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RESEARCH

Outcomes in surgical management of microprolactinomas: an international multi-institutional series

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Abstract

Background Prolactinomas represent the most common pituitary adenoma subtype, the majority of which are microprolactinomas. Dopamine agonists (DAs) remain the first-line intervention for microprolactinomas, however, many patients either cannot tolerate DAs or require lifelong therapy to maintain hormonal control. As endoscopic endonasal surgery (EES) continues to revolutionize the surgical management of sellar lesions, we sought to reassess the feasibility and efficacy of early surgical resection for microprolactinoma.

Methods Retrospective chart review from 2010 to 2021 of adults who underwent EES for microprolactinoma was performed across three medical centers. Surgical failure was defined as a need to restart DAs, a serum prolactin level greater than 30ng/mL at last follow-up, tumor recurrence, or a need for reoperation.

Results A total of 56 patients were identified with a mean age of 32.9 years and an average of 26.4 months of follow-up. The majority had been on DAs preoperatively (98.2%). The most common surgical indications were DA intolerance (73.2%), tumor unresponsiveness (19.6%), and desire for pregnancy (7.1%). Gross total resection was achieved in 51 (91.1%) cases. The overall surgical remission rate was approximately 70% with failures observed in 17 (30.4%) patients. Multivariate logistic regression identified subtotal resection as the only independent predictor of surgical failure ($p=0.038$*). The most common postoperative complication was transient arginine vasopressin deficiency (AVP-D) (21.4%). There were no cases of permanent AVP-D, new visual deficits, or cerebrospinal fluid leak.

Conclusions With a surgical remission rate of nearly 70%, EES represents a safe and viable alternative strategy to long-term DA treatment for microprolactinomas.

Keywords Pituitary adenoma · Microprolactinoma · Prolactin · Dopamine agonist · Endoscopic endonasal surgery

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Introduction

Prolactinomas, benign prolactin-secreting tumors derived from lactotrophs in the anterior pituitary gland, represent the most common pituitary adenoma subtype and account for approximately 50% of all pituitary adenomas [1]. The vast majority (over 90%) are microprolactinomas, lesions less than 10 mm in diameter, and have an incidence three times greater in women than in men [1, 2]. These small secretory tumors typically present with symptoms of hormonal and sexual dysfunction from hyperprolactinemia including menstrual irregularity, infertility, decreased libido, and galactorrhea. Over the past several decades, primary management with surgical resection or radiation has largely been replaced by pharmacotherapy with dopamine agonists (DA), such as cabergoline. DAs are associated with normalization of prolactinemia in 80–90% of cases and tumor shrinkage in two-thirds of cases [3]. However, tumor regrowth and the recurrence of hyperprolactinemia while weaning or after cessation of DAs are well-documented phenomena, and a significant portion of patients that start DAs require life-long treatment [4]. Additionally, approximately 4% of patients cannot tolerate chronic cabergoline, and over 26% complain of undesired side effects [5, 6]. Subtle complaints of fatigue, sinus congestion, gastrointestinal problems, and even behavioral changes as extreme as psychosis or compulsive gambling have been reported with DA therapy [7].

Endoscopic endonasal surgery (EES) has revolutionized the field of pituitary surgery and the treatment of pituitary adenomas. Evidence continues to mount with increasing gross total resection rates and improved remission or cure rates for secretory tumors with cumulative experience [8, 9]. Only recently, however, has there been an interest in promoting a paradigm shift towards considering earlier surgical resection of microprolactinomas, especially in younger patients who would otherwise likely require decades of medical therapy [6]. Microprolactinomas tend to occur in surgically favorable locations in the sella without significant extension into the cavernous sinus. Furthermore, surgical resection is a potentially curative alternative to prolonged medical therapy, and there is some evidence that preoperative DA use can generate intratumoral fibrotic changes that can make subsequent surgical resection more challenging [10, 11].

In a 2014 review of microprolactinoma surgical series, a pooled outcomes analysis revealed an 83% rate of immediate postoperative prolactinemia normalization, and a 74% long-term remission rate [12]. In comparison to the estimated 21–48% long-term remission rate after withdrawal of DAs, the relative durability and efficiency of surgical resection for microprolactinoma in the modern era of EES should be reconsidered [4, 13, 14]. Health-related quality-of-life studies have also favored surgical resection given the previously discussed side effect profile of DAs [15]. Additionally, surgical resection has been shown to be more cost-effective, especially in younger patients [16]. Given these potential benefits, the efficacy of EES for microprolactinoma deserves further study and potentially earlier consideration—even as an alternative first-line intervention—in the existing multidisciplinary treatment paradigm.

Methods

Study design and patient population

An international multi-institutional retrospective cohort of patients who underwent EES for the resection of suspected microprolactinomas from 2010 to 2021 was reviewed for this retrospective cohort study. Three tertiary academic medical centers (two in the United States and one in the Netherlands) were included, and Institutional Review Board approval to conduct this retrospective study was obtained at all sites with a data-sharing agreement as previously described [17]. Patients included were at least 16 years old, had a visible pituitary lesion on magnetic resonance imaging (MRI) that was less than 10 mm in diameter, demonstrated hyperprolactinemia on serum testing (not presumed to be stalk effect), and had no other potential cause for hyperprolactinemia outside of their pituitary lesion. Patients with incomplete documentation of their DA use, missing serum prolactin values either pre- or postoperatively, or without a postoperative MRI were excluded. Additionally, patients with dually or multiply secretory pituitary lesions (i.e. co-secreting another hormone) based on serum testing were also excluded.

Preoperative evaluation, surgical resection, and postoperative care

Diagnosis of microprolactinoma was based on preoperative clinical and biochemical assessment in conjunction with MRI. Clinical presentation of hormonal dysfunction was followed by endocrinological evaluation with a complete serum hormone panel to confirm hyperprolactinemia. If an MRI additionally revealed the presence of a pituitary lesion with a diameter less than 10 mm, a diagnosis of microprolactinoma was made. Patients who did not have an absolute contraindication to DAs were started on DA therapy. Patients with lesions that were hormonally unresponsive (defined as demonstrating an insufficient biochemical response to the maximally tolerated DA dose, as previously described [17]) or that continued to enlarge despite DA

treatment, who developed pituitary apoplexy, progressive vision loss, or an extraocular movement deficit, who desired pregnancy, or who were either intolerant of DA side effects or preferred not to be on long-term medical therapy were offered surgical intervention after interdisciplinary discussion among endocrinologists, neuroradiologists, neurosurgeons, and otolaryngologists. Serum prolactin levels were additionally assessed immediately preoperatively.

All surgical resections were performed consistently across centers via EES in a multidisciplinary fashion involving both neurosurgeons and otolaryngologists using a binostril approach as previously published and exemplified in **Video 1** [18, 19]. In brief, after a posterior septectomy is performed to maximize maneuverability, a wide sphenoidotomy is then performed using a 0-degree endoscope. After a bony window is made exposing the sella, and anatomical landmarks are confirmed by stereotactic navigation and intraoperative Doppler, the sellar dura is opened. The normal pituitary gland is sharply incised and explored to identify the tumor-gland interface and the tumor is removed by primarily extracapsular dissection using a two-handed traction-counter traction technique. Prior to closure, a 30-degree endoscope is employed to help detect and resect any residual tumor. The sellar defect is repaired using any combination of an inlay and/or onlay of dural substitute, an adhesive dural sealant, and, if there is an intraoperative cerebrospinal fluid (CSF) leak, a fat or fascia autograft or a pedicled nasoseptal flap is employed.

The day after surgery, all patients had a random serum prolactin level checked. Additionally, a full endocrine panel was performed both prior to discharge and during endocrinological follow-up within three months of surgery to assess for hypopituitarism. Postoperative MRI was obtained 3–5 days postoperatively to assess the extent of resection prior to discharge. A routine follow-up MRI was also obtained to monitor for recurrence or regrowth within 3–6 months as well as at any additional timepoints if a resurgence of hyperprolactinemia was noted during follow-up serum testing.

Data collection and outcomes

Patient demographics, preoperative DA use, and endocrinological dysfunction based on serum testing were recorded from the medical record. Panhypopituitarism was defined as a complete anterior pituitary hormone and posterior pituitary hormone (usually assessed by arginine vasopressin deficiency or AVP-D) deficiency. Single-axis deficiencies were otherwise noted individually, and any deficiency of either luteinizing hormone or follicle-stimulating hormone was termed hypogonadism. Both the highest preoperative serum prolactin level recorded and the immediate preoperative serum prolactin level were assessed. Patient-specific indications for surgery and any preoperative neurological deficits were likewise recorded.

Preoperative MRIs were reviewed to assign a Knosp classification and to assess maximal tumor diameter, presence of apoplexy, presence of a cystic component, optic chiasm impingement and involvement of adjacent anatomical spaces [20]. Postoperative MRIs were assessed for the extent of resection and follow-up MRIs were assessed for tumor regrowth or recurrence based on the neuroradiologist's documented MRI interpretation at the time of imaging. Intraoperative and postoperative CSF leak, length of the hospitalization, postoperative neurological deficits, and new or persistent hormonal dysregulation were recorded as well as any other postoperative complications. Serum prolactin levels from postoperative day one and the value at last follow-up were assessed. Histopathological findings as well as any additional microprolactinoma treatment required, such as restarting DAs or additional surgery, were also recorded. A composite outcome for surgical failure was defined as a need to restart DAs, a serum prolactin level > 30ng/mL at the last follow-up, tumor recurrence, or a need for reoperation. Data extraction during systematic review of medical records was blinded to all outcomes, including the composite outcome for surgical failure.

Statistical analysis

All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.). Baseline characteristics and outcomes were primarily analyzed with descriptive statistics as follows: Means and standard errors (± SE) or medians with interquartile ranges were reported for continuous variables. For categorical variables, the number (N) and percentage (%) of patients associated with each parameter was given. To determine predicting variables for the dichotomous composite outcome of surgical failure, multivariable logistic regression was performed. In the regression model, variables with a significance of $p < 0.3$ in relevant univariate analyses were then tested in the multivariate model using a backwards stepwise selection method, and those with a contributing significance of $p < 0.1$ were retained in the model to ensure adjustment for any major confounders. A value of $p < 0.05$ based on two-tailed hypothesis testing was considered statistically significant.

Results

Patient population

A total of 56 patients who underwent EES for microprolactinoma were included. Baseline clinical characteristics

Table 1 Patient demographics and presentation

Parameter	Total Cohort *N* (%) (*n* = 56)	(Range)
Age (years) (mean ± SE)	32.9 ± 1.1	(17.0–53.0)
Sex:		
Female	49 (87.5%)	
Male	7 (12.5%)	
Follow-up (months) (mean ± SE)	26.4 ± 3.2	(1.0–111.0)
Preop prolactin (ng/mL) (mean ± SE)	88.0 ± 13.4	(3.9–698)
On a dopamine agonist (DA)	55 (98.2%)	
Hypopituitarism (any deficit):	16 (28.6%)	
Panhypopituitarism	0 (0%)	
GH deficiency	0 (0%)	
Hypogonadism (LH/FSH deficiency)	12 (21.4%)	
TSH deficiency	4 (7.1%)	
ACTH deficiency	3 (5.4%)	
AVP-D	1 (1.8%)	
Visual deficit	2 (3.6%)	
Extraocular movement deficit	0 (0%)	

SE = standard error; GH = growth hormone; LH = luteinizing hormone; FSH = follicle stimulating hormone;

TSH = thyroid stimulating hormone; ACTH = adrenocorticotropic hormone; AVP−D = arginine vasopressin deficiency

Table 2 Imaging, Surgical, and pathological characteristics

Parameter	Total Cohort *N* (%) (*n* = 56)	(Range)
Maximum tumor diameter (mm) (mean ± SE)	6.5 ± 0.3	(1.0–9.9)
Knosp grade:		
0	38 (67.9%)	
≥1	18 (32.1%)	
Other imaging features:		
Apoplexy	4 (7.1%)	
Cystic component	9 (16.1%)	
Suprasellar extension	1 (1.8%)	
Optic chiasm impingement	2 (3.6%)	
Clival invasion	0 (0.0%)	
3rd ventricular involvement	0 (0.0%)	
Indication for surgery:		
Tumor unresponsive to DA	11 (19.6%)	
DA intolerance	41 (73.2%)	
Vision loss	1 (1.8%)	
Apoplexy	1 (1.8%)	
Desire for pregnancy	4 (7.1%)	
Patient preference	4 (7.1%)	
Extent of resection:		
Gross total resection	51 (91.1%)	
Subtotal resection	5 (8.9%)	
Intraop CSF leak	6 (10.9%)	
Length of hospital stay (days) (mean ± SE)	2.9 ± 0.1	(1.0–5.0)
Histopathologic findings:		
IHC negative	8 (14.6%)	
Prolactin +	46 (83.6%)	
GH +	15 (27.3%)	
LH / FSH +	1 (1.8%)	
TSH +	0 (0%)	
ACTH +	0 (0%)	

SE = standard error; DA = dopamine agonist; CSF = cerebrospinal fluid; IHC = immunohistochemistry; GH = growth hormone;

LH = luteinizing hormone; FSH = follicle stimulating hormone; TSH = thyroid stimulating hormone; ACTH = adrenocorticotropic hormone;

ADH = antidiuretic hormone

are shown in Table 1. The mean age of the cohort was 32.9 years (range 17–53 years) and the majority of patients were female (*n* = 49, 87.5%). Two (3.6%) patients presented with a visual deficit at the time of surgery. Nearly all patients (*n* = 55, 98.2%) were on DAs preoperatively. The mean preoperative prolactin was 88 ng/mL (range 3.9–698 ng/mL). In terms of other endocrinological dysfunction, 16 patients (28.6%) had some form of hypopituitarism; most commonly hypogonadism (*n* = 12, 21.4%), followed by thyroid stimulating hormone (TSH) deficiency (*n* = 4, 7.1%), adrenocorticotropic hormone (ACTH) deficiency (*n* = 3, 5.4%), and AVP-D (*n* = 1, 1.8%). There were no cases of preoperative panhypopituitarism or growth hormone (GH) deficiency. The mean clinical follow-up was 26.4 months (range 1–111 months).

Imaging features and surgical characteristics

Tumor measurements were performed on preoperative MRI for all patients and a Knosp classification was also assigned (Table 2). The average maximum tumor diameter was 6.5 mm (range 1.0–9.9 mm). The majority of cases were Knosp 0 (*n* = 38, 67.9%), with the remainder being Knosp 1 or greater (*n* = 18, 32.1%). A portion of the microprolactinomas were cystic (*n* = 9, 16.1%) or had evidence of apoplexy on MRI (*n* = 4, 7.1%). Two (3.6%) lesions demonstrated optic chiasm impingement and one (1.8%) had suprasellar extension. There were no lesions demonstrating extension into other compartments such as the clivus or third ventricle. Additionally, while dissection was extended to the medial cavernous sinus wall for lesions with a Knosp grade > 1, invasive cavernous sinus exploration was not performed in any cases.

The most common primary indication for surgical resection was DA intolerance (*n* = 41, 73.2%) followed by tumor unresponsiveness to DA therapy (tumors that were either biochemically unresponsive or demonstrated progressive growth, *n* = 11, 19.6%) (Table 2). A small percentage of patients had surgery based on patient preference (*n* = 4, 7.1%). Gross total resection was achieved in the majority of cases (*n* = 51, 91.1%). There were 6 intraoperative CSF

leaks, but no postoperative CSF leaks during the follow-up period. On histopathological assessment, 83.6% of tumors were proven to be of lactotroph origin and stained positive for prolactin. Another significant portion (27.3%) also stained positive for GH, while a handful were immunohistochemically negative (14.6%). The mean length of hospital stay for the surgical admission was 2.9 days (range 1–5 days).

Surgical outcomes and complications

The primary outcome was a composite outcome for surgical failure involving tumor recurrence on MRI, reoperation for residual (or recurrence), restarting DAs during follow-up, or a last follow-up serum prolactin level greater than 30ng/mL. There were 17 (30.4%) surgical failures overall, indicating a 69.6% surgical remission rate (Table 3). Most patients failed either due to an elevated serum prolactin level at the last follow-up ($n=11$, 64.7%) or because DAs were restarted during the follow-up period ($n=7$, 41.2%). Three (17.6%) patients demonstrated tumor recurrence on imaging and three (17.6%) required reoperation for further resection. Multivariate logistic regression was employed to determine any independent clinical, surgical, or radiographic predictors of surgical failure: In univariate analysis, preoperative hypopituitarism of any hormonal axis (OR 3.444, $p=0.049$*) was associated with surgical failure, while achieving a gross total resection (OR 0.086, $p=0.035$*) predicted surgical remission. In multivariate analysis, after adjusting for preoperative hypopituitarism, subtotal resection was the only independently significant predictor of surgical failure (OR 0.083, $p=0.038$*) (Table 4). Patient age, preoperative prolactin level, tumor size, Knosp classification, and cystic tumoral appearance were not associated with surgical failure.

Serum prolactin levels on postoperative day one (mean 15.6 ± 5.5ng/mL), and at last follow-up (mean 30.3 ± 7.7ng/mL), were both significantly decreased from immediate preoperative prolactin levels (mean 88.0 ± 13.4ng/mL) for the overall cohort (One-way ANOVA, Tukey's Multiple Comparisons Test, $p<0.0001$*) (Fig. 1A). When comparing patients that achieved surgical remission versus those with surgical failure, there were no differences in mean serum prolactin levels at any timepoints, but the differences between preoperative, postoperative, and follow-up prolactin levels seen in the overall cohort analysis persisted across the two groups (Two-way ANOVA, Tukey's Multiple Comparisons Test, $p<0.05$*) (Fig. 1B).

Of the 12 patients with hypogonadism on preoperative serum testing, 9 patients (75%) demonstrated resolution of their hypogonadism on follow-up testing (Table 3). There were 12 cases of transient postoperative AVP-D, but no

Table 3 Surgical outcomes and complications

Parameter	Total Cohort *N* (%) (*n* = 56)
Failure	**17 (30.4%)**
Last follow-up prolactin > 30ng/mL	11 (19.6%)
Tumor recurrence	3 (5.4%)
Required reoperation	3 (5.4%)
Restarted DA during follow-up period	7 (12.5%)
Resolution of preop hypogonadism (*n* = 12)	9 (75.0%)
Postop prolactin (ng/mL) (mean ± SE):	
Postop day 1 prolactin	15.6 ± 5.5
Last follow-up prolactin	30.3 ± 7.7
Complications:	
Transient AVP-D	12 (21.4%)
Permanent AVP-D	0 (0%)
Postop CSF leak	0 (0%)
Postop hyponatremia	5 (8.9%)
Postop new hypopituitarism	2 (3.6%)
Postop visual deficit	0 (0%)
Epistaxis	1 (1.8%)
Headache requiring ER visit	1 (1.8%)
Postop radiation	0 (0%)

SE = standard error; DA = dopamine agonist; AVP–D = arginine vasopressin deficiency; CSF = cerebrospinal fluid; ER = emergency room

Table 4 Multivariate logistic regression for predictors of surgical failure for microprolactinomas

	UNIVARIATE			MULTIVARIATE		
Parameter	**OR**	**95% CI**	**p Value**	**OR**	**95% CI**	**p Value**
Age	0.972	[0.905—1.043]	0.427			
Sex (F vs. M)	0.533	[0.106—2.695]	0.447			
Immediate Preop Prolactin Level	1.007	[0.998—1.016]	0.124			
Hypopituitarism (any deficiency)	3.444	[1.008—11.776]	**0.049***	3.514	[0.955—12.932]	0.059
Maximum Tumor Diameter	0.867	[0.644—1.168]	0.348			
Cystic Tumor Appearance	0.242	[0.028—2.110]	0.199			
Knosp Grade (≥ 1 vs. 0)	1.782	[0.541—5.865]	0.342			
Extent of Resection Gross total vs. subtotal	0.086	[0.009—0.836]	**0.035***	**0.083**	**[0.008—0.870]**	**0.038***

Multivariate regressions performed by stepwise subtraction of all variables with a significance of $p<0.3$ in the univariate analysis; contributing variables with a significance level of $p<0.1$ remained in the multivariate model to confirm independently predicting variables after adjustment. "*" = indicates statistical significance for $\alpha=0.05$

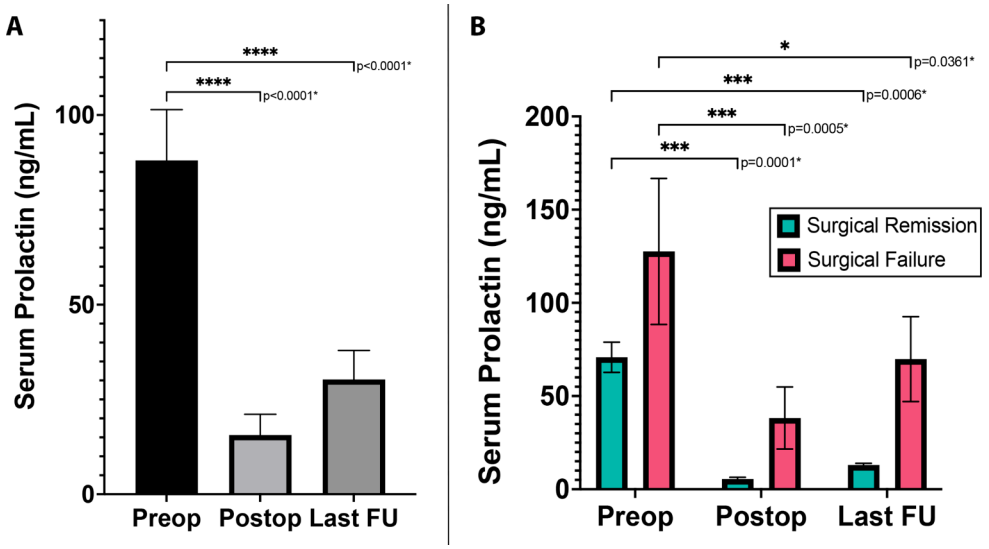

Fig. 1 Serum prolactin levels. **(A)** Overall cohort mean serum prolactin levels (ng/mL) and the associated standard error are shown at three time points; immediately preoperatively, postoperatively (on postoperative day one), and at the last follow-up. A one-way ANOVA for repeated measures was performed to compare means across the three timepoints, demonstrating significance for the overall variance across the three means ($F = 53.3$, $p < 0.0001$*). Tukey's post-hoc multiple comparison tests revealed statistically significant differences between both preoperative and postoperative ($p < 0.0001$*) and preoperative and last follow-up ($p < 0.0001$*) serum prolactin levels, and the respective p-values are displayed on the diagram. **(B)** Mean serum prolactin levels (ng/mL) and the associated standard error for both the subgroup of patients that achieved surgical remission (green) and the subgroup that experienced surgical failure (red) are shown at three time points; immediately preoperatively, postoperatively (on postoperative day one), and at the last follow-up. A two-way ANOVA for repeated measures was performed to compare means across the three timepoints, which was significant for overall variance across timepoints ($F = 18.5$, $p < 0.0001$*). Tukey's post-hoc multiple comparison tests revealed statistically significant differences both between preoperative and postoperative and between preoperative and last follow-up serum prolactin levels from the surgical remission and surgical failure groups. The respective p-values for the above comparisons are shown on the diagram

permanent cases requiring desmopressin supplementation during follow-up. There were two cases of new postoperative hypopituitarism that required supplementation during follow-up, but no cases of panhypopituitarism or new visual field deficits. Other complications included one case of epistaxis and a severe postoperative headache that provoked an emergency room visit (Table 3).

Discussion

For the last several decades, DAs have represented first-line treatment for prolactinomas. Cabergoline has largely replaced bromocriptine as the preferred agent due to better tolerance, improved tumor response, and a less burdensome dosing schedule [3, 5, 21]. Cabergoline can effectively normalize serum prolactin levels in over 90% of prolactinoma patients and, most notably in macroprolactinomas, causes tumor shrinkage in over two-thirds of cases [3, 22]. After weaning off of DAs, however, long-term remission rates of hyperprolactinemia are quite poor, with a 50–80% recurrence rate in larger series and meta-analyses [4, 13]. Additionally, DAs are associated with a host of side effects ranging from gastrointestinal disturbances and generalized fatigue to psychiatric symptoms [7]. At higher doses and after prolonged courses, cabergoline may also increase the risk of developing valvular heart disease [23].

In the modern era of improved surgical outcomes for pituitary adenomas after EES, a revisiting of the role of surgical resection in the prolactinoma management algorithm is warranted. According to current guidelines, surgical resection is reserved only for patients who do not respond to DAs, have acute and persistent vision loss, or who have contraindications to DA therapy (such as being on a dopamine-modulating antipsychotic agent) [1]. Nonetheless, the growing surgical literature continues to demonstrate greater safety and efficacy of EES for pituitary adenomas, especially with increasing experience or at specialized centers. For example, despite the availability of medical therapies, surgical resection has become first-line for GH-secreting pituitary adenomas and has been shown to be particularly effective at achieving surgical remission for GH-secreting microadenomas (compared to macroadenomas or giant adenomas) [8, 9]. In large or giant prolactinomas, initial management with DA therapy can provide early symptom control and potentially generate tumor shrinkage in lesions that tend to be invasive and are not as easily resectable [24]. Microprolactinomas, however, may be more reliably and durably treatable with surgical resection alone. In this international multi-institutional series of microprolactinoma patients who

underwent EES for resection, we demonstrated that a majority of patients, nearly 70%, can achieve surgical remission. Surgical morbidity was minimal, with transient AVP-D (21.4%) being the most common complication observed in our series (with a 0% rate of permanent AVP-D), followed by hyponatremia (8.9%), similar to findings in other contemporary surgical prolactinoma series [17, 25, 26]. There were no cases of postoperative CSF leak, no new visual field or other cranial nerve deficits, and no mortalities, but the low incidence of new postoperative hypopituitarism of one or more axes (3.6%) should be discussed when counselling patients regarding surgery. Nonetheless, these findings suggest that microprolactinoma patients may benefit from earlier consideration of surgical resection during their treatment course with relatively low associated risk.

The 70% long-term remission rate reported in our study is consistent with the limited existing literature. A 2014 review that aggregated outcomes data from 627 microprolactinoma patients who underwent either endoscopic or microscopic resection quoted an immediate postoperative rate of prolactinemia normalization of 83.2%, and a long-term remission rate of 74.4% [12]. Notably, our composite outcome for surgical failure likely represents a stricter definition of surgical failure than simply the resolution of hyperprolactinemia reported in these older series. A more contemporary series investigating EES for microprolactinoma by Micko et al. similarly described an overall endocrinological remission rate of 67% after a mean follow-up of 37 months [27]. In a slightly larger series by Uzuner et al. evaluating EES in 105 microprolactinoma patients and also advocating for a potential paradigm shift favoring surgical resection, the authors observed a comparable long-term remission rate of 74.3% at a median of 74.9 months of follow-up [11].

The only contemporary series to observe a surgical remission rate of over 80% was published by Baussart et al. in 2021. The authors evaluated EES in 114 microprolactinomas with a much shorter median follow-up of 18.2 months and observed an 81% "long-term" remission rate. Like in our series, Baussart et al. similarly determined that gross total resection was a key predictor of surgical remission [28]. However, there is a known phenomenon of delayed endocrinological or tumor recurrence (after initial remission) after microprolactinoma resection in 15–20% of cases at approximately 27 months postoperatively [29]. The mean follow-up in our series was nearly 27 months, and, accordingly, our series may better capture some of these delayed recurrences. Baussart et al. also noted that lateral cavernous sinus adherence or invasion was predictive of surgical failure in their multivariate analysis [28]. Additional recent studies likewise noted significantly improved surgical remission rates in tumors that either were enclosed fully by the pituitary gland and did not invade the cavernous sinus or were graded as Knosp 0 (versus Knosp $\geq$ 1) on preoperative imaging [26, 27]. In our dataset (Table 4), we suspect that our limited sample size was underpowered to find a significant influence of Knosp grade on surgical remission outcomes. Additionally, cavernous sinus exploration for further resection was deferred in these cases given the well-described elevated risk of neurovascular injury and current paucity of evidence supporting its use to achieve meaningful hormonal control in prolactinoma [30]. Nonetheless, the aggregate literature seems to report favorable surgical outcomes for smaller, non-expansile, secretory pituitary lesions and earlier consideration of surgical resection in these anatomically favorable cases should be revisited for microprolactinoma.

In our series, all patients except for one (who had a medical contraindication) were pre-treated with DAs prior to surgical resection. Some of the highest reported surgical remission rates for microprolactinoma in the literature, however, are from series in which the patients were DA treatment naïve [11, 31]. For example, Uzuner et al. determined that the length of preoperative DA use was the strongest predictor of postoperative long-term remission; patients with a 3-year or longer preoperative DA use history demonstrated a significantly lower remission rate (29.5%) compared to those who had a shorter history of DA use (50%) or no DA use history at all (94.1%). They additionally noted that these results correlated to how fibrotic the tumor was intraoperatively, as more fibrotic tumors demonstrated a 28.6% remission rate while softer tumors were associated with an 85.7% remission rate [11]. The connection between DAs and the development of intratumoral fibrosis (and diminished resectability) has been previously hypothesized, although the association with cabergoline, in particular, is less obvious [10, 32]. Unfortunately, granular information regarding the length of preoperative DA treatment and intraoperative tumoral consistency were unavailable from our retrospective cohort for comparison. Further studies remain necessary to better elucidate the influence of prior DA use on surgical outcomes in microprolactinoma, although the existing literature is already suggestive of a potentially negative effect on surgical remission.

While only a handful of patients in our series sought surgical intervention due to a desire for pregnancy, fertility remains a critical issue in the multidisciplinary management of prolactinomas in female patients. Many prolactinoma patients have concomitant gonadal axis dysfunction (in our series, 21.4% of patients had hypogonadism at the time of surgery) and struggle with infertility [33]. Primary management with surgical resection offers a pathway to restoring normal ovulatory cycles in women without dependence on DAs and with minimal risk of new or worsened pituitary dysfunction (only a 3.6% risk in our series). Even in cases in which the postoperative remission period is transient,

women can still take advantage of this early postoperative period to pursue pregnancy [12]. DAs are still not approved for use in pregnancy and once a pregnancy is confirmed, women are advised to stop DA treatment. Approximately 40% of pregnant women with microprolactinomas are thought to experience asymptomatic tumor growth, with a 2–5% rate of symptomatic tumor enlargement leading to vision loss or apoplexy [34]. With the continually improving safety profile of EES, upfront surgical resection of microprolactinomas seems especially reasonable in women of reproductive age.

Long-term or lifetime DA therapy for microprolactinoma patients also represents a significant cost both financially and to quality-of-life, which can introduce barriers to medication adherence and potentially compromise therapeutic efficacy. A United States-based cost-utility analysis of surgery versus lifetime DA therapy determined that surgical resection is most cost-effective with an estimated lifetime cost of $40,473 compared to bromocriptine therapy ($41,601) and cabergoline therapy ($70,696) [16]. Of note, these figures consider a patient diagnosed at age 40, but each additional year of therapy with bromocriptine ($2,622) or cabergoline ($4,729) could represent substantial additional cost and therefore may make early surgery a more economical option in younger patients [16]. These findings are further supported by another cost analysis based on Medicare reimbursement fees that again demonstrated significant savings after surgical resection of microprolactinomas in patients with a life expectancy greater than 10 years [35], and by an Italian national cost-effectiveness analysis with similar findings [36]. Additionally, health-related quality-of-life (HR-QoL) evaluations in microprolactinoma patients have consistently shown faster resolution of various quality measures after surgery [15, 37, 38]. Given the potential healthcare cost savings and the high remission rate provided by surgical resection compared to DA therapy, further study of the benefits of first-line surgical intervention for microprolactinomas remains warranted.

Limitations

The results of this study should be interpreted in the context of its limitations which include, but are not limited to, the retrospective nature of data collection, relatively limited sample size, and limited follow-up to a mean of 26.4 months. Our study identified gross total resection as the sole significant predictor of surgical remission in this cohort, however, this study was likely underpowered to demonstrate the influence of preoperative hypopituitarism or Knosp classification in multivariate analysis. Additionally, postoperative and follow-up imaging assessments of extent of resection, tumor progression, and tumor recurrence were based on the neuroradiologist's read at the time of imaging without explicit protocols for blinding to patient history. While the multi-institutional nature of this study improves external validity and generalizability, the institutions included in this study are tertiary care centers with multidisciplinary care teams with specific expertise in EES, as evidenced by the high rate of gross total resection and favorable complication profile. Therefore, these results may not be applicable to surgeons or to centers with less experience in EES. Moreover, the slight variability, albeit minimal, in surgical technique and closure materials expected across centers could have had some effect on outcomes and adverse event rates. Our series also incorporated a majority female (87.5%) and young adult (mean age 33 years) patient population, which, while reflective of the expected epidemiology of prolactinoma patients, must be considered when generalizing our outcomes [1, 39]. For example, male prolactinoma patients tend to have more invasive tumors with lower associated rates of surgical remission and are underrepresented in our cohort [40, 41]. Additionally, the relatively low surgical morbidity in our cohort may be somewhat driven by a generally younger patient population, as there is a known graded increase in EES complication rates with increasing age [42]. Preoperative DA use was also classified dichotomously as we were unable to evaluate or control for the duration of DA treatment prior to surgery due to the retrospective and heterogeneous nature of the data collection. As previously mentioned, the length of DA pretreatment has been hypothesized to influence both extent of resection and long-term prolactinemia remission rates after surgery; additional prospective and larger cohort studies incorporating detailed DA pretreatment data remain necessary for more definitive recommendations on the timing of surgical versus medical intervention. Despite these limitations, however, our study adds substantially to the body of literature exemplifying a high surgical remission rate for microprolactinomas with minimal complications.

Conclusions

Overall, our results suggest that EES facilitates durable symptomatic improvement in patients with microprolactinomas with high rates of surgical remission, especially when gross total resection is achieved, and few complications. Given the well-described side effects, financial costs, and quality-of-life drawbacks associated with long-term DA therapy, early surgical intervention for microprolactinomas with EES should be strongly considered.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics Statement Institutional Review Board (IRB) approval for this multi-center retrospective chart review study to review individual patient charts for data capture was obtained by the lead author under the guidelines set forth by the Northwell Health Human Research Protection Program. A data-sharing agreement was established for anonymized data sharing across the three involved medical centers. Given the retrospective nature of the research and supervised anonymization process for data collection under IRB guidelines, individual patient consent to participate and consent to publish were not required. All authors contributed sufficiently to the development of this work and have approved of its submission to *Pituitary*. This manuscript is a unique submission and is not being considered for publication, in part or in full, with any other source in any medium. This work received no funding or other material supplementation, and there are no conflicts of interest to disclose. This work was performed with ethical approval from the institutional review boards of the three participating centers in accordance with the declaration of Helsinki.

Competing interests The authors declare no competing interests.

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