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Clinical Research Article

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Cure and Hormonal Control After Prolactinoma Resection: Case Series and Systematic Review

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Abbreviations:CSI, cavernous sinus invasion; DA, dopamine agonist; DI, diabetes insipidus; EMR, electronic medical record; EOR, extent of resection; GTR, gross total resection; MRI, magnetic resonance imaging; POD, postoperative day; SRS, stereotactic radiosurgery; STR, subtotal resection; TSSR, transsphenoidal surgical resection; USC, University of Southern California.

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Abstract

Context: Surgical management of prolactinomas is an important treatment for patients intolerant of dopamine agonist therapy. However, predictors of postoperative outcomes remain unclear.

Object: While transsphenoidal surgical resection (TSSR) is important second-line therapy in prolactinoma patients, predictors of surgical cure and biochemical remission following TSSR remain sparse.

Methods: A retrospective review of prolactinoma patients undergoing TSSR at the USC Pituitary Center from 1995 to 2020 was conducted. Participants were categorized as surgical cure (normalization of serum prolactin without medical treatment), surgical noncure, biochemical control (prolactin normalization with or without adjuvant therapy), and nonbiochemical control. A systematic review of the outcomes of surgically managed prolactinomas was performed.

Results: The 40 female and 16 male participants had an average age of 35.6 years. Prior treatment included transsphenoidal resection (6, 11%) and dopamine agonist treatment (47, 84%). The 40 macroadenomas and 15 microadenomas exhibited suprasellar extension (24, 43%) and parasellar invasion (20, 36%). Fifteen (27%) were purely intrasellar. Gross total resection was achieved in 25 patients (45%) and subtotal in 26 (46%). Surgical cure was achieved in 25 patients (46%) and biochemical control in 35 (64%). Surgical cure was more likely in smaller, noninvasive tumors, those that were fully resected, and patients with lower preoperative (< 1000 ng/mL) and immediately postoperative (< 7.6 ng/

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mL) prolactin levels. Ten of 26 patients (38%) undergoing adjuvant therapy achieved biochemical control, which was less likely in men and those with higher preoperative prolactin or invasive tumors.

Conclusion: Surgical resection of prolactinomas is a safe procedure that, when offered judiciously, can achieve symptom and/or biochemical control in a majority of patients. A variety of predictors may be useful in advising patients on likelihood of postoperative remission.

Key Words: prolactinoma, neurosurgery, pituitary adenoma, pituitary tumor

Prolactinomas are prolactin-secreting adenomas arising from lactotroph cells of the pituitary gland, and comprise approximately 40% of pituitary tumors [1]. There are 2 predominant categories of symptoms with which prolactinoma patients present: those due to elevated prolactin and its inhibition of gonadotropin-releasing hormone and those due to tumor mass effect [2]. An increase in prolactin secretion commonly results in reproductive and sexual dysfunction, including oligomenorrhea, galactorrhea, and amenorrhea in women and decreased libido in men [3]. Symptoms of mass effect include headaches, vision loss, and hypopituitarism and are usually seen in patients with macroprolactinomas [3].

Standard of care for treatment of prolactinomas centers around dopamine agonist (DA) therapy, which in the majority of cases is remarkably effective [4, 5]. Surgical resection is usually reserved for patients who are intolerant or resistant to DA therapy, as well as for some women harboring tumors who are considering pregnancy [6]. Prior studies have reported postsurgical biochemical control rates ranging between 50% and 93% for microprolactinomas and between 30% and 80% for macroprolactinomas [7-13] with mean follow-up of 19.6 to 138 months.

Although the effectiveness of surgical resection as a second-line therapy for prolactinomas has been reported, predictors of surgical cure (hormonal remission without postoperative DA therapy) and biochemical control with or without adjuvant postoperative DA therapy have not been extensively studied.

Objectives

We report a retrospective analysis of clinical and neuroimaging features of surgically treated prolactinoma patients at the University of Southern California (USC) Pituitary Center over the last 2 decades to identify predictors of persistent disease after surgery, with special attention given to identifying predictors of surgical cure as well biochemical control either with or without adjuvant postoperative DA therapy. To supplement our analysis, we conducted a systematic literature review of surgically managed prolactinoma cases through the PubMed database using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [14].

Materials and Methods

Patient Selection and Preoperative Assessment

This study was approved by the USC Institutional Review Board (IRB HS-11-00702). Patients surgically treated by authors M.W. and G.Z. for prolactinomas at the USC Pituitary Center from 1995 to 2020 were identified from a prospectively maintained RedCap database and retrospectively reviewed. All patients had prolactinomas confirmed by histopathological assessment. One patient did not have pathology available because the tumor was suspected to be suctioned before a sample could be obtained; however, it did have preoperative prolactin greater than 200 ng/mL that was reduced with DA therapy and exhibited biochemical remission postoperatively. Resection was offered as second-line treatment for patients who failed DA therapy or had persistent significant symptoms secondary to mass effect. In some cases, the preoperative diagnosis was indeterminate and the diagnosis of prolactinoma was made following histopathological analysis. In rare cases, resection was offered as a first-line treatment if patients expressed a strong preference for surgery and a clinical decision was made that the tumor could be completely resected and potentially cured. All patients underwent a thorough preoperative workup including a complete history, physical examination, endocrine laboratory testing, ophthalmological exam when appropriate, and magnetic resonance imaging (MRI) to assess the size of the tumor and determine the extent of invasion when present. Extrasellar extension was defined on MRI as tumor growth into the cavernous sinus, frontal lobe, clivus, sphenoid sinus, or suprasellar region. Degree of invasion was determined and scored by an independent neuroradiologist for this analysis. The minimum follow-up time for inclusion was 3 months.

Surgical Technique

All patients underwent a standard direct microscopic or endoscopic endonasal transsphenoidal approach based on surgeon preference. Intraoperative cerebrospinal fluid leaks were repaired using autologous adipose grafts for packing of the sella and/or fascial reconstruction of the sellar dura using a 2-layer fascial apposition technique [15].

Follow-up and Outcome Measurements

In the immediate postoperative period, patients were monitored for diabetes insipidus (DI), hyponatremia secondary to syndrome of inappropriate antidiuretic hormone secretion, and other electrolyte imbalances. Prolactin and electrolyte levels were drawn on postoperative days (POD) 1 and 2, and serum sodium levels were checked on POD7. After discharge, patients were followed by clinical assessment, MRI, measurement of prolactin levels, and visual field testing at intervals of 1.5, 3, and 6 months for the first year after surgery. Patients with residual tumor were evaluated for adjuvant medical therapy and radiation therapy or stereotactic radiosurgery (SRS), which was offered at the discretion of the treating radiation oncologist and neurosurgeon based on residual tumor size and location. Degree of resection was determined by an independent neuroradiologist.

Patients were divided into 4 groups for the purposes of analysis: surgical cure, surgical noncure, biochemical control, and nonbiochemical control. Surgical cure was defined as normalization of prolactin levels following surgery without the need for postoperative DA, whereas biochemical control was defined as normalization of prolactin levels following surgery, either with or without the use of postoperative DA. These determinations were based on laboratory data and medical history at the time of the patient's last known clinical visit. These categorizations are consistent with those used in prior literature and allow for overlap between outcome groups.

Whenever possible, postoperative MRI results and serum prolactin levels were used to determine prolactinoma recurrence (elevation of prolactin above normal) and progression (tumor growth on MRI). When postoperative MRI results were not available within the electronic medical record (EMR), recurrence/progression was determined by review of evaluations made by board-certified endocrinologists, adhering to these definitions.

Statistical Analysis

Descriptive statistics were used to summarize patient characteristics. Categorical variables were analyzed with chi-square analysis. Continuous variables were analyzed with independent *t* test (for normally distributed data) or Mann-Whitney *U* test (if distribution was not normal). SPSS 25.0 statistical software (IBM Corp) was used to perform the statistical analysis and generate receiver operating characteristic curves. *P* values less than .05 were considered to be statistically significant.

Prolactin Level Analysis

Preoperative prolactin levels were defined as the most recent prolactin level of patients while they were undergoing DA therapy prior to surgery (n = 47). Individuals who did not undergo DA therapy prior to surgery were excluded from analysis of preoperative prolactin level calculations because they had disproportionally elevated prolactin levels that were not predictive of the surgical response to treated prolactinomas relative to the other patients in our study (n = 9). For these patients, it is possible that DA therapy was either discontinued or not recorded in the EMR. POD1 prolactin was measured as a morning laboratory draw the first day after surgical resection using the Elecys Prolactin II immunoassay (Roche Diagnostics).

Systematic Review

To aid in analysis of our results, a systematic review of studies reporting the surgical management of prolactinomas through the PubMed and Google Scholar databases was conducted. Articles were included in the analysis if all cases in the series were surgically managed either as a primary mode of treatment, along with DA therapy, radiotherapy, or a combination of these treatment modalities. Series of patients managed solely by DA therapy or radiosurgery were excluded. Case reports, mixed-pituitary tumors, systematic and literature reviews, and cases looking at special populations, such as articles focused on pregnancy, pediatric adenomas, or multiple endocrine neoplasia type 1 syndrome, patients were excluded. For practicality, all articles not in English and series that did not examine predictors of hormonal remission were also excluded. A total of 160 studies were identified through PubMed and 17 additional studies were identified through Google Scholar and from citations of included papers, for a total of 177 initial records after duplicates were removed (Figure 1). Of these, 38 full-text articles were assessed for eligibility, and 19 studies published from 1992 to 2020 were included in the analysis.

Results

Patient Characteristics on Presentation

Of the 56 patients in this study, 40 were female (71%) and 16 were male (29%) with an average patient age of 35.6 years at surgery (SD 13.3). Fifty-three patients (95%) underwent surgery at Keck Hospital of USC and 3 patients (5%) were operated on at Los Angeles County + USC Medical Center. Nineteen patients (34%) underwent endoscopic endonasal

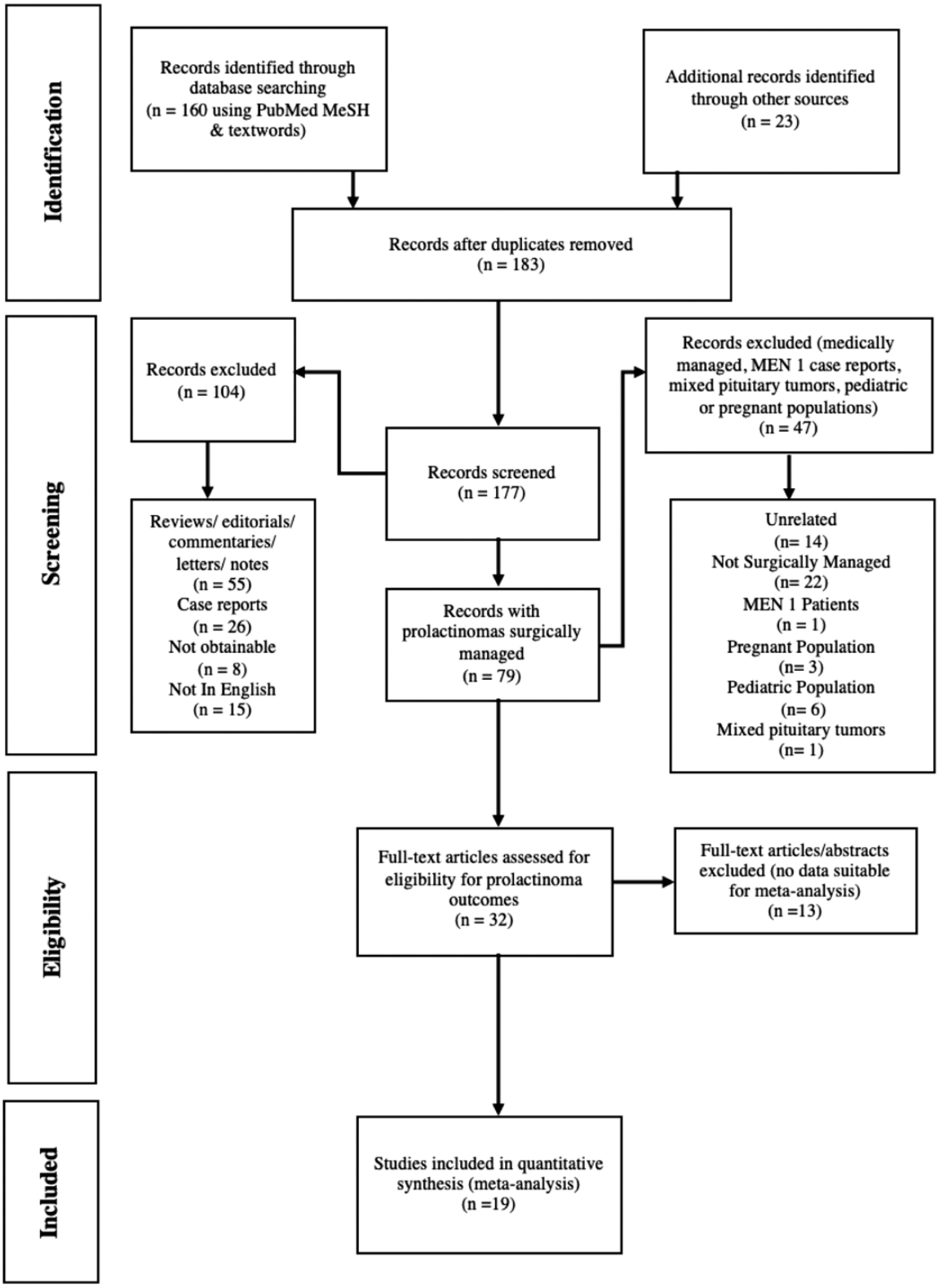

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for systematic review of surgical management of prolactinomas. The flow diagram template was adopted from the PRISMA statement [24].

transsphenoidal resection and the other 37 (66%) underwent a microscopic endonasal transsphenoidal procedure. Common presenting symptoms included amenorrhea/oligomenorrhea (34 patients, 61%), galactorrhea (19 patients, 34%), headache (25 patients, 45%), visual loss (11 patients, 20%), decreased libido (11 patients, 20%), fatigue

(8 patients, 14%), and dizziness (5 patients, 9%). Six patients (11%) had undergone prior transsphenoidal resection and 47 patients (84%) had prior DA treatment. Only 9 patients (16%) had received no treatment prior to surgery, either because of DA intolerance or a preference for surgery as a first-line treatment (Table 1). Mean preoperative prolactin levels in patients on a DA was 251.8 ng/mL (SD 522.2).

Preoperative Tumor Neuroimaging Characteristics

Maximal tumor diameter was available for 45 patients with a mean of 1.6 cm (SD 0.86). Forty were macroadenomas (73%) and 15 were microprolactinomas (27%), with 1 being a giant prolactinoma (> 4 cm). Twenty-four (43%) demonstrated suprasellar extension, 9 (16%) exhibited infrasellar extension into the sphenoid sinus, 1 (2%) extended to the clivus, and 20 (36%) invaded one or both of the cavernous sinuses. Fifteen prolactinomas (27%) were purely intrasellar (see Table 1).

Table 1. Overview of presenting patient and tumor characteristics

Patient characteristic	No. (%)
Female	40 (71%)
Male	16 (29%)
Age at surgery, mean ± SD, y	35.6 ± 13.3
Mean clinical follow-up time, mo	39.4 ± 42.1
Mean neuroimaging follow-up time, mo	33.3 ± 36.2
Type of surgical resection	
Endoscopic endonasal transsphenoidal	19 (34%)
Microscopic endonasal transsphenoidal	37 (66%)
Presenting symptoms	
Amenorrhea/oligomenorrhea	34 (61%)
Galactorrhea	19 (34%)
Headache	25 (45%)
Visual loss	11 (20%)
Decreased libido	11 (20%)
Fatigue	8 (14%)
Dizziness	5 (9%)
Prior treatment	
Prior DA therapy	47 (84%)
Prior transsphenoidal resection	6 (11%)
No prior treatment	9 (16%)
Neuroimaging characteristics	
Maximal tumor diameter, cm	1.6 ± 0.86
Macroadenomas	40 (73%)
Microadenomas	15 (27%)
Giant prolactinoma	1 (2%)
Suprasellar extension	24 (43%)
Sphenoid sinus invasion	9 (16%)
Clival extension	1 (2%)
Cavernous sinus invasion	20 (36%)
Purely intrasellar	15 (27%)

Abbreviation: DA, dopamine agonist.

Pituitary Adenoma Pathology and Immunostaining

All except 3 tumors in this study were classified as prolactinomas (53, 95%). Of the 3 patients whose tumors did not stain positively for prolactin, one was a very small microprolactinoma that was suctioned before pathology could be sent and 2 had tumors that were negative for all hormonal markers. In all 3 cases, patients had documented pretreatment prolactin levels greater than 200 ng/mL. In addition to prolactin (53, 95%), tumors also stained for adrenocorticotropin hormone (8, 14%), luteinizing hormone (6, 11%), growth hormone (6, 11%), follicle-stimulating hormone (3, 5%), and thyrotropin (2, 4%).

MIB-1 labeling index was performed in 21 cases (38%) demonstrating a mean of 2.43 (SD 1.47). Staining for p53 was performed in 12 cases (21%), with 6 prolactinomas staining positively (50%) and 6 staining negatively (50%). Neither MIB-1 labeling index nor p53 staining was correlated with hormonal remission.

Postoperative Complications

The majority of patients (45, 80%) experienced no postoperative complications. Three patients (5%) experienced cerebrospinal fluid leak, 2 of which required surgical repair and the other self-resolved. Three patients (5%) became hyponatremic, 4 (7%) had transient DI, 2 experienced epistaxis (4%), and 2 (4%) had meningitis (Table 2). No patients experienced permanent DI and no patient deaths occurred.

Surgical Outcomes

The mean neuroimaging follow-up time was 33.3 months (SD 36.2). Follow-up imaging was available for 51 patients (91%) and showed gross total resection (GTR) in 25 patients (49%) and subtotal resection (STR) in 26 patients (51%). Five patients (9%) experienced tumor progression after STR at a mean time of 41.3 months, and 3 patients (5%) had tumor recurrence after GTR at a mean time of 30.7 months (see Table 2).

Hormonal Outcomes

POD1 prolactin levels were available for 42 patients (75%) with a median of 10.2 ng/mL (interquartile range, 3.4-67.2 ng/mL). The mean clinical follow-up time for all patients was 39.4 months (SD 42.1) with a median prolactin level of 16.7 ng/mL (interquartile range, 9.1-60.4 ng/

mL) in the 48 patients with available follow-up levels. Hormonal outcome data were available for all but one patient demonstrating biochemical control with or without adjuvant therapy in 35 patients (64%) and surgical cure (hormonal remission without postoperative DA therapy) in 25 patients (46%) (see Table 2). This amounted to surgical cure of 73% of microadenomas (11 of 15) and 36% of macroadenomas (14 of 39) and biochemical control of 87% of microadenomas (13 of 15) and 56% of macroadenomas (22 of 39). No significant differences in surgical cure or biochemical control were noted between patients undergoing microscopic vs endoscopic transsphenoidal resection.

Table 2. Postoperative outcomes and adjuvant therapy

Postoperative complications	No. (%)
Transient DI	4 (7)
Hyponatremia	3 (5)
CSF leak	3 (5)
Epistaxis	2 (4)
Meningitis	2 (4)
Surgical outcomes	
Gross total resection	25 (49)
Subtotal resection	26 (51)
Tumor progression	5 (9)
Tumor recurrence	3 (5)
Hormonal outcomes	
Surgical cure	25 (46)
Biochemical control	35 (64)
Adjuvant therapy	
DA therapy	14 (25)
SRS	5 (9)
DA therapy + SRS	5 (9)
DA therapy + additional resection	1 (2)
DA therapy + SRS + additional resection	1 (2)

Abbreviation: CSF, cerebrospinal fluid; DA, dopamine agonist; DI, diabetes insipidus; SRS, stereotactic radiosurgery.

Adjuvant Therapy

Adjuvant therapy in the patients who did not experience surgical cure consisted of DA therapy, SRS, additional surgery, or a combination of treatments. Fourteen patients (25%) were prescribed DA alone, 4 of whom (7%) exhibited biochemical remission. Five patients (9%) underwent SRS alone, 2 of whom (4%) experienced biochemical control. Five patients (9%) had combination DA therapy and SRS, 3 of whom exhibited hormonal remission. One patient (2%) had combination DA therapy and repeat surgical resection and continued to be in nonremission, and one patient (2%) achieved remission after combination DA therapy, SRS, and repeat resection (see Table 2). Four patients (7%) did not undergo adjuvant therapy in the follow-up period.

Differences Based on Patient Sex

Men were significantly older than women at the time of surgery (45.8 vs 31.6 years; 95% CI, –21.2 to –7.3; $P < .001$) and presented with larger tumors (2.2 cm vs 1.4 cm; 95% CI, –1.4 cm to –0.28 cm; $P = .004$). Additionally, men were less likely to undergo surgical cure (19% vs 57%, $P = .011$). There were no significant differences between patient sex and preoperative or POD1 prolactin levels, prolactinoma invasion characteristics, extent of resection (EOR), or rate of biochemical cure (Table 3).

Predictors of Surgical Cure

Male patients were less likely to remit from surgery alone (19% of men remitted vs 57% of women, $P = .011$). Additionally, patients with prior transsphenoidal surgery were less likely to experience surgical cure than those who had not (0% vs 51%, $P = .018$). There was an insignificant trend of lower mean preoperative prolactin levels

Table 3. Comparison of male and female patients

	Male (n = 16)	Female (n = 40)	95% CI	*P*
Mean age at time of surgery, y	45.8	31.6	–21.2 to –7.3	< .001[a]
Preoperative prolactin, ng/mL	307 ± 798	231 ± 388	–436 to 285	.675[a]
Mean maximal tumor diameter, mm	2.2cm	1.4cm	–1.4 to –0.28	.004[a]
Suprasellar extension	9 (56%)	23 (56%)	–	.932[b]
Cavernous sinus invasion	8 (50%)	28 (70%)	–	.158[b]
Purely intrasellar	13 (81%)	28 (70%)	–	.39[b]
Postoperative d 1 prolactin	46 ± 76	62 ± 112	–55 to 87	.652[b]
Gross total resection	5 (31%)	20 (50%)	–	.148[b]
Surgical cure	3 (19%)	22 (57%)	–	.011[b]
Biochemical control	8 (50%)	27 (68%)	–	.178[b]

[a]Independent samples *t* test.
[b]Chi-square analysis 95% CI.

in patients that experienced surgical cure (96.8 ng/mL vs 361 ng/mL; 95% CI, –4.8 ng/mL to 533 ng/mL; $P = .054$). Patients with smaller prolactinomas were more likely to achieve surgical cure (1.3 cm vs 1.9 cm; 95% CI, 0.064 cm to 1.1 cm; $P = .013$). Cavernous sinus invasion (CSI) was more common in the surgical failure group (57% vs 12% in surgical cure group, $P = .001$). There were no significant associations between surgical failure and suprasellar, infrasellar, clivus, or frontal lobe extension, although this may be because of limited sample size. POD1 prolactin level was also a significant predictor of surgical cure (95.5 ng/mL in the surgical failure group vs 4.7 ng/mL in the surgical cure group, 95% CI, 39 ng/mL to 142 ng/mL; $P = .001$). Specifically, we found a POD1 prolactin level greater than 7.6 ng/mL predicted nonsurgical cure with a sensitivity of 79% and a specificity of 77% (area under the curve = 0.89; 95% CI, 0.79 to 0.99; Figure 2). Patients who underwent GTR of their tumor were more likely to experience surgical cure than those who underwent STR (75% vs 8%, $P < .001$; Table 4).

Predictors of Biochemical Control

Mean preoperative prolactin levels were higher in the nonbiochemical control group than the biochemical control (with or without adjuvant therapy) group (512 ng/mL vs 89 ng/mL; 95% CI, 23 ng/mL to 823 ng/mL; $P = .032$). Biochemical control was more likely to be achieved in patients with smaller prolactinomas (1.4 cm vs 2.0 cm; 95% CI, 0.02 cm to 1.1 cm; $P = .042$). POD1 prolactin levels were a significant prognosticator for biochemical control with or without adjuvant therapy (19 ng/mL in the biochemical control with or without adjuvant therapy group vs 125 ng/mL in the nonbiochemical control group; 95% CI, 25 ng/mL to 186 ng/mL; $P = .014$). Patients who had undergone prior transsphenoidal surgery were less likely to achieve biochemical control than those who had not (17% vs 69%, $P = .011$). Additionally, biochemical control was more likely to be achieved in patients who underwent GTR than those who underwent STR (88% vs 35%, $P < .001$). No significant differences were noted between biochemical control and patient sex or tumor invasion characteristics.

Patients who experienced biochemical control after adjuvant therapy were more likely to have lower preoperative prolactin levels (69 ng/mL vs 673 ng/mL; 95% CI, 48 ng/mL to 1159 ng/mL; $P = .036$) and have tumors that invaded the cavernous sinuses (81% vs 18%, $P = .048$). There were no differences in POD1 prolactin levels and biochemical control in patients who underwent additional treatment (see Table 4).

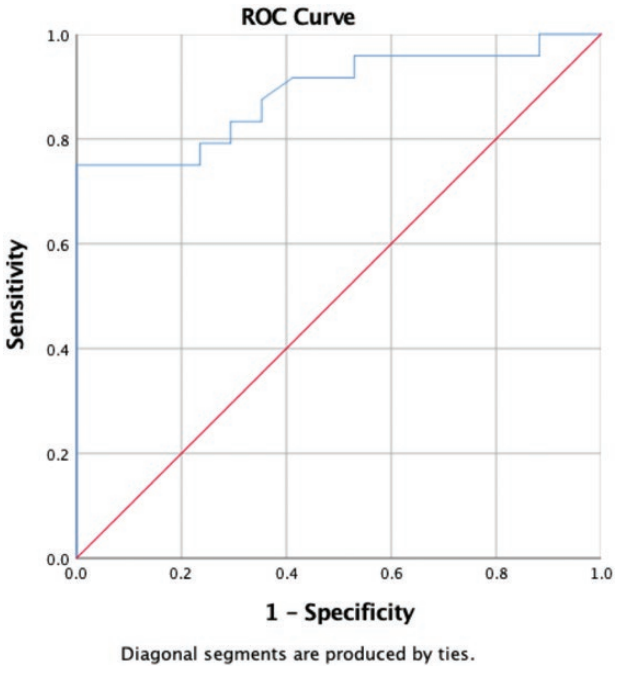

Figure 2. Receiver operating characteristic (ROC) curve demonstrating the ability of postoperative day 1 prolactin to predict need for adjuvant treatment in our patient population.

Systematic Review

The 19 articles in our systematic review included 1536 prolactinoma cases treated via surgical resection [8, 12, 16-32]. These studies identified tumor size (11 of 19) [8, 16-19, 21-23, 25, 29, 31] preoperative prolactin levels (10 of 19) [8, 12, 16-18, 21, 22, 24, 25, 31] postoperative prolactin levels (10 of 19) [12, 19-24, 26, 28, 29, 32] prior treatment (9 of 19) [12, 16, 17, 20, 21, 23, 26, 28], extrasellar invasion (7 of 19) [8, 12, 18, 20, 25, 27, 31], CSI (7 of 19) [12, 16, 18, 19, 23, 28, 29] and surgical approach (6 of 19) [18, 19, 22, 25, 28, 32] as main predictors of postoperative hormonal remission. Other significant predictors included patient age (1 of 19) [8] sex (1 of 19) [8] cystic tumor (1 of 19) [16] infiltration into the dura (1 of 19) [8] tumor encasement by the pituitary gland (1 of 19) [30] and plurihormonal vs pure lactotroph adenoma on immunohistochemistry (1 of 19) [29] (Table 5). Pooled analyses were performed on available data.

Fourteen studies reported patient sex, demonstrating 761 men and 560 women. All but one study [30] reported patient age with mean ages ranging from 30 to 44 years and reported follow-up times in all but 2 studies [28, 32] ranging from 3 to 196 months. While not every study clearly delineated the number of patients receiving each treatment, in the studies that reported numbers 788 patients received surgical resection alone, 433 underwent surgical resection and postoperative DA therapy, and 68 received surgery with adjuvant DA and radiotherapy. Overall, hormonal remission occurred in 780 (50.7%) out of 1536 cases. In

Table 4. Comparison of patients with and without surgical cure and patients with and without biochemical control

	Surgical cure (n = 25)	No surgical cure (n = 30)	*P*, 95% CI	Biochemical control (n = 35)	Nonbiochemical control (n = 20)	*P*, 95% CI
Sex	3 (12%) male, 22 (88%) female	13 (43%) male, 17 (57%) female	.011[b]	8 (23%) male, 27 (77%) female	8 (40%) male, 12 (60%) female	.178[b]
Mean age at surgery, y	33.3 ± 13	37.7 ± 13.6	.228[a], –2.8 to 11.7	36.3 ± 14	34.5 ± 12.7	.63[a], –9.4 to 5.8
Prior transsphenoidal resection	0 (0%)	6 (20%)	.018[b]	1 (3%)	5 (25%)	.011[b]
Mean preoperative prolactin level, ng/mL	96.7 ± 96.9	361 ± 658	.054[a], –4.8 to 533	89.3 ± 38.3	512 ± 776	.04[a],22.8 to 823
Mean postoperative d 1 prolactin level, ng/mL	4.7 ± 4.1	95.5 ± 122.5	.001[a], 39 to 143	19.3 ± 36.4	125 ± 144	.014[a],25 to 186
Maximal diameter, cm	1.3 ± 7.3	1.9 ± 9.2	.028[a], 0.064 to 1.1	1.4 ± 0.72	2.0 ± 1.1	.042[a],0.02 to 1.1
Suprasellar extension	8 (32%)	16 (53%)	.11[b]	13 (37%)	11 (55%)	.20[b]
Cavernous sinus invasion	3 (12%)	17 (57%)	.001[b]	12 (34%)	8 (40%)	.67[b]
Purely intrasellar	11 (44%)	3 (10%)	.004[b]	11 (31%)	3 (15%)	.18[b]
Gross total resection(n = 50)	18 (90%)	2 (10%)	< .001[b]	21 (70%)	9 (30%)	< .001[b]

[a]Independent samples *t* test.
[b]Chi-square analysis 95% CI.

studies that reported outcomes by treatment group, 256 of 646 patients (39.6%) remitted from surgery alone, 170 of 273 patients (62.3%) achieved remission from surgery and DA therapy, and 42 of 59 patients (71.2%) remitted after surgery, DA, and radiotherapy. Eleven patient mortalities were reported.

The 14 studies that reported prolactinoma size classification included 727 macroprolactinomas, 629 microprolactinomas, and 99 giant prolactinomas (> 40 mm) [8, 12, 16, 17, 19, 21, 22, 24-26, 28-31]. In studies that reported outcomes by prolactinoma size, 422 of 629 patients with microprolactinomas (67%), 260 of 727 patients with macroprolactinomas (36%), and 19 of 99 patients with giant prolactinomas (19%) achieved hormonal remission [8, 12, 16-19, 21-26, 28, 31].

Six studies [12, 16, 18, 21, 24, 32] reported their findings according to sex, with a total of 145 surgically treated prolactinoma patients in 104 men and 41 women (47.7% and 28.3%, respectively). A total of 73.1% of men and 61.0% of women achieved remission at long-term follow up.

CSI was investigated as a predictive factor of remission for surgically managed prolactinomas in 7 studies, with 3 providing details amenable for pooled analysis [12, 16, 23]. In these studies, there were 110 prolactinoma patients, 48.2% of whom had adenomas with CSI.

Discussion

We report a retrospective clinical analysis of our 2.5-decade experience with the surgical treatment of patients with prolactinomas, demonstrating surgical cure or biochemical control in a majority of patients. Surgical resection of prolactinomas is typically reserved for tumors refractory to DA therapy, patients who are unable to tolerate medical therapy, or for those who are seeking to improve chances of successful pregnancy. In concordance with this standard of practice, our study of 56 patients in large part consisted of patients who presented with invasive tumors after failure of DA therapy. Our findings suggest surgical intervention for prolactinoma should be recommended on a judicious basis, particularly when clinical predictors, such as smaller preoperative size and lower prolactin levels, support a favorable outcome of surgical cure or biochemical control. However, patients with large, highly invasive prolactinomas and prolactin levels greater than 500 ng/mL rarely benefit from surgical intervention unless it is for treatment of rapid neurological deterioration. Multimodal treatment with DA

Table 5. Systematic review of series reporting outcomes after surgical resection of prolactinomas

Study authors	No.	% Female	No. of patients achieving hormonal remission			Criteria for hormonal remission	Follow-up time, mo	Prognostic variables
			Micro (%)	Macro (%)	All (%)			
Ogiwara et al	5	60.00	5/5 (100%)	–	100%	Surgical w/ chemical cure	Mean: 3	Preoperative prolactin levels, tumor size, cavernous sinus invasion, previous treatment, cystic nature
Képénékian et al	20	44.68	–	15/17 (88.24%)	75.00%	Surgical w/ chemical cure	Mean: 196 ± 100	Preoperative baseline prolactin levels, tumor size, previous treatment
Shimon et al	8	11.11	–	4/8 (50.00%)	50.00%	Surgical w/ chemical cure	Mean: 93.6 ± 61.2	Giant prolactinoma (tumor size), cavernous sinus invasion, extrasellar involvement, surgical approach, preoperative prolactin levels
Vale et al	13	61.54	1/1 (100.00%)	9/12 (75.00%)	76.92%	Surgical w/ chemical cure	Mean: 48	Tumor size, cavernous sinus invasion, postoperative prolactin levels, previous treatment
Vroonen et al	56	60.98	–	–	32.14%	Surgical w/ chemical cure	88.5	Extrasellar involvement, previous treatment, postoperative prolactin level
Tamasauskas et al	32	100	19/32 (59.38%)	–	59.38%	Surgical w/ chemical cure	Median: 88.5	Tumor size, previous treatment, preoperative prolactin levels, postoperative prolactin levels, postoperative treatment
Sinha et al	122	41.28	10/12 (83.33%)	40/83 (48.19%)	77.05%	Surgical w/ chemical cure	Mean: 50.4 ± 32.4	Tumor size, surgical approach, preoperative prolactin levels, postoperative prolactin levels
Qu et al	87	0	13/18 (72.22%)	24/69 (34.78%)	72.41%	Surgical w/ chemical cure	Median: 45.0	Extrasellar involvement, cavernous sinus invasion, previous treatment, preoperative prolactin level, postoperative prolactin level
Yu et al	18	13.33	–	4/18 (22.22%)	22.22%	Surgical w/ chemical cure	Mean: 31.7	Giant prolactinoma (tumor size), cavernous sinus invasion, preoperative medical treatment, surgical approach, postoperative prolactin levels
Asano et al	8	0	–	8/8 (100.00%)	100%	Surgical w/ chemical cure	Mean: 42.48 ± 14.52	Preoperative prolactin levels, postoperative prolactin levels
Gökalp et al	550	28.36	200/311 (64.31%)	15/222 (6.76%)	38.74%	Surgical cure	Mean: 86.4	Tumor size, extrasellar involvement, surgical approach, preoperative baseline prolactin levels
Jho et al	5	80.00	–	–	40.00%	Surgical w/ chemical cure	Not reported	Postoperative prolactin levels, surgical approach

Table 5. Continued

Study authors	No.	% Female	No. of patients achieving hormonal remission			Criteria for hormonal remission	Follow-up time, mo	Prognostic variables
			Micro (%)	Macro (%)	All (%)			
Merola et al	49	75.40	24/25 (96.00%)	23/24 (95.83%)	91.84%	Surgical w/ chemical cure	60	Postoperative prolactin levels, preoperative medical treatment
Zada et al	20	Not reported	–	–	40.00%	Surgical cure	Median: 16	Extrasellar involvement, preoperative medical treatment
Gsponer et al	52	77.48	16/25 (64.00%)	10/26 (38.46%)	46.15%	Surgical w/ chemical cure	Not reported	Surgical approach, cavernous sinus invasion, preoperative medical treatment, postoperative prolactin levels
Zielinski et al	48	92	–	–	71%	Surgical w/ chemical cure	84	Cavernous sinus invasion (Knosp score), tumor size, plurihormonal vs pure lactotroph adenomas, postoperative prolactin levels
Losa et al	120	77.5	46/59 (78%)	31/61 (50.8%)	64.2%	Surgical cure	Mean: 50.2 ± 3.0	Age, sex, preoperative prolactin levels, tumor size, extrasellar involvement, dural infiltration
Micko et al	60	83	–	–	67%	Surgical cure	Mean: 37	Tumor enclosed by pituitary gland or not
Kreutzer et al	212	63	47/56 (84.8%)	–	42.7%	Surgical cure	Mean: 19.6	Preoperative prolactin levels, tumor size, extrasellar involvement
Present study	56	71.0	11/15 (73%)	14/39 (36%)	46%	Surgical cure	Median: 39.4	Cavernous sinus invasion, postoperative d 1 prolactin levels, tumor size, sex, prior transsphenoidal resection, extent of resection
Present study	56	71.0	13/15 (87%)	22/39 (56%)	64%	Surgical w/ chemical cure	Median: 39.4	Preoperative prolactin levels, postoperative d 1 prolactin levels, tumor size, prior transsphenoidal surgery, extent of resection, cavernous sinus invasion

Abbreviation: w/, with.

therapy and fractionated radiation therapy may offer better long-term tumor control in these patients without the need for invasive surgery. Importantly, we suggest a POD1 prolactin level greater than 7.6 ng/mL predicts a patient will not undergo biochemical control from surgical resection alone with a sensitivity of 79% and a specificity of 77%. In these patients, plans for adjuvant therapy can be made shortly after surgery to readily achieve biochemical control.

Our cohort consisted of patients of similar age and an average proportion of female patients compared to other surgical series; however, our patients had fewer microprolactinomas and more macroprolactinomas. Our surgical cure rates were comparable to the higher rates found in the current literature both for microprolactinomas and macroprolactinomas as was the overall rate of biochemical control we achieved with or without adjuvant therapy. The surgical complication rate and incidence of major morbidity and mortality were extremely low.

Presently, there remains a paucity of US studies investigating the role of transsphenoidal resection in

achieving biochemical control in previously treatment-refractory prolactinomas. Our formal systematic review demonstrated studies have most commonly found tumor size, prolactin levels, and extrasellar invasion to be significant predictors of biochemical control after surgical intervention. Microprolactinomas were associated with better outcomes than macroprolactinomas and giant prolactinomas, and those with CSI were associated with poorer outcomes, suggesting size and invasion are predictors of success. Sex also played a significant role in patient outcomes, with men more likely to achieve biochemical control. Although DA therapy remains the primary treatment option for prolactinomas, our review suggests surgery is an effective adjuvant treatment to DA therapy in carefully selected cases. A recent systematic review on the efficacy of surgical resection for prolactinoma treatment demonstrated biochemical control in up to 81% of patients and surgical cure in up to 67% of patients [33]. Unlike our systematic review, Zamanipoor Najafabadi et al did not assess predictors of remission and focused solely on the success of transsphenoidal resection in the literature [33].

In contrast to the findings of our systematic review, we found prior surgical resection, tumor size, preoperative and POD1 prolactin levels, and EOR, but not tumor invasiveness or patient sex, significantly predicted postoperative biochemical control. Although predictors of surgical cure were similar, there were some key differences. Specifically, preoperative prolactin levels were not significantly associated with surgical cure, whereas patient sex and tumor invasiveness were. These findings are likely explained in part by the significant role EOR plays in surgical cure. Larger and more invasive tumors, especially those tumors invading the cavernous sinuses, are more difficult to fully resect. In our study male patients had larger tumors, and although there was not a significant difference between EOR and patient sex, men may have had more advanced disease that was less amenable to cure via surgical resection alone. Additional investigation is merited to determine whether sex is an independent predictor for failure to achieve surgical cure or if other factors influence outcomes in male prolactinoma patients. With adjuvant therapy, the outcome disparity between sexes was eliminated in our patients. Our finding that preoperative prolactin levels were not significantly associated with surgical cure but were associated with biochemical control may be a factor of limited sample size.

No patients in our study with preoperative prolactin above 500 ng/mL achieved surgical cure, and no patients with preoperative prolactin levels greater than 1000 ng/mL remitted irrespective of adjuvant therapy. Importantly, patients who eventually exhibited biochemical control after adjuvant therapy had lower preoperative prolactin levels and were more likely to have tumors that invaded the cavernous sinuses. This latter finding is likely indicative of a more aggressive adjuvant therapy strategy in patients with known residual tumor in the cavernous sinuses that leads to improved disease control. In patients in whom prolactin normalization is not expected, goals of surgical treatment include tumor control and/or reduction in medication dose requirements.

An analysis comparing our male and female prolactinoma patients revealed differences consistent with the recent literature [12, 16, 18, 23, 26, 27]. Men were more likely to be older and have larger tumors than their female counterparts. These differences in age likely result from differing surgical indications, whereby men undergo surgery because of DA resistance and symptoms of mass effect, whereas women are more frequently intolerant of DA or desire pregnancy [34]. However, despite the more progressed state of prolactinomas in men, no association was observed between sex and biochemical control rates in our study. Furthermore, despite having larger tumors with greater tumor symptomology, prolactinomas in men were not more likely to invade outside the sella than prolactinomas in women. This finding may be limited to patients who proceed to surgical resection. Alternatively, the large, noninvasive prolactinomas found in men may lack tumor markers that promote invasion. This finding differs from some prior studies that have suggested that sex plays a predictive role in biochemical control [8, 10]; however, a recent systematic review of pituitary adenoma outcomes also concluded that sex did not play a significant role in postoperative remission [35].

Limitations

This study is primarily limited by its retrospective nature and sample size. Additionally, our mean clinical and imaging follow-up times were complicated by multiple factors, including a transition to an EMR system with loss of original records and losing patients to follow-up. Owing to sample size, conclusions about the role of SRS and sites of tumor invasion other than the cavernous sinus (frontal lobe, clivus, suprasellar, infrasellar) in surgical cure and biochemical control were unable to be drawn. We suspect this may have additionally affected the lack of significance we noted between preoperative prolactin levels in patients who achieved surgical cure vs those who did not. Of note, 8 patients in our study were missing long-term follow-up prolactin levels. Biochemical control status for these 8 patients was made by review of clinical notes from board-certified endocrinologists and confirmed via follow-up phone call.

Data from phone follow-up for these patients were patient reported and assessed for normalization of prolactin levels and presence of symptomatology.

Conclusions

This retrospective series of 56 prolactinoma patients treated surgically at a tertiary pituitary center suggests that surgical resection can be an effective treatment for prolactinoma patients. CSI status, tumor size, POD1 prolactin levels, and EOR can be used to predict surgical cure. In particular, POD1 prolactin levels greater than 7.6 ng/mL can reliably predict that a patient will not attain surgical cure. We suggest that significant preoperative prolactin elevations (> 500 ng/mL for surgical cure and > 1000 ng/mL for biochemical control regardless of postoperative DA therapy) may decrease the likelihood of surgical cure or biochemical control irrespective of DA therapy. Although surgical resection of prolactinomas is safe at experienced pituitary centers, it should be reserved for selected cases in which patients can achieve disease control, relief of symptoms of mass effect, or reduction of DA dosage. Realistic outcomes regarding biochemical control and ongoing dependence on medications should be provided to patients to aid in decision making.

Additional Information

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