Long-term surgical outcomes following transsphenoidal surgery in patients with Rathke's cleft cysts

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OBJECTIVE Rathke's cleft cysts (RCCs) are benign epithelial lesions of the sellar region typically treated via a transsphenoidal approach with cyst fenestration and drainage. At present, there is limited evidence to guide patient selection for operative treatment. Furthermore, there is minimal literature describing factors contributing to cyst recurrence.

METHODS The authors conducted a retrospective analysis of 109 consecutive cases of pathology-confirmed RCCs treated via a transsphenoidal approach at a single center from 1995 to 2016. The majority of cases (86.2%) involved cyst fenestration, drainage, and partial wall resection. Long-term outcomes were analyzed.

RESULTS A total of 109 surgeries in 100 patients were included, with a mean follow-up duration of 67 months (range 3–220 months). The mean patient age was 44.6 years (range 12–82 years), and 73% were women. The mean maximal cyst diameter was 14.7 mm. Eighty-eight cases (80.7%) were primary operations, and 21 (19.3%) were reoperations. Intraoperative CSF leak repair was performed in 53% of cases and was more common in reoperation cases (71% vs 48%, $p < 0.001$). There were no new neurological deficits or perioperative deaths. Two patients (1.8%) developed postoperative CSF leaks. Transient diabetes insipidus (DI) developed in 24 cases (22%) and permanent DI developed in 6 (5.5%). Seven cases (6.4%) developed delayed postoperative hyponatremia. Of the 66 patients with preoperative headache, 27 (44.3%) of 61 reported postoperative improvement and 31 (50.8%) reported no change. Of 31 patients with preoperative vision loss, 13 (48.1%) reported subjective improvement and 12 (44.4%) reported unchanged vision. Initial postoperative MRI showed a residual cyst in 25% of cases and no evidence of RCC in 75% of cases. Imaging revealed evidence of RCC recurrence or progression in 29 cases (26.6%), with an average latency of 28.8 months. Of these, only 10 (9.2% of the total 109 cases) were symptomatic and underwent reoperation.

CONCLUSIONS Transsphenoidal fenestration and drainage of RCCs is a safe and effective intervention for symptomatic lesions, with many patients experiencing improvement of headaches and vision. RCCs show an appreciable (although usually asymptomatic) recurrence rate, thereby mandating serial follow-up. Despite this, full RCC excision is typically not recommended due to risk of hypopituitarism, DI, and CSF leaks.

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KEYWORDS Rathke's cleft cyst; transsphenoidal; complications; microsurgery; endoscopy; pituitary surgery

RATHKE'S cleft cysts (RCCs) are benign cystic lesions of the sellar and suprasellar space. These cysts are often found incidentally during routine imaging for unrelated neurological complaints. On MRI, RCCs typically appear as homogeneous, minimally enhancing ovoid lesions, or they are discovered as microscopic lesions dur-

ing autopsy.^{5,28} RCCs may cause symptoms secondary to mass effect on the optic chiasm and/or pituitary gland. In such instances, patients can present with vision loss, headaches, and/or endocrinopathy.

RCCs are believed to be the embryological remnants of the pars intermedia within Rathke's pouch, a conflu-

ABBREVIATIONS dDAVP = desmopressin acetate; DI = diabetes insipidus; RCC = Rathke's cleft cyst; SIADH = syndrome of inappropriate antidiuretic hormone; USC = University of Southern California.

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ence formed from ectodermal tissue, as evidenced by a characteristic simple ciliated cuboidal epithelium on histopathology. They have been proposed to exist on both a clinical and histological continuum, with the more aggressive form being a craniopharyngioma.^{5,9,12,21,31}

In symptomatic patients, transsphenoidal fenestration of RCCs remains the mainstay of treatment. Surgical management has been shown to be effective in alleviating headaches and visual impairment. Although recurrence is known to occur in patients with RCCs, this appears to be a function of follow-up duration. In this series, we present our institutional experience with transsphenoidal surgical management of RCCs with an average follow-up of more than 5 years.

Methods

Patient Population

A retrospective chart review was conducted following a search of the University of Southern California (USC) Pituitary Center REDCap database. We identified 132 consecutive surgical cases of RCCs treated at USC's Pituitary Center from 1995 to 2016. Of these, 109 cases (83%) had sufficient data for inclusion, mostly due to poor patient compliance with follow-up at the Los Angeles County + USC Medical Center (LAC+USC), which is a county hospital. The minimum follow-up period for inclusion was 3 months, and the mean follow-up duration was 67 months. Only patients with histologically confirmed RCCs were included. Preoperative patient evaluation included history and physical examination, endocrine lab testing, and an ophthalmological examination. High-resolution MRI, with thin-section sellar slices, with and without Gd was obtained for all patients. All patients with endocrinopathies were medically managed pre- and postoperatively. Indications for surgery included symptomatic disease or significant interval cyst progression on interval MRI.

Surgical Technique

All patients were treated with either microscopic or endoscopic transsphenoidal operations. The microscopic approach was routinely used at USC from 1995 to 2011, and since then the endoscopic approach has predominated. Cyst fenestration, drainage, and marsupialization were performed in 86.2% of cases. Full cyst resection was not typically performed to avoid hypopituitarism, diabetes insipidus (DI), and CSF leaks. Cyst wall biopsies were taken from the cyst lining the sellar floor or occasionally cavernous sinus wall. Following cyst drainage and partial wall resection for pathological analysis, a Valsalva maneuver was performed to assess for an iatrogenic CSF leak. If a CSF leak was identified, repair was performed using an autologous subcutaneous adipose graft from the abdomen or thigh, with or without rectus abdominis fascia or tensor fascia lata to reconstruct the sellar dura. An absorbable hemostatic agent (Surgicel, Ethicon) tucked as a bony sellar inlay ("cargo net" technique) was used to hold the graft in place. In patients without evidence of intraoperative CSF leaks, the sellar floor was minimally constructed using a monolayer of Surgicel, packing of dead space with gelatin sponge, and a subsequent Surgicel "cargo net."

Postoperatively patients went to the intensive care unit for approximately 24 hours, and during this time were monitored for DI and other causes of electrolyte abnormalities. On postoperative day 7, outpatient serum sodium levels were checked in all patients to assess for hyper- or hyponatremia.

Pathological Tissue Assessment

Histopathological staining was performed in all cases. Each biopsied specimen was fixed in formalin and sent to the pathology department in a singular cassette. Specimens were embedded in paraffin, sliced into 4-micron sections, mounted, and stained with H & E for light microscopy examination.

Follow-Up and Outcome Measurement

Standard follow-up consisted of routine MRI, visual field testing (in most patients), and physical examination. Follow-up outpatient physical examinations were performed at 2 weeks, 3 months, and 12 months following surgery. In asymptomatic patients, subsequent follow-up was recommended annually for 5 years and then every 2 years thereafter. Patients with significant postoperative progression were monitored with neuroimaging at 6- to 9-month intervals. Levels of prolactin, insulin-like growth factor-1, morning cortisol (AM cortisol), follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, and when indicated, free thyroxine (fT4) were obtained in patients preoperatively. Patients with hormonal deficiencies were followed by either their own endocrinologists or a specialist at our institution. In patients with symptoms or laboratory values concerning for pre- or postoperative endocrinopathy, follow-up appointments with a specialized endocrinologist were performed at 2 weeks, 6 weeks, 3 months, 6 months, and 1 year postoperatively. Patients were subsequently followed on an annual basis or as needed. Retrospective chart reviews and direct patient inquiry were used to obtain long-term follow-up of the disease state.

Statistical Analysis

Perioperative details were populated into REDCap, a secure, standardized electronic database. Epidemiological data were processed within REDCap's previously validated, embedded statistical tool.³ Categorical recurrence and morbidity data were calculated with a standard chi-square test. Probability values less than 0.05 were considered statistically significant.

Results

Preoperative Characteristics

One hundred nine surgical cases in 100 patients were included in the analysis with a mean follow-up duration of 67 months, ranging from 3 to 220 months. Eighty (73.4%) surgical cases were performed on female patients and 29 (26.6%) were performed on male patients. The mean patient age at surgery was 44.6 years (range 12–82 years) with a median age of 40 years. Patient characteristics are listed in Table 1. Preoperatively, 16 cases (18.0%) had cysts

TABLE 1. Patient characteristics

Characteristic	No. of Cases (%)
Sex	
Female	80 (73.4)
Male	29 (26.6)
Cyst diameter*	
<10 mm	16 (18.0)
≥10 mm	73 (82.0)
Prior operations	
1st operation	88 (80.7)
2nd operation	16 (14.7)
3rd operation	5 (4.6)
Surgical procedure†	
Microscopic sublabial	44 (43.6)
Microscopic endonasal	42 (41.6)
Endoscopic endonasal	14 (13.9)
Endoscopic extended	1 (1)

* Missing data points (n = 89 cases).

† Missing data points (n = 101 cases).

less than 10 mm in greatest diameter whereas 73 cases (82.0%) harbored lesions equal to or greater than 10 mm in diameter. Twenty cases did not have sufficient preoperative imaging information for assessment of lesion size. The mean maximal cyst diameter was 14.7 mm. Of the 89 cases with preoperative imaging available, 75 (84.3%) exhibited suprasellar extension and optic chiasm compression. Eighty-eight cases (80.7%) underwent a first operation and 21 cases (19.3%) were reoperations. Fifteen cases undergoing reoperation had undergone 1 prior operation, while 5 cases underwent multiple prior operations for recurrent RCC. Presenting preoperative symptoms are shown in Table 2. In the majority of cases surgical indications were visual deterioration or progressive endocrinopathies. Of the cases in which patients were harboring cysts less than 10 mm in size (n = 16), 4 had worsening endocrinopathies accompanied by an inability to tolerate dopamine agonists for hyperprolactinemia. Three cases of suprasellar cysts less than 10 mm in size developed progressive loss of visual acuity. Six cases had debilitating headaches refractory to multiple lines of medical management. There were 3 patients with “incidentalomas” who presented more than 20 years ago, prior to the establishment of robust guidelines for surgical indication, who underwent surgical management per patient preference and psychological discomfort regarding the presence of a cystic lesion in his or her pituitary.

Initial Surgical Outcomes and Complications

RCCs were fenestrated via microscopic sublabial transsphenoidal approach in 44 cases (43.6%), microscopic endonasal transsphenoidal approach in 42 cases (41.6%), and endoscopic endonasal transsphenoidal approach in 14 cases (13.9%). In 1 case the patient had marked suprasellar extension of the RCC requiring an extended endoscopic endonasal transtuberulum approach (Table 1). The majority of cases (94, 86.2%) consisted of a simple fenestration procedure for cyst decompression, followed by subtotal

TABLE 2. Presenting symptoms

Symptom	No. of Patients (%)*
Headache	66 (62.9)
Vision loss	31 (29.5)
Cranial nerve palsy	3 (2.9)
Dizziness	11 (10.5)
Apoplexy	4 (3.8)
Fatigue	18 (17.1)
Hypopituitarism	15 (14.3)
Hypogonadism	
Decreased libido	7 (6.7)
Amenorrhea/oligomenorrhea	19 (18.1)
Galactorrhea	8 (7.6)
Incidental	3 (2.8)

* Missing patient data points (n = 105 patients).

cyst wall biopsy and resection. Intraoperative autologous graft placement for repair of a CSF leak was required in 53% of cases. Lumbar drains were placed preoperatively in 7 cases (6.4%) to divert CSF postoperatively in the setting of a leak. Reoperations carried a significantly higher probability of developing an intraoperative CSF leak than in patients undergoing first-time operations (71% vs 48%, $p < 0.001$). In 42 cases in which CSF leak was not evident, absolute ethanol was instilled in the cyst bed with no ensuing complications.

The mean hospital stay was 3.9 days with a median of 3 days (range 2–13 days). There were no new neurological deficits follow surgery, and there were no perioperative deaths. In 2 cases (2%) patients developed postoperative CSF leaks: 1 required reoperation for CSF leak repair after failure of leak resolution with a lumbar drain, and 1 CSF leak resolved with a lumbar drain. There were 2 (2%) cases of meningitis. One resolved with a prolonged course of intravenous antibiotics. A second patient presented to the clinic with headaches, nausea, and vomiting 6 days after surgery and was readmitted for syndrome of inappropriate antidiuretic hormone (SIADH) and meningitis. Workup revealed a sphenoid sinus abscess and an asymptomatic anterior thalamic stroke. Symptoms resolved with surgical drainage of the abscess, strict fluid restriction, and antibiotics. Another patient sustained an internal carotid artery injury that required reoperation. Both patients were ambulating independently and had no significant neurological deficits at discharge.

The most common complication was transient DI, which developed in 24 cases (22%). In 6 cases (5.5%), patients developed new-onset postoperative permanent DI requiring long-term management with desmopressin acetate (dDAVP). There was no difference in rates of transient DI ($p = 0.285$), permanent DI ($p = 0.296$), or other complications ($p = 0.235$) between patients undergoing microscopic versus endoscopic procedures. The preoperative cyst size also had no bearing on the risk of developing transient DI ($p = 0.340$) or permanent DI ($p = 0.338$). There were 7 cases (6.9%) of delayed postoperative hypo-

TABLE 3. Response to surgery

Symptom	No. of Patients	Improved	Stabilized	Worsened	Symptomatic FU Unavailable	New Onset (%)
Headache	66	27 (44.3%)	31 (50.8%)	3 (4.9%)	5 (7.6%)	
Vision	31	13 (48.1%)	12 (44.4%)	2 (7.4%)	4 (12.9%)	
Hypopituitarism	15		15 (100%)			
Hyperprolactinemia	16	14 (87.5%)	2 (12.5%)			
Hypogonadism*	17	3 (21.4%)	11 (78.6%)			
Hypothyroidism	19		19 (100%)			
Hypocortisolemia	8		8 (100%)			
DI	8		8 (100%)			Transient 24 (22.0%), permanent 6 (5.5%)

FU = follow-up.

Response following surgery is reported as percentage of patients with the respective preoperative symptoms and greater than 3 months of clinical follow-up regarding this particular symptom, who demonstrated clinical improvement following operation.

* Three patients with preoperative hypogonadism did not have postoperative endocrine records available for reviews.

natremia consistent with SIADH, all of which normalized with fluid restriction and/or hypertonic saline. Six of these 7 cases of SIADH were treated within the initial hospital stay and 1 case required early readmission.

Long-Term Outcomes and Cyst Recurrence

Of 66 cases in which patients had preoperative headache, 61 of them had clinical follow-up available: 27 (44.3%) reported postoperative improvement and 31 (50.8%) reported long-term stabilization of their headache (Table 3). Of 31 cases in which patients had preoperative vision loss and visual field deficits, 13 (48.1%) reported long-term improvement and 12 (44.4%) experienced subjective stabilization of vision.

Preoperative hyperprolactinemia ($n = 16$) resolved in 14 (87.5%) cases following surgery while 2 cases (12.5%) remained on dopamine agonists (Table 3). There were 17 cases with symptomatic hypogonadism without concurrent hyperprolactinemia. Of these cases, 3 experienced resolution as evidenced by normalization of laboratory values or resumption of regular menses, 11 cases remained on hormone replacement, and there were 3 cases for which there was no follow-up hormone status available. All cases ($n = 8$) with preoperative central adrenal insufficiency (defined as AM cortisol < 4.6 mcg/dl) remained on steroids postoperatively. Of the 19 cases with preoperative hypothyroidism, all remained on levothyroxine replacement therapy. There were 3 cases of patients with isolated neurogenic DI and 5 cases of DI concurrent with deficiencies in other hormonal axes, and all aforementioned patients remained dependent on dDAVP following surgical management. Similarly, all 15 cases with preoperative panhypopituitarism (defined as deficiencies in greater than 2 hypothalamic pituitary axes) remained on his or her respective hormonal replacement regimen despite adequate decompression. Clinical response to surgery is summarized in Table 3.

Twenty-nine cases (26.6%) demonstrated evidence of radiological recurrence or residual cyst enlargement on follow-up imaging. Average latency to radiologically detectable disease progression was 28.8 months. Of these, only 10 (9.2% of the total 109 cases) were symptomatic recurrences requiring reoperation. There was no appre-

ciable difference ($p = 0.78$) in recurrence rate following alcohol cauterization (10/42, 23.8%) compared with cases in which alcohol instillation was not performed (16/61, 26.2%; Table 4). Presence of a graft for sellar floor reconstruction conferred no statistically significant difference ($p = 0.10$) in recurrence rates (17/54, 31.5%) compared with cases with no autologous grafts (9/51, 17.7%). The use of microscopic versus endoscopic approaches also conferred no significant difference on recurrence rates ($p = 0.38$) or presence of postoperative residual cysts ($p = 0.15$). An operative goal of more aggressive resections did not ($p = 0.618$) decrease the risk of recurrence (2/11, 18.2%) in comparison with cyst fenestration and capsular wall biopsy alone (23/92, 25.0%). Furthermore, there was no difference ($p = 0.519$) in the percentage of residual cysts appreciated on MR images 3 months after surgical intervention when comparing cases that underwent more aggressive resections (2/9, 22.2%) versus those that received conservative fenestrations (16/62, 25.8%). However, in cases in which imaging demonstrated residual cysts, the rate of recurrence was notably higher ($p < 0.001$). The presence of squamous metaplasia on histopathology was associated with a higher rate of recurrence ($p = 0.028$) and squamous metaplasia was also appreciated at a higher rate in cases undergoing reoperation ($p = 0.009$). These rates have been summarized in Table 4. Progression-free survival curves are provided in Fig. 1.

Discussion

We present a large series of patients with RCCs treated via transsphenoidal surgery at a single tertiary-care pituitary center with considerable follow-up. Cyst fenestration, drainage, and partial wall excision were safely performed with very few major complications and a low incidence of permanent DI. Headaches and visual dysfunction improved in nearly half of patients with preoperative symptoms.

Clinical Presentation

In agreement with the literature, the majority of our patients presented with headaches, visual deficits, and endo-

TABLE 4. Surgical characteristics associated with recurrence

Surgical Characteristic	Recurrence/ Progression				p Value
	No	Yes	Total	%	
Chemical cauterization					0.78
Alcohol instillation	32	10	42	23.8	
No alcohol use	45	16	61	26.2	
Sellar floor reconstruction					0.10
Presence of fascial/fat graft	37	17	54	31.5	
Continuous drainage	42	9	51	17.7	
Extent of resection					0.62
Capsular wall resection	9	2	11	18.2	
Cyst fenestration & biopsy	69	23	92	25	
3-mo postop MRI					<0.001
Presence of residual cyst	10	8	18	44.4	
No residual appreciated	52	1	53	1.9	
Surgical approach					0.38
Microscopic	61	25	87	28.7	
Endoscopic	10	2	12	16.7	
Histopathology					0.03
Presence of squamous metaplasia	6	4	10	40	
No squamous metaplasia	73	25	98	25.5	

crinopathies.^{2,10,14–16,19,22,25–27,31} Vision deficits are frequently only detected on formal vision testing, therefore we recommend routine ophthalmological screening, including a dilated eye examination and formal visual field testing. While hyperprolactinemia secondary to mass effect preventing prolactin release inhibitory factor transmission down on the pituitary stalk resolved in all patients, patients who required hormonal supplementation prior to surgery continued to require supplementation after surgery.^{25,30}

Surgical Morbidity

Our institution has adopted a surgical philosophy of simple cyst fenestration and capsular wall biopsy due to the high rate of surgical morbidities, particularly new-onset DI, following gross-total resection.¹ There were no new neurological deficits attributable to surgery despite transient complications, and no deaths in our series, which is consistent with other published series regarding the safety of both microscopic and endoscopic approaches to the sella in high-volume centers.^{4,6–8,18,20} Despite the use of a conservative surgical technique consisting of simple cyst fenestration, the development of transient DI was the most common endocrine morbidity, with 6 patients developing permanent DI.^{1,2,17,24} Careful monitoring of postoperative serum sodium levels are crucial given the propensity for development of transient SIADH, which was noted in 7 patients in this series. We routinely obtain outpatient serum sodium levels 1 week after surgery to facilitate detection of delayed sodium abnormalities.³²

Postoperative Symptom Resolution

In agreement with other reports in the literature, the

FIG. 1. Kaplan-Meier plot of recurrence- and reoperation-free survival over 120 months. Figure is available in color online only.

majority of our patients experienced long-term stabilization or resolution of intractable headaches (58/61, 95.1%) and visual symptoms (25/27, 92.6%) hypogonadism following resection.^{2,15,16,27} The majority of our patients with preoperative endocrinopathies required ongoing medical replacement for hormonal deficiencies following successful resection.^{14–16} However, similar to other reports, all patients in our series had resolution of hyperprolactinemia, likely due to decompression of the stalk.^{14–16} The limited postoperative improvement of other endocrinopathies may be due to capsular wall inflammation that results in chronic hypophysitis leading to irreversible damage, surgical trauma, or irreparable harm from prolonged compression of the gland.^{11,12,22,23}

Recurrence

Despite the benign nature of RCCs, a significant percentage of patients will experience recurrence following resection, necessitating long-term observation. Roughly one quarter of our series experienced a recurrence in agreement with previously reported recurrence rates of 0%–33%.^{2,9,10,15,16,19,21,24,26,27} The wide range of reported recurrence rates may be attributable to a poorly standardized definition of recurrence and the significant variability in follow-up duration. The relationship between various surgical characteristics and the rate of recurrence are summarized in Table 4. Employment of alcohol cauterization, presence of fat and fascial graft for CSF leak repairs, extent of resection, and endoscopic versus microscopic approach were not associated with increased rates of recurrence. A finding of squamous metaplasia on histopathology was correlated with an increased rate of recurrence. This is consistent with previous studies in the literature.¹ The presence of residual cyst on postoperative imaging was also correlated with an increased rate of recurrence. However, an operative goal of more aggressive capsular wall resection did not decrease the rate of residual cysts noted on postoperative imaging. Given the robust evidence of increased endocrinopathy following attempts at capsular wall resection and equivocal contributions of gross-total resections toward decreasing recurrence rate,

TABLE 5. RCC surgical series

Authors & Year	No. of Patients	Recurrence Rate (%)	Gross Total vs Decompression	Alcohol Instillation	Fat & Fascial Packing
Aho et al., 2005	118	18	No (p = 0.473)	NA	Yes (p < 0.001)
Benveniste et al., 2004	62	16	Yes (p = 0.317)	No (p = 1.000)	No (p = 0.608)
Higgins et al., 2011	61	18	No (p = 0.36)	NA	NA
Kim et al., 2004	53	11	Yes (p = 0.012)	NA	NA
Current study	109	24	No (p = 0.62)	No (p = 0.78)	No (p = 0.10)
Lillehei et al., 2011	82	11	NA	No (p = 0.2)	NA
Wait et al., 2010	73	11	No (p = 1.000)	NA	NA

NA = not applicable.

our institution advocates for cyst fenestration and capsular wall biopsy alone. Our findings have been examined in the context of other comparable surgical series in Table 5.

Conclusions

Transsphenoidal cyst fenestration is a safe and effective treatment for a majority of patients with symptomatic RCCs. Surgery may decompress the optic apparatus and alleviate intractable headaches as well as hyperprolactinemia in patients with RCCs. These operations carry a small risk of causing permanent DI. Furthermore, patients with endocrinopathies should have a tempered expectation regarding postoperative relief of hypopituitarism. Although benign, RCCs show an appreciable recurrence rate, mandating careful follow-up for disease recurrence or progression. Despite this, full RCC excision is not recommended secondary to known complications associated with this maneuver, namely hypopituitarism, DI, and CSF leaks.

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Disclosures

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Author Contributions

Conception and design: Zada, Lin, Wedemeyer, Bradley, Donoho, Weiss, Carmichael. Acquisition of data: Zada, Lin, Wedemeyer, Bradley, Donoho. Analysis and interpretation of data: all authors. Drafting the article: Zada, Lin, Wedemeyer, Bradley, Donoho, Fredrickson. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Zada. Statistical analysis: Zada, Lin, Wedemeyer, Bradley, Donoho. Study supervision: Lin, Weiss.

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