

# Repeat Operations in Pediatric Patients with Recurrent Craniopharyngiomas

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## Key Words

Craniopharyngioma · Recurrence · Radiotherapy

## Abstract

**Background:** Controversy continues over the optimal management of recurrent craniopharyngiomas. Our strategy for approaching repeatedly recurrent craniopharyngiomas in pediatric patients has been to decompress vital structures and relieve the symptoms as early as possible. The purpose of this study was to present our experiences of repeatedly recurrent craniopharyngiomas and the pattern of failure associated with treatment. **Methods:** A retrospective review was conducted on 7 pediatric patients who underwent resection >2 times in a single institution between 1990 and 2004. Resections were performed 3–8 times for each patient. Variables including tumor size, consistency and location, extent of resection, adjuvant therapy and morbidity were evaluated. **Results:** Thirty-two operations were performed in 7 pediatric patients. Total resection was not achieved by the third surgery and thereafter, and the interval between each surgery became shorter. Appetite disorders, neurocognitive disorders and behavioral disorders occurred following repeat surgeries. **Conclusion:** Repeat operations are associated with a high failure rate of tumor control, even though they can help relieve neurologic symptoms. It is suggested that the number of repeat operations should be limited.

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## Introduction

Craniopharyngiomas are rare intracranial tumors in childhood, representing 1.2–4.4% of tumors of the central nervous system. Although the histology is benign and the mortality rate low, craniopharyngiomas are associated with a high rate of recurrence, which, in turn, is associated with a high rate of morbidity [1]. Although the optimal management of craniopharyngiomas remains controversial, the extent of surgical resection has been considered the most significant predictive factor of tumor cure and good functional outcome [2, 3]. The rationale for maximal resection has been challenged because surgical complications such as hypothalamo-pituitary dysfunction or optic nerve damage are serious morbidities. Therefore, studies have supported the trend toward less surgical aggressiveness and the broad use of irradiation after subtotal resection or at the time of progression [4, 5]. However, subtotal resection is associated with a higher number of recurrences, which bear a poor prognosis [6, 7]. Morbidity caused by recurrence and the surgical results after repeat procedures are thus an important parameter for the long-term evaluation of the management of craniopharyngiomas [8, 9].

Repeat operations for recurrent craniopharyngiomas have been the subject of only few studies. In cases of recurrent craniopharyngiomas after primary surgery and radiation therapy, we performed repeat surgeries for the

relief of symptoms such as increased intracranial pressure, visual disturbances and mental deterioration. Based on our strategy, we have operated on 87 patients with craniopharyngiomas since 1990. In this study, we focused on pediatric patients with repeatedly recurrent tumors who underwent surgery more than 2 times. We evaluated the failure pattern and associated factors of repeated recurrences.

### Clinical Material and Methods

We conducted a database search for patients who had been diagnosed with craniopharyngiomas at a single institution since 1990 after the advent of MR imaging. Eighty-seven patients underwent surgery for the initial treatment of craniopharyngiomas. The purpose of the initial surgery was total resection whenever possible without risking damage to the hypothalamus or visual pathway. In cases resulting in subtotal resection at the first operation, we subsequently performed radiotherapy. When recurrence was accompanied by signs and symptoms such as intracranial hypertension, focal neurologic deficits, seizures and mental deterioration, we opted to perform a reoperation. The purpose of the reoperation was total tumor resection with the preservation of functioning and the relief of symptoms. In cases involving tumor recurrence or progression, even following reoperation and radiotherapy, a repeat reoperation was performed with the goal of maximal resection and relief of symptoms. The extent of resection was determined based on the surgeon's report and postoperative MR images.

Based on our policy, 7 (5 males and 2 females) of 87 patients underwent operations >2 times. Data were extracted from clinical notes, surgical reports and radiologic reports. The ages of the 7 patients ranged from 6 to 16 years (mean: 12 years). The median number of surgeries was 4 (range: 3–8). The median follow-up duration was 10 years (range: 5–14 years).

### Results

Between 1990 and 2004, we operated on 87 patients with the diagnosis of craniopharyngioma; 61 were adult and 26 pediatric patients. The age ranged between 5 and 80 years. During craniopharyngioma surgery, gross total resection was achieved in 28 patients (32.2%). Three of the 28 patients (10.7%) had tumor recurrences, and the mean time between the first surgery and recurrence was 84 months. Of the other patients (n = 59) with subtotal and partial resections, adjuvant radiotherapy and radiosurgery was performed in 34 and 4 patients, respectively. Fifteen patients were followed without adjuvant therapy. Six patients were treated with bleomycin via an Ommaya valve reservoir. Eighteen of the 59 patients (30.5%) had tumor recurrences, and the mean

time between the first surgery and recurrence was 11.5 months. In our institution, symptomatic recurrence has been an indication for reoperation irrespective of adjuvant therapy.

Seven pediatric patients with tumor recurrences underwent craniotomies >2 times. The patient characteristics are summarized in table 1. The tumor height in the midline ranged from 2.8 to 6.3 cm. The consistency of tumors included 2 cystic, 1 solid and 4 mixed components. Calcifications and hydrocephalus accompanied 57.1% and 71.4% of the tumors at the time of initial presentation, respectively. The extent of the first surgical resection was a gross total resection in 2 patients, a subtotal resection in 4 patients and a partial resection in 1 patient (table 2). Adjuvant radiotherapy was delivered within 5 months after the initial operation; the radiation dosage ranged from 4,500 to 5,040 cGy. Radiotherapy was performed following the second operation in 2 patients. The indications for radiation after the second operation were a rapid growth of a remnant tumor in case 1, and a staged operation in case 3. In the second operation, gross total, subtotal and partial resections were achieved in 2 and 4 patients, and 1 patient, respectively. In the third operation, subtotal and partial resections were achieved in 5 and 2 patients, respectively. Gross total resection was not achieved with the third operation and beyond.

A total of 32 operations were performed in 7 pediatric patients. The median interval between the first and second operations was 58 months; between the second and third operations it was 11 months, and between the third and fourth operations 12.5 months. The interval between the fourth and fifth operations was 8.5 months (table 3). A longer interval between the first and second surgeries was associated with total resection (cases 2 and 5) and early irradiation (cases 6 and 7).

After the first and second surgeries, all 7 patients developed panhypopituitarism, requiring lifelong hormone supplementation of all pituitary hormones including vasopressin, cortisol, and thyroxine. The other complications associated with repeat surgeries included appetite disorders and hypothalamic obesity (100%), neurocognitive disorders and learning disabilities (100%), neuropsychological and behavioral disorders (42.9%), and sleep disorders (42.9%). Four of 5 patients presenting with visual disturbances had visual deterioration at the last follow-up visit. There were no surgery-related mortalities.

**Table 1.** Patient characteristics

No.	Age/sex years	Presenting symptom and sign	Tumor size, cm	Tumor location	Tumor consistency	Calcification	Hydrocephalus	Follow-up, years
1	6/M	headache	3.5 × 4 × 5	sellar, suprasellar	mixed	+	+	6
2	11/M	headache, vision deterioration	6 × 5 × 5.5	suprasellar	cystic	-	+	14
3	11/F	headache, vision deterioration	6 × 6 × 5.3	suprasellar, parasellar	mainly cystic	-	+	10
4	12/M	growth retardation	4 × 6 × 6.3	sellar, suprasellar	multicystic, small solid	+	+	5
5	13/F	headache, vision deterioration	5 × 3 × 3.8	sellar, suprasellar	mainly solid	+	+	14
6	15/M	headache, vision deterioration	3.4 × 3.2 × 2.8	suprasellar	mixed	-	-	14
7	16/M	vision deterioration	3.2 × 3 × 3	sellar, suprasellar	mixed	+	-	8

**Table 2.** Extent of repeated surgery and timing of radiation therapy

No.	Number of surgeries	1st surgery	Dose cGy	2nd surgery	Dose cGy	3rd surgery	4th surgery	Interval between 1st surgery and RT, months
1	3	subtotal	-	subtotal	RT(5,040)	subtotal	-	3
2	7	total	-	total	-	subtotal	partial	-
3	4	partial	-	partial	RT(5,040)	partial	partial	4
4	3	subtotal	RT (4,500)	subtotal	-	subtotal	-	0.4
5	4	total	RT (4,500)	subtotal	-	subtotal	partial	5
6	8	subtotal	RT (5,040)	total	-	subtotal	partial	2
7	3	subtotal	RT (5,040)	subtotal	-	partial	-	2

RT = Radiation therapy.

**Table 3.** Surgical approaches and intervals between each surgery

No.	Number of surgeries	1st	Interval months	2nd	Interval months	3rd	Interval months	4th	Interval months	5th	Interval months	6th	Interval months	7th	Interval months	8th
1	3	FT	0.5	FT	9	BIH										
2	7	FT	82	FT	7	FT	1	FT	10	FT	18	FT	0.5	FT		
3	4	FT	3	FT	110	BIH	14	FT								
4	3	FT	3	FT	5	BIH										
5	4	FT	84	FT	50	FT	36	BIH								
6	8	FT	66	BIH	128	FT	11	FT	7	FT	4	FT	21	FT	4	FT
7	3	FT	58	FT	11	BIH										

FT = Frontotemporal approach; BIH = bifrontal interhemispheric approach.

## Discussion

The treatments available for the recurrence of craniopharyngiomas include reoperation, irradiation and radiosurgery [10, 11]. In the case of a cystic recurrence, intracystic bleomycin or intracystic irradiation is effective

[12]. Radiotherapy has been the proposed management either after subtotal resection or at the time of recurrence [13]. However, there is no consensus on the optimal management of a recurrence or progression after maximal resection and irradiation. Our strategy for approaching repeatedly recurrent craniopharyngiomas in pediatric pa-

tients has been to decompress close anatomic structures and relieve the symptoms as early as possible.

Recurrent craniopharyngiomas grow along the path of least resistance, extending into the basal cisterns, third ventricle and cerebral hemispheres. The tumor can also displace the optic nerves and chiasm and grow superiorly into the hypothalamus and brain stem. At the first surgery, there is usually a natural cleavage plane between the tumor and the surrounding normal brain that results from a dense peritumoral gliotic reaction. However, at recurrence after radical surgery, this gliotic reaction is not present, and this renders further surgical resection very challenging, with a high risk of complications and a low rate of local control [14]. In our series, total resection was not achieved with the third surgery and thereafter, and the interval between each surgery became shorter. Most surgical complications occurred after the first and second surgeries, which were performed in order to achieve total or radical resection. The purpose of a repeat reoperation was maximal resection and a relief of symptoms, which was different from that of the first and second operation. A candidate for repeat reoperation was a patient who developed a rapid regrowth of tumor accompanied by neurological symptoms.

Repeat surgeries after the second surgery were not related to serious morbidities, except for wound complications. There was no evidence of tumor seeding during repeat surgeries. Repeat operations were better tolerated than the first and second attempts in terms of symptom relief and surgical morbidity because endocrine disturbances were already established and balanced by medical treatments. In our series, all patients were followed up for >5 years. Tumor progression itself was not the main cause of death. The quality of life of long-term survivors was less because of visual disturbances and endocrinopathies such as obesity and diabetes insipidus. Obesity has a marked impact on the patient's quality of life and is associated with diminished motility and impaired school-

ing. The relation of obesity to surgical damage has been debated. Obesity, unlike hypopituitarism, results from preoperative damage rather than from surgery itself [15]. In our series, subtotal resection, tumor recurrence and obesity are closely correlated. Although no patients died during the perioperative period, 3 patients died after the perioperative period of endocrine disorders caused by hypothalamic damage.

The appropriate time point and dose of irradiation after incomplete resection are controversial in the literature as well as in the clinical setting. Moon et al. [16] suggested that early radiation therapy should be highly recommended for a better quality of life and longer survival. In this series, the total radiation dose ranged from 45 to 55.8 Gy, with a median dose of 54 Gy using a conventional fractionation dose (1.8 Gy per fraction a day, 5 days a week). Habrand et al. [17] showed that a high dose of radiation ( $\geq 55$  Gy) significantly influenced the outcome of patients who were irradiated with a total dose between 45 and 56 Gy (median: 50 Gy). Regine et al. [18] reported a 44% risk of relapse below 54 Gy versus 16% above 54 Gy. In our series, radiation therapy was given within 5 months after the first surgery. A relatively low dose of radiation (<50.4 Gy) has been suggested to lead to poor tumor control. Conversely, other series have found no such dose-effect relationship [19].

From this limited experience, it is crucial to reduce the number of repeat surgeries in the management of craniopharyngiomas. To accomplish this goal, the initial operation to remove the tumor needs to be as aggressive as possible so as not to develop critical, irreversible or uncontrollable complications such as visual deterioration and hypothalamus-related neurologic dysfunctions. In conclusion, repeat operations for recurrent craniopharyngiomas are associated with a high failure rate of tumor control, even though repeat operations can help relieve neurologic symptoms.

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