0163-769X/06/$20.00/0
*Printed in U.S.A.*

Endocrine Reviews 27(5):485–534

doi: 10.1210/er.2005-9998

# Advances in the Treatment of Prolactinomas

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**Prolactinomas account for approximately 40% of all pituitary adenomas and are an important cause of hypogonadism and infertility. The ultimate goal of therapy for prolactinomas is restoration or achievement of eugonadism through the normalization of hyperprolactinemia and control of tumor mass. Medical therapy with dopamine agonists is highly effective in the majority of cases and represents the mainstay of therapy. Recent data indicating successful withdrawal of these agents in a subset of patients challenge the previously held concept that medical therapy is a lifelong requirement. Complicated situations, such as those encountered in resistance to dopamine agonists, pregnancy, and giant or malignant prolactinomas, may require multimodal therapy involving surgery, radiotherapy, or both. Progress in elucidating the mechanisms underlying the pathogenesis of prolactinomas may enable future development of novel molecular therapies for treatment-resistant cases. This review provides a critical analysis of the efficacy and safety of the various modes of therapy available for the treatment of patients with prolactinomas with an emphasis on challenging situations, a discussion of the data regarding withdrawal of medical therapy, and a foreshadowing of novel approaches to therapy that may become available in the future. (*Endocrine Reviews* 27: 485–534, 2006)**



**First Published Online May 26, 2006**

Abbreviations: BMD, Bone mineral density; BMI, body mass index; CSF, cerebrospinal fluid; CT, computed tomography; ER, estrogen receptor; LINAC, linear accelerator; MEN 1, multiple endocrine neoplasia type 1; MRI, magnetic resonance imaging; NGF, nerve growth factor; PRL, prolactin; SCRT, stereotactic conformal radiotherapy; SERM, selective ER modulator; SSTR, somatostatin receptor; TK, thymidine kinase.

***Endocrine Reviews* is published by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.**

## I. Introduction

### *A. Historical overview*

IN THE LATE 1920s and early 1930s, a number of groups found that pituitary extracts could induce milk secretion. Riddle *et al*. (1–3) found that this substance, which they named prolactin (PRL), was different from other known growth- and gonadal-stimulating substances. They found that this PRL stimulated production of a milk-like substance from the crop sacs of pigeons and doves, and they developed the pigeon crop sac assay (1–3) that became the standard assay procedure for PRL over the next 30 yr. Eventually, this assay was replaced by specific RIAs in a number of species.

In humans, however, because of the high lactogenic activity of even very highly purified preparations of human GH (4, 5), it was impossible to separate human PRL from GH using the relatively crude pigeon crop assay, and the very existence of a distinct PRL isoform in humans was questioned (5). On the other hand, at the same time, it was observed that most patients with pituitary tumors in whom galactorrhea and amenorrhea were the cardinal clinical features did not have acromegalic features (6) and patients who were known to have isolated, congenital GH deficiency were able to lactate postpartum (7). In 1970, Frantz and Kleinberg (8) developed a sensitive bioassay in which they used excess antibody to GH to neutralize any potential lactogenic effects it had and, for the first time, were able to demonstrate measurable PRL levels in women with puerperal and nonpuerperal galactorrhea but not in most normal men. Subsequently, further purification of human PRL led to the development of RIAs that could finally measure PRL levels in the sera of normal individuals (9).

At the same time that PRL was initially being characterized in the early 1930s by Riddle *et al*. (1–3), so too were appearing the first clinical reports of a syndrome of amenorrhea coupled with galactorrhea (10, 11). Over the ensuing 20 yr, three distinct clinical syndromes were described: 1) the Chiari-Frommel Syndrome—amenorrhea, galactorrhea, and low urinary gonadotropins occurring postpartum (12); 2) the Ahumada-Argonz-del Castillo syndrome—nonpuerperal amenorrhea, galactorrhea, and low urinary gonadotropins with no evidence of a pituitary tumor on standard skull x-rays (13); and 3) the Forbes-Henneman-Griswold-Albright syndrome—nonpuerperal amenorrhea, galactorrhea, and low urinary gonadotropins in association with a chromophobe adenoma (6). Overproduction of PRL was postulated in both of the last two syndromes (6, 13). Friesen *et al.* (14) then demonstrated elevated radioimmunoassayable PRL levels in the serum of a patient with a prolactinoma, the fall in such levels with partial tumor resection, and the production of PRL by the tumor *in vitro*. The now recognized insensitivity of standard skull x-rays and a better understanding of the pathophysiology of prolactinomas have rendered obsolete this early eponymic classification of PRL disorders.

### *B. Epidemiology*

Prolactinomas are the most frequent pituitary tumors, with an estimated prevalence in the adult population of 100 per million population (15). However, recently Beckers *et al.* (16) found a much higher prevalence at 55 per 71,000 (775 per million) inhabitants in Belgium. Their frequency varies with age and sex, occurring most frequently in females between 20 and 50 yr old, when the ratio between the sexes is estimated to be 10:1. After the fifth decade of life, the frequency of prolactinomas is similar in both sexes (17, 18). In the pediatric/adolescent age, prolactinomas are rare, but represent about half of all pituitary adenomas, which, overall, account for less than 2% of intracranial tumors (19, 20). One possible explanation for the increased prevalence of prolactinomas in women may be related to the fact that the clinical presentation in women is more evident, usually the classical amenorrhea-galactorrhea syndrome, whereas men may ignore the symptoms of impotence and decreased libido and the diagnosis is often made when signs of compression due to the tumor develop (17). However, studies comparing the clinical and pathological correlates of growth of these tumors in both sexes are lacking, and a more aggressive course of the disease in men has not been ruled out. Delgrange *et al. (*21*)* showed a greater growth potential of macroprolactinomas in men than in women as well as a male preponderance of aggressive forms of the disease (*i.e.*, giant, invasive, and malignant prolactinomas).

Prolactinomas cause gonadal and sexual dysfunction related to the hyperprolactinemia and may cause other symptoms related to the tumor expansion. The major objectives of treating patients with prolactinomas are: 1) to suppress excessive hormone secretion and its clinical consequences, such as infertility, sexual dysfunction, and osteoporosis; 2) to control tumor mass, thereby relieving visual field defects, cranial nerve function, and possibly hypopituitarism; 3) to preserve or improve residual pituitary function; and 4) to prevent disease recurrence or progression. Treatment goals for micro- and macroprolactinomas are similar; however, for the majority of microprolactinomas, control of tumor size is a less clinically important endpoint because microprolactinomas do not cause neurological defects, nor are they at substantial risk for growth over time. In larger macroprolactinomas that are at risk for neurological sequelae, control of tumor growth or reduction in size takes priority over the treatment of hypogonadism. Furthermore, patients with macroprolactinomas and hypopituitarism should receive standard hormonal replacement therapy for hypopituitarism as in other types of macroadenomas. The initiation of GH replacement should be delayed if there is a reasonable likelihood that hypopituitarism will resolve and/or normoprolactinemia can be achieved, because GH deficiency can resolve with pharmacotherapy-induced PRL normalization (22). If substantial tumor reduction is not observed after initiating treatment for

the prolactinoma and reversal of GH deficiency does not appear realistic, GH therapy should be considered. Because of a theoretical risk of GH/growth factor-induced tumor enlargement, GH therapy in this situation must be done cautiously.

This review provides a critical analysis of the efficacy and safety of the various modes of therapy available for the treatment of patients with prolactinomas. Special attention will focus on challenging situations, including the treatment of patients resistant to dopamine agonists, the treatment of children and adolescents, and management of women who become pregnant. We will review the evidence of the efficacy of withdrawal from dopamine agonists after long-term treatment and, finally, highlight experimental therapies currently under investigation.

## II. Observation

### *A. Treatment indications*

Asymptomatic patients with prolactinomas do not have an absolute requirement for treatment of their prolactinomas. Indications for therapy in patients with prolactinomas may be divided into two categories: 1) effects of tumor size, and 2) effects of hyperprolactinemia (Table 1). Studies examining the natural history of untreated microprolactinomas have shown that significant growth of these tumors is uncommon (Table 2). Six series of patients with microadenomas who were found to have computed tomography (CT) or tomographic evidence of prolactinomas were observed without treatment for a period up to 8 yr (23–28). Of 139 women, only nine (7%) microprolactinomas had evidence for growth. Thus, the simple argument that therapy is indicated for a microadenoma to prevent it from growing is fallacious. On the other hand, an untreated prolactinoma should be followed closely to determine whether it is enlarging. It is very unlikely for a prolactinoma to grow significantly without an increase in serum PRL levels, although this phenomenon has been reported (29). Therefore, most patients with microadenomas verified by imaging may be monitored with serial PRL levels. Although there is no consensus on the frequency of imaging after the achievement of normoprolactinemia, most clinicians monitor with pituitary magnetic resonance imaging (MRI) periodically to verify the absence of tumor growth and to ensure that PRL levels are reliable indicators of tumor size. If PRL levels rise or symptoms of mass effects develop (such as headaches), then repeat scanning is indicated to evaluate for the possibility of significant tumor growth. Significant increases in PRL levels usually, although not always (30), reflect tumor growth. A microadenoma with documented evidence of growth demands therapy for the size change alone, because it may be one of the 7% that will grow to be a macroadenoma.

TABLE 1. Indications for therapy

| |
|---|
| Mass effects |
| Hypopituitarism |
| Visual field defects due to pressure on the optic chiasm |
| Cranial nerve deficits |
| Headaches |
| Effects of hyperprolactinemia |
| Hypogonadism |
| Amenorrhea or oligomenorrhea |
| Infertility |
| Impotence |
| Osteoporosis or osteopenia |
| Relative indications |
| Bothersome hirsutism |
| Bothersome galactorrhea |

TABLE 2. Studies examining the natural history of microprolactinomas

| Study | Ref. | Patients (n) | Evidence of tumor growth | Length of follow-up (yr) |
|---|---|---|---|---|
| Von Werder *et al.* | 27 | 10 | 1 | 4 |
| March *et al.* | 24 | 43 | 2 | 4 |
| Weiss *et al.* | 28 | 27 | 3 | 6 |
| Koppelman *et al.* | 23 | 8 | 1 | 2.5–7.5 |
| Sisam *et al.* | 26 | 38 | 0 | 4 |
| Schlechte *et al.* | 25 | 13 | 2 | 5.3 |
| TOTAL | | 139 | 9 (6.5%) | 2.5–8.0 |

The presence of a macroadenoma raises the probability for the tumor in question to have biological characteristics that confer a propensity to grow. Moreover, most macroprolactinomas are associated with PRL elevations significant enough to elicit symptoms that would warrant treatment. Therefore, unless there are specific contraindications, therapy is usually advisable for these tumors. Local or diffuse invasion and compression of adjacent structures, such as the stalk or optic chiasm, are additional indications for therapy.

Other indications for therapy are relative, being due to the hyperprolactinemia itself. These include: decreased libido, menstrual dysfunction, galactorrhea, infertility, hirsutism, impotence, and premature osteoporosis. Eugonadal women with nonbothersome galactorrhea do not have specific reasons for therapy. On the other hand, a woman harboring a prolactinoma with amenorrhea and anovulation who wishes to become pregnant has a clear indication for therapy. However, if such a woman does not wish to become pregnant, then therapy may be warranted to prevent osteoporosis or to improve libido.

### *B. Oral contraceptives for hypogonadism*

Hypogondal women with microprolactinomas may be treated for their hypogonadism with oral contraceptives, provided that their PRL levels do not increase substantially and there is no evidence of tumor enlargement (31). Series of patients with prolactinomas who are treated with oral contraceptives for hypogonadism have not shown substantial risk for tumor enlargement (32). Individual case reports of tumor enlargement during estrogen therapy have been documented, but whether tumor enlargement in these cases was related to use of estrogen or reflected the natural progression of these particular tumors is not known. Because of this uncertainty, it is advisable to monitor patients who use oral contraceptives carefully with periodic measurement of PRL levels (33–35).

The ability to follow patients closely with PRL levels, MRI scans, and bone mineral density (BMD) studies and the knowledge of the efficacy of various modes of therapy allow

a highly individualized way of managing patients and choosing the proper mode of their therapy.

## III. Surgery

### *A. Surgical approaches*

Historically, surgical resection of prolactinomas was the preferred mode of therapy until the mid-1980s, when bromocriptine became available and was shown to be effective in the control of these tumors. Most, although not all, authorities reserve surgical treatment of prolactinomas for special circumstances. A list of surgical indications is presented in Table 3.

Pituitary apoplexy is a potentially life-threatening clinical syndrome caused by infarction or hemorrhage into an existing pituitary tumor (36). These patients may develop visual disturbance, associated with severe headache, altered consciousness, and vascular collapse. Under certain circumstances, *i.e.*, severe, progressive visual loss, it represents the most urgent indication for surgical intervention. There is solid evidence, however, that apoplexy in patients with stable visual field deficits may be managed medically under careful monitoring, with complete resolution of neuroophthalmological signs and visual deficits (37–39). An effort to manage patients with pituitary apoplexy nonsurgically is particularly important for prolactinomas, because surgical intervention and decompression do not ensure long-term cure of these tumors. Neurosurgical and endocrine expertise is required to safely manage and monitor patients with apoplexy nonsurgically. Other indications include failure of medical therapy, defined as inadequate PRL reduction on high doses of dopamine agonists, or tumor enlargement, even if accompanied by sufficient PRL lowering. Finally, surgery may be necessary in pregnant women with expanding prolactinomas associated with unstable neuroophthalmological deficits that do not respond to bromocriptine (see *Section IX*).

When surgery is undertaken, the transsphenoidal approach represents the standard of care for microprolactinomas and the overwhelming majority of macroprolactinomas (40). Craniotomy, which is rarely indicated, is reserved for tumors that are inaccessible via the transsphenoidal approach. Such cases might include patients with large tumors with suprasellar, parasellar, or unusual intracranial extensions, such as those extending toward the frontal or temporal lobes (41). Favorable experience with variations of the standard transsphenoidal approach have recently been described and provide alternatives to transcranial approaches, even for previously unapproachable lesions involving the cavernous sinus and parasellar region (42). Giant and invasive prolactinomas cannot be cured by surgery, regardless of the surgical technique employed or the experience of the neurosurgeon; therefore, if undertaken, the goal of surgery under these circumstances is to debulk with the prospect of improving symptoms related to mass effects (43).

TABLE 3. Indications for surgery

| |
|---|
| Unstable pituitary apoplexy |
| Failure of medical therapy |
| Inadequate reduction of PRL to restore gonadal function |
| Tumor enlargement |
| Tumor enlargement despite sufficient PRL reduction |
| Desire for pregnancy |
| Previous pregnancy complicated by symptomatic tumor expansion |
| Personal choice to avoid dopamine agonist therapy during estation (macroadenomas) |
| Symptomatic, unstable tumor enlargement during pregnancy that does not respond to reinstitution of dopamine agonist treatment |

### *B. Endoscopy*

Recent technological advances have catapulted minimally invasive endoscopic techniques to the forefront of transsphenoidal surgery (41). The main advantage afforded by endoscopy is the superior panoramic view. Some surgeons exploit endoscopy as an adjunctive visualizing tool, but increasingly, the endoscope is being used as a stand-alone operating instrument, used in one of several different ways. The most common method consists of an endoscopic endonasal unilateral approach, permitting removal of the entire tumor through the nostril. In addition to the wide surgical view, endoscopy provides three additional potential benefits, including: 1) avoidance of submucosal transseptal dissection, thus eliminating nasoseptal perforations; 2) less patient discomfort due to the lack of nasal packing; and 3) reduced operative time and hospital stay (44). For the neurosurgeon, the major obstacle to adopting the endoscopic technique is that of the need to acquire novel surgical skills (45, 46). Although the number of reported cases and follow-up duration are limited, preliminary studies suggest that complication rates of the endonasal endoscopic approach may be comparable to, or perhaps slightly lower than, those observed using the traditional operating microscope (47–51). Two studies comparing outcomes of endonasal endoscopic microsurgery and sublabial microsurgery specifically for prolactinomas found no differences in initial surgical remission rates but fewer minor complications associated with endoscopic or endoscopic-assisted procedures (52, 53).

### *C. Intraoperative imaging*

Currently, intraoperative imaging is used by most neurosurgical centers, both for guidance to reach the sphenoid sinus and sella and to assess the extent of tumor resection. C-arm videofluoroscopy is the most widely used guidance device. Frameless stereotaxy, or "neuronavigation", is a newer intraoperative computer-guided imaging system that assists the surgeon in the identification of anatomical landmarks and allows referral to preoperative MRI images in several planes of view simultaneously. This technique is achieved by segmentation and three-dimensional reconstruction of the tumor and adjacent structures. Neuronavigation is most valuable in reoperations where the anatomy may be distorted, but it is also helpful in surgeries involving large, invasive or suprasellar tumors and in cases where the carotid arteries are closely approximated or kinked (40, 54). Because the morphology of the tumor and neurovascular structures shift during tumor resection, frameless stereotaxy cannot be used to estimate the extent of tumor removal.

Moreover, these systems have the disadvantage of requiring greater set-up time. Whether the use of neuronavigational systems improves surgical cure rates or reduces the frequency of complications is unknown.

Intraoperative MRI has been used in some centers to delineate tumor borders and to accurately monitor the extent of tumor resection (55). This imaging modality is in an evolving stage of development and improvement. A comprehensive evaluation of the different available MRI systems has been reported by Albayrak *et al.* (55). The predominant opinion is that intraoperative MRI will have limited use in resecting purely sellar microadenomas but may be beneficial for assessing the adequacy of resection of supra- and parasellar extensions (40). Long-term results are not available to determine whether this application improves surgical outcomes.

Use of ultrasonography is chiefly used in transcranial procedures performed in the resection of giant macroadenomas. The advantage of ultrasound over MRI is the provision of real-time feedback to the surgeon during tumor removal. Because indications to resect giant invasive prolactinomas requiring craniotomy are extraordinarily rare, this imaging modality, in its current form, is suspected to have limited application for the surgical management of prolactinomas.

Regardless of the innovative operative techniques and imaging modalities emerging, the specific surgical treatment plan of a patient with a prolactinoma ultimately depends upon the availability, familiarity, and expertise of these instruments for the neurosurgical center and neurosurgeon to which one refers their patients. Definitive data on the impact of these advances on surgical outcomes are not yet available.

### *D. Surgical success rates*

Surgical outcomes are highly dependent upon the expertise and experience of the neurosurgeon, as well as the size of the tumor. Surgical results from 50 published series are summarized in Table 4. Only results from the latest series from a given neurosurgical/endocrine team are included, omitting data from earlier studies. Criteria for inclusion in this analysis consists of the following: 1) cure or remission rates are reported with respect to size of the tumor (microadenoma *vs.* macroadenoma); 2) normalization of PRL levels defines surgical remission; and 3) surgical cure rates are reported on the basis of the number of patients with documented follow-up. Combining data from all 50 series, 1596 of 2137 (74.7%) microadenomas and 755 of 2226 (33.9%) macroadenomas were classified as achieving initial surgical remission, *i.e.*, having PRL levels normalized by 1–12 wk after surgery. Within these series, the surgical success rates were highly variable. For series with at least 10 patients, the surgical remission rate varied from 38 to 100% for microadenomas and from 6.7 to 80% for macroadenomas. Similar data were obtained from a mail survey of 80 neurosurgeons, which found surgical cure rates of 74% of 1518 PRL-secreting microadenomas and 30% of 1022 PRL-secreting macroadenomas (56). In this latter report, criteria for the assignment of patients to micro- or macroadenoma status was made on the basis of imaging and/or PRL levels ($<$ or $>$ 200 ng/ml, respectively). Clearly, for the macroadenomas the success rate in large part was dependent on the size of tumors chosen for surgery. In many series, the objective was, appropriately, debulking of a very large tumor rather than cure, and in other series very large tumors were not operated upon.

Although surgical series reported from the last decade have used some of the newer techniques described above, the results from these series cannot be strictly compared with those of early series because of differences in the patient populations. In the past 10–15 yr, most patients were treated with dopamine agonists first, and only those resistant to or intolerant of these drugs or whose tumors did not decrease in size were referred for surgery. In some series, it was reported that prior use of dopamine agonists made it more difficult to remove the tumor (see *Section III.E* for a more extensive discussion of this). Overall, it does not appear that surgical outcomes are substantially different now compared with 20 yr ago, but a formal analysis cannot be carried out for the above-stated reasons.

In a number of series, it was the impression that PRL levels were more predictive of surgical success than actual size of the tumor. Patients with serum PRL levels above 200 ng/ml were found to have a decreased chance for cure at surgery even when stratified within micro- and macroadenoma groups (57–62). Thus, PRL levels above 200 ng/ml appear to be a risk factor for poor surgical outcome independent of tumor size. An obvious explanation for this finding is lacking, because one would expect higher PRL levels in more highly differentiated tumors, which might thereby impart a greater likelihood of complete tumor resection. It is unknown whether the extent of dural invasion and the degree of histological differentiation of a tumor correlate with PRL levels in prolactinomas.

Gonadal function is almost uniformly restored in both sexes upon achievement of normoprolactinemia after successful surgical resection (63–66). In young women, normal LH pulsatility is restored as early as the eighth postoperative day (66, 67). Often normal reproductive function is obtained even with PRL levels slightly above normal, but because such patients appear to have a much greater chance of recurrence of more significant hyperprolactinemia (see *Section III.F*), they cannot be deemed definitively cured. Patients with macroadenomas of all types may be hypopituitary before surgery and, because of the extent of surgery sometimes performed, may have significant changes in pituitary function postoperatively. In an analysis of 84 patients with macroadenomas (36 were prolactinomas), Nelson *et al.* (68) found that of those with normal preoperative pituitary function, only 78% retained normal function postoperatively. One third with some pituitary deficits before surgery improved, and one third with such deficits had worsened pituitary function after surgery. None of the panhypopituitary patients improved after surgery (68).

### *E. Recurrence and long-term cure*

One of the most controversial areas regarding the surgical management of prolactinomas involves the likelihood of a recurrence of hyperprolactinemia in patients who have undergone an initial remission. Rates of recurrence, as observed

TABLE 4. Surgical outcomes for prolactinomas

| First author of series | Ref. | Tumors operated | | Tumors in remission | | % in remission | | Recurrence | | % Recurrence | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Micro | Macro | Micro | Macro | Micro | Macro | Micro | Macro | Micro | Macro |
| Antunes | 114 | 9 | 8 | 3 | 3 | 33.3 | 37.5 | | | | |
| Wiebe | 62 | 13 | | 5 | | 38.5 | | | | | |
| Aubourg | 578 | 23 | 67 | 13 | 26 | 56.5 | 38.8 | | | | |
| Domingue | 433 | 67 | 25 | 46 | 10 | 68.7 | 40.0 | | | | |
| Grisoli | 436 | | 20 | | 6 | | 30.0 | | | | |
| Nicola | 579 | 70 | 40 | 47 | 16 | 67.1 | 40.0 | | | | |
| Rawe | 61 | 21 | 9 | 17 | 3 | 81.0 | 33.3 | | | | |
| Samaan | 580 | 26 | | 20 | | 76.9 | | | | | |
| Landolt | 59 | 33 | 37 | 25 | 10 | 75.8 | 27.0 | | | | |
| Pelkonen | 438 | 6 | 53 | 3 | 6 | 50.0 | 11.3 | | | | |
| Tucker | 581 | 27 | 18 | 20 | 8 | 74.1 | 44.4 | 3 | | 15.0 | |
| Faria | 582 | 72 | 28 | 55 | 13 | 76.4 | 46.4 | 4 | 4 | 13.3 | 36.4 |
| Giovanelli[a] | 583 | 48 | | 38 | | 79.2 | | 10 | | 26.3 | |
| Smallridge | 584 | 19 | 5 | 12 | 0 | 63.2 | 0.0 | | | | |
| Von Werder | 27 | 31 | | 20 | | 64.5 | | | | | |
| Woosley | 585 | 22 | 14 | 16 | 5 | 72.7 | 35.7 | 1 | 0 | 6.3 | 0.0 |
| Ciric | 465 | | 41 | | 11 | | 26.8 | | | | |
| Nelson | 586 | 28 | 11 | 21 | 4 | 75.0 | 36.4 | 8 | 1 | 38.1 | 25.0 |
| Randall | 60 | 54 | 46 | 39 | 13 | 72.2 | 28.3 | | | | |
| Dupuy | 434 | 2 | 78 | 2 | 7 | 100.0 | 9.0 | | | | |
| Hardy | 75 | 186 | 89 | 143 | 34 | 76.9 | 38.2 | 12 | 4 | 50.0 | 80.0 |
| Rodman | 587 | 42 | 23 | 37 | 9 | 88.1 | 39.1 | 5 | 1 | 17.2 | 20.0 |
| Brabant | 588 | 19 | 37 | 11 | 14 | 57.9 | 37.8 | | | | |
| Charpentier | 57 | 58 | 289 | 35 | 134 | 60.3 | 46.4 | 2 | 10 | 5.7 | 7.5 |
| Fahlbusch | 58 | 108 | 139 | 66 | 15 | 61.1 | 10.8 | 8 | 1 | 16.0 | 6.7 |
| Scanlon | 69 | 15 | 20 | 10 | 16 | 66.7 | 80.0 | 0 | 0 | 0.0 | 0.0 |
| Arafah | 589 | 74 | 46 | 67 | 29 | 90.5 | 63.0 | 5 | 10 | 7.5 | 34.5 |
| Parl | 590 | | | 13 | 11 | | | 4 | 10 | 30.8 | 90.9 |
| Schlechte | 336 | 30 | 24 | 20 | 11 | 66.7 | 45.8 | 8 | 4 | 40.0 | 36.4 |
| Bevan | 85 | 39 | 28 | 27 | 8 | 69.2 | 28.6 | 1 | 1 | 3.7 | 12.5 |
| Guidetti | 466 | 34 | 120 | 20 | 11 | 58.8 | 9.2 | 8 | 4 | 40.0 | 36.4 |
| Ciccarelli | 71 | | | 18 | 4 | | | 4 | 4 | 22.2 | 100.0 |
| Webster | 80 | 42 | 37 | 35 | 28 | 83.3 | 75.7 | 6 | 2 | 17.1 | 7.1 |
| van't Verlaat | 591 | 11 | | 11 | | 100.0 | | 5 | | 45.5 | |
| Thomson | 592 | 61 | 8 | 46 | 4 | 75.4 | 50.0 | 8 | 0 | 19.5 | 0.0 |
| Massoud | 73 | 64 | | 58 | | 90.6 | | 25 | | 43.1 | |
| Soule | 593 | 11 | 23 | 5 | 4 | 45.5 | 17.4 | 1 | 0 | 20.0 | |
| Giovanelli[a] | 88 | 92 | 118 | 71 | 26 | 77.2 | 22.0 | | | | |
| Biller | 594 | 23 | 14 | 21 | 6 | 91.3 | 42.9 | 2 | | 9.5 | 0.0 |
| Inoue | 133 | 13 | | 7 | | 53.8 | | | | | |
| Turner | 92 | 32 | | 25 | | 78.1 | | 1 | | 4.0 | |
| Tyrrell | 72 | 84 | 129 | 69 | 83 | 82.1 | 64.3 | | | | |
| Gokalp | 76 | 311 | 239 | 200 | 16 | 64.3 | 6.7 | | | | |
| Acquati | 595 | | 83 | | 15 | | 18.1 | | 2 | | 13.3 |
| Abe | 596 | 5 | 9 | 4 | 2 | 80.0 | 22.2 | | | | |
| Amar | 82 | 107 | 115 | 97 | 79 | 90.7 | 68.7 | 0 | 41 | 0.0 | 51.9 |
| Kristof | 79 | 5 | 32 | 2 | 8 | 40.0 | 25.0 | 1 | 1 | 50.0 | 12.5 |
| Wolfsberger | 81 | 11 | | 9 | | 81.8 | | 1 | | 11.1 | |
| Esposito | 597 | 20 | 22 | 15 | 6 | 75.0 | 27.3 | 5 | 0 | 33.3 | 0.0 |
| Mortini | 598 | 69 | 82 | 52 | 41 | 75.4 | 50.0 | 9 | 6 | 17.3 | 14.6 |
| Totals | | 2137 | 2226 | 1596 | 755 | 74.7 | 33.9 | 147 | 106 | | |

[a] These appear to be separate series of patients.

with rates of surgical remissions, are highly variable among neurosurgical centers, ranging from 0 (69) to 50% (70). In part, this reflects differences in the level of neurosurgical expertise. Unfortunately, the surgical literature is confounded by variable follow-up times, drop-out rates, and definitions of cure/recurrence. It is possible, and even likely, that surgical series with relatively short follow-up times will underestimate the true recurrence rate because the time to recurrence of hyperprolactinemia in some tumors may be lengthy (71). As for surgical cure, most often, recurrence is defined as the discovery of an elevated PRL level at any point in the postoperative surveillance period after an initial surgical remission. On the other hand, some authors use less stringent criteria, regarding patients with mild asymptomatic hyperprolactinemia as in remission (72). Given all of these factors, a true assessment of recurrence rates is difficult to establish.

Adding further confusion to the controversy are series reporting that recurrence of mild hyperprolactinemia in some women after adenomectomy for prolactinomas resolves with time, and therefore may not definitively reflect operative failure (73, 74). One important study described the

course of eight patients who developed recurrent hyperprolactinemia 2 to 10 yr postoperatively and who were monitored thereafter without treatment (74). One patient was found to have primary hypothyroidism and became normoprolactinemic with L-$T_4$ therapy, thus accounting for her PRL elevation. Of the remaining seven patients, four underwent a spontaneous remission of hyperprolactinemia. This course of relapse, followed by a second remission, has not been widely reported. It is unknown whether these experiences are atypical or whether they reflect a more frequent outcome that has simply gone unrecognized thus far.

From the series compiled in Table 4, recurrence rates for microadenomas [147 of 809 (18.2%)] and macroadenomas [106 of 465 (22.8%)] are similar. It should be emphasized that under most circumstances, the recurrence is detected biochemically (hyperprolactinemia), not necessarily with radiographic documentation of tumor regrowth. Recurrence of the hyperprolactinemia is usually accompanied by sexual/reproductive dysfunction, which thereby serves as an indication for medical therapy to reduce PRL hypersecretion. In a series of patients with microadenomas operated upon by Dr. Jules Hardy, of 58 patients with a normal PRL postoperatively, 25 had a relapse of hyperprolactinemia after a mean of 3.3 yr, but only 10 of these 25 had a recurrence of amenorrhea or galactorrhea, and CT scans showed evidence of a recurrence of the microadenoma in only two (75).

Overall long-term surgical cure rates may be calculated based upon series that have reported both initial remission rates and recurrence rates, understanding that these numbers reflect somewhat of a reporting bias, because they are derived from neurosurgeons who are willing to publish their data. Based on the initial remission rate of 74.7% and the recurrence rate of 18.2% cited above, an overall long-term surgical cure rate for microadenomas among these selected series, using a normal PRL level as the criterion, is 61.1%. For patients with macroadenomas, with an initial remission rate of 33.9% and a recurrence rate of 22.8%, the long-term cure rate is 26.2%. These general numbers may be given to patients when counseling them with respect to choices of therapy. Neurosurgeons who have compiled their own data on surgical cures and remission may provide patients with more meaningful personal estimates for cure, based upon their individual statistics. For patients with giant prolactinomas and those with considerable cavernous sinus invasion, the chance for surgical cure is essentially zero (76–78).

### *F. Predictors of remission and cure*

A number of studies have analyzed factors that might predict initial surgical remission and likelihood for long-term cure. As discussed above, several studies have identified an inverse relationship between preoperative PRL levels and chances for initial surgical remission (57, 60–62, 72, 79–81). Initial surgical success is also correlated with adenoma stage (58, 72). A low immediate postoperative PRL level has been shown to be an excellent predictor of long-term surgical cure (82, 83). For example, one large analysis of surgical outcomes of 339 surgically resected prolactinomas showed that when a postoperative PRL level below 5 ng/ml was achieved, 80.5% of the cohort remained in remission over a mean follow-up of 9.2 yr (83).[1] In this series, the immediate postoperative PRL level was a better predictor of long-term surgical cure than the preoperative PRL level. A separate (5-yr follow-up) study found that a postoperative PRL below 10 ng/ml predicted biochemical cure with 100% accuracy for both micro- and macroadenomas; cure was unlikely to be obtained in patients with postoperative PRL levels between 10 and 20 ng/ml (*i.e.*, the high normal range) (82). Repeat transsphenoidal surgery for persistent tumor after failed surgery or radiotherapy is curative in less than 50% of the cases (83).

An extensive debate regarding the effects of pretreatment with dopamine agonists on surgical outcomes for prolactinomas has pervaded the surgical literature in the past. Landolt *et al.* (84) were the first to report better surgical cure rates for microadenomas that had not been exposed to dopamine agonists before surgery. In the hands of some neurosurgeons, it is the impression that dopamine agonist treatment induces tumor fibrosis, creating a tough tumor consistency that made surgical removal difficult. However, the majority of other series investigating this issue have not corroborated these results (72, 85–89). Because surgery for prolactinomas in the present era most often follows a trial of dopamine agonist therapy, the decision of whether or not to use a dopamine agonist has already been made.

### *G. Complications*

Complications from transsphenoidal surgery for microadenomas are quite infrequent, the mortality rate being at most 0.6%, the major morbidity rate being about 3.4% (visual loss 0.1%, stroke/vascular injury 0.2%, meningitis/abscess 0.1% and oculomotor palsy 0.1%) and cerebrospinal fluid (CSF) rhinorrhea occurring in 1.9% (41, 56, 90, 91). The mortality rate for transsphenoidal surgery for all types of secreting and nonsecreting macroadenomas is 0.9%, the major morbidity rate is 6.5% (visual loss 1.5%, stroke/vascular injury 0.6%, meningitis/abscess 0.5%, and oculomotor palsy 0.6%), and the rate of CSF rhinorrhea is 3.3% (41, 56, 90, 91). Transient diabetes insipidus is quite common with transsphenoidal surgery for both micro- and macroadenomas, and permanent diabetes insipidus occurs in about 1% of surgeries on macroadenomas (56, 91). Hypopituitarism is common in patients with macroadenomas before surgery as a result of mass effects, occurring in more than 50% of patients. With surgery, either further worsening or improvement may occur (68). GH deficiency after transsphenoidal surgery for microprolactinomas was reported as high as 30% in one series (92). Surgery involving craniotomy is much more hazardous. Although visual field defects and reduction in visual acuity can be improved in 74% of patients whose macroadenomas abut the optic chiasm (93), a small number of patients with normal visual fields may have a reduction of vision after surgery due to herniation of the chiasm into an empty sella, direct injury or devascularization of the optic apparatus, fracture of the orbit, postoperative hematoma, or cerebral vasospasm (94).

[1] These data were not incorporated into the present analysis of surgical remission and recurrence rates because percentages of cure were reported based on the number of individuals in the initial cohort, rather than on patients who truly followed up.

*H. Surgical vs. medical therapy*

Although most authorities recommend transsphenoidal surgery as a second line option for prolactinomas, some experts continue to advocate surgery as a potentially curative procedure in selected patients (72, 92, 95, 96). These experts propose that young patients with microadenomas who have a good chance of cure could avoid the need for extended medical therapy. Enthusiasm for this perspective is tempered by recent evidence that withdrawal of cabergoline may lead to sustained remission in some cases (97, 98). Couldwell and Weiss (99) make an economic argument that surgical intervention is less expensive than lifelong medical therapy. On the other hand, a surgery complicated by hypopituitarism has the potential to incur significantly higher costs (with replacement of pituitary hormones) and lead to higher morbidity (secondary adrenal insufficiency) over many years. Admittedly, hypopituitarism is an unlikely complication for the resection of a microprolactinoma in the hands of an experienced neurosurgeon. One should also bear in mind that with the expected upcoming availability of cabergoline in generic form, even an uncomplicated transsphenoidal surgery may prove to be more expensive than the cost of medical therapy. Given its efficacy and safety, as discussed in *Section V*, medical therapy remains the first line therapy for the treatment of prolactinomas.

## IV. Radiotherapy

*A. Delivery of radiotherapy*

The availability of highly effective medical and surgical therapies for the majority of prolactinomas has rendered the role of radiotherapy in the management of prolactinomas as one of adjunctive therapy. In most cases, radiotherapy is used after failed transsphenoidal surgery and medical therapy. Rarely, in a few centers, it has been administered postoperatively as a prophylactic measure to prevent growth of a remnant tumor.

Today, several methodologies for the delivery of radiotherapy are available. Conventional fractionated external beam radiotherapy involves the use of several ports to concentrate an x-ray beam on the pituitary fossa by a crossfire technique while the patient is immobilized in an individually shaped plastic mask. Supravoltage radiotherapy is delivered in daily doses of 200 cGy 4–5 d/wk over a period of 5–6 wk up to a total dose of 4500–5000 Gy (100). Stereotactic conformal radiotherapy (SCRT) is also a fractionated form of radiotherapy, but uses stereotactic techniques to deliver radiation with higher precision. The underlying principle of SCRT is to shape the radiation beams to conform to the shape of the tumor, thereby reducing radiation exposure to surrounding normal brain (101). Most SCRT is delivered with linear accelerators (LINAC) that generate photon beams focusing on a stationary target, using a moving gantry system (102). Most recently, single dose radiotherapy has become widely available and is being increasingly used. This form of radiotherapy delivers a necrotizing dose to the tumor, which has been stereotactically defined using three-dimensional image processing. The hallmark of this type of radiotherapy is the sharp dose gradient of radiation at the treatment field edges, which reduces the dose of radiation to the surrounding normal brain tissue. Most single-dose radiotherapy uses cobalt-60 gamma radiation emitting sources ("gamma-knife" radiotherapy) arranged in a hemisphere to focus on a central target. This results in multiple small radiation spheres that are combined in a multiple isocenter technique to conform to the shape of nonspherical pituitary tumors (103). An alternative method of delivering single-dose radiation therapy is with the use of a LINAC-based system that has been modified to limit mechanical instability and inaccuracy (104, 105). There is no clear advantage for either of these single-dose techniques (gamma knife *vs.*, LINAC) in terms of their ability to spare normal tissue from high radiation doses (106). Treatment of pituitary adenomas with single-dose radiation therapy using heavy-charge particle proton beams is very limited, because few centers have the facilities to provide this form of radiotherapy, due to its high operational and maintenance costs (107). As of yet, there are no adequate studies to conclude whether there is one mode of single dose radiotherapy that has superior efficacy or safety.

Regardless of the delivery system, the aim of all high precision techniques is to minimize radiation exposure to the surrounding normal tissue. The combination of better immobilization and high-definition three-dimensional imaging has been the most important determinant of improvements in modern radiotherapy—less so the technique of delivery (103). The two general therapeutic goals for performing radiotherapy in prolactinomas are: 1) arrest of tumor growth and prevention of further problems from mass effects; and 2) normalization of hyperprolactinemia (108–112). However, it is possible that persistent postradiotherapy elevations of PRL in patients with prolactinomas are due to a radiation effect and are not caused by hypersecretion from residual tumor (113). Although these arguments may hold true, the variable definitions of "mildly elevated PRL levels" and "improvement" preclude an accurate assessment of radiotherapy efficacy.

*B. Analysis of radiotherapy studies*

There are several important caveats regarding the critical interpretation of data in clinical studies of the efficacy of radiotherapy for the treatment of prolactinomas. The first relates to the definitions of tumor control endpoints. Tumor control may be defined with either endocrinological (normalization of PRL levels) or volumetric (long-term radiographic assessment of tumor size) parameters. Many series report a tumor "control" rate, which often refers to the stable PRL levels or the absence of radiographic progression. Moreover, many of the series do not report the mean or median duration of follow-up. Under these circumstances, the data do not provide an appropriate measure of efficacy. The second important observation is that the majority of the studies are retrospective, single-arm analyses. Few of them report the rate of decline of PRL. Finally, and most importantly, many of the studies are confounded by the inclusion of patients who were receiving concomitant medical therapy. A number of patients in whom cure was reported continued to require dopamine agonist therapy. Therefore, in some cases,

TABLE 5. Efficacy of single dose stereotactic radiotherapy on prolactinomas

| Study | Ref. | Device | Associated therapy | No. of patients | No. cured | Median or mean follow-up (months) | Margin dose (Gy) |
|---|---|---|---|---|---|---|---|
| Levy *et al.* | 140 | Proton beam | TSS (6/20) | 20 | 12 | 12 | NR-50–150 Gy in 4 fractions |
| Ganz *et al.* | 131 | GK | TSS (2/3) | 3 | 0 | 18 | 13.7 |
| Lim *et al.* | 141 | GK | TSS, DA(9) | 18 | 10 | 26 | 25 |
| Martinez *et al.* | 142 | GK | TSS (1/5) | 5 | 1 | 36 | 33 |
| Mitsumori *et al.* | 127 | LINAC | TSS | 4 | 0 | 47 | 15 |
| Morange-Ramos *et al.* | 144 | GK | TSS | 4 | 0 | 20 | 28 |
| Yoon *et al.* | 149 | LINAC | NR | 13[b] | 11 | 12 | 17 |
| Hayashi *et al.* | 132 | GK | NR | 13 | 2 | 16 | 24 |
| Inoue *et al.* | 133 | GK | NR | 2 | 1 | >24 | 20 |
| Kim MS *et al.* | 135 | GK | TSS (1), ?DA[a] | 13 | 3 | 12 | 22 |
| Kim SH *et al.* | 136 | GK | TSS (4), ?DA[a] | 18 | 3 | 27 | 29 |
| Laws and Vance | 139 | GK | NR | 13 | 1 | >6 | 18 |
| Mokry *et al.* | 143 | GK | BRC, TSS | 21[b] | 4 | 31 | 14 |
| Izawa *et al.* | 134 | GK | NR | 15 | 3 | 28 | 22 |
| Landolt and Lomax | 138 | GK | DA(9), TSS | 20 | 5 | 29 | 25 |
| Pan *et al.* | 146 | GK | None | 77 | 16 | 33.2 | 31.5 |
| Feigl *et al.* | 130 | GK | TSS or TCS | 18 | NR | 55 | 15 |
| Pollock *et al.* | 148 | GK | BRC (3/7) | 7 | 2 | 20 | 20 |
| Choi *et al.* | 129 | GK | TSS, ?DA[a] | 21 | 5 | 42.5 | 28.5 |
| Muramatsu *et al.* | 145 | LINAC | NR | 1 | 0 | 30 | 15 |
| Kuo *et al.*, Petrovich *et al.* | 137, 147 | GK | TSS, CRT[c] (3) | 15 | 11 | 42 | 15 |

TSS, Transsphenoidal surgery; NR, not reported; GK, gamma-knife; DA, dopamine agonist; BRC, bromocriptine; TCS, transcranial surgery; CRT, conventional radiotherapy.

[a] It is unclear whether dopamine agonist therapy was used concomitantly in any of these patients.

[b] Some patients in these cohorts had normal PRL levels prior to RT.

[c] Three patients also received conventional radiotherapy following $\gamma$ knife for tumor remaining near optic chiasm.

it is impossible to separate out any PRL-lowering effects of radiotherapy from the effects of dopamine agonists. In the present review, we have chosen to confine the analysis to the normalization of hyperprolactinemia. It should nevertheless be acknowledged that in many cases the goal of radiotherapy for treatment-resistant tumors was control of growth or alleviation of mass effects. To accurately assess the efficacy of radiotherapy for these situations, standard criteria for growth control would be necessary.

### *C. Efficacy—conventional radiotherapy*

Approximately 250 patients have been reported who have undergone treatment with conventional radiotherapy alone, or after failure of medical and/or surgical therapy (114–126). In all of these settings, normalization of hyperprolactinemia was infrequent, with an overall normalization rate for the entire series of 34.1%. When normal PRL levels were achieved, it was only with an extended latency in most cases.

Conventional radiotherapy after noncurative surgery rarely normalizes PRL levels. A total of three studies report PRL normalization rates of 1 of 11 (9%) (119), 0 of 11 (0%) (115), and 3 of 13 (23%) (121) when radiotherapy was administered after incomplete surgical resection. Two series of patients who received LINAC-based fractionated radiotherapy after unsuccessful transsphenoidal surgery achieved PRL normalization rates similar to those receiving conventional fractionated radiotherapy (36.3 and 25%) (127, 128).

The remainder of the studies in this group included patients treated with a dopamine agonist or with all three modalities (surgery, dopamine agonists, and radiotherapy). Thus, it is uncertain what specific effect radiotherapy had in PRL lowering, or normalization, in these patients. Because these prolactinomas often represent the most therapy-resistant tumors, normalization of hyperprolactinemia may not have been feasible. Therefore, the rates of normalization are expected to be poor. In many of these cases, the goal of radiotherapy may have been to control further growth or to relieve mass effects on cranial nerves.

### *D. Efficacy—single-dose stereotactic radiotherapy*

Almost 300 patients (Table 5) have been reported who have undergone treatment with single-dose stereotactic radiotherapy alone, or after failure of medical and/or surgical therapy (127, 129–149). In all of these settings, normalization of hyperprolactinemia was infrequent, with an overall normalization rate for the entire series of 31.4%. One could argue that the short follow-up duration among these series may have underestimated the complete response rate for these tumors treated with single-dose radiotherapy.

Only one study reported the outcomes of patients treated with single-dose stereotactic radiotherapy as primary therapy for prolactinomas (146). Follow-up beyond 2 yr was available for 77 patients who were not receiving bromocriptine. Normalization of PRL in the absence of concomitant medical therapy was attained in 16 (20.8%) of these patients.[2] The data obtained from this single center would indicate that single-dose stereotactic surgery is not a highly effective mode of therapy if the goal is normalization of hyperprolactinemia.

[2] Authors report a "cure" rate of 52%, which appears to include patients treated with medical therapy following gamma knife radiotherapy.

A second notable study by Landolt and Lomax (138) reported the outcomes of 20 patients who underwent gamma-knife radiosurgery after unsuccessful transsphenoidal surgery and/or "failed" medical therapy. Normoprolactinemia was achieved in five patients, all of whom were able to discontinue medical therapy. For 11 patients, PRL levels normalized or declined by at least 20%, but only with continuation of medical therapy. These subjects were regarded as "improved", although clearly in the absence of a control group, any improvement attributed to the effects of radiotherapy cannot be distinguished from effects of medical therapy. Furthermore, the clinical significance of a 20% decline in hyperprolactinemia is uncertain, because it would not be expected to alter dopamine agonist therapy continuation or dosage under these circumstances. Treatment with radiosurgery failed entirely in four patients. Therefore, a 25% complete response rate was achieved for gamma-knife radiotherapy in this series.

### *E. Selecting the mode of radiotherapy*

The advantages and disadvantages of various modes of radiotherapy are important considerations when referring a patient with a prolactinoma to a radiotherapist. Although it is true that a large single dose of radiation is more effective in cell death than the same dose delivered in several smaller fractions, large single doses of radiation are more toxic to normal tissue than similar doses given in a fractionated manner. In the early days of single-dose radiotherapy, high doses for large pituitary adenomas near the optic apparatus resulted in a high incidence of optic neuropathy (150). The risk of damage is dose dependent, with a 78% risk of optic neuropathy in patients receiving more than 15 Gy and a 27% risk for those receiving 10–15 Gy to the optic apparatus (151, 152). To achieve an acceptable fall-off gradient with single-session therapy, current practice aims at limiting irradiation of the optic apparatus to single doses of less than 8 Gy (103, 112, 113, 139). As a result, pituitary adenomas with significant suprasellar extension, or those with less than 5-mm clearance between the tumor margin and the optic apparatus are poor candidates for single-dose radiotherapy (103, 112, 139). On the other hand, tumors with cavernous sinus invasion can be good candidates for single-dose radiotherapy, because the cranial nerves in the cavernous sinus are relatively radioresistant (112, 153, 154). Fractionated radiotherapy is also preferable to single-dose radiotherapy when the tumor volume is so large (>3 cm) that an effective radiation dose cannot be safely delivered in a single session (112, 113, 139). It is estimated, based upon extrapolation from an integrated logistical formula, that the maximum diameter of a spherical tumor that is treatable with a risk of complications less than 3% is approximately 35 mm (155).

Prospective evaluations of the rate of PRL normalization in head-to-head comparisons of fractionated *vs.* single-dose radiotherapy for prolactinomas have not been published. Even if such series were to exist, one would need to critically analyze the comparability of the tumors in each group. For conventional radiotherapy, there is no restriction as to the size of the tumor or the proximity to the optic apparatus. As noted above, prolactinomas treated with single-dose radiotherapy will largely consist of intrasellar adenomas well away from the optic apparatus. In contrast, prolactinomas treated with fractionated radiotherapy consist of not only intrasellar adenomas, but also large adenomas with suprasellar extension that may lie in close proximity to the optic apparatus. Complete hormonal and tumor growth responses are undoubtedly more difficult to achieve in this latter category of tumors.

In addition to patient convenience, one of the proposed advantages of single-dose radiotherapy over fractionated radiotherapy is its shorter latency to hormonal and tumor size responses. It appears likely that single-dose radiotherapy lowers PRL levels more rapidly than conventional external beam radiotherapy, although prospective comparative studies are not available to verify this claim. Six of the 21 series listed in Table 5 reported the latency to normalization of PRL levels for their patients with prolactinomas treated with single-dose radiotherapy; these responses ranged from 1 to 2 yr (129, 137, 139, 147–149). The latency to normalization of hyperprolactinemia for conventional external beam radiotherapy is on the order of several years.

### *F. Complications*

The most frequent long-term morbidity of conventional radiotherapy is radiation-induced hypopituitarism, with a cumulative actuarial risk of approximately 50% at 10–20 yr (111, 156, 157). Hypopituitarism is likely secondary to hypothalamic and pituitary damage, although the former is considered of primary importance (158). Recently, it has been discovered that the consequences of hypopituitarism may be more significant than issues related to hormone replacement dosing and monitoring. A recent large prospective study from the United Kingdom showed that the standardized mortality rate was higher in patients with hypopituitarism that had been treated with radiotherapy compared with those who had not received radiotherapy (159). A large proportion of this excess was due to a significant increase in cerebrovascular disease-associated deaths in the radiotherapy group.

Additional complications that occur months to years after radiotherapy of pituitary adenomas include cerebrovascular accidents, optic nerve damage, neurological dysfunction, and soft tissue reactions (157, 160–162). Conventional radiotherapy is associated with an increased risk of secondary radiation-induced intracranial malignancies, with a cumulative risk of 2.0% at 10 yr and 2.4% risk at 20 yr (163–165).

The incidence of hypopituitarism after single-dose stereotactic radiotherapy is difficult to establish at present. The reported rates of hypopituitarism vary widely, ranging from 0–36%, after single-dose radiotherapy (132, 134, 136, 141–143, 148). These analyses are confounded by factors such as previous pituitary surgery in some individuals. A long-term follow-up study with a mean follow-up of 17 yr determined a relatively high cumulative incidence of hypopituitarism at 72% (108). Cranial neuropathies have been reported after single-dose radiotherapy. A high incidence of optic neuropathies was reported in the early use of single-dose therapy when higher doses were administered. With dose changes and technical improvements, these adverse effects are less

frequent. The risk of damage to the optic apparatus is approximately 1%. The severity of these cases ranges from nonspecific visual loss to blindness (113, 148, 166). Cranial neuropathies involving nerves that traverse the cavernous sinus (III, IV, V, VI) are less common and often transient (113, 153, 166). Radiation necrosis of surrounding brain tissue occurs in approximately 0.2–0.8% of cases (113, 160). As of yet with limited follow-up, there have been no reported cases of secondary intracranial malignancies who have undergone single-dose radiotherapy.

### *G. Conclusions with regard to radiotherapy*

Overall, radiotherapy has a very limited role in the treatment of patients with prolactinomas. The very high rate of efficacy of dopamine agonists (see *Section V*) along with the high complication rates of radiotherapy render treatment with this modality rarely necessary. The few patients who now require radiotherapy are those who do not respond to dopamine agonists and who cannot then be cured by surgery. When a large tumor remains after surgery, then conventional radiotherapy is the best modality. However, a small residual tumor, especially when involving the cavernous sinus, may be better treated with stereotactic radiotherapy.

## V. Medical Therapy

The compounds used in clinical practice to treat prolactinomas are all dopamine receptor agonists. Among these, bromocriptine, cabergoline, pergolide, and quinagolide are the most commonly used. The dopamine agonists lisuride and terguride are less frequently used, as is metergoline, a serotonin antagonist.

### *A. Pharmacological profile*

Bromocriptine, pergolide, and cabergoline are all ergot derivatives. The only nonergot derivative that is used in clinical practice is quinagolide. The chemical structures of the most used compounds are shown in Fig. 1. The ergot-derivative dopamine agonists comprise a group of indole alkaloids that are predominantly found in various species of the ascomycete *Claviceps* (167). The ergot alkaloids can all be considered derivatives of the tetracyclic ergoline skeleton and can be divided into two main groups based on their structural characteristics (167). The first group includes all lysergic acid derivatives of the acid amide types, such as amine alkaloids (ergonovine) and the structurally more complex ergopeptines (ergotamine, ergocristine). The second group includes the so-called "clavine alkaloid" derivatives that contain either a methyl or a hydroxymethyl group at position 8 (167). The ergot alkaloids and their derivatives have a wide spectrum of pharmacological actions that include central, neurohumoral, and peripheral effects, mediated by norepinephrine, serotonin, and dopamine receptors. The diversity of biological properties of ergot derivatives is likely due to diverse mechanisms of action at the cellular and molecular levels (167). Because ergot derivatives interact with different receptor sites, it is not surprising that the drugs developed (as well as the natural alkaloids) display a number of side effects (167). The clinical application of ergot derivatives in the treatment of other clinical conditions, such as postpartum hemorrhage, migraine, and other vascular headaches, orthostatic hypotension, and Parkinson's disease will not be discussed here.

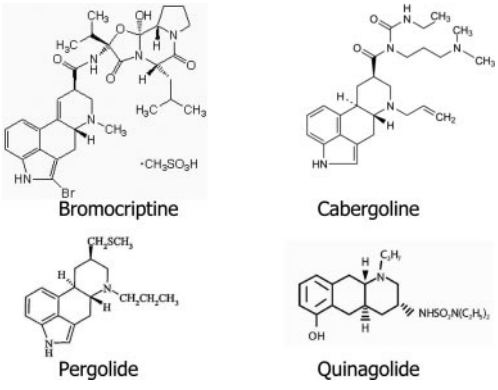


FIG. 1. Biochemical structure of dopamine agonists. Bromocriptine, pergolide, and cabergoline are all ergot derivatives. Quinagolide is a nonergot derivative.

The octahydrobenzyl(g)-quinolines are a group of nonergot oral medications that also function as dopamine agonists with specific $D_2$ receptor activity (168–170). Quinagolide and SDZ 205–503 are slightly less active than their ergoline counterparts, CPQ 201–403 and pergolide, in inhibiting basal PRL secretion in rats (171, 172). Quinagolide is the most active octahydrobenzyl(g)-quinoline and is about 35 times more potent than bromocriptine. The octahydrobenzo(g)-quinolines bind more specifically to dopamine receptors than the ergot derivatives bromocriptine, CQP 201–403, and pergolide (167–174).

### *B. Mechanisms of action*

In contrast to the other pituitary hormones, PRL secretion is mainly regulated by the inhibitory tone exerted by dopamine with minor additional inhibitory activity played by γ-aminobutyric acid and cholinergic pathways (175). TSH-releasing hormone, serotonin, estrogens, endogenous opiates, and vasoactive intestinal polypeptide stimulate PRL secretion, but their role is clearly minor compared with that of dopamine (175).

Classically, dopamine receptors have been divided into $D_1$ receptors, which stimulate adenylyl cyclase activity, and $D_2$ receptors, which inhibit this enzyme (176–178); three further discrete receptor subtypes have been described ($D_3$, $D_4$, and $D_5$) with less activity on PRL secretion (177). Dopamine inhibition of PRL secretion is mediated by the $D_2$ dopamine receptors expressed by normal and tumorous lactotrophs (176–178). $D_2$ receptors belong to the family of G protein-coupled receptors, characterized by a single polypeptide chain containing seven hydrophobic transmembrane domains: besides their effect on adenylyl cyclase, they are able to inhibit inositol phosphate production (179) with an effect that involves G proteins sensitive to pertussis toxin (176–179). Additionally, dopamine inhibits arachidonic acid release from pituitary cells independently from the other trans-

duction mechanisms (180). Two isoforms generated by alternative splicing of the $D_2$ dopamine receptor have been described (181). These two isoforms differ by a 29-amino acid additive sequence located within the third intracytoplasmic loop that interacts with G proteins: dopamine inhibition of adenylyl cyclase activity is observed with both isoforms. Stimulation of $D_2$ receptors by dopamine reduces adenylyl cyclase activity that consequently reduces intracellular cAMP levels in normal as well as in tumoral lactotrophs (182). The inhibition of cAMP levels is a key step in the inhibition of PRL release by dopamine (183). It is likely that all dopaminergic ergot derivatives share similar mechanisms of action (175).

Dopamine agonists reduce the size of prolactinomas by inducing a reduction in cell volume (via an early inhibition of secretory mechanism, and a late inhibition of gene transcription and PRL synthesis), as well as causing perivascular fibrosis and partial cell necrosis (184). There may also be a true antimitotic effect of these drugs. Histologically there is a reduction in secretory activity and cell size, an increase in immunoreactive PRL cellular content and inhibition of exocytosis (185).

### *C. Therapeutic profile of dopamine receptor agonists*

*1. Bromocriptine.* More than 25 yr ago, bromocriptine was introduced into clinical practice as the first medical treatment for prolactinomas (186–188). Bromocriptine-mesylate is a semisynthetic ergot derivative that has $D_2$ receptor agonist and $D_1$ antagonist properties. It has a relatively short elimination half-life, so that it is usually taken two or three times daily, although once daily may be effective in some patients. Generally, the therapeutic doses are in the range of 2.5–15 mg/d, and most patients are successfully treated with 7.5 mg or less. However, doses as high as 20–30 mg/d may be necessary for patients who demonstrate resistance. For microprolactinomas bromocriptine is successful in 80 to 90% of patients in normalizing serum PRL levels, restoring gonadal function, and shrinking tumor mass (175). For macroprolactinomas, normalization of serum PRL levels and tumor mass shrinkage occur in about 70% of patients treated with bromocriptine even when given at low doses; visual field defects improve in the majority of patients (175). In most patients, headache and visual field defects improve dramatically within days after the first administration of bromocriptine, with gonadal and sexual function improving even before complete normalization of serum PRL levels. Although prolactinomas usually remain sensitive to bromocriptine, this drug usually does not "cure" these pituitary adenomas, and the withdrawal of therapy often results in recurrent hyperprolactinemia; tumor regrowth may occur later, with the consequent risk for compromised vision (see *Section VIII*). Prolonged bromocriptine treatment has been associated with increased fibrosis of prolactinomas (189) and with increasing tumor consistency. PRL normalization with bromocriptine is also associated with an increase in bone density both in women (190) and in men (191) and with improvement of semen quality in men (192). Other formulations of bromocriptine, long-acting and the long-acting repeatable forms for im injections, an intranasal powder, and an intravaginal tablet, were developed to overcome side effects such as nausea, vomiting, postural hypotension, and headache (see *Section VI*). These reactions were considered to be due to the rapid absorption of bromocriptine, which is administered two or three times a day, thus causing high blood levels. However, despite promising data (190–195), none of these formulations were ever introduced in the pharmaceutical market for hyperprolactinemia. Bromocriptine (as a first-generation dopamine receptor agonist) has been largely superseded by more potent compounds with longer lasting effects and improved side effect profiles. Nevertheless, bromocriptine is still widely used to treat prolactinomas, primarily in young women desiring pregnancy (see *Section IX*).

*2. Cabergoline.* Cabergoline is a $D_2$ selective agonist widely used to treat prolactinomas. It strongly suppresses PRL secretion both *in vivo* and *in vitro* and preliminary studies showed a significant PRL inhibition within 12 h after treatment with cabergoline and bromocriptine in cultured pituitary cells from estradiol-induced rat pituitary tumors (196, 197). Inhibition of *de novo* PRL synthesis was more pronounced with cabergoline than bromocriptine treatment (196). The continued oral administration of cabergoline significantly reduced both PRL levels and the weight of the pituitary during 15–60 d of treatment as compared with bromocriptine (197). One single dose of cabergoline (0.2–0.6 mg) in healthy male volunteers induced a dose-dependent PRL inhibition (198). In healthy men, single doses of 0.5, 1, and 1.5 mg of cabergoline completely suppressed PRL levels ($<1$ $\mu$g/liter) (199). In healthy women with regular menses, cabergoline at doses of 0.4–0.6 mg induced a 43–76% PRL suppression; PRL levels returned to baseline within 24 h after the low 0.4-mg dose but remained suppressed until 5 d after the administration of 0.6 mg (200).

The beneficial effects of cabergoline in resolving hyperprolactinemia are widely known (201) (Table 6). Significant decreases in serum PRL levels occur in as many as 95% of hyperprolactinemic women during chronic cabergoline treatment at a dose of 1 mg twice weekly (202). In a multicenter, randomized, 24-wk trial conducted in 459 hyperprolactinemic women (203), cabergoline induced normal PRL levels in 83% compared with 59% with bromocriptine; ovulatory cycles or pregnancies were recorded in 72% *vs.* 52%, and side effects were less frequent, less severe, and shorter lived. In a retrospective study of 455 patients (204), cabergoline treatment normalized PRL levels in 86% of 425 patients with available follow-up (92% of 244 patients with idiopathic hyperprolactinemia or microprolactinoma, and 77% of 181 patients with macroprolactinoma); 13% had side effects but only 4% discontinued cabergoline therapy because of side effects (204). Generally, the median dose of cabergoline at the start of therapy was 1 mg/wk in patients with macroprolactinomas and 0.5 mg/wk in those with idiopathic hyperprolactinemia or microprolactinomas (0.5 mg/wk) (201). A remarkable tumor-shrinking effect of cabergoline has been observed in patients with macroprolactinomas (205): 12–24 months of treatment with cabergoline induced a greater than 20% decrease of baseline tumor size in more than 80% of cases, with complete disappearance of tumor mass in 26–36% of cases. Moreover, Colao *et al.* (206)

TABLE 6. Overview of efficacy of cabergoline treatment in patients with hyperprolactinemic disorders.

| Author | Year | Ref. | Total patients | Micro | Macro | % PRL normalization | % Tumor reduction | % Side effects |
|---|---|---|---|---|---|---|---|---|
| Prospective study | | | | | | | | |
| Ciccarelli | 1989 | 599 | 30 | 27 | 3 | 81 | 71 | 48 |
| Ferrari[a] | 1989 | 600 | 46 | 38 | 8 | 85 | 83 | 15 |
| Ferrari | 1992 | 347 | 127 | 108 | 19 | 90 | 79 | 23 |
| Webster | 1993 | 202 | 162 | 161 | 1 | 92 | | 40 |
| Webster[a] | 1994 | 203 | 223 | 223 | 0 | 83 | | 68 |
| Biller | 1996 | 353 | 15 | 0 | 15 | 73 | 73 | ~0 |
| Ciccarelli | 1997 | 392 | 48 | 26 | 9 | 91 | 70 | 4 |
| Colao | 1997 | 323 | 27 | 8 | 19 | 85 | 48 | 22 |
| Colao | 1997 | 205 | 23 | 0 | 23 | 83 | 61 | 4 |
| Muratori | 1997 | 348 | 26 | 26 | 0 | 96 | 68 | 24 |
| Cannavò | 1999 | 349 | 37 | 26 | 11 | 92 | 100 | 8 |
| Colao | 2000 | 206 | 110 | 0 | 110 | 89 | 55 | 4.6 |
| Di Sarno | 2001 | 207 | 116 | 60 | 56 | 86 | 79 | 3.3 |
| Colao[b] | 2003 | 98 | 272 | 155 | 117 | 92 | 74[c] | |
| Retrospective study | | | | | | | | |
| Ferrari | 1997 | 354 | 65 | 0 | 65 | 61 | 66 | 25 |
| Verhelst | 1999 | 204 | 455 | 249 | 181 | 86 | 67 | 13 |

[a] Indicates series that include data from double-blind studies. All other studies were open-label.
[b] This series also contains data derived from an extension of the published study.
[c] Tumor reduction in this study was defined as >50%.

showed that cabergoline treatment induced further tumor shrinkage in 60% of patients previously treated with other dopamine-agonists compared with 82.3% of previously untreated patients (Fig. 2A). Cabergoline treatment is also effective and safe in patients with prolactinomas with onset in childhood or adolescence (see *Section X*). The superiority of cabergoline over bromocriptine was supported by a comparative retrospective study by Di Sarno *et al.* (207). Based on these data, cabergoline treatment is clearly indicated as the primary approach to macroprolactinomas. Lastly, cabergoline seems to induce fewer side effects than other dopamine agonists (see *Section VI*). At present, cabergoline is certainly the most effective compound to treatment prolactinomas, with very good patient compliance with long-term treatment regimens.

*3. Pergolide.* Pergolide is a synthetic ergoline derivative with long-acting $D_2$ and $D_1$ agonist properties. This dopamine agonist is approximately 100 times more potent than bromocriptine and suppresses PRL secretion for up to 24 h after a single dose (208–211), allowing effective control of hyperprolactinemia with once daily dosing. Pergolide is approved in the United States only for the therapy of Parkinson's disease, where it has been used at doses more than 10 times those used for PRL-secreting tumors (212). Pergolide has advantages over bromocriptine in that it only requires once-a-day dosing and is approximately one fifth of the cost. In short-term studies, pergolide has been shown to effectively lower PRL levels. In an open-label, randomized, controlled, multicenter study, Lamberts and Quik (213) reported that bromocriptine and pergolide were equally effective in lowering serum PRL levels and in inducing tumor shrinkage; a high incidence of adverse events, such as nausea, dizziness, vomiting, asthenia, headache, and decrease in blood pressure, was reported with both drugs. Data concerning the reduction of macroprolactinoma size by pergolide are limited (214–217). In the series of 22 patients with macroprolactinomas treated with pergolide reported by Freda *et al.* (218), PRL levels normalized in 15 patients and approached normal in two others. Prior studies of pergolide therapy of both micro- and macroprolactinomas have shown high rates of PRL normalization; PRL levels were normalized in 37 of 41 (218), 17 of 18 (219), and 16 of 25 (208) subjects treated for periods from 6–24 months. The ability of pergolide and bromocriptine to lower PRL also seems to be similar (208, 213, 220), but some patients who have not responded well to bromocriptine have been reported to achieve better suppression of hyperprolactinemia with pergolide (221). In a recent study enrolling 22 *de novo* patients with macroprolactinomas, Orrego *et al.* (222) reported that after a mean of 12 months of treatment with pergolide at a dose ranging from 0.05–0.5 mg/d, a mean PRL suppression of 88% was obtained, with PRL levels being normalized in 15 patients and decreased to 25–40 ng/ml in another three. Shrinkage of tumor volume by at least 75% of baseline was achieved in 10 patients (45.4%), and shrinkage by at least 25% was achieved in 19 patients (86.4%).

*4. Quinagolide.* Quinagolide is an octahydrobenzyl(g)-quinoline nonergot oral dopamine agonist with specific $D_2$ receptor activity. Several studies demonstrated that once-daily quinagolide treatment in women with hyperprolactinemia reduced PRL levels and tumor size and relieved gonadal dysfunction, thereby restoring fertility (223–230). In analogy with the results of cabergoline, treatment with quinagolide effectively reduced PRL levels, with normalization of sperm parameters within 3 months in 13 of 14 men (231). In addition, tumor mass was reduced by at least 30% in eight of 13 men with macroprolactinomas (231). In a prospective, multicenter trial conducted in 26 patients with macroprolactinomas who received once-daily quinagolide for 24 wk, tumor size decreased in 21 patients, regular menses were restored in 11 of 15 premenopausal women, and sexual function improved in five of seven males (229). From this study, it appears that quinagolide is at least as effective as bromocriptine. In fact, 81% of patients achieved normal PRL

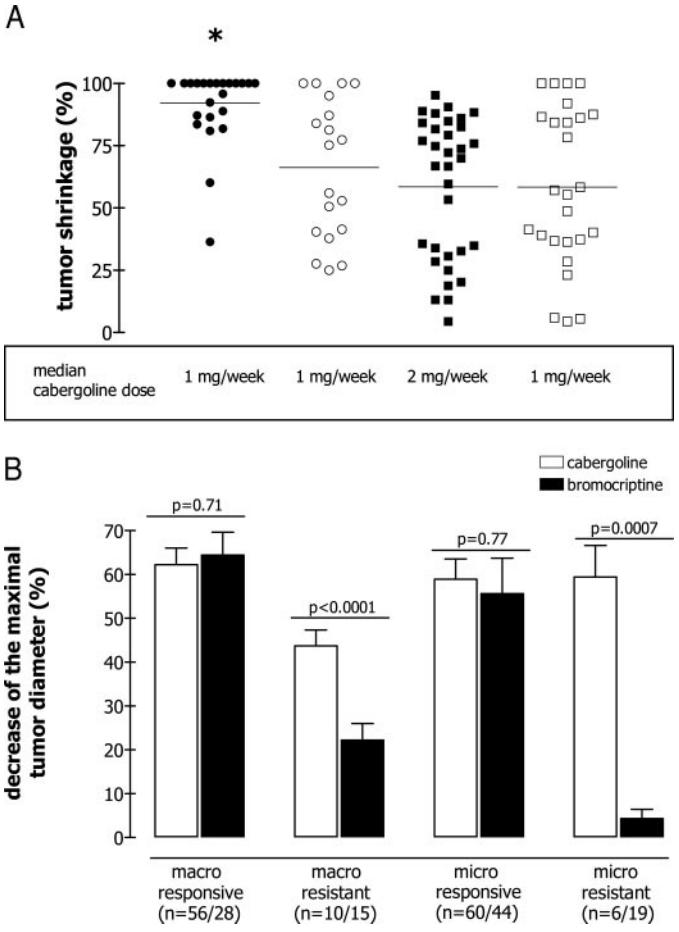


FIG. 2. Tumor shrinkage with cabergoline. A, Cabergoline induced further tumor shrinkage in 60% of patients previously treated with other dopamine-agonists, compared with 82.3% of previously untreated patients. ●, *De novo* patients; ○, patients intolerant to bromocriptine; ■, patients resistant to bromocriptine; □, patients responsive to a previous treatment course of bromocriptine and treated with cabergoline. Data are derived from Ref. 206. B, Comparison of tumor reduction responses in micro- and macroprolactinoma with bromocriptine or cabergoline. Data are derived from Ref. 207.

levels after 24 wk of quinagolide treatment compared with 70% of bromocriptine-treated patients. However, there was no significant difference between the treatment groups with respect to the PRL levels at the end of the study. Both drugs were able to restore menses and fertility and reduce the incidence of galactorrhea in similar proportions of patients (229). Side effects, however, limited the continuation of bromocriptine but not of quinagolide treatment in another comparative study (226).

In a randomized, cross-over study, 20 patients with hyperprolactinemia received once-daily quinagolide or twice-weekly cabergoline for 12 wk, with the two treatment phases separated by a washout period of 12 wk with placebo (232). A higher percentage of patients achieved normal PRL levels with cabergoline compared with quinagolide (90 *vs.* 75%; $P < 0.05$), but clinical efficacy, such as amenorrhea, oligomenorrhea, galactorrhea, and impotence, was similar as was the occurrence of side effects (232). In another study, Di Sarno *et al.* (224) compared the outcome of quinagolide and cabergoline in a sequential treatment administered to 39 patients. Treatment with quinagolide for 12 months was followed by a 12-month washout period, and then cabergoline treatment was given for a further 12-month period. The 12-month withdrawal of dopamine agonist therapy was introduced in this protocol to evaluate the recurrence of hyperprolactinemia. After treatment with quinagolide for the first 12 months, PRL levels normalized in 100% of patients with microprolactinomas and in 88% of patients with macroprolactinomas; tumor volume was reduced by more than 80% in 22% of patients with microprolactinomas and 25% of patients with macroprolactinomas. At the end of the washout period, PRL levels increased in all patients, but were significantly lower than the PRL levels measured at baseline before initiation of quinagolide therapy. After 12 months of cabergoline treatment, PRL levels normalized in 96% of patients with microprolactinomas and 88% with macroprolactinomas; tumor volume reductions of more than 80% were noted in 30 and 31% of patients with micro- and macroprolactinomas, respectively. After 12 months of withdrawal from cabergoline treatment, recurrence of hyperprolactinemia was observed in all patients with macroprolactinomas and 19 of the 23 patients with microprolactinomas.

Giusti *et al.* (233) compared once-daily quinagolide (0.075 mg) with twice-weekly cabergoline (0.5 mg) in 12 patients enrolled in a randomized cross-over study where treatment with the second dopamine agonist was initiated after the recurrence of hyperprolactinemia. Nine patients completed both treatment cycles; the clinical effects were similar with the two drugs and, interestingly, only one patient remained resistant to both dopamine agonists. Quinagolide is currently available in several European countries and in Canada but is not available in the United States.

*5. Other dopamine agonist compounds.* Lisuride hydrogen maleate is another synthetic ergot derivative, with PRL-inhibitory activity in experimental models of hyperprolactinemia (234). Liuzzi *et al.* (235) showed a potent inhibition of PRL but not GH with 0.2 mg of lisuride in 12 patients with acromegaly. At a dose of 0.3–0.6 mg/d for 7 d, lisuride effectively inhibited lactation and also suppressed the serum PRL levels in 53 women with no untoward side effects (236). In another study enrolling patients with macroprolactinomas, Liuzzi *et al.* (186) showed that lisuride and bromocriptine had similar tumor shrinking effects, but withdrawal from treatment induced recurrence of hyperprolactinemia in all cases.

Terguride, an analog of lisuride, binds to $D_2$ receptors. In a cohort of 20 patients with hyperprolactinemia, Dallabonzana *et al.* (237) showed that terguride, given for at least 6 months in divided doses ranging from 0.25–1.50 mg/d, normalized PRL levels in 55% and induced tumor shrinkage in three of five patients with a macroprolactinoma and in one of three patients with a microprolactinoma. Neither lisuride nor terguride is currently used in the treatment of prolactinomas.

### *D. Serotonin receptor antagonists*

Metergoline is a nonselective antagonist for 5-hydroxytryptamine-1B and 5-hydroxytryptamine-1D receptors that

has been used to treat hyperprolactinemia in the past. In a group of lactating women, metergoline treatment induced significantly higher responses of PRL to metoclopramide as compared with those treated with either bromocriptine or lisuride (238). Metergoline 8 mg/d given to 69 women within 24 h after delivery and continued for 5 d was able to prevent lactation (239). Similar results were reported by Crosignani *et al.* (240). In another study by the same group (241), 20 patients with hyperprolactinemic amenorrhea-galactorrhea were treated with one or more of the following serotonin antagonists: metergoline, methysergide, and cyproheptadine. Among the 11 patients without evidence of pituitary tumor, resumption of menses was observed in five, two of whom had ovulatory cycles; one patient became pregnant; ovulation occurred only during treatment with metergoline. In the group of nine patients with enlarged sellae, three experienced isolated episodes of bleeding, whereas two had three and four menses each, respectively; all cycles were anovulatory. In another study, metergoline, in a dosage of 4 to 24 mg/d, was administered for 1 to 8 months to 42 patients with hyperprolactinemic amenorrhea. Metergoline treatment restored menses in 37 patients; 28 patients ovulated, and eight of them became pregnant (242). Although these studies reported an efficacy of metergoline in normalizing gonadal function and in restoring fertility in women, no data are available in patients with macroprolactinomas or in men with hyperprolactinemia. Metergoline is seldom, if ever, used today in the treatment of prolactinomas.

### *E. Conclusions with regard to medical therapy*

By far, the greatest experience in treating patients with prolactinomas has been with bromocriptine and cabergoline. In head-to-head randomized, prospective comparison studies (202), retrospective analyses (207), and general clinical experience, cabergoline has been shown to be more effective in lowering PRL levels to normal, reducing tumor size, and having less adverse effects. As noted below, patients are less likely to be resistant to the therapeutic effects of cabergoline; furthermore, most patients found to be resistant to bromocriptine subsequently respond to cabergoline. Finally, treatment with cabergoline affords a greater chance of obtaining permanent remission and successful withdrawal of medication, compared with treatment with bromocriptine (see *Section VIII.C*). Thus, in general, cabergoline is preferable to bromocriptine as an initial therapeutic agent.

There is much less experience with pergolide and quinagolide in the primary treatment of patients with prolactinomas. However, these drugs appear to have similar efficacy and adverse event profiles compared with bromocriptine (see *Section VI.C*). When used in very high doses, pergolide appears to have an increased association with organ fibrosis, including cardiac valve fibrosis. Therefore, pergolide should be avoided if high doses are needed. Depending upon pricing in some countries, pergolide may be less expensive than other dopamine agonists, and this may factor into its use. Pergolide has not been approved by the U.S. Food and Drug Administration (FDA) for use in patients with prolactinomas, and quinagolide is not approved for use in the United States.

The single exception to a preference for cabergoline may be for treatment of women who wish to become pregnant. As discussed in *Section VI.C* , the safety database for bromocriptine is far larger than that for cabergoline for fetal outcomes. Although there are no particular worrisome aspects of this smaller database for cabergoline, some clinicians and patients feel more comfortable using bromocriptine when fertility is the desired outcome. On the other hand, the small safety databases for pergolide and quinagolide are worrisome, and we specifically recommend avoiding their use when fertility is the desired outcome.

## VI. Safety of Dopamine Agonists

### *A. Bromocriptine*

The adverse effects of bromocriptine may be grouped into three categories: gastrointestinal, cardiovascular, and neurological (243). Symptoms tend to occur after the initial dose and with dosage increases, but can be minimized by introducing the drug at a low dosage (0.625 or 1.25 mg/d) at bedtime, by taking it with food, and by very gradual dose escalation (175). Sometimes, tolerance develops to the adverse effects, but occasionally, therapy withdrawal or dose reduction followed by a more gradual reintroduction is required. Up to 12% of patients are unable to tolerate therapeutic doses of bromocriptine (244). The most common gastrointestinal effects are nausea (~30%) and vomiting (~20%) (175, 243). Nausea tends to be more persistent. Constipation is also frequent, with an incidence of up to 10%. Other reported gastrointestinal effects include dry mouth, dyspepsia, and symptoms suggestive of reflux esophagitis (175, 243). In approximately 25% of patients, postural hypotension develops when initiating therapy and can result in dizziness and even syncope (244). The syncope is rare, although it may be observed even after a small initial dose (1.25–2.5 mg/d) at the start of treatment. These symptoms can often be avoided by taking the drug at bedtime or while recumbent, but tolerance usually develops rapidly making this precaution unnecessary after the first few days. Up to 30% of patients receiving high doses of bromocriptine (30 to 75 mg/d) experience a syndrome of painless digital vasospasm causing blanching of the extremities in response to cold (245, 246). However, this reaction is rare at the low doses used to control PRL hypersecretion. Other less frequent side effects include leg cramps, flushing, and nasal congestion (31, 247).

The most frequent neurological adverse effects include headache and drowsiness. Psychiatric adverse effects are infrequent at the bromocriptine doses required to control PRL hypersecretion; however, low doses have been associated with mania in postpartum patients (243, 244, 248). Signs and symptoms of psychosis or exacerbation of preexisting psychosis have been associated with the use of bromocriptine (249–251). Turner *et al.* (251) observed *de novo* psychotic reactions in eight of 600 patients treated with bromocriptine or lisuride, another dopamine agonist. The symptoms, which included auditory hallucinations, delusional ideas, and mood alterations, entirely remitted when the drug was reduced in dosage or discontinued (252). In a short-term trial in which bromocriptine was given to 16 individuals with

psychiatric disorders who were previously stabilized on neuroleptic agents, exacerbation of psychoses was not observed (252). Although these data are reassuring, this study included a small number of subjects with a limited exposure to bromocriptine (10 wk). Thus, the safety of dopamine agonists in this population remains to be established. Other symptoms, usually associated with higher doses of bromocriptine, include anxiety, depression, confusion, auditory hallucinations, hyperactivity, disinhibition, insomnia, daytime somnolence, and paranoia (244, 251, 253). Moreover, dyskinesias similar to those observed with levodopa are well-recognized effects of high-dosage treatment (244). Other reported adverse effects include paraesthesia, nightmare, blurred vision, diplopia (at high doses) and reversible ototoxicity (in patients with chronic hepatic disease) (243, 244).

CSF rhinorrhea has been reported during treatment of adults with bromocriptine, not only postsurgically, but also in the absence of prior radiotherapy or surgical intervention due to tumor shrinkage, when the tumor previously served as a "cork" for the tumor-induced defect in the skull base (254–259).

Individual case reports of postpartum women and other adults treated with bromocriptine have suggested a causal association between the use of bromocriptine and hypertension, thromboembolic events, severe leukopenia, hyponatremia, and edema (260–264). However, conclusive evidence that these events were drug-induced is lacking. In the United States, the FDA has determined that bromocriptine should not be used to treat postpartum lactation.

Rarely, in patients with Parkinson's disease treated with very high doses of bromocriptine, pulmonary infiltrates, fibrosis, pleural effusions, pleural thickening, and retroperitoneal fibrosis have been described (244); however, these adverse effects appear to be dose-dependent and are unlikely to occur at the low doses used for treatment of prolactinomas.

In a small group of patients at low doses of bromocriptine (5–10 mg/d), transient asymptomatic increases in serum alkaline phosphatase and/or transaminases have been reported (243, 244). Hyponatremia has been associated with the use of bromocriptine in patients with cirrhosis and hepatic encephalopathy (264).

### *B. Cabergoline*

Side effects associated with the use of cabergoline are similar to those reported for the other dopamine agonists, but are generally less frequent, less severe, and of shorter duration (31). Some effects subside with dose reduction or continued use in many patients (203). The long half-life of cabergoline, which results in a relatively flat plasma drug concentration, may be advantageous with respect to the induction of side effects (265). The most common adverse event is nausea or vomiting (~35%), followed by headache (~30%), and dizziness or vertigo (~25%) (244, 265). Diarrhea, drowsiness, somnolence, paresthesias, and dyspnea are less commonly reported. Withdrawal of cabergoline treatment due to side effects is reported in less than 3% of patients (244, 265). Hypotension has been reported in approximately 50% of women with hyperprolactinemia during cabergoline or bromocriptine treatment with a median decrease in blood pressure of 10 mm Hg (203). Generally, hypotension is asymptomatic, because only one of 136 patients treated with cabergoline for the inhibition of lactation (266) and three of 254 patients treated with cabergoline for hyperprolactinemia (203) developed symptomatic hypotension. Side effects such as thromboembolic events (265) or psychosis have not been reported in patients with pituitary adenomas treated with cabergoline. Pleuropulmonary inflammatory-fibrotic syndrome has been described in a few patients (267–269). Constrictive pericarditis was diagnosed in a patient with Parkinson's disease receiving cabergoline therapy at the dose of 10 mg/d (270).

Recently, a number of case reports have been published describing the occurrence of valvular insufficiency in patients who have been treated with high doses of cabergoline (~4 mg total daily dose) or pergolide (see *Section VI.C*) for Parkinson's disease. Both multivalvular (271) and single mitral valve (272) heart disease have been described. In these cases, the echocardiographic and/or microscopic features resembled those found in valvular disorders associated with ergot alkaloid agents and appetite suppressants (273, 274). In one case of cabergoline-associated valvular disease, cardiac symptoms improved with discontinuation of the drug (271); mitral valve replacement was required in the second (272). Although causality has not been proven, the similarity of the echocardiographic findings, time course, and partial reversal of symptoms in these cases suggests that the use of the dopamine agonists in high doses may have been responsible for these adverse cardiac effects. Therefore, extreme caution should be exercised in titrating patients to high doses of cabergoline or pergolide, and patients treated with higher doses should be monitored for this adverse effect when the drug is prescribed.

### *C. Pergolide*

In general, the nature and incidence of most side effects reported with pergolide are similar to those of bromocriptine (208, 213, 275). Nausea, vomiting, dizziness, headache, and postural hypotension are the most commonly reported effects. In one study, however, flushing, fever, and flu-like symptoms were reported more commonly in adults treated with pergolide than in those treated with bromocriptine (213). As with the other dopamine agonists, daytime somnolence is commonly reported at very high doses (276). Children with Tourette syndrome treated with pergolide in doses of 150–450 $\mu$g daily for tic reduction experience side effects that are similar in nature and frequency to placebo (277). Mild insomnia and mild rashes were the only side effects observed more commonly in pergolide-treated children compared with placebo. As discussed above, cases of pergolide-associated valvular heart disease have been reported in adults with Parkinson disease treated with doses much higher than those used for the treatment of hyperprolactinemia (219, 278–280). An FDA survey of reported cases of pergolide-associated valvular heart disease did not establish causality, as a result of insufficient information and absence of histological data (281). Nonetheless, the growing number of reported cases of valvular heart disease at higher doses

warrants routine clinical cardiac assessment of patients who are treated with higher doses.

### *D. Quinagolide*

Most adverse effects reported in adults taking quinagolide are consistent with those reported for other dopamine agonists, although they occur perhaps less frequently than with bromocriptine (226, 233, 282–285). As with bromocriptine, psychotic symptoms have been observed rarely, including personality or behavioral changes, hypomania, and delusions (286, 287). In one double-blind, randomized 6-month study in 22 women with persistent hyperprolactinemia, quinagolide was significantly better tolerated compared with bromocriptine (226). No changes in blood biochemistry, hematology, blood pressure or pulse rate were reported in trials performed with quinagolide, confirming the favorable safety profile (226, 283–285, 288, 289). Less frequent side effects include anorexia, abdominal pain, constipation and/or diarrhea, insomnia, flushing, edema, nasal congestion, hypotension, and rare psychotic reactions (244).

## VII. Dopamine Agonist Resistance

Although dopamine agonists have been proven to be successful in normalizing PRL levels, alleviating symptoms of hyperprolactinemia, and reducing tumor size, a subset of individuals with prolactinomas do not respond satisfactorily to these agents (290). In general, prolactinomas exhibit varying degrees of responsiveness to the class of dopamine agonists, ranging from complete response at one end of the spectrum to total resistance at the other. In addition, individual prolactinomas may respond variably to selected dopamine agonists, such that tumors that respond poorly or incompletely to one dopamine agonist may respond well to another. The concept of dopamine agonist resistance must be distinguished from that of dopamine agonist intolerance, in which adverse effects of the medication prevent the achievement of an effective response.

### *A. Definition of dopamine agonist resistance*

Varying definitions of dopamine agonist responsiveness and resistance are used throughout the literature, including failure to normalize PRL levels, failure to reduce PRL levels sufficiently to achieve ovulation, or failure to enable a 50% reduction of hyperprolactinemia (207, 282, 291, 292). In addition, there are no standard dose thresholds to which a dopamine agonist should be titrated to assign an individual to the status of "dopamine agonist resistant". Obviously, the percentage of patients deemed resistant to a particular drug will depend upon this dose threshold.

The desired biological response in the treatment of hyperprolactinemia in women is the achievement of ovulation regardless of the actual PRL level achieved. However, because this level varies on an individual basis, is difficult to define, and is not provided in most papers, for the purposes of the present analysis, dopamine agonist resistance with respect to hormone levels will be defined as the failure to achieve normoprolactinemia. Similarly, in an effort to achieve uniformity, for the purposes of the present analysis, dopamine agonist resistance with respect to tumor size will be defined as the failure to achieve tumor size reduction of 50%.

### *B. Features and mechanisms*

The molecular factors underlying the ability of some prolactinomas to escape dopaminergic control are not fully understood. It is worth noting that the overall number of human prolactinomas that have been characterized on a molecular level, directly comparing resistant and responsive prolactinomas, is limited. These studies are inherently challenging for the following reasons. First, human-derived prolactinoma cell lines are relatively unavailable (293). Therefore, *in vitro* studies of these tumors are largely restricted to the use of primary (short-term) cultures. Second, as noted by their insensitivity to inhibitory signals and histologically aggressive nature, these particular tumors have acquired multiple intrinsic molecular defects that result in autonomous capabilities, such as escape from apoptosis and/or an unrestrained replicative potential, which are likely to have a diverse molecular basis (294). The substantial genetic heterogeneity among these tumors complicates our ability to dissect out individual factors that are responsible for the development of drug resistance.

The obvious candidate for a molecular alteration leading to dopamine agonist resistance is the lactotroph dopamine $D_2$ receptor itself (Fig. 3). Thus far, mutations in the $D_2$ receptor have not been identified in human prolactinomas, although it should be noted that a limited number of these tumors have been subject to such a molecular analysis (295). Several studies have examined the expression and affinity of $D_2$ receptors in resistant prolactinomas, as well as proximal downstream signaling effectors of the $D_2$ receptor (296).

There is experimental evidence that some dopamine agonist-resistant prolactinomas have a reduced density of $D_2$ receptors (292, 297, 298). The initial studies documenting this finding were reported by Pellegrini *et al.* (292), who compared dopamine receptor density and affinity in primary cell cultures of prolactinomas derived from bromocriptine-sensitive (n = 10) and resistant (n = 8) patients. The density of dopaminergic binding sites, as assessed by [$^3$H]spiroperidol (a selective $D_2$ receptor antagonist) was reduced by 50% in the group of resistant prolactinomas overall compared with the group of bromocriptine-sensitive adenomas. The binding affinity, nonetheless, was similar. On an individual basis, the dopamine receptor density was highly variable, so that a clear distinction in dopamine receptor expression between sensitive and resistant tumors was not discernible. Five of the resistant prolactinomas that actually grew during therapy showed a dramatic reduction in $D_2$ receptor sites, exhibiting only 10% of the number of dopaminergic binding sites found in normally responsive tumors. In the majority of tumors, adenyl cyclase activity within the cells paralleled the changes in $D_2$ receptor number proportionately, demonstrating that although reduced in number, the $D_2$ receptors from the resistant prolactinomas couple normally to adenyl cyclase. However, for the tumors that grew during therapy, dopamine paradoxically stimulated adenyl cyclase activity. For

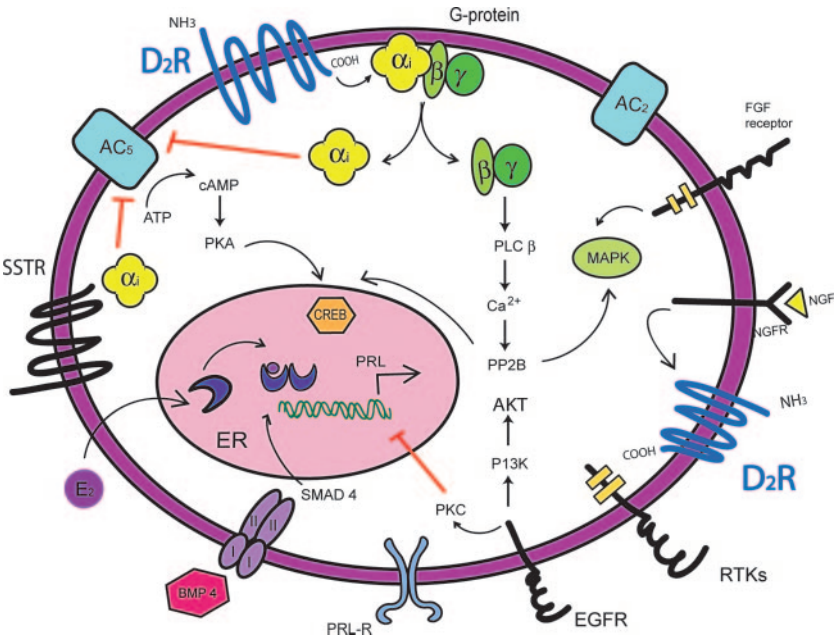


FIG. 3. Schematic illustration of signaling pathways in pituitary lactotrophs. For simplicity, major pathways are illustrated, and the reader is referred to recent reviews for more extensive detail (183, 520, 626). Alterations in several of these signaling pathways have been identified in human prolactinomas (see Tables 14 and 15). Activation of the $D_2$ receptor, and to a lesser extent the somatostatin receptor (SSTR), results in the inhibition of PRL synthesis and secretion through a number of pathways mediated by several G proteins. G$\alpha$i2 mediates $D_2$-induced adenyl cyclase 5 inhibition and subsequent reduction in intracellular cAMP, probably the major pathway involved in the inhibition of PRL gene transcription, as well as the inhibition of phospholipase C activity, which is necessary for activation of phosphoinositide pathways. $D_2$ receptor activation also stimulates MAPK, ERK1, and ERK2, thereby inhibiting cell proliferation. Estradiol ($E_2$) stimulates PRL gene transcription (in a classic mechanism) by binding to estrogen response element located in the PRL promoter. NGF receptor (NGFR) signaling stimulates expression of $D_2$ receptor. AC5, Adenyl cyclase type 5; AC2, adenyl cyclase type 2; FGF, fibroblast growth factor; PLC $\beta$, phospholipase B; PP2B, protein phosphatase 2B; RTK, receptor tyrosine kinase; EGFR, epidermal growth factor receptor; PRL-R, PRL receptor; BMP 4, bone morphogenetic protein 4; CREB, cAMP element binding protein; PKA, protein kinase A; PKC, protein kinase C; P13K, phosphatidylinositol 3-kinase; AKT, protein kinase B; $\alpha$, $\alpha$-subunit of G protein; $\beta$, $\beta$-subunit of G protein; and $\gamma$, $\gamma$-subunit of G protein.

this subset of resistant tumors, the possibility of abnormal coupling of the $D_2$ receptor to second messengers (G$\alpha$i2 proteins), in addition to an overall reduction in $D_2$ receptor expression, cannot be excluded. Unexpectedly, in this subset of tumors, the bromocriptine-induced stimulation of adenyl cyclase was not associated with a further increase in PRL release. The significance of this finding remains uncertain, although it raises speculation that the increase in adenyl cyclase activity may have reflected preserved activation of adenyl cyclase subtype 2, which is stimulated by $D_2$ receptor activation and lies upstream of mitogenic signaling pathways (299, 300).

Since this initial report documenting a reduction in $D_2$ receptor expression among bromocriptine-resistant prolactinomas, some (298, 301), but not all (302, 303), studies have corroborated these findings. For example, Caccavelli *et al.* (301) found a 4-fold lower level of $D_2$ receptor mRNA and 5-fold lower number of $D_2$ binding sites among bromocriptine-resistant compared with bromocriptine-sensitive prolactinomas, but Kovacs *et al.* (302), demonstrated preservation of both $D_2$ receptor mRNA and protein expression in their prolactinoma resistant to dopamine agonist therapy. Thus, the absence of $D_2$ receptor expression is not a universal finding among prolactinomas resistant to dopamine agonist therapy. It may, however, be associated with the progression to a more dedifferentiated state (41).

A second area of investigation into the mechanism of dopamine agonist resistance has focused on differences in the proportion of short ($D_{2S}$) and long ($D_{2L}$) dopamine receptor variants and correlating this with the degree of dopamine agonist responsiveness. As noted earlier, the $D_2$ receptor exists as two different isoforms generated by alternative splicing: the long ($D_{2L}$) and the short ($D_{2S}$) isoforms, which differ in the presence or absence of a stretch of 29 amino acids within the third cytoplasmic loop. The two molecular forms of the receptor display comparable binding characteristics, but they are regulated differently (297, 304) and may couple selectively to different G proteins (305, 306). The $D_{2S}$ receptor may be more efficient than the $D_{2L}$ at coupling to adenyl cyclase (307, 308). Using quantitative RT-PCR, both the short and long isoforms were found in sensitive prolactinomas, in equivalent proportions to that reported for normal pituitary lactotrophs (301). By contrast, the proportion of mRNA corresponding to the $D_{2S}$ was lower in resistant compared with responsive prolactinomas ($D_{2S}/D_{2L}$ ratio = 0.74 and 1.00, respectively). The significance of this altered ratio is uncertain, because the magnitude of the decrease in $D_{2S}$ receptor expression is of limited amplitude, compared with a 4-fold overall lower expression of the $D_2R$. Consequently, alterations in the ratio of the receptor variants may contribute to (but are unlikely to solely determine) the spectrum of dopamine agonist responsiveness observed among prolactinomas (309).

A few studies have investigated alterations in G protein

subunits as contributing factors to bromocriptine resistance. Two rat PRL-secreting pituitary tumor cell lines (7315a and MtTTW15) that are resistant to dopamine agonists display a reduction in $G\alpha i_2$ and $G\alpha o$ content, compared with normal rat pituitary (310, 311). A study of human bromocriptine-resistant prolactinomas corroborated the finding of a reduction in $G\alpha i_2$ among resistant prolactinomas, although no differences in $G\alpha o$ or $Gs\alpha$ mRNA levels were observed (312). The relative $G\alpha i_2$ expression correlated with the $D_2$ receptor expression, as well as the ability of bromocriptine to inhibit PRL secretion *in vitro*. Therefore, a common regulatory element involved in $D_2$ receptor and $G\alpha i_2$ subunit expression may contribute to dopamine agonist resistance in some prolactinomas.

A third major area of investigation has focused on the role of autocrine pathways of inhibitory growth signaling in the development of dopamine agonist resistance in human prolactinomas. Missale and Spano (313) have identified a nerve growth factor (NGF)-mediated autocrine loop that controls cell proliferation and differentiation in pituitary lactotrophs. This autocrine loop is present in dopamine-sensitive prolactinomas but lost in dopamine-resistant tumors. A thorough analysis and comparison of the NGF system has revealed that dopamine-sensitive prolactinomas secrete high levels of NGF and express both $p75^{NGFR}$ and trkA receptors for NGF (314). In contrast, dopamine-resistant prolactinomas do not produce NGF and express the trkA but not the $p75^{NGFR}$ receptor (314). Exposure of the dopamine-resistant cells to exogenous NGF induces expression of NGF mRNA, production and secretion of biologically active NGF, and the expression of $p75^{NGFR}$ receptors, thus restoring the autocrine loop. More impressively, treatment of the dopamine-resistant cells with NGF promotes their differentiation, induces expression of both the $p75^{NGFR}$ receptor and $D_2R$, inhibits proliferation, and abrogates the tumorigenic potential of these cells *in vivo* (298, 315). Conversely, ablation of NGF production in dopamine-responsive cells leads to transformation and $D_2R$ loss (314). Purportedly, the reestablishment of the NGF-mediated autocrine loop induced a permanent effect, because it was maintained in daughter cells even upon withdrawal of exogenous NGF. The molecular mechanisms underlying the "redifferentiating" effects of NGF are under investigation but appear to involve two events. First, NGF appears to regulate $D_2R$ expression by inducing $p75^{NGFR}$ receptor-mediated nuclear translocation and activation of nuclear factor-$\kappa$B (316). Second, NGF promotes a conformational change in the tumor suppressor p53 that permits its nuclear translocation and reconstitutes its DNA binding activity (317).

To summarize, there is solid evidence that some dopamine agonist-resistant prolactinomas are associated with a reduction in $D_2$ receptor density but not an alteration in binding affinity. Some dopamine agonist-resistant prolactinomas may exhibit disruptions in the autocrine growth factor signaling pathway mediated by NGF, which may contribute to the progression of these tumors. Whether alterations in $D_2$ receptor isoform ratios are altered, related to differences in G protein specificity, or of major significance in mediating dopamine agonist resistance remains to be determined. Finally, it should be emphasized that additional undiscovered molecular alterations further downstream of the $D_2$ receptor, and/or alterations altogether unrelated to $D_2$ receptor signaling, may contribute or cause insensitivity to inhibitory dopaminergic influence, especially in more dedifferentiated tumors.

### *C. Unusual presentations*

Under most circumstances, the normalization of PRL levels achieved with a dopamine agonist is accompanied by substantial tumor size reduction. However, unusual cases of selective dopamine agonist resistance have been reported in a few patients exhibiting discordant responses to the PRL-lowering and tumor size-reducing effects of bromocriptine. Because of the discordance of response seen in many patients, both the PRL response and the tumor size response will be discussed separately, where appropriate, using the definitions of dopamine agonist resistance outlined above, *i.e.*, failure to normalize PRL levels and failure to decrease tumor size by at least 50%.

Rarely, patients who initially respond to dopamine agonist therapy later become resistant (318–320). For example, Delgrange *et al.* (321) reported an unusual case of a macroadenoma that responded well to bromocriptine for 5 yr, yet later became resistant. The mechanism for this late loss of responsiveness is not known. Rarely, a benign prolactinoma will develop dopamine agonist resistance upon malignant transformation (322), a phenomenon that should be investigated in patients who develop late resistance to dopamine agonists (320). Noncompliance with medications can lead to a clinical situation that mimics resistance, as a result of side effects generated by discontinuing a drug, followed by resumption of the full dose. Under these circumstances, drug intolerance, rather than tumoral resistance, is responsible for the unsatisfactory response.

### *D. Resistance to prolactin-lowering effects*

On the basis of the efficacy data presented in *Section IV* (Medical Therapy), it is possible to estimate the prevalence of resistance to the specific dopamine agonists with respect to the normalization of PRL. Overall, approximately 24, 13, and 11% of patients demonstrate resistance to bromocriptine, pergolide, and cabergoline, respectively. Resistance to quinagolide is difficult to ascertain, because there are no large published series in which quinagolide was given to totally drug-naïve patients, which would allow determination of the percentage of patients responding with a normalization of PRL levels in the absence of any prior drug therapy. Virtually all of the studies testing the efficacy of quinagolide were conducted in patients who had previously been treated with bromocriptine.

It is of clinical interest to know whether resistance to dopamine agonists represents a class effect. Most of the clinical data regarding dopamine agonist resistance involve studies investigating whether another dopamine agonist may be effective in patients resistant to bromocriptine. Of all the dopamine agonists, cabergoline has been shown to be most effective in normalizing PRL levels in patients resistant to bromocriptine. Approximately 80% of bromocriptine-resis-

tant patients obtain a normalization of PRL on cabergoline (204, 323). Colao *et al.* (323) showed that 85% of 20 patients resistant to both bromocriptine and quinagolide responded with a normalization of PRL levels, and 70% responded with some change in tumor size. A subgroup analysis from a large study of patients treated with cabergoline found that 70% of 58 patients in whom bromocriptine failed to normalize PRL were controlled with cabergoline (204). These patients did require higher doses of cabergoline (1.5 mg/wk) compared with the overall cohort (0.5 mg/wk). Seven (12%) of the patients previously found to be resistant to bromocriptine were completely resistant to cabergoline (<50% decrease in PRL levels). It is not known for certain why cabergoline can be effective in patients resistant to bromocriptine, but possible explanations include the higher affinity of cabergoline for dopamine binding sites, its greater occupancy of the receptor, and slower elimination from the pituitary (324).

Two large, prospective European randomized studies compared bromocriptine to cabergoline with respect to drug efficacy, thus allowing a comparison of the prevalence of resistance to each drug within the same study. In the European Cabergoline Collaborative Study, PRL was normalized in 48 of 74 (65%) women taking bromocriptine and in 66 of 72 (92%) women taking cabergoline (203). In a multicenter study conducted in France, 27 of 58 (48%) women taking bromocriptine and 56 of 60 (93%) women taking cabergoline normalized their PRL levels (325). A third retrospective analysis by Di Sarno *et al.* (207) compared rates of drug resistance between a group of patients who were taking bromocriptine initially in the 1980s to another group of patients taking cabergoline initially (in the same clinic) when it became available in the late 1980s. Of patients with microadenomas, 57% of 44 patients taking bromocriptine and 90% of 60 patients taking cabergoline normalized their PRL levels (207). Similarly, of patients with macroadenomas, 46% of 28 patients taking bromocriptine and 82% of 46 taking cabergoline normalized their PRL levels (207).

Quinagolide (CV 205–502) has been shown to be effective in improving hyperprolactinemia in some patients resistant to bromocriptine, although the ability of quinagolide to normalize hyperprolactinemia in these patients varies widely among the studies (225, 282, 284, 326–329). There are sporadic reports of using pergolide in bromocriptine-resistant patients that show only modest efficacy (221, 330).

### *E. Resistance to mass-reducing effects*

There are no prospective, randomized series that have compared one dopamine agonist to another with respect to their abilities to decrease tumor size. Therefore, three series have been selected that are comparable in many aspects with respect to relative abilities of tumor size lowering (Table 7). In these series, PRL levels could be lowered to normal in 66, 68, and 100% and tumor size decreased by at least 50% in 64, 86, and 96% of patients receiving bromocriptine (187), pergolide (218), and cabergoline (206), respectively. However, it should be noted that the times of final assessment of the efficacy of these drugs were different; the effects of pergolide and cabergoline were assessed at comparable times at 27 and 24 months, whereas the effects of bromocriptine were assessed at 12 months. Because the process of tumor mass reduction may continue after 1 yr, it is possible that the efficacy of bromocriptine in reducing tumor size is underestimated by the figures presented in Table 7.

On the basis of the studies cited above for PRL level reduction and tumor size reduction, it is possible to make a rough, overall comparison of the three evaluable dopamine agonists. With respect to lack of normalization of PRL levels, resistance can be expected in 25–50% of patients taking bromocriptine, 10–30% taking pergolide, and 5–18% taking cabergoline. With respect to failure to achieve at least a 50% decrease in tumor size, resistance can be expected in about one third of those taking bromocriptine, about 15% of those taking pergolide, and 5–10% of those taking cabergoline.

### *F. Treatment approaches*

The possible treatment approaches for patients with prolactinomas that demonstrate dopamine agonist resistance include: 1) trial of an alternative dopamine agonist; 2) escalation of the dopamine agonist beyond conventional doses; 3) surgical tumor resection; 4) radiotherapy; and 5) experimental treatments. As noted above, some patients who respond do not respond to one dopamine agonist will respond to another, and *vice versa*. Another approach is simply to continue increasing the dose of the medication as long as a continued response can be documented. About 80–90% of patients who respond to dopamine agonists will do so rapidly and with low doses. However, about 5% of patients respond with a step-wise reduction in PRL levels with each increase in dose. Di Sarno *et al.* (207) found that incremental increases in cabergoline doses led to step-wise reduction in PRL levels in 18% of patients with macroadenomas and 10% of those with microadenomas. Increasing the weekly dose of cabergoline to 7 mg/wk permitted recovery of gonadal and sexual function in 30% of those with macroadenomas and all of those with microadenomas (207). A patient we recently reported required up to 3 mg/d of cabergoline to reduce PRL levels to less than 100 $\mu$g/liter (331). In general, large doses of cabergoline are very well tolerated, as demonstrated by the many studies in which this drug has been used to treat Parkinson's disease (56–58). As long as adverse effects from

TABLE 7. Tumor size reduction with various dopamine agonists

| Drug | Bromocriptine | Pergolide | Cabergoline |
|---|---|---|---|
| Ref. | 187 | 218 | 206 |
| No. of patients | 27 | 22 | 26 |
| Baseline PRL ($\mu$g/liter) | 2260 ± 539 | 2938 ± 780 | 1013 ± 278 |
| Normalization of PRL (%) | 66 | 68 | 100 |
| % with 50% tumor shrinkage | 64 | 86 | 96 |
| Time of assessment (months) | 12 | 27 | 24 |

higher doses do not develop, dose escalations are reasonable, with the awareness that doses of cabergoline greater than 2.0 mg/wk are beyond what is recommended in the package insert. Thus, once a patient has been switched to the most efficacious and well-tolerated drug (usually cabergoline), the dose may be raised cautiously. However, as noted above, cardiac valvular fibrosis may occur in patients taking large doses, and patients should be monitored for this possibility.

Transsphenoidal surgery remains an option if the tumor is potentially resectable and an experienced neurosurgeon is available. Radiotherapy may be effective in controlling tumor growth, although its efficacy in restoring PRL levels to normal is limited. If fertility is a major concern, induction of ovulation is possible in hyperprolactinemic patients even without lowering PRL levels, using clomiphene citrate, gonadotropins, and pulsatile GnRH (332–334). A number of experimental therapies in various phases of development are available, as discussed in *Section XII* (Experimental Therapy), although these methods should be reserved for situations in which all other standard therapies have failed.

## VIII. Dopamine Agonist Withdrawal

### A. Overview

As already discussed in detail, the primary medical treatment of prolactinomas with dopamine agonists is highly effective in controlling the hyperprolactinemic syndrome, *i.e.*, recovery of gonadal function, control of tumor growth, and recovery of neurological symptoms (15). The appreciation for medical therapy with dopamine agonist compounds is based not only on excellent clinical results but also on the evidence that surgery resulting in normal PRL levels has a high risk of recurrence of hyperprolactinemia (85, 335, 336). Previously, cure of a prolactinoma has been defined and regarded as the complete removal of tumor through surgical resection (31). In the past, withdrawal from medical therapy has been generally reported to result in a greater incidence of recurrent hyperprolactinemia compared with that observed after surgery (Table 8). As a result, the principal shortcoming of dopamine agonist treatment has been perceived to be its supposed lifelong requirement. In fact, in the first study reporting results of bromocriptine withdrawal, Johnston *et al.* (337) showed that PRL levels remained significantly lower than those before initiating therapy, but they remained within the normal range in only two of 37 treated patients. Several other studies have evaluated recurrence after discontinuation of bromocriptine, all of which have reported quite disappointing results, as detailed in the following sections. More recently, in an prospective, observational, analytical study conducted in 200 patients with hyperprolactinemia undergoing cabergoline withdrawal, Colao *et al.* (98) reported a prevalence of persistent normoprolactinemia, independent of baseline tumor size, in more than 60% of the patients, thus providing anticipation for greater long-term successful withdrawal with this drug. Overall, in that prospective study, over the time of follow-up using MRI scans, complete disappearance occurred in 46 of 117 (39.3%) patients with macroadenomas and 63 of 194 (32.5%) patients with microadenomas. This section focuses on the possibility of withdrawing dopamine agonist therapy in patients with prolactinoma, first analyzing the results reported in the literature, followed by a highlight of the authors' personal experience and perspective, ending with a proposed protocol for withdrawal of treatment that may be applied in clinical practice.

### B. Bromocriptine withdrawal

After withdrawal of bromocriptine (Table 8), remission rates have been reported from as low as 0 to 9% (337–340) to as high as 20 to 44% (97, 125, 341–344). In the only study restricted to patients with macroprolactinomas, van't Verlaat and Croughs (345) reported a remission rate in 8% of 12

TABLE 8. Literature review on dopamine agonist withdrawal

| Author | Ref. | No. of subjects | | | | Drug | Treatment duration (months) | Normal PRL (%) | Follow-up duration (months) |
|---|---|---|---|---|---|---|---|---|---|
| | | Total | Micro | Macro | NTH | | | | |
| Johnston *et al.* | 337 | 37 | | | 19 | BRC | 12–72 | 5.4 | 0.5 |
| Zarate *et al.* | 344 | 16 | | | 0 | BRC | Mean 24 | 37.5 | 24 |
| Moriondo *et al.* | 341 | 36 | 36 | 0 | 0 | BRC | Mean 12 | 22 | Up to 30 |
| Johnston *et al.* | 339 | 13 | 5 | 6 | 2 | BRC | Mean 44 | 7.7 | 1–12.5 |
| Johnston *et al.* | 339 | 2 | 1 | 1 | 0 | PER | 24 | 0 | 2 |
| Maxson *et al.* | 340 | 7 | 7 | 0 | 0 | BRC | >12 | 0 | 2 |
| Wang *et al.* | 125 | 24 | 15 | 4 | 5 | BRC | Mean 24 | 21 | 12–48 |
| Winkelmann *et al.* | 343 | 40 | | | | BRC | | 18.4 | 5–25 |
| Rasmussen *et al.* | 283 | 75 | | | | BRC | Mean 24 | 44 | >6 |
| van't Verlaat *et al.* | 345 | 12 | 0 | 12 | 0 | BRC | Median 60 | 8.3 | 12 |
| Ferrari *et al.* | 347 | 65 | 42 | 7 | 15 | CAB | Median 14 | 31.3 (yr 1)<br>66.7 (yr 2) | 3–24 |
| Muratori *et al.* | 348 | 26 | 26 | 0 | 0 | CAB | 12 | 19 | 38–60 |
| Cannavò *et al.* | 349 | 37 | 26 | 11 | 0 | CAB | 24 | 13.5 | 12 |
| Di Sarno *et al.* | 224 | 39 | 23 | 16 | 0 | CV | 12 | 0 | 0.5–2 |
| Di Sarno *et al.* | 224 | 39 | 23 | 16 | 0 | CAB | 12 | 10.2 | 12 |
| Passos *et al.* | 342 | 131 | | | | BRC | Mean 47 | 20.6 | Mean 44 |
| Colao *et al.* | 98 | 200 | | | | CAB | >24 | | 24–60 |
| Biswas *et al.* | 97 | 22 | 22 | 0 | 0 | BRC | Median 36 | 50 | >12 |
| Biswas *et al.* | 97 | 67 | 67 | 0 | 0 | CAB | Median 36 | 31.3 | >12 |

BRC, Bromocriptine; CAB, cabergoline; NTH, nontumoral hyperprolactinemia; PER, pergolide; CV, quinagolide.

patients after 12 months. Importantly, an increase of tumor volume with clear-cut reexpansion has been found in less than 10% of cases (188, 222, 346) after bromocriptine discontinuation. Tumor regrowth appears to depend upon the duration of previous treatment, although the cumulative data to this point are too sparse to draw definitive conclusions (97, 98, 125, 337–345).

### *C. Cabergoline withdrawal*

As noted above, cabergoline has been associated with substantial success with respect to tumor mass reduction in macroadenomas. In light of its efficacy in this regard, it was anticipated that cabergoline might achieve a greater likelihood of remission of hyperprolactinemia (compared with bromocriptine) after treatment withdrawal. Results of studies investigating withdrawal from cabergoline treatment remain limited. Persistent normoprolactinemia was found by Ferrari *et al.* (347) in 31.2% of 32 patients; by Muratori *et al.* (348) in 24% of 25 patients; by Cannavò *et al.* (349) in one patient with a macroprolactinoma (11%) and four with microprolactinomas (22%); and by Biswas *et al.* (97) in 31.3% of 67 patients (Table 8). In a sequential study aiming at comparing the efficacy of a 12-month course of treatment with quinagolide and cabergoline in 39 patients (23 with microprolactinoma and 16 with macroprolactinoma), Di Sarno *et al.* (224) also found persistent normoprolactinemia in none of the patients during the treatment with quinagolide and in 10.2% (17.4% of 23 microprolactinomas) treated with cabergoline (Table 8). All the studies reporting the results of cabergoline withdrawal, with the exception of the one by Biswas *et al.* (97), were prospective. The limitations of the studies above were both the small series of patients studied and the lack of criteria for treatment withdrawal. Moreover, the study by Di Sarno *et al.* (224) did not have the goal of investigating the effects of treatment withdrawal but was focused on the comparison of the efficacy between the two drugs. Therefore, the outcome of cabergoline treatment and withdrawal could be biased by the previous treatment with quinagolide.

The more recent study by Colao *et al.* (98) reported a Kaplan-Meier estimate of recurrence rate of hyperprolactinemia after 5 yr of cabergoline withdrawal of only 24% in patients with nontumoral hyperprolactinemia, 32.6% in patients with microprolactinomas, and 43.3% in those with macroprolactinomas. MRI evidence of tumor regrowth was not found in any patient; only 10 women (22.2%) and seven men (38.9%) with recurrent hyperprolactinemia redeveloped gonadal dysfunction. In accord with previous studies, PRL levels at recurrence were significantly lower than at diagnosis in all groups. The patients showing small remnant tumors on MRI at treatment withdrawal, with either macro- or microprolactinomas at their diagnosis, had a higher estimated recurrence rate after 5 yr than those without evident tumor (macroprolactinomas 77.5 *vs.* 32.6%, $P = 0.001$; microprolactinomas 41.5 *vs.* 26.2%, $P = 0.02$). Age, basal PRL levels, nadir PRL levels (Fig. 4), percent PRL suppression, nadir tumor diameter after cabergoline (Fig. 5), treatment duration, and cabergoline dose were all higher before treatment withdrawal in patients developing a recurrence of hyperprolactinemia compared with those achieving persistent control (98). A Cox regression analysis (Fig. 6) indicated that the nadir value of maximal tumor diameter during cabergoline treatment was the best predictor of persistent hyperprolactinemia after withdrawal ($\chi^2 = 12$; $P < 0.001$); the hazard rate for each millimeter of maximal tumor diameter measured on MRI before treatment withdrawal on recurrence of hyperprolactinemia was 19% (98). These results support the concept of periodic treatment withdrawal, especially in the patients with no tumor visible on MRIs during treatment. However, until longer follow-up data are available, particularly in patients with macroadenomas for whom tumor regrowth may compromise vision, patients should be closely monitored for recurrent hyperprolactinemia and tumor regrowth.

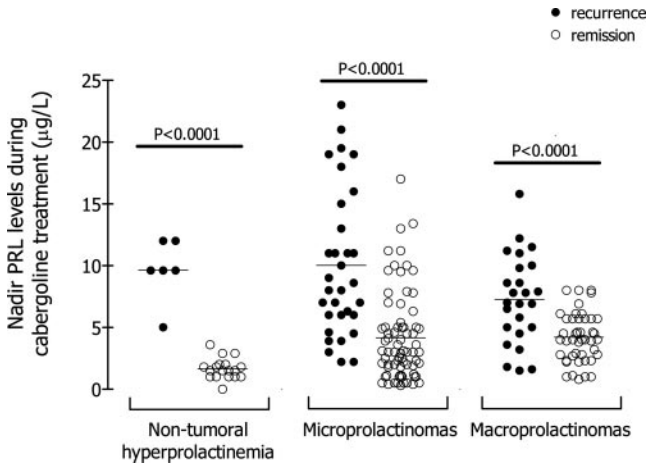


FIG. 4. Side-by-side demonstration of nadir PRL levels achieved during treatment with cabergoline in those patients who developed recurrence of hyperprolactinemia (●) after treatment withdrawal and those who sustained remission (○) after treatment withdrawal. The nadir PRL was higher before treatment withdrawal in those patients who developed recurrence of hyperprolactinemia. Data are derived from Ref. 98.

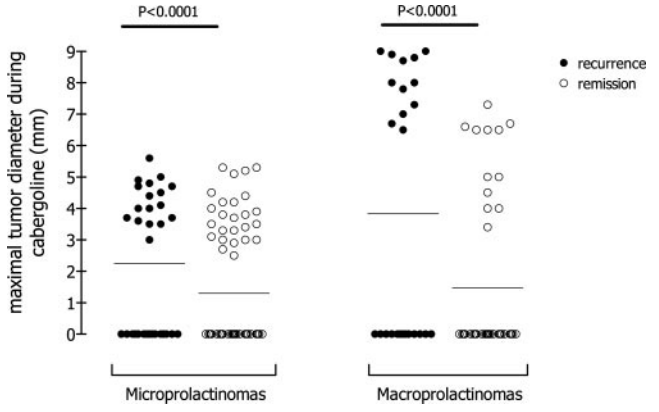


FIG. 5. Side-by-side demonstration of maximal tumor diameter achieved during treatment with cabergoline in those patients who developed recurrence of hyperprolactinemia (●) after treatment withdrawal and those who sustained remission (○) after treatment withdrawal. The nadir tumor diameter was larger before treatment withdrawal in those patients who developed recurrence of hyperprolactinemia. Data are derived from Ref. 98.

*D. Withdrawal of other dopamine agonists*

The results of treatment withdrawal with other dopamine agonists are limited. As shown in Table 8, the outcomes of only two patients have been reported after pergolide withdrawal (339) and of 39 patients after quinagolide withdrawal (224); PRL levels did not remain normal in any of these cases (224, 339). The latter study was not designed to address the issue of quinagolide withdrawal, which was performed only as a washout period before changing to cabergoline treatment. Therefore, the paucity of the data does not permit conclusive statements on treatment withdrawal with other dopamine agonists.

*E. Other conditions associated with remission of hyperprolactinemia*

Two other conditions, apart from previous surgery and/or radiotherapy and bromocriptine or cabergoline withdrawal, are known to facilitate the remission of hyperprolactinemia: pregnancy (350, 351) and menopause (352). Among the 200 patients (156 women) we enrolled in the study of cabergoline withdrawal (98), recurrence of hyperprolactinemia was not found to be associated with gender ($P = 0.928$) or with menopause (27.5% in premenopausal and 36% in postmenopausal women; $P = 0.5$). In our study, we excluded the patients undergoing treatment discontinuation for pregnancy. Nevertheless, remission of hyperprolactinemia has also been described in untreated tumors during their natural history. Spontaneous regression of hyperprolactinemia has been reported in 32% (23), 33% (351), 35% (25) and up to 55% of cases (26), but the great majority of these patients had microadenomas. Therefore, even considering that natural history might have a relevant role in the outcome of microprolactinomas, it is less likely that macroadenomas would spontaneously regress.

*F. Authors' personal experience*

Because the possibility of inducing a long-lasting control of hyperprolactinemia in the absence of continuing pharmacological treatment has profound consequences not only for the patients' compliance but also for pharmacoeconomics, we started a project in January 1994 to analyze the remission rate of hyperprolactinemia after withdrawal of cabergoline therapy given as exclusive treatment for the disease. In the absence of previous criteria for bromocriptine treatment withdrawal, as described in Table 9, we chose to adopt two conditions for the inclusion criteria for cabergoline withdrawal: the normalization of PRL levels and the shrinkage of the tumor on MRI. As a further precaution, once the patients fulfilled our criteria, cabergoline treatment was continued for another 12 months. Based on results in the literature on bromocriptine and cabergoline withdrawal (Table 8), the achievement of normoprolactinemia as the first inclusion criterion was a mandatory requisite that does not require further explanation. We also decided to consider the amount of tumor shrinkage as a further criterion, because cytocidal effects of bromocriptine have been previously shown (184) and disappearance of prolactinomas during cabergoline treatment has also been well documented (205, 206, 353, 354). On this basis, we performed the analysis of the results dividing the patients with hyperprolactinemia achieving stable normalization during cabergoline treatment into those having tumor disappearance on MRI and those having a consistent reduction of tumor mass, which we arbitrarily set at at least 50% of baseline. An exclusion criterion was the invasion of critical structures such as cavernous sinuses, optic chiasm, III ventricle, *etc.*; thus, patients with at least 50% shrinkage of their tumors that invaded critical structures were excluded from treatment withdrawal. Interestingly, although patients with negative MRI had a lower rate of recurrence than those with visible adenomas, more than half of the patients showing remnant tumors on MRI had persistent normoprolactinemia after drug withdrawal. This suggests that some of these patients have abnormalities on MRI other than prolactinomas, such as small nonfunctioning lesions, fibrotic scar, or other nontumoral abnormalities (incidentalomas).

In the first analysis of our series of patients, there were no cases of recurrence of hyperprolactinemia after 3 yr of withdrawal. Because the number of patients with an available follow-up after 36 months was still limited compared with the entire series (97 of 200), to provide further information on this topic, we have extended the follow-up of the 200 patients enrolled in the study of 2003 (98) up to 90 months. Table 9 provides details of the population at this second analysis. Of the initial 200 patients, 14 patients were lost at follow-up, and 26 women became pregnant during the study: all these 40 patients were in remission of hyperprolactinemia at the time of study exit. Remission rate after prolonged discontinuation of cabergoline treatment (median follow-up, 72–90 months) was 68.4% in patients with nontumoral hyperprolactinemia, 51.8% in patients with microprolactinomas, and 52.5% in patients with macroprolactinoma. However, as already demonstrated by the first analysis (98), the highest remission rates were found in patients with nontumoral hyperprolactinemia or with either microprolactinomas or macroprolactinomas that had disappeared on MRI during cabergoline therapy (Fig. 7). The 7-yr Kaplan-Meier estimation of recurrence showed that the remission rates in the patients with small

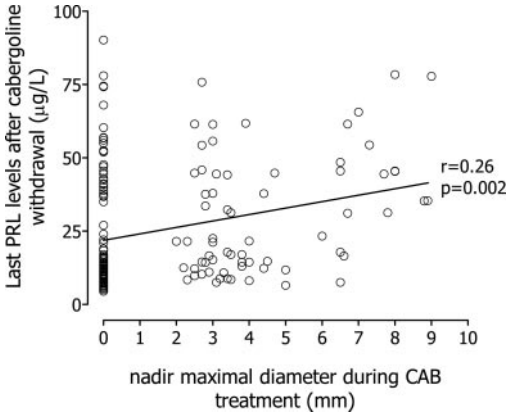


FIG. 6. Cox regression analysis indicating that the nadir value of maximal tumor diameter during cabergoline treatment is the best predictor of hyperprolactinemia after withdrawal ($\chi^2 = 12$; $P < 0.001$). ○, Individual results in the 200 patients of last PRL levels after withdrawal correlated with nadir maximal diameter during treatment. Data are derived from Ref. 98.

TABLE 9. Remission rates of hyperprolactinemia after at least 48 months of cabergoline withdrawal

| | PRL levels (μg/liter) | | Maximal tumor diameter (mm) | | Median time of follow-up (months) |
|---|---|---|---|---|---|
| | Baseline | Nadir | Baseline | Nadir | |
| Nontumoral hyperprolactinemia | | | | | |
| Recurrence (n = 6) | 70.4 ± 5.2 | 9.6 ± 2.6 | Negative | Negative | 18 |
| Remission (n = 13) | 74.1 ± 8.1 | 1.8 ± 0.8 | Negative | Negative | 90 |
| Pregnancy (n = 3)[a] | 51.7 ± 3.0 | 1.5 ± 0.5 | Negative | Negative | 48 |
| Lost at follow-up (n = 3) | 59.3 ± 0.6 | 1.2 ± 1.0 | Negative | Negative | 24 |
| Microadenomas | | | | | |
| Recurrence (n = 39) | 178.1 ± 35.6 | 8.9 ± 5.9 | 6.9 ± 1.4 | 2.5 ± 2.2 | 12 |
| Remission (n = 42) | 143.5 ± 45.4 | 4.2 ± 3.3 | 6.5 ± 1.8 | 1.0 ± 1.6 | 72 |
| Pregnancy (n = 18)[a] | 167.5 ± 64.6 | 4.0 ± 4.8 | 7.3 ± 1.6 | 0.6 ± 1.4 | 36 |
| Lost at follow-up (n = 6) | 173.3 ± 48.9 | 4.7 ± 3.0 | 7.3 ± 1.9 | 2.6 ± 2.1 | 42 |
| Macroadenomas | | | | | |
| Recurrence (n = 39) | 1131 ± 1147 | 6.3 ± 3.3 | 18.3 ± 5.6 | 3.4 ± 3.8 | 24 |
| Remission (n = 21) | 814 ± 2046 | 4.0 ± 1.9 | 16.0 ± 8.3 | 1.1 ± 2.1 | 72 |
| Pregnancy (n = 5)[a] | 481 ± 210 | 2.8 ± 1.2 | 15.0 ± 4.2 | 0.8 ± 1.9 | 24 |
| Lost at follow-up (n = 5) | 400 ± 209 | 5.2 ± 2.9 | 14.3 ± 3.7 | 0 ± 0 | 36 |

Inclusion criteria for cabergoline withdrawal were as follows: 1) serum PRL normalization (≤25 μg/liter in women or 15 μg/liter in men) during cabergoline treatment; 2) disappearance of the tumor or reduction in tumor size by 50% or more from baseline; to minimize the risk of errors in reading MRI scans, treatment was continued before stopping in all patients for another 12 months after fulfilling the specified withdrawal criteria; 3) follow-up after withdrawal of at least 24 months to characterize early and delayed recurrences. Exclusion criteria for cabergoline withdrawal were as follows: 1) serum PRL levels above 25 μg/liter in women or 15 μg/liter in men during cabergoline treatment; 2) tumors increasing in size during cabergoline treatment or not decreased in size by 50% or more from baseline; tumors whose outer border was 5 mm or less from the optic chiasm; tumors with MRI evidence of invasion of one or both cavernous sinuses or any other critical area.

[a] All women who became pregnant during the study were excluded from further analysis. Data are shown as mean ± SD. $\chi^2$/Fisher's exact tests were used to analyze proportions. Data are derived from an extension study of Ref. 98.

remnant tumors on MRI were much lower, *i.e.*, 20% in microprolactinomas and 0% in macroprolactinomas (Fig. 7). Importantly, at the last follow-up (48–90 months after cabergoline withdrawal), no recurrence of hyperprolactinemia was documented in the patients who had no evident tumor on MRI later than 36 months.

### *G. Practical implications and approaches*

To avoid unnecessary treatment, cabergoline withdrawal can be performed in patients with normoprolactinemia after at least 2 yr of treatment and when the MRI demonstrates complete disappearance of the tumor. If small remnants are still visible, we do not suggest withdrawing treatment. Alternatively, in patients with microprolactinomas, treatment can be withdrawn, but the higher recurrence rate should be considered and a more careful follow-up performed. In any case, the follow-up should be very strict during the first year after withdrawal, because the recurrence rate is highest during this period. It can subsequently be tailored on the basis of an individual patient's history and severity of disease. Because pregnancy and menopause are both physiological events associated with remission of hyperprolactinemia, these events should receive special attention with regard to the need for continuing therapy.

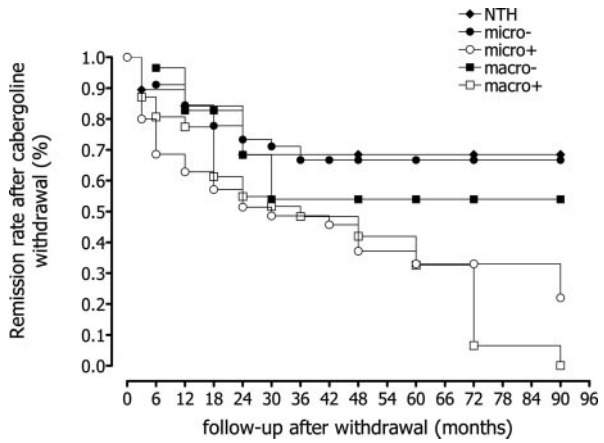


FIG. 7. Kaplan-Meier estimation of recurrence rates over 7 yr. Remission rates in patients with small remnant tumors evident on MRI are much lower than those without tumor remnants or those with nontumoral hyperprolactinemia (NTH). ♦, NTH; ●, microprolactinomas without tumor remnant; ○, microprolactinomas with tumor remnant; ■, macroprolactinomas without tumor remnant; □, macroprolactinomas with tumor remnant. The difference among the Kaplan-Meier curves is significant ($P < 0.0001$).

## IX. Pregnancy

The management of prolactinomas in pregnant women can be complex. Three major issues arise in the treatment of prolactinomas in pregnancy: 1) the effect of the pregnancy on the prolactinoma; 2) the effects of the dopamine agonist on early fetal development occurring before a pregnancy is diagnosed; and 3) the safety and efficacy of dopamine agonists after reintroduction for symptomatic tumor growth.

### *A. Effect of pregnancy on prolactinoma growth*

During pregnancy, estrogen stimulates PRL synthesis and secretion and promotes lactotroph cell hyperplasia (355). PRL levels in the maternal circulation rise throughout normal pregnancy, reaching a mean concentration of 150 ng/ml at term (356, 357). Autopsy studies showing lactotroph cell hyperplasia during pregnancy have been corroborated *in vivo* by MRI scans showing a gradual increase in pituitary volume over the course of gestation, beginning in the second month, peaking the first week postpartum, and achieving a

final mean height of 11.8 mm (358–360). After delivery, the gland rapidly involutes and returns to its normal size by 6 months postpartum (358, 359).

Reports of enlargement of prolactinomas associated with pregnancy began over 30 yr ago, shortly after the introduction of bromocriptine as an effective medical therapy for these tumors (334, 361–369). Early on, many of the symptomatic patients underwent surgery for visual defects (334, 363, 365, 367). However, the observation was soon made that in those who were managed without surgery, symptoms resolved shortly after parturition (334, 364, 366, 368). The enlargement of macroadenomas during pregnancy is therefore due to two factors: 1) discontinuation of the dopamine agonist that had caused the tumor to shrink; and 2) the stimulatory effect of the high estrogen levels produced by the placenta.

The potential for the enlargement of a prolactinoma during pregnancy is highly dependent upon two factors: its size, and the patient's history of prior radiotherapy or surgery. A total of five studies have compiled data analyzing the risk of symptomatic tumor enlargement in pregnant women with prolactinomas, divided according to their status as micro- or macroprolactinomas (370–374) (Table 10). These studies do not include case reports, only patients who were part of a larger subset being evaluated. According to these data, the risk of symptomatic tumor enlargement for microadenomas is low. Only 12 of 457 pregnancies (2.6%) were complicated by symptoms of tumor enlargement (headaches and/or visual disturbances). Surgical intervention was not required in a single case. Medical therapy with bromocriptine was instituted in five individuals, which was followed by the resolution of their symptoms. A few of these studies assessed the possibility of asymptomatic tumor growth by CT or MRI scans. In one review, 11 of 246 women (4.5%) with microprolactinomas demonstrated asymptomatic tumor growth (372). Another series documented tumor growth at similar low frequency in two of 41 microprolactinomas (5%) (373).

The risk of tumor enlargement in pregnancy is substantially greater for patients with macroprolactinomas. It is particularly high in women who have not undergone prior surgery or radiotherapy for their macroprolactinomas. According to the series included in Table 10, 45 of 142 pregnancies (31%) were complicated by symptoms of tumor enlargement (headaches and/or visual disturbances). Surgical intervention was undertaken in 12 of these cases (8.5%). Seventeen symptomatic patients with macroadenomas (who had not undergone prior surgery or radiotherapy) received medical therapy with bromocriptine, leading to resolution of their symptoms. Asymptomatic growth of macroprolactinomas was demonstrated by CT or MRI scans in a further four of 45 individuals (8.9%) in one series (372) and in a further four of 23 (17%) in another series (373). A total of 140 women with macroadenomas have been identified who have undergone surgery or radiation before pregnancy. In these individuals, the risk to tumor enlargement was low (2.5%).

Thus, the overall risk of clinically significant enlargement of microprolactinomas is low. It is similarly low for macroprolactinomas that are surgically resected or irradiated pregestationally (5%). There is a moderate risk of clinically significant tumor enlargement for macroprolactinomas that have only been treated with dopamine agonists pregestationally (31%). These data serve as the basis for management recommendations that are suggested below.

It should be emphasized that surgery was undertaken in many of these symptomatic women (25–50%) in the earliest studies before it was recognized that bromocriptine could reduce tumor size. Several reports have now documented the successful and safe use of bromocriptine and cabergoline to control tumor growth and alleviate visual symptoms during pregnancy, without adverse effects on the infants (371, 372, 375–382).

### *B. Effects of dopamine agonists on fetal development*

As discussed previously, hyperprolactinemia is usually associated with anovulation and infertility; correction of the hyperprolactinemia with dopamine agonists restores ovulation in about 90% of cases. Most patients with prolactinomas that come to clinical attention will require treatment of hyperprolactinemia to ovulate and conceive. Therefore, under these circumstances, the fetus is likely to be exposed to one of these drugs for at least 3–4 wk of gestation, until a pregnancy test can verify conception and allow discontinuation of the medication. Because all of the dopamine agonists have been shown to cross the placenta in humans and/or animals, it is advised that fetal exposure to the dopamine agonists be limited to as short a period as possible. The following section presents data regarding the effects of dopamine agonists when used in the early stages of gestation and when used throughout the pregnancy.

The use of bromocriptine, when it is taken for only the first few weeks of gestation, has not been associated with an increase in the rates of spontaneous abortions, ectopic pregnancies, trophoblastic disease, multiple pregnancies, or congenital malformations in a very large number of pregnancies (Table 11) (383, 384). Long-term follow-up studies of 64 children, between the ages of 6 months and 9 yr, who were born to mothers who took bromocriptine for a limited duration in early pregnancy have shown no adverse effects on childhood development (385). There is less data available on the effects of continuous bromocriptine (used throughout gestation) on fetal/infant development. An analysis of the infant outcomes of approximately 100 women who used bromocriptine throughout gestation revealed abnormalities in two infants,

TABLE 10. Effect of pregnancy on prolactinomas

| | Total no. of patients | Symptomatic enlargement | % Symptomatic enlargement | No. requiring surgery (%) |
|---|---|---|---|---|
| Microadenomas | 457 | 12 | 2.6 | |
| Macroadenomas | 142 | 45 | 31 | 12 (8.5%) |
| Macroadenomas, prior surgery or radiation | 140 | 7 | 5 | |

Data compiled from Refs. 370–374.

TABLE 11. Effect of bromocriptine on pregnancies

| | Bromocriptine (n) | Bromocriptine (%) | Normal population (%) |
|---|---|---|---|
| Pregnancies | 6239 | 100 | 100 |
| Spontaneous abortion | 620 | 9.9 | 10–15 |
| Terminations | 75 | 1.2 | |
| Ectopic | 31 | 0.5 | 0.5–1.0 |
| Hydatidiform moles | 11 | 0.2 | 0.05–0.7 |
| Deliveries (known duration) | 4139 | 100 | 100 |
| At term (>38 wk) | 3620 | 87.5 | 85 |
| Preterm (<38 wk) | 519 | 12.5 | 15 |
| Deliveries (known outcome) | 5120 | 100 | 100 |
| Single births | 5031 | 9.3 | 8.7 |
| Multiple births | 89 | 1.7 | 1.3 |
| Babies (known details) | 5213 | 100 | 100 |
| Normal | 5030 | 96.5 | 95 |
| With malformations | 93 | 1.8 | 3–4 |
| With perinatal disorders | 90 | 1.7 | >2 |

Data are derived from Ref. 384. Bromocriptine (n) refers to the number of patients treated with bromocriptine who experience the event listed in the first column. Bromocriptine (%) refers to the percentage of patients treated with bromocriptine who experience the listed event. Normal population (%) refers to the percentage of the normal population that experiences the listed event.

one born with an undescended testicle and one with a talipes deformity (386).

Few data are available on the safety of pergolide in pregnancy. Detailed data on the safety of pergolide during early gestation has only been reported in one woman treated with pergolide for Parkinson disease (387). The child of this pregnancy had no evidence of developmental abnormalities. According to statements made in this report, two major and three minor congenital abnormalities were described among 38 pregnancies in women receiving pergolide in premarketing studies, but a causal relationship was not definitively established (387). The manufacturer of pergolide, Eli Lilly & Co. (Indianapolis, IN), reports limited data on pregnancies in which the fetus was exposed to pergolide but did find that 7.2% of pregnancy outcomes resulted in spontaneous abortions, 7.2% in minor malformations, 14.3% in intentional abortions, 28.6% in healthy infants, and 43.4% with no information available (388). This limited information seems sufficient to recommend against the use of pergolide for a woman desiring pregnancy.

Quinagolide does not appear to be safe during pregnancy. Some early publications reported no detrimental effects on pregnancy or fetal development in women who became pregnant during treatment with quinagolide (327). However, a recent review of 176 pregnancies, in which quinagolide was maintained for a median duration of 37 d, reported 24 spontaneous abortions, one ectopic pregnancy, and one stillbirth at 31 wk gestation (244). Furthermore, nine fetal malformations were reported in this group, including spina bifida, Trisomy 13, Down syndrome, talipes, cleft lip, arrhinencephaly, and Zellweger syndrome (244). Therefore, quinagolide should also not be used if pregnancy is desired.

Experience with the use of cabergoline in pregnancy is accumulating. Data on exposure of the fetus or embryo during the first several weeks of pregnancy have been reported in just over 350 cases, and such use has not shown an increased percentage of spontaneous abortion, premature delivery, multiple pregnancy, or congenital abnormalities (204, 349, 373, 389–392). No alterations in the newborns' weights were observed (204, 373, 389–391). Short-term follow-up studies of 107 infants born to mothers who used cabergoline during pregnancy indicate normal neonatal physical and mental development (391).

Taken together, the following may be concluded with respect to the use of a dopamine agonist to facilitate ovulation and fertility. Bromocriptine has the largest safety database and has a proven safety record for pregnancy. The database for the use of cabergoline in pregnancy is much smaller, but there is no evidence at present indicating that it exerts deleterious effects on pregnant women. The incidence of malformation in their offspring is not greater than in the general population. For the woman who is intolerant to bromocriptine and who is doing well with cabergoline, continuation of cabergoline for facilitating pregnancy appears to be reasonable. Although the safety databases for pergolide and quinagolide are limited, the number of abortions and malformations associated with the reported pregnancies raises serious concern. Therefore, quinagolide and pergolide should not be used when fertility is desired, and all premenopausal women treated with these medications should be apprised of these data. If reinstitution of a dopamine agonist is needed later in gestation to control tumor growth, bromocriptine is favored over the other dopamine agonists due to greater experience with this drug in this setting.

### *C. Recommendations for management of prolactinoma in pregnancy*

The optimal management approach for a woman with a prolactinoma who desires pregnancy may depend on tumor size and individual tumor characteristics. Irrespective of these factors, the risks and benefits of surgical *vs.* medical therapy should be explained in detail to each patient.

A hyperprolactinemic woman harboring a microprolactinoma has three options to restore fertility: a dopamine agonist alone, transsphenoidal selective adenomectomy, or bromocriptine after surgery or irradiation. Pregnancy can be achieved in 80–85% of women with microadenomas treated with either bromocriptine or surgery (393–396). Transsphenoidal surgery of microprolactinomas is curative (long-term)

in approximately 60% of cases; nevertheless, it entails morbidity and mortality, albeit at very low rates (see *Section III.G*). For patients with microprolactinomas (or intrasellar macroprolactinomas), bromocriptine or cabergoline therapy is generally preferred to surgery because it is safe for the fetus when discontinued early in gestation and poses only a very low risk of tumor enlargement for the mother. Rare patients who remain infertile with failure to respond to either modality may need additional hormonal therapy to facilitate ovulation, such as clomiphene citrate plus human chorionic gonadotropin, pulsatile GnRH therapy, or recombinant gonadotropins (334, 397–401). Although radiotherapy has been advocated for patients with microadenomas before bromocriptine-induced pregnancy, this strategy is unwarranted, because the risk of tumor enlargement without radiotherapy is much lower than the risk of known, long-term sequelae of hypopituitarism associated with pituitary radiotherapy (108, 156, 157).

A patient with a microadenoma treated only with a dopamine agonist pregestationally should be carefully followed throughout pregnancy. PRL levels do not always rise during pregnancy in women with prolactinomas, as they do in normal women. Usually PRL levels rise over the first 6–10 wk after discontinuing bromocriptine and then do not increase further (402). PRL levels may also not rise with tumor enlargement (403). For these two reasons, periodic assessment of PRL levels is not beneficial. Because of the low incidence of tumor enlargement in microprolactinomas, routine periodic visual field testing is not cost effective. Visual field testing and MRI scans should be performed, however, in patients who develop visual changes or symptoms of mass effects. If tumor enlargement occurs, reinstitution of a dopamine agonist is often successful in reducing the size; however, persistent visual defects may necessitate transsphenoidal surgery or early delivery.

For the patient with a small intrasellar or inferiorly extending macroadenoma, bromocriptine is also favored as the primary therapy. The likelihood that such a tumor will enlarge sufficiently to cause clinically serious complications is probably only marginally higher than the likelihood in patients with microadenomas.

In a woman with a larger macroadenoma that may have suprasellar extension, there is a 15–35% risk of clinically serious tumor enlargement during pregnancy when only bromocriptine is used. There is no clear-cut answer as to the best therapeutic approach, and this has to be a highly individualized decision that the patient has to make after a clear, documented discussion of the various therapeutic alternatives. The most conservative approach is to perform a prepregnancy transsphenoidal surgical debulking of the tumor. This should greatly reduce the risk of serious tumor enlargement, but cases with massive tumor expansion during pregnancy after such surgery have been reported (378). After surgical debulking, bromocriptine is required to restore normal PRL levels and allow ovulation. Although radiotherapy before pregnancy, followed by bromocriptine, reduces the risk of tumor enlargement to only 5%, it is rarely curative. Radiotherapy may also result in long-term hypopituitarism (see *Section IV.F*), so that this approach seems much less desirable than transsphenoidal surgery plus bromocriptine. A third approach entails administration of bromocriptine continuously throughout gestation (404). The safety of the last approach has not been established, but based on the small number of cases cited earlier, it probably is not harmful (395). Should pregnancy at an advanced stage be discovered in a woman taking bromocriptine, the existing data are reassuring and would not justify therapeutic abortion. The most common approach is just to stop bromocriptine after pregnancy is diagnosed, as is done in patients with microadenomas.

For patients with macroadenomas treated with bromocriptine alone or after surgery or irradiation, careful follow-up with 1-month to 3-month visual field testing is warranted. Repeat scanning is reserved for patients with symptoms of tumor enlargement and/or evidence of a developing visual field defect or both.

Should symptomatic tumor enlargement occur with any of these approaches, reinstitution of bromocriptine is probably less harmful to the mother and child than surgery. There have been a number of cases reported where such reinstitution of bromocriptine has worked quite satisfactorily, causing rapid tumor size reduction with no adverse effects on the infant (see *Section IX.B*). Any type of surgery during pregnancy results in a 1.5-fold increase in fetal loss in the first trimester and a 5-fold increase in fetal loss in the second trimester, although there is no risk of congenital malformations from such surgery (405). Thus, bromocriptine reinstitution would appear to be preferable to surgical decompression. However, such medical therapy must be very closely monitored, and transsphenoidal surgery or delivery (if the pregnancy is far enough advanced) should be performed if there is no response to bromocriptine and vision is progressively worsening.

## X. Prolactinomas in Children and Adolescents

### *A. Epidemiology*

Pituitary adenomas are less common in children than in adults, but they become increasingly more frequent during the adolescent years (406–408). Pituitary adenomas constitute less than 3% of supratentorial tumors in children (406–408) and 2.3–6% of all intracranial tumors treated surgically (19, 20, 406–412). However, most published series included patients with onset of symptoms before the age of 20 yr as pediatric patients (19). The average annual incidence of pituitary adenomas in childhood has been estimated to be 0.1 per million children (413). Pituitary carcinomas are rare in adults and extremely rare in children (414).

There appears to be a greater invasiveness of prolactinomas in children compared with adults (407, 412, 415). Macroadenomas at presentation are more likely in boys than in girls (20, 407, 416). In the series reported by Colao *et al.* (417), microprolactinomas were more frequent in females (10 of 17), whereas macroprolactinomas were slightly, but not significantly, more frequent in males (7 of 9) than in females (7 of 17).

*B. Presentation*

Prepubertal children generally present with a combination of headache, visual disturbances, growth failure, and primary amenorrhea (Table 12). However, growth failure has been reported to be common in some series (416, 418, 419), but not others (17, 22). In fact, Colao *et al.* (417) found growth arrest only in one male patient with microprolactinoma (4%), whereas all the remaining 25 patients had normal heights, and pubertal development was appropriate for their age. Cannavò *et al.* (420) reported short stature in three of 30 adolescents with either micro- or macroprolactinoma (10%). Growth and pubertal development were reported to be normal also in a 16-yr-old boy with multiple endocrine neoplasia type 1 (MEN 1) syndrome with a pituitary adenoma accompanied by mild elevation of PRL and GH that was identified through family screening (421). In a reevaluation of the young/adolescent patients with hyperprolactinemia admitted to the University Federico II Hospital from January 1, 1995, to December 31, 2004, we found short stature in seven of 50 patients (14%), five girls and two boys, and another two, one girl and one boy, had their height below or at the 5th percentile. As expected, the percentiles of height in the patients with extrasellar/invasive macroprolactinomas were lower than in patients bearing smaller tumors ($P = 0.015$ comparing microprolactinomas *vs.* extrasellar tumors; Table 12). Macroadenomas were slightly more frequent at diagnosis in boys than in girls (76.2 *vs.* 48.3%; $P = 0.09$).

The most common symptoms of prolactinomas in the peripubertal age range are those associated with deficiency of the pituitary-gonadal axis. Menstrual irregularities in girls are common in all types of pituitary adenomas, except those causing Nelson's syndrome (418). As in the adults (17), the size of the prolactinomas is reported to correlate well with baseline PRL levels (417). In 50 patients, we found a high correlation between PRL levels and tumor volume ($r = 0.84$; $P < 0.0001$) and PRL levels and body mass index (BMI) ($r = 0.48$; $P = 0.024$). Weight gain has been reported to occur in patients with hyperprolactinemia (17, 422–424) but has not been described previously in children. However, among our 50 children, 23 had a normal BMI (<25 kg/m$^2$), 25 were overweight (BMI, 25.1–30 kg/m$^2$), and two were obese (BMI, >30 kg/m$^2$). Headache and/or visual field defects were common first symptoms in the majority of patients with macroadenomas (417). This finding was confirmed in the reevaluation of these 50 patients: in 28 of 29 girls, the first symptoms were amenorrhea, primary or secondary, or oligomenorrhea. The remaining girl, 10.5 yr old at diagnosis, had a large tumor (volume, 1982.6 mm$^3$; maximal diameter, 17.9 mm) that was diagnosed because of headache and bilateral galactorrhea in a context of panhypopituitarism (Table 12). In young patients, galactorrhea should be carefully investigated on breast examination, because teenagers may not voluntarily refer to it as a symptom, and frequently it is not spontaneous (415). Cannavò *et al.* also reported galactorrhea in 91% of their patients (420). In boys, the most common symptoms were headache (15 of 21 patients) and gynecomastia (12 of 21 patients).

Impairment of other pituitary hormone secretion was previously reported to occur in only a minority of patients at diagnosis (417, 420) and in some patients hypopituitarism developed after surgery. Our recent reevaluation allowed us to confirm that pituitary deficiencies in the context of a microprolactinoma are very rare (4.7%), whereas deficiencies are common in patients with macroadenomas with extrasellar extension (77.8%; Table 12). Additionally, 33.3% of the patients with enclosed macroadenomas presented with some degree of pituitary deficiency. Reduction of tumor size by

TABLE 12. Presentation of prolactinomas in children and adolescents

| | Microadenomas | Enclosed macroadenomas | Extrasellar and/or invasive macroadenomas |
|---|---|---|---|
| N | 20 | 21 | 9 |
| No. of girls/boys | 15/5 | 11/10 | 3/6 |
| Age at diagnosis (yr) | 14.4 ± 0.5 | 14.8 ± 0.4 | 13.8 ± 1.1 |
| Height (percentile) | 35.5 ± 4.0 | 26.9 ± 5.7 | 16.2 ± 6.3 |
| BMI (kg/m$^2$) | 24.4 ± 0.5 | 26.1 ± 0.4 | 27.6 ± 1.2 |
| Basal PRL levels (μg/liter) | 138.4 ± 21.6 | 671.4 ± 161.9 | 2123 ± 279 |
| Tumor volume on MRI (mm$^3$) | 113.0 ± 15.1 | 1145 ± 145 | 2826 ± 330 |
| Symptoms (%) | | | |
| Amenorrhea[a] | 53.3 (33.3/20) | 72.7 (9.1/63.6) | 66.7 (33.3/33.3) |
| Oligomenorrhea[a] | 46.7 | 18.2 | 0 |
| Gynecomastia[b] | 100 | 55.6 | 16.7 |
| Galactorrhea | 42.8 | 60 | 33.3 |
| Visual field defects | 0 | 50 | 66.7[c] |
| Headache | 33.2 | 80 | 66.7 |
| Pituitary hormone defects (%)[d] | | | |
| Isolated GH deficiency | 4.7 | 5 | 0 |
| Isolated TSH deficiency | 0 | 0 | 0 |
| Isolated ACTH deficiency | 0 | 10 | 0 |
| Multiple hormone deficiencies | 0 | 20 | 77.8 |

Data represent the experience of the Department of Endocrinology and Oncology, University 'Federico II' of Naples, reported as mean ± SEM or percentage.

[a] Calculated only in girls.

[b] Calculated only in boys.

[c] All boys.

[d] FSH and LH deficiency were not assessed.

dopamine agonists or surgery may result in a restoration of normal pituitary function (22, 425).

Lastly, the most frequent complication of hyperprolactinemia in adult patients is decreased BMD, resulting in osteoporosis in some patients (426–428). Di Somma *et al.* (191) reported a more severe impairment of BMD in young male patients compared with those in whom hyperprolactinemia occurred at an older age. In 20 patients with hyperprolactinemia during adolescence, Colao *et al.* (429) found significantly lower BMD values both in adult and in adolescent patients with hyperprolactinemia than in their sex- and age-matched controls and also lower BMD values, corrected for age, in the adolescent patients with hyperprolactinemia than in the young adult patients. This finding is confirmed in a large cohort of patients (Fig. 8). In 22 patients all having a diagnosis of prolactinomas before the age of 18 yr, the BMD at lumbar spine was significantly lower than in age-matched controls ($0.78 \pm 0.06$ *vs.* $0.96 \pm 0.02$ g/cm$^2$). Z-scores at lumbar spine ranged from $-0.8$ to $-3.5$. The z-score was significantly correlated with BMI ($r = 0.48$; $P = 0.024$) but not with PRL levels or tumor volume.

During childhood, prolactinomas can also represent the first tumor in MEN 1 syndrome. In two recently reported juvenile patients (421), a 14-yr-old girl developed prolactinoma and manifested delayed puberty and growth arrest, whereas a 16-yr-old boy was asymptomatic, as already commented above.

### *C. Treatment strategy*

As for adult patients, in the absence of complications requiring immediate surgery, such as visual loss, hydrocephalus, or CSF leak, pharmacotherapy with dopamine agonists should be considered the first-line treatment approach. However, surgery in children poses no additional risks compared with surgery in adults. In children and adolescents, bromocriptine has been used successfully by several investigators (19). In our series, bromocriptine at doses ranging from 2.5–20 mg/d orally, induced normoprolactinemia in 38.5% of patients (417). Compliance issues and intolerance of side effects were problems. Cabergoline, at doses ranging from 0.5–3.5 mg/wk orally, is also effective in adolescent patients with large tumors and symptoms of tumor expansion. In our cases, cabergoline induced normalization of PRL levels in all but three cases, and in two of those three PRL levels were reduced by more than 95%. Overall, cabergoline was much better tolerated than bromocriptine. Twelve of our 50 patients (one with enclosed macroprolactinoma and 11 with microprolactinoma) achieved the disappearance of the tumor, so they were withdrawn from treatment according with our protocol.

As shown in Fig. 9, PRL normalization was followed by an increase in BMD at L1-L4, and osteocalcin levels (from $3.0 \pm 0.2$ to $7.9 \pm 0.3$ $\mu$g/liter) were completely normalized. Bisphosphonates probably should not be used in patients who have not even achieved full bone maturity.

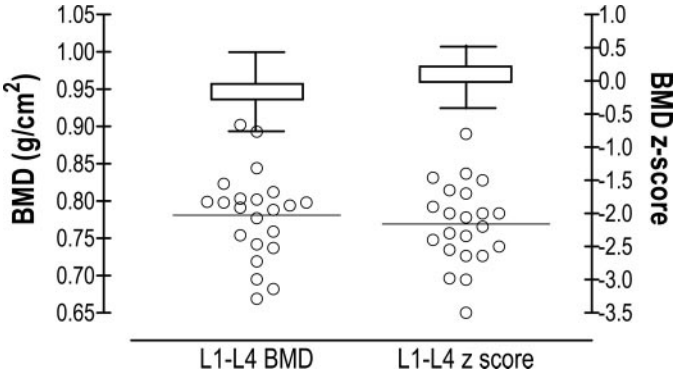


FIG. 8. BMD and Z-scores at the lumbar spine (L1–L4). ○, Individual adolescent patients of the series studied in Naples at the University "Federico II". *Boxes* refer to sex- and age-matched controls.

## XI. Special Situations

### *A. Prolactinomas in males*

A considerably greater proportion of males with prolactinomas that come to clinical attention have macroprolactinomas, compared with women (17, 430). Although symptoms of hypogonadism are still the most prevalent, symptoms due to mass effects commonly serve as those that prompt medical attention and lead to the diagnosis. A summary of 16 series comprising 444 men with prolactinomas indicates that 77.9% were impotent, 36.6% had visual field defects, 33.8% had partial or complete hypopituitarism, 29.1% complained of headaches, and only 10.9% had galactorrhea (60, 64, 75, 85, 114, 115, 431–441). Thus, about one third of men have symptoms due to tumor size.

Although it has been speculated that gender-specific differences in tumor size may be related to a delay in diagnosis in men (440), this theory is irreconcilable with data regarding the infrequency of tumor growth in studies evaluating the natural history of these tumors, as previously described. There are some clinical and pathological data which indicate that proliferative activity and tumor aggressiveness are greater in prolactinomas from men compared with those from women (21, 442). The molecular basis of these differences has not been determined.

Data on the efficacy of medical therapy in the treatment of hyperprolactinemia in men are still limited, with few studies comparing results in men *vs.* women (21, 191, 431, 436, 437, 440–445). The only prospective analysis evaluating differences in treatment efficacy between males and females found

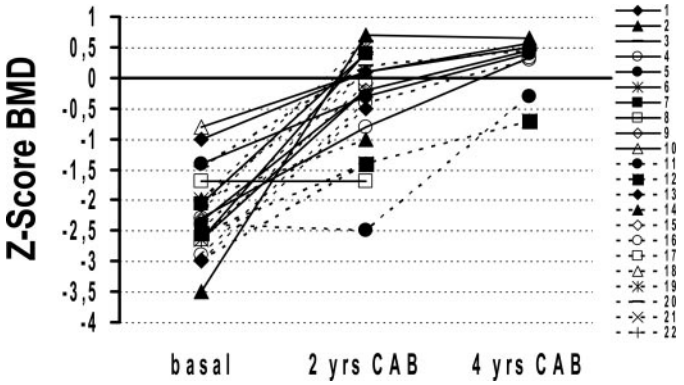


FIG. 9. Rise in BMD Z-scores 2 and 4 yr after treatment with cabergoline in 22 adolescent patients.

that normalization of PRL after 6-month treatment with cabergoline in 219 patients (145 females, 74 males) was similar in women and men (17). As expected, successful treatment was greater in patients with microprolactinomas than in those with macroprolactinomas. In a retrospective study of 455 patients treated with cabergoline, which included 102 men, the male patients were less likely than females to achieve normoprolactinemia (75% *vs.* 90%) (204). However, when considering the fact that the large majority of males in this study had macroprolactinomas (86 for males *vs.* 38% for females), gender did not have an independent influence on success of treatment. In a subset analysis that only included microprolactinomas, normalization of PRL was similar in males and females (92 *vs.* 93%, respectively). On the other hand, Pinzone *et al.* (444) determined in a retrospective study that a similar percentage of their medically managed patients (n = 46) achieved a normalization of serum PRL.

Recovery from sexual dysfunction is possible with medical therapy when normoprolactinemia is achieved, although it is not universal and is dependent upon recovery of adequate testosterone secretion. In a series of male patients treated for up to 24 months with cabergoline, PRL levels normalized in 75.6% of patients with macroadenomas and in 80% of those with microprolactinomas (425). The maximal tumor diameter was reduced by 73.7 ± 22.6% in macro- and 72.8 ± 28.3% in microprolactinomas. In this study, testosterone levels normalized in 68.6% of patients. Sperm volume and count normalized in all patients who achieved normal testosterone levels, whereas sperm motility normalized in more than 80% (425). Nocturnal penile tumescence (abnormal in 96.7% of patients at baseline) normalized in 60.6% of the patients who achieved normal PRL levels, but normalized in only 7.7% of patients who remained hyperprolactinemic (446). Other studies have shown a significant increase of number, motility, forward progression, and normal morphology of sperm after PRL normalization with bromocriptine, quinagolide, or cabergoline treatment (192, 231). Use of cabergoline may facilitate more rapid improvement in the number and the motility of sperm compared with use of bromocriptine (192). More recent reports also confirm the beneficial effects of cabergoline treatment on the number of erectile events and the recovery of semen quality in men with prolactinoma (425, 446).

These data demonstrate that medical therapy, particularly with cabergoline, is effective and safe in men with prolactinoma and can be successfully used as primary therapy even in men bearing large macroprolactinomas. For men who remain hypogonadal despite normalization of PRL, or for men who do not achieve normoprolactinemia using maximal doses of dopamine agonists, testosterone replacement should be considered. Exogenous testosterone has the potential to further increase PRL levels by aromatization to estradiol; however, the frequency of this phenomenon is not known (331, 447).

### *B. Prolactinomas in multiple endocrine neoplasia*

Prolactinomas occur in about 20% of patients with MEN 1 and represent the most frequent type of pituitary adenoma observed in this syndrome (448–450). There is evidence to suggest that prolactinomas arising in patients with MEN 1 behave more aggressively than those that develop sporadically (448, 450). This issue was specifically addressed in the France-Belgium multicenter study of 136 individuals with MEN 1 harboring pituitary adenomas (450). Of the 136 adenomas, prolactinomas accounted for 63% of all tumor types. Compared with a control group consisting of individuals with sporadic pituitary adenomas, prolactinomas in patients with MEN 1 were larger and more aggressive at presentation. For example, macroprolactinomas were more frequent in MEN 1 patients than in non-MEN 1 subjects (84 *vs.* 24%), and a high proportion of the MEN 1 prolactinomas were classified as invasive (24%). Over a median of 11.4 yr of follow-up, the response to treatment was less satisfactory in the MEN 1 adenomas, with PRL level normalization achieved in 44% of MEN 1 cases compared with 90% in sporadic cases. Although it is uncertain whether the two groups compare with respect to specific mode of therapy employed or the aggressiveness of their treatment regimens, these data suggest that prolactinomas in MEN 1 may be relatively more resistant to treatment. In general, the treatment strategy for prolactinomas in patients with MEN 1 does not differ from that for sporadic prolactinomas. However, in light of the above data, treating physicians should be aware of the potential need for more intensive pharmacological therapy or the use of multiple therapeutic modalities to achieve satisfactory outcomes.

### *C. Giant prolactinomas*

Giant prolactinomas are traditionally defined as PRL-secreting adenomas greater than 4 cm in diameter and/or those with more than 2 cm of suprasellar extension (77, 451–454). The exact prevalence of giant prolactinomas is not known for certain, but two recent retrospective analyses of prolactinomas at single institutions indicate that they are uncommon, reporting prevalences of 0.5 and 4.4% among all pituitary tumors (78, 455). Because of their rarity, relatively few series are available describing treatment outcomes, although many individual case reports have been documented in the literature.

Giant prolactinomas are usually associated with very high serum PRL concentrations, in the range of 20–100,000 ng/ml when measured with two-site monoclonal immunoradiometric or chemiluminometric assays (77, 451, 456). Occasionally, these assays will report inaccurately that PRL concentrations are normal or only mildly elevated, due to a phenomenon referred to as the "hook effect" (457–459). This effect occurs when hormone concentrations are exceedingly high, causing independent saturation of binding sites on both antibodies and interference with antibody-antigen-antibody sandwich formation. Because the capture antibody is fully occupied, the signal antibody remains in the liquid phase and, as a result, becomes discarded during the washing step of the assay protocol. The remaining weak signal on the solid phase is falsely indicated as corresponding to a low hormone concentration. The presence of the hook effect can be determined by measurement of PRL at 10- or 100-fold dilutions. Failure to recognize this effect has led to misdiagnoses of giant prolactinomas or large macroprolactinomas as non-

functioning pituitary adenomas with mild hyperprolactinemia representing stalk disruption and, consequently, also led to unnecessary neurosurgical intervention (460–463).

Giant prolactinomas represent a special management and treatment situation for two reasons. First, in some circumstances, the therapeutic goals for these tumors may differ from those held for more common micro- or smaller macroprolactinomas. Second, specific complications may arise during the treatment of giant prolactinomas that may alter initial therapeutic plans, requiring alternative or additional modes of therapy. Although the therapeutic goals for most micro- and macroprolactinomas include normalization of hyperprolactinemia, restoration of eugonadism, and reduction in tumor size, these goals may not be realistic for all giant prolactinomas. Because PRL levels must be reduced to near normal levels to restore normal reproductive function, a reduction of 50% or even 90% (although substantial) may not be great enough to restore sexual and reproductive function in severe hyperprolactinemia. Rather, in those giant tumors that are not responsive to dopamine agonist therapy, encroachment upon or invasion into critical neural structures may represent the most pressing concern. Furthermore, in some situations, particularly in long-standing tumors, substantial reduction of tumor size may not reverse visual field defects or hypopituitarism, and a more feasible goal may be prevention of further growth. The benefits of any form of treatment designed to achieve these goals must be balanced against risks associated with the specific therapy (464).

Patients with giant prolactinomas can develop pituitary apoplexy if their tumors do not reduce in size substantially with a chosen form of therapy. In addition, rapid size reductions in large prolactinomas that are highly sensitive to dopamine agonist therapy can precipitate CSF rhinorrhea (254, 257–259, 455). Both of these complications may require timely surgical intervention and correction, although this may not obviate the need for further medical and/or radiotherapy postoperatively.

The absolute indications for surgical intervention in patients with giant prolactinomas are the same for all prolactinomas and include continued tumor growth on medical therapy, acute neurological defects that do not respond rapidly to medical therapy, and unstable pituitary apoplexy. Surgical cure is not a realistic attainable goal for giant prolactinomas, but tumor debulking may be necessary in the aforementioned specific situations.

Surgical cure rates have been reported in a limited number of patients with giant pituitary tumors operated via the transsphenoidal, craniotomy, and combined transsphenoidal-craniotomy routes. Mohr *et al.* (452) described an exceptionally high hormonal improvement in a cohort of 14 patients with giant prolactinomas who underwent transsphenoidal surgery. In this series, it was reported that only six of 14 patients required bromocriptine for persistent hyperprolactinemia postoperatively. However, it was not explicitly stated whether normoprolactinemia (or mild hyperprolactinemia) was in fact attained or sustained in the eight other patients, so whether these eight individuals actually achieved remission or cure, or perhaps opted for radiotherapy, cannot be ascertained from their data. There has been no other series restricted to patients with giant prolactinomas treated with surgery alone that has reported hormonal cure or complete resection of tumor mass in a single patient. Ciric *et al.* (465) reported that of 14 cases of giant prolactinoma operated transsphenoidally, "such a removal [was] difficult or impossible," although specific figures were not detailed. Guidetti *et al.* (466) found that normalization of PRL levels was not achieved in any of six patients operated for giant prolactinomas. Of four patients reported by Davis *et al.* (451) and two reported by Murphy *et al.* (77), none had return of PRL to normal levels postoperatively, and all had significant residual tumor after surgery.

The morbidity and mortality rates associated with surgical intervention are considerably higher for giant pituitary adenomas than for smaller, noninvasive adenomas, especially those that require transfrontal approaches. Complication rates specific to surgery for giant prolactinomas are not available, but may be estimated on the basis of rate complications found after surgical resection of giant pituitary adenomas in general. Of 16 cases of giant pituitary adenoma operated via craniotomy by Symon *et al.* (454), three died in the immediate postoperative period, and two others died within 6 months of surgery. In a series of 77 patients operated upon by Pia *et al.* (453), there were eight operative deaths and considerable morbidity, including increased visual loss in four, oculomotor disturbances in eight, diabetes insipidus in 15, mental deterioration in 14, and CSF fistulas in five. Fewer complication rates are reported in more recent series that use transsphenoidal approaches, although they are still higher than those observed in other surgical series. For example, Mohr *et al.* (452) reported a transsphenoidal operative mortality of 5.2%, primarily resulting as a consequence of postoperative hematomas. The risk of significant organic brain syndrome in this series of transsphenoidal surgeries was 3% and that of permanent diabetes insipidus was 6.5% (452). Even the most recent surgical series still report significant complication rates. In a series of 92 giant pituitary tumors operated on via the transsphenoidal or combined transsphenoidal/transfrontal routes, surgical morbidity was 3.3%, CSF leak was 5.4%, and worsening vision on follow-up was 7.6% (467). Another recent surgical series of 43 giant pituitary adenomas reported by Garibi *et al.* (468) found a mortality of 4.7%, with permanent diabetes insipidus in 9.3% and meningitis with CSF fistula formation in 14.0%.

Thus, surgery for giant prolactinomas can be successful in debulking tumors but actual cure is uncommon in almost all series. However, complication rates are high, with mortality rate ranging from 3.3% (467) to 31.2% (454) and the major morbidity rate ranging from 10% (452) to 62% (454).

Radiotherapy has been used as adjunctive therapy in patients with giant prolactinomas; however, the effects of radiotherapy alone are difficult to discern from the effects of either prior surgery or concomitant medical therapy. One study of four giant prolactinomas that were treated initially with conventional radiotherapy (41.4–50 Gy) before medical therapy reported that no patient had been endocrinologically or radiologically cured with radiotherapy after an interval varying from 1 month to 7 yr (before any medical therapy) (456). Nevertheless, radiotherapy may be indicated for those who demonstrate absolutely no response to dopamine agonists or whose tumors were documented to actually grow on

dopamine agonists or after incomplete surgical removal (469).

Normalization of PRL and even radiological disappearance of tumor is possible in some giant prolactinomas. Data on the efficacy of medical therapy for giant prolactinomas has been reported in seven series consisting of at least two patients (Table 13). Some of these patients underwent prior surgery or radiotherapy, which in most cases was associated with little change in PRL levels or tumor mass. Of patients reported in these series who were treated with either bromocriptine or cabergoline, 32 of 49 (65%) achieved a normal PRL level, and 29 of 45 (64%) experienced at least 50% reduction in tumor size. In the 35% of patients who did not normalize PRL levels on medical therapy, partial responses (PRL reductions ~95%) were possible in many cases.

Because of the excellent potential results with dopamine agonists and largely poor results of surgery in most patients, the authors recommend dopamine agonists as initial therapy for patients with giant prolactinomas and reserve surgery for those patients who demonstrate inadequate responses to medical therapy. Even if subsequent surgery is necessary for tumor debulking, it rarely is curative, and a dopamine agonist is usually necessary for treatment of the hyperprolactinemia. In some extreme cases, complete tumor removal may not be achievable by any means, and control of further tumor growth may be acceptable. Given the relatively high complication rates associated with surgery in these patients, it is important to balance benefits of therapy with potential complications. Whether surgery should be considered for removal of a shrunken tumor during dopamine agonist treatment is not established. Some tumors become fibrotic after treatment with a dopamine agonist, and, as discussed previously, tumor removal has been found to be impaired in some series (84, 85) but not others (72, 86, 87). However, because complete surgical removal is rarely achieved and dopamine agonists will still be necessary for controlling the hyperprolactinemia, there seems to be little reason for surgical intervention if the tumor mass has been reduced to a sufficient size that neurological symptoms have been attenuated. Reduction in dopamine agonist doses may be possible in patients taking large doses of dopamine agonists after normoprolactinemia has been achieved and sustained for a duration sufficient enough to ascertain a reasonable chance for success. Successful dopamine agonist withdrawal has been reported in a few patients. However, when therapy is discontinued, the prolactinoma may return to its original size, often within days to weeks. This potential return to pretherapy size dictates extreme caution when withdrawing dopamine agonists in giant prolactinomas, because rapid tumor expansion may produce more severe clinical symptoms than slow tumor enlargement.

TABLE 13. Efficacy of dopamine agonist therapy in giant prolactinomas

| Series | Ref. | Drug | No. of patients | Normal PRL | 50% tumor reduction |
|---|---|---|---|---|---|
| Murphy | 77 | BRC | 2 | 1 | 2 |
| Davis | 451 | BRC | 9 | 4 | 3 |
| Grebe | 456 | BRC | 4 | 3 | NR |
| Saeki | 601 | BRC | 10 | 7[a] | 6 |
| Minniti | 602 | CAB | 4 | 3 | 1 |
| Shrivastava | 78 | BRC | 10 | 9 | 10 |
| Corsello | 455 | CAB | 10 | 5 | 7 |
| TOTAL | | | 49 | 32 (65%) | 29 (64%) |

BRC, Bromocriptine; CAB, cabergoline; NR, tumor shrinkage not reported.

[a] One case required surgical intervention due to tumor growth despite PRL normalization.

### *D. Malignant prolactinomas*

Malignant prolactinomas are rare tumors. Their exact incidence is not known for certain, but overall pituitary carcinomas represent less than 0.5% of symptomatic pituitary tumors (470). Approximately 40 cases of malignant prolactinoma have been published in the English literature (286, 303, 320, 322, 471–497). Most commonly, malignant prolactinomas are indistinguishable from invasive macroadenomas at presentation (498). The diagnosis of pituitary carcinoma can only be made upon demonstration of metastatic spread; reliable distinction between carcinoma and adenoma cannot be made on the basis of standard histological criteria (499). At this time, there are no methods to accurately identify those invasive pituitary tumors most likely to metastasize, thus permitting early aggressive treatment before progression to pituitary carcinomas (499).

Knowledge of the natural history of malignant prolactinomas may be helpful for disease management. Typically, the primary tumor is treated with medical, surgical, and/or radiation therapy, followed by a long latency (years) before recurrence or progression of residual tumor occurs and metastases become apparent (489, 498, 500). Less commonly, a malignant prolactinoma will exhibit early aggressive behavior with multiple recurrences and early development of metastases (489). Once metastases are diagnosed, survival is usually very short, with a mean survival time of approximately 10 months (488). However, prolonged, asymptomatic survival has been reported in a few patients (484, 488). Where possible, dopamine agonists should be employed because they can occasionally be effective in reducing the mass of tumor (484, 488). Unfortunately, once craniospinal or systemic metastases become obvious, therapeutic options are limited in efficacy, and treatment is mainly palliative (498, 501). Surgery may be useful in debulking the lesion and relieving local compressive effects (497). Chemotherapy with somatostatin infusion, procarbazine, vincristine, cisplatine, lomustine, carboplatin, and etoposide has been attempted but as yet has not been demonstrated to be effective (322, 492, 496). A single case report detailed the dramatic response of a patient with craniocervical metastases to the alkylating agent, temozolomide (502), and other anecdotal reports of its successful use have been described. However, with the exception of this case and isolated others (488, 502), there is no evidence that either radiotherapy or chemotherapy prolongs survival to any major extent (498).

## XII. Experimental Therapy

### *A. Somatostatin analogs*

Somatostatin analogs are widely used for the primary and secondary treatment of somatotroph adenomas, for which

they have been shown to be effective for the biochemical and clinical control of acromegaly (503). The success of somatostatin analog therapy for acromegaly is attributable both to the high density of somatostatin receptor subtype 2 (SSTR2) among somatotroph adenomas and the high affinity of the available somatostatin analogs for this receptor subtype (504). Somatostatin suppresses *in vitro* PRL secretion from some prolactinomas in culture (292, 505, 506). However, somatostatin and octreotide do not reduce serum PRL levels in patients with prolactinomas (507, 508) and therefore have not been useful therapy for these patients. Despite the ineffectiveness of somatostatin and SSTR2 subtype-specific analogs for the treatment of prolactinomas, the recent introduction of novel variants of somatostatin analogs has opened the door for the use of these agents in patients with prolactinomas who are resistant to standard (dopamine agonist) medical therapy.

In addition to their expression in pituitary somatotrophs, multiple SSTR subtypes have been identified in the normal pituitary, as well as in other types of pituitary adenomas, including prolactinomas. The normal pituitary predominantly expresses SSTR1, -2, and -5 (509, 510). All five SSTR subtypes have been found in human prolactinomas, with SSTR5 exhibiting the highest level of expression among the receptor subtypes, and SSTR3 and SSTR4 exhibiting minimal expression (509–516). Although the abundance of the five SSTR subtypes found in prolactinomas varies among different studies, it appears, from both a quantitative and functional perspective, that the dominant SSTR in human prolactinomas is SSTR5 (504, 514).

Shimon *et al.* (504) compared the *in vitro* effects of SSTR2 *vs.* SSTR5 analogs in primary cultures of human prolactinomas. Although the clinically available somatostatin analogs, octreotide and lanreotide, did not suppress PRL release from these prolactinoma cell cultures, newer SSTR5 subtype-selective analogs (BIM 23052 and BIM 23268) did suppress PRL secretion by 30–40% in four of six prolactinomas, including two tumors that exhibited dopamine agonist resistance. Jaquet *et al.* (514) confirmed the functional selectivity of the SSTR5 agonist BIM 23268 in their *in vitro* study of 10 prolactinomas, showing 26–90% inhibition of PRL release, which correlated with the expression of SSTR5 transcripts. However, the degree of PRL suppression afforded by BIM 23268 was no greater than that achieved by quinagolide, and additive inhibitory effects of quinagolide plus BIM 23268 were not observed. Therefore, further *in vitro* and *in vivo* testing of SSTR5 subtype-selective analogs will be necessary to determine whether these agents will serve a useful role for the treatment of patients with dopamine agonist-resistant prolactinomas.

The novel compound SOM230 has a broad somatostatin binding profile, exhibiting high-affinity binding to SSTR1, -3, and -5. SOM 230 has a 40 times higher binding affinity to SSTR5 receptors, compared with octreotide, thus providing rationale for a trial of this agent in reducing PRL secretion in prolactinomas. Hofland *et al.* (517) found that SOM230 was more potent than octreotide in suppressing PRL secretion in primary cultures from both mixed GH-PRL-secreting adenomas and pure PRL-secreting adenomas. Murray *et al.* (518) reported similar results in primary cultures of two human prolactinomas (30–40%). These results suggest a potential role for SOM230 for the treatment of dopamine agonist-resistant prolactinomas, primarily in those showing a high level of SSTR5 expression.

Finally, a number of chimeric compounds have been developed that contain structural elements of both somatostatin and dopamine in a single molecule. These hybrid molecules exhibit potent, selective agonist activity at both the SSTR2 subtype receptor and the $D_2$ receptor. The SSTR and $D_2$ receptors have been shown to heterodimerize in the presence of appropriate ligands, generating a hybrid receptor that enhances the inhibitory activity of adenyl cyclase (519). Although it is known that the two receptors colocalize in pituitary cells, the specific intracellular signaling pathways by which the hybrid receptors mediate GH and PRL suppression have not been fully elucidated (520). As for SOM230, these hybrid compounds were initially developed for the potential use in patients with acromegaly resistant to the clinically available somatostatin analogs and thus far have primarily been tested in cell cultures of GH-secreting or mixed GH-PRL-secreting adenomas (521–523). The chimeric somatostatin-dopamine molecule BIM 23A387 produced a 73% inhibition of PRL in six mixed GH plus PRL-secreting adenomas (523). The chimera was more effective in suppressing PRL secretion than a SSTR2 subtype analog alone, $D_2$ receptor agonist alone, or the two combined. Jaquet *et al.* (521) tested a number of these compounds for their ability to suppress PRL secretion and found maximal PRL suppression of 46 to 74%, all of which were greater than octreotide. This study did not, however, report a direct comparison of the PRL-lowering effects of these chimeric compounds to any of the available dopamine agonists. Thus, results of preliminary studies of SSTR-$D_2$ receptor chimeric agonists support further investigation of their effects in humans with prolactinomas.

### *B. Therapy directed against estrogen/estrogen receptor*

Estrogen may play a role in the development and/or progression of a subset of lactotroph tumors. Estrogen stimulates PRL secretion and mitogenesis in pituitary lactotrophs in both *in vitro* and *in vivo* models (524). In addition to the well-known lactotroph hyperplasia that develops during pregnancy, several cases of lactotroph adenoma have been reported in male-female transsexuals given pharmacological doses of unopposed estrogen, emphasizing the proliferative effects of estrogen on these cells (35, 525, 526). In human prolactinomas, multiple estrogen receptor (ER) variants generated by alternative splicing are coexpressed with ER$\alpha$ and ER$\beta$. One tumor-specific splice variant, $\Delta$5delER, which has been identified in human prolactinomas, potently induces the activity of estrogen-responsive genes in the presence of ER$\alpha$, and this increased activity could conceivably confer a pathophysiological role in promoting estrogen-regulated tumor proliferation and/or PRL secretion in some patients (527, 528). It should be emphasized that epidemiological analyses of women taking oral contraceptives or hormone replacement therapy have not shown associations with estrogen and prolactinoma development. It is the authors' theory that estrogen may play a permissive role in the growth of a subset of prolactinomas that may have acquired genetic

defects in pathways involving estrogen signaling or action. Thus, estrogen represents one of several pituitary growth factors that may serve as a therapeutic target to inhibit hormone secretion and cell growth.

Strategies aimed at inactivating the ER or modulating estrogen signaling provide an experimental approach to reduce PRL hypersecretion and control lactotroph adenomatous growth. Most of the studies investigating the effects of selective ER modulators (SERMs) on prolactinomas have been performed in cell cultures derived from rat prolactinoma cell lines or human prolactinomas (529–538). However, the reported *in vitro* effects of tamoxifen and raloxifene have been inconsistent from study to study, precluding definitive conclusions on their potential use at this time. Although several studies have shown inhibitory effects of these agents on PRL secretion and cell proliferation, some have shown no effects, or even stimulatory effects, in others. Two recent studies have shown differential effects of tamoxifen and raloxifene on PRL secretion (539) and cell proliferation (540). It is possible that the discordant findings reported in studies involving SERMs are due to variations in SERM dosages, duration of treatment, and differences in the molecular behavior/characteristics of individual tumors. Fulvestrant, a new type of ER antagonist devoid of any agonist activity that binds to, blocks, and degrades the ER (541), has been shown to have PRL-reducing and antiproliferative effects in experimental models (540, 542). For example, Heaney *et al.* (542) found that the administration of fulvestrant to rats with sc somatolactotroph (GH3) tumors decreased PRL levels by 88% and attenuated tumor growth by 41%. Kansra *et al.* (540) showed similar *in vitro* results, albeit only in nonphysiological (*i.e.*, estrogen-deprived) conditions. In one short-term human study of eight patients with giant invasive PRL-secreting pituitary adenomas, tamoxifen given over 5 d modestly suppressed PRL secretion and had a slight but significant potentiating effect on bromocriptine-mediated inhibition of PRL secretion (535). Neither raloxifene nor fulvestrant has been tested *in vivo* in humans with prolactinomas.

A second experimental approach aimed at mitigating the proliferative effects of estrogen on prolactinomas involves reduction of endogenous estradiol levels through aromatase inhibition. A single case report describes the ability of anastrazole to augment PRL suppression when combined with very high doses of cabergoline (331). Long-term effects of aromatase inhibitors are uncertain, however, and chronic estrogen deficiency may have important adverse consequences on bone (543, 544). Therefore, this therapeutic approach should be reserved for specific situations that are not amenable to standard therapy and in particular for those prolactinomas that show evidence for exquisite sensitivity to estradiol.

### *C. Prolactin receptor antagonists*

Several PRL receptor antagonists are under development as potential therapies for the treatment of breast and prostate cancer (reviewed in Ref. 545). The rationale for PRL receptor antagonism in this context is to block the proliferative effects of autocrine-derived PRL on these tissues (546, 547). The PRL receptor could represent a theoretical target to disrupt the adverse peripheral effects of hyperprolactinemia due to prolactinoma, and PRL receptor antagonists have been proposed as potential agents to treat dopamine agonist-resistant prolactinomas (545). However, any effects of PRL receptor antagonism on PRL secretion and cell growth are uncertain—both in normal and adenomatous human lactotrophs. It appears that the expression of the PRL receptor is up-regulated in human prolactinomas, but the functional consequences of this alteration are unknown (548, 549). In mice, the targeted disruption of the PRL receptor results in hyperprolactinemia, lactotroph hyperplasia, and ultimately, prolactinomas (550, 551). Whether a long feedback loop exists in humans that regulates PRL secretion and cell growth has not been determined.

### *D. Gene therapy*

Gene therapy represents a potential future therapy for the treatment of pituitary adenomas, although it remains at an early stage of investigation. The underlying concepts of gene therapy and a summary of preclinical studies in pituitary tissue and adenomas are the subject of several recent reviews, to which the reader is referred for further information (552–554). In view of the fact that most prolactinomas are benign microadenomas that are successfully and safely treated with available medical or surgical methods, and that sustained hyperprolactinemia is not associated with mortality, as hormonal hypersecretion is for other pituitary tumor subtypes, the gene therapy approach will have limited applicability for the majority of these tumors. However, gene therapy could play a role in the treatment of large aggressive prolactinomas, locally invasive postsurgical residual disease, or pituitary carcinomas (555).

Most preclinical gene therapy models for the treatment of pituitary adenomas have used adenoviral vectors as the delivery system because of their high efficiency in infecting nondividing cells (556). A number of different strategies have been attempted to ablate pituitary tumors by varying the therapeutic gene delivered. These therapeutic genes fall into the following categories: suicide gene/prodrugs, toxins, tumor suppressors, apoptosis inhibitors, growth inhibitors, and inhibitors of specific signaling pathways. Equally important to the success of gene therapy are the achievement of cell-type specificity for transgene delivery and the ability to regulate transgene expression. Targeting strategies have taken advantage of the highly specialized profile of transcription factors, hormones, and receptors to specifically target a particular pituitary cell type. Cell type specificity for transgene delivery has already been achieved by placing transgenes under the control of cell-specific promoters (*i.e.*, the human PRL promoter). Regulation of transgene expression is at an earlier stage of investigation, but some initial studies have shown that expression of the therapeutic gene can be temporally or situationally regulated (557–559).

A number of preclinical *in vivo* models of gene therapy have been designed that specifically target lactotroph adenomas. Many of these models are based upon the method of gene-directed enzyme prodrug therapy in which the gene

encoding thymidine kinase (TK) is delivered to tumor cells, followed by the systemic administration of a nucleoside analog such as gancyclovir, which is converted locally to a cytotoxin by TK (560, 561). In applications of gene therapy targeting prolactinomas, the gene encoding TK is placed under the control of the human PRL (or cytomegalovirus) promoter (562–564). Other models have used adenovirus to overexpress genes encoding tyrosine hydroxylase (559) or a dominant-negative ER (565) with the goal of inhibiting growth of sc lactotroph tumors in mice. Together, these models have demonstrated the feasibility of preventing tumor growth, reducing tumor mass, and attenuating hyperprolactinemia using gene therapy approaches. Nevertheless, it appears that systemic injection of adenoviral vectors carrying cell-specific therapeutic genes may not be able to generate high enough transgene expression in the pituitary to be efficacious. Systemic administration of adenoviral vector is only effective using strong viral promoters that are accompanied by ubiquitous expression; adenoviral constructs using cell-specific promoters have thus far required direct stereotaxic intrapituitary injection. Therefore, at the present time, only direct surgical approaches using injection into the body of the tumor or tumor remnant appear imminently feasible (555). A number of additional issues will need to be addressed before gene therapy becomes a reality, including the development of safer and more effective gene delivery vectors, the refinement of strategies to regulate transgene expression, and the identification of specific gene targets that do not require a high rate of proliferation to induce cell death.

### *E. Nerve growth factor*

NGF has been proposed as potential redifferentiation therapy for the treatment of dopamine agonist-resistant prolactinomas lacking $D_2$ receptor expression (see *Section VII.B*). The inspiration for this therapy is based upon previous *in vitro* studies demonstrating the effectiveness of NGF in restoring $D_2$ receptor expression, reducing tumor proliferation, and abolishing the tumorigenicity of dopamine-resistant prolactinoma cells that were implanted sc into mice (298, 314, 315, 566).

The therapeutic use of recombinant NGF has been explored in other areas, including the treatment of diabetic polyneuropathy and HIV-related neuropathy (567, 568). However, clinical application of nerve growth treatment in humans has been limited due to challenging issues related to the safe and effective delivery of NGF to the tissue of interest. NGF does not cross the blood-brain barrier when administered peripherally and can cause intolerable and unacceptable side effects at high doses (568, 569). Recently, NGF therapy was investigated in a phase 1 trial of NGF gene delivery for Alzheimer's disease, wherein autologous fibroblasts genetically modified to express human NGF were stereotaxically implanted into the forebrain (570). In this trial, long-term adverse effects of NGF were not observed after a mean follow-up of 22 months. Pending further verification of NGF efficacy and the development of safe, effective, and acceptable gene delivery systems for the treatment of pituitary tumors, NGF may represent a potential means of redifferentiating therapy in highly selected cases.

TABLE 14. Genetic alterations identified in human prolactinomas[a]

| | Gene | Protein | Identified defect | Human tumors | Animal model | Ref. |
|---|---|---|---|---|---|---|
| Gain of function events | *CCND1* | Cyclin D1 | Overexpression | Aggressive adenomas | NA | 603 |
| | *RAS* | Ras | Somatic mutation | Pituitary carcinomas | NA | 604–607 |
| | *PTTG1* | Pituitary tumor-transforming protein 1 | Overexpression | All classes of pituitary adenomas | Multipotential focal hyperplasia → adenomas (LH, FSH, TSH, under control of α−subunit promoter) | 606, 607 |
| | *FGFR4* | Truncated ptd-FGF4 receptor | Alternative transcriptional initiation | All classes of pituitary adenomas | Lactotroph adenomas (under control of the PRL promoter) | 608–610 |
| | *HMGA2* | High mobility group AT-hook 2 | Gene amplification → HMGA2 overexpression | Prolactinomas | Somatolactotroph adenomas | 611, 612 |
| | BMP4 | Bone morphogenetic protein 4 | Overexpression | Prolactinomas | Lactotroph adenomas[b] | 613 |
| | Δ5delER | Truncated ER | Alternative splice variant | Prolactinomas | NA | 527, 614 |
| Loss of function events | *MEN1* | Menin | Inactivating germline mutation followed by somatic mutation | All (prolactinomas most common) | Adenomas | 615 |
| | *RB1* | Retinoblastoma | Promoter methylation | Aggressive adenomas | Intermediate lobe hyperplasia → adenomas | 616, 617 |
| | *CDKN2A* | INK4a (p16) | Promoter methylation | Adenomas | KO: sarcomas, lymphomas, melanoma | 618–620 |
| | *DRD2* | Dopamine receptor D2 | Decreased expression | DA resistant prolactinomas | Lactotroph hyperplasia → adenomas | 621, 622 |

NA, Not applicable; FGF, fibroblast growth factor; KO, knockout.
[a] Only genetic defects for which there is experimental evidence that the defects are also identified in human prolactinomas are listed.
[b] *BMP4* is overexpressed in prolactinomas derived from dopamine $D_2$ receptor-deficient female mice.

TABLE 15. Other protooncogene/tumor suppressor gene alterations in genetically modified mouse models

| | Protein | Pituitary defect | Ref. |
|---|---|---|---|
| Transgenic mice | | | |
| *Gal* | Galanin | Lactotroph hyperplasia → adenomas | 623 |
| *Ngf* | NGF | Lactotroph hyperplasia | 624 |
| *Tgfa* | TGF-α | Lactotroph hyperplasia, adenomas in females only | 625 |
| Knockout mice | | | |
| *Prlr* | PRL receptor | Lactotroph hyperplasia → adenomas | 550 |

*F. Molecular therapeutics*

Recent advances in the understanding of signaling pathways controlling pituitary hormone production and in the delineation of underlying molecular defects involved in pituitary tumorigenesis have provided a source of potential therapeutic targets for the treatment of pituitary tumors that are not responsive to standard therapy (571, 572). Several candidate factors have been implicated in the pathogenesis and progression of prolactinomas (Tables 14 and 15). The discovery of these genetic alterations may offer the opportunity to develop highly targeted and effective therapeutic approaches that are directed at processes fundamentally involved in tumorigenesis.

The concept of molecular therapeutics aims at developing treatments that modulate a specific factor or cellular pathway thought to play a critical role in the survival, proliferation, or invasion of a tumorous cell (573). Although there are many genetic aberrations that can be identified in pituitary adenomas, only a subset of these are critically involved in cell proliferation, cell survival, and tumor progression. One of the challenges for the development of successful targeted therapy will be the ability to distinguish which genetic alterations are truly pathogenetic from those that are epiphenomena that arise secondarily, accompanying the process of tumorigenesis (294, 574). Thus, validation that a proposed genetic aberration has tumorigenic causality using stringent criteria with multiple lines of scientific evidence is essential for the selection of "critical targets" (575). Although it remains to be proven as a general principle, most authorities believe that interference with tumor-initiating events will ultimately be necessary for effective targeted therapy (573, 576). The optimal implementation of this type of approach will require the development of molecular diagnostic markers able to identify patients with tumors whose growth is governed by the chosen therapy. Although this area of investigation remains in the very early stages of discovery, the promise of these technologies may lead to a new era of individualized molecular medicine, wherein each patient is treated on the basis of the underlying genetic aberrations, resulting in more effective and less toxic therapy (577).

## XIII. Concluding Remarks

In the present era, most prolactinomas are successfully treated with medical therapy with minimal morbidity. The extraordinary response of these tumors to medical therapy represents one of the most remarkable and satisfying achievements in the field of endocrinology. However, the small proportion of prolactinomas that are unresponsive to dopamine agonists represent the most severe aspect of this disease and unfortunately, are often associated with poor response to nonmedical approaches, including transsphenoidal surgery and radiotherapy. For these patients, a combination of medical, neurosurgical, and radiation therapies may be necessary to control tumor growth. Investigative therapies targeting underlying molecular defects involved in the pathogenesis of these tumors hold promise for devising strategies to treat prolactinomas that remain therapeutic challenges.

## Acknowledgments

The authors express their gratitude to Peter Kopp, M.D., for helpful comments on the manuscript, and Sabine Schnyder, M.D., for assistance with figures. We are grateful to Marco Losa, M.D., for providing follow-up data on recurrence in his surgical series.

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This work was supported in part by National Institutes of Health Grant K08 DK066044 (to M.P.G.) and by the Italian Ministry of University and Research (Grant FIRB 2001 RBAU01FMEY, to A.C.). This study has been partially supported by a grant of the Italian Ministry of University and Research (M.I.U.R.) to A.C. (no. 2005 069841).

Disclosure Statement: M.P.G., G.L., and A.C. have nothing to disclose. M.E.M. consults for and has equity interest in Pfizer.

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