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Surgery for prolactinomas: a better choice?

Jürgen Honegger[1] · **Isabella Nasi-Kordhishti**[1] · **Nuran Aboutaha**[1] · **Sabrina Giese**[1]

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Abstract

Purpose Renewed interest in transsphenoidal surgery (TSS) as a therapeutic option for prolactinomas has emerged.

Methods Based on contemporary literature and own experience, the changing role of surgery for treatment of prolactinomas is discussed.

Results Today, TSS is performed by minimally invasive microscopic or endoscopic techniques. Normoprolactinemia is obtained in 71–100% of patients with microprolactinomas by TSS. Almost equal results are found in circumscribed intrasellar macroprolactinomas. In experienced hands, pituitary function is preserved in TSS. The risk of cardiac valve disease is still a concern with ergot-derived dopamine-agonists (DAs) in patients requiring long-term, high-dose dopamine-agonist (DA) treatment. Cost-utility analysis favors TSS over DA treatment. The possible negative impact of DA treatment on future surgical results is still a controversial and unsettled issue. In patients who wish to become pregnant, the advantages of microprolactinoma removal to avoid DAs and macroprolactinoma debulking to avoid symptomatic enlargement during pregnancy should be discussed with the patients. Young patients' age is an argument for surgery to circumvent the unpredictable sequelae of long-term DA treatment. Surgery should be discussed in male gender because of a higher likelihood of DA resistance and aggressive behavior of prolactinoma.

Conclusion Given excellent results of TSS and concerns about medical treatment, the scale of indications for TSS as an alternative to DAs has increased. The patient's wishes concerning a chance at a cure with TSS instead of a long-term treatment with DAs has become an important and accepted indication. With DA medication and TSS, two effective treatment modalities for prolactinomas are available that can be used in a complementary fashion.

Keywords Prolactinoma · Hyperprolactinemia · Transsphenoidal surgery · Dopamine-agonists · Hypopituitarism · Endocrinological outcome

Introduction

With discovery of bromocriptine (BC) in 1965 and subsequent market approval, medical treatment became the therapy of first choice in prolactinomas. Medical treatment was then improved with the introduction of cabergoline (CAB) in the 1990s, a second generation dopamine-agonist (DA) with better efficacy and tolerability compared to BC [1]. Transsphenoidal surgery remained a second-line treatment for those prolactinomas resistant to dopamine-agonists (DAs) or patients who do not tolerate DAs [2–4]. The scope of additional accepted indications for prolactinoma surgery became restricted to some specific clinical circumstances. These included progressive visual loss [2, 5] and spontaneous or DA-induced CSF rhinorrhea [6].

Since the beginning of the new millennium, the pendulum has been swinging back towards surgery for several reasons. New concerns about long-term safety and efficacy of DAs have emerged. It became obvious that most prolactinomas recur once DAs are withdrawn [7]. In parallel, surgical techniques and results have improved with minimal invasiveness, high cure rates and low surgical morbidity.

This review article addresses the evolving role of surgery in the management of prolactinomas. The current indications for transsphenoidal surgery (TSS) are presented and discussed in the context of contemporary literature and personal experience.

✉ Jürgen Honegger
juergen.honegger@med.uni-tuebingen.de

[1] Department of Neurosurgery, University of Tübingen, Hoppe-Seyler-Straße 3, 72076 Tübingen, Germany

Advances of transsphenoidal surgery

The first transsphenoidal operation was performed by Hermann Schloffer in 1907 [8] via a rhinotomy. In the following years, TSS was refined. Sublabial and transnasal approaches avoided external incisions. With the introduction of the operating microscope by Jules Hardy from Montreal in the late 1960s [9], TSS gained worldwide recognition. With magnification under the microscope, microadenomas could be identified and selective adenomectomy with preservation of the pituitary gland became feasible.

A further milestone of microscopic pituitary surgery was the introduction of the so-called "septum-pushover technique" which was first described by Griffith and Veerapen [10] which avoids extensive nasal septum mucosa dissection and removal of the bony nasal septum and guarantees minimal postoperative nasal discomfort and pain.

The concept of pure endoscopic transnasal surgery was introduced by Hae Dong Jho in the 1990s [11]. Subsequently, endoscopy has become a widely accepted alternative to microsurgery for removal of pituitary adenomas.

With microscopic and endoscopic pituitary surgery, two minimally invasive techniques with equally low complication rates are available for surgical treatment of pituitary adenomas [12]. With attention to gentle nasal dissection, postoperative nasal packing can be avoided. Nasal breathing is immediately restored after surgery which is much appreciated by the patients.

Outcome of transsphenoidal surgery in prolactinomas

Surgical cure rates in prolactinomas

Almost all operations for prolactinomas are performed by TSS [13] and the transsphenoidal route is the only appropriate approach to microprolactinomas. A recent review on microprolactinoma surgery based on literature published in the past 15 years showed favorable rates of postoperative normoprolactinemia in 71–100% of the cases [14]. Remission rates ranged from 71 to 93% for microscopic series and from 82 to 100% for endoscopic series [14].

Best results have been reported from single-center series and from centers with a high caseload of pituitary operations [14, 15]. An 82% remission rate was reported for the largest series of 400 microprolactinomas operated by one surgeon [16]. A literature review showed mean remission rates of 77% in centers with a low caseload of microprolactinoma operations and of 91% in centers with a high caseload [15]. These results underline the importance of continuous surgical experience. The results also indicate that remission rates for microprolactinoma in pituitary centers of excellence compare favorably with the remission rates of DA therapy.

In prolactinomas, surgical cure rates are inversely correlated to tumor size and preoperative prolactin (PRL) level [3, 4, 13, 17]. For macroprolactinomas, overall surgical cure rates up to 74% have been reported [18]. The results are particularly good in enclosed macroprolactinomas [19]. In this subtype of prolactinomas, early remission in 95% [77/81] and long-term remission in 89% [72/81] of the cases has been found [18]. In intrasellar macroprolactinomas, cure rates comparable to microprolactinomas have been reported [13]. In contrast, surgery alone is rarely curative in giant prolactinomas (≥ 4 cm) [3, 17].

The cure rate dramatically drops with invasive character of prolactinomas [20]. Still, normoprolactinemia in around 30% of invasive prolactinomas has been reported [3, 18, 21]. Kreutzer et al. [3] have nicely shown the relation of tumor extension and remission rates. They found early remission in 78.1% of intrasellar prolactinomas (including microprolactinomas), in 59.4% of suprasellar prolactinomas without visual deficits, in 13.5% of suprasellar prolactinomas with visual deficits, in 24.3% of parasellar and/or sphenoidal prolactinomas, and in 0% of giant prolactinomas.

Similar, recurrence rates are also correlated to prolactinoma size [2, 3]. Kreutzer et al. [3] reported on a recurrence rate of 7.1% in microprolactinomas, of 11.9% in intrasellar prolactinomas (including microprolactinomas), of 24.2% in suprasellar prolactinomas without visual deficits, and of 33.3% in suprasellar prolactinomas with visual deficits with a median follow-up of 12 months. Interestingly, a long-term study after TSS for microprolactinoma with follow-up of at least 5 years did not show any recurrence among 97 patients [2]. We have to mention that the reported recurrence rates are heterogeneous with a wide range from between 0 and 58% [13, 14]. In our experience, an early postoperative PRL level in the low normal range indicates complete removal and a low risk of recurrence.

Preservation of pituitary function in prolactinoma surgery

As mentioned earlier, an important goal of TSS is selective adenomectomy with preservation of pituitary function. Today, the rate of postoperative pituitary failure is low. Mainly patients with large adenomas are at risk while the rate of pituitary failure is very low in small adenomas. In the large study on postoperative hormonal loss from Santa Monica [22], new postoperative hypopituitarism occurred in 0% of patients with adenoma diameters < 20 mm, and in 13.6% with adenoma diameters ≥ 30 mm.

In the large prolactinoma series from Erlangen [3], the rate of new postoperative hypopituitarism was 7% (12/171) at follow-up. None of the patients suffered from permanent

postoperative diabetes insipidus. Surgery-related hypopituitarism exclusively occurred in macroprolactinomas.

Microprolactinomas prevail in female patients in childbearing age. Particularly in patients with desire to have children, utmost attention must be paid to preserve pituitary function when performing pituitary surgery. In all but one study on microprolactinoma surgery, the outcome of pituitary function was most favorable [14]. The majority of series reported 0% of postoperative anterior pituitary failure. Permanent postoperative diabetes insipidus rarely occurred [14].

On the other hand, improvement of pituitary function following transsphenoidal adenoma surgery is relatively frequent [22]. Kreutzer et al. [3] observed postoperative improvement of preoperatively impaired pituitary function in 35% of prolactinoma patients.

Regarding hyperprolactinemia-related amenorrhea in female patients, menstrual cycles are usually restored if postoperative normalization of PRL is obtained [18].

Complications

The complication rate of transsphenoidal prolactinoma surgery is low. In the Erlangen series on 212 consecutive prolactinoma cases including microprolactinomas and macroprolactinomas, the mortality rate was 0% and the morbidity rate was 3.8% [3] e.g. one patient with a nasal bleeding requiring operative electrocauterization, two patients with meningitis, one patient with deep venous thrombosis, two patients with febrile sinusitis, and two patients with a postoperative CSF leak. In the Milano series on 120 consecutive transsphenoidal operations for prolactinomas [13], no operative mortality occurred. Major morbidity occurred in six patients (5%) and consisted of permanent visual damage in one eye, transient worsening of vision in one eye, deep venous thrombosis, epistaxis requiring emergency nasal tamponade, mucocele requiring evacuation, and renal colic in one patient each. In a series on 138 female patients undergoing TSS for prolactinoma, no mortality and no major complications occurred [18]. In the review on transsphenoidal microprolactinoma surgery, the mortality rates were 0% both for microscopic and endoscopic series [14]. Other neurosurgical complications occurred in 0–1.8% of microscopic series and in 0% of endoscopic series [14].

Concerns regarding DA treatment

Side effects and resistance

DA treatment is effective in prolactinomas with a higher success rate in microprolactinomas compared to macroprolactinomas [23]. The second generation DA cabergoline (CAB) is superior compared to bromocriptine (BC) in terms of efficacy and tolerability [1]. However, adverse effects are relatively frequent. Typical side effects are orthostatic hypotension, nausea, headache, dizziness, vertigo, abdominal discomfort or pain, constipation, weakness, fatigue, nasal obstruction, and psychiatric disorders [1, 24]. In the study by Webster et al. [1] who compared CAB and BC in a double-blind fashion, 68% of women on CAB and 78% of women on BC reported adverse events. However, adverse events occurred in only 15–20% of patients in each group beyond the first 2 weeks of treatment. DA treatment had to be discontinued because of side effects in 3% of patients on CAB in contrast to 12% on BC. In the Belgian retrospective multicenter study on CAB treatment of hyperprolactinemia [23], 8.5% (38/455) of the patients reported on minor DA-related side effects and 4% (18/455) on major or persisting symptoms. In a study from Leiden on the long-term outcome of patients with macroprolactinomas initially treated with DAs, side-effects were reported in 42% due to DA treatment and 18% had to discontinue treatment due to intolerance [24].

Primary and secondary resistances are another concern of DA treatment. An association of resistance to CAB with large initial prolactinoma size, invasive character and male gender has been shown [25]. In the above mentioned study from Leiden [24], 23 out of 72 patients initially treated with bromocriptine (n = 30), quinagolide (n = 26), cabergoline (n = 9), or terguride (n = 7) eventually underwent surgery because of resistance to DAs. According to the literature, resistance to DAs occurs in one-third of patients with macroprolactinomas treated with BC, and in 10–20% of those treated with CAB [24]. Surgery becomes necessary as a second line treatment in 14–38% of prolactinoma patients. However, systematic data on the frequency of secondary resistance to DAs are still scarce.

Cardiac valvular fibrosis

Studies in Parkinson's disease demonstrated a dose-dependent risk of restrictive valvular heart disease with the use of ergot-derived DAs, as for example CAB [26]. The complication is mediated by the serotonin receptor subtype 5-HT_{2B} whose stimulation results in fibrotic changes causing valve regurgitation.

Although higher doses of DAs are administered in Parkinson's disease than in treatment for hyperprolactinemia, the endocrinologists treating prolactinoma patients with DAs were alarmed. Subsequently, extensive research focused on the issue. While most studies did not find an increased risk of clinically relevant valvulopathy, some studies demonstrated increased valvular regurgitation under DAs [27].

A concern is the young age of most prolactinoma patients who might need lifelong DA treatment. DA intake could be required over decades. The treatment duration of the available studies on this issue is limited ranging from 44.8 to

79 months in a literature review [27]. Prospective studies have not shown an increased risk of valvular dysfunction. However, the prospective phase of these studies only ranged between 24 and 62.5 months [28, 29] and the use of the term "long-term" study does not appear to be appropriate for these studies.

Valassi et al. [27] concluded from their review of the literature that caution must be exercised, especially in patients requiring long-term, high-dose DA regimens.

Negative impact of DA treatment on future surgery

Inferior surgical remission rates after pre-treatment of microprolactinomas with BC were first described by Landolt et al. [30]. Postoperative normoprolactinemia was found in 81% of microprolactinoma patients without previous BC treatment but in only 33% following BC. Among patients with previous BC, results were significantly inferior if BC intake exceeded 1 year. The authors concluded that BC should not be used in patients with microprolactinomas unless the patient and his physician accept that such treatment may render later surgery less effective.

In a study on 32 female patients undergoing surgery for prolactinoma, the major independent factor associated with favorable outcome in terms of remission was the absence of preoperative DA therapy [31]. Postoperative remission was achieved in 90% of the patients who did not receive DA therapy compared to 45.5% who were treated with DAs prior to surgery.

Fibrosis secondary to DA treatment is discussed as a main reason for impaired surgical results [30–32]. Apparently, fibrosis is less pronounced following CAB treatment than following BC treatment. In the study performed by Menucci et al. [32], 77% of prolactinomas previously treated with BC were documented with fibrous consistency according to the operative notes while 22% of those previously treated with CAB were fibrous. In that study, only one of the patients with fibrous prolactinomas versus 37% of non-fibrous prolactinomas were brought into remission with surgery.

It has to be mentioned that the issue of DA pre-treatment is still controversial. Other studies have not found a negative influence of DA treatment on outcome of prolactinoma surgery [13, 18, 19]. However, having the concern of reduced surgical success rate in patients with previous DA treatment in mind, upfront TSS for prolactinoma should be discussed at initial presentation with each patient in an individualized manner.

Superior control of hyperprolactinemia with transsphenoidal surgery in addition to DA

Primeau et al. [19] analyzed the outcome of TSS in 25 patients suffering from DA-resistant prolactinomas. Most of them were pre-treated with CAB. Ten of them were brought into remission by surgery without the need of postoperative DA administration. Among the 15 patients who needed postoperative DA treatment, a significant reduction of the lowest PRL level on DAs was obtained by surgery (mean PRL on DAs: preoperative 70 ng/ml versus postoperative 26 ng/ml). This higher efficacy was observed with a significant lower mean dose after surgery (mean CAB dose: preoperative 2.4 mg/week versus postoperative 1.4 mg/week). In 7 out of the 15 patients, preoperatively elevated PRL was normalized on DA treatment after surgery. Interestingly, the authors observed the same percentage of PRL reduction under DA when preoperative treatment with DA and postoperative re-commencement with DA were compared. A significant debulking effect was also reported from a multicenter study of 92 patients resistant to CAB [25]. In a subgroup of patients who received CAB before and after surgery treatment, surgery resulted in a significant reduction in PRL levels while reducing the CAB dose by 50%.

These findings indicate that PRL reduction by surgery is in any case beneficial. PRL levels are either lowered under postoperative maintenance of DA or DA can be reduced in dose or even be withdrawn after surgery.

Quality of life (QoL) has been assessed in women with microprolactinomas under DA treatment using the short form-36 health survey (SF-36) [33]. QoL was inversely associated with the PRL levels. The patients with normal PRL levels had superior QoL in all categories except for the category "physical role" than those patients with elevated PRL. The authors emphasized the importance of providing adequate disease control in order to avoid the adverse consequences of hyperprolactinemia on QoL. The study underlines that additional surgery should be considered if residual hyperprolactinemia persists under DA treatment.

CSF leakage

Invasive prolactinomas frequently erode the bony structures of the skull base but the defect is plugged by the tumor mass. CSF leakage is a well-known and severe complication of DA treatment in this type of prolactinomas. Once tumor shrinkage occurs under DAs, CSF may escape through the emerging gap and rhinorrhea occurs. CSF leakage can also occur spontaneously in prolactinomas invading the skull base. A nasal CSF fistula may precipitate the potentially life-threatening sequelae of meningitis, encephalitis and pneumencephalus [34]. From 1980 to 2011, 42 prolactinomas with spontaneous or DA-induced CSF-leakage have been reported in the literature [6]. In macroprolactinoma, an incidence of CSF rhinorrhea as high as 8.7% has been reported [35]. Conservative management is rarely successful. Reduction or cessation of DA therapy has been attempted but CSF leakage

commonly recurred once medical therapy was re-started [6]. CSF leakage requires surgical repair which is mostly performed by a transsphenoidal approach [6]. In nearly 90% of pituitary adenoma patients with spontaneous or medication-induced rhinorrhea, surgical repair was eventually required. Meningitis without CSF-rhinorrhea as a presentation of invasive macroprolactinoma has also been described and surgical repair of the skull base defect was required [36]. In view of the existing literature, surgical skull base repair is mandatory in prolactinomas if spontaneous or DA-induced CSF leakage occurs.

Management of prolactinoma during pregnancy

In female patients with prolactinoma under DA therapy, the most common attitude is to withdraw DA once pregnancy has been confirmed. Short-term exposure to BC or CAB has not been shown to increase the risk for spontaneous abortions, multiple pregnancies, or congenital malformations with reported experience for BC in > 6000 females and for CAB in > 900 females. Administration of BC or CAB throughout pregnancy should be considered with caution as data on extended use during pregnancy are still limited [37].

During pregnancy, high estrogen levels produced by the placenta are responsible for lactotroph hyperplasia preparing for post-partum lactation. Accordingly, estrogens stimulate PRL-secreting adenoma cells which can result in tumor growth. The risk of symptomatic enlargement with progressive headache and/or visual decline during pregnancy is only 2.4% for microprolactinoma [38]. However, the literature shows a 21% risk of symptomatic macroprolactinoma enlargement during pregnancy [38]. The risk is particularly high in macroprolactinoma with suprasellar extension. One option would be to demonstrate tumor response with DAs, to stop treatment after conception and to re-initiate DAs in those patients with symptomatic re-growth. It is easily understandable that the circumstances of symptomatic enlargement and re-commencement of DAs are troublesome for an afflicted pregnant woman. Therefore, pre-pregnancy debulking of macroprolactinoma appears an alternative and successful strategy to prevent symptomatic enlargement. If TSS is performed prior to pregnancy, the risk of symptomatic enlargement in macroprolactinomas is reduced to only 4.7%.

Given the high cure rate, TSS is also a successful option for females with microprolactinoma before they fulfill their wish to become pregnant. It enables becoming pregnant without DA medication and an unburdened pregnancy. Neurosurgeons are aware of an increasing tendency of endocrinologists to refer female patients with newly diagnosed microprolactinoma and desire for pregnancy to undergo TSS prior to conception.

Cost-effectiveness: prolactinoma surgery vs DA treatment

Turner et al. [39] performed a cost-comparison of prolactinoma surgery versus DA treatment in the setting of the UK health system. For hypothetical patients with uncomplicated, curative surgery or with medical treatment using 1 mg CAB per week, comparable costs of 4925 £ for surgery and 4534 £ for CAB treatment were found during a follow-up of 10 years. Surgery is associated with high upfront surgical costs and inpatient stay while DA treatment is associated with accumulating, on-going costs. For the described setting, it means that surgery is cheaper compared to medical treatment with a follow-up greater than 10 years. Jethwa et al. [40] used a theoretical model with a 2-armed decision tree to assess the cost-effectiveness of microscopic transsphenoidal surgery (mTSS) and endoscopic transsphenoidal surgery (eTSS) versus medical therapy in the management of microprolactinoma in the United States. Cure rates of DA treatment were obtained from the literature. Surgical cure rates were obtained from series by experienced pituitary surgeons and surgical complication rates were obtained from those series that reported on surgical outcome. The costs were analyzed from the perspective of the U.S. health care third-party payer. At the 5-year time horizon, the expected costs for mTSS were $13,650, for eTSS $15,473, for CAB $19,621, and for bromocriptine $16,580. At the 10-year time horizon, the expected costs for mTSS were $15,029, for eTSS $16,576, for CAB $31,201, and for BC $24,845. At both time horizons, DA treatment was found to be more costly and less effective than TSS. The authors describe, as a limitation of their study, that the decision analysis model is a simplified framework and that the findings may not be generalized to all patients with prolactinomas and to different economic environments in other countries [40].

Zygourakis et al. [41] performed a real-life cost-utility analysis of surgical versus medical treatment for prolactinomas and calculated the entire actual costs of care at the University of California, San Francisco. The basic assumption was a 60% surgical response rate and an 80% medical response rate. For all calculated ages of diagnosis (20–80 years), surgery was cheaper and produced higher quality-adjusted life years (QALYs) compared to medical treatment with CAB. Only with an assumed, theoretical surgical cure rate ≤ 30%, a preference for CAB over surgical treatment was found.

Surgery was superior to BC in terms of QALYs for all age groups and cheaper if diagnosis was made at the age of 40 years or younger.

Summary of indications for surgery

The classical indication for TSS in the DA era is resistance or intolerance to DA medication [2–4]. If both DA and surgery are not sufficiently effective, fractionated radiotherapy or radiosurgery should be considered.

Patient preference has emerged as an indication for surgery. In 2006, the guidelines of the Pituitary Society described that "In centers with experienced neurosurgeons, the possibility of cure by surgery versus long-term DA therapy should be discussed with the patient, and patient preference is also an indication for surgery" [42]. This statement provided official approval to enlarge the indication for surgery in prolactinomas. The personal wish of the informed patient became an important indication for first line TSS in prolactinoma patients [4, 43]. Surgery should particularly be considered in microprolactinomas where a cure rate of about 90% can be anticipated [14]. We give the advice to perform surgery only if the microprolactinoma is well-defined on magnetic resonance imaging (MRI) which is a pre-requisite for surgical success. Surgery can also be considered in circumscribed macroprolactinomas given the relatively high cure rates [18]. In contrast, surgery is not primarily indicated in large prolactinomas with invasive character due to the low cure rate [3] and the increased risk of surgery [17] and primary DA therapy is preferred in this subtype of prolactinomas.

Prolactinomas in male patients behave more aggressively and show an increased likelihood of resistance to DA treatment [25]. Hence, male gender is a further argument that could influence the decision in favor of surgery [44].

We consider young patient's age as an important aspect to offer surgical treatment in order to minimize the dose of DAs, to achieve best possible control of hyperprolactinemia and to avoid the individually unpredictable sequelae of long-term DA treatment [14, 40].

The patients' wish to become pregnant is a re-enforcing argument if surgery is considered [2, 18]. In microprolactinomas, surgery offers a high likelihood of cure and the opportunity to become pregnant without DA medication. In macroprolactinomas, pre-pregnancy debulking significantly reduces the risk of symptomatic enlargement during pregnancy [38]. The alternative strategy in macroprolactinoma is withdrawal of DA once pregnancy has been confirmed and re-commencement in case of symptomatic prolactinoma enlargement during pregnancy.

Surgery is indicated if progressive visual loss occurs in large prolactinomas in order to decompress the optic chiasm [2, 5]. Particularly in the presence of cystic prolactinomas or in hemorrhagic or ischemic pituitary apoplexy, rapid relief of the optic chiasm is unlikely under DAs.

In our opinion, surgical repair of the skull base defect together with prolactinoma resection is mandatory if a spontaneous or DA-induced nasal CSF leak occurs.

Conclusion

Transsphenoidal surgery has regained acceptance for the treatment of prolactinomas and is an option for a wide scale of prolactinoma subtypes. Surgical experience is an important determinant of the outcome and surgery for prolactinomas should be performed by experienced pituitary surgeons.

With DA medication and TSS, two effective treatment modalities for prolactinomas are available that can be used in a complementary fashion. The treatment concept for each individual prolactinoma patient should be defined by an interdisciplinary team. The patient should be widely informed about the therapeutic options with their pros and cons and the patient's preference should be taken into consideration for decision making.

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