Outcomes of transsphenoidal surgery in prolactinomas: improvement of hormonal control in dopamine agonist-resistant patients

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Abstract
Context: Few studies have recently re-examined the efficacy of neurosurgery in prolactinoma patients operated for various indications.
Objective: To analyze outcomes of patients with a prolactinoma treated by transsphenoidal surgery, to identify factors associated with remission and relapse, and to evaluate if surgical debulking allows for better hormonal control in patients with preoperative resistance to dopamine agonists (DAs).
Patients and methods: This was a retrospective review of patients with a benign prolactinoma followed preoperatively and postoperatively in our department and treated by transsphenoidal surgery (n=63; 45 women; mean age: 31 ±14 years).
Results: Postoperative remission was obtained in 63% of microprolactinomas, 60% of noninvasive macroprolactinomas, and none of the invasive macroprolactinomas. Better remission rate was independently predicted by lower diagnostic prolactin (PRL) levels and by the lack of abnormal postoperative residual tissue (P<0.05). A recurrence of hyperprolactinemia was observed in 34% of patients after a median follow-up period of 36 (7–164) months. In patients with preoperative DA resistance treated again after surgery, there was a significant reduction in PRL levels postoperatively (26 (6–687) ng/ml) vs preoperatively (70 (22–1514) ng/ml; P<0.01) under a lower DA dose, and about half of the patients had PRL normalization.
Conclusions: Recurrence of hyperprolactinemia is observed in one-third of prolactinoma patients after surgical remission and may occur as late as 13 years after surgery. Resistance to DA can be considered as a good surgical indication, as partial tumor resection allows for better hormonal control with a lower dose of DAs.

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Introduction
Prolactinomas are the most frequent pituitary tumors, with a prevalence estimated to be 35–60 cases per 100 000 individuals (1, 2, 3). Women are predominantly affected and generally have symptoms of hypogonadism and/or galactorrhea (4, 5), whereas men are more likely to present with larger adenomas at the time of diagnosis and show drug resistance (6). Dopamine agonist (DA) therapy is recommended as first-line treatment (7). Its high efficacy has been well demonstrated in lowering prolactin (PRL) levels, reducing prolactinoma size, and restoring gonadal function (7, 8, 9). Since DAs are so highly effective, recognized indications for surgery of prolactinoma have become rare, usually targeting specific situations where medical treatment is failing.

Surgical tumor resection is indeed indicated in the few prolactinoma patients with severe intolerance or resistance to DA and in patients with acute complications such as apoplexy or cerebrospinal fluid (CSF) leak (7, 8). Recently, several studies have raised the concern of an increased risk for cardiac valve disease with the prolonged use of DA with partial serotonergic activity (10, 11, 12, 13, 14). Also, emerging evidence has been provided for a link between chronic DA therapy and impulsive behavior disturbances such as gambling, hypersexuality, or bulimia (15, 16). Because of these problems, surgery might become a reasonable treatment alternative in young patients who do not wish to take prolonged, eventually lifelong medical treatment and in patients who require protracted use of higher-than-standard doses of bromocriptine or cabergoline.

Few studies have recently re-examined the outcome of patients treated by transsphenoidal surgery for a prolactinoma (17, 18, 19, 20, 21, 22, 23, 24). They reported variable remission rates for microprolactinomas (between 50 and 93%) and macroprolactinomas...
(between 30 and 80%), as well as a highly variable frequency of recurrences between 5 and 58%, the latter variability being mainly dependent on the length of the follow up and the indication retained for surgery. The aim of our study was to retrospectively analyze the clinical characteristics and outcome of patients with a prolactinoma treated by transsphenoidal surgery for various indications. We also wished to identify factors associated with tumoral relapse and evaluate if surgical treatment allows a better response to DA therapy in patients with preoperative DA resistance.

**Subjects and methods**

**Patients**

This was a retrospective chart review that included all patients with a prolactinoma treated by transsphenoidal surgery between April 1979 and June 2011 (n=71) and who were regularly followed by the Department of Endocrinology of our institution. We, however, excluded all patients (n=7) who had not been seen in our institution preoperatively in order to avoid any recruitment bias in outcome analysis. Another patient was excluded because of a diagnosis of malignant prolactinoma. Information on patients not seen for follow up over the last 2 years was collected by contacting the patient, the patient’s endocrinologist, or the patient’s family physician. This cohort study represented about 16% of a larger population of 452 prolactinoma patients regularly seen in our center.

Data recorded included age at diagnosis, gender, results of magnetic resonance imaging (MRI) at diagnosis and 3 months after surgery, symptoms at presentation, history and efficacy of DA therapy before and after surgery, indication, time and place of surgery, surgical complications, duration of follow up after surgery, and PRL level values at diagnosis, under DA therapy, before surgery, 2−4 months after surgery, and at each following endocrine visit.

**Definitions**

PRL-secreting tumors were classified as microprolactinoma (diameter ≤10 mm), macroprolactinoma (diameter >10 mm), and invasive macroprolactinoma in case of extrasellar extension of the macroadenoma in at least one of the cavernous sinuses. The total cumulative dose of DA was calculated for each patient before and eventually after surgery. Resistance to DA was defined as a lack of normalization of PRL levels and a failure to decrease tumor size by 50% or more despite adequate doses of the DA (at least 15 mg bromocriptine daily or 2 mg cabergoline weekly) administered for at least 6 months (7, 25, 26). The majority of patients (39/56) had been treated with cabergoline preoperatively. In subjects treated with other DAs, we arbitrarily converted doses of bromocriptine (12 patients) and quinagolide (five patients) into ‘cabergoline-equivalent’ doses (bromocriptine 2.5 mg two times/day and quinagolide 150 µg/day were considered equivalent to cabergoline 0.5 mg two times/week).

**Assays**

Serum PRL concentrations were measured by an in-house RIA before 1996 and by conventional immunochemiluminescence assays thereafter (Immulite, Diagnostic Products Corporation, Los Angeles, CA, USA, until August 2002; Elecsys, Roche Diagnostics, until January 2009; and Access, Beckman Coulter, Brea, CA, USA, thereafter). The converting factor was 1 ng/ml = 25 mU/l.

**Statistical analysis**

Data were analyzed using ANOVA with post hoc comparison tests or by χ²-tests as appropriate. A multivariate logistic regression analysis was performed to determine factors independently predicting immediate and long-term postsurgical remission and recurrence. Several variables were first included in a univariate analysis: age, gender, type of prolactinoma (microprolactinoma, macroprolactinoma, or invasive macroprolactinoma), PRL level at diagnosis, use of DA before surgery, preoperative DA resistance, site of surgery (UCL, Brussels or elsewhere), and postoperative residue at MRI. Those with a P value <0.10 were further included in the multiple logistic regression analysis using a stepwise process. Statistical significance was defined as a P value of <0.05. Kaplan–Meier survival curves were calculated to evaluate the relapse-free evolution probability and differences between subgroups were analyzed by the log-rank test. All statistical tests were performed using the Software SPSS 18.0 (SPSS, Inc., Chicago, IL, USA).

**Results**

**General characteristics and surgical indications**

Of the 63 patients operated for their prolactinoma and included in this study, 45 (71%) were women and their mean age was 31 ± 14 years. Twenty-seven patients...
(43%) had been operated for a microprolactinoma, 20 (32%) for a macroprolactinoma, and 16 (25%) for an invasive macroprolactinoma (Table 1). At the time of diagnosis, median PRL level was 195 ng/ml (extreme values: 38–9302 ng/ml). Patients with an invasive macroprolactinoma were older than patients with microprolactinoma or noninvasive macroprolactinoma ($P<0.01$). There were only women in the microprolactinoma group, while men represented 30 and 75% of the noninvasive and invasive macroprolactinoma groups respectively ($P<0.01$). Male patients were older at diagnosis (40±16 vs 27±11 years; $P<0.001$), had larger prolactinomas (height: 24±12 vs 11±11 mm; $P<0.001$) and higher median PRL level (1435 vs 114 ng/ml; $P<0.01$) than female patients. Fifty-two patients (83%) had symptoms of hypogonadism and/or galactorrhea and 13 patients (21%) had compression symptoms (visual loss and/or headache).

The vast majority of patients (89%) had received DA prior to the surgery, less often in the invasive macroprolactinoma group (69%) than in the other two groups (95 and 96%; $P<0.05$). Twelve patients had received bromocriptine preoperatively while 39 and 5 patients had been treated with cabergoline and quinagoline respectively. Eighty-four percent of patients (53/63) underwent surgery in our institution, whereas twenty patients had surgery elsewhere (13 with DA resistance and 25 without medical treatment). Twelve patients had had surgery (36%) due to drug intolerance, 29 (47%) for acute complications, 13 patients (21%) had DA resistance, and 26 (41%) had a noninvasive macroprolactinoma or noninvasive macroprolactinoma ($P<0.01$). There were only women in the microprolactinoma group, while men represented 30 and 75% of the noninvasive and invasive macroprolactinoma groups respectively ($P<0.01$). Male patients were older at diagnosis (40±16 vs 27±11 years; $P<0.001$), had larger prolactinomas (height: 24±12 vs 11±11 mm; $P<0.001$) and higher median PRL level (1435 vs 114 ng/ml; $P<0.01$) than female patients. Fifty-two patients (83%) had symptoms of hypogonadism and/or galactorrhea and 13 patients (21%) had compression symptoms (visual loss and/or headache).

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Indications for surgery were drug intolerance in 13 patients (21%), DA resistance in 26 (41%), patient’s choice in 14 (22%), and acute complications in 10 (16%; Table 2). Patients who had surgery because of acute complications were older (46±17 years), mostly men, and had larger prolactinoma (height: 31±15 mm), compared with patients with other surgical indications ($P<0.01$).

### Table 1 Patient characteristics and surgical outcome according to tumor size. Values are shown as mean±s.d. or as median (P5–P95).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n=63)</th>
<th>Microprolactinoma (n=27)</th>
<th>Macroprolactinoma (n=20)</th>
<th>Invasive macroprolactinoma (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>31±14</td>
<td>26±7</td>
<td>29±10</td>
<td>43±18</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>18/45</td>
<td>0/27</td>
<td>6/14</td>
<td>12/4</td>
</tr>
<tr>
<td>Initial PRL (ng/ml)</td>
<td>195 (38–9302)</td>
<td>91 (35–250)</td>
<td>403 (65–2379)</td>
<td>2043 (68–11542)</td>
</tr>
<tr>
<td>Preop DA (%)</td>
<td>56/63</td>
<td>26/27 (96)</td>
<td>19/20 (95)</td>
<td>11/16 (69)</td>
</tr>
<tr>
<td>Preop resistance (%)</td>
<td>25/55 (45)</td>
<td>9/26 (35)</td>
<td>9/18 (50)</td>
<td>7/11 (64)</td>
</tr>
<tr>
<td>Follow up (months)</td>
<td>85±62</td>
<td>75±59</td>
<td>97±57</td>
<td>87±76</td>
</tr>
<tr>
<td>Postop remission (%)</td>
<td>29/63 (46)</td>
<td>17/27 (63)</td>
<td>12/20 (60)</td>
<td>0/16 (0)</td>
</tr>
<tr>
<td>Recurrence (%)</td>
<td>10/29 (34)</td>
<td>4/17 (24)</td>
<td>6/12 (50)</td>
<td></td>
</tr>
<tr>
<td>Long-term remission (%)</td>
<td>19/63 (30)</td>
<td>13/27 (48)</td>
<td>6/20 (30)</td>
<td>0/16 (0)</td>
</tr>
</tbody>
</table>

*P<0.05, †P<0.01, ‡P<0.001 vs microprolactinoma; §P<0.05, †P<0.01, ‡P<0.001 vs macroprolactinoma.

*Missing information for one patient in the macroprolactinoma group.

## Postoperative remission
Remission, defined as persistent normoprolactinemia without any treatment for at least 6 months after surgery, was obtained in 63% (17/27) of patients with a microprolactinoma and in 60% (12/20) of patients with a noninvasive macroprolactinoma. As expected, there was no remission in patients with invasive macroprolactinoma. Remission rate was lower in the case of surgery for an acute complication (1/10, 10%; $P<0.05$) and slightly higher when surgical indication was patient’s choice (71%), although this difference did not reach statistical significance (Table 2). There was also no significant difference in the rates of postoperative remission between patients treated with DA preoperatively (48%) and those without medical treatment (29%, NS). At postoperative MRI, abnormal intrasellar or parasellar residual tissue was observed in not only 23 out of 34 patients with persistent hyperprolactinemia (68%), but also in 11 out of 29 patients in remission (28%; $P=0.003$).

Univariate analysis revealed that gender, age, diagnostic PRL levels, size and invasiveness of prolactinoma, and postoperative residue at MRI were all associated with the probability of remission, whereas no relation between DA resistance and surgical indication was observed (data not shown). In a multiple logistic regression analysis, however, only diagnostic PRL levels ($P<0.001$) and postoperative residue ($P<0.05$) were independently associated with remission, while initial PRL concentration was the only predictive factor of persistent remission at the last visit ($P=0.003$).

Nine postoperative complications (14%) were observed in a total of eight patients (live with a macroprolactinoma and three with a microprolactinoma), including partial pituitary insufficiency in three patients, permanent diabetes insipidus (DI) in two, CSF leak in two with one case of secondary meningitis, and severe epistaxis requiring hemostatic intervention in two patients. One macrolactinoma patient had both partial pituitary insufficiency and CSF leak. In addition, two subjects showed prolonged (> 6 months) but finally
reversible DI. Of the three microprolactinoma patients with a surgical complication, all had been treated preoperatively with a DA for 12–139 months and two of them had a tumor which was described as fibrous and adherent by the neurosurgeon.

**Recurrence of hyperprolactinemia**

Ten (34%) out of the 29 patients in remission had a relapse of their hyperprolactinemia over time, after a median period of 36 months (extreme values: 7–164 months). Kaplan–Meier analysis also showed a higher probability of recurrence in male than in female patients (5-year relapse rates of 100 and 35% respectively; P<0.05; Fig. 1A). The probability of recurrence was also twofold higher in patients with abnormal postoperative residual tissue at MRI (64 vs 34% in those without residue), but this difference was not significant (Fig. 1C). Only one patient with an aggressive tumor.

**DA resistance and effects of surgery**

Out of the 55 patients treated medically before surgery, 25 patients (45%) had resistance to DAs. There was no significant difference in the rate of preoperative resistance among microprolactinoma, macroprolactinoma, and invasive macroprolactinoma (Table 1). Patients with DA resistance had, however, higher diagnostic PRL levels (Fig. 2), and univariate and multivariate analyses revealed an association between diagnostic PRL level and preoperative DA resistance (P<0.05).

Thirty-eight patients required DA treatment after surgery and 24 of them (63%) normalized their PRL level. In 15 patients with preoperative DA resistance who needed medical treatment again after surgery, there was a significant difference between the lowest PRL levels on preoperative DA treatment (70 (22–1514) ng/ml) and postoperative DA treatment (26 (6–687) ng/ml; P<0.01; Fig. 3A). Moreover, medical treatment allowed PRL normalization in seven out of 15 previously DA-resistant patients (47%; Fig. 3B), and this higher efficacy of DA treatment was observed with a significantly lower mean dose after surgery (1.4 mg/week of cabergoline) than before surgery (2.4 mg/week of cabergoline; P<0.01). There were, however, no differences in the relative reduction of PRL levels under DA treatment before (mean decrease of
Discussion

In this retrospective study of 63 patients operated for a benign prolactinoma, remission was obtained in 63% of patients with a microprolactinoma and in 60% of patients with a noninvasive macroprolactinoma. A high recurrence rate of hyperprolactinemia (34%) was also observed, occurring throughout a prolonged mean postoperative follow-up period of 94 months. We also show that in the nonsurgically cured DA-resistant patients, tumor resection allowed normalization of hyperprolactinemia in nearly 50% of cases, with a lower dose of DAs.

DAs represent the undisputed treatment of choice for all types of prolactinomas. Clinical Practice Guidelines recently published by the Endocrine Society indeed reinforced the recommendation of DA administration as first-line treatment, and the use of cabergoline over other DAs (7). Because medical treatment is so highly efficient, transphenoidal surgery has become less and less used, thus explaining the fact that recent surgical series are rare and often contain a limited number of patients. Also, as illustrated in our study, the clinical characteristics of patients in these surgical series are different from those of the general prolactinoma population, with a relative selection of male patients with larger tumors and a higher rate of DA resistance, thus precluding any valid comparison between the relative effectiveness of medical and surgical treatment of prolactinomas.

The clinical characteristics of our patients were similar in many other aspects to those reported in recent surgical series (17, 18, 19, 20, 21). As also shown here, the mean age of operated patients usually ranges between 30 and 38 years, men represent 25–40% of them and have higher PRL levels and larger tumors (19, 20). An interesting finding was that our male patients were significantly older than our female patients, which likely results from differences in the surgical indications selected in men (mainly DA resistance and acute complications) and women (more frequent DA intolerance or personal wish). In our study, microprolactinomas accounted for 43% of resected tumors, a proportion similar to those reported by Losa et al. (19) (49%) and by Raverot et al. (21) (46%), but higher than those reported by Kreutzer et al. (17) (26%) and Hamilton et al. (20) (32%). Our mean follow up was longer (85 months) than in most other studies, only...
Raverot et al. (21) reporting a longer follow up with a mean of 138 months.

Kreutzer et al. (17) reported changes in their surgical indications over time. With the availability of cabergoline, which is more efficient and better tolerated than bromocriptine, the rate of surgeries done for DA intolerance or DA resistance has decreased and new indications have emerged, like cystic prolactinomas or patient’s preference which accounted for 20% of their indications between 2000 and 2005. In our study, patient’s preference indeed represented a significant proportion (22%) of indications for neurosurgery, while cystic tumors were not particularly prominent. On the other hand, DA resistance remains the most frequent indication, accounting here for 41% of surgeries, a proportion similar to that observed by Kreutzer et al. (37%).

The rate of postoperative complications of 14% (17%) if we also consider the two patients with prolonged but reversible DI) was similar to those reported by Hamilton et al. (13%) and Kreutzer et al. (17%). While most complications occurred in patients with a macroprolactinoma, they were also observed in three subjects with a microprolactinoma. All of them had received presurgical DA treatment and two of them had a tumor which was reported as fibrous and adherent by the neurosurgeon. Interestingly, Menucci et al. (24) reported a very high rate of postoperative complications (10/13 or 77%) in patients with a fibrous prolactinoma. It is, however, not possible to conclude from the present study whether tumor fibrosis did or did not a negative impact on surgical outcomes or whether preoperative DA treatment may or may not have favored this pathological feature, as has been previously reported (4, 24).

In the present series, postoperative remission was obtained in only 63% of microprolactinomas but in 60% of noninvasive macroprolactinomas, with definition of invasiveness restricted to cavernous sinus extension. The remission rate observed here for microprolactinomas is lower compared with those (78–93%) reported in several recent series (17, 18, 19, 21, 22, 23), but similar to the success rate reported in one study (20) and higher than that reported by Menucci et al. (24). In fact, our study included patients who underwent surgery in different institutions over a long timespan between 1979 and 2010, while most recent studies were from single experienced centers and included patients treated after 1990. The probability of remission was much lower (33%) when considering all macroprolactinomas (noninvasive and invasive) altogether. This rate is comparable with those reported in previous studies. In a multiple logistic regression analysis, a lower PRL level at diagnosis was independently associated with a successful surgical outcome, as already reported by previous authors (17, 19, 21, 27). Also, as found in other studies (19, 24, 27, 28), preoperative DA therapy seems to have no significant influence on the probability of surgical success.

In our study, about 34% of patients with postoperative remission relapsed 7–164 months after initial surgery, a recurrence rate higher than those reported in recent studies (17, 18, 19, 20, 21) but similar to findings from older publications with long follow-up periods of up to 148 months (29, 30, 31, 32). Noticeably, recurrence of hyperprolactinemia seems to occur at a constant rate over time and half of the relapsing patients did so 3 years or more after surgery. Thus, the longer the follow up, the higher the relapse rate, an observation which is similar to what has been reported for patients with nonfunctioning pituitary adenomas (33, 34). Our findings thus emphasize the necessity to follow these patients for many years after apparent surgical remission.

Another important and new finding in our study is the significant improvement with surgery of hormonal control under DA therapy in previously drug-resistant patients. It has been shown in several studies that debulking of GH-secreting pituitary adenomas further improved hormonal control of acromegaly by somatostatin analogs (35, 36), but this debulking effect had not been convincingly demonstrated until now for PRL-secreting pituitary adenomas. We demonstrate here that surgery allowed a subsequent normalization of PRL concentrations, with a lower dose of DA in nearly half of the resistant patients. Resistance to DAs or even the need to utilize a higher-than-standard dose of cabergoline to control PRL and tumor volume may therefore be considered as valid indications for surgical resection of prolactinomas. There was, however, no difference in the percentage of reduction of PRL levels under DA treatment before or after surgery. This indirectly suggests that the sensitivity of the tumoral cells to dopaminergic inhibition most likely did not change with surgery. As shown by Caccavelli et al. (37), intrinsic sensitivity of the tumor to DA is essentially related to D2 dopamine receptor expression on pituitary tumor cells, a parameter which should not be affected by partial resection of the adenoma.

Our study has several limitations, most of them related to the retrospective analysis of the data. DA treatment was not systematically stopped 4 weeks before surgery, as was done in most recent surgical series. However, since we did not consider patients in remission if recurrence of hyperprolactinemia occurred within the first 6 months after surgery, the fact that patients were or were not on DA at the time of surgery should not have affected our results. Our series also contains a limited number of patients. We, however, excluded patients who had not been seen in our institution preoperatively to prevent any recruitment bias that would have affected our outcome analysis. The fact that our patients have been operated in different institutions simply reflects daily life practice. Despite these shortcomings, we believe that our main
conclusions remain valid and likely correspond more closely to the ‘real-life’ situation.

In conclusion, we show here that transsphenoidal surgery may offer a reasonably good chance of post-operative remission to patients with a microprolactinoma or a non-invasive macroadenoma. Recurrence of hyperprolactinemia, however, occurs in one-third of the patients, at a rather constant rate over time, with relapse still found up to 13 years after surgery. We also demonstrate that complete or even partial resistance to DAs can be considered as valuable surgical indications. Indeed, even if the surgery is not curative, 50% of our operated patients had normal levels of PRL with a lower dose of DA. This debulking effect of surgery can therefore be very useful to achieve PRL control and to eventually diminish the risk of long-term dose-related side-effects of DA.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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