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Adam Mamelak

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REVIEW



Surgery as a first-line option for prolactinomas

Adam Mamelak

Surgical Director, Pituitary Center & Center for Minimally Invasive Skull Base Surgery, Cedars-Sinai Medical Center, Los Angeles

ABSTRACT

Introduction: Treatment of prolactinomas with dopamine agonists has been the established first-line treatment option for many years, with surgery reserved for refractory cases or medication intolerance. This approach may not be the best option in many cases.

Areas covered: Review of the epidemiology, biology, and treatment options available for prolactinomas, including best available data on outcomes, costs, and morbidities for each therapy. These data are then used to propose a 'surgery-first' treatment approach for a subset of prolactinomas as an alternative to primary medical management.

Expert opinion: Based on the available data, there is a strong rationale that transsphenoidal surgery should be considered a first-line treatment option for both micro- and macro-prolactinomas that do not demonstrate high grade cavernous sinus invasion on MRI imaging, with dopamine agonists administered as a secondary therapy for tumors not in remission following surgery, and for giant tumors. This 'surgery-first' approach assumes the availability of skilled and experienced pituitary surgeons to ensure optimal outcomes. This approach should result in high cure rates and reduced DA requirements for patients not cured from initial surgery. Further, it will reduce medical costs over a patient's lifetime and the chronic morbidities associated with protracted dopamine agonist usage.

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1. Introduction

Despite prolactinoma being the most common hormone secreting pituitary tumor [1] it is often among the least commonly operated, ranging from 7% to 20% of tumors in several large series [2–5]. This observation is historically attributed to both the efficacy of non-surgical treatment by dopamine agonists (DA) as well as a prevalence for later term recurrence following initial remission. The goal of this review is to reevaluate the most current data on this topic and determine if indeed the role for surgery has been underestimated.

2. Epidemiology and clinical presentation

Pituitary adenoma is the third most common brain tumor [6]. The prevalence of pituitary adenomas in the general population is surprisingly high. Prevalence based on autopsy studies [7] and incidental identification on MRI studies both suggest that approximately 10–20% of the general population harbor an adenoma [8]. The overwhelming majority of these tumors are incidental microadenomas (>99%), with very low growth potential. Immunostaining data from autopsy specimens suggests that the majority of these 'incidentalomas' are lactotroph (i.e. prolactin producing) tumors [7]. The prevalence of clinically significant pituitary adenomas is far lower. Population studies indicate that symptomatic tumors occur in approximately 1 in 865 to 1 in 2628 people [9]. Several large epidemiological studies, largely from European countries with national health care registries aimed at detecting clinically

symptomatic adenomas indicate a prevalence ranging from 0.49% to 1.15% of the population [10–16]. Tumors with a cross-sectional diameter greater than 10 mm are considered macroadenomas, while those smaller than 10 mm considered microadenomas. This distinction has practical significance because microadenomas have a low probability of growing over extended periods of time, while the majority of macroadenomas will grow [8,9,17,18]. Therefore, macroadenomas are more likely to produce compressive symptoms such as visual deficits or hormonal deficits, while only microadenomas that secrete excess hormone tend to have clinical relevance.

It is estimated that about two-third of pituitary adenomas are secretory and one-third are non-secretory (commonly referred to as nonfunctioning) [19]. Of note, many nonfunctioning adenomas demonstrate immunostaining for hormones. These include the most common types of nonfunctioning adenomas: gonadotroph (LH and/or FSH); silent corticotrope (ACTH positive); silent somatotroph (GH) and combinations of these. Amongst tumors that produce excess bio-active hormones prolactinomas (PRL secreting) are the most common, representing 46–66% of tumors [13–16]. In turn this also makes prolactin (PRL) secreting tumors the most common hormonally active tumor. Microprolactinomas (microadenomas that produce PRL) have a prevalence of approximately 40 per 100,000 people, and macroprolactinomas 10 per 100,000 [20]. Because macroadenomas have a propensity to grow over time, they can produce a variety of symptoms including hormonal deficiencies due to gland compression, visual defect due to optic nerve

Article highlights

- Dopamine agonists are established first-line therapy for the treatment of prolactinomas
- Prolactin levels are normalized in 73–96% of patients with treated with dopamine agonists, and tumor shrinkage is observed in 47–97%
- Long term dopamine agonist withdrawal after prolactin normalization is accomplished in only 16–21% of patients, often leading to protracted or even life-long use.
- Transsphenoidal surgical cure rates for microadenomas range from approximately 65–93% (up to 100% in some reports), and for macroadenomas approximately 45–60%, with patients in both groups who were not cured requiring less DA to achieve long-term remission.
- Transsphenoidal surgery for prolactinoma is very safe, with new hormonal deficiencies reported in less than 3% of patients, and major morbidity and mortality below 1%.
- Extent of cavernous sinus invasion, not tumor size, is the single most important independent primary predictor of surgical remission, with high rates of remission in tumors with low grade cavernous sinus invasion.
- Transsphenoidal surgery may be a more cost effective, easier, and equally effective treatment for prolactinomas without cavernous sinus invasion. It should be considered a first-line treatment in appropriate situations and when expert pituitary surgery is available.

compression, diplopia, hydrocephalus, and a variety of other mass-effect related phenomena. In contrast, microprolactinomas typically only produce symptoms related to excess PRL. The detection of symptomatic prolactinomas varies dramatically between sexes, predominantly due to the presence of overt symptoms in pre-menopausal women, and the relative lack of symptoms in men until tumors are larger. Women are most likely to be diagnosed with a prolactinomas in their 30s, while in men in their 50's [14]. Furthermore, while microadenomas predominate in woman (85%), macroadenomas represent 80% of PRL-secreting tumors in men. This disparity may reflect a different underlying biology of these tumors in men, making them more aggressive and prone to growth [21,22]. Alternatively, there may be a detection bias for identifying more aggressive tumors in men simply because if they remain small, they are unlikely to come to clinical attention. Pre-menopausal women come to medical attention due to secondary oligomenorrhea, amenorrhea and galactorrhea [23,24]. In contrast, post-menopausal women may be more difficult to detect early [20,25,26]. In the absence of these early signs attributable to elevated PRL, men often only come to attention due to compressive etiology such as visual loss, or hypogonadal symptoms of diminished libido, erectile dysfunction, or weight changes [27].

3. Overview of prolactin biology

Cells within the anterior pituitary gland are subdivided based on their secretory hormones. There are specific cell types in the gland cells that secrete adrenocorticotrophic hormone (ACTH), gonadotrophs (LH and FSH), prolactin (PRL) growth hormone (GH) and thyroid-stimulating hormone (TSH). Pituitary stem cells give rise to 3 main lineages. Differentiation is determined by the expression of transcription factors for lineage commitment and terminal differentiation. Cell containing the POU1F1 gene express the transcription

factor protein PIT1 and differentiate into GH, PRL, and TSH expressing cells while those expressing the TBX19 gene and TPIT transcription factor differentiate into ACTH secreting cells. LH and FH secreting cells derive from cells expressing the SF1 gene and associated SF01 transcription factor. Thus, prolactinomas arise from PIT1 expressing stem cells. (See [28] for an excellent overview).

Prolactin is a 22 kilodalton peptide produced by lactotroph cells in the anterior pituitary gland [29]. Prolactin, via interaction with its transmembrane receptor PRLR, stimulates the mamillary cells in breast tissue to hypertrophy and proliferate, resulting in galactorrhea and gynecomastia [30]. In addition, it suppresses gonadotroph production resulting in diminished estrogen and progesterone in women, and testosterone in both men and women [31]. Over 300 discrete physiological functions have been related to PRL production [32–34]. Lactotroph cells preferentially express dopamine receptor type 2 (D₂R). Under normal conditions hypothalamic dopamine transmitted to the anterior pituitary via the portal system binds to D₂R and inhibits PRL synthesis and lactotroph proliferation. High levels of circulating estradiol, such as seen in pregnancy, inhibit dopamine production, in turn leading to increased PRL secretion and lactotroph cell proliferation. Pathological hyperprolactinemia predominately results in oligo- or amenorrhea in menstruating females and can also cause infertility and galactorrhea. In males it typically causes diminished testosterone production and associated symptoms of hypogonadism.

Prolactinoma can be associated with genetic syndromes [35]. Multiple endocrine neoplasia type I (MEN1) is the most common one. Heterozygous inactivating mutations have been found in 90% of cases with loss of heterozygosity at 11q.p13. Approximately 30% to 40% of patients with MEN1 develop pituitary tumors of which approximately 60% are prolactinomas [36,37]. Less common genetic syndromes in which prolactinomas can occur include familial isolated pituitary (FIP) adenoma. The genetic cause of this syndrome is poorly defined with greater than 90% of FIP families having no clear gene identified. The AIP gene has been identified in 10% [38]. Most recently, a somatic mutation in splicing factor 3 subunit B1 has been associated with tumors demonstrating higher levels of prolactin and shorter progression free survival [39].

4. Causes of hyperprolactinemia

Disruption of tonic outflow of dopamine from the hypothalamus to the pituitary gland through the pituitary stalk portal venous system reduces the normal inhibitory influence of dopamine on lactotrophs. In turn this elevates serum PRL levels due to increased production of PRL by lactotroph ('stalk effect') [40]. Stalk effect typically attributable to compression of the gland by a nonfunctioning adenoma, Rathke's cleft cyst, or other sellar mass, is a well-established cause of hyperprolactinemia [41]. Compression of the gland presumably inhibits dopamine outflow from the portal system in turn resulting in elevated prolactin. Interestingly, there is no clear correlation between the size of the tumor, degree of gland compression, or degree of stalk deviation, and measured levels

of hyperprolactinemia [42]. Medication such as anti-psychotics, anti-depressants, or anti-emetics can also cause hyperprolactinemia [43] as can chronic renal failure, and other illnesses [31]. These non-tumoral causes of hyperprolactinemia only produce modest elevations in serum prolactin.

Because stalk effect from non-PRL secreting tumors is common, and nonfunctioning adenomas are almost as common as prolactinomas, it is critical to differentiate between these two to determine correct therapy. Many studies have been looked at the relationship between prolactin level and tumor type [44–46]. Current guidelines suggest that a prolactin level above 250 µg/L is diagnostic of a prolactin secreting macroadenoma, with levels about 1000 µg/L commonly observed in giant tumors [43–47]. Microadenomas typically present with levels in the range of 50–150 µg/L [20]. However, there is reasonably strong data to suggest that lower levels of prolactin can differentiate a prolactin secreting microadenoma from a non-secreting tumor. For example, in a series of 226 nonfunctioning adenomas, 39% had pre-operative elevated serum prolactin levels of which 99% had a prolactin level <94 ng/ml [45]. We have observed a similar correlation in our practice. Given the reliability of modern assays, this study suggests that a PRL level above approximately 100 ng/ml is very likely indicative of a PRL secreting tumor, while levels below this indicate other causes for hyperprolactinemia. For very small or cystic tumors, PRL values may be misleading, but for tumors with a volume greater than 5 mm diameter, PRL levels are a reliable measure of tumor type. And while the degree of stalk deviation or gland compression does not correlate well with the extent of stalk effect, the prolactin level in true prolactinomas is correlated with tumor size, with increasing tumor size predicting increasing higher levels of serum prolactin above 100 ng/ml [48].

5. Treatment options

Prolactinoma is managed using several treatment strategies with the primary ones being observation, medication, surgery, and radiation. There continues to be quite significant debate over the optimal initial treatment option for newly diagnosed prolactinomas, with traditional views of treatment coming under new scrutiny based on improved surgical method and recognized limits of medical therapy.

5.1. Observation

Natural history studies demonstrated that persistent and progressive growth of microprolactinomas is quite uncommon [49–51], with close to 90% remaining stable over a 10-year follow-up period and up to 30% regressing [51]. Therefore, for patients who are asymptomatic, even if PRL is elevated, observation with serial imaging and serial measurement of PRL levels is a reasonable and widely recommended strategy [52]. Differentiating non-functioning microadenomas from prolactinoma with serum PRL levels below 100 ng/ml can often be difficult, and therefore in patients that are hormonally intact, therapy is generally not indicated. This approach is rarely reasonable for patients with macroadenomas or giant

tumors where the need to reduce mass effect must also be taken into consideration [20]. In contrast, in post-menopausal women, women not interested in pregnancy, or women that are not bothered by the lack of a normal menstrual cycle there is no urgency to normalize serum prolactin levels even if oligo or amenorrhea is present, as evidence suggest mild hyperprolactinemia is not dangerous in women [53,54].

5.2. Dopamine agonists

Dopamine, predominately released in the hypothalamus, is the agent that regulates prolactin secretion by lactotrophs and subsequent dopamine receptor down regulation of cAMP driven PRL production [55]. Not surprisingly, long lasting dopamine agonists (DA) reduce prolactin secretion from lactotrophs via sustained binding to PRLR cell surface receptors inducing down-stream inhibition of lactotroph function. The D₂R subtype is the most common receptor found on lactotrophs [56], and a variety of D₂R receptor agonist have proven to be very effective in treating prolactinoma. Like dopamine itself, DA preferentially bind to D₂R and reduces PRL secretion via inhibition of cAMP.

Dopamine agonists have long been considered a first-line therapy for prolactinomas based on responsiveness and the opportunity to avoid surgery. Several sets of guidelines from endocrine societies have supported this view including a most recent update in 2019 [1,28]. The goals of DA therapy are normalization of prolactin level, tumor shrinkage and/or stabilization in size, and restoration of normal gonadal function. Several DA have been developed for clinical use including bromocriptine, cabergoline, quinagolide, lisuride, pergolide, dihydroergocryptine and mesulergine. The most tested of these agents in clinical practice are bromocriptine, cabergoline and quinagolide [20]. All these medications dramatically reduce PRL levels with cabergoline demonstrating the greatest overall affect and most tolerable side effects [57]. Bromocriptine and cabergoline are currently approved by the FDA and are the most widely used in clinical practice.

5.2.1. Bromocriptine

Bromocriptine was introduced to medical practice over 40 years ago [58] and binds to both D₁R and D₂R receptors. Bromocriptine can normalize PRL in approximately 78–90% of microadenomas and 72% of macroadenomas [20,43,59]. Amenorrhea is resolved in approximately 80% of women. Tumor reduction is noted in 77% of patients, with 25–50% having a tumor reduction of greater than 50%, and minimal reduction in close to 30% [1,60,61]. For large tumors with prominent visual field deficits, bromocriptine can produce profound improvements in vision over a short period of time, well correlated with tumor volume reduction [20,62]. Typical starting dose of Bromocriptine are 0.625–1.25 mg daily, increased at intervals of 1.25 mg weekly until a dose of 2.5 mg two to three times daily. Side effects occur frequently with bromocriptine. Common side effects include upper gastrointestinal upset, postural hypotension, nausea, fatigue and headaches. These symptoms are related to incidental activation of 5HT_{1A} and D₁R receptors [1,63].

5.2.2. Cabergoline

Cabergoline has been shown to be at least as effective as bromocriptine, and better tolerated by patients [1,46,64]. Prolactin normalization has been reported in 73% to 96% of patients, with tumor shrinkage in 48% to 83% [65]. A meta-analysis of 26 studies indicated cabergoline treatment resulted in normal prolactin levels in 50% to 100%, with tumor reduction 47% to 97% [64]. Over 90% of patients will have a rapid response at doses less than 2 mg/week (typically 0.5 mg twice weekly). Like bromocriptine, results are relatively similar for both micro- and macroadenomas, with a slightly better response in smaller tumors [65]. Even when higher doses are required, most patients will respond to treatment. The markedly better side effect profile of cabergoline as well as lesser frequency of dosing has led this agent to be most popular with both patients and physicians.

For patients with macroadenomas, invasive tumors and giant tumors, a higher dose regime has been proposed to achieve more rapid response. However, a prospective randomized trial demonstrated no superiority to higher doses to achieve a 50% tumor reduction or normalize prolactin levels [66]. These data demonstrate the extreme efficacy of DA for the treatment of prolactinoma and why this may be considered a logical choice for initial therapy. Doses of up to 7–12 mg/week are considered safe, although higher doses have been used in resistant cases [67].

5.3. Dopamine agonist side effects

Despite these impressive results, there are some substantial downsides to DA therapy [68,69,70–73]. DA are not always well-tolerated with known side effects of headache, nausea, and confusion [60,65]. Generally underappreciated is the risk for developing impulse control disorders such as gambling, hypersexuality, or repetitive behaviors [74–76]. While the true incidence of these disorders is not fully understood, these side effects are likely under-reported, and may cause more morbidity than the prolactinoma itself.

Long-term side effects of DA use such as pulmonary and cardiac fibrosis have been reported but are largely associated with significantly higher doses (10–100-fold higher) used to treat Parkinson's disease [77–79]. Valvular heart disease arising from chronic DA use has also been reported [80,81]. This effect was reported to be more likely with cabergoline. Despite these initial concerns, large multicenter follow up studies have failed to demonstrate any association between the risk of valvular heart disease and low dose cabergoline usage in prolactinoma patients [82]. However, it remains unclear what cumulative dose of DA is associated with valvular heart disease, and the avoidance of long-term therapy seems prudent [65].

Induction of tumor fibrosis via the use of DA is a well-appreciated phenomenon, although surprisingly poorly documented. Landolt et al. were the first to demonstrate poorer surgical outcomes in patients pretreated with bromocriptine [83], who noted normal serum prolactin levels in 81% of surgical patients who were not pre-treated with bromocriptine, but only 33% in those that had previously been treated with it, especially if treatment was greater than one year.

Menucci et al. compared 24 consecutive patients with prolactinoma to 34 patients with growth hormone (GH) secreting tumors to determine extent of fibrosis [84]. 87.5% of prolactinomas were treated with DA for at least 1 month. Fibrosis was noted in 54% of prolactinomas compared with only 6% of GH secreting tumors. In contrast, tumor fibrosis was noted in only one tumor not treated with DA. Only 18% of non-fibrous prolactinomas had been exposed to bromocriptine and only 3 patients in that series had long term remission. Previous exposure to DA was the only major predictor of poor outcome in patients with microadenomas. Other studies have not found this relationship to be true [85–87], although surgeons commonly note tumor fibrosis in surgical specimens of prolactinomas following long term DA use [88]. Fibrosis is reported to be more associated with bromocriptine than cabergoline. These data, along with several older series [84] indicate that bromocriptine can induce tumor fibrosis and that fibrosis is associated with poor rates of surgical remission below those reported in larger surgical series. While less published data support the view that cabergoline induces fibrosis, this has been commonly observed in my surgical practice, and has been noted by others as well [89,90]. When present, fibrosis renders most tumors difficult to remove without damaging the pituitary gland itself or surrounding structures, and rates of remission are relatively low.

A relatively uncommon but well-documented complication of DA treatment is the development of CSF fistulae due to tumor shrinkage. This phenomenon is almost exclusively observed in macroadenomas and/or giant tumors that have eroded through the diaphragma sellae. A rate of spontaneous leakage as high as 8.7% has been reported [91], although selection bias likely resulted in an over-estimate of this occurrence. Nonetheless, a CSF fistula is a potentially serious complication that can result in meningitis, ventriculitis, subdural hematoma formation and even death. Most CSF fistulae require urgent or semi-urgent surgical repair.

Pituitary apoplexy, or sudden hemorrhagic infarction of a pituitary tumor, can also occur. An extensive review including 25 retrospective series of pituitary apoplexy since 2000 indicated that PRL-secreting tumors were the underlying tumor type in an average of 22% (range 1–63%) of cases, second only to nonfunctioning tumors [92]. There is no indication that the use of DA agonists increases the risk of apoplexy, even for large or giant tumors. In a retrospective series of 368 patients with documented prolactinoma undergoing MRI imaging, any evidence of hemorrhage was identified in 6.8%, but only 3 patients (0.8%) had apoplexy [50]. Hemorrhage was higher in macroadenomas (64% of all cases) and in women (88% of all cases). The majority were treated with DA, resolved, and were asymptomatic.

5.4. Withdrawal of dopamine agonists

Many prolactinoma patients require years to lifelong therapy with DA. In patients with macroadenomas, dose de-escalation once tumor reduction and normalized PRL levels are obtained has proven to be an effective strategy for over 91% of patients [68]. However, a comprehensive meta-analysis of patients that had DA withdrawal after treatment of prolactinoma noted

successful long-term discontinuation in only 21% of patients with microadenomas and 16% of patients with macroadenomas [69]. Smaller tumors seem more amenable to medication withdrawal [70]. Even in patients with no observable tumor and PRL levels normalized at the lowest treatment dose of 0.25 mg/week, remission after withdrawal was only noted in 41–47% [71–73]. Only 60% of patients in a strict protocol of DA withdrawal had normal prolactin levels after more than 5 years, even when no tumor could be visualized. 22% of women and 39% of men developed gonadal dysfunction [93].

Stated otherwise, while most patients can dose-reduce the DA over time, a smaller percentage are able to completely discontinue, leading to essentially life-long medical therapy [69].

5.5. Dopamine resistance

While a full discussion of DA resistance is beyond the scope of this review, a brief mention of this phenomenon is important to understanding treatment options. Dopamine resistance is a broadly used term, with several definitions applied in the literature. The most generally accepted definition refers to an inability to reduce PRL level to normal range despite increasing doses of DA, and/or a failure to reduce a tumor by at least 50% of its initial size [64]. Dopamine resistance is more commonly observed with bromocriptine compared to cabergoline, and 70–80% of patients who are resistant to bromocriptine will become responsive to cabergoline [64]. There are several proposed mechanisms of dopamine resistance, the most recognized one involving reduction in D₂R receptor expression [94]. Dopamine resistance to cabergoline is estimated to occur in less than 10% of microprolactinomas and 15–20% of macroprolactinomas, although inadequate dosing in some cases raises the suspicion the actual numbers of true resistance are even lower [64]. Inability to bring about normal PRL levels with doses of more than 3–7 mg/week of cabergoline, or 20–40 mg/day of bromocriptine is the primary evidence for dopamine resistance. Surgery is often used in the setting of dopamine resistance to reduce tumor burden and attempt a surgical cure if possible. Radiation can also be used in this setting but overall results for normalize PRL have been sub-optimal (see below).

6. Surgery

Since DA were introduced, the surgical management of prolactinomas has largely been relegated to a second-line treatment. Interestingly, the available evidence does not clearly justify this approach. In fact, there is substantial data to support the rationale for surgery as a first line treatment option. There are many published series describing neurosurgical outcomes from surgery of prolactinomas, with a variability in both initial remission rates and long-term recurrence rates [95–98]. A comprehensive review of series reported through 2005 classified remission or cure as a normalized serum prolactin level [64]. The overall initial remission rate for microadenomas was 74.7% (1596 out of 2137) and 33.9% for macroadenomas (755 of 2226). A more recent review encompassing series published between 2006 – 2015, largely utilizing endoscopic

techniques, reported overall remission rates of 81% for microadenomas and 41% for macroadenomas, with remission rates as high as 93–100% reported by some [43]. An important meta-analysis comparing results of surgery to medical management indicated 36% disease remission with medical management followed by drug withdrawal, but 83% remission with surgery [99]. They also noted that while biochemical control was maintained in 81% of patient on DA, 26% experienced side effects. These numbers can be difficult to generalize as variability in neurosurgical expertise is well recognized to play an important role in outcome [100].

Transsphenoidal surgery can be carried out with extremely low morbidity in experienced hands. The risk of developing new hormonal deficiencies for tumors <20 mm is 0–7% [101,102] and 1.5% to 3% or less in tumors >20 mm [4,19,101]. In other words, in most reports there is no substantial difference in new hormonal deficits following surgery for micro- or macroadenomas. A comprehensive review of the surgical literature for microadenomas indicated that in most series the rate of new hypopituitarism reported for any axis was close to 0% [103].

Other complications of transsphenoidal surgery are also very low for prolactinoma [99,104,105]. In one series of 212 consecutive patients the mortality rate was 0% and morbidity rate 3.8%. In other series no operative mortality was reported and morbidity was similarly low at 5% [86,103]. The most common complications of surgery are listed in Table 1 [106,107]. Iatrogenic CSF rhinorrhea is a relatively common side effect of transsphenoidal surgery, occurring in approximately 15% of cases. Fortunately, intraoperative repair is easily performed with only 0.3–2% of patients requiring a reoperation to further repair the leak. Similarly, meningitis from pituitary surgery is quite infrequent, with a reported incidence of 0.1–0.5% of cases in large series. Carotid artery injury, a dreaded fear, is also a very rare event, reported in less than 1% of cases. Other complications such as hematoma

Table 1. Complications of transsphenoidal surgery for pituitary tumors*.

Complication	Percentage	Comment
CSF rhinorrhea	15	
CSF rhinorrhea requiring surgical repair	2	
Sinusitis	8	
Epistaxis	2	
New anterior pituitary hormone deficiency	1	
Panhypopituitarism	1	
Transient Diabetes Insipidus	11	
Permanent Diabetes Insipidus	1.4	
Vision loss (new)	0.4	
Oculomotor Nerve Palsy (CN III, IV, or VI)	8	All transient
Carotid artery Injury	0.7	
Vascular Occlusion, Stroke	1	Includes carotid injury
Hydrocephalus	0.3	
Sellar/ Suprasellar hematoma	0.5	Requiring intervention
Meningitis	0.5	
Symptomatic hyponatremia (SIADH)	13	Requiring Readmission
Death (all causes)	< 0.3%	

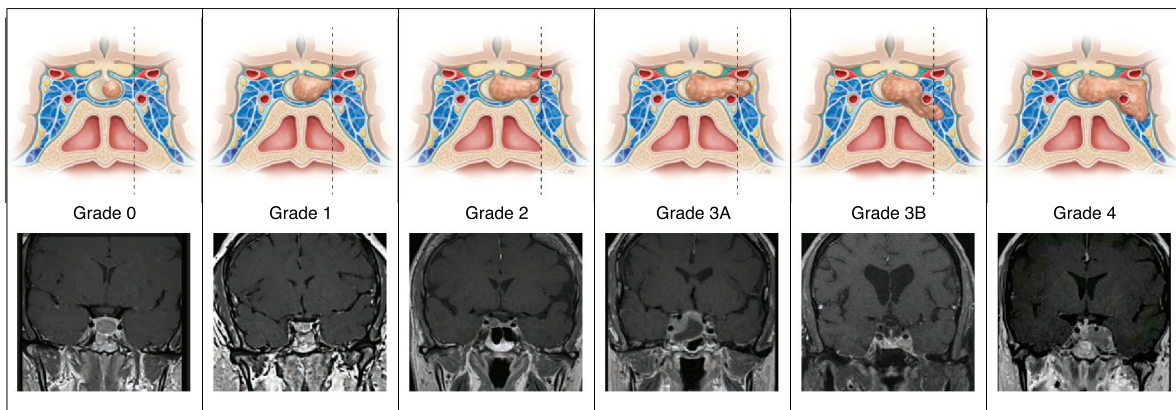
*From the author's personal series of 897 pituitary adenomas [19]. Results are like those reported by other series [106]

requiring evacuation or visual loss all occur in less than 1% of cases. These numbers reflect outcomes with macroadenomas, with even less morbidity reported for smaller tumors. Further, tumors that are invasive of the cavernous sinuses are associated with a higher rate of serious complications such as carotid injury (2%) or cranial nerve palsy (6.8%) [108]. Thus, surgical strategies to minimize operation for high grade tumors seems justified. The most frequent complication of pituitary surgery is delayed symptomatic hyponatremia due to the syndrome of inappropriate antidiuretic hormone (SIADH). This is the leading cause of hospital readmission, with a reported incidence of 10–15% of cases. However, the use of 750 ml–1500 ml fluid restriction protocols in the early postoperative period (4–10 days after surgery) has been demonstrated to dramatically reduce the rate of symptomatic hyponatremia and readmission by at least 3-fold [109]. Repeat transsphenoidal surgery is associated with slightly higher complication rates, especially meningitis, diabetes insipidus, and CSF leaks requiring repair, but not with higher mortality [110]. Outcomes from both microscopic and endoscopic surgeries for microadenomas appear quite similar [20,43,103,111]. Thus, the surgical literature demonstrates that prolactinoma surgery is highly effective and safe [110]. Of note, both the medical and surgical morbidity and mortality for giant adenomas, defined as tumors with a diameter greater than 4 cm, is markedly higher than for micro- or macro-adenomas, generally reported to be 3–5 times higher [107,112].

Honing down on remission rates based on tumor size and anatomic location, especially extent of cavernous sinus invasion, provides critical insight into the advantages and limits of surgery. The cavernous sinus is a triangular shaped venous cavity formed by the walls of the dura mater medial to the temporal lobe, lateral to the pituitary fossa, and inferior to the frontal lobe. It is a bilateral structure that sits just lateral to the sella turcica and therefore directly adjoined to the pituitary gland itself. This complex structure is part of the venous drainage system of the brain, collecting blood from the brain and carrying it to the inferior petrosal sinus and then jugular veins. The cavernous sinus envelops a portion of the internal

carotid artery, and cranial nerves III, IV, V, and VI. Surgical removal of lesions within the cavernous sinus is well known to carry significant surgical risks, and there is a vast neurosurgical literature describing surgical approaches and outcomes, ranging from cranial nerve palsies to carotid injury, stroke, and death. Given the complex nature of the cavernous sinus and substantial potential morbidity associated with aggressive surgical resection in this area, it is not surprising that cavernous sinus invasion is a very important predictor for surgical cure.

The most widely used and universally accepted grading tool for measuring cavernous sinus involvement is the Knosp grading scale [113], which divides tumors into grades 0–4 based on coronal T1 weighted MRI imaging criteria (Figure 1). Grades 0–2 tumors are generally considered to not invade the cavernous sinus but can put pressure on the medial wall. In contrast grades 3–4 invade through the medial wall of the cavernous sinus. Grade 4 tumors circumferentially encase the intra-cavernous portion of the carotid artery. More recent correlation studies between Knosp grade and surgical finding support further subdivision of grade 3 into those tumors that invade only the superior cavernous component (3A) and those that invade the inferior cavernous component (3B) [114]. In one study of GH-secreting tumors a remission rate of 47.6% was noted for tumors invading the cavernous sinus (all grades), compared to 76.4% for those not invading and 74.2% for noninvasive microadenomas. In that study, only cavernous sinus invasion, not tumor size, predicted surgical remission [115]. Numerous other studies support the view that even in experienced hands, total removal of tumors with high grade cavernous sinus invasion (Grades 3B and 4) is rarely accomplished [116–119]. Table 2 summarizes results from some recent series of prolactinomas in which remission rates in the subset of tumors with cavernous sinus invasion could be clearly teased out from the overall remission rates. In tumors with cavernous sinus invasion remission rates were markedly lower (23%) that overall remission rates for all microadenomas (78%) and macroadenomas (56%). Even in the groups that did go into remission, Knosp high grade patients had higher recurrence rates than those with grade 0. Several



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Figure 1. Knosp Grading Scale for determining extent of cavernous sinus invasion by pituitary tumors. Grade 0–2 tumors are considered not invasive of the cavernous sinus. Grade 3–4 tumors are considered invasive. Grade 3 is frequently subdivided into grade 3A (above the inferior aspect of the intra-cavernous carotid artery) and 3B (below the inferior aspect of the intra-cavernous carotid artery). The Knosp grading schema is well validated and has proven to be a strong predictor of extent of surgical resection for pituitary adenomas. Grade 4 tumors are rarely able to be totally removed, while grade 0–2 tumors have a high rate of total removal by experienced surgeons. Results for Grade 3 are more variable (see text for details). © Giovanna Santoni, CMI. Used by permission.

Table 2. ~TC~

Reference	TTS	N	M/F	Remission (%)		Remission in tumors with cavernous sinus invasion (%)
				Micro	Macro	
Ikeda [82] Reported outcomes of transsphenoidal surgery for prolactinomas.	Micro	138	0/138	86	74	24
Akin [133]	Endo	142	66/76	74	41	24
Andereggen [119]	Micro	71	0/71	67	60	1
Han [134]	Endo	52	14/38	100	59	29
Micko [102]	Endo	60	Oct-50	82	-	45
Park [116]	Micro	96	22/74	43	31	13
Zielinski [120]	Endo	48	Apr-44	92	68	20*

*Evaluated grades 0–4 and considered grades 2–4 invasive. No remission in patient with grade 3–4

N = number of patients; TTS = method of transsphenoidal surgery; Endo = endoscopic; Micro = microscopic.

studies in GH secreting tumors [120,121], nonfunctioning adenomas [122,123], and prolactinomas [124] support the observation that Knosp score remains the dominant predictor of surgical outcome. More recent surgical techniques have described removing the medial wall if the cavernous sinus [125], with at least one report detailing very high (97%) remission rates for hormonally active tumors [126]. However, this report excluded patients with extension beyond the medial cavernous wall (i.e. not grade 3B or 4), and thus may not be truly representative of cavernous invasion. Some papers report high rates of radiographic gross total removal for high Knosp grade tumors, but these studies tend to have limited follow up of 3 months or less, and are not specific to hormone secreting tumors for which cure is more reflected in hormonal status rather than evidence of tumor on MRI [127]. These high-risk procedures have not been clearly correlated with improved surgical outcomes in terms of hormonal complete cure and carry with them the potential for significant morbidity. In general, the long and complex history of cavernous sinus surgery suggests this approach should be considered in only very select cases, and by surgeons highly experienced in the technique. Even then, it is unlikely to substantially impact surgical cure rates for hormone secreting tumor such as prolactinoma. This approach may not be overall worth the potential risk, especially when highly effective medical therapies and radiation are available. A larger body of data with long-term follow-up will be required to validate this more aggressive approach.

Park et al. [128] looked at surgical outcomes for micro and macroprolactinomas in which any evidence of cavernous sinus invasion was excluded and noted normalization of PRL in 83% or microadenomas and 58.8% of macroadenomas, both results that were essentially identical to those patients with similar tumors receiving DA therapy. Long-term DA-free control rates were 75% for microadenomas and 47% for macroadenomas. Tampourlou et al. [103] reported a surgical remission rate for microadenomas of 71–93% after microscopic surgery and 81–100% after endoscopic surgery. A meta-analysis by Zamanipour et al. [99] also reported better long-term remission rate with transsphenoidal surgery (67%) compared to DA treatment (34%), although the DA-mediated normalization rate of the PRL was 81%. Remission rates across reports varied from 60% to 93% for microadenomas and 10–74% for macroadenomas, demonstrating the difficulty in grouping together many series to arrive at a meaningful average. Further, various centers used

different assays or measures of remission. It is also difficult to determine in this meta-analysis how many patients were pre-treated and failed DA, how long they were treated, and how many went directly to surgery.

Long-term remission data is harder to fully evaluate. The primary quantitative measure of recurrence is elevation of serum PRL outside of normal range. Recurrence rates of 18–20% over 10 years have been reported by several groups [95,102,129]. However, supra-normal PRL levels may not be clinically relevant for many patients. In fact, supra-normal PRL in a post-menopausal woman or a woman not seeking pregnancy may not have any impact. Radiographic changes may also not be present so mass effect is not an issue. Further, elevation of prolactin and subsequent renormalization has been observed [49].

However, even in those not cured from surgery, patients undergoing primary surgery have lesser long-term DA requirements and overall better remission rates than those treated with DA alone. Andereggen et al. [130] evaluated 100 patients in which 34% received DA therapy and 66% underwent surgery as a primary therapy, including both micro and macroadenomas. At 10 years 64% of patients treated using primary medical therapy with DA required ongoing treatment while only 32% of those undergoing primary surgery required DA therapy. Logistic regression analysis of the data set indicated that primary intervention (surgery vs medical therapy) was the main independent variable to predict DA therapy requirements at 10 years, with the only other significant variable being tumor invasiveness (i.e. higher Knosp grade). As previously discussed, Knosp score has repeatedly been demonstrated to predict the rates of surgical cure for a variety of hormonally active tumors and prolactinomas is no different. In a prospective analysis, Zielinski et al. [131] determined that Knosp score was the only variable predicting remission following multivariate stepwise logistic regression. Similar observations have been noted in many other series [123]. Even where extended surgical approaches specifically aimed at tumors invading the cavernous sinuses have been evaluated, immediate surgical remission rates for grade 4 tumors were only 53.8% [132]. Long-term endocrine data was not available and remission rates are likely far lower. Some debate remains as to whether higher Knosp score is a marker of aggressiveness. Hage noted that patients likely to be able to discontinue DA therapy started out with smaller tumors, indirectly arguing that tumor debulking may improve chances of discontinuing DA therapy over time for tumors not cured by initial surgery [70,132].

6.1 Giant prolactinomas

Giant prolactinomas (>4 cm diameter) represent only 5% of adenomas and occur in men 9 times more commonly than in women. Surgery is rarely curative for these tumors [112,133]. Only 15% of patients with giant prolactinomas undergo surgery, which is usually used to help reduce mass effect in slowly responsive tumors, or to assist with normalization of PRL for resistant cases. Data supporting surgery as the initial therapy for giant tumors is sparse and weak, unless it is being used to reduce long-term DA requirements, which remains a theoretical and yet unproven observation. There is no formal analysis demonstrating that tumor debulking impacts long-term DA requirements. Further, surgical complications are dramatically higher for giant adenomas than for macroadenomas, with several series reporting major complication rates of 15% or more, and mortality rates of 2–3% [134]. These statistics make a strong argument to avoid surgical intervention for giant tumors unless medical therapy fails, or perhaps to assist with reduction in tumor volume. While the distinction between a large macroadenoma and a giant adenoma is somewhat arbitrarily set at 4 cm, this distinction serves as a useful guideline for determine where the risk to benefit ratio of surgery versus medical management for prolactinomas can be drawn.

7. Cost of surgical versus medical therapy

Relatively few studies have assessed the costs associated with therapy of prolactinomas, although the available studies are quite informative. Turner et al. [98] evaluated outcomes of transsphenoidal surgery for microprolactinoma from a single surgeon between 1976 and 1997 where surgery was offered due to drug intolerance, resistance, or lack of availability of medication. They noted a 78% cure rate with only 1 recurrence at 12 years. They estimated the cost of surgery to be equivalent to the cost of DA therapy at ten years. A smaller analysis [135] calculated an average yearly cost for cabergoline therapy to be approximately \$3306, and the cost for a single microscopic transsphenoidal surgery to be \$9865. Based on their observed 91% initial remission rate for microprolactinomas, they concluded that surgery is more cost effective than 4 years of cabergoline therapy, with equal clinical efficacy and reduced side effects. A more recent and comprehensive cost effectiveness analysis [136] used a decision tree analysis and included quality adjusted life years (QALYS) as a surrogate measure of the value of medical versus surgical remission for microprolactinomas. A single QALY is a year lived with no health issues. Their analysis considered the frequency of various surgical complications and medication side effects, cost of treatment, as well as data supporting the view that quality of life is reported to be diminished in many patients taking DA [63,137–139]. They assumed a surgical cure rate of 90% with a 2.5% complication rate for microscopic surgery and 92–100% cure rate for endoscopic methods with similar rates of complications. Based on these assumptions they calculated a 5-year costs of \$13,649 for microscopic and \$15,474 for endoscopic surgery (including imaging, hormone testing, and post-operative follow up visits). They calculated an expected 5-year cost of \$19,620 for cabergoline and

\$16,579 for bromocriptine. Based on these numbers and related QALY assumptions, they determined that at both five- and ten-year time points transsphenoidal surgery was less costly and more cost effective than treatment with either cabergoline or bromocriptine, with the effect amplified by including impact on quality of life. While this analysis may be a bit over-optimistic, largely attributable to the extremely high surgical cure rates, it is consistent with other studies suggesting that in the hands of experienced pituitary surgeons, transsphenoidal surgery is likely cheaper, more cost effective, and results in better long-term quality of life than primary DA therapy. Of course, these results are limited to micro-prolactinomas with minimal or no cavernous sinus invasion. No such analysis exists for intrasellar macroadenomas.

8. Radiation therapy

Radiation therapy is rarely used as a first line therapy for prolactinomas due to the efficacy of DA and surgery in controlling disease in most patients. Further, radiotherapy carries with it substantial risks for further damage to the pituitary gland and loss of hormonal function over time [140]. Radiation has been used as a second-line therapy for resistant tumors, most commonly employing stereotactic radiosurgery techniques. These data indicate a low rate of PRL normalization ranging from 17% to 25% [140–142]. In some cases, radiotherapy may improve responsiveness to DA [142]. Radiation is more effective at controlling tumor growth than normalizing PRL. Based on current available data radiation therapy is likely to remain a secondary and limited treatment option for patients with prolactinoma. A more detailed discussion of the role of radiation in prolactinomas management is beyond the scope of this review, but can be found elsewhere [142,143]

9. Expert opinion

Based on extensive clinical data collected over many decades evaluating the safety and efficacy both of medical and surgical interventions for the treatment of prolactinomas, in addition to substantive evidence regarding the natural history of these tumors, a re-assessment of optimal treatment strategies seems warranted. An optimal treatment is one that provides the best patient outcome, in the most cost effective and safe manner. For prolactinomas these goals can be generally best stated as long-term normalization of serum prolactin levels, elimination of prolactin induced sex-hormone deficiencies; prevention of injury to the pituitary gland itself or related anatomical structures; and reduction in any mass effect caused by the tumor. The use of DA as a first-line therapy for all prolactinomas has been the predominate approach since the 1970s, for valid reasons. These medications are effective and safe, with normalization of prolactin levels in up to 96% of patients. Tumor volume reduction is seen in up to 83% and occurs quickly in most patients. Further, if successful, these medications may avoid the need for surgery and its attendant risks.

However, as surgical experience and techniques have improved, and a deeper appreciation of the potential negative side effects of long-term DA use have become apparent, there

is good reason to re-assess these options. The advantages of successful initial surgery are that it can achieve the same goals as DA therapy, while simultaneously mitigating risks, and side effects of long-term, or even lifetime, DA therapy. Further, it may be a more cost-effective approach.

If one were to consider both medication and surgery as first line options, the primary determinant is arguably the extent of cavernous sinus invasion. Surgical cure in tumors with high grade cavernous sinus invasion (Grade 3/4) is low (<23%) even in experienced hands. However, surgery in the cavernous sinus increases risks for carotid injury, cranial nerve palsies and other complications. Additional factors in this equation would be overall tumor size, surgical experience, and contraindications to one therapy or the other. Based on these considerations, an algorithm for using surgery as a first-line treatment strategy is proposed in Figure 2.

For microprolactinomas without high grade cavernous sinus invasion, there is a substantial body of evidence to suggest that surgical removal by an experienced pituitary surgeon may be the most optimal treatment option. Results of surgical remission rates for microprolactinomas with no overt cavernous sinus invasion over the past 20 years indicates that surgery provides similar remission rates to medication and frequently avoids the need for many years of medical therapy. Surgical remission rates for microprolactinomas range from 75% to 100% in many series, essentially identical to remission rates from medical therapy alone (75–90%). A representative example is shown in Figure 3. The high upfront cost of surgery is counterbalanced by the cumulative cost of DA therapy, which reaches a 'break-even' point at

about 4 years of drug therapy. Given the extremely high safety profile of surgery in the modern era, reduced hospital stay and recovery time, and the low rates of surgical complication and/or hormonal dysfunction, surgery is a very appealing solution. Using this approach microadenomas with a Knosp grade 0–3A should be considered for surgery at time of diagnosis, while those with Knosp grade 3B/4, are best treated with DA upfront. Debulking of high-grade invading tumors could then be considered if patients are intolerant or resistant to medication, but not as primary therapy.

For macroprolactinomas a similar line of reasoning can be employed. For tumors with no or relatively minimal (Knosp grade 0–3A) cavernous extension, upfront surgical excision aimed at remission is well supported by the medical literature. For patients with high grade (grade 3B/4) cavernous sinus invasion, if a substantial tumor debulking of at least 75% can be obtained, it is likely to allow better hormonal control with reduced DA requirements over lifetime, and the attendant reduced risks of medication related side effects. This applies specifically to macroadenomas, and not giant (>4 cm) adenomas, as no far less definitive data supporting the role of debulking to reduce DA requirements is available for giant tumors. A representative example is shown in Figure 4.

Importantly, surgery should be considered as primary, not secondary therapy. This opinion contrasts with current endocrine society guidelines indicating primary medical therapy in the majority of prolactinomas (regardless of size), with surgery reserved for patients with DA intolerance or resistance. The algorithm proposed is similar to the approach already

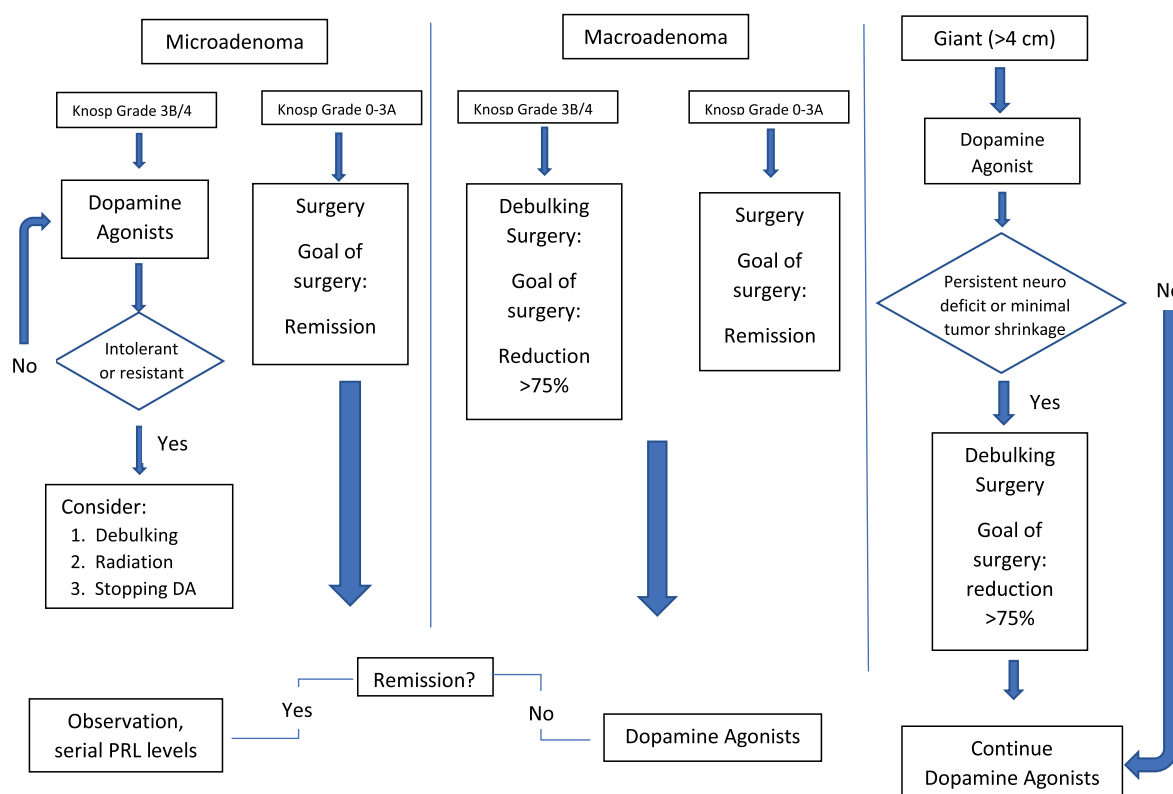


Figure 2. Proposed decision-making algorithm for first-line surgical approach. In this schema Knosp grade is used as the primary determinant of whether surgery should be considered an initial treatment option.

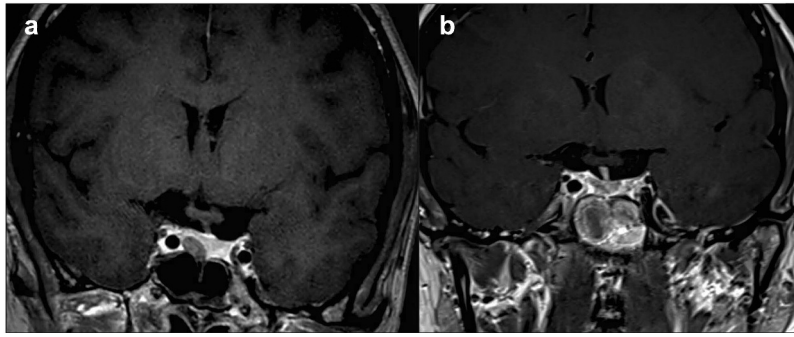


Figure 3. A) Intrasellar (Knosp grade 0) micro-prolactinoma. This 36-year-old female presented with secondary amenorrhea, headaches and a PRL level of 95 ng/ml. She did not tolerate even low doses of cabergoline. B) Surgery was carried out demonstrating total removal at 3 months. An immediate post-operative PRL level was 1.7 ug/L which remained in normal range no medication with resumption of normal menses and resolution of headaches.

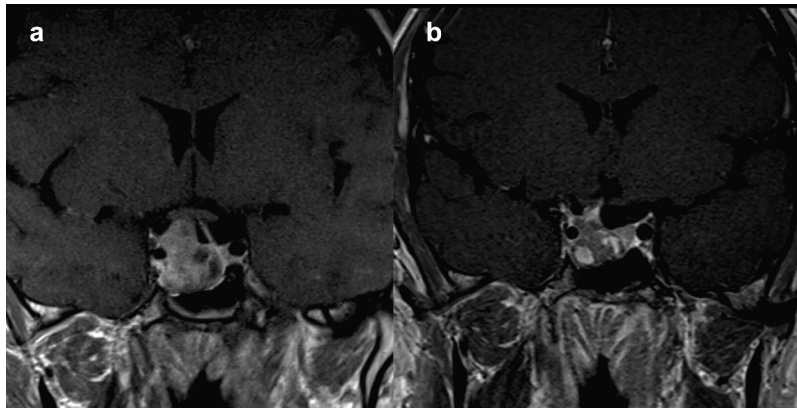


Figure 4. A) Macroprolactinoma with grade 3 cavernous sinus invasion. A 26-year-old male presented with hypogonadism and headaches. Initial prolactin level was 2248 ng/ml. Despite increasing doses of cabergoline and some tumor shrinkage (B), prolactin never normalized. He subsequently underwent surgery where prominent fibrosis and hemorrhage was noted. Postoperative PRL was 31 ng/ml and he his PRL level has remained normal on cabergoline 0.5 mg weekly.

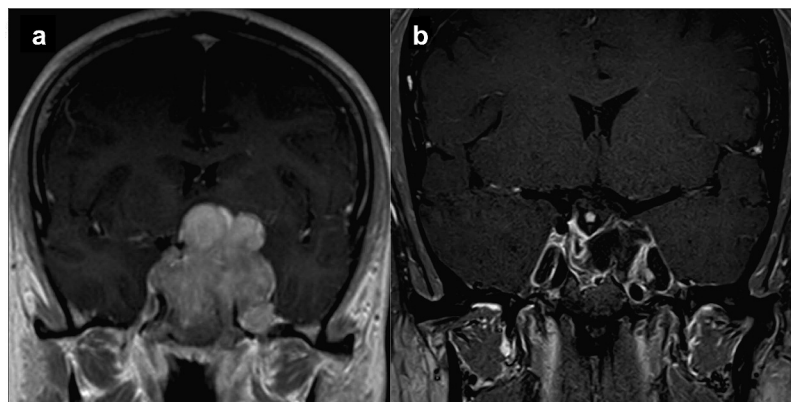


Figure 5. A) Giant prolactinoma is an 18 year old male with a serum prolactin > 20,000 ng/ml, bitemporal hemianopsia, and hypopituitarism. MRI demonstrates a large mass with bilateral Grade 4 cavernous sinus invasion. B) Treatment with cabergoline resulted in normalization of prolactin and massive tumor regression with restoration of vision in 6 weeks. No surgery was performed. It is unlikely initial surgical resection would have benefitted the patient.

commonly used for GH and ACTH secreting adenomas. For these tumors an initial attempt at surgical cure or substantial debulking is considered a first-line option, and there is little reason to suggest that prolactinomas are different. Primary surgery also avoids the potential for DA therapy-induced tumor fibrosis, thereby making later surgical excision more

complicated, higher risk, and less effective. Thus, the drug-naïve prolactinoma patient is a better surgical candidate than one on long-term medical therapy.

For giant adenomas, surgical cure remains very low, regardless of surgical expertise or cavernous invasion. A representative example is shown in [Figure 5](#). It is therefore reasonable to treat

these tumors with DA upfront and monitor them closely for tumor regression and hormonal remission. If patients have persistent neurological deficits from compression or not showing signs of rapid tumor remission, then surgical debulking can be considered, with the goals of reducing mass effect, reducing DA requirements, and accelerating hormonal remission. Primary surgical intervention is rarely indicated in these tumors.

The line of reasoning presented here represents a contrast to what has been accepted dogma for many years, namely, to treat with DA and consider surgery only for drug intolerance or drug resistance. In this paradigm, surgery is offered as the primary option, before initiation of medical therapy, for both micro- and macroadenomas without high grade cavernous sinus invasion, with the understanding that once medical therapy has been initiated surgical remission is less likely.

This approach makes more sense when one considers that patients that undergo surgery and later require DA often require lower doses to achieve PRL normalization. For some older or asymptomatic patients, even if there is a later recurrence of hyperprolactinemia it may not require intervention.

10. Conclusion

There is currently relative equivalency between the outcomes of transsphenoidal surgery and medical therapy for prolactinomas without high grade cavernous sinus invasion. Assuming there is an experienced, and competent pituitary neurosurgeon available, surgical therapy should no longer be relegated to second-line therapy in appropriately selected cases, and in fact should be considered a first-line option offered to patients upfront. A prospective randomized trial comparing primary surgical and primary medical therapy would be the ideal way to resolve this issue. As a shift toward primary surgery occurs, careful reevaluation of data will prove invaluable to make a final determinant on the benefits of each approach.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (⇨) to readers.

1. Casanueva FF, Molitch ME, Schlechte JA, et al. Guidelines of the pituitary society for the diagnosis and management of prolactinomas. *Clin Endocrinol (Oxf)*. 2006 Aug;65(2):265–273.

- **2006 guidelines for treatment of prolactinomas from the Pituitary Society.**
- 2. Loyo-Varela M, Herrada-Pineda T, Revilla-Pacheco F, et al. Pituitary tumor surgery: review of 3004 cases. *World Neurosurg*. 2013 Feb;79(2):331–336.
- 3. Younus I, Gerges MM, Uribe-Cardenas R, et al. How long is the tail end of the learning curve? Results from 1000 consecutive endoscopic endonasal skull base cases following the initial 200 cases. *J Neurosurg*. 2020;7:1–11.
- 4. Mamelak AN, Carmichael J, Bonert VH, et al. Single-surgeon fully endoscopic endonasal transsphenoidal surgery: outcomes in three-hundred consecutive cases. *Pituitary*. 2013 Sep;16(3):393–401.
- 5. Fahlbusch R, Buchfelder M. Pituitary surgery. In: editor, Melmed S. The pituitary. 4th ed. Vol. 1. Philadelphia: Elsevier; 2017:671–687.
- 6. Ostrom QT, Patil N, Cioffi G, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2013–2017. *Neuro Oncol*. 2020 Oct 30;22(12Suppl 2):iv1–iv96.
- 7. Buurman H, Saeger W. Subclinical adenomas in postmortem pituitaries: classification and correlations to clinical data. *Eur J Endocrinol*. 2006 May;154(5):753–758.
- 8. Molitch ME. Pituitary tumours: pituitary incidentalomas. *Best Pract Res Clin Endocrinol Metab*. 2009 Oct;23(5):667–675.
- 9. Molitch ME. Diagnosis and treatment of pituitary adenomas: a review. *JAMA*. 2017 Feb 7;317(5):516–524.
- 10. Day PF, Loto MG, Glerean M, Day PF, Loto MG, Glerean M, et al. Incidence and prevalence of clinically relevant pituitary adenomas: retrospective cohort study in a health management organization in Buenos Aires, Argentina. *Arch Endocrinol Metab*. 2016 Nov-Dec;60(6):554–561.
- 11. Agustsson TT, Baldvinsdottir T, Jonasson JG, et al. The epidemiology of pituitary adenomas in Iceland, 1955–2012: a nationwide population-based study. *Eur J Endocrinol*. 2015 Nov;173(5):655–664.
- 12. Gruppeta M, Mercieca C, Vassallo J. Prevalence and incidence of pituitary adenomas: a population based study in Malta. *Pituitary*. 2013 Dec;16(4):545–553.
- 13. Fontana E, Gaillard R. Epidemiology of pituitary adenoma: results of the first Swiss study. *Rev Med Suisse*. 2009 Oct 28;5(223):2172–2174.
- 14. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clin Endocrinol (Oxf)*. 2010 Mar;72(3):377–382.
- **Excellent epidemiological study on tumor incidence.**
- 15. Raappana A, Koivukangas J, Ebeling T, et al. Incidence of pituitary adenomas in Northern Finland in 1992–2007. *J Clin Endocrinol Metab*. 2010 Sep;95(9):4268–4275.
- 16. Daly AF, Rixhon M, Adam C, et al. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *J Clin Endocrinol Metab*. 2006 Dec;91(12):4769–4775.
- 17. Dekkers OM, Hammer S, de Keizer RJ, et al. The natural course of non-functioning pituitary macroadenomas. *Eur J Endocrinol*. 2007 Feb;156(2):217–224.
- **A nice study indicating the slow growth potential of most pituitary tumors.**
- 18. Dekkers OM, Pereira AM, Roelfsema F, et al. Observation alone after transsphenoidal surgery for nonfunctioning pituitary macroadenoma. *J Clin Endocrinol Metab*. 2006 May;91(5):1796–1801.
- 19. Mamelak AN. Pituitary surgery. In: Melmed S, editor. The pituitary. 2022. Vol. 1. Philadelphia PA: Elsevier. p. 723–752.
- 20. Chanson P, Maiter D. The epidemiology, diagnosis and treatment of Prolactinomas: the old and the new. *Best Pract Res Clin Endocrinol Metab*. 2019 Apr;33(2):101290.
- **An authoritative review of all aspects of prolactinoma therapy, with focus on medical therapy.**
- 21. Ramot Y, Rapoport MJ, Hagag P, et al. A study of the clinical differences between women and men with hyperprolactinemia. *Gynecol Endocrinol*. 1996 Dec;10(6):397–400.

22. Delgrange E, Trouillas J, Maiter D, et al. Sex-related difference in the growth of prolactinomas: a clinical and proliferation marker study. *J Clin Endocrinol Metab.* **1997** Jul;82(7):2102–2107.
23. Touraine P, Plu-Bureau G, Beji C, Touraine P, Plu-Bureau G, Beji C, et al. Long-term follow-up of 246 hyperprolactinemic patients. *Acta Obstet Gynecol Scand.* **2001** Feb;80(2):162–168.
24. Berinder K, Stackenas I, Akre O, et al. Hyperprolactinaemia in 271 women: up to three decades of clinical follow-up. *Clin Endocrinol (Oxf).* **2005** Oct;63(4):450–455.
25. Shimon I, Bronstein MD, Shapiro J, et al. Women with prolactinomas presented at the postmenopausal period. *Endocrine.* **2014** Dec 47(3):889–894.
26. Santharam S, Tampourlou M, Arlt W, et al. Prolactinomas diagnosed in the postmenopausal period: clinical phenotype and outcomes. *Clin Endocrinol (Oxf).* **2017** Nov;87(5):508–514.
27. Delgrange E, Donckier J. Gonadal dysfunction in males with prolactinoma: from functional modification to irreversible damage? *Eur J Endocrinol.* **1997** Jun;136(6):630.
28. Melmed S, Longo DL. Pituitary-tumor endocrinopathies. *N Engl J Med.* **2020** Mar 5;382(10):937–950.
29. Root AW, Reiter EO, Weisman Y. Current status and clinical application of the hypothalamic hormones. *Adv Pediatr.* **1976**;23:151–211.
30. Bernard V, Young J, Chanson P, et al. New insights in prolactin: pathological implications. *Nat Rev Endocrinol.* **2015** May;11(5):265–275.
31. Bernard V, Young J, Binart N. Prolactin — a pleiotropic factor in health and disease. *Nat Rev Endocrinol.* **2019** Jun;15(6):356–365.
32. Bole-Feysoy C, Goffin V, Edery M, et al. Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. *Endocr Rev.* **1998** Jun;19(3):225–268.
33. Goffin V, Binart N, Clément-Lacroix P, Goffin V, Binart N, Clément-Lacroix P, et al. From the molecular biology of prolactin and its receptor to the lessons learned from knockout mice models. *Genet Anal.* **1999** Nov;153–5:189–201.
34. Goffin V, Bouchard B, Ormandy CJ, et al. Prolactin: a hormone at the crossroads of neuroimmunoendocrinology. *Ann N Y Acad Sci.* **1998** May;1(840):498–509.
35. Barry S, Korbonits M. Update on the genetics of pituitary tumors. *Endocrinol Metab Clin North Am.* **2020** Sep;49(3):433–452.
36. Lemmens I, Van de Ven WJ, Kas K, et al. Identification of the multiple endocrine neoplasia type 1 (MEN1) gene. The European consortium on MEN1. *Hum Mol Genet.* **1997** Jul 6;(7):1177–1183. [10.1093/hmg/6.7.1177](https://doi.org/10.1093/hmg/6.7.1177)
37. Chandrasekharappa SC, Guru SC, Manickam P, et al. Positional cloning of the gene for multiple endocrine neoplasia-type 1. *Science.* **1997** Apr 18;276(5311):404–407.
38. Marques P, Caimari F, Hernandez-Ramirez LC, et al. Significant benefits of AIP testing and clinical screening in familial isolated and young-onset pituitary tumors. *J Clin Endocrinol Metab.* **2020** 1; 105(6): Jun.
39. Li C, Xie W, Rosenblum JS, et al. Somatic SF3B1 hotspot mutation in prolactinomas. *Nat Commun.* **2020** May 19;11(1):2506.
40. Park SS, Kim JH, Kim YH, et al. Clinical and radiographic characteristics related to hyperprolactinemia in nonfunctioning pituitary adenomas. *World Neurosurg.* **2018** Nov;119:e1035–e1040.
41. Kruse A, Astrup J, Gyldensted C, et al. Hyperprolactinaemia in patients with pituitary adenomas The pituitary stalk compression syndrome. *Br J Neurosurg.* **1995**;9(4):453–457.
- **Classic description of stalk effect.**
42. Bergsneider M, Mirsadraei L, Yong WH, et al. The pituitary stalk effect: is it a passing phenomenon? *J Neurooncol.* **2014** May;117(3):477–484.
43. Chanson P, Maiter D. Prolactinoma. In: Melmed S, editor. *The pituitary.* United Kingdom: Elsevier; **2017**. p. 467–514.
44. Behan LA, O'Sullivan EP, Glynn N, et al. Serum prolactin concentration at presentation of non-functioning pituitary macroadenomas. *J Endocrinol Invest.* **2013** Jul-Aug;36(7):508–514.
45. Karavitaki N, Thanabalasingham G, Shore HC, et al. Do the limits of serum prolactin in disconnection hyperprolactinaemia need re-definition? A study of 226 patients with histologically verified non-functioning pituitary macroadenoma. *Clin Endocrinol (Oxf).* **2006** Oct;65(4):524–529.
46. Melmed S. Pathogenesis of pituitary tumors. *Nat Rev Endocrinol.* **2011** May;7(5):257–266.
47. Chahal J, Schlechte J. Hyperprolactinemia. *Pituitary.* **2008**;11(2):141–146.
48. Faje A, Jones P, Swearingen B. The prolactin per unit tumor volume ratio accurately distinguishes prolactinomas from secondary hyperprolactinemia due to stalk effect. *Endocrine Practice.* **2022**;28(6): 572–577. DOI:[10.1016/j.epr.2022.03.013](https://doi.org/10.1016/j.epr.2022.03.013)
- **Excellent documentation fo relationship between tumor size and serum PRL level.**
49. Schlechte J, Dolan K, Sherman B, et al. The natural history of untreated hyperprolactinemia: a prospective analysis. *J Clin Endocrinol Metab.* **1989** Feb;68(2):412–418.
- **Ipportant study documenting natural history of untreated tumors.**
50. Sarwar KN, Huda MS, Van de Velde V, et al. The prevalence and natural history of pituitary hemorrhage in prolactinoma. *J Clin Endocrinol Metab.* **2013** Jun;98(6):2362–2367.
51. Bonert V. Do nothing but observe microprolactinomas: when and how to replace sex hormones? *Pituitary.* **2020** Jun;23(3):307–313.
- **Data supporting lack of need to treat many PRL secreting tumors at hormonal recurrence.**
52. Melmed S. Pituitary tumors. *Endocrinol Metab Clin North Am.* **2015** Mar;44(1):1–9.
53. Krogh J, Selmer C, Torp-Pedersen C, et al. Hyperprolactinemia and the association with all-cause mortality and cardiovascular mortality. *Horm Metab Res.* **2017** Jun;49(6):411–417.
54. Dekkers OM, Romijn JA, de Boer A, et al. The risk for breast cancer is not evidently increased in women with hyperprolactinemia. *Pituitary.* **2010** Sep;13(3):195–198.
55. Grattan DR, Kokay IC. Prolactin: a pleiotropic neuroendocrine hormone. *J Neuroendocrinol.* **2008** Jun;20(6):752–763.
56. Kelly MA, Rubinstein M, Asa SL, et al. Pituitary lactotroph hyperplasia and chronic hyperprolactinemia in dopamine D2 receptor-deficient mice. *Neuron.* **1997** Jul;19(1):103–113.
57. Boguszewski CL, CM DS, KS S, et al. A comparison of cabergoline and bromocriptine on the risk of valvular heart disease in patients with prolactinomas. *Pituitary.* **2012** Mar;15(1):44–49.
58. Thorner MO, McNeilly AS, Hagan C, et al. Long-term treatment of galactorrhoea and hypogonadism with bromocriptine. *Br Med J.* **1974** May 25;2(5916):419–422.
59. Biller BM, Grossman AB, Stewart PM, et al. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab.* **2008** Jul;93(7):2454–2462.
60. Colao A, Somma CD, Lombardi G, di Sarno A, Pivonello R, et al. Dopamine receptor agonists for treating prolactinomas. *Expert Opinion on Investigational Drugs.* **2002** Jun;11(6):787–800. DOI:[10.1517/13543784.11.6.787](https://doi.org/10.1517/13543784.11.6.787)
61. Bevan JS, Webster J, Burke CW, et al. Dopamine agonists and pituitary tumor shrinkage. *Endocr Rev.* **1992** May;13(2):220–240.
62. Thorner MO, Martin WH, Rogol AD, et al. Rapid regression of pituitary prolactinomas during bromocriptine treatment. *J Clin Endocrinol Metab.* **1980** Sep;51(3):438–445.
- **Landmark paper describing efficacy of bromocriptine for treatment of PRLomas.**
63. Webster J, Piscitelli G, Polli A, et al. A comparison of cabergoline and bromocriptine in the treatment of hyperprolactinemic amenorrhea cabergoline comparative study group. *N Engl J Med.* **1994** Oct 6;331(14):904–909.
64. Gillam MP, Molitch ME, Lombardi G, et al. Advances in the treatment of prolactinomas. *Endocr Rev.* **2006** Aug;27(5):485–534.
65. Colao A, Savastano S. Medical treatment of prolactinomas. *Nat Rev Endocrinol.* **2011** May;7(5):267–278.
66. Rastogi A, Bhansali A, Dutta P, et al. A comparison between intensive and conventional cabergoline treatment of newly diagnosed patients with macroprolactinoma. *Clin Endocrinol (Oxf).* **2013** Sep;79(3):409–415.

67. Olafsdottir A, Schlechte J. Management of resistant prolactinomas. *Nat Clin Pract Endocrinol Metab.* 2006 Oct;2(10):552–561.
68. Paepegaey AC, Salenave S, Kamenicky P, et al. Cabergoline tapering is almost always successful in patients with macroprolactinomas. *J Endocr Soc.* 2017 Mar 1;1(3):221–230.
69. Dekkers OM, Lagro J, Burman P, et al. Recurrence of hyperprolactinemia after withdrawal of dopamine agonists: systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2010 Jan;95(1):43–51.
- **Important analysis demonstrating difficulty of DA withdrawal in PRL secreting tumors.**
70. Hage C, Salvatori R. Predictors of the response to dopaminergic therapy in patients with prolactinoma. *J Clin Endocrinol Metab.* 2020 1;105(12):Dec.
71. Kharlip J, Salvatori R, Yenokyan G, et al. Recurrence of hyperprolactinemia after withdrawal of long-term cabergoline therapy. *J Clin Endocrinol Metab.* 2009 Jul;94(7):2428–2436.
72. Barber TM, Kenkre J, Garnett C, et al. Recurrence of hyperprolactinemia following discontinuation of dopamine agonist therapy in patients with prolactinoma occurs commonly especially in macroprolactinoma. *Clin Endocrinol (Oxf).* 2011 Dec;75(6):819–824.
73. Anagnostis P, Adamidou F, Polyzos SA, et al. Long term follow-up of patients with prolactinomas and outcome of dopamine agonist withdrawal: a single center experience. *Pituitary.* 2012 Mar;15(1):25–29.
74. Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. *JAMA Intern Med.* 2014 Dec;174(12):1930–1933.
- **Paper documenting some under-reported aspects of DA related psychiatric disorders.**
75. Noronha S, Stokes V, Karavitaki N, et al. Treating prolactinomas with dopamine agonists: always worth the gamble? *Endocrine.* 2016 Feb;51(2):205–210.
76. Bancos I, Nannenga MR, Bostwick JM, et al. Impulse control disorders in patients with dopamine agonist-treated prolactinomas and nonfunctioning pituitary adenomas: a case-control study. *Clin Endocrinol (Oxf).* 2014 Jun;80(6):863–868.
77. Su J, Simonsen U, Carlsen J, et al. Pulmonary artery occlusion and mediastinal fibrosis in a patient on dopamine agonist treatment for hyperprolactinemia. *Front Pharmacol.* 2017;8:492.
78. Townsend M. Constrictive pericarditis and pleuropulmonary fibrosis secondary to cabergoline treatment for Parkinson's disease. *Heart.* 2004 Aug;90(8):e47.
79. Levin J, Neudert J, Zwermann L, et al. Reversible cardiac valve fibrosis secondary to treatment with high-dose cabergoline for Parkinson's disease. *J Neurol.* 2011 Nov;258(11):2097–2099.
80. Bogazzi F, Manetti L, Raffaelli V, et al. Cabergoline therapy and the risk of cardiac valve regurgitation in patients with hyperprolactinemia: a meta-analysis from clinical studies. *J Endocrinol Invest.* 2008 Dec;31(12):1119–1123.
81. Roth BL. Drugs and valvular heart disease. *N Engl J Med.* 2007 Jan 4;356(1):6–9.
82. Stiles CE, Tetteh-Wayoe ET, Bestwick J, et al. A meta-analysis of the prevalence of cardiac valvulopathy in patients with hyperprolactinemia treated with cabergoline. *J Clin Endocrinol Metab.* 2018;104(2):523–538. DOI:10.1210/jc.2018-01071
- **Important analysis of impact of low dose cabergoline on valvular heart disease.**
83. Landolt AM, Keller PJ, Froesch ER, et al. Bromocriptine: does it jeopardise the result of later surgery for prolactinomas? *Lancet.* 1982 Sep 18;2(8299):657–658. DOI:10.1016/S0140-6736(82)92756-8
84. Menucci M, Quinones-Hinojosa A, Burger P, et al. Effect of dopaminergic drug treatment on surgical findings in prolactinomas. *Pituitary.* 2011 Mar;14(1):68–74.
85. Losa M, Mortini P, Barzaghi R, et al. Surgical treatment of prolactin-secreting pituitary adenomas: early results and long-term outcome. *J Clin Endocrinol Metab.* 2002 Jul;87(7):3180–3186.
86. Ikeda H, Watanabe K, Tominaga T, et al. Transsphenoidal microsurgical results of female patients with prolactinomas. *Clin Neurol Neurosurg.* 2013 Sep;115(9):1621–1625.
87. Primeau V, Raftopoulos C, Maiter D. Outcomes of transsphenoidal surgery in prolactinomas: improvement of hormonal control in dopamine agonist-resistant patients. *Eur J Endocrinol.* 2012 May;166(5):779–786.
88. Honegger J, Nasi-Kordhishti I, Aboutaha N, et al. Surgery for prolactinomas: a better choice? *Pituitary.* 2020 Feb;23(1):45–51.
- **Nice analysis of surgical advantages for microadenomas.**
89. Mohan N, Chia YY, Goh GH, et al. Cabergoline-induced fibrosis of prolactinomas: a neurosurgical perspective BMJ case rep. 2017;3. DOI:10.1136/bcr-2017-220971
90. Kawabata Y, Ueno Y, Horikawa F, et al. Remarkable effects of cabergoline in a patient with huge prolactinoma resistant to high-dose bromocriptine: case report. *Surg Neurol.* 2008 Jan;69(1):85–8; discussion 88.
91. Lam A, Holbrook E. Skull base anatomy and CSF rhinorrhea. *Adv Otorhinolaryngol.* 2013;74:1–11.
92. Briet C, Salenave S, Bonneville JF, et al. Pituitary Apoplexy. *Endocr Rev.* 2015 Dec;36(6):622–645.
93. Colao A, Di Sarno A, Cappabianca P, et al. Withdrawal of long-term cabergoline therapy for tumoral and nontumoral hyperprolactinemia. *N Engl J Med.* 2003 Nov 20;349(21):2023–2033.
- **Key study evaluating efficacy of DA withdrawal in patients with hyperprolactinemia, indicating withdrawal less effective for long-term control.**
94. Caccavelli L, Feron F, Morange I, et al. Decreased expression of the two D2 dopamine receptor isoforms in bromocriptine-resistant prolactinomas. *Neuroendocrinology.* 1994 Sep;60(3):314–322.
95. Tyrrell JB, Lamborn KR, Hannegan LT, et al. Transsphenoidal microsurgical therapy of prolactinomas: initial outcomes and long-term results. *Neurosurgery.* 1999 Feb;44(2):254–261. discussion 261–3.
96. Donoho DA, Laws ER Jr. The role of surgery in the management of prolactinomas. *Neurosurg Clin N Am.* 2019 Oct;30(4):509–514.
97. Couldwell WT, Weiss MH, Laws ER Jr. Prolactinomas. *N Engl J Med.* 2004 Mar 4;350(10):1054. author reply.
98. Turner HE, Adams CB, Wass JA. Trans-sphenoidal surgery for microprolactinoma: an acceptable alternative to dopamine agonists? *Eur J Endocrinol.* 1999 Jan;140(1):43–47.
99. Zamanipoor Najafabadi AH, Zandbergen IM, de Vries F, et al. Surgery as a viable alternative first-line treatment for prolactinoma patients: a systematic review and meta-analysis. *J Clin Endocrinol Metab.* 2020;105(1):Mar.
- **Recent well-performed meta-analysis of surgical advantages for prolactinomas.**
100. Casanueva FF, Barkan AL, Buchfelder M, et al. Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): a pituitary society statement. *Pituitary.* 2017 Oct;20(5):489–498.
101. Fatemi N, Dusick JR, de Paiva Neto MA, et al. The endonasal microscopic approach for pituitary adenomas and other parasellar tumors: a 10-year experience. *Neurosurgery.* 2008 Oct;63(4 Suppl 2):244–256. discussion 256.
102. Kreutzer J, Buslei R, Wallaschofski H, et al. Operative treatment of prolactinomas: indications and results in a current consecutive series of 212 patients. *Eur J Endocrinol.* 2008 Jan;158(1):11–18.
103. Tampourlou M, Trifanescu R, Paluzzi A, et al. Therapy in endocrine disease: surgery in microprolactinomas: effectiveness and risks based on contemporary literature. *Eur J Endocrinol.* 2016 Sep;175(3):R89–96.
104. Barker FG 2nd, Klibanski A, Swearingen B. Transsphenoidal surgery for pituitary tumors in the United States, 1996–2000: mortality, morbidity, and the effects of hospital and surgeon volume. *J Clin Endocrinol Metab.* 2003 Oct;88(10):4709–4719.
105. Gondim JA, Almeida JP, Albuquerque LA, et al. Endoscopic endonasal approach for pituitary adenoma: surgical complications in 301 patients. *Pituitary.* 2011 Jun;14(2):174–183.
106. Jane JJ, Thapar K, Laws E. Pituitary tumors: functioning and non-functioning. In: Winn H, editor. Youman's neurologic surgery. 2011. Vol. 2. Philadelphia PA: Elsevier. p. 1476–1510.
107. Sudhakar N, Ray A, Vafidis JA. Complications after trans-sphenoidal surgery: our experience and a review of the literature. *Br J Neurosurg.* 2004 Oct;18(5):507–512.

108. Ouyang T, Zhang N, Xie S, et al. Outcomes and complications of aggressive resection strategy for pituitary adenomas in knosp grade 4 with transsphenoidal endoscopy. *Front Oncol.* **2021**;11:693063.
109. Winograd D, Staggers KA, Sebastian S, et al. An effective and practical fluid restriction protocol to decrease the risk of hyponatremia and readmissions after transsphenoidal surgery. *Neurosurgery.* **2020** Sep 15;87(4):761–769.
110. Jahangiri A, Wagner J, Han SW, et al. Morbidity of repeat transsphenoidal surgery assessed in more than 1000 operations. *J Neurosurg.* **2014** Jul;121(1):67–74.
111. Gondim JA, Schops M, de Almeida JP, et al. Endoscopic endonasal transsphenoidal surgery: surgical results of 228 pituitary adenomas treated in a pituitary center. *Pituitary.* **2010**;13(1):68–77.
112. Shimon I. Giant prolactinomas: multi-modal approach to achieve tumor control. *Endocrine.* **2017** May;56(2):227–228.
113. Knosp E, Steiner E, Kitz K, et al. Pituitary adenomas with invasion of the cavernous sinus space: a magnetic resonance imaging classification compared with surgical findings. *Neurosurgery.* **1993** Oct;33(4):610–617. discussion 617–8.
114. Micko ASG, Wohrer A, Wolfsberger S, et al. Invasion of the cavernous sinus space in pituitary adenomas: endoscopic verification and its correlation with an MRI-based classification. *J Neurosurg.* **2015** Apr;122(4):803–811.
115. Briceno V, Zaidi HA, Doucette JA, et al. Efficacy of transsphenoidal surgery in achieving biochemical cure of growth hormone-secreting pituitary adenomas among patients with cavernous sinus invasion: a systematic review and meta-analysis. *Neurol Res.* **2017** May;39(5):387–398.
- **Assesment of role of cavernous sinus involvement in achieving biochemical control for GH secreting tumors.**
116. Dehdashti AR, Ganna A, Karabatsou K, et al. Pure endoscopic endonasal approach for pituitary adenomas: early surgical results in 200 patients and comparison with previous microsurgical series. *Neurosurgery.* **2008** May;62(5):1006–1015. discussion 1015–7.
117. Jho DH, Biller BM, Agarwalla PK, et al. Pituitary apoplexy: large surgical series with grading system. *World Neurosurg.* **2014** Nov;82(5):781–790.
118. Lonser RR, Wind JJ, Nieman LK, et al. Outcome of surgical treatment of 200 children with Cushing's disease. *J Clin Endocrinol Metab.* **2013** Mar;98(3):892–901.
119. Mortini P, Losa M, Barzaghi R, et al. Results of transsphenoidal surgery in a large series of patients with pituitary adenoma. *Neurosurgery.* **2005** Jun;56(6):1222–1233. discussion 1233.
120. Babu H, Ortega A, Nuno M, et al. Long-term endocrine outcomes following endoscopic endonasal transsphenoidal surgery for acromegaly and associated prognostic factors. *Neurosurgery.* **2017** Aug 1;81(2):357–366.
121. Jane JA Jr., Starke RM, Elzoghby MA, et al. Endoscopic transsphenoidal surgery for acromegaly: remission using modern criteria, complications, and predictors of outcome. *J Clin Endocrinol Metab.* **2011** Sep;96(9):2732–2740.
122. Mooney MA, Sarris CE, Zhou JJ, et al. Proposal and validation of a simple grading scale (TRANSSPHER Grade) for predicting gross total resection of nonfunctioning pituitary macroadenomas after transsphenoidal surgery. *Oper Neurosurg (Hagerstown).* **2019** Nov 1;17(5):460–469.
123. Little AS, Chicoine MR, Kelly DF, et al. Evaluation of surgical resection goal and its relationship to extent of resection and patient outcomes in a multicenter prospective study of patients with surgically treated, nonfunctioning pituitary adenomas: a case series. *Oper Neurosurg (Hagerstown).* **2020** Jan 1;18(1):26–33.
124. Zielinski G, Sajjad EA, Maksymowicz M, et al. Double pituitary adenomas in a large surgical series. *Pituitary.* **2019** Dec;22(6):620–632.
125. Fernandez-Miranda JC, Zwagerman NT, Abhinav K, et al. Cavernous sinus compartments from the endoscopic endonasal approach: anatomical considerations and surgical relevance to adenoma surgery. *J Neurosurg.* **2018** Aug;129(2):430–441.
126. Cohen-Cohen S, Gardner PA, Alves-Belo JT, et al. The medial wall of the cavernous sinus Part 2: selective medial wall resection in 50 pituitary adenoma patients. *J Neurosurg.* **2018** Sep 7;131(1):131–140.
127. Fang Y, Pei Z, Chen H, et al. Diagnostic value of Knosp grade and modified Knosp grade for cavernous sinus invasion in pituitary adenomas: a systematic review and meta-analysis. *Pituitary.* **2021** Jun;24(3):457–464.
128. Park JY, Choi W, Hong AR, et al. Surgery is a safe, effective first-line treatment modality for noninvasive prolactinomas. *Pituitary.* **2021** Dec;24(6):955–963.
129. Babey M, Sahli R, Vajtai I, et al. Pituitary surgery for small prolactinomas as an alternative to treatment with dopamine agonists. *Pituitary.* **2011** Sep;14(3):222–230.
130. Andereggen L, Frey J, Andres RH, et al. 10-year follow-up study comparing primary medical vs surgical therapy in women with prolactinomas. *Endocrine.* **2017** Jan;55(1):223–230.
- **Important study validating utility of surgical approach over medical therapy for subset of prolactinomas.**
131. Zielinski G, Ozdarski M, Maksymowicz M, et al. Prolactinomas: prognostic factors of early remission after transsphenoidal surgery. *Front Endocrinol (Lausanne).* **2020**;11:439.
132. Bao X, Deng K, Liu X, et al. Extended transsphenoidal approach for pituitary adenomas invading the cavernous sinus using multiple complementary techniques. *Pituitary.* **2016** Feb;19(1):1–10.
133. Shimon I, Sosa E, Mendoza V, et al. Giant prolactinomas larger than 60 mm in size: a cohort of massive and aggressive prolactin-secreting pituitary adenomas. *Pituitary.* **2016** Aug;19(4):429–436.
134. Marigil Sanchez M, Karekezi C, Almeida JP, et al. Management of giant pituitary adenomas: role and outcome of the endoscopic endonasal surgical approach. *Neurosurg Clin N Am.* **2019** Oct;30(4):433–444.
135. Couldwell WT, Weiss MH. Medical and surgical management of microprolactinoma. *Pituitary.* **2004**;7(1):31–32.
136. Jethwa PR, Patel TD, Hajart AF, et al. Cost-effectiveness analysis of microscopic and endoscopic transsphenoidal surgery versus medical therapy in the management of microprolactinoma in the United States. *World Neurosurg.* **2016** Mar;87:65–76.
- **Cost and cost-efficacy analysis of surgery versus medical therapy for microprolactinomas.**
137. Cesar de Oliveira Naliato E, Dutra VAH, Caldas D, et al. Quality of life in women with microprolactinoma treated with dopamine agonists. *Pituitary.* **2008**;11(3):247–254.
138. Zanettini R, Antonini A, Gatto G, et al. Valvular heart disease and the use of dopamine agonists for Parkinson's disease. *N Engl J Med.* **2007** Jan 4;356(1):39–46.
139. Ono M, Miki N, Kawamata T, et al. Prospective study of high-dose cabergoline treatment of prolactinomas in 150 patients. *J Clin Endocrinol Metab.* **2008** Dec;93(12):4721–4727.
140. Sheehan JP, Jagannathan J, Pouratian N, et al. Stereotactic radiosurgery for pituitary adenomas: a review of the literature and our experience. *Front Horm Res.* **2006**;34:185–205.
141. Pouratian N, Sheehan J, Jagannathan J, et al. Gamma knife radiosurgery for medically and surgically refractory prolactinomas. *Neurosurgery.* **2006** Aug;59(2):255–266. discussion.
142. Tanaka S, Link MJ, Brown PD, et al. Gamma knife radiosurgery for patients with prolactin-secreting pituitary adenomas. *World Neurosurg.* **2010** Jul;74(1):147–152.
143. Kowalchuck RO, Trifiletti DM, Brown PD. Radiotherapy in the management of pituitary adenomas. Melmed S, editors. *The Pituitary*. Fifth ed. Cambridge MA:Elsevier; **2022**. p.753–764.