Surgical management of the recurrence and regrowth of craniopharyngiomas

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Object. The authors performed a retrospective analysis of a consecutive series of craniopharyngiomas and their recurrences, which were managed with surgery alone.

Methods. In the past 20 years, 37 consecutive patients with craniopharyngiomas underwent surgery without adjuvant radiotherapy. During that period there was a consistent strategy that surgical management was the first choice of treatment whenever possible.

Of these 37 patients, 11 experienced tumor recurrence (29.7%) during the mean follow-up period of 11.1 years. Of these 11 patients, seven experienced recurrence after neuroimaging-confirmed total removal, and four patients experienced recurrence after partial or incomplete removal. In these 11 patients, surgical removal was performed 17 times. Using a proper surgical approach (mainly a basal interhemispheric approach) and meticulous microsurgical techniques, total removal of the recurrent tumor was achieved in nine surgeries (52.9%). The mortality and morbidity rates associated with these 17 surgeries were 0% and 9.1%, respectively. In most cases, visual function was preserved or improved and intellectual performance was also preserved.

Conclusions. Recurrence of craniopharyngioma can be safely managed by using meticulous contemporary microsurgical techniques without additional radiotherapy. The role of surgery and adjuvant radiotherapy for craniopharyngiomas may vary in the future, depending on innovations in treatment and technology. Nevertheless, surgery can be still a major therapeutic option in the management of recurrent craniopharyngiomas.

KEY WORDS • craniopharyngioma • recurrence • outcome

Surgical management of craniopharyngioma, despite its histologically benign nature, remains challenging because of the tumor’s proximity to vital structures, including the optic apparatus, pituitary stalk, hypothalamus, and vessels in the circle of Willis. In addition, the high frequency of this tumor’s recurrence and regrowth is a challenge for neurosurgeons during long-term follow-up periods. Various strategies have been advocated to improve outcomes in patients with craniopharyngiomas. Some neurosurgeons have stressed total removal of the tumor without additional radiotherapy to avoid the potential side effects of irradiation.

Other neurosurgeons have emphasized the combination of conservative surgery and radiotherapy because the risks of morbidity and mortality associated with aggressive surgery are not negligible. In addition, adjuvant radiotherapy is considered useful to control the high frequency of recurrence and regrowth when only a subtotal resection is performed. Recently, multimodal management including stereotactic radiotherapy and intracavitary radiation has also been introduced as another treatment option.

Among many unresolved problems regarding craniopharyngioma, the most important one is the high rate of recurrence associated with this lesion. Surgical management of a recurrent craniopharyngioma occasionally causes serious complications because scars produced by previous surgery may enhance the technical difficulty of secondary surgery and, therefore, increase the risks of mortality and morbidity.

As a result, many authors who prefer to perform radical resection in the first surgery recommend radiotherapy or a multimodal approach as a salvage treatment for patients with recurrent craniopharyngiomas.

For 20 years we have treated patients with craniopharyngiomas based on a policy of surgical management alone, without radiotherapy, even in cases of recurrent tumors. In this study we performed a retrospective analysis of the recurrence of craniopharyngiomas that had been surgically treated without radiotherapy, and we studied the current role of surgery in the management of recurrent craniopharyngiomas.

Clinical Material and Methods

Patient Population

Between January 1985 and August 2004, 37 patients underwent surgery for craniopharyngiomas in our department.
Cranioopharyngioma recurrence

There were 21 male and 16 female patients ranging in age at the primary surgery from 1 to 72 years (mean 29.7 years); eight children were younger than 16 years of age. The goal of our surgery was excision of as much of the tumor as possible without incurring neurological and neuropsychological complications. We attempted to preserve the pituitary stalk whenever possible. Thirty-three patients underwent craniotomy—either bifrontal or frontotemporal craniotomy—and only four patients with intrasellar tumors underwent transphenoidal surgery. Thirty primary operations were performed by the senior author (K. Hashi) and the seven remaining surgeries were performed by another author (Y.M.). Total resection, which was defined as no residual tumor left behind, as viewed both intraoperatively and on postoperative neuroimages (both CT scans and MR images\(^{14,46,56}\)), was obtained in 26 patients (70.3%). Subtotal resection, which was defined as small but definite signs of residual tumor seen intraoperatively or on neuroimages, was performed in seven patients (18.9%). Small flecks of calcification observed to have been left behind on postoperative CT scans were deemed residual tumor. Partial resection, which was defined as the finding of definite residual tumor both intraoperatively and on neuroimages, was performed in four patients (10.8%). The decision to perform a subtotal or partial tumor removal was made by the surgeon during the operation, based on the difficulty of each surgery.

For the various surgical approaches, total resection was achieved in 80% of surgeries in which the basal interhemispheric approach was used, 75% in which the pterional approach was selected, and 25% in which the transsphenoidal approach was used. There was no incidence of perioperative mortality at the primary surgery. Surgery-related morbidity was experienced in two patients (5.4%): visual deterioration in one patient and neuropsychological disturbance caused by hypothalamic damage in another. In 18 patients the pituitary stalk was resected, resulting in permanent panhypopituitarism. In patients with a preserved stalk, the endocrinological findings were panhypopituitarism in five patients, partial deficiency in seven patients, and normal endocrine function in seven patients. Histological examinations of the tumors documented the adamantinomatous type in 22 patients (59.5%), the papillary type in 13 patients (35.1%), and a mixed type of lesion in two patients (5.4%).

Radiation therapy was never prescribed as a primary treatment following surgery. Nevertheless, it was performed in patients who could not undergo surgical removal due to poor general condition or an inaccessible tumor location; these patients were excluded from this study.

In all patients, preoperative neuroimaging evaluations, including CT and MR imaging studies, were performed. Within 6 months after surgery, all patients underwent neuroimaging as part of their reassessment. Ophthalmological examinations, including tests of visual acuity and visual field, were performed both pre- and postoperatively in all patients. Both pre- and postoperative endocrinological evaluations were performed in all patients, and the KPS\(^{12}\) and WAIS-R\(^{30}\) were used for the neuropsychological evaluation.

Follow-Up Study

After discharge, all patients routinely underwent neuroimaging and clinical examinations every 6 to 12 months.

Clinical information on each patient was obtained by a review of the medical record. Thirty-six of 37 patients participated in follow-up review for at least 12 months. Four of these patients were eventually lost to follow up. Consequently, complete follow-up data were available for 32 patients. The long-term follow-up data, including overall survival rate, recurrence-free survival rate, and disease control rate, were examined. The mean follow-up period was 11.1 years (range 1–19 years).

Two patients died during the follow-up period. One died of a shunt-related infection approximately 3 years after the operation, and the other died of a cardiovascular event 10 years after surgery. The tumor-related mortality rate during the follow-up period was 3.1%, and the tumor-unrelated mortality rate was 3.1%.

Therapeutic Strategy for Recurrent Cranioopharyngiomas

Our strategy for treatment of recurrent cranioopharyngiomas was excision whenever possible, and radiotherapy was not administered unless resection was impossible. If the intraoperative findings indicated that complete removal could not be achieved without a significant risk of morbidity, incomplete resection was performed. The age of the patient, location of the tumor, previous modalities of treatment, and severity of symptoms and signs were assessed when making decisions about treatment.

The selection of the surgical approach to use in a repeated operation was based on the previous approach(es) and the extent of tumor. In most cases, the basal interhemispheric approach\(^{40}\) was preferred by surgeons in our department. The pituitary stalk was resected when tumor invasion into the stalk was suspected. All surgical treatments for recurrence were performed by the two authors mentioned previously (K. Hashi and Y.M.).

Statistical Analyses

Comparisons of discrete variables between outcome groups were made using chi-square tests,\(^ {40}\) and comparisons of continuous variables were made using the Wilcoxon rank-sum test.\(^ {12}\) The cumulative probability of recurrence was estimated as a function of time after surgery by using the Kaplan–Meier survivorship method.\(^ {23}\) Comparisons of survivorship curves were made using log-rank tests.\(^ {21}\)

Results

Tumor Recurrence

Among the 37 patients who underwent surgery at our institution, 11 patients were later found to have tumor recurrence or regrowth (Table 1). The overall recurrence and regrowth rate in the present series was 29.7%. When we considered tumor regrowth and tumor recurrences separately based on neuroimaging findings after primary surgery, recurrence after total resection of a tumor was observed in four (15.4%) of 26 patients, and regrowth after incomplete resection and partial removal was observed in seven (63.6%) of 11 patients. Complete total resection was associated with a lower recurrence rate, compared with incomplete resection (\(p = 0.04\)). In children following the initial surgery, four (50%) of eight patients experienced a recurrence of the disease. In adolescents, seven (24.1%) of 29 patients had a recurrence. All these patients were male.
Table 1

| Case No. | Follow-Up (yrs) | No. of Recurrences | Previous Surgery | Interval (yrs) | Site of Recurrence | Surgical Approach | Resectability | History of Type of Granulopharyngioma | Visual Outcome | Postop KPS | Pretop KPS | Pathology of Tumor | Surgical Success |
|----------|----------------|--------------------|-----------------|---------------|-------------------|------------------|--------------|-------------------------------|---------------|------------|------------|-------------------|-----------------|----------------|
| 1        | 29, M          | 1                  | TR              | 18.7          | subchiasmatic     | BI               | STR          | pap                           | 90            | 90         | improved  | BI Persistent resection | STR total resection |
| 2        | 40, M          | 2                  | TR              | 4.5           | retrochiasmatic   | BI               | STR          | pap                           | 90            | 90         | no change | BI Partial resection    | STR total resection |
| 3        | 72, M          | 1                  | PR              | 10            | intrasellar       | TS               | PR           | pap                           | 70            | 70         | no change | TS Persistent resection | PR partial resection |
| 4        | 45, M          | 1                  | TR              | 17.6          | retrochiasmatic   | BI               | TR           | Ad                            | 90            | 90         | improved  | BI Persistent resection | TR total resection |
| 5        | 46, M          | 2                  | STR             | 0.8           | retrochiasmatic   | BI               | STR          | pap                           | 90            | 90         | no change | BI Partial resection    | STR total resection |
| 6        | 4, M           | 1                  | TR              | 4.1           | retrochiasmatic   | BI               | TR           | Ad                            | 90            | 90         | improved  | BI Persistent resection | TR total resection |
| 7        | 9, M           | 3                  | PR              | 3             | intrasellar       | TS               | PR           | pap                           | 90            | 90         | improved  | TS Persistent resection | PR partial resection |
| 8        | 17, M          | 2                  | STR             | 18.5          | retrochiasmatic   | BI               | STR          | pap                           | 90            | 90         | no change | BI Partial resection    | STR total resection |
| 9        | 3, M           | 1                  | STR             | 18.4          | retrochiasmatic   | BI               | STR          | pap                           | 90            | 90         | no change | BI Partial resection    | STR total resection |
| 10       | 18.7           | 1                  | STR             | 18.7          | retrochiasmatic   | BI               | STR          | pap                           | 90            | 90         | no change | BI Partial resection    | STR total resection |

- Ad = adamantinomatous; BI = basal interhemispheric; pap = papillary; PR = partial resection; PT = pterional; SPS = same as that found at previous surgery; STR = subtotal resection; TR = total resection.
- * Age at initial treatment.
- † Interval between previous surgery and recurrence.
- ‡ Preoperative neuroimaging, including both CT scans and MR images in all patients.

Surgical Outcomes

Resectability following surgery was confirmed not only by operative findings but also by interpretation of postoperative neuroimages, including both CT scans and MR images in all patients. Total resection was accomplished in nine of 17 operations for recurrent tumors (52.9%). In six (54.5%) of the 11 second operations total resection was accomplished, and in three (60%) of the five third operations total resection was achieved. Six operations resulted in subtotal resection and two resulted in partial resection because of the tight adhesion of the tumor to the optic apparatus. As to surgical approaches, total resection was accomplished in...
nine (69.2%) of 13 operations in which the basal interhemispheric approach was used, in none (0%) of two operations in which the pterional approach was used, and in none (0%) of two operations in which the transsphenoidal approach was used. The site of recurrence, which was determined by reviewing preoperative neuroimaging studies and surgical findings, was the retrochiasmatic region in 10 patients, the subchiasmatic region in five patients, and the intrasellar region in two. Total resection was accomplished in seven (70%) of 10 patients whose lesions were in the retrochiasmatic region, in two (40%) of five patients whose lesions were in the subchiasmatic region, and in none (0%) of the two patients whose lesions were in the intrasellar region.

The reasons for incomplete resection in eight operations were analyzed according to the patient’s records. In two patients who underwent transsphenoidal surgery, total resection was not attempted, because the goal of surgery was decompression of the optic apparatus. In three patients firm adherence of the lesion to vital structures, including the optic apparatus (in three) and major vessels (in one) was a reason why complete resection could not be achieved. In one patient the surgeon had an impression of complete removal after surgery; however, a small residual lesion was detected on the postoperative MR image. An inadequate view of the tumor during surgery interfered with total resection in one patient. During a basal interhemispheric approach, an excellent view into the retrochiasmatic region was obtained through the window of the lamina terminalis; however, the view just behind the optic chiasm was restricted. Recently a neuroendoscope was used to confirm whether the residual tumor was present behind the optic chiasm after completion of microsurgical resection.

There were seven patients in whom total resection could not have been achieved at the primary operation, but could be achieved at the following operation. In three patients (Cases 5, 9, and 10), the surgical approach was changed from a pterional approach to a basal interhemispheric approach. In one patient (Case 1), the reason for incomplete resection at the previous operation was injury to the anterior communicating arteries complex; however, it was possible to dissect the tumor from these vessels at the following surgery (Fig. 2). In two patients (Cases 2 and 8), a small residual tumor had been left in the retrochiasmatic region, as seen on the postoperative MR image, and regrowth of the tumor occurred. Nevertheless, total resection was accomplished at the following operation with the aid of a neuroendoscope. Total resection was achieved by sacrificing the pituitary stalk at a subsequent operation in one patient (Case 11).

An ophthalmological examination was performed in all patients regardless of their visual symptoms. We found that visual symptoms had worsened in seven patients at the preoperative evaluation of the first recurrence and in three patients at the preoperative evaluation of the second recurrence. Postoperative visual function was improved in most patients in whom visual function had deteriorated and was worsened in only one patient (9.1%), who had a tumor that was hard and calcified. There was no damage to visual function postoperatively in patients who had no visual symptoms preoperatively.

To determine neuropsychological function, the WAIS-R was used to examine seven patients both pre- and postoperatively. The mean preoperative IQ in these patients was 106.9 (range 62–128) and the mean postoperative IQ was 101.1 (range 58–124), slightly lower than the preoperative scores. The performance status was evaluated in all pa-
In each case the postoperative KPS score was the same as the preoperative one in all patients. The mean KPS score was 87.1 (range 70–90). All patients returned to their normal daily and social activities after their surgeries. There was no significant difference between pre- and postoperative IQs and KPS scores.

Preoperatively, the pituitary stalk had been preserved in six (54.5%) of 11 patients; however, during subsequent surgeries it had to be sacrificed in four patients because of tumor invasion and, finally, it could only be preserved in two patients. Regarding endocrinological outcomes, all nine patients in whom the pituitary stalk had been resected experienced permanent panhypopituitarism. Normal pituitary function was maintained in only one patient, and the other

![Fig. 2. Case 1. Magnetic resonance images obtained in a representative case in which repeated surgical treatment was required for a recurrent craniopharyngioma. Pre-ope = preoperative; post-ope = postoperative.](image)

![Fig. 3. Graph depicting the overall survival rate over time in all patients in the series, as analyzed using the Kaplan–Meier method.](image)
experienced partial hypopituitarism, including diabetes insipidus and adrenal failure, despite preservation of the pituitary stalk. Compared with preoperative endocrine function, postoperative function was deteriorated in four patients (36.4%) and unchanged in seven patients (63.6%).

In the surgical treatment of recurrent craniopharyngiomas, the operative mortality rate was 0% and no tumor-related or-unrelated death was experienced during the entire follow-up period. The surgical morbidity rate was 9.1%. Although most complications were controlled without any sequela, one patient with a hard calcified tumor suffered mild deterioration of visual function. This patient had already lost visual function in his left eye preoperatively. His preoperative visual acuity was 0.6 and worsened to 0.3 postoperatively; however, these values were sufficient to allow him to continue his normal educational activities.

Long-Term Outcomes

As of the last follow-up period, patient data had been obtained in 32 patients who were observed for at least 1 year. We analyzed long-term outcomes, including the overall survival rate, recurrence-free survival rate, and disease control rate. The cumulative survival and probability of recurrence were estimated using the Kaplan–Meier survivorship method. Comparisons of survivorship curves were made using log-rank tests.

The 5-, 10-, and 15-year overall survival rates were 97, 94, and 94%, respectively (Fig. 3), and the corresponding recurrence-free survival rates were 79.9, 75.2, and 59.1% (Fig. 4). In patients in whom total resection was accomplished during the primary surgery, the 5-year recurrence-free survival rate was 90.4% and the corresponding 10-year rate was 90.4%; in patients in whom total resection could not be achieved, the 5-year recurrence-free survival rate was 51.9 and the corresponding 10-year rate was 38.9% (Fig. 4). Total resection at the primary surgery affected the recurrence-free survival rate, but did not affect the overall survival rate. The 5-, 10-, and 15-year disease control rates at the last follow up were 83, 92, and 76%, respectively. The recurrence-free survival rate was significantly different between patients in whom complete tumor resection was accomplished and those in whom tumor resection was incomplete. Nevertheless, the overall survival rate was not significantly different between these two groups.

After surgical treatment for the first recurrent tumor, five patients experienced a second or third recurrence. All these patients underwent repeated operations, and tumor control was eventually achieved in most of them.

Discussion

Recurrence of Craniopharyngioma

Tumor recurrence is a very common event in the management of craniopharyngiomas, even after complete resection and postoperative radiotherapy. Its recurrence is considered a major cause of morbidity in long-term outcome studies. If craniopharyngioma recurrence can be managed in a safe manner, long-term outcome may be dramatically improved.

The extent of resection and the use of postoperative radiotherapy are the most significant factors affecting the recurrence rate. In our series, the recurrence rate after complete resection was 15% during a mean follow-up period of 10 years. This rate is comparable to recurrence rates after complete resection cited for other modern series. In our series, the recurrence rate after complete resection was 15% during a mean follow-up period of 10 years. This rate is comparable to recurrence rates after complete resection cited for other modern series. In our series, the recurrence rate after complete resection was 15% during a mean follow-up period of 10 years. This rate is comparable to recurrence rates after complete resection cited for other modern series.
was 4.2 years. Despite this discrepancy, the difference between the two groups was not statistically significant. The reason why the interval to recurrence in our series is somewhat longer than those reported in the literature cannot be specified, but the extent of tumor resection may affect the latent interval of recurrence.

In the 1960s, because of significant incidences of morbidity and mortality in patients after attempts at radical surgery, Kramer, et al., reported the efficacy of combining limited surgery and radiotherapy in the treatment of craniopharyngioma. After this report, many authors asserted that radiotherapy both increased survival and lengthened the interval before tumor recurrence. Nevertheless, the hazards of radiotherapy, including radiation necrosis, optic neuritis, and dementia, should not be overlooked.  

**Management of Recurrent Craniopharyngiomas**

There is no consensus on the optimal management of recurrent craniopharyngiomas after surgery. Surgical treatment for recurrent craniopharyngiomas is considered more challenging than primary surgery. In primary tumors, there is usually a dense gliotic reaction separating the tumor from the normal neural tissue of the hypothalamus. This gliotic reaction forms a natural cleavage plane during surgery. At recurrence after radical surgery, however, this gliotic reaction is not present, rendering additional resection more challenging, with a high risk of complications and a low local control rate. The rate of complete resection of recurrent craniopharyngioma surgery has been determined to be between 40 and 70%. In numerous reports the authors have highlighted the increase in the rates of mortality and morbidity after surgery for recurrent craniopharyngiomas. Considering the difficulty encountered in new operations for recurrences and the morbidity and mortality rates associated with these procedures, many authors have recommended radiotherapy as the choice of treatment for recurrent craniopharyngiomas.

No patient received radiotherapy during the follow-up period in the present series. Our policy is that radiotherapy should be limited to patients with tumors that cannot be controlled by surgical treatment alone. Radiotherapy may enhance the technical difficulties following surgery and have an adverse effect on surgical outcomes.
Cranioopharyngioma recurrence

A morbid condition following surgery was experienced in only one patient, in whom visual function slightly deteriorated. In a comparison between our data and data obtained from literature on surgical treatment for recurrent craniopharyngiomas, patient outcomes in our series were favorable. It is interesting that the resectability of recurrent craniopharyngiomas was affected by the site of recurrence and previous surgical approaches used in the present series, as mentioned earlier. Total resection was achieved in 70% of patients with recurrences in the retrochiasmatic region and in 69.2% of patients in whom the basal interhemispheric approach was performed. The technical difficulties of repeated surgery can be attributed to arachnoidal scars from previous surgery and the loss of a gliotic reaction between the tumor and the surrounding neural tissues. Nevertheless, arachnoidal scars and adhesion can be safely dissected using a meticulous microsurgical technique, and a cleavage plane can become detectable even after radical excision.42–58 In our series, data on surgical treatment for recurrent craniopharyngiomas are encouraging, and the role of surgical treatment in contemporary neurosurgery should be reconsidered.

With regard to functional outcomes, three patients, including two patients after primary surgery and one patient after additional surgery, experienced a neurological deterioration or a psychological disorder. The mean KPS score at the last follow up in patients with recurrences was 86.2. All these patients were able to return to their daily or social activities.

The efficacy of radiotherapy in the control of craniopharyngiomas has been documented in many reports.1,3,5,7,15,31,35,37,38,41,43,54,56,57,60 Radiotherapy is an important adjuvant treatment for partially removed or recurrent craniopharyngiomas. On the other hand, patients who undergo radiotherapy are at risk for radiation-induced adverse effects in the long term,1,3,7,15,41 and the options of further treatment in patients with tumor recurrence are limited.

Intracavitary radiotherapy is used to treat cystic craniopharyngiomas42,25,1 however, visual outcome is not satisfactory and treatment failure may occur. Stereotactic radiosurgery is increasingly used in the management of intracranial tumors, and the efficacy of radiosurgery has been shown in cases of craniopharyngioma.1,3,10,26,50 Although we have not yet used radiosurgery, its role is increasing in the management of craniopharyngiomas, especially for small residual tumors left at surgery and small solid recurrences.

As we see from the results of the present series, the role of surgery is important in the treatment of craniopharyngiomas, even in cases of recurrences. We emphasize the use of radical surgery as the initial treatment of choice in patients with craniopharyngiomas whenever possible. Total resection may offer a chance for long-term recurrence-free survival. Nevertheless, in some patients subtotal or partial resection may be acceptable if total resection is believed to carry a risk of significant sequelae. In addition to surgical treatment, special attention should be paid to the management of endocrine disorders, and careful follow-up review of cases is mandatory for early detection of tumor recurrence.

Conclusions

Recurrence of craniopharyngioma can be safely treated with meticulous microsurgery without the need for additional radiotherapy. Long-term follow up of patients by performing periodic neuroimaging studies is strongly indicated for patients with craniopharyngiomas after surgical treatment, even in asymptomatic patients. Stereotactic radiosurgery may be a treatment option in these cases. The role of surgical treatment for craniopharyngiomas may vary in the future, depending on the progress of other modalities of treatment and technology. Nevertheless, surgery can still be a major therapeutic option in the management of recurrent craniopharyngiomas.