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ORIGINAL ARTICLE

Efficacy and Safety of Endoscopic Transsphenoidal Resection for Prolactinoma: A Retrospective Multicenter Case-series

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Background. Endoscopic transsphenoidal surgery (ETSS) for prolactinoma is reserved for dopamine agonist (DA) resistance, intolerance, or apoplexy. High remission (overall 67%, microprolactinoma up to 90%), low recurrence (5–20%) rates highlighted that surgery might be first-line treatment.

Aims. To report on outcomes of ETSS in a cohort of prolactinomas.

Methods. Multicenter retrospective cohort of 137 prolactinoma patients (age 38.2 ± 13.7 years; 61.3% female, median follow-up 28.0 [15.0–55.5] months) operated between 2010–2019 with histopathological confirmation.

Results. Median preoperative prolactin levels were 166 (98–837 μg/L; males 996 [159–2145 μg/L] vs. females 129 [84–223 μg/L], $p < 0.001$). 56 (40.9%) microprolactinomas, 69 (50.4%) macroprolactinomas, and 7 (5.1%) giant prolactinomas were included, whereas no adenoma was detected in 5 (3.6%) patients. Males had larger tumors (macroprolactinomas: 38, 71.7%) vs. 31 (36.9%), $p < 0.001$; giant prolactinomas: 7 (13.2%) vs. 0 (0.0%), ($p < 0.001$). Prolactinomas were graded as KNOSP-3 in 15 (11.5%), and KNOSP-4 in 20 (15.3%) patients. Primary indication was DA intolerance (59, 43.1%); males 14 (26.4%) vs. females 45 (53.6%), $p = 0.006$. Long-term remission (i.e., DA-free prolactin level <1xULN) was achieved in 87 (63.5%) patients, being higher in intended complete resection (69/92 [75.0%]), and lower in males (25 [47.2%] vs. 62 females [73.8%], $p = 0.002$). Transient DI ($n = 29$, 21.2%) was the most frequent complication.

Conclusions. Despite high proportions of macroprolactinoma and KNOSP 3–4, long-term remission rates were 63.5% overall, and 83.3% in microprolactinoma patients. Males had less favorable remission rate compared to females. These findings highlight that ETSS may be a safe and efficacious treatment to manage prolactinoma.

Key Words: Prolactinoma, Dopamine agonist, Endoscopic trans-sphenoidal resection, Efficacy, safety, Remission.

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Introduction

Although a rare disease, prolactinomas are the most common type of pituitary adenoma (prevalence 37–115/100,000 individuals), accounting for 32–66% of cases (1,2). Prolactinomas are found three times more frequently in women than in men, with a peak-incidence at 25–35 years (2,3). Characterized by prolactin hypersecretion, prolactinomas are usually diagnosed when symptoms such as galactorrhea and hypogonadism -resulting in subfertility and in menstrual cycle disorders in women- become apparent (1). Moreover, larger tumors extending beyond the sellar region may cause visual field defects due to mass effects on the optic system (2). Additionally, non-specific symptoms such as fatigue, headache, weight gain, psychological symptoms, and neurocognitive complaints might occur (1). Prolactinomas are subcategorized as microprolactinomas (<10 mm; 80% of cases), macroprolactinomas (10–40 mm), or giant prolactinomas (>40 mm) based on Magnetic Resonance Imaging (MRI) (2).

Physiologically, prolactin production and secretion is regulated by dopamine, which inhibits prolactin secretion (1). Therefore, treatment with dopamine agonists (DAs) is recommended as first-line treatment in current guidelines (1,4). For all other types of functional pituitary adenoma, surgical resection is first-line treatment (5–7). Typically, in response to DAs, serum prolactin levels decline and normalize, hypogonadism restores, and prolactinomas shrink in size, and in 26–46% even disease remission is reported >1 year after DA withdrawal (1,8,9). Therefore, surgical treatment is reserved for patients who experience severe side effects of DAs, in case of a DA-resistant prolactinoma, or when an acute decompression of surrounding structures is warranted, e.g. in case of apoplexy or severe optic chiasm compression (1,4).

Recently, outcomes of endoscopic transsphenoidal surgery (ETSS) have improved and a greater role for surgery in the management of prolactinomas is being discussed. Reviews and meta-analyses suggested that surgery may be a viable alternative first-, or early second-line treatment for selected prolactinomas, also Supplementary Table 1 (9–11). Although DA treatment normalizes prolactin in 81% of patients, remission rate after withdrawal following two years of treatment is only 34% (9). Therefore, most patients need prolonged, often lifelong, medical treatment. By contrast, surgical resection resulted in remission $\geq$1 year after surgery in 67% of patients, and remission rates increased to 80–90% in microprolactinoma patients (9,11–14), with recurrence rates varying from 5–20% (11,15). The overall complication rate after prolactinoma surgery is low, with severe complications occurring seldomly (9–14), especially when performed by experienced pituitary surgeons (16). Interestingly, previously published studies on surgically treated prolactinoma patients rarely include long-term follow-up (>2 years) (9). Furthermore, current literature mostly contains single-center observational data on small, or selective cohorts, e.g. describing only male patients or giant prolactinomas (9), while representative outcome data are important for clinical counseling of prolactinoma patients considering surgery.

Therefore, this multicenter, retrospective study aimed to assess the effectivity and safety of ETSS for prolactinoma patients in a large cohort of surgically treated patients from three tertiary referral centers. Clinical efficacy, and safety outcomes, including short- (<6 months) and long-term (>1 year postoperatively) biochemical remission, resolution of hypogonadism and visual deficiencies, and recurrence and complication rates were assessed.

Methods

Study Design and Population

A retrospective chart review of all prolactinoma patients undergoing endoscopic trans-sphenoidal surgery between January 1st, 2010, and December 31st, 2019, was performed in three tertiary referral centers from the USA and the Netherlands. All data was collected either for previous studies (17,18), or with a waiver from medical ethical review from institutional medical ethical review boards (G19.011, and IRB 2020H0221). All centers signed a data sharing agreement.

In- and Exclusion Criteria

In all patients, initial prolactinoma diagnosis was based on symptomatic hyperprolactinemia. Indications for surgery were either DA intolerance, resistance, or an acute surgery indication (i.e., apoplexy, vision loss, or CSF leakage). Postoperatively, prolactinoma diagnosis was confirmed by immunohistochemistry (i.e., presence of prolactin-secreting tumor cells), in most patients. Patients were not included in case of clinical diagnosis of co-secretion of growth hormone (GH).

Surgical Technique and Pre- and Post-operative Work-up

Preoperatively, all patients underwent an MRI and CT-scan, and routine assessment of endocrine function. In case of corticotroph or thyrotroph pituitary deficiency, hormone replacement therapy was initiated preoperatively. In all three centers, transsphenoidal adenoma resection was performed endoscopically. After surgery patients remain hospitalized for 3–5 d, during which they are monitored for early complications (e.g., central spinal fluid leakage, hypo- or hypernatremia). Postoperative endocrine assessment was performed to assess remission, restoration of preoperative hypopituitarism and occurrence of new-onset hypopituitarism. A routine MRI was performed in all patients within 6 months postoperatively.

Study Parameters

All data was retrospectively extracted from the electronic patient files.

Clinical Parameters

The following data was extracted from electronic patient records: age, sex, preoperative dopamine agonist treatment and its outcomes, i.e. intolerance (clinically relevant side effects), resistance (insufficient biochemical response to maximally tolerated DA dosage) or other, surgical indication (i.e. DA intolerance, resistance, acute indication and/or patient preference), intent of surgery (complete resection or debulking/optic decompression), pre- and postoperative laboratory measurements, pre- and postoperative endocrine deficiencies, radiological and pathology characteristics, and surgical outcomes.

Radiological Measurements

Radiologic characteristics were based on the last preoperative MRI. Tumor size was categorized as giant (≥40 mm), macro- (10–40 mm), or microprolactinoma (<10 mm) based on maximum diameter. Cavernous sinus involvement was graded according to KNOSP-grading (19), and for analyses, tumors with KNOSP score >3 were considered invading the cavernous sinus.

Prolactin Measurements

The highest and immediate preoperative (≤1 d; POD1) serum prolactin levels were documented (non-pregnant or -lactating). Furthermore, serum prolactin levels at 1 week postoperatively, lowest values postoperatively, and last follow-up were recorded. Upper limit of normal (ULN) for serum prolactin was 15.3 (Leiden and NY) or 17.7 (OSU) μg/L for males, and 23.3 (Leiden and NY) or 29.2 (OSU) μg/L for non-pregnant, postmenopausal females.

Outcome Definitions

Outcomes following surgery were extent of tumor resection, biochemical remission, disease recurrence, recovery of gonadal axis, pituitary function, and visual deficiencies (i.e., visual field defects and/or visual acuity defects), and complications.

Tumor resection was judged at the postoperative MRI (performed within 3–6 months) and was defined as gross total resection (GTR) or subtotal resection (STR). Remission was defined as normoprolactinemia (<1xULN), or asymptomatic mild (≤1.5x ULN) hyperprolactinemia combined with GTR, without the need for DA treatment. Short-term remission was measured ≤6 months, and long-term at last follow-up (≥1 year after surgery). Recurrence was defined as recurrence of symptomatic hyperprolactinemia after an episode of remission, regardless of tumor growth on MRI.

Restoration of hypogonadism was defined as restoration of menstrual cycle/fertility and/or libido/erectile function, if available supported by biochemistry. Restoration of preoperatively existing pituitary deficiency(-ies) was defined as normalization of endocrine function, without the need for substitution therapy.

Safety assessment included evaluation of all observed complications occurring within 30 d after surgery, based on clinical diagnoses and included at least the following complications of interest: cerebrospinal fluid (CSF)-leakage, transient (<6 months) and permanent (≥6 months) diabetes insipidus (DI), hyponatremia, new pituitary deficiencies, and new vision deficiencies.

Statistical Analyses

Statistical analyses were performed using IBM SPSS statistics 25 (IBM Corp. Armonk, NY, USA). Baseline characteristics were calculated using descriptive statistics. Data was reported as means with standard deviation (± SD) or median (interquartile range) for continuous variables, and as frequencies (N) with percentage (%) for dichotomous variables. As sex differences are well-established in patients with prolactinoma, data is reported for males and females separately, and the two sexes were compared regarding outcomes (significant results reported in text). *T*-tests or non-parametric Mann-Whitney-*U*-tests were used as appropriate, for the analyses of continuous variables. Analyses of categorical variables consisted of χ^2 or Fisher's exact tests, as appropriate. *p*-values <0.025 were considered significant.

Results

Preoperative Characteristics

We identified 137 consecutive prolactinoma patients, with a mean age of 38.2 ± 13.7 years, of whom 84 patients (61.3%) were female. A complete overview of preoperative characteristics and sex differences is shown in Table 1. A comparison was made between study sites for key characteristics, revealing only differences in patient age (data not shown) and the indication for surgery (see *Surgical indication and goals* below).

Endocrine Characteristics

Median prolactin level at or just before admission for surgery (with or without DA), available for 132 patients, was 94 μg/L (41–228 μg/L; males 166 μg/L [43–514 μg/L] vs. females 72 μg/L [41–147 μg/L], $p = 0.014$). Data regarding pituitary functioning was available in 135

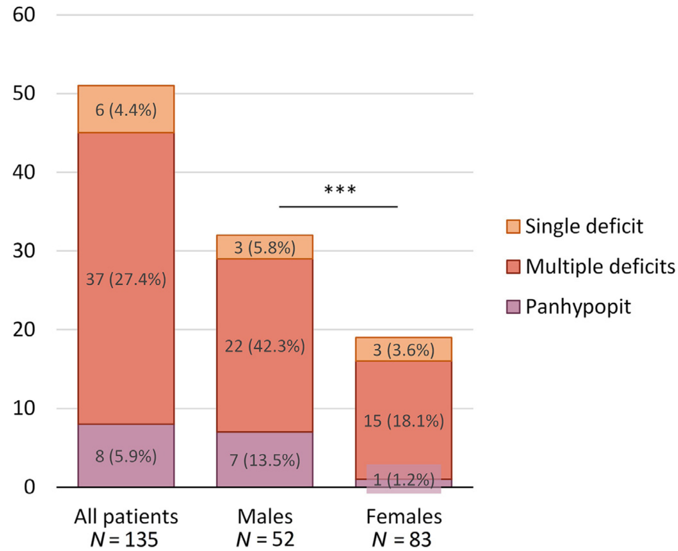

Figure 1. Pituitary deficiencies, data are presented as *n* (%).

Table 1. Baseline characteristics

		All patients $N = 137$	Males $N = 53$ (38.7)	Females $N = 84$ (61.3)	p
Age at surgery (years)		38.2 (± 13.7)	46.5 (± 15.0)	33.0 (± 9.6)	<0.001
Serum prolactin (µg/L)	Highest pre-operatively	N =115	$N = 45$ (84.9)	$N = 70$ (83.3)	
		169 (98–837)	996 (159–2145)	129 (84–223)	<0.001
	Last pre-operatively	$N = 132$	$N = 48$ (90.6)	$N = 84$ (100.0)	
		94 (41–228)	166 (43–514)	72 (41–147)	0.016
Max diameter (mm)		15.2 (± 12.4)	23.8 (± 14.5)	9.8 (± 6.8)	<0.001
Cystic tumor		32 (23.4)	12 (22.6)	20 (23.8)	0.875
KNOSP		$N = 131$	$N = 48$ (90.6)	$N = 83$ (98.8)	
	0.	60 (45.8)	11 (22.9)	49 (59.0)	<0.001
	1.	25 (19.1)	7 (14.6)	18 (21.7)	
	2.	11 (8.4)	6 (12.5)	5 (6.0)	
	3A and 3B.	15 (11.5)	8 (16.8)	7 (8.4)	
	4.	20 (15.3)	16 (33.3)	4 (4.8)	
Apoplexy		12 (8.8)	4/53 (7.6)	8/84 (9.5)	0.766
Vision deficit		27 (19.7)	19/53 (35.8)	8/84 (9.5)	<0.001
EOM deficit		1 (0.7)	1 (1.9)	0 (0.0)	

Data are presented as mean (± SD), median (IQR),or n (%) unless specified otherwise.

Table 2. Type of pituitary deficit(s)

	All patients $N = 135$	Males $N = 52$	Females $N = 83$	p
GH	13 (9.5)	11 (21.1)	2 (4.8)	<0.001
LH	43 (31.9)	30 (57.7)	13 (15.7)	<0.001
FSH	41 (30.4)	28 (53.8)	13 (15.7)	<0.001
TSH	25 (18.5)	16 (30.8)	9 (10.8)	<0.005
ACTH	15 (11.1)	12 (23.1)	3 (3.6)	<0.001
ADH	10 (7.4)	8 (15.4)	2 (2.4)	0.013

Data are presented as n (%).

patients (52 males and 83 females), showing 51 patients (37.8%) with any pituitary deficit, of whom 6 (4.4%) had a single deficit, 37 (27.4%) multiple deficits, and 8 patients (5.9%) had panhypopituitarism, Figure 1, and Table 2 for a complete overview of types of pituitary deficits. Of the pituitary axes, the gonadal axis was most often deficient, with LH deficiency in 43 patients (31.9%) combined with FSH deficiency in 41 patients (30.4%). Males were more likely to have any pituitary deficit (32 [61.5%], vs. 19 females [22.9%], p <0.001), showed multiple deficits more often (22 [42.3%], vs. 15 females [18.1%], p <0.001), and were more likely to have panhypopituitarism (7 [13.5%], vs. 1 female [1.2%], $p = 0.001$).

Imaging and Ophthalmological Data

Pituitary imaging showed a mean maximal diameter of 15.2 ± 12.4 mm, with 56 patients (40.9%) having microprolactinoma, 69 (50.4%) macroprolactinoma, and 7 (5.1%) giant prolactinoma, and in 5 patients (3.6%) no adenoma was visible, also Figure 2. Males more often showed

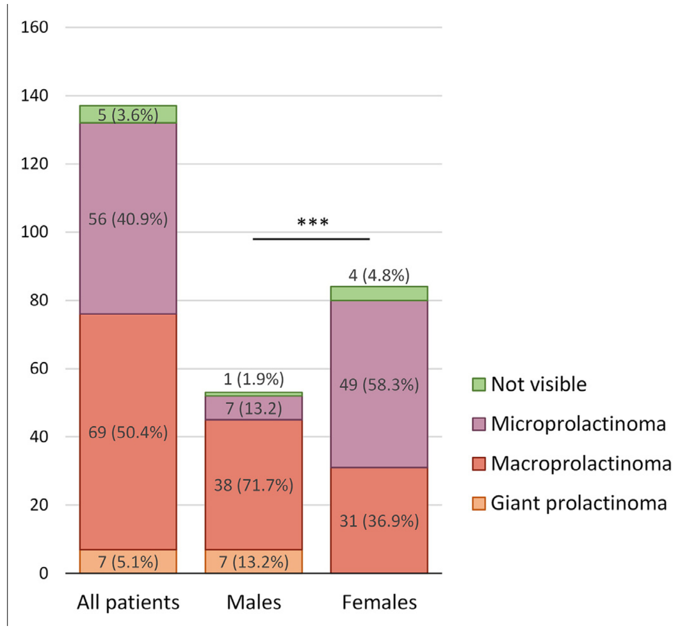

Figure 2. Prolactinoma size based on maximum tumor diameter on the last preoperative MRI. Characterized as not visible on MRI, microprolactinoma (<10 mm), macroprolactinoma (10–40 mm), or giant prolactinoma (≥40 mm). Data are presented as *n* (%).

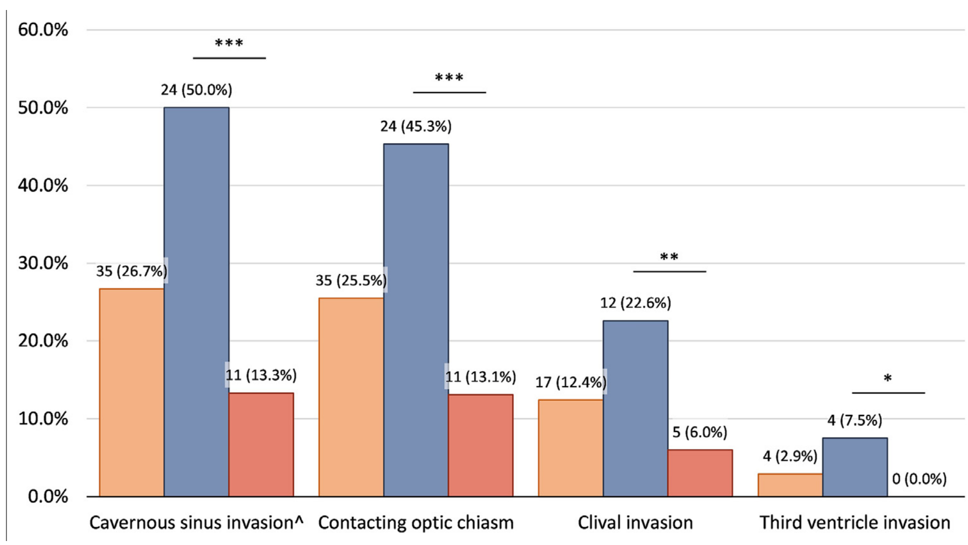

Figure 3. Prolactinoma invasiveness characteristics based on last preoperative MRI. Cavernous sinus invasion defined as KNOSP score 3 or higher. Data are presented as *n* (%), with orange bars for the entire population, blue bars for males, and red bars for females. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

macroprolactinomas (38 [71.7%] vs. 31 females [36.9%]) and giant prolactinomas (7 [13.2%] vs. 0 females [0.0%]), compared to microprolactinoma (7 [13.2%] vs. 49 females [58.3%]), $p < 0.001$. 32 patients (23.4%) had a cystic prolactinoma.

A complete overview of tumor invasiveness is shown in Figure 3. KNOSP scores were available for 131 patients, showing 15 patients (11.5%) with KNOSP-3, and 20 (15.3%) with KNOSP-4. As expected, males more often showed invasive tumors. Moreover, 39 patients (28.5%) showed suprasellar growth, whereas in 35 patients (25.5%) the prolactinoma contacted the optic chiasm.

Vision deficits were observed in 27 patients (19.7%), of whom only 1 patient (0.7%) had extraocular muscular deficits noted on exam. Males were more likely to have a vision deficit (19 [35.8%] vs. 8 females [9.5%], $p < 0.001$).

Surgical Indications and Goals

For a complete overview of surgical indications and goals, Table 3. As expected, the majority of patients (123

Table 3. Surgical indication and goals

		All patients N = 137	Males N=53	Females N = 84	*p*
Received preop DA treatment		123 (89.8)	45 (84.9)	78 (92.9)	0.135
Indication for surgery	DA intolerance	59 (43.1)	14 (26.4)	45 (53.6)	0.024
	No tumor response	28 (20.4)	15 (28.3)	13 (15.5)	
	Vision loss	16 (11.7)	10 (18.9)	6 (7.1)	
	Apoplexy	8 (5.8)	3 (5.7)	5 (6.0)	
	Multiple reasons	15 (10.9)	7 (13.2)	8 (9.5)	
	Other reasons[a]	11 (8.0)	4 (7.5)	7 (8.3)	
Intent of surgery	Complete resection	109 (79.6)	33 (62.3)	76 (90.5)	<0.001
	Debulking/optic decompression	28 (20.4)	20 (37.7)	8 (9.5)	

Data are presented as *n* (%).
[a]e.g. patient preference, CSF-leak.

[89.8%]) had received DA treatment prior to surgery, and the indication for ETSS most often was DA intolerance (59 patients [43.1%]), and DA resistance in 28 patients (20.4%). Acute surgical indications were vision loss, occurring in 16 patients (11.7%), and apoplexy, occurring in 8 patients (5.8%) (apoplexy in total observed in 12 [8.8%] patients). In 15 patients (10.9%) multiple indications were observed (mostly combination of DA intolerance and/or no tumor response, either with or without patient preference). In 11 patients (8.0%), a variety of “other reasons” were observed as single indication for ETSS, including at least 2 patients with patient preference observed as single indication. There was no difference between males and females in indication for ETSS. Interestingly, in the LUMC, DA intolerance was reported more often as the indication for surgery (49 patients [61.3%] vs. OSU 15 [35.9%] and Northwell 4 [28,6%], $p = 0.005$). OSU and Northwell were more likely to report no DA response as the surgical indication, respectively in 19 patients (44.2%) and 7 patients (50.0%) vs. LUMC 15 (18.8%), $p < 0.005$.

In 109 patients (79.6%), complete prolactinoma resection was the main surgical intent, as opposed to 28 patients (20.4%) in whom debulking (e.g., for decompression of the optic system) was primarily intended because total resection was deemed not feasible.

Surgical Outcomes

Extent of Resection

An overview of surgical outcomes is shown in Table 4. In total, in 96 patients (70.1%) GTR was accomplished, whereas in 41 patients (29.9%) STR was observed. In 91 out of 109 patients (83.4%) in whom complete resection was the intent of surgery, GTR was achieved. Interestingly, GTR was observed in 5 patients (17.9%) in whom the intent of surgery was debulking. As expected, GTR was less often seen in males (28 [52.8%], vs. 68 females [81.0%], $p < 0.001$), opposed to STR in 25 males (47.2%), compared to 16 females (19.0%), $p < 0.001$.

Short-term Remission

Median prolactin levels at POD1, available for 132 patients, were <1xULN in 92 patients (67.2%), (males 29/51 [56.9%], females 63/81 [77.8%], $p = 0.011$). Interestingly, short-term remission was observed in 102 patients (76.7%) overall, data available for 133 patients (50 males [53%], 83 females [98.8%], $p < 0.001$). As expected, the short-term remission rate was slightly higher among patients in whom complete resection was the intent of surgery (95 patients [87.2%]). Although still a reasonable remission rate, males showed lower short-term remission rates compared to females (males 33 [66.0%] vs. females 69 [83.1%], $p = 0.024$).

Resolution of Hypogonadism

Resolution of hypogonadism was observed in 16/36 patients (44.4%), of whom 3 patients were not in short-term biochemical remission and 4 patients underwent STR. Similar proportions for males and females.

Resolution of Hypopituitarism

Complete resolution of hypopituitarism was observed in 44/50 patients (88.0%), similar for males and females, 3 patients (6.0%, all males) showed partial resolution, and 3 patients no resolution (6.0%; 1 male [3.2%], 2 females [10.5%]), $p < 0.001$.

Complications of Surgery

For an overview of all observed complications, Table 5. A total of 61 complications occurred in 41 patients (29.9%). Transient DI was the most frequently re-

Table 4. Short-and long-term surgical outcomes

		All patients $N = 137$	Males $N = 53$	Females $N = 84$	p
Extent of surgery	GTR	96 (70.1)	28 (52.8)	68 (81.0)	<0.001
	STR	41 (29.9)	25 (47.2)	16 (19.0)	
Length of stay (days)		3.60 (± 3.03)	4.32 (± 4.47)	3.14 (± 1.40)	0.067
Short-term remission	Total	102/133 (76.7)	33/50 (66.0)	69/83 (83.1)	0.024
	Intended CR	82/109 (75.2)	22/33 (66.7)	60/76 (78.9)	0.172
DA-free remission at last follow-up		87 (63.5)	25 (47.2)	62 (73.8)	0.002
Long-term remission	Total	73/118 (61.9)	21/48 (43.8)	52/70 (74.3)	0.001
	Intended CR	69/92 (75.0)	19/30 (63.3)	50/62 (80.6)	0.072
Time of follow-up (months)		28.0 (15.0–55.5)	35.0 (21.0–61.0)	26.0 (14.0–50.0)	0.092
Prolactin <ULN	POD1	92/132 (67.2)	29/51 (56.9)	63/81 (77.8)	0.011
	At last follow-up	66/135 (48.2)	17/52 (32.6)	49/83 (59.0)	0.003
Resolution of symptoms					
Hypopituitarism	No	3/50 (6.0)	1/31 (3.2)	2/19 (10.5)	<0.001
	Partially	3/50 (6.0)	3/31 (9.7)	0/19 (0.0)	
	Complete	44/50 (88.0)	27/31 (87.1)	17/19 (89.5)	
Hypogonadism		16/36 (44.4)	8/23 (34.8)	8/21 (38.1)	0.051
Additional therapy post-op	Total	48 (35.0)	29 (54.7)	19 (22.6)	<0.001
	RTx	11/136 (8.1)	9/52 (17.3)	2/84 (2.4)	0.003
	DA treatment	42 (30.7)	24 (45.3)	18 (21.4)	0.003
	Reoperation	7/93 (7.5)	4/36 (11.1)	3/57 (5.3)	0.424

Data are presented as mean (± SD), median (IQR), or *n* (%) unless specified otherwise.

Table 5. Complications of surgery

	All patients $N = 137$	Males $N = 53$	Females $N = 84$	p
Any complication (no. of patients)	41 (29.9)	15 (28.3)	26 (31.0)	0.741
Any permanent complication (no. of patients)	7 (5.1)	4 (7.5)	3 (3.6)	0.430
CSF-leak	1 (0.7)	1 (1.9)	0 (0.0)	NA
Transient DI	29 (21.2)	9 (17.0)	20 (23.8)	0.150
Permanent DI	2 (1.5)	2 (3.8)	0 (0.0)	0.148
Hyponatriemia	10 (7.3)	2 (3.8)	8 (9.5)	0.315
New Hypopituitarism	8/129 (6.2)	4/46 (8.7)	4/83 (4.8)	0.008
New visual complaint	2/109 (1.8)	2 (3.8)	0 (0.0)	NA
Meningitis	1/95 (1.1)	1/36 (2.7)	0/59 (0.0)	NA
Epistaxis	5/95 (5.3)	2/36 (5.6)	3/59 (5.1)	NA
Other[a]	3/95 (3.2)	2/36 (5.6)	1/59 (1.7)	NA

Data are presented as *n* (%), counted as no. of complications, unless specified otherwise.
[a]I.e. 2 patients with headache (1 male, 1 female), 1 male patient hematoma and nerve damage.

ported surgical complication ($N = 29$ [21.2%]). Transient postoperative hyponatremia occurred in 10 patients (7.3%). Post-operative CSF-leakage was observed only in 1 male patient (0.7%). Permanent DI was observed in 2 male patients (1.5%). New hypopituitarism was observed in 8/128 patients (6.3%), including 1 male patient (0.9%) with novel panhypopituitarism, 3 patients (2 males, 1 female) with novel TSH deficiency and 3 patients (1 male, 2 females) with novel ACTH deficiency. Although similar for micro-, macro- and giant prolactinoma patients, male patients developed new hypopituitarism more frequently (4/46 [8.7%] vs. 4/83 females [4.8%], $p = 0.008$). Permanent complications all involved new hypopituitarism, and were observed in 7 patients (5.1%), equally divided between males and females.

Long-term Remission

Long-term follow-up (>1 year) was available for 118/137 patients, of whom 73 (61.9%) showed DA-free remission. Interestingly, of 135 patients with available data, 66 patients (48.2%) had prolactin levels <1xULN at last follow-up (17/52 males [32.6%], 49/83 females [59.0%], $p = 0.003$). Formal recurrence rates could not reliably be evaluated, since DA treatment was restarted even though the present definition of recurrence was not (yet) met in a small number of patients (exact number unknown).

As expected, males had lower long-term DA-free remission rates (21/48 [43.8%] vs. 52/70 females [74.3%], $p = 0.001$). Within the group of patients in whom complete resection was the intent of surgery, long-term remission was observed in 69/92 (75.0%), not different for males and females. Furthermore, patients with microprolactinoma had higher long-term DA-free remission rates (35/42 [83.3%] vs. macroprolactinomas 37/65 [56.9%], giant prolactinomas 1/7 [14.3%], and non-visible prolactinomas 0/4 [0.0%], p <0.001). Moreover, patients with adenomas with cavernous sinus invasion (KNOSP>3) were less likely to reach DA-free remission (10/32 [31.3%] vs. 62/80 [77.5%], p <0.001).

Additional Treatment Strategies

During a median follow-up of 28.0 (15.0–55.5) months, 42 patients (30.7%) had received DA treatment postoperatively, of whom 35 patients (25.5%) still received DA treatment at last follow-up. Males were more likely to receive DA treatment, both at any point postoperatively (24 [45.3%] vs. 18 females [21.4%], p = 0.003), and at last follow-up (23 [43.4%] vs. 12 females [14.3%], p <0.001). Overall, 11 patients (8.1%, data available for 136 patients) received radiotherapy, and 7 patients (7.5%, data available for 93 patients) underwent reoperation. Although proportions of males and females who underwent reoperation were similar, males were more likely to receive radiotherapy (9 [17.3%], available for 52 males) vs. 2 females (2.4%), (p = 0.003).

Discussion

In this multinational retrospective case-series of 137 prolactinoma patients who underwent surgery, mostly as second-line treatment, long-term DA-free remission was achieved in 61.9% of patients, with transient DI being the most frequent complication, and permanent new hypopituitarism occurring in 5.1%, despite the large proportion of macro- or giant prolactinomas. Furthermore, sex differences in both clinical characteristics and surgical outcomes were observed. We present outcomes of three high-volume neurosurgical expert centers.

Preoperative Characteristics

Since ETSS is not standard treatment in all prolactinoma patients, it is worthwhile to understand the characteristics of this surgical cohort. We describe a case-series consisting of 61.3% females and a mean age at surgery of 38.2 (± 13.7) years. Previously published surgical cohorts tend to report higher proportions of male patients compared to general prolactinoma patient population (2,3,9,20–22). The proportion of females and age at the time of surgery in our case-series is in line with other surgically treated prolactinoma cohorts, especially compared to cohorts consisting of similar proportions of microprolactinoma patients (9,20–22). Up to 26.7% of the patients in our case-series showed invasion of the cavernous sinus (KNOSP score 3 or higher), which is in line with other studies reporting similar amounts of patients with larger tumors (21,22).

As DA treatment is recommended as first-line treatment for prolactinoma, the vast majority of patients in our case-series were pretreated with DA, which is similar to most other published cross-sectional surgical cohorts (22–24). We found that the indication for surgery was DA intolerance or resistance in most patients, and even a combination of the two in a handful of patients. Of DA naïve patients' surgical indications were mostly acute loss of vision or apoplexy. Interestingly, in Leiden DA intolerance was more often reported as an indication for surgery than the other two centers, and no tumor response was more often reported as an indication in Columbus and Long Island. We hypothesize this reflects a national difference, as the two centers from the United States have similar proportions. To our knowledge, there are no previous studies that could make such a comparison. Furthermore, the mean age was different between the participating centers, as the patients in Long Island were the oldest and those in Columbus the youngest (data not shown). The reason for this difference in age, and its implications, as well as that of the difference in surgical indication, for our study are unclear, as there were no differences in other preoperative characteristics, or other outcomes of interest. Furthermore, although our study was not powered to detect a difference between study sites, the similarities between patient characteristics add to the strength of combining our patient data.

Interestingly, only two patients were treated surgically because of patient preference as the only indication, and in a number of patients patient preference was registered as a co-indication, which is in line with multiple recent studies reporting varying proportions of patients undergoing surgery because of their preference either with or without DA pretreatment (20,23,24). This reflects a growing interest in patient preference as a valid indication for surgical treatment.

In up to 79.6% of patients the intent of surgery was complete resection, which is in line with Force BK, et al. (2022), who report complete resection as the goal of surgery in 80.0% of their patients.

Surgical Outcomes

Long-term remission was achieved in 61.9% of patients, which is slightly lower than remission rates reported in literature (mainly of selected cases) (9,22–29). Although sex differences are a potential confounding factor in our cohort, higher long-term remission rate of 83.3% was observed in microprolactinoma patients. The higher proportion of macro- and giant prolactinomas in our cohort compared to most previous reports (23–25,30) could therefore explain our lower overall remission rate. Moreover, Abou-Al-Shaar H, et al. (2022) report even lower remission rates, especially for patients with KNOSP-3 and -4, which may further contribute to our lower remission rate, as our cohort had higher proportions of patients with KNOSP-3 and -4 lesions compared to previous studies (22–24). The slightly lower overall remission rate in our case-series could thus be explained by the relatively high amount of larger and invasive tumors, which is supported by previous observations that tumor size and invasiveness are associated with remission rate (20–22,30–32). Interestingly, none of the patients with a clear clinical prolactinoma diagnosis but non-detectable tumors showed remission, of whom histopathological analyses showed negative results in 2 patients, and prolactin and GH co-staining in the other 2 patients. Unfortunately, preoperative functional imaging was not available at that time. Based on our findings, alternative diagnosis (e.g., hyperplasia) cannot be ruled out, and should be considered.

As expected, among patients in whom complete remission was the intent of surgery, we found a higher remission rate of 75.2%. Force BK, et al. (2022) report long a term remission rate of 84.8% for the patients in whom complete remission was the goal of surgery. Interestingly, when they compared these remission rates between micro- and macroprolactinoma patients, they found remission in 75.0% of macroprolactinoma patients, which is similar to the remission rate we found (22).

Remission rates in our cohort could furthermore be impaired by our stringent criteria for remission, as even prolactin levels slightly above the reference range were categorized as active disease or started on DA treatment and therefore reported as not in remission.

Moreover, there are some studies that have showed that longer DA pretreatment may be associated with worse outcomes of surgery (23,24). Although we did not record the time of DA pretreatment in our case-series, we do know that the vast majority of our patients had received DA treatment.

With overall small numbers of permanent complications, surgery was well tolerated. The most frequent complication was transient DI, with new hypopituitarism being observed in 6.3% of patients, which is in line with previous reports in literature (9–14,20,22,24,30).

Sex Differences

In our case-series, males were older and more often showed macro- and giant prolactinomas, which is in line with previous reports in literature (23,33–35). Moreover, males were more likely to have invasive tumors, higher preoperative prolactin levels and were more likely to have pituitary deficits, which reflects a general notion that males have more complicated tumors (2,3,9,23,33–35).

Interestingly, in males DA resistance was more often the indication for surgery compared to females, and debulking was more often the intent of surgery, which is likely due to the higher ratio of larger and invasive tumors in males. To our knowledge, there are no other recent studies that compared these characteristics between males and females.

Furthermore, we found that males were less likely to achieve long-term DA-free remission, which confirms some previous reports in literature (23,30,33–35). It should be noted that there are also reports that show no difference in remission between males and females, or described differences are not significant in multivariate analyses (20,22,24,25). However, as mentioned these studies rarely report testing for sex differences in their baseline characteristics, while, based on our results, sex may pose as is an important confounding factor, impairing their analyses. Moreover, studies could be underpowered for determining any effect, as the proportions of male patients vary greatly (20,22–25,30,33–35). Furthermore, as described above, assuming that remission rates after surgery are lower in patients with larger and/or invasive tumors (9,20–22,30–32), we hypothesize that the lower remission rate in our male patients, is a reflection of their worse clinical characteristics. However, based on our data, we cannot completely rule out that sex independently influences the chance for remission.

Current Perspective and Future Directions

An updated definition of modern surgical indications for prolactinoma is lacking, while awareness of a more vital role for surgery as (first-line) treatment for prolactinoma is increasing. Moreover, prospective studies and RCT's remain scarce, but are expected (36). Additional analyses of our data, focusing one distinct groups of interests, or attempting quantification of the effects of tumor size and grade on surgical outcomes may provide at least a framework that could be used in anticipation of these studies. Furthermore, our results warrant a clear description of sex differences in any characteristic or outcome in studies with prolactinoma patients.

Updated definitions of surgical outcomes may be warranted, as the clinical relevance of slightly elevated prolactin levels are unclear, especially in patients in whom restoration of hypogonadism was reached following surgery. Further studies focusing on the long-term recurrence and remission rates, and the potential predictive value of slightly elevated postoperative prolactin levels are therefore needed.

Limitations

Several limitations need to be addressed. Although the present data provide an insight in real-life clinical care, the study was limited by its retrospective nature. All patient data was anonymized prior to USA-Netherlands exchange, which may limit answering additional questions regarding unclear and non-interpretable data fields during data analysis. Fortunately, this did not pose any problems in the interpretation of our main outcome data for this manuscript. Data was collected separately by the three study centers after careful discussion how to define parameters. Nonetheless, as discussed above, a comparison of key characteristics showed only differences between centers in age and indication for surgery, of which the implications for our study remain unclear. Although our study is not powered to fully detect difference between study sites, the differences are thought to be of low clinical importance. To compensate for potential bias, outcome definitions were predefined based on consensus between centers and frequent study meetings were held. In the present study, as in most previously published studies, all patients were treated in three high-volume reference centers, resulting in a more complex patient population with potentially lower a priori chances for remission rates. Furthermore, it is known that surgical outcomes are better when surgeons are more experienced, hampering extrapolation of the reported outcomes to all patients with prolactinoma, especially to centers with lower surgical volumes (37). However, long-term remission rates were reported for the first multicenter surgical cohort, combining surgically treated patients with prolactinoma from different continents.

Conclusions

In this multinational retrospective case-series of 137 prolactinoma patients who underwent ETSS, with high proportions of macroprolactinoma and KNOSP 3–4, the majority achieved long-term remission, with low complication rates. Both preoperative clinical characteristics and remission rates were significantly different between males and females, which is probably at least in part due to the worse clinical characteristics in males, but should be taken into account when providing patient education.

Conflicts of Interest

The authors declare that they have no competing interests. There was no external funding for this study.

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Supplementary Materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.arcmed.2023.102919.

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