



Paradigm Shift in the Management of Prolactinoma: Is Primary Surgery Better than Medical Management in Select Patients?

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Abstract

Prolactinomas, benign hormone-secreting tumours of the anterior pituitary, are traditionally treated with dopamine agonists (DAs), such as cabergoline, due to their high efficacy in normalizing prolactin levels, alleviating symptoms, and reducing tumour size. However, DA therapy often necessitates long-term use, with potential adverse effects and variable remission rates after discontinuation. Surgical resection, primarily via endoscopic transsphenoidal approaches, offers an alternative and increasingly reconsidered option. This review explores the evolving paradigm in prolactinoma management, emphasizing primary surgery's role in select cases. Surgery demonstrates high remission rates, especially for Macroprolactinoma and non-invasive macroprolactinomas, and presents the potential for a permanent cure. Expanding indications for surgery include DA resistance, intolerance, patient preference, and certain tumour characteristics. Advancements in surgical techniques and improved outcomes further support its use. The review underscores the importance of individualized treatment plans, considering tumour characteristics, patient factors, and the expertise available. Future clinical trials comparing surgical and medical approaches aim to refine evidence-based pathways in prolactinoma care.

Keywords: Prolactinoma; Macroprolactinoma; Transsphenoidal Surgery; Endoscopic Surgery; Dopamine Agonist

Introduction

Prolactinomas are the most common type of hormone-secreting pituitary tumours, arising from the lactotroph cells of the anterior pituitary gland [1,2]. They are benign tumours, classified as World Health Organization Grade I [3,4], and are characterized by the overproduction of prolactin (PRL(3)). Prolactinomas account for a significant proportion of all pituitary adenomas, with estimates ranging from 30% to 60% [5–8]. Studies suggest a prevalence of 35 to 775 cases per million people [6,8]. The over secretion

of prolactin leads to hyperprolactinemia, which manifests with a variety of clinical symptoms [3,9]. In women, common presentations include menstrual disturbances (such as amenorrhea and oligomenorrhea), galactorrhoea (breast milk production), and infertility [1,2,9]. Men may experience sexual dysfunction, including decreased libido and erectile dysfunction, and less frequently, gynecomastia, osteoporosis [1,5,9-11]. Additionally, larger tumours can cause mass effect symptoms such as headaches and visual field defects due to compression of adjacent structures [1-3]. Prolactinomas are typically categorized based on their

size into macroprolactinomas (diameter < 10 mm) and macroprolactinomas (diameter ≥ 10 mm) [5,11,12]. A subset of macroprolactinomas, known as giant prolactinomas, are defined as being greater than 4 cm in diameter and/or having more than 2 cm of suprasellar extension [12-14]. Macroprolactinomas are more frequent and rarely proliferate, while macroprolactinomas, particularly in men, may exhibit different clinical prognoses and require closer monitoring [12]. The general consensus is that dopamine agonists (DAs) are the first-line medical therapy for most prolactinomas due to their effectiveness in lowering prolactin levels and reducing tumour size [8,15,16]. However, surgery plays an important role in specific situations [8,15].

History of Management of Prolactinoma

The history of prolactinoma treatment has evolved significantly. Historically, surgical resection was the primary treatment for prolactinomas [14]. However, the landscape dramatically shifted with the discovery and introduction of dopamine agonists (DAs) in the mid-1980s, particularly bromocriptine, which proved effective in controlling these tumours [14]. The ability of bromocriptine to normalize prolactin levels and reduce tumour size marked a turning point, making medical therapy the mainstay of treatment for most prolactinomas [14,17-19].

Subsequent advancements in medical therapy included the development of cabergoline in the 1990s, a second-generation DA with better efficacy, tolerability, and less frequent dosing compared to bromocriptine [4,17,18]. Studies demonstrated cabergoline's superiority in normalizing prolactin and achieving tumour shrinkage, even in patients resistant to other DAS [17]. Quinagolide also emerged as another DA option with a different tolerability profile [17].

Despite the success of medical therapy, surgery continues to play a crucial role in specific circumstances [14,18,20]. Indications for surgery include resistance or intolerance to DAs, tumour enlargement despite medical therapy, and certain situations during pregnancy with unstable neuro-ophthalmological deficits [14,21]. Furthermore, with advancements in transsphenoidal surgical techniques, particularly endoscopic approaches, surgery is increasingly considered a viable option, even as a potential first-line treatment for macroprolactinomas in some centres or based on patient preference for a chance of cure without long-term medication [9,17,19].

Therefore, while DAs represent the primary treatment approach for most prolactinomas, surgery remains an important alternative and is experiencing a reappraisal of its role in the modern era, particularly for macroprolactinomas and DA-resistant cases [17,18,20].

Role of Medical therapy

Advantages of Dopamine Agonist Treatment

Dopamine agonists (DAs) offer several advantages as a primary treatment for prolactinomas:

- **First-Line Therapy:** Dopamine agonists are the recommended initial treatment for most prolactinomas. This is based on their established effectiveness in managing the condition.
- **Effective Prolactin Lowering:** DA therapy is highly effective at reducing serum prolactin levels. Studies have shown that following primary treatment, prolactin levels significantly decrease in patients treated medically. Cabergoline, in particular, has demonstrated high efficacy in achieving normoprolactinemia in a large percentage of patients [3,7,9,11,12,14,22-28].
- **Symptom Improvement:** By normalizing prolactin levels, DAs can alleviate clinical symptoms of hyperprolactinemia, such as galactorrhoea, hypogonadism, menstrual disturbances, sexual dysfunction, and infertility.
- **Tumour Size Reduction:** Dopamine agonists can lead to a reduction in the size of prolactinomas. Significant tumour shrinkage occurs in a high proportion of patients within 12-24 months of cabergoline treatment. In some cases, especially with microadenomas, complete tumour disappearance can occur.
- **Generally Well-Tolerated:** Dopamine agonists are generally considered safe and well-tolerated by most patients.
- **Cabergoline Preference:** Cabergoline is often the preferred dopamine agonist due to its longer half-life, higher efficacy in normalizing prolactin and inducing tumour shrinkage, and better tolerability compared to bromocriptine and quinagolide. It has also been shown to be more effective in normalizing prolactin levels in patients who are resistant to bromocriptine.
- **Visual Field Improvement:** In patients with macroprolactinomas experiencing vision damage, dopamine agonist therapy can lead to an improvement in visual fields in a significant percentage of cases.
- **Standard of Care:** Medical management with dopamine agonists is considered the standard of care for prolactinomas by many healthcare providers due to the high rates of biochemical and radiographic remission achieved.
- **Physiological Mechanism:** Dopamine agonist therapy works by capitalizing on the natural response of prolactin-secreting cells (lactotrophs) in the pituitary gland to dopamine, which leads to a decrease in prolactin secretion. Dopamine agonists bind to dopamine D2 receptors on these cells, inhibiting prolactin synthesis and release, and reducing tumour size.
- **Minimizing Side Effects:** Common side effects associated with DA use can often be minimized by using

strategies such as preferring cabergoline, starting at a low dose and gradually increasing it, taking medication with food or before bedtime, and splitting or reducing the dose if side effects develop.

- **Restoration of Gonadal Function and Fertility:** In cases of microadenomas where observation alone is not suitable, medical treatment with dopamine agonists is effective in restoring gonadal function and fertility in most patients.
- **Post-Surgical Benefit:** In some instances, dopamine agonist dose reduction can be achieved after surgical intervention for prolactinomas.
- Overall, dopamine agonist therapy is a highly effective and generally well-tolerated first-line treatment for prolactinomas, addressing both the hormonal and tumour aspects of the condition in most patients.

Disadvantages of Dopamine Agonist Treatment

Dopamine agonist (DA) therapy, while a first-line treatment for prolactinomas, has several disadvantages, including [3,7,9,12,14,17,22–25,27–31].

- **Potential Need for Long-Term Treatment:** Many patients may require DA treatment for an extended period, potentially lifelong, as sustained remission after withdrawal occurs in only about one-third of patients after two years of treatment. Long-term disease remission after DA withdrawal (34%) is notably lower compared to transsphenoidal surgery (64%).

Possible Adverse Effects: DAs can cause various side effects.

- Common side effects include gastrointestinal issues like nausea, vomiting, abdominal discomfort, and constipation; symptoms related to vasodilation such as postural hypotension, headache, nasal congestion, and flushing; and neurological effects like mood changes, sleep disturbance, and fatigue. These side effects usually improve over time but can persist and be disabling for some individuals.
- Less common side effects at typical doses include digital vasospasm.
- Bromocriptine is associated with increased side effects compared to cabergoline and quinagolide. In one study, adverse events occurred in 78% of women on bromocriptine versus 68% on cabergoline, leading to discontinuation in 12% and 3% respectively.
- Other symptoms associated with higher doses of bromocriptine include anxiety, depression, confusion, auditory hallucinations, hyperactivity, disinhibition, insomnia, daytime somnolence, and paranoia. Dyskinesias similar to those seen with levodopa are also recognized with high-dosage treatment. Paraesthesia, nightmares, blurred vision, diplopia (at high doses), and reversible ototoxicity (in patients with chronic hepatic disease) have also been reported.

Rare but Serious Risks: DA use carries rare but serious risks.

- **Cardiac Valvopathy:** There is a debated risk of cardiac valvopathy, which appears to be related to lifetime cabergoline exposure. Concerns exist about the potential for interaction with serotonin 5-hydroxytryptamine 2B (5-HT_{2B}) receptors, similar to drugs known to cause fibrotic disease. However, recent literature does not strongly support a clinically concerning association between DAs for hyperprolactinemia and cardiac valvopathy, although concerns about long-term cumulative doses remain. Studies have investigated the prevalence of cardiac valvular abnormalities in hyperprolactinaemic patients treated with ergot-derived dopamine agonists.
- **Impulse Control Disorders (ICDs):** ICDs have been reported in 8-24% of patients. These include pathological gambling, hypersexuality, and compulsive shopping. The prevalence of ICDs was significantly higher in patients with prolactinomas on DA therapy compared to those with non-functioning pituitary adenomas not on DAs, and the general population. Male patients with prolactinomas treated with DAs showed a higher risk of ICDs. Risk factors for ICDs include male sex, a eugonadal state, less invasive tumours, and psychiatric comorbidities. ICDs are associated with bromocriptine, quinagolide, and cabergoline.
- **Psychosis:** Psychosis is another rare but serious risk.
- New-onset psychosis may rarely occur after starting DAs.
- Cerebrospinal fluid (CSF) rhinorrhoea.
- **Tumour Fibrosis:** DA treatment may induce tumour fibrosis, which some neurosurgeons believe can make surgical removal more difficult, although this remains controversial.
- **Impact on Quality of Life:** Quality of life can remain impaired in some patients despite effective DA treatment.
- **Limited Chances of Permanent Cure:** DA therapy has limited chances of a permanent cure. Long-term remission rates after DA withdrawal are lower than after surgery.
- **Potential for Dopamine Agonist Resistance:** A subset of individuals with prolactinomas do not respond satisfactorily to DAs. Resistance is defined as the failure to achieve normoprolactinemia and/or 50% tumour shrinkage. Approximately 80% of bromocriptine-resistant patients may respond to cabergoline. Resistance to one DA does not necessarily mean resistance to all, as some patients may respond to an alternative DA. Higher dose of DAs may be needed in some cases of partial resistance.
- **Adverse Effects can Lead to Discontinuation:** Intolerable adverse events can necessitate stopping DA treatment in some patients. Cessation of therapy was required in a small minority of patients due to side

effects, with a higher rate for bromocriptine (12%) than cabergoline (3%). In one macroprolactinoma study, 18% of patients stopped treatment due to side effects.

- **Cost:** The lifelong costs associated with medical therapy can be a significant consideration compared to surgical options. Patients in developing countries might take suboptimal doses due to cost.
- **May Induce Tumour Fibrosis:** As mentioned earlier, some neurosurgeons believe that DA treatment can induce tumour fibrosis, potentially complicating subsequent surgical removal. However, this remains a point of debate.
- These disadvantages highlight the importance of careful patient selection, thorough discussion of potential risks and benefits, and close monitoring during DA therapy for prolactinomas. In cases of intolerance or resistance, or due to patient preference, surgery may be considered as an alternative.

Role of surgery

Traditional Indications for Surgery

Historically, before the widespread use of dopamine agonists (DAs), surgery was the primary treatment for prolactinomas [14,24]. However, with the advent of effective medical therapy, surgery became reserved for specific situations [9,14,18,20]. These traditional indications include [4,9,14,16-18,20,32].

- **Resistance to Dopamine Agonists (DA Resistance):** Surgery is indicated in patients whose prolactin levels do not normalize or whose tumours do not shrink adequately despite being on maximally tolerated doses of DAS [4,14,16,18]. This was the most common indication for surgery in some series [21].
- **Intolerance to Dopamine Agonists (DA Intolerance):** Patients who experience significant and intolerable side effects from DAs are candidates for surgical treatment. DA intolerance was a more frequent reason for surgery in microprolactinoma patients than in macroprolactinoma patients in one study.
- **Pituitary Apoplexy with Neurological Worsening:** In cases of haemorrhage or infarction into the tumour causing acute symptoms like severe headache and visual disturbance, urgent surgical decompression may be necessary. However, some cases with stable visual field deficits might be managed medically.
- **Progressive Visual Loss or Other Neurological Deficits:** Patients experiencing worsening vision or cranial nerve defects due to tumour compression, especially if not responding to medical therapy, are surgical candidates.
- **Cerebrospinal Fluid (CSF) Leak:** Surgery is indicated to repair CSF leaks that may occur spontaneously or as a result of tumour shrinkage after DA therapy.

- **Certain Situations During Pregnancy:** Expanding prolactinomas causing unstable neuro-ophthalmological deficits that do not respond to bromocriptine may require surgery during pregnancy, particularly in the second trimester. Debulking surgery may also be considered prior to pregnancy in women with macroprolactinomas to reduce the risk of symptomatic enlargement.

Expanding Indications for Surgery

Over time, with advancements in surgical techniques (especially endoscopic transsphenoidal surgery) and a greater understanding of the limitations and potential long-term issues with DA therapy, the indications for considering surgery have broadened. These expanding indications include:

- **Patient Preference:** The patient's informed decision to pursue surgery as a potential chance for cure and avoid long-term medication has become an increasingly recognized and accepted indication, particularly for macroprolactinomas. This was the prevailing indication for surgery in macroprolactinomas in some contemporary series [3,4,7,9,14,16,17,19-21].
- **Cystic Prolactinomas:** Tumours with a significant cystic component are often less likely to respond effectively to DA therapy alone, making surgery a more viable option.
- **Young Patients:** In younger individuals, surgery might be considered to circumvent the potential unpredictable long-term sequelae of DA treatment.
- **Discordance Between Prolactin Levels and Tumour Size:** When there is a significant tumour mass with only modestly elevated prolactin levels, suggesting a possible non-functioning adenoma causing a stalk effect, surgery may be preferred as DAs are unlikely to shrink the tumour.
- **Prior to Attempting Pregnancy (in some cases):** For women with microprolactinomas, surgery offers a high probability of remission, potentially eliminating the need for DA therapy to induce ovulation.
- **Debulking in DA-Resistant or Aggressive Prolactinomas:** Surgery can be used to reduce tumour size in patients with resistant or aggressive prolactinomas, often as part of a multimodality treatment approach.
- **Potential for Long-Term Remission:** Studies suggest higher long-term remission rates after surgery compared to DA withdrawal, especially in microprolactinomas.

Surgery as a First-Line Option in the Recent Era

The role of surgery as a potential first-line treatment for prolactinomas, rather than solely a second-line option, has been increasingly discussed and supported by recent literature and advancements. This shift is driven by [3,5,7,9,10,16-20,24,33-35].

- **High Remission Rates, Especially in Microprolactinomas:** Contemporary surgical series, particularly with experienced pituitary surgeons and endoscopic techniques, report high initial and long-term remission rates in microprolactinomas, often comparable to or even exceeding those after DA withdrawal.
- **Lower Morbidity in Experienced Centres:** Advances in surgical techniques have led to lower complication rates associated with transsphenoidal surgery in experienced hands.
- **Limitations and Side Effects of Long-Term DA Therapy:** Concerns about the need for prolonged DA treatment, potential side effects (including rare but serious ones like impulse control disorders and cardiac valvopathy), and the possibility of recurrence after DA withdrawal have prompted consideration of surgery as an initial option.
- **Patient Preference for a Chance of Cure:** Many patients, particularly younger individuals, may prefer the possibility of a surgical cure over the prospect of years or even a lifetime of medical therapy.
- **Potential Cost-Effectiveness:** Some analyses suggest that surgery may be more cost-effective than lifelong medical management, especially when considering younger patients.
- **Better Outcomes in DA-Naive Patients:** Some studies suggest that surgical remission rates may be higher in patients who have not received prior DA treatment, possibly due to the lack of tumour fibrosis.
- The following Table 1 highlights the ongoing clinical trials focusing on dopamine agonist (DA) therapy versus surgery.

Trial Name	Type	Comparison	Status	Estimated Completion	Key Outcomes	Additional details
PRolaCT-1,2,3	Randomized Controlled Trials	Surgery vs. DA therapy	Ongoing	Post-2025	Remission rates, HRQoL	Includes pre and post treatment imaging assessments; subgroups analysed for patient age, gender and tumour size
PRolaCT-O	Observational Cohort	Surgery vs. DA therapy (non-randomized)	Ongoing	Post-2025	Real-world outcomes, patient preference	Tracks long term recurrence rates and tumor progression; geographic diversity in patient demographics

Table 1: Ongoing clinical trials and their status:[36]

Evidence-based Clinical Pathway

The clinical treatment paradigm Figure 1 illustrates how dopamine agonists remain the cornerstone of prolactinoma treatment, with surgery reserved for specific cases such as DA resistance, progressive symptoms, or patient preference.

Diagnosis and Initial Evaluation

The diagnosis of prolactinoma may be triggered by hormonal investigations for symptoms like menstrual disturbances and galactorrhoea in females, or erectile dysfunction and loss of libido in males. It can also be an incidental finding on neuroimaging or due to symptoms of pituitary mass effect, such as visual field defects [3,12,13,17].

- Biochemical diagnosis involves measuring serum prolactin levels. It's important to be aware of potential pitfalls in prolactin immunoassays, such as the high-dose hook effect. Macroprolactinoma, where prolactin exists in a large molecular mass, should also be considered as a cause of elevated prolactin that may not be clinically

significant.

- Once hyperprolactinemia is confirmed, pituitary magnetic resonance imaging (MRI) with contrast is essential to visualize the pituitary gland and identify the presence and size of a prolactinoma. MRI is also crucial for follow-up to monitor tumour size. Physicians' awareness of gadolinium retention and MRI timing practices in the longitudinal management of pituitary tumours is important.
- Algorithms exist to differentiate prolactinoma from non-functional adenomas causing a stalk effect, which can also lead to mild hyperprolactinemia.

First-Line Treatment

Dopamine Agonists (DAs): Dopamine agonists (DAs) are the first-line treatment for most prolactinomas. This is supported by their high efficacy in lowering prolactin levels and reducing tumour size [3,11-13].

- Cabergoline is generally the preferred DA due to its

better tolerance and superior efficacy in normalizing prolactin levels and causing tumour involution compared to bromocriptine. Cabergoline has a longer half-life, allowing for less frequent dosing.

- Dopamine agonist therapy capitalizes on the physiologic response of lactotrophic cells to dopamine, decreasing

prolactin secretion.

- In some cases of microadenomas, observation or hormone replacement therapy (HRT) can be considered depending on menopausal and gonadal status, along with patient preference.

Evidence Based Clinical Pathway

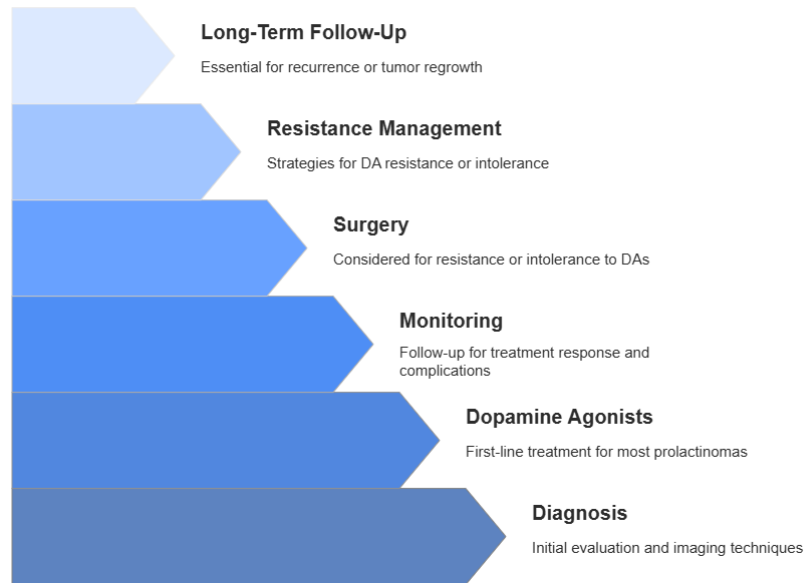


Figure 1: Existing clinical treatment paradigm: This figure visually represents the traditional approach to prolactinoma management, highlighting dopamine agonists (DAs) as the first-line treatment. It outlines pathways involving medical therapy, monitoring, and alternative options like surgery in cases of DA resistance or intolerance.

Monitoring Response to Medical Therapy

Follow-up should include monitoring serum prolactin levels, changes on MRI, the need for HRT, and any complications or adverse effects of DA treatment [3,8,11,12,29].

- Significant tumour shrinkage with DA therapy can occur. Macroadenoma shrinkage is often more pronounced in DA-naïve patients compared to those pre-treated with other DAs.
- The Pituitary Society consensus defined 'resistance' as a lack of normalization of prolactin serum levels or lack of relevant mass shrinkage ($\geq 30\%$ reduction in maximum diameter) when treated with standard dopamine agonist doses (7.5–10 mg per day of bromocriptine or 2.0 mg per week of cabergoline) for at least 6 months [12]. If prolactin levels do not normalize or tumour size does not adequately reduce with maximum tolerated doses of DAs, dopamine agonist resistance should be considered. Switching to a different DA (e.g., cabergoline for bromocriptine resistance) or increasing the dose

may be attempted.

Consideration of Surgery:

Surgery, mainly via the transsphenoidal route, is considered in specific situations [3,4,7,11-13,23,24,37,38].

- Traditional indications for surgery include:
 1. Resistance to dopamine agonists.
 2. Intolerance to dopamine agonists.
 3. Pituitary apoplexy with neurological worsening.
 4. Progressive visual impairment while on medication.
 5. Cystic tumours that may be less responsive to DAs.
 6. Intratumorally haemorrhage.
 7. Cerebrospinal fluid (CSF) leak. Prolactinoma extension can be a contributing factor in DA-induced CSF rhinorrhoea.
- Expanding indications for surgery and the consideration of surgery as a viable alternative first-line treatment in selected cases, particularly for non-invasive macroprolactinomas, are gaining recognition. This is

supported by systematic reviews and meta-analyses. Factors supporting this include:

1. High remission rates reported in contemporary surgical series, especially for microprolactinomas.
2. Patient preference to avoid long-term medication and seek a potential cure. The PRolaCT study is a randomized clinical trial comparing DA treatment against neurosurgical counselling with surgery in consenting patients as a first-line approach.
3. Potential for higher long-term remission rates after surgery compared to DA withdrawal. Recurrence rates after DA withdrawal can exceed 50%.
4. Cost-effectiveness analyses suggesting surgery may be more cost-effective in the long run compared to medical therapy, especially for microprolactinomas.
5. Surgery may be considered prior to pregnancy in women with macroprolactinomas to reduce the risk of symptomatic enlargement during gestation.
 - Surgery for giant prolactinomas is challenging and often requires multimodal therapy involving surgery, radiotherapy, or both. Primary medical therapy is often preferred for giant prolactinomas.
 - The effect of pre-operative DA use on surgical outcomes is debated. Some believe it may induce tumour fibrosis, potentially making surgery more difficult, while others suggest pre-operative DA therapy may improve post-operative tumour control.

Management of Dopamine Agonist Resistance or Intolerance

For patients resistant to or intolerant of standard doses of cabergoline, higher doses may be considered [7,11,12,26,39,40].

- Surgery is a viable option for DA-resistant prolactinomas and can lead to hormonal control in a subset of patients. Surgical outcomes of medically failed prolactinomas have been reviewed.
- Radiotherapy (e.g., Gamma Knife radiosurgery) may be considered for medically and surgically refractory prolactinomas.
- Novel molecular therapies may be developed in the future for treatment-resistant cases based on understanding the pathogenesis of prolactinomas.

Dopamine Agonist Withdrawal

Withdrawal of DA therapy may be attempted in patients who have maintained normal prolactin levels for a sustained period (e.g., 2-3 years) with significant tumour reduction or absence on MRI [3,7,10,26,39-42].

- However, the recurrence rate after DA withdrawal is substantial, often exceeding 50%. Long-term disease remission is lower after DA withdrawal compared to primary surgery.

- Factors predicting successful DA withdrawal are being investigated.

Long-Term Follow-Up

Long-term follow-up is essential for all patients with prolactinomas, regardless of the primary treatment modality. This includes regular monitoring of prolactin levels and periodic MRI scans to assess for recurrence or tumour regrowth [7,11,12,29,38].

- The long-term impact of primary medical or surgical therapy on factors like BMI and metabolic profile is also being studied.

Role of Pituitary Tumour Centres of Excellence

Pituitary Tumour Centres of Excellence (PTCOE) play a crucial role in enhancing surgical outcomes and promoting standardized, multidisciplinary care for patients with prolactinomas [3,7,12,17,28].

Emphasis on Multidisciplinary Teams: PTCOEs are characterized by the presence of experienced multidisciplinary teams. These teams typically include endocrinologists, neurosurgeons with expertise in pituitary surgery, radiologists, pathologists, and other specialists who collaborate to provide comprehensive care. This multidisciplinary approach ensures that patients benefit from the collective expertise of various specialists, leading to more informed decision-making and tailored treatment plans [7,12,17,23,35].

Enhanced Surgical Outcomes due to Experienced Surgeons and High Volume Centres: The surgical outcomes for prolactinomas are significantly influenced by the experience of the pituitary surgeon and the volume of pituitary surgeries performed at the centre. PTCOEs typically concentrate expertise, with surgeons dedicated to pituitary operations performing a higher volume of these procedures. Studies have shown that higher surgical volume is associated with better remission rates and lower complication rates. For instance, one review noted that mean remission rates for macroprolactinoma surgery were 91% in high-caseload centres compared to 77% in lower-volume centres. Selective transsphenoidal adenectomy performed by experienced pituitary neurosurgeons in high-volume centres can achieve remission rates similar to dopamine agonist therapy for macroprolactinomas and enclosed macroprolactinomas. Therefore, PTCOEs, by centralizing specialized surgical expertise, contribute to improved surgical outcomes [3,8,17-20,23,28,35,43].

Promotion of Standardized Care: PTCOEs also foster standardized care through the development and implementation of best practice guidelines and protocols.

The interdisciplinary nature of these centres facilitates the creation of consensus-based approaches to diagnosis, treatment selection, surgical techniques, and post-operative management. By adhering to these standardized protocols, PTCOEs aim to reduce variability in care and ensure that all patients receive evidence-based treatment [8,12,17,18,20,23,24,28,34,35,43].

Discussion of Surgical Options: In PTCOEs with experienced teams and expert pituitary surgeons, the possibility of surgical remission versus long-term dopamine agonist therapy should be discussed with patients, especially when mass morphology favors surgical success. This comprehensive discussion ensures that patients are well-informed about all available treatment options and can actively participate in the decision-making process, aligning treatment with their preferences. Therefore, management

of prolactinomas within a PTCOE is likely to lead to more favorable outcomes and a higher quality of care [12,18,19].

Rationale for Surgery as First-Line Option in Recent Era

While dopamine agonists (DAs) are the established first-line treatment for most prolactinomas, there is increasing discussion and evidence supporting surgery as a viable and potentially superior first-line option in selected cases [3,7,9-13,23-25,37,40,42]. The low surgical threshold approach Figure 2 provides a framework for expanding surgery indications, especially for microprolactinomas, emphasizing the importance of tailored, patient-centric treatment decisions. The rationale for considering surgery as a first-line option includes:

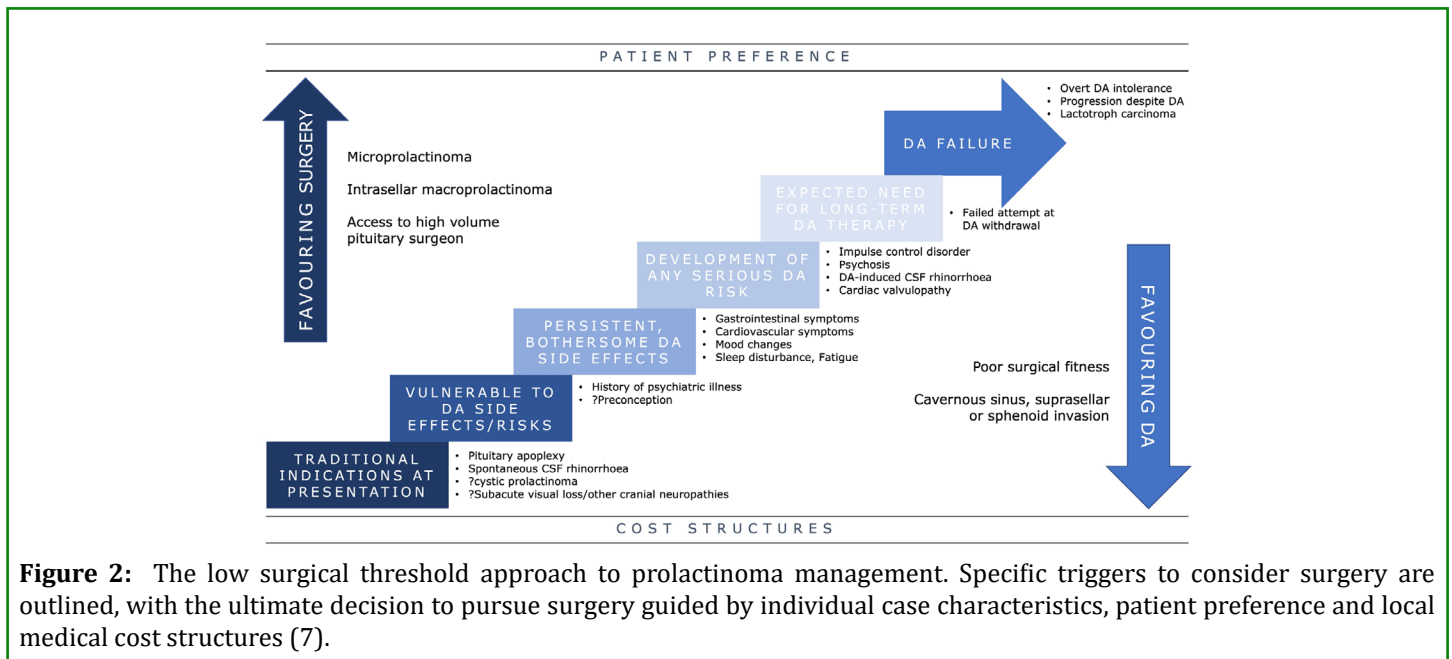


Figure 2: The low surgical threshold approach to prolactinoma management. Specific triggers to consider surgery are outlined, with the ultimate decision to pursue surgery guided by individual case characteristics, patient preference and local medical cost structures (7).

High Remission Rates, Especially for Macroprolactinomas: Several studies and meta-analyses suggest that surgery can achieve high remission rates, particularly in macroprolactinomas [3,5,7-11,14,23-26,37,42,44]. Remission rates of 71-100% have been reported for macroprolactinomas after transsphenoidal surgery (TSS) [9,18,41]. A meta-analysis showed a higher long-term remission rate with surgery (67%) compared to DA treatment (34%), particularly for macroprolactinomas (83% vs 36%) [7,9]. Another meta-analysis comparing initial surgical and medical treatment in treatment-naive macroprolactinoma patients showed a high remission rate after surgery [42]. A study with long-term follow-up reported a 72% long-term remission rate after first-line surgery for macroprolactinomas [27].

Potential for Long-Term Cure and Avoidance of Long-Term Medication: Surgery offers the possibility of a permanent cure without the need for long-term DA therapy [5,12,18,20,40]. Patients may prefer this to the potential adverse effects and inconvenience of lifelong medication [5,18,45]. Recurrence rates after DA withdrawal can be high (over 50%) [5,7,42].

Patient Preference: Patient preference itself is now a recognized indication for surgery, especially in centres with experienced neurosurgeons [7,10,43,46]. The possibility of cure by surgery versus long-term DA therapy should be discussed with the patient [18,43].

Superiority in Long-Term Remission Compared to DA Withdrawal: Some non-randomized data and meta-analyses

indicate that long-term remission is higher after surgery than after DA withdrawal [7,9].

Cost-Effectiveness: Cost-utility analysis has favoured TSS over DA treatment, particularly if diagnosis is made at a younger age (e.g., 40 years or younger) [12,18].

Pregnancy Considerations: In women desiring pregnancy, surgery for macroprolactinomas offers a high chance of cure, potentially eliminating the need for DA therapy to induce ovulation. For macroprolactinomas, debulking surgery can reduce the risk of symptomatic enlargement during pregnancy [9,14,17,18].

DA Intolerance or Resistance: While traditionally a second-line indication, considering surgery earlier for patients with persistent and bothersome DA side effects or concerns about long-term DA risks is part of a proposed “low surgical threshold” approach [9,11,14,25,40,44,46].

Specific Tumour Characteristics: Surgery might be preferred for well-defined, non-invasive microprolactinomas, and some suggest it should be discussed for circumscribed intrasellar macroprolactinomas as well. Tumours not located laterally from the gland, without cavernous sinus invasion, may have better surgical outcomes [9,18,24,25,27,28,39].

Potential Avoidance of DA-Induced Tumour Fibrosis: There is a suggestion that preoperative DA treatment might lead to tumour fibrosis, potentially making surgery more

difficult and affecting outcomes. Some studies have shown better surgical outcomes in patients without prior DA treatment [24,27,42].

Age and Gender: Young patients’ age is considered an argument for surgery to potentially avoid the unpredictable long-term sequelae of DA treatment. Some suggest surgery should be discussed more readily in male patients due to a higher likelihood of DA resistance and potentially more aggressive tumour behaviour [6,18,24,41].

It’s important to note that the decision for first-line surgery should be made on an individual basis, considering tumour size and characteristics (including Knosp grade and invasiveness), patient preference, availability of experienced pituitary surgeons in specialized centres, local cost structures, and a thorough discussion of the risks and benefits of both medical and surgical treatment options [6,7,9,12,18,20,23-25,27,37,42,43]. A strategic SWOT analysis Figure 3 emphasizes the efficacy of DAs while identifying long-term treatment concerns. It also highlights evolving surgical techniques as opportunities for addressing DA limitations. While DAs remain highly effective for many, surgery is increasingly being recognized as a safe and effective first-line alternative for carefully selected patients, particularly those with non-invasive microprolactinomas. Ongoing randomized trials are expected to provide further clarity on the comparative effectiveness of these two approaches [7,9,17,18,24,25,27].

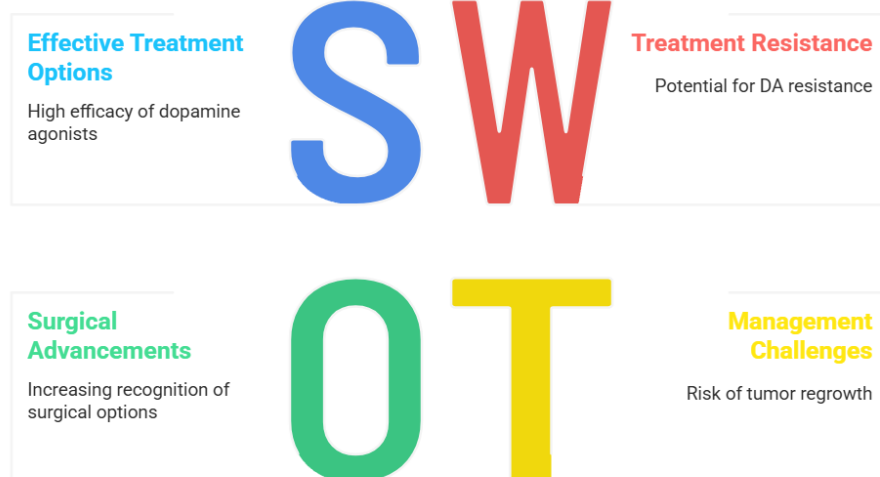


Figure 3: ‘SWOT’ analysis of existing treatment paradigm: The SWOT analysis outlines the strengths, weaknesses, opportunities, and threats in the current management strategies. Strengths include DA efficacy, while limitations such as potential side effects and long-term dependency are acknowledged. Opportunities lie in surgical advancements, while threats include non-compliance and recurrence risks.

Conclusion

While dopamine agonists remain the cornerstone of prolactinoma treatment, the evolving role of surgery as a first-line option is gaining attention, especially for selected cases such as microprolactinomas. Surgery offers potential long-term remission and freedom from medication, supported by advancements in techniques and individualized patient care. Future research and patient-centred discussions will further clarify the optimal treatment pathways, ensuring a balanced approach that prioritizes efficacy, safety, and quality of life.

Conflict of Interest

No conflict of interests to report.

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