# Surgical outcomes in 118 patients with Rathke cleft cysts

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Object. Microscopic Rathke cleft cysts are a common incidental autopsy finding, but some Rathke cleft cysts can become sufficiently large to cause visual impairment, hypothalamic–pituitary dysfunction, and headaches. In this study patients were evaluated pre- and postoperatively to ascertain the clinical significance of surgical intervention on endocrine and visual improvement. Factors correlated with cyst recurrence were also evaluated.

Methods. A retrospective analysis was conducted in 160 patients with Rathke cleft cysts who were treated between 1984 and 1995 and completed at least a 5-year follow-up period. Of these 160 patients, 118 initially exhibited symptoms of visual impairment or endocrine dysfunction, became symptomatic during the follow-up period, or were found to have cyst enlargement. These 118 patients underwent transsphenoidal surgery. Forty-two patients with incidental lesions that demonstrated no growth on magnetic resonance (MR) images were followed up without an operation.

Complete resection, as observed on MR images 3 months postoperatively, was obtained in 114 (97%) of 118 patients. Vision improved postoperatively in 57 (98%) of 58 patients. Hypogonadism improved in 11 (18%) of 62 patients, growth hormone deficiency resolved in 14 (18%) of 78 patients, and hypocortisolemia resolved in one (14%) of seven patients. Twenty-two patients (19%) began to exhibit symptoms of diabetes insipidus, which had not been present preoperatively. The total 5-year recurrence rate was 18% (21 of 118 patients), with 12 patients requiring a repeated operation. Surgical and pathological factors that were found to be statistically associated with recurrence were the use of a fat and/or fascial graft for closure (p < 0.01) and the presence of squamous metaplasia in the cyst wall (p < 0.01). The extent of resection of the cyst wall was not associated with an increased rate of recurrence. In 42 (69%) of 61 patients the incidental cysts did not progress on imaging studies or clinically.

Conclusions. This is the largest series of patients with symptomatic Rathke cleft cysts who received operative intervention and participated in the longest postoperative follow up reported in the literature. The high recurrence rate (18%) supports the theory that a relationship exists between a symptomatic Rathke cleft cyst and craniopharyngioma. Improvements in visual and endocrine dysfunction can be expected after surgical decompression of the optic apparatus and the hypothalamic–pituitary axis.

KEY WORDS • Rathke cleft cyst • intrasellar cyst • endocrine dysfunction • pituitary • transsphenoidal craniotomy

Rathke cleft cyst is a nonneoplastic cyst derived from glandular rests of the Rathke cleft in the region of the intermediate lobe of the pituitary gland. The cysts are commonly found at autopsy on a microscopic scale, and 80% of them lie at the interface between the anterior and posterior lobes of the pituitary. Occasionally, Rathke cleft cysts are sufficiently large to cause visual or endocrine disorders. These disorders are caused by compression of the visual apparatus, pituitary gland, or hypothalamus by the cyst

Histologically, Rathke cleft cysts consist of a single or pseudostratified epithelium with an underlying layer of connective tissue. The epithelium may contain ciliated, goblet, squamous, and/or basal cells. <sup>14</sup> These cysts are classified as a distinct category among other cystic epithelial lesions including dermoid cysts, epidermoid cysts, and craniopharyngiomas.

The embryological development of Rathke cleft cysts has been well reviewed previously. 5.6.8.17 It is thought that a ros-

Abbreviations used in this paper: CSF = cerebrospinal fluid; DI = diabetes insipidus; MR = magnetic resonance.

tral outpouching of the primitive oral cavity in the 3rd or 4th week of gestation meets a downward projection from the diencephalon. Both structures are ectodermal in origin. Together these structures give rise to the anterior lobe, pars tuberalis, and pars intermedia of the pituitary gland. He formation of the adenohypophysis and neurohypophysis, a cleft remains in the region of the pars intermedia. This cleft has been named the Rathke cleft. A symptomatic Rathke cleft cyst develops when this cleft fails to regress. Other theories of derivation of these lesions have included an endodermal origin 19,14 or reverse metaplasia of pituitary cells 16,19

Resection of Rathke cleft cysts generally offers improved endocrine as well as visual function;<sup>11</sup> however, aggressive resection of Rathke cleft cysts can result in postoperative endocrine dysfunction, most commonly DI. The purpose of this study was to assess our surgical technique for treating symptomatic Rathke cleft cysts in a large series of patients who participated in at least 5 years of follow-up review so that we could gain a more accurate expectation of outcomes with this lesion. We also endeavored to ascertain whether our data support the theory that the Rathke cleft cyst and

TABLE 1
Criteria for surgical intervention

Presenting Symptom	No. of Patients (%)
incidental finding (cyst <1 cm)	61 of 160 (38)
no growth during follow up (≤9 yrs)	42 of 61 (69)
development of visual loss, endocrinopathy,	19 of 61 (31)
or cyst growth > 1.5 cm on MR imaging*	
visual loss (99 eyes)	58 of 118 (49)
both eyes	41 of 58 (71)
l eve	17 of 58 (29)
endocrinopathy	63 of 118 (53)

<sup>\*</sup> These patients initially had an incidental finding of Rathke cleft cyst and later symptoms began to develop. These patients are also included in the symptomatic groups.

craniopharyngioma both arise from an ectodermal origin and lie on a continuum of the same disease process.<sup>6,10</sup> Finally, we analyzed the development of recurrences in surgically treated patients to determine whether any surgical technique or pathological factors were correlated with higher rates of cyst recurrences.

#### Clinical Material and Methods

#### Patient Population

A consecutive series of 160 patients harboring Rathke cleft cysts were treated between 1984 and 1995 at the University of Southern California Medical Center. A diagnosis of Rathke cleft cyst was determined based on findings on MR images in all 160 patients and was confirmed by histopathological analysis in the 118 surgically treated patients. The minimal follow-up period for inclusion in the study was 5 years. The initial patient workup included detailed general and neurological histories and physical examinations, along with analyses of pertinent ophthalmological, endocrinological, and MR imaging data. High-resolution, thin-section (2–3 mm) MR images were obtained in all patients. Patients were chosen for surgery if they experienced visual loss, endocrinopathy, or progression of the size of the cyst (Table 1). Surgery was performed in 50 males and 68 females ranging in age from 15 to 68 years. The patients' preoperative endocrine findings are summarized in Table 2.

# Surgical Technique

Microsurgical transsphenoidal drainage of the cyst was performed via the sublabial transsphenoidal approach in all patients, as described previously.3 The surgical objective was to drain the contents of the cyst and remove as much capsule as possible. Initially, our efforts included resecting nonadherent portions of the capsule and coagulating the capsule margins aggressively. In patients treated later, in an attempt to decrease complications we modified our surgical technique and performed a less aggressive resection of the capsule by stripping less of the membrane. In all patients in whom the arachnoid membrane was preserved, absolute alcohol was instilled in the tumor bed to treat potential microscopic rests of columnar epithelial cells (adapted from CB Wilson, personal communication, 1984). In patients in whom perforation of the arachnoid and egress of CSF were encountered, no alcohol was used. In these patients, we per-

TABLE 2
Preoperative hormonal deficiencies in 118 patients

Finding	No. of Patients (%)
GH deficiency (IGF-I)	78 (66)
hypogonadism	62 (53)
hypothyroidism	8 (7)
hypocortisolemia	7 (6)
DÏ	0 (0)

formed grafting by using autologous adipose tissue and/or rectus abdominis fascia. Some patients also underwent lumbar puncture to prevent the development of a CSF fistula.

During the perioperative period, patients were treated according to our standard protocol. For the first 24 hours, the patients remained in the intensive care unit for neurological observation and surveillance for DI. Nasal packings were removed on the 1st postoperative day, and most patients were transferred to the ward. Patients were discharged on the 2nd or 3rd postoperative day.

#### Pathological Tissue Analysis

Tissue specimens obtained during these operations were fixed in formalin, embedded in paraffin, sectioned, and stained in hematoxylin and eosin. The specimens were then examined with the aid of a light microscope.

## Treatment Follow Up and Outcome Measures

Relevant studies (contrast-enhanced MR imaging, visual field testing, and laboratory studies), interval medical history, and physical examinations were obtained as part of routine follow-up examinations, which were scheduled at 1.5-, 3-, and 6-month intervals for the first 12 months and thereafter annually. Magnetic resonance imaging with 2- to 3-mm spacing between images was performed in all patients treated surgically at 3 months postoperatively. If there was no evidence of a residual cyst, repeated MR imaging was performed annually for 5 years, and approximately every 2 years thereafter. If a residual cyst was noted, repeated MR imaging studies were performed every 6 to 9 months for up to 5 years and then annually for the next 5 years if there was no change. Chart reviews and direct contacts with the patients were used to derive the follow-up and outcome data.

# Statistical Analysis

Recurrence data were analyzed using the Student t-test with probability values less than 0.05 considered statistically significant.

# Results

# Incidental Cases

In this series, an initial diagnosis of incidental Rathke cleft cyst was made in 61 patients. Of these, 19 patients demonstrated cyst growth, visual loss, or endocrinopathy on follow-up MR images and proceeded to surgical treatment. Forty-two patients (69%), with incidental lesions in whom there was no sign of endocrine dysfunction and no growth was detected on MR images, were observed for up to 9 years without surgical intervention.

TABLE 3			
Findings following surgery	in	118	patients

Finding	No. of Patients (%)
complete resection per MR imaging	114 of 118 (97)
postop radiotherapy	0 of 118 (0)
postop visual loss	0 of 118 (0)
improved vision	57 of 58 (98)*
postop hypogonadism†	2 of 56 (4)
improved hypogonadism	11 of 62 (18)
postop hypothyroidism†	0 of 118 (0)
resolved hypothyroidism	0 of 8 (0)
postop hypocortisolemia†	0 of 118 (0)
resolved hypocortisolemia	1 of 7 (14)
postop GH deficiency†	0 of 118 (0)
resolved GH deficiency	14 of 78 (18)
postop DI†	22 of 118 (19)

- \* Eighty-eight (89%) of 99 eyes.
- † Endocrinopathy not present preoperatively.

#### Surgical Experience

On average the duration of surgery ranged from 42 to 73 minutes. Blood loss during the operations ranged from 30 to 150 ml. The average duration of hospitalization was 3.8 days. No blood transfusions were necessary. The diagnosis of a Rathke cleft cyst was confirmed by histopathological evaluation in all surgical cases.

## Initial Response to Surgery

Complete cyst resection was achieved in 114 patients (Table 3). Complete resection was defined as no evidence of a Rathke cleft cyst on postoperative MR images, which was confirmed by a neuroradiologist 3 months postoperatively. Fifty-seven (98%) of 58 patients with preoperative visual loss experienced an improvement in their vision following surgery. Some patients also experienced an improved endocrine status. Hyperprolactinemia resolved in 100% (34 of 34) of patients postoperatively. Preoperative growth hormone deficiency completely resolved in 14 (18%) of 78 patients. Hypocortisolemia resolved in one (14%) of seven patients, and hypogonadism improved in 11 (18%) of 62 patients.

#### Surgical Complications

Postoperative DI occurred in 22 patients. Fourteen of these patients were among the first 33 patients whom we treated surgically; given this high rate of DI (42%) we decided to modify our approach to lower the endocrinological complication rate. Only eight (9%) of 85 patients undergoing less radical resection experienced postoperative DI. Two patients displayed symptoms of hypogonadism postoperatively that had not been present before the operation. One patient experienced a CSF leak and one patient had meningitis. Forty-three patients required grafts for violation of the arachnoid and egress of CSF. No patient required a repeated operation for a CSF leak. There were no perioperative deaths or complications leading to new neurological deficits in this series.

#### Cyst Recurrence

All recurrences occurred within 5 years; they were found in 21 (18%) of 118 patients by performing MR imaging.

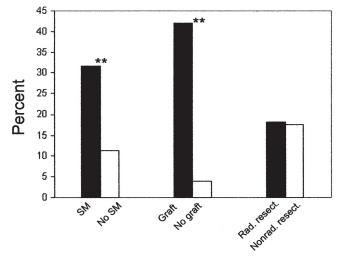


Fig. 1. Graph demonstrating surgical and pathological correlates of recurrence. *Double asterisks* indicate a highly statistically significant difference between the factors. Nonrad. = nonradical; rad. = radical; resect. = resection; SM = squamous metaplasia.

Nineteen of 114 patients who had no evidence of a residual cyst on 3-month postoperative MR images experienced a recurrence. Two of four patients in whom a residual cyst was identified on the initial (3-month) postoperative MR image also experienced regrowth of the cyst. Twelve (57%) of the 21 patients underwent a repeated operation after showing progressive growth on MR images. Of these 21 patients, nine (43%) were observed for up to 12 years without progression of the cyst.

Recurrences were associated with surgical and pathological factors (Fig. 1). Most significant among these factors was the use of a graft. Eighteen of 43 patients who required a graft during surgery experienced a recurrence, whereas only three of 75 patients without a graft experienced a recurrence (p = 0.000007). Recurrence was associated to a lesser extent with squamous metaplasia. Of the 38 patients with squamous metaplasia, 12 (32%) experienced a recurrence, whereas only nine (11%) of 80 patients without squamous metaplasia experienced a recurrence. This difference was also statistically significant (p = 0.009). The extent of resection was not associated with an increased rate of recurrence. Six of 33 patients undergoing radical resection experienced a recurrence, whereas recurrence occurred in 18 of 85 patients who underwent a less radical resection (p = 0.473).

## Discussion

#### Incidental Rathke Cleft Cysts

With the advent of modern neuroimaging, the Rathke cleft cyst is becoming a more common incidental finding. These cysts are usually benign and require only conservative management. In their recent survey, Sanno, et al., 18 found that only 5.4% of Rathke cleft cysts increased in size during follow up. Our data support the assertion that growth of these small, incidental Rathke cleft cysts is uncommon and that most do not require an operation (Table 1). Among patients with an incidental finding of a cyst in our series, 69% demonstrated no growth for up to 9 years. Thus, re-

currence of disease can be followed by using MR imaging without a repeated operation if no progression of cyst growth is demonstrated.

#### Resolution of Symptoms

Although incidental asymptomatic lesions can be followed conservatively, symptomatic Rathke cleft cysts are most successfully managed surgically. Headache, visual field defect, decreased visual acuity, hyperprolactinemia, and amenorrhea-galactorrhea syndrome have resolved or improved according to previous reports. Hypopituitarism and DI, however, have generally failed to improve. Our results reconfirm that visual dysfunction improves with surgical decompression. Our data also indicate that preoperative hypopituitarism improves after removal of the Rathke cleft cyst (Table 3). This improvement was most impressive in patients with a growth hormone deficiency or hypogonadism, who represented 66 and 53% of our patients, respectively. Improvement was less common but still present in patients with hypocortisolemia, whereas no improvement was seen in the eight patients with preoperative hypothyroidism. These results show that preoperative endocrinopathy might improve in response to surgical inter-

# Surgery-Related Morbidity

Aggressive resection of Rathke cleft cysts can result in postoperative endocrine dysfunction. Diabetes insipidus has been reported to be the most common postoperative complication in surgically treated patients. Our results were similar, with 22 cases of DI developing in patients in whom it was not present preoperatively. In our experience, radical resection of the cyst wall was associated with a higher rate of endocrine morbidity. Forty-two percent (14 of 33) of the patients undergoing radical resection in our series began to experience DI postoperatively compared with only 9% of those patients undergoing nonradical resection. Similarly, 6% of patients had developed postoperative hypogonadism following radical resection, whereas only 2.5% of patients undergoing less radical resection did.

# Surgical Management and Recurrence

Recurrences of symptomatic Rathke cleft cysts are considered rare; however, confirmation of this fact is difficult to ascertain from the published literature. In a recent study, 53 patients underwent surgery for Rathke cleft cysts at three different institutions where various surgical techniques were used.<sup>12</sup> The authors reported an 11% recurrence rate during a mean follow-up period of 31 months (2 months minimum).12 Voelker and colleagues21 surgically treated eight patients and reviewed 147 case reports with varying surgical techniques in the literature to arrive at a 5% recurrence rate following transsphenoidal surgery and a 10% rate following craniotomy. How they arrived at that number was not explained. Some studies have focused on symptom improvement without indicating the duration of the follow-up period.<sup>4</sup> In one study the authors retrospectively reviewed 16 cases of Rathke cleft cyst without recurrence but did not include the duration of the follow up.13 Forty patients undergoing a transsphenoidal approach were presented in a study by Ross, et al., <sup>17</sup> in which the mean follow-up period was 62

months. The authors mentioned one patient who experienced recurrence requiring repeated surgery, but they did not reveal whether other recurrences arose that did not require intervention. Our series revealed an 18% recurrence rate in patients in whom the duration of follow up was at least 5 years. We believe the discrepancy between our recurrence rate and those of other studies is due to the short follow-up time periods or low numbers of patients in the other studies. Interestingly, in one other study in which 12 patients were followed up over a median follow-up period of 30 months, there was a 33% recurrence rate. <sup>15</sup> A recurrence rate of 19% in 26 patients were presented by Shin, et al., <sup>20</sup> with a mean follow-up period of 70 months.

The question that naturally arises from these observations is whether aggressive surgical intervention, including resection of the symptomatic cyst contents and wall, is necessary. Full evacuation of the contents and liberal opening of the cyst wall was recommended by Fager and Carter<sup>5</sup> in 1966. Voelker and colleagues<sup>21</sup> found that it was the most common form of treatment used in the cases they reviewed. This approach was supported by other authors who identified and drained the cyst in conjunction with a biopsy of the cyst wall. Ross, et al., 77 advocated the use of cauterization of the cyst wall and application of absolute alcohol if no violation of the subarachnoid space was seen, in an attempt to kill the cellular wall of the cyst and thus potentially decrease recurrence. This was done in their series of 40 patients undergoing transsphenoidal surgery for Rathke cleft cyst without any complication. In our 118 patients treated surgically, 75 patients received absolute alcohol when the arachnoid membrane was intact. This technique has been adopted by the senior author with no claim as to its efficacy at reducing recurrence. No apparent complication resulted from this technique in our experience. Recently, however, a case report was published in which the authors described blindness, anosmia, and partial third cranial nerve damage in a patient who underwent four surgical procedures for a recurrent Rathke cleft cyst. The authors of that report stated that the subarachnoid membrane was violated and that the alcohol mixed with the patient's CSF, causing the complication.8

We did not find that radical resection was associated with a decreased recurrence rate. Combined with our improved endocrinological complication rates for less radical resection, it appears that attempting total resection of the wall may not be the optimal treatment for a symptomatic Rathke cleft cyst. Instead, we found that squamous metaplasia and the use of a fat and/or fascial graft during surgery were more highly associated with recurrences in our patients. We postulate that the use of a graft may increase the chances of loculation and reformation of the cyst.

Relationship Between a Symptomatic Rathke Cleft Cyst and Craniopharyngioma

The intrasellar cyst differential diagnosis includes epithelial cyst, epidermoid cyst, dermoid cyst, Rathke cleft cyst, and craniopharyngioma. It is well known that these lesions frequently cannot be distinguished radiographically and that microscopic diagnosis can be difficult. This was well described by Harrison and colleagues, 6 who suggested that all of these cysts are best viewed as a continuum of epithelial-lined cystic lesions. Although these authors provided an extremely thorough histological presentation, they only allud-

ed to a few series of surgical outcomes. As argued earlier, those series were either not supported by a large number of patients with adequate follow-up periods or their recurrence rates could not be confirmed. Based on our large number of patients with a 5-year follow-up period, we postulate that our recurrence results support the closer relationship between craniopharyngioma and the Rathke cleft cyst proposed by Harrison and colleagues. Of the 38 patients with squamous metaplasia, 12 (32%) experienced a recurrence, supporting the theory that Rathke cleft cysts with squamous metaplasia represent a more aggressive pathological entity that may approach the natural history of craniopharyngioma. Our recurrence rate even exceeds the 7% in 144 patients with craniopharyngioma reported by Yasargil, et al.,<sup>22</sup> who specifically aimed to remove these lesions aggressively at surgery. This raises the question as to whether complete radical resection is necessary to remove a Rathke cleft cyst to reduce recurrence.

#### Conclusions

To date, we present the largest series reported in the literature of Rathke cleft cysts that required surgical intervention as well as a large number of incidental cases that were followed conservatively. Visual improvement can be expected postoperatively with low complications. Resolution of endocrine dysfunction is possible in some patients. It is important to note that a recurrence rate of approximately 18% can be expected if the surgical technique described in this paper is used. In our opinion, a more aggressive resection, which can cause increased complications, may not be justified, given that repeated surgical drainage may be necessary in some recurrent cases. Instead, a less radical resection, which may be associated with a lower complication rate despite a similar recurrence rate, may be preferable.

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