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# SURGERY IN MICROPROLACTINOMAS: EFFECTIVENESS AND RISKS BASED ON CONTEMPORARY LITERATURE

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**Abstract**

Microprolactinomas are the most common pituitary adenomas. In symptomatic patients, dopamine agonists are the first treatment of choice; when cabergoline is used, biochemical control rates between 85 and 93% have been reported. Long-term treatment is needed in most of the cases with compliance, patient convenience and potential adverse effects representing areas requiring attention. Based on the literature published in the last 15 years, transsphenoidal surgery can lead to normal prolactin in the post-operative period in usually 71-100% of the cases with very low post-operative complication rates. Surgical expertise is the major determinant of the outcomes and it may be a cost-effective option in young patients with life expectancy greater than ten years (provided it is performed by experienced surgeons at high volume centres with confirmed optimal outcomes). Larger series of patients with adequate follow-up could further validate the place of transsphenoidal surgery (particularly through the endoscopic approach for which long-term results are currently limited) in the management algorithm of patients with microprolactinoma.

**Abbreviations:** DA: Dopamine agonist, PRL: Prolactin

## I. Introduction

Prolactinomas are the most common pituitary adenomas accounting for 51-66% of these tumours; recent epidemiological studies suggest prevalence 44-62 cases/100,000 population (1). The median age at diagnosis is 32 years with 76-81% of them being microadenomas (1,2). The clinical manifestations of microprolactinomas are attributed to PRL excess and include galactorrhoea and those of hypogonadotropic hypogonadism. The main aims of their treatment include normalization of PRL and amelioration of the clinical consequences of the hyperprolactinaemia, prevention of tumour growth, as well as improvement of the quality of life. The adoption of a treatment option with the highest success rate, less side effects/complications and optimal cost-effectiveness is of major importance. Currently, dopamine agonists (DA) are the first line therapy for symptomatic microprolactinomas and transsphenoidal surgery is recommended to symptomatic patients who cannot tolerate high doses of cabergoline or who are not responsive to DA therapy (3).

Resistance to DA includes a failure to achieve normal PRL on maximally tolerated doses of DA and a failure to achieve tumour shrinkage more than 50% (4). The second criterion would be considered clinically important mainly for macroprolactinomas due to their potential to exert pressure effects to surrounding structures. Decreased number of dopamine receptors 2 ($D_2$) has been reported in DA resistant prolactinomas but the mechanism of DA resistance has not been completely elucidated (3,4). The prevalence of resistance to DA treatment differs between the various agonists and has is less common in microprolactinomas and in women (3,5,6). The reported rates of PRL normalization in patients with microprolactinoma are around 57% with bromocriptine and 85-93% with cabergoline (5-8) with the latter agent leading to normoprolactinaemia in a significant number of bromocriptine resistant patients (4). A recent meta-analysis suggested that persisting normoprolactinaemia after withdrawal of DA is expected in only 21% of the cases with the probability been higher when cabergoline had been used for at least two years and pituitary MRI had shown normal appearances prior to DA discontinuation (9,10). Side

effects of these agents are mainly gastrointestinal with nausea and vomiting, as well as headaches and drowsiness; these can be minimized by gradual titration of the dose offered at bed time. Mood alterations (anxiety and depression), psychosis or behavioural changes including impulse control disorders may also occur and are considered to be reversible when the medication is stopped (4,11). Discontinuation of treatment due to intolerance has been described in 4% of the cases on cabergoline and 12% on bromocriptine (6,7). Although a clinically concerning association between the use of DAs for the treatment of hyperprolactinaemia and cardiac valvulopathy is not supported by the recently published literature (12), concerns remain on the impact of long-term use of cabergoline, even in low weekly doses, resulting in large cumulative doses.

A systematic review of the outcomes of surgery specifically in patients with microprolactinomas based on the contemporary published literature is not available. Given the advances in transsphenoidal surgical techniques, and especially the minimally invasive ones, that have taken place in the last years, such an analysis is of major importance and will facilitate therapeutic decisions relying on existing evidence. We have, therefore, reviewed the available literature on the surgical management of microprolactinomas (microscopic and endoscopic) published between 2000 and 2015 and we have extensively assessed the data on biochemical remission and recurrence rates, predictive factors of recurrence, peri-operative complications and cost implications.

## II. Transsphenoidal surgery for microprolactinomas

Surgery for microprolactinomas is currently performed through the transsphenoidal route with a microscope, endoscope or both. The endoscopic endonasal approach - a minimally invasive technique offering superior panoramic view and the benefits of avoiding submucosal transseptal dissection (thereby eliminating nasoseptal perforations), as well as

less patient discomfort due to the lack of nasal packing - has been applied in the latest years with less available published literature.

**i) Remission and recurrence rates after transsphenoidal surgery**

A summary of the surgical success rates from 45 studies published between 1977-2005 (84.4% of them prior 2000) showed high variability in the achievement of normal PRL (38-100%) possibly reflecting differences in the neurosurgical expertise; the remission rate, as estimated based on the total number of included patients, was 74.7% and the recurrence of hyperprolactinaemia (affected by the variable definitions of cure/recurrence, observation periods and drop-out rates) was 18.2% (4). Studies published during the period covered in this review on patients with microprolactinoma treated with the microscopic transsphenoidal technique and with main indications resistance/intolerance to DAs or patient's choice suggest that biochemical remission with normoprolactinaemia is achieved usually in 71-93% of the cases; serum PRL had been checked shortly after or within the first weeks following surgery (13-24) (Table 1). In a large series of 400 patients treated by the sublabial transsphenoidal approach by a single neurosurgeon, post-operative remission was reported in 82% of the cases; information on previous treatment with DAs was not available (14). Raverot *et al.* in a collaborative multicenter study of 43 patients who stopped the DAs one month prior to the operation found a 93% remission rate (18). In two series with 46 (20) and 59 (24) patients operated on by two experienced neurosurgeons in a single center, early postoperative normoprolactinaemia was reported in 91% and 78% of the cases, respectively; DAs had been stopped before surgery [at least four weeks in the first and at least two months (in almost half of the patients) in the second study]. Mortini *et al.* in a series of 69 patients operated on in a single centre by two surgeons (21), showed post-operative remission rate 75% (off DA for at least two months). Lower post-operative remission rates (40-63%) have been reported in three series with, however, small number of patients (5, 27 and 32)

affecting the estimation of the relevant rates (25-27). Most studies with mean/median follow-up period ranging between 12 and 84 months suggest that recurrence of the hyperprolactinaemia is observed between 0 and 13% of the cases (15-17,20,23). In one study, however, recurrence rate of 33% was described during a median observation period of 33 months (22). It should be noted that information on the timing of stopping DA treatment was not available in this report and the possibility that the rate of early biochemical remission may also reflect the impact of DA cannot be excluded.

Series reporting the outcomes of endoscopic transsphenoidal surgery in microprolactinomas are rather limited (Table 2). The post-operative remission rates range between 81-100% and in all but one of the studies there is no available information on previous DA administration (19,28-35). Given that the main advantages of the endoscopic approach involve invasive adenomas, it would be anticipated that the remission rates should not differ between microscopic and endoscopic techniques in microprolactinomas. Recurrence rate of 0% has been described in two series with 7 (32) and 12 (34) patients within a median follow-up period of 62 months and 15 months, respectively. Tanei *et al.* (29) reported relapse rate of 25% but this relies on a group of only 4 patients.

Series confirming that the operations were carried out by one or two surgeons in a single center or by surgeons each performing 80 pituitary operations per year, mostly show higher remission rates (82-100%) (13-16,18,20,30-32) pointing out the importance of surgical expertise. Other factors affecting biochemical remission are not clearly defined specifically for the microprolactinomas as the reported results include analyses for both micro- and macroprolactinomas. Tamasauskas *et al.* (26) suggested that lack of pre-operative therapy with DAs was an independent factor associated with optimal surgical outcome in microprolactinomas; perivascular fibrosis in the adenoma (36) introduced by the medical treatment was a possible mechanism. However, a number of series including both micro- and macroprolactinomas did not confirm this finding (13,16,24,25). The pre-operative PRL levels have been negatively associated with remission in all types of

prolactinomas (16,20,24,25,27); nonetheless, the impact of previous DA treatment on the PRL values used for the statistical analyses is not clear. Finally, Primeau *et al.,* (25) in a series of 63 patients operated on for a prolactinoma (43% micro-), showed that absence of adenoma tissue on MRI performed 3 months post-operatively was positively related with remission of the hyperprolactinaemia.

Main drawbacks of the published literature include the small number of patients and the short observation period in many series (particularly the endoscopic ones), as well as the variable protocols for the confirmation of biochemical remission and detection of recurrence (timing of blood sampling after surgery, duration of stopping DAs). Furthermore, the specific indications for surgery may have introduced a bias in the selection of patients studied; the impact of this (positive or negative) in the reported outcomes is not clear. Finally, the available literature may not necessarily reflect the "real life" outcomes, as the published data tend to represent experience of large centers with usually optimal results.

**ii) Peri- and post-operative complications in microprolactinomas**

The reported peri- and post-operative complications in microscopic series include mortality 0% (13,15-17,19-22,24,27), visual deterioration 0% (13,15,27) and other neurosurgical complications 0-1.8% (febrile sinusitis, epistaxis requiring emergency nasal tamponade and mucocele requiring evacuation one year later) (20,24). Outcomes of pituitary function are shown in Table 3 and in all (15,19,20,22,24,26) but one (with a very small number of patients) (23) studies they look rather optimal; hypogonadism or permanent diabetes insipidus were found between 0 and 6%.

The reported peri- and post-operative complications in endoscopic series include mortality 0% (19,29-31,33-35,37), visual deterioration 0% (32,34,37) and other neurosurgical complications 0% (37). Outcomes of pituitary function are shown in Table 3;

new pituitary hormone deficits range between 0 and 6% (19,29,30,37). Notably, no cases of permanent diabetes insipidus have been described.

**iii) Quality of life and costs**

Data on the quality of life of patients with microprolactinomas treated by surgery are not currently available.

Based on a study from the UK published in 1999 (38), the costs for a hypothetical patient with microprolactinoma undergoing surgery and cure with no complications and followed-up for 10 years did not differ from those required for a patient receiving cabergoline 1 mg/week for 10 years.

In a very recently published study (39) Jethwa *et al.* performed a cost-effectiveness analysis comparing transsphenoidal surgery (microscopic or endoscopic) and medical therapy (bromocriptine or cabergoline) in microprolactinomas using decision analysis modelling. Each probability (cure rates, complications) in the model was based on data gathered from the published literature and costs were taken from the perspective of the US healthcare third-party payer. Base case analysis revealed that medical therapy was more costly and less effective than surgery in young patients with life expectancy greater than 10 years. The authors propose that the costs of medications continue to accumulate with time, whereas the costs of surgery are realized upfront and do not recur on a continuous basis, unless the patient has post-operative hypopituitarism requiring hormone replacement therapy. They point out though that the operation should be performed only by experienced surgeons at high volume centers with optimal biochemical cure and low complications rates. It should be noted, however, that in this study a number of assumptions had to be made in order to complete the model; these may not be a perfect reflection of the real world, thereby introducing errors and may not necessarily apply to different medical economic environments in other countries.

## III. Conclusions and Future Perspectives

In the last decades, medical treatment has been considered the mainstay in the management of microprolactionomas. This relies on the well established high biochemical control and low drug intolerance rates (particularly for cabergoline, 85-93% and 4%, respectively) leading physicians to overlook the option of surgical removal and often not to discuss this with the patient at the time of diagnosis. Based on the literature published in the last 15 years and keeping in mind its limitations as described above, surgery by experienced hands can achieve biochemical control in 82-100% of the cases with practically minimum complication rates; amongst them, permanent diabetes insipidus (up to 6%) is probably the one requiring more attention. The reported recurrence rates (derived mostly from microscopical transsphenoidal operations) need to be taken into account, although at present, they do not seem to be particularly high (mostly 0-13%).

Therefore, in centers with neurosurgical expertise in which the chance of successful and safe removal of a symptomatic microprolactinoma can be high, the adoption of this route is not an unreasonable approach and needs at least to be discussed with the patient or even offered as primary therapy to selected, suitable patients. This is of particular relevance for young patients with a favourable surgical target who may require decades of medical therapy or for those non-compliant to DA treatment (provided surgery is not complicated by hypopituitarism requiring replacement).

Areas that need to be further clarified in this field include the impact of longer observation periods on sustaining biochemical remission and the timing of recurrence (if detected long after the operation allowing a female to reach menopause, it may not be of clinical significance). Such data should be generated from large series of non-selected (if possible) patients followed-up by robust protocols. Also, quality of life, financial strains on

patients and their families and cost-effectiveness issues remain to be elucidated. Finally, further outcomes of endoscopic surgery in microprolactinomas are eagerly awaited.

**Declaration of interest**

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

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**Table 1.** Outcomes of series including patients with microprolactinoma treated by the microscopic transsphenoidal approach**.**

| Ref. | Total N Age (yrs) (range) | Males N Age (yrs) (range) | Females N Age (yrs) | Indications for surgery | Follow-up (months) (range) | N of patients with remission of hyperPRLaemia post-operatively (%) | N of patients with recurrence of hyperPRLaemia (%) |
|---|---|---|---|---|---|---|---|
| **(13)** | 21<br>All <40 | 0 | 21 | DA resistance or intolerance<br>Patient's preference<br>Intratumoural haemorrhage[a] | Mean<br>144[a] | 18 (86%)[b] | - |
| **(14)** | 400 | - | - | - | - | 328 (82%)[c] | - |
| **(25)** | 27 | 0 | 27<br>Mean 26±7 | DA resistance or intolerance<br>Patient's preference | Mean<br>75±59 | 17 (63%)[d] | 4/17 (24%)[d] |
| **(26)** | 32 | 0 | 32<br>Mean 31±8 | DA resistance or intolerance<br>Patient's preference | Mean<br>50±32 | 19 (59%)[e] | - |
| **(15)** | 24<br>Median 30<br>(18-52) | 4<br>Median 39<br>(18-52) | 20<br>Median 29<br>(18-46) | Patient's preference (no DA previously) | Median<br>30<br>(6-77) | 22 (91%) | 0/22 (0%) |
| **(16)** | 18 | 18<br>Median 38<br>(17-69)[a] | 0 | DA resistance or intolerance<br>Tumour apoplexy<br>Patient's preference | Median<br>45<br>(13-121)[a] | 15 (83%)[f] | 2/15 (13%)[f] |
| **(17)** | 12<br>Median 32<br>(17 - 65)[a] | - | | DA resistance or intolerance<br>Patient's preference<br>Tumour apoplexy[a] | Mean<br>39<br>(1-62)[a] | 11 (92%)[g] | 1/11 (9%)[g] |
| **(18)** | 43<br>Mean 38±13[a] | - | | DA resistance or intolerance<br>Patient's preference | Mean<br>138 ± 46[a] | 40 (93%)[h] | - [h] |
| **(19)** | 21 | - | | - | Mean<br>61<br>(1 – 144)[i] | 15 (71%)[j] | - |
| **(20)** | 46<br>Median 32<br>(12-69)[a] | - | | DA resistance or intolerance<br>Patient's preference [a] | Median<br>12<br>(3–132)[a] | 42 (91%)[k] | 3/42 (7%)[k] |
| **(21)** | 69<br>Mean 30±1[a] | - | | - | Mean<br>53±4[a] | 52 (75%)[m] | - |
| **(22)** | 20<br>Mean 33±3[a] | - | | DA resistance or intolerance<br>Patient's | Median<br>33[a] | 15 (75%) | 5/15 (33%)[n] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | preference [a] | | | |
| **(23)** | 11 | 11<br>Median 41<br>(32 - 54) | 0 | - | Median<br>84<br>(24-156) | 8 (73%) | 0/8 (0%) |
| **(27)** | 5<br>Median 31[a] | - | | DA resistance or intolerance<br>Patient's preference[a] | Mean<br>44[i] | 2 (40%)[p] | 1/2 (50%)[p] |
| **(24)** | 59<br>Mean 30±1<br>(12-67)[a] | - | | DA resistance or intolerance<br>Patient's preference | Mean<br>50±3<br>(1-132)[a] | 46 (78)[q] | - [q] |

In the above series the authors report microscopic or do not confirm endoscopic approach.

**a:** Data for both micro- and macroprolactinomas.
**b:** PRL was measured 7-10 days, 6 months and 1-5 years after surgery. The patients were instructed to visit the hospital in case of menstrual irregularities. Information of timing of stopping the DA prior to surgery not available.
**c:** The authors use the term "cured microprolactinomas" and no further details are provided. Information on previous DA treatment not reported.
**d:** Remission was defined as normoprolactinaemia without any treatment for at least 6 months post-operatively. Recurrence was defined as the re-detection of hyperprolactinemia 6 months or longer after surgery (if the recurrence occurred within the first 6 months, patients were not considered to have had remission).
**e:** Information of timing of stopping the DA prior to surgery not available.
**f:** Remission was defined as normal PRL without DA for at least 4 weeks before surgery. Recurrence was based on detection hyperprolactinaaemia during the follow-up period.
**g:** Remission post-operatively was defined as normal PRL on day 7 post-operatively off DA for at least 6 weeks before surgery. Remission during long-term follow-up was defined as normal PRL in the absence of DA treatment for 3 months. Follow-up data were available for 12 patients with microprolactinomas and these have been included in the Table.
**h:** DA treatment was stopped one month prior to surgery. Serum PRL was measured 1-2 weeks after surgery and yearly for at least 10 years. Long-term follow-up data specifically for microprolactinomas are not reported.
**i:** Data for all adenomas included in this series.
**j:** Remission was defined as normalization of PRL checked at least 6 weeks post-operatively and after withdrawal of DA within the same period.
**k:** Remission was defined as normal PRL on day 7 post-operatively (off DA therapy for at least 4 weeks prior to surgery). Recurrence was defined as hyperprolactinaemia at last follow-up; long-term data were available for 46 patients and these have been included in the Table.
**m:** Remission was defined normalization of PRL off DA for at least 2 months. PRL levels had to remain normal for a minimum of 6 months, otherwise patients were not included in the remission group. Data on long-term remission specifically for microprolactinomas are not reported.
**n:** Information of timing of stopping the DA prior to surgery not available. Recurrence of hyperprolactinaemia occurred within 4 years after surgery.
**p:** DAs were stopped the day before surgery. Remission was defined as the resolution of hyperprolactinaemia three months post-operatively.
**q:** Remission was defined as normalization of PRL measured 5-6 days after surgery. If patients had received DA or had discontinued this shortly before surgery, the earlier postoperative value used for classifying surgical outcome was that obtained at least 2 months after surgery. Patients were not considered in remission if hyperprolactinaemia recurred within 6 months of surgery. Follow up data specifically for microprolactinomas are not reported.

**Table 2.** Outcomes of series including patients with microprolactinoma treated by the endoscopic transsphenoidal approach (as confirmed by the authors of the papers).

| Ref. | Total N Age (yrs) (range) | Males N Age (yrs) | Females N Age (yrs) (range) | Indications for surgery | Follow-up (months) (range) | N of patients on remission of hyperPRLaemia post-operatively (%) | N of patients with recurrence of hyperPRLaemia (%) |
|---|---|---|---|---|---|---|---|
| **(28)** | 11 | - | | DA resistance or intolerance | -[a] | 10 (91%)[a] | - |
| **(29)** | 4 | 0 | 4 (18-35) | - | Mean 34±13 | 4 (100%)[b] | 1/4 (25%)[b] |
| **(30)** | 39 Mean 29±9 | - | | DA resistance or intolerance Cystic adenoma Patient's preference | - | 39 (100%)[c] | - |
| **(31)[d]** | 13 Mean 37±3[e] | - | | DA resistance or intolerance | Mean 22±3[e] | 12 (92%) | - |
| **(32)** | 7 | - | | DA resistance or intolerance Patient's preference | Median 62 (8-132)[f] | 7 (100%) | 0/7 (0%) |
| **(19)** | 16 | - | | - | Mean 18 (1-76)[f] | 13 (81%)[g] | - |
| **(33)[h]** | 17 | - | | - | - | 16 (94)[h] | |
| **(34)[i]** | 12 | - | | DA resistance or intolerance | Median 15 (4-31)[e] | 12 (100%)[i] | 0/12 (0%) |
| **(35)[j]** | 28 Mean 36 (7-82)[e] | - | | - | Median 54 (19-54)[f] | 24 (86%)[j] | - |

**a:** Follow-up data specifically for microprolactinomas are not reported. Remission was defined as normal PRL off DA in the last follow-up appointment.

**b:** Remission was defined as normal PRL 3 months post-operatively. The recurrence in the one patient was detected 16 months post-operatively.

**c:** Remission was defined as normoprolactinaemia on the 7$^{th}$ post-operative day. Information on previous treatment with DAs and timing of stopping it not available.

**d:** The study included 35 patients with prolactinoma (13 with micro- and 22 with macroprolactinoma). Eight patients had been previously operated but it is not clarified if amongst them there were ones with microprolactinoma. Information of timing of stopping the DA prior to surgery not available.

**e:** Data for both micro- and macroprolactinomas.

**f:** Data for all pituitary tumours included in this series. Information on previous treatment with DAs and timing of stopping it not available.

**g:** Remission was defined as normalization of PRL checked at least 6 weeks post-operatively and after withdrawal of DA during the same period.

**h:** The series included 194 patients with 77 functioning and 131 non-functioning pituitary adenomas. Thirty tumours were operated on after recurrence; there is no information if microprolactinomas were included in this group. PRL was checked intra-operatively. Information on previous treatment with DAs and timing of stopping it not available.

**i:** The study included 25 patients with prolactinoma (12 with micro- and 13 patients with macroprolactinoma). One of them had undergone prior microscopic transsphenoidal surgery but it was not clarified if this patient had a

micro- or a macroprolactinoma. Remission was defined as normal PRL the day after surgery. Information on previous treatment with DAs and timing of stopping it not available.

**j:** The series included 418 patients with pituitary adenomas, 79 of whom were operated after tumour recurrence; there was no information if microprolactinomas were included in this group. Remission was defined as normal PRL levels at the latest check and off DA for at least 2 months.

**Table 3.** Pituitary function after transsphenoidal surgery for microprolactinomas.

| Ref. | N | Anterior pituitary hormone deficits | Posterior pituitary dysfunction |
|---|---|---|---|
| **Microscopic series** | | | |
| **(26)** | 32 | - | 5/32 (16%) Transient DI<br><br>2/32 (6%) Permanent DI |
| **(15)** | 24 | 1/24 (4%) [a] Hypogonadotropic hypogonadism | 1/24 (4%) [b] Transient SIADH |
| **(19)** | 21 | 0 (0%) | - |
| **(20)** | 56 | 0 (0%) | - |
| **(22)** | 20 | 0 (0%) | - |
| **(23)** | 11 | 5/11 (46%) [c] Hypogonadotropic hypogonadism (testosterone deficiency)<br><br>1/11 (9%) [d] Central hypothyroidism | 2/11 (18%) Transient DI |
| **(24)** | 59 | 0 (0%) | - |
| **Endoscopic series** | | | |
| **(29)** | 4 | 0 (0%) | - |
| **(37)** | 16 | 1/16 (6%) ACTH and reported TSH deficiency (diagnosed on 7th postoperative day) | - |
| **(30)** | 39 | 0 (0%) [e] | 1/39 (3%) Transient DI |
| **(19)** | 16 | 0 (0%) | - |

**a:** Permanent hypogonadotropic hypogonadism despite post-operative normal PRL levels.

**b**: Re-hospitalization was required.

**c:** Post-operatively, 5 patients were testosterone deficient (central hypogonadism) despite being normoprolactinaemic (3 after surgery alone and 2 on additional DA therapy).

**d:** Post-operatively, central hypothyroidism was reported in one patient but pre-operative assessment was not available.

**e:** No permanent adrenal insufficiency was reported. Adrenal function recovered 6 months after surgery in 29 patients and 18 months after surgery in the remaining ones.