

Therapy Of Endocrine Disease: Surgery In Microprolactinomas: Effectiveness And Risks Based On Contemporary Literature

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1 **SURGERY IN MICROPROLACTINOMAS: EFFECTIVENESS AND RISKS BASED**
2 **ON CONTEMPORARY LITERATURE**

3

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23

24 **Abstract**

25 Microprolactinomas are the most common pituitary adenomas. In symptomatic patients,
26 dopamine agonists are the first treatment of choice; when cabergoline is used, biochemical
27 control rates between 85 and 93% have been reported. Long-term treatment is needed in most
28 of the cases with compliance, patient convenience and potential adverse effects representing
29 areas requiring attention. Based on the literature published in the last 15 years,
30 transsphenoidal surgery can lead to normal prolactin in the post-operative period in usually
31 71-100% of the cases with very low post-operative complication rates. Surgical expertise is
32 the major determinant of the outcomes and it may be a cost-effective option in young patients
33 with life expectancy greater than ten years (provided it is performed by experienced surgeons
34 at high volume centres with confirmed optimal outcomes). Larger series of patients with
35 adequate follow-up could further validate the place of transsphenoidal surgery (particularly
36 through the endoscopic approach for which long-term results are currently limited) in the
37 management algorithm of patients with microprolactinoma.

38

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

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47 I. Introduction

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

60 Resistance to DA includes a failure to achieve normal PRL on maximally tolerated
61 doses of DA and a failure to achieve tumour shrinkage more than 50% (4). The second
62 criterion would be considered clinically important mainly for macroprolactinomas due to
63 their potential to exert pressure effects to surrounding structures. Decreased number of
64 dopamine receptors 2 (D₂) has been reported in DA resistant prolactinomas but the
65 mechanism of DA resistance has not been completely elucidated (3,4). The prevalence of
66 resistance to DA treatment differs between the various agonists and has is less common in
67 microprolactinomas and in women (3,5,6). The reported rates of PRL normalization in
68 patients with microprolactinoma are around 57% with bromocriptine and 85-93% with
69 cabergoline (5-8) with the latter agent leading to normoprolactinaemia in a significant
70 number of bromocriptine resistant patients (4). A recent meta-analysis suggested that
71 persisting normoprolactinaemia after withdrawal of DA is expected in only 21% of the cases
72 with the probability been higher when cabergoline had been used for at least two years and
73 pituitary MRI had shown normal appearances prior to DA discontinuation (9,10). Side

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

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

93

94 **II. Transsphenoidal surgery for microprolactinomas**

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

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

101

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

103 A summary of the surgical success rates from 45 studies published between 1977-
104 2005 (84.4% of them prior 2000) showed high variability in the achievement of normal PRL
105 (38-100%) possibly reflecting differences in the neurosurgical expertise; the remission rate,
106 as estimated based on the total number of included patients, was 74.7% and the recurrence of
107 hyperprolactinaemia (affected by the variable definitions of cure/recurrence, observation
108 periods and drop-out rates) was 18.2% (4). Studies published during the period covered in
109 this review on patients with microprolactinoma treated with the microscopic transsphenoidal
110 technique and with main indications resistance/intolerance to DAs or patient's choice
111 suggest that biochemical remission with normoprolactinaemia is achieved usually in 71-93%
112 of the cases; serum PRL had been checked shortly after or within the first weeks following
113 surgery (13-24) (Table 1). In a large series of 400 patients treated by the sublabial
114 transsphenoidal approach by a single neurosurgeon, post-operative remission was reported in
115 82% of the cases; information on previous treatment with DAs was not available (14).
116 Raverot *et al.* in a collaborative multicenter study of 43 patients who stopped the DAs one
117 month prior to the operation found a 93% remission rate (18). In two series with 46 (20) and
118 59 (24) patients operated on by two experienced neurosurgeons in a single center, early
119 postoperative normoprolactinaemia was reported in 91% and 78% of the cases, respectively;
120 DAs had been stopped before surgery [at least four weeks in the first and at least two months
121 (in almost half of the patients) in the second study]. Mortini *et al.* in a series of 69 patients
122 operated on in a single centre by two surgeons (21), showed post-operative remission rate
123 75% (off DA for at least two months). Lower post-operative remission rates (40-63%) have
124 been reported in three series with, however, small number of patients (5, 27 and 32)

125 affecting the estimation of the relevant rates (25-27). Most studies with mean/median
126 follow-up period ranging between 12 and 84 months suggest that recurrence of the
127 hyperprolactinaemia is observed between 0 and 13% of the cases (15-17,20,23). In one
128 study, however, recurrence rate of 33% was described during a median observation period of
129 33 months (22). It should be noted that information on the timing of stopping DA treatment
130 was not available in this report and the possibility that the rate of early biochemical
131 remission may also reflect the impact of DA cannot be excluded.

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

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

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

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

165

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

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

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

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

179

180 **iii) Quality of life and costs**

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

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

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

203

204 **III. Conclusions and Future Perspectives**

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

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

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

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

230

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

234

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- 1 **Table 1.** Outcomes of series including patients with microprolactinoma treated by the
2 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 All <40	0	21	DA resistance or intolerance Patient's preference Intratumoural haemorrhage ^a	Mean 144 ^a	18 (86%) ^b	-
(14)	400	-	-	-	-	328 (82%) ^c	-
(25)	27	0	27 Mean 26±7	DA resistance or intolerance Patient's preference	Mean 75±59	17 (63%) ^d	4/17 (24%) ^d
(26)	32	0	32 Mean 31±8	DA resistance or intolerance Patient's preference	Mean 50±32	19 (59%) ^e	-
(15)	24 Median 30 (18-52)	4 Median 39 (18-52)	20 Median 29 (18-46)	Patient's preference (no DA previously)	Median 30 (6-77)	22 (91%)	0/22 (0%)
(16)	18	18 Median 38 (17-69) ^a	0	DA resistance or intolerance Tumour apoplexy Patient's preference	Median 45 (13-121) ^a	15 (83%) ^f	2/15 (13%) ^f
(17)	12 Median 32 (17 - 65) ^a	-	-	DA resistance or intolerance Patient's preference Tumour apoplexy ^a	Mean 39 (1-62) ^a	11 (92%) ^g	1/11 (9%) ^g
(18)	43 Mean 38±13 ^a	-	-	DA resistance or intolerance Patient's preference	Mean 138 ± 46 ^a	40 (93%) ^h	- ^h
(19)	21	-	-	-	Mean 61 (1 - 144) ⁱ	15 (71%) ^j	-
(20)	46 Median 32 (12-69) ^a	-	-	DA resistance or intolerance Patient's preference ^a	Median 12 (3-132) ^a	42 (91%) ^k	3/42 (7%) ^k
(21)	69 Mean 30±1 ^a	-	-	-	Mean 53±4 ^a	52 (75%) ^m	-
(22)	20 Mean 33±3 ^a	-	-	DA resistance or intolerance Patient's	Median 33 ^a	15 (75%)	5/15 (33%) ⁿ

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

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

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a: Data for both micro- and macroprolactinomas.

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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.

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c: The authors use the term "cured microprolactinomas" and no further details are provided. Information on previous DA treatment not reported.

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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).

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e: Information of timing of stopping the DA prior to surgery not available.

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f: Remission was defined as normal PRL without DA for at least 4 weeks before surgery. Recurrence was based on

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detection hyperprolactinaemia during the follow-up period.

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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.

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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.

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i: Data for all adenomas included in this series.

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

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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.

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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.

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n: Information of timing of stopping the DA prior to surgery not available. Recurrence of hyperprolactinaemia occurred within 4 years after surgery.

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p: DAs were stopped the day before surgery. Remission was defined as the resolution of hyperprolactinaemia three months post-operatively.

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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.

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- 1 **Table 2.** Outcomes of series including patients with microprolactinoma treated by the
 2 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	-

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

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

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

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

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

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

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

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

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

24 micro- or a macroprolactinoma. Remission was defined as normal PRL the day after surgery. Information on
25 previous treatment with DAs and timing of stopping it not available.
26 **j:** The series included 418 patients with pituitary adenomas, 79 of whom were operated after tumour recurrence;
27 there was no information if microprolactinomas were included in this group. Remission was defined as normal
28 PRL levels at the latest check and off DA for at least 2 months.
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1 **Table 3.** Pituitary function after transsphenoidal surgery for microprolactinomas.

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Ref.	N	Anterior pituitary hormone deficits	Posterior pituitary dysfunction
Microscopic series			
(26)	32	-	5/32 (16%) Transient DI 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) 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%)	-

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4 **a:** Permanent hypogonadotropic hypogonadism despite post-operative normal PRL levels.5 **b:** Re-hospitalization was required.6 **c:** Post-operatively, 5 patients were testosterone deficient (central hypogonadism) despite being normoprolactinaemic (3 after surgery alone and 2 on additional DA therapy).7 **d:** Post-operatively, central hypothyroidism was reported in one patient but pre-operative assessment was not available.8 **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.

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