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Effect of dopaminergic drug treatment on surgical findings in prolactinomas

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Abstract

It has been reported that prolactinomas treated with Bromocriptine (BROM) show fibrosis that may interfere with complete surgical resection. The same has not been reported for Cabergoline (CAB). We retrospectively studied 24 consecutive patients (13 females, mean age 40 years, range 16–60) with histopathologically confirmed prolactinomas undergoing surgical resection at Johns Hopkins Hospital between 1992 and 2009. We compared these prolactinomas to 34 patients (22 females, mean age 42.9 years, range 15–75) with GH-secreting adenoma. The operative notes from 7 different neurosurgeons were reviewed to catalog the tumors as fibrous or not fibrous. Of the 24 prolactinomas, 21 (87.5%) were previously treated with DA. Indication for surgery was: DA resistance (n.5), DA intolerance (n.6), persistent mass effect (n.7) and CSF leak (n.3). Five (14.7%) of GH-secreting adenomas, were exposed to DA and/or somatostatin analogs. We found that 54% of prolactinomas and only 6% of GH-secreting adenomas were described as fibrous. 10/12 (77%) of prolactinomas exposed to BROM for at least 1 month, 2/9 (22%) exposed to CAB only, and 1/3 (33%) not previously treated were fibrous ($P < 0.05$). The mean BROMcumulative dose was 406 mg (range 75–1,375), while CAB dose was 28 mg (range 6–70). Only 18% of non-fibrous prolactinomas had been exposed to BROM. Only 3 patients had persistent biochemical remission (2 treated with CAB and 1 not treated). Patients exposed to BROM for at least 1 month are more likely to have tumor fibrosis than patients that are untreated or treated with CAB.

Keywords

Prolactinoma; Pituitary adenoma; Dopamine agonist; Cabergoline; Tumor fibrosis

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Introduction

Pituitary adenomas are the most common intrasellar tumors and prolactinomas account for 40% of all pituitary tumors [1]. The estimated prevalence of prolactinomas is of 62 cases per 100,000 individuals [2]. The majority of prolactinomas are small at the time of diagnosis in women, while men typically present with macroprolactinomas which may cause local neurologic symptoms and hypopituitarism [1]. The main objectives of treatment are to normalize prolactin (PRL) secretion, and to avoid or reduce neurologic compressive symptoms, while preserving pituitary function [3].

Prior to the discovery of dopaminergic agents (DAs), these tumors were treated surgically [4]. DAs, due to their clinical effectiveness and low toxicity profile, have become the first line treatment, reserving surgery for patients who failed medical therapy [5, 6] or for neurosurgical emergencies such as apoplexy or neurologic deficit involving the visual pathways.

Bromocriptine (BROM) was the first DA used to treat prolactinomas; it normalizes prolactin in approximately 80% of patients with microadenomas and restores menses and fertility in over 90% of women [5]. Cabergoline (CAB) has better tolerance profile as well as higher success rates and easier administration thanks to its longer half life [7–9]. It has been reported that prolactinomas exposed to BROM may develop tumor fibrosis [5, 10–16], which has generated a renewed interest in surgical treatment of prolactinomas, and has promoted some controversy regarding first line therapy [17–23]. No tumor fibrosis has been reported in patients treated with CAB. In this retrospective study we analyzed the relationship between tumor fibrosis and treatments with CAB only versus BROM (alone, or in combination with CAB).

Patients and methods

Patient population

We retrospectively studied the records of 24 patients with histopathologically confirmed prolactinomas who underwent surgery between 1992 and 2009 at Johns Hopkins Hospital (2 patients via craniotomy and 22 transsphenoidal). They were compared with 34 patients with GH-secreting adenoma undergoing surgery in the same period of time in the same institution.

Patients with prolactinomas—Six patients (25%) had microprolactinomas and 18 patients (75%) had macroprolactinomas. Demographics are shown in Table 1. Twenty-one (87.5%) were previously treated with DA and 3 (12.5%) needed urgent surgery due to tumor local compression at the time of diagnosis without exposure to any therapeutic agent. Nine patients were treated only with CAB and 12 were exposed to BROM for at least 1 month. Of the 12 patients exposed to BROM, 4 (33%) were also treated with CAB for a period of time ranging from 30 to 790 days, with a mean cumulative dose of 288 mg, ranging from 2.5 to 1,080 mg and a median cumulative dose of 35 mg. One patient was also exposed to Quinagolide for a short period of time. The rest of the patients (66%, n.8) were only exposed to BROM. The total mean BROM cumulative dose in all these 12 patients was 406 mg

(range 75–1,375 mg) in a time period between 30–550 days, with a median cumulative dose of 491 mg. The 9 patients exposed only to CAB had a mean cumulative dose of 28 mg, ranging from 6 to 70 mg in a time period of 42–989 days, with a median cumulative dose of 24 mg. The mean follow up period was 49 months. Indication for surgery in DA-treated patients is shown in Table 2.

Patients with GH-secreting adenomas—Of the patients presenting with GH-secreting adenomas 28 (82%) had macroadenomas. A total of 22 patients (64%) were female. The mean age was 42 years, range15–71 (Table 2). Only 5 patients (14%) were treated medically before surgery: one with BROM, 1 with CAB, 2 with octreotide and 1 with multiple agents.

Data collection

Data collection for these patients was done retrospectively by review of medical records. The Operative Notes from 7 different neurosurgeons were reviewed. Pre and postoperative laboratory data were obtained from Johns Hopkins Hospital records and from clinic notes of referring and consulting physicians. Initial prolactin levels refer to the earliest known documented level prior to initiating medical therapy. Preoperative prolactin levels were obtained within 7 days of surgery; the majority of patients were receiving medical therapy at this time. The prolactin levels in the post operative period reflect the most recent follow up value with or without medical therapy.

Data analysis

Patients were separated in 2 groups: “fibrous” and “nonfibrous” according to surgeon’s description and according to histopathological evidences. Fibrous tumors were described by the surgeons in the operative notes as: “firm”, “not typical”, “semi soft with fibrous bands”, “not classic pituitary tumor”, “solid”, “broad areas of fibrosis”, “very tenacious tumor”, “very fibrous in the center”. When the adenoma was described as “soft”, “typical”, or was not otherwise described, we classified it as non fibrous. In addition the following data were collected:

1. Preoperative tumor size percentage reduction: comparing data from tumor size at diagnosis with tumor size before surgery.
2. Preoperative PRL percentage reduction: comparing initial PRL level with preoperative PRL level.
3. Intra-operative complications: CSF leak limited bleeding.
4. Postoperative complications: SIADH, diabetes insipidus (DI), sinusitis, vein thrombosis, nerve palsy, hypopituitarism.
5. Postoperative treatment: some patients required further treatment after surgery, which were classified as: DA (on DA therapy), radiation therapy, and second surgery.
6. Postoperative biochemical outcome: the outcomes were separated in 4 groups according to the data from the last postoperative clinic note available: normoprolactinemia on DA (patients requiring medical treatment with DA),

biochemical remission (normoprolactinemia without any therapeutic agent), and persistent hyperprolactinemia (per patient preference or clinician judgment, no further treatment attempt up to the last clinic note).

Pathology analysis

Routine H&E and immunostaining for prolactin, GH and ACTH were performed and read by a single pathologist (PB) who was blinded to the operative findings. The number of slides analyzed per case ranged between was 1 and 9, and the mean number per case was 2.5.

Statistical analysis

Data compared between groups using the Fisher's exact test or chi-square test. P values of <0.05 were considered statistically significant. All continuous variables are presented as mean or percentages.

Results

Presurgical treatment in relationship with tumor consistency

In the prolactinomas group, 21/24 patients were exposed to DA therapy: Nine only to CAB, 8 only to BROM, and 1 both to CAB and BROM with an exposure to BROM for more than 30 days; One patient was treated with BROM, CAB and Quinagolide. Three patients were not exposed to any DA before surgery; they all had macroprolactinomas that required urgent intervention. One of these patients had a "fibrous" tumor.

Eighty-three percent of tumors in the BROM group, 22% in the only CAB group and 33% of the tumors without exposure to DA were described as "fibrous" in the operative notes. There was a statistically significant difference favoring the presence of fibrosis at the time of surgery in patients exposed to BROM for at least one month ($P < 0.05$ by χ^2 test) (Fig. 1).

Ten of the 13 "fibrous" tumors and 8/11 "non-fibrous" tumors were macroadenomas, demonstrating that the prevalence of fibrosis was similar among micro and macroprolactinomas.

The GH-secreting tumors were divided in 2 groups: those undergoing surgery as first line therapy (29 patients), and those in which medical treatment with somatostatin analogs (SA) and/or DA therapy was attempt first (5 patients) "DA/SA". In the "DA/SA" group, all 5 patients had "non fibrous" tumors. Of the 29 patients in the no treatment group, only 2 were classified as "fibrous".

Implications of tumor consistency of prolactinomas on other parameters

Preoperative PRL percentage reduction—Data from 16 patients was available to calculate the preoperative PRL percentage reduction. Nine of these patients were in the "fibrous" group and 7 in the "non fibrous" group. In the "fibrous" group 8 patients (88.8%) had a PRL percentage reduction >25%, whereas in the "non fibrous" group, 57% (4 patients) had a PRL percentage reduction >25% (difference not statistically significant).

Preoperative tumor size modification—Data from 15 patients was available to calculate the preoperative tumor size percentage reduction. Eight were in the “fibrous” group and 7 in the “non fibrous” group. In the “fibrous” group, 6 patients (75%) had a decrease in the tumor size, whereas 1 had no changes and 1 had actually an increase in size. In the “non fibrous” group 3 (43%) had a reduction in the tumor size, 3 (43%) had an increase in the size and 1 patient (14%) had no changes (difference not statistically significant).

Intra-operative complications—Five (38%) of the 13 patients in the “fibrous” group had intra-operative complications. One patient had a minor episode of bleeding and 4 had CSF leak, one of them requiring lumbar shunt drainage placement. In the “non fibrous” group, only 2 patients (18%) had intra-operative complications and in both cases it was a minor CSF leak, not requiring further treatment (difference not statistically significant).

Postoperative complications—Ten out of 13 patients (77%) with “fibrous” tumors had postoperative complications. Five patients (38%) had some degree of hypopituitarism, and 4 (30%) had diabetes insipidus (DI). One patient developed SIADH, one sinusitis and one cortical vein thrombosis followed by hemorrhagic stroke (later diagnosed with antiphospholipid antibody syndrome). In the “non fibrous group”, 8 patients (72%) had postoperative complications. Five (45%) had DI, and 3 (27%) had hypopituitarism; In addition, one patient had SIADH and one-third and fourth cranial nerves palsy (difference not statistically significant).

Postoperative treatment—Four patients with a follow up of less than 30 days were excluded from this analysis (1 with a “fibrous” and 3 with “non-fibrous” adenomas). Sixteen patients (80%) needed further treatment after surgery. All of them received DA’s, except for 1 who could not tolerate it. Only one patient needed a second surgery and radiotherapy in addition to DA agents, (this patient had a “fibrous” tumor). None of the patients with non-fibrous tumors required second surgery or radiotherapy.

Postoperative biochemical outcome—Four patients with a follow up of less than 30 days were excluded from this analysis. None of the patients with “fibrous” tumors had a complete biochemical remission, whereas 3 (37%) of the patients with non-fibrous tumors did. This difference was statistically significant, with a two-tailed *P* value of 0.0214 by χ^2 test (Fig. 2). Interestingly, 2 of the 3 patients who went into biochemical remission were preoperatively treated with CAB (one for 42 days and the other one for 133 days, they both had a reduction in PRL levels before surgery, indication for surgery was DA intolerance).

Pathology findings

Pathology slides were available for 19 cases. The neuropathologist judged “fibrous” 6/10 of tumors classified as such by surgeon, and “non fibrous” 7/9 of tumors not reported to be fibrous by the surgeon, with an overall 68% concordance between surgical finding and histopathology. Two representative photographs (one without and one with fibrosis) are shown (Fig. 3).

Discussion

In this study, we present data suggesting that prolactinomas pre-surgically treated with BROM have greater probability of developing fibrosis compared with tumors exposed only to CAB or without any medical therapy. The fact that BROM is associated with perivascular tumor fibrosis has been reported [5, 10–16], but whether fibrosis has a positive or a negative impact on the management of prolactinomas is still debated [17, 23]. While some neurosurgeons refer that harder tumors may be more difficult to resect, and this may increase the risk of intraoperative and postoperative complications, many series investigating this issue do not corroborate this opinion [24, 25]. Conversely, it has been reported that pre-surgical treatment with BROM, possibly by inducing tumor regression, seemed to improve the surgical outcome [26]. In our analysis there was no difference between “fibrous” and “non fibrous” adenomas in intra-operative or post-operative complications. On the other hand, “fibrous” tumors had lower probability of going into biochemical remission than “non-fibrous” tumors (0% vs. 37%). These results suggest that fibrosis may indeed interfere with complete hormonal cure. In light of these findings, the presence of fibrosis at surgery could be used as a prognostic factor of biochemical remission after surgery.

There has been discussion on whether the development of fibrosis is related to greater reduction on tumor size and/ or PRL secretion instead of being related to the use of DA’s itself, suggesting that those tumors that have greater response to medical treatment are those that are more prone to develop fibrosis. We could not find any significant difference in tumor size reduction or PRL level reduction in our two groups. This finding suggests that the development of fibrosis is independent from tumor regression or reduction in secretion.

Of note is that our population includes mostly patients with tumors that in one way or other failed medical therapy. Our sample may not be representative of what happens in those tumors that do respond to medical treatment by tumor shrinkage and reduction of PRL level. Obviously, such patients never undergo surgery, and therefore no pathology data can be collected. Since it is impossible to identify which patients will require surgery down the road, we advocate for the “dopamine agonist first” approach, particularly for large tumors that are unlikely to be fully cured by surgery. Furthermore, it has been recently shown in a prospective study done by Ono et al. [27] that virtually all tumors are medically treatable, and the existence of “resistant prolactinomas” has been questioned since highdose aggressive treatment with CAB was effective in 99% of their prolactinoma patients (using doses as high as 12 mg/week). We tried to determine whether CAB has the same effects in inducing tumor fibrosis as BROM. Our findings suggest that CAB has less probabilities of inducing tumor fibrosis. This, in addition to its superiority in normalizing PRL secretion and restoring ovulatory cycles [28–31], is another reason to prefer it to BROM. It is worth mentioning, that CAB used in doses of 0.25–2 mg weekly has not been reported to cause systemic fibrosis [32] or clinically significant fibrotic cardiac valve disease [33, 34], but doses as high as the one used by Ono et al. have yet to be proven safe from the cardiac point of view.

This study is limited by its retrospective nature and small sample, particularly when trying to analyze each treatment group separately. However, the findings do not contradict what has been observed for almost 30 years and it adds data on the outcome of surgery.

Conclusion

Prolactinomas exposed to BROM for at least 1 month are more likely to have tumor fibrosis than adenomas that are treated only with CAB, or are not treated with any DA agent. Finding fibrosis at the time of surgery can be used as a negative prognostic factor indicating less likelihood of biochemical remission.

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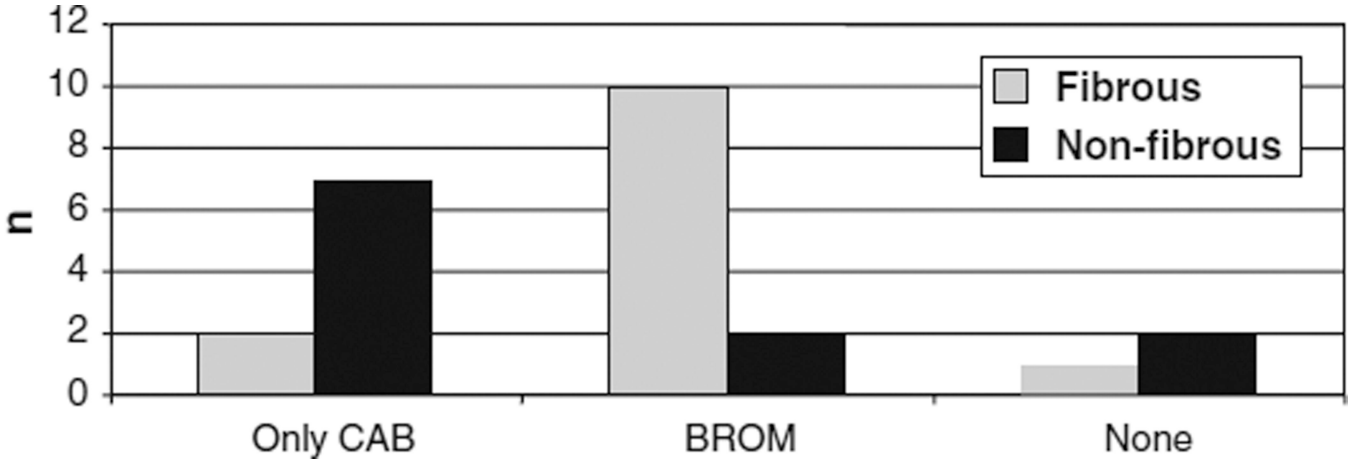

Fig. 1.

Tumor consistency of prolactinomas in relationship with presurgical therapy. Patients treated with bromocriptine (BROM) for at least 1 month showed increased probability of developing tumor fibrosis compared with patient treated with cabergoline only (only CAB) or untreated (None). $P < 0.05$ by χ^2 test

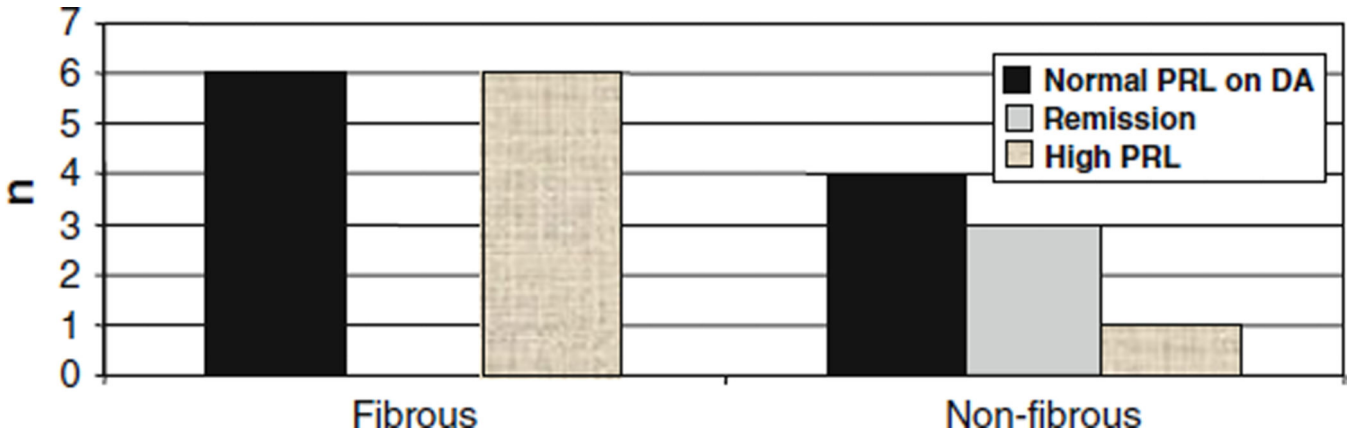

Fig. 2.

Number f patients who have normal serum prolactin (PRL) on DA (patients requiring medical treatment), on biochemical remission (normal PRL without any therapeutic agent), and persistent hyperprolactinemia (patient preference or clinician judgment, no further treatment attempt) classified according to tumor appearance ("fibrous" or "non-fibrous". $P < 0.05$ by χ^2 test, related to percentage of biochemical remission)

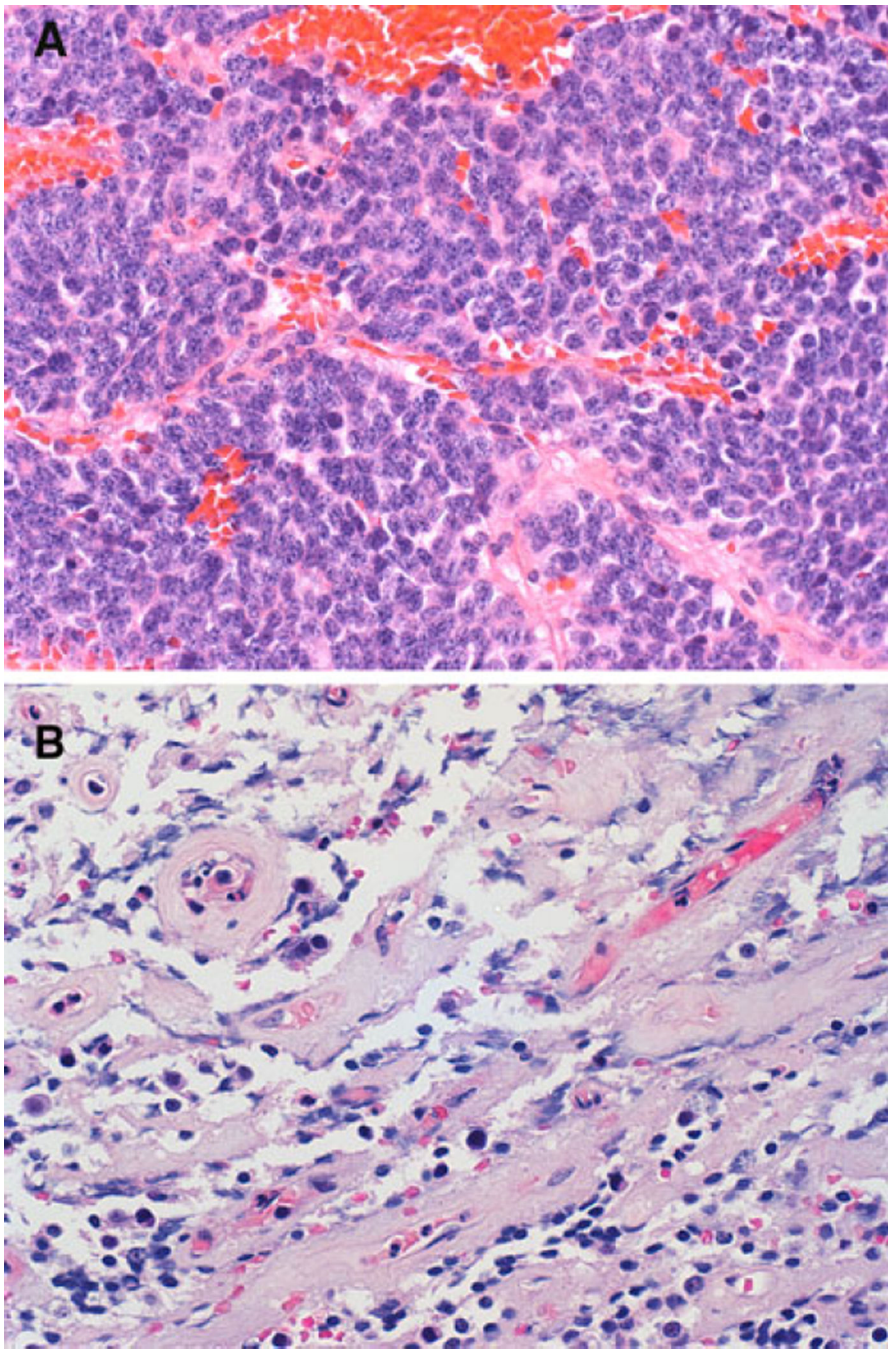

Fig. 3.
Representative slides from a case without **a** (treated with cabergoline) and with **b** (treated with bromocriptine) fibrosis. H&A staining, magnification × 160

Table 1

Preoperative clinical characteristics of the patient population

	Prolactinomas				GH-secreting tumors			
	Fibrous	**Non-fibrous**	**Total**	**%**	**Fibrous**	**Non-fibrous**	**Total**	**%**
Gender								
Female	7	6	13	54.2	1	21	22	64.7
Male	6	5	11	45.8	1	11	12	35.3
Age								
15–30	5	2	7	29.2	0	5	5	14.7
31–62	8	9	17	70.8	2	27	29	85.3
Other pituitary axis affected[a]								
Yes	2	6	8	33.3	0	3	3	8.8
No	11	5	16	66.6	2	29	31	91.2
Symptoms[b]								
Local compression	6	4	10	41.7	1	9	10	29.4
Endocrine	2	3	5	20.8	12	12	35.3	
Both	5	4	9	37.5	1	11	12	35.3
Tumor size								
<=1 cm	3	3	6	25	0	6	6	17.5
>1 cm	10	8	18	75	2	26	28	82.3

All data is from the time of diagnosis

[a] Including: LH, FSH, TSH, ACTH

[b] Local compression: visual field cut, headaches, seizures, CSF leak. Endocrine symptoms refer to symptoms from hyperprolactinemia or hypopituitarism confirmed by abnormal laboratory findings

Table 2

Indications for surgery in patients with prolactinomas.

	n	%
Vision path compression	7	29.2
DA resistance	5	20.8
DA intolerance	6	25.0
CSF leak	4	16.7
Patient's preference	1	4.2
Temporal lobe seizures	1	4.2
Total	24	100

DA = dopamine agonist