

# Trans-sphenoidal surgery for microprolactinoma: an acceptable alternative to dopamine agonists?

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## Abstract

**Aims:** Reported cure rates following trans-sphenoidal surgery for microprolactinoma are variable and recurrence rates in some series are high. We wished to examine the cure rate of trans-sphenoidal surgery for microprolactinoma, and to assess the long-term complications and recurrence rate.

**Design:** A retrospective review of the outcome of trans-sphenoidal surgery for microprolactinoma, performed by a single neurosurgeon at a tertiary referral centre between 1976 and 1997.

**Patients:** All thirty-two patients operated on for microprolactinoma were female, with a mean age of 31 years (range 16–49). Indications for surgery were intolerance of dopamine agonists in ten (31%), resistance in six (19%) and resistance and intolerance in four (12.5%). Two patients were from countries where dopamine agonists were unavailable.

**Results:** The mean pre-operative prolactin level was 2933 mU/l (range 1125–6000). All but 1 had amenorrhoea or oligomenorrhoea, with galactorrhoea in 15 (46.9%). Twenty-five (78%) were cured by trans-sphenoidal surgery, as judged by a post-operative serum prolactin in the normal range. During a mean follow-up of 70 months (range 2 months to 16 years) there was one recurrence at 12 years. Post-operatively, one patient became LH deficient, two patients became cortisol deficient and two became TSH deficient. Out of 21 patients tested for post-operative growth hormone deficiency, 6 (28.6%) were deficient. Five patients developed post-operative diabetes insipidus which persisted for greater than 6 months. There were no other complications of surgery. The estimated cost of uncomplicated trans-sphenoidal surgery, and follow-up over 10 years, was similar to that of dopamine agonist therapy.

**Conclusion:** In patients with hyperprolactinaemia due to a pituitary microprolactinoma, trans-sphenoidal surgery by an experienced pituitary surgeon should be considered as a potentially curative procedure. The cost of treatment over a 10 year period is similar in uncomplicated cases to long-term dopamine agonist therapy.

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## Introduction

Dopamine agonists have been recognised as medical treatment for prolactinomas for over two decades (1, 2). A review of more than 400 patients with hyperprolactinaemia who were treated with bromocriptine found that 80–90% developed normal prolactin levels or a return of menses (3). Cabergoline, a long-acting dopamine agonist is tolerated in some patients who are bromocriptine intolerant (4) and may be more efficacious (5). Cabergoline was shown to reduce prolactin levels in 114/127 (90%) hyperprolactinaemic patients, of whom 71 had microprolactinomas (6). Twenty-nine patients (23%) described adverse effects. Cabergoline has also been shown to be a successful treatment for patients with microprolactinomas that are bromocriptine and quinagolide resistant, defined as absent or poor response (normalisation of prolactin and or tumour mass shrinkage) to 15 mg bromocriptine for at least 3 months (7). However, dopamine agonists are

not always effective, may have side-effects limiting their use, and the better tolerated ones (such as cabergoline) as yet lack adequate safety profiles to allow licensing in pregnancy.

Trans-sphenoidal surgery is currently seen as second-line treatment for the majority of patients with microprolactinomas, although this is a controversial issue (8). Most patients will be treated with dopamine agonists as initial therapy, with surgery reserved for those who either fail to respond or who cannot tolerate treatment. Variable cure rates judged by normalisation of prolactin levels following trans-sphenoidal surgery for microprolactinomas have been reported: 85% (9), 67% (10), 75% (11), 88% (12) and 70% (13). Recurrence rates following trans-sphenoidal surgery for microprolactinomas have been reported as high as 50% of those with initially normal prolactin levels following surgery (9). Other published series have shown lower but still significant recurrence rates: 12% (14), 21% (12) and 17.4% (3).

## Method and patients

Thirty-six patients were identified from the database of endocrine patients as having trans-sphenoidal surgery for microprolactinomas between 1976 and 1997. Four patients were excluded, two because of insufficient data, and two because they were operated on elsewhere. The patients were all female, with a mean age of 31 years (range 16 to 49 years). All operations were performed by a single surgeon (CBTA). The mean duration of follow-up was 5.8 years (range 2 months to 16 years, median 4.5 years). A retrospective analysis of the data was performed.

Pituitary microadenomas were diagnosed on the basis of sustained hyperprolactinaemia, with a mean prolactin level of 2933 mU/l (range 1125–6000), and pituitary imaging (either computed tomography (CT) or magnetic resonance imaging (MRI)) in 27 patients, which showed a pituitary microadenoma (diameter 10 mm or less) in 18 patients. There was no significant change in the prolactin normal range (<600 mU/l) during the period of study.

At time of referral, prior to dopamine agonist treatment, 31 patients (96.8%) had menstrual disturbance, galactorrhoea was present in 15 (46.9%) and infertility a presenting problem in 15 (46.9%). Bromocriptine intolerance (such that patients could not continue to take a dopamine agonist at the dose necessary for restoration of menses and ovulation and/or normalisation of prolactin) was the indication for surgery in the majority of cases (ten patients (31%)), and three of these patients were also intolerant of cabergoline. Six patients (18%) were resistant (failure to suppress prolactin to greater than half the starting level, despite escalating doses of dopamine agonist) to bromocriptine, and one was also resistant to cabergoline. Four patients (12%) were resistant and intolerant of bromocriptine. Two patients were from countries where dopamine agonists were not easily available, and in others, where specified, the indication was patient preference. Nineteen patients (59%) received pre-operative treatment with dopamine agonists, and this was bromocriptine in the majority of cases, although one patient also received quinagolide and four also tried cabergoline. The duration of treatment varied from 10 days to 10 years, but was intermittent in many patients.

The data were analysed using the chi-squared test and Wilcoxon's rank sum test, using  $P < 0.05$  as significant.

## Results

### Surgical outcome

Surgical cure, following selective adenectomy, defined as a post-operative prolactin in the normal biochemical range in the absence of dopamine agonist therapy, was achieved in 25 (78%) patients (Table 1). The mean

**Table 1** Surgical outcome.

	Number of patients	Mean prolactin (mU/l)
Remission	25 (78%)	253
Uncured	7 (22%)	1897
Recurrence	1 (4%)	3885

post-operative prolactin level was 253 mU/l (range, from not detected to 470 mU/l) in the cured group and 1897 mU/l (range 1772–1850) in the uncured group.

Surgery was well-tolerated, and was complicated by diabetes insipidus that was temporary in two patients and permanent in five (15.6%).

One patient with a normal post-operative prolactin (346 mU/l) had evidence of persistent hyperprolactinaemia (prolactin 817 mU/l) and galactorrhoea at 3 months. She underwent a second operation that was curative.

One patient developed recurrent hyperprolactinaemia at 12 years with no evidence of tumour on imaging.

Two patients had a suboptimal cortisol response during an insulin tolerance test post-operatively, but all other patients had normal adrenocorticotrophin (ACTH) reserve as judged by an insulin tolerance test in 26 patients, short synacthen test in 2 patients, and random cortisol >600 nmol/l in 1 patient. There was no information available on one patient.

Two patients were thyrotrophin (TSH) deficient post-operatively and one developed primary hypothyroidism, but the remainder had normal thyrotroph function. Out of 21 patients tested for growth hormone reserve with an insulin tolerance test, 6 (28.6%) were growth hormone deficient. Nine patients had luteinising hormone (LH)-releasing hormone tests, and 17 patients had LH in the normal range. Two had day 21 progesterone levels checked and these were both compatible with ovulation. There was no information on LH reserve in three patients, although one of these was documented to be having regular periods. Only one patient (cured) had post-operative LH deficiency.

Twenty-one of 28 patients (75%) were documented to be menstruating regularly, two were taking the oral contraceptive pill and two had other causes for amenorrhoea (hysterectomy, absent vagina). Ten of these patients were known to have had successful pregnancies following surgery. Three patients were not menstruating regularly and these were all uncured.

### Characteristics of patients who were not cured by surgery

Seven patients (22%) were not cured by surgery (Table 2), although one of these patients was 'clinically' cured with restoration of menses, ovulation and fertility. There was no significant difference between pre-operative prolactin in the cured (2717 mU/l) and uncured (3704 mU/l) groups.

**Table 2** Characteristics of patients cured and not cured by surgery.

	Cured	Uncured
Number of patients	25/32 (78%)	7/32 (22%)
Pre-operative prolactin (mU/l)	2717	3704
Pre-operative bromocriptine	14/25 (56%)	5/7 (71%)
Tumour detected on imaging	14/25 (56%)	4/7 (57%)
Tumour detected by surgeon	22/22 (100%)	6/6 (100%)
Confirmatory histology	14/19 (74%)	1/5 (20%)

There was no significant difference in terms of pre-operative bromocriptine treatment when the uncured group were compared with the cured patients: 4 patients (80%) had received pre-operative bromocriptine for between 3 weeks and 6 months, whereas 14 (73.7%) of the cured patients had received bromocriptine prior to surgery, for a period of 10 days up to 10 years ( $P > 0.05$ ).

Whether a microadenoma was demonstrated on either CT or MRI, or whether a tumour was detected by the surgeon, was not significantly associated with outcome ( $P > 0.05$ ). Neither resistance to treatment with bromocriptine nor intolerance was predictive of lack of cure.

Histology confirmed the presence of pituitary adenoma in 14/19 of the cured patients. Immunostaining for prolactin was confirmatory in 13 cases and unavailable in 1. In contrast, pituitary adenoma was only demonstrated histologically in one of five uncured patients with available histological records, and immunostaining was not performed at this time. Microscopic

examination of the other cases showed normal pituitary gland only.

### Estimated costs

A comparison of costs of trans-sphenoidal surgery or drug treatment is shown in Table 3. This considers a hypothetical patient undergoing surgery and cure with no complications, and followed up for 10 years, and compares this with the cost of a patient receiving treatment with cabergoline 1 mg/week for 10 years.

### Discussion

Our data show that trans-sphenoidal surgery for microprolactinoma is associated with a 78% cure rate and recurrence rate of only 1/25 cases (4%). This cure rate is comparable with other series (9–13) and the recurrence rate of only 4% is lower than that often quoted: 12% (14), 17.4% (3), 21% (12) and 50% (9). There were few complications of surgery: five patients developed permanent diabetes insipidus (15.6%), two developed TSH deficiency, and two had reduced ACTH reserve on insulin tolerance test post-operatively. The commonest post-operative hormonal deficiency was growth hormone in 28.6% of the patients. There are no comparable data on growth hormone deficiency following trans-sphenoidal surgery for microprolactinoma in other surgical series, but it is clearly important to counsel patients about this possibility prior to surgery. It is not clear why the incidence of diabetes insipidus was higher than that found in patients operated on for acromegaly, by the same surgeon

**Table 3** Relative costs of surgery and medical treatment.

	Surgery	Drug treatment
New patient appointment	£77	£77
MRI pituitary	£105	£105
Follow-up appointments in first year		3 × £39 = £117
Pituitary function tests		£60
Inpatient stay (includes pituitary function tests and visual fields)	£2580	
Trans-sphenoidal surgery	£1362	
Antibiotics	£61	
Post-operative assessment (includes pituitary function tests)	£165	
Post-operative MRI	£105	
Post-operative visual fields	£70	
Annual prolactin for:		
5 years	£5	£5
10 years	£10	£10
Outpatient appointments for:		
5 years	£39	£39
10 years	£195	£195
Cabergoline 1 mg/week for:		
5 years		12 × £31.46 =
10 years		£1887.60
Total		£3775.20
5 years	£4725	£2446.60
10 years	£4925	£4534.20

at the same institution over the same time period (5.8%).

A summary of the results from 31 series shows that 872/1224 (71.2%) of patients with microprolactinomas had normal prolactin levels after surgery, although the range varied from 38 to 91% (3). This series reports a recurrence rate of 82/471 (17.4%), so reducing the long-term normalisation of prolactin levels with surgery from this review to 52.8%. Others have reported higher recurrence rates of up to 50% (9), although a further assessment of 57 patients with microprolactinomas showed that although 25 women relapsed with hyperprolactinaemia during a mean follow-up of 3 years, many of the women were asymptomatic, making a clinical remission rate of 75%, 10–20 years after initial successful trans-sphenoidal surgery for microprolactinomas (15). A 10 year follow-up study of 61 patients who underwent trans-sphenoidal surgery for microprolactinoma demonstrated a cure rate of 73% in terms of hyperprolactinaemia, with a recurrence rate of 12% (14). This study, like the series reported by Serri *et al.* (15), showed that recurrences continued to occur up to 10 years post-operatively. It may be that our recurrence rate will rise as the duration of follow-up increases.

A comparison of dopamine agonist treatment showed that 5 of the 7 uncured had received prior unsuccessful treatment with dopamine agonists (intolerance in 4 of 5), compared with 14 of the patients who were cured ( $P > 0.05$ ). These data do not confirm the suggestion that a lack of response to dopamine agonists or poor tolerability is characteristic of an active form of tumour and therefore resistance to surgical cure (16). It is difficult to judge duration of treatment and compliance in retrospective analyses. Many patients had taken bromocriptine intermittently, and true bromocriptine resistance is often difficult to differentiate from intolerance. This may partly explain the difference from the work of Soule *et al.* (16), but it is also important to note that their study included patients with micro- and macroprolactinomas, and that all 11 patients with microprolactinomas had received dopamine agonist treatment pre-operatively. Since it is the patient with a tumour resistant to dopamine agonist treatment, or who is intolerant of such treatment, who is more likely to be referred for trans-sphenoidal surgery, it is important that our data demonstrate that they do not necessarily fall into a group with an adverse prognosis.

It is perhaps surprising that the identification of a microadenoma on pituitary imaging was not significantly associated with cure following trans-sphenoidal surgery. Many feel that an essential pre-requisite to surgery is the finding of a definite lesion on pituitary imaging (10). Trans-sphenoidal surgery in patients with no demonstrable tumour carried a poor success rate of 54% in one series (17). However, approximately 10% of asymptomatic subjects harbour pituitary incidentalomas detectable either at autopsy or on imaging (18, 19), and therefore scans may produce

false positive results (17). Thus based on our data, where tumours were only identified in 18/27 patients imaged, the lack of a demonstrable microadenoma on imaging in a patient with a significantly elevated prolactin level where other causes of hyperprolactinaemia have been excluded, should not alter the decision as to whether to ask an experienced surgeon to operate. In these cases the surgeon is often able to identify a clear microadenoma despite the lack of positive imaging. It is interesting to compare imaging and outcome between the two decades. During the first 10 years, 15/20 patients had CT scans performed. (The remainder had skull X-rays and metrimazole cisternograms.) Only just over half (8/15 (53.3%)) of the scans demonstrated the tumour. During the second decade, all patients had CT or MRI scanning and 10/12 (83%) of these investigations were 'positive', showing the tumour. Interestingly, there was no significant difference in cure rate between the two decades (80 and 75%,  $P > 0.05$ ).

The estimates for cost that we have made take an uncomplicated patient receiving either dopamine agonist treatment or trans-sphenoidal surgery. Clearly lack of cure or hypopituitarism including symptomatic growth hormone deficiency would add significant costs to surgical treatment, while increased dosage requirements or a couple of pregnancies requiring monitoring of visual fields and possibly a post-partum MRI, would increase the cost of medical treatment. We have not compared oestrogen treatment alone as fertility is an important issue for many of these patients, but this would usually be a cheaper option. There is also the possibility of remission in one-third of patients with hyperprolactinaemia following pregnancy (20). It is interesting to note that, despite these caveats, the two modalities of treatment do not differ significantly in terms of cost over 10 years.

This study shows that trans-sphenoidal surgery in the dopamine agonist era, in the hands of an experienced pituitary surgeon, is associated with a high cure rate with few post-operative complications and a low recurrence rate. These data compare favourably with the outcome following dopamine agonist treatment, with the advantage that surgery obviates the need to continue drug treatment which may be associated with unpleasant side-effects and may lack adequate safety data during pregnancy. Clearly we do not advocate trans-sphenoidal surgery for everyone with a microprolactinoma. These data obviously cannot be extrapolated to all centres treating patients with microprolactinomas, as dopamine agonists work well in most cases when prescribed by anyone, in contrast to surgery. However, where there is access to an expert in trans-sphenoidal surgery, and where dopamine agonist tolerance/resistance is a problem, then the option of trans-sphenoidal surgery should be strongly considered. Perhaps the time has come for a randomised trial, or at least the consideration of surgery earlier in the management strategy.

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