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Treatment of Recurrent Craniopharyngiomas

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One of the most common complications of craniopharyngioma treatment is recurrence. The outcomes of treatment for recurrent tumors with different modalities were evaluated. Of the 61 patients treated initially, 24 had recurrence during follow-up period (1-29 years, mean 11years). Twenty-two patients underwent a total of 35 additional operations for recurrence. With reoperation, total surgical removal was achieved for four occasions (Group a), subtotal resection was achieved with 31 surgical procedures. Nineteen procedures (Group b) were done without radiotherapy and seven were followed by radiotherapy (Group c). Seven patients were treated with radiosurgery (Group d) with or without surgical resection. The surgical mortality rate for Group a was 50% which was higher than for initial operation, while for Group b 10.5% and none for Groups c and d. Good functional status was maintained at follow-up in 50% of survived patients for Group a, 14% for Group b, 57% for Group c and 86% for Group d. The 5-year recurrence free survival rate was 50% for Group a, 16% for Group b, 80% for Group c, and 83.3% for Group d. The rate of recurrence free survival for Group b was significantly lower than Group c ($P = 0.004$) and Group d ($P = 0.001$).

The recurrence free survival rates were higher for Groups c and d than for Group b. The mortality and morbidity higher in the Group a. Radiotherapy and radiosurgery are useful adjuncts for the treatment of recurrence, resulting in a high recurrent-free survival rate with better functional outcome.

Craniopharyngiomas are tumors of nonglial origin, histologically benign and constitute 2.5 to 4% of all intracranial tumors (1, 2, 8). The growth characteristics of craniopharyngiomas show considerable variation and often they behave as aggressive tumors. As recurrence rates depend on the efficacy of the surgical treatment and the growth potential of the tumor itself, anything short of total excision will cause recurrence. The recurrence rates vary greatly from 0% to nearly 100% (3, 4, 8, 28, 30, 31, 32) depending on the surgical treatment and adjuvant therapy.

The optimal treatment of recurrent craniopharyngioma is remains controversial. Surgery should be considered as the first choice of treatment among therapeutic modalities for recurrent craniopharyngiomas although it is more difficult than primary operation (6, 24) and increase in morbidity and mortality. Radiation therapy is said to play an important role in reducing the rate of recurrence. Recently, gamma knife surgery is reported to be effective for achieving long-term control of tumors without compromising the quality of patient survival. However, there were few reports which analyzed the treatment outcomes of recurrent craniopharyngiomas comparing with each modality.

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In this paper, we retrospectively analyzed the results obtained with surgery for patients presenting with recurrence of craniopharyngiomas, as well as outcome compared with additional treatment modalities in Kobe University Hospital over the last 35 years.

MATERIALS AND METHODS

From 1966 to 2001, 61 consecutive patients underwent surgical treatment for their craniopharyngiomas at Kobe University Hospital. Data are collected and analyzed from their medical records. There were 35 males and 26 females with an age range from 2 to 67 years (Table 1). Sixteen patients were children below the age of 18 years, nine boys and seven girls. The mean age of the children was 8.1 years and that of the adults was 43.3 years. The initial operative approach was directly related to the anatomy and size of the tumor. Fifteen patients required a shunting procedure for accompanied hydrocephalus.

Three patients with subtotal resection died during the early postoperative period. Remaining patients are divided into 3 groups according to their treatment. Group A (n = 10) comprised the patients with total surgical resection, Group B (n = 25) those who underwent subtotal resection only and Group C (n = 23) those who underwent subtotal resection followed by radiotherapy. Tumor removal was considered complete when reported as such by the surgeons in their operative notes, which was confirmed by neuroimaging including CT scan and MRI. Subtotal removal was defined as an excision of the tumor of more than 75%. The radiation dose was between 40 to 50 Gy for children and 50 to 70 Gy for adults in 1.5 to 2 Gy fractions. For radiosurgery, the mean marginal tumor dose was 14.2 Gy (range 10.6-18 Gy) and the mean maximum dose was 26.6 Gy (range 13.3-36 Gy). However dose to the optic nerve was always reduced to less than 10 Gy. Visual acuity and field were evaluated before and after surgery. Need of hormonal replacement after surgery was also studied.

Patients were followed-up and functional status of each patient was evaluated with the Karnofsky functional outcome scale based on the activity of daily living. A score of 90 or 100 was interpreted as an excellent functional condition, a score of 70 or 80 as good, a score of 50 or 60 as fair and a score below 40 was interpreted as a poor functional condition. The follow-up outcome for non-recurrent tumor was evaluated at their last follow-up while for recurrent tumor it was defined at the last follow-up after previous treatment but before recurrence.

TABLE 1. Age and sex distribution at initial operation.

	No. of cases	Age (mean ± SD)	No. of patients under 18 years	Sex (male:female)
Group A	**10**	**37.2 ± 20.4**	**3 (30%)**	**7:3**
Group B	**28**	**39.4 ± 16.9**	**4 (14%)**	**17:11**
Group C	**23**	**26.7 ± 18.7**	**9 (39%)**	**11:12**
Total	**61**	**34.2 ± 18.8**	**16 (26%)**	**35:26**

Any evidence of tumor growth on neuroimaging was defined as tumor recurrence. Tumor recurrence was found in 24 patients. Twenty-two patients underwent a total of 35 additional operations for recurrence. Eight patients needed a third, three a fourth and two a fifth operation. In each time of recurrence, treatment modalities are categorized into 4 groups as

follows, Group a: total surgical resection only (n = 4), Group b: subtotal resection only (n = 19), Group c: subtotal resection and radiotherapy (n = 7), and Group d: radiosurgery with regardless of surgical resection (n = 7).

Survival probabilities were computed with the technique of Kaplan-Meier. For the Kaplan-Meier analysis, we defined the end point as recurrence of the tumor or death determined at follow- up examinations. The statistical significance of the recurrence-free survival rate was analyzed by Log rank test.

RESULTS

Outcome after Initial treatment

As for the initial operation, total tumor removal was achieved for 10 patients (Group A), three were children and seven adults. Subtotal tumor removal was achieved for the remaining 51 patients. Three patients of them (Group B) died within 30 days after operation. Surgical mortality was 4.9%. Operative morbidity occurred in 8% of the patients. CSF leakage occurred in 4 patients, in 2 of whom it resolved conservatively while remaining two patients developed meningitis managed with antibiotic therapy. One patient developed transient third nerve palsy that improved within 6 months.

The patients were followed up from 1 to 29 years. Final outcomes at the last follow-up indicate that among the Group A patient, six patients were functionally in good, one in fair and one in poor condition (Table 2). Two patients died; one after one year due to pneumonia and the other due to cerebrovascular accident after 23 years later. The functional status of the patients in Group B showed that 12 patients were in functionally good, five in fair and four in poor condition, and four patients died within two years of their first operation in addition to 3 surgical mortalities. The functional status of the patients in Group C at long-term follow-up showed that 17 patients were functionally in good, three in fair and one in poor condition (Table 2). Two patients died, one after five years due to pneumonia and the other after 16 years due to a road traffic accident.

TABLE 2. Final functional outcome at long-term follow-up after initial operation and reoperation.

	Number	Excellent or Good	Fair	Poor	Death*	Recurrence	Mean follow up (yrs.)
Initial operation							
Group A	**10**	**6**	**1**	**1**	**2 (0)*** **	**2**	**9.0 (1- 23)**
Group B	**28**	**12**	**5**	**4**	**7 (3)**	**15**	**8.6 (1- 27)**
Group C	**23**	**17**	**3**	**1**	**2 (0)*** **	**7**	**14.5 (1- 29)**
Total	**61**	**35**	**9**	**6**	**11 (3)*** **	**24**	**11 (1-29)**
Recurrence							
Group a	**4**	**1**	**1**	**0**	**2 (2)**	**0**	**8.5 (8 - 9)**
Group b	**19**	**2**	**5**	**7**	**5 (2)**	**10**	**3.0 (1 - 10)**
Group c	**7**	**4**	**0**	**3**	**0**	**2**	**6.3 (3 - 12)**
Group d	**7**	**6**	**0**	**1**	**0**	**1**	**4.2 (2 - 7)**
Total	**37****	**13**	**6**	**11**	**7 (4)**	**13**	**4.1 (1 - 12)**

*** (): surgical mortality**

****: 35 surgical procedures were undertaken for 22 patients and two patients treated with radiosurgery o**

***** death due to unrelated cause (2 cases of Group A and 2 of Group C)**

Postoperative visual improvement or normal vision was seen in 45 (77.6%) of the patients (Table 3). Group A showed improved or normal visual function in 80% and no

TABLE 3. Results of visual acuity and visual field.

	Number	Normal or Improved	No Change	Worse
Initial operation				
Group A	10	8 (80%)	2 (20.0 %)	0
Group B	25	19 (76%)	6 (24.0 %)	0
Group C	23	18 (78.3%)	5 (21.8%)	0
Total	58*	45 (77.6%)	13 (22.4%)	0
Recurrence				
Group a	4	2 (50%)	1 (25%)	1 (25%)
Group b	19	15 (78.9%)	2 (10.5%)	2 (10.5%)
Group c	7	5 (71.4%)	2 (28.6%)	0 (0%)
Group d	7	6 (85.7%)	1 (14.3%)	0 (0%)
Total	37	28 (75.7%)	6 (16.2%)	3 (8.1%)

*Three patients were excluded because of post-operative death.

change in visual function in 20%. Almost the same results were seen in Group B and C. Hormonal replacement was required in 53 patients (86%) (Table 4). Hormone replacement therapy was required for 90% of the patients in Group A, 79% of those in Group B and 96% of those in Group C. All the patients in Group A, 50% of Group B and 74% of Group C developed postoperative diabetes insipidus (DI) and were treated with desmopressin

TABLE 4. Hormone replacement required after operation

	Number	**None**	**Ant. Pituitary hormone**	**Desmopressin**
Initial operation				
Group A	**10**	**0 (0%)**	**9 (90%)**	**10 (100%)**
Group B	**28**	**5 (18%)**	**22 (79%)**	**14 (50%)**
Group C	**23**	**1 (4%)**	**22 (96%)**	**17 (74%)**
Total	**61**	**6 (10%)**	**53 (86%)**	**41 (67%)**
Recurrence				
Group a	**4**	**0 (0%)**	**4 (100%)**	**4 (100%)**
Group b	**19**	**0 (0%)**	**19 (100%)**	**18 (95%)**
Group c	**7**	**0 (0%)**	**7 (100%)**	**7 (100%)**
Group d	**7**	**0 (0%)**	**7 (100%)**	**5 (71%)**
Total	**37**	**0 (0%)**	**37 (100%)**	**34 (92%)**

(DDAVP). Thus DI was unavoidable after total removal.

Two of 10 patients in Group A, 15 of 25 patients in Group B, and 7 of 23 patients in Group C experienced recurrence during the mean follow-up period of 11years (Table 2). Recurrence-free survival probabilities were computed with the Kaplan-Meier technique (Figure 1). The cumulative 10-20 years rate of recurrence-free survival was 79% for Group A, 15% for Group B and 67% for Group C, respectively. For Group B, the 5-year rate was 36%. Log rank statistical analysis demonstrated a statistically significant difference both between Group A and B ($p = 0.013$) and between Group B and C ($p = 0.002$).

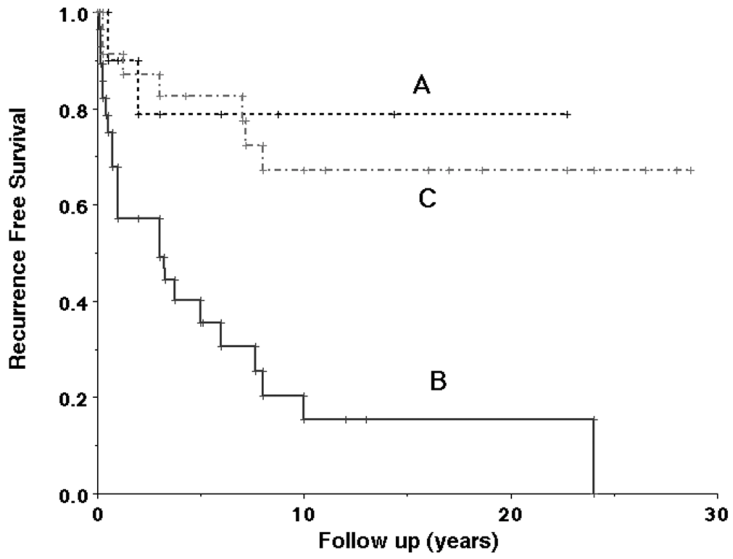

Figure 1. Recurrence-free survival rate after initial therapy as calculated with the Kaplan Meyer method. Group A represents patients who underwent total surgical resection, Group B those who were treated with subtotal surgical resection only and Group C those who were treated with subtotal surgical resection followed by radiotherapy. The graph demonstrates recurrence-free survival was 79% for Group A, and 67% for Group C at 10- 20 years. For Group B the recurrence-free survival was 36% at 5 years and 15% at 10 years. Log rank analysis indicated a correlation between Groups A & B of $P = 0.013$ and between Groups B and C of $P = 0.002$. Both values of P are statistically significant.

Outcome after recurrence

Twenty-two patients underwent a total of 35 additional operations for recurrence. Four patients died in the postoperative period (Table 2). The surgical mortality was 11.4%. The survival rate for Group a was 50% and for Group b 73.7% while 100% for Groups c and d. At follow-up, patients were in satisfactory condition of 35%, in fair 16% and in poor 30%, respectively. Functional status at the follow-up in Group a was good in one patient and fair in the other. In Group b, two patients were in good, five in fair and seven in poor functional condition. The numbers for Group c were four patients in good and three in poor functional condition, and for Group d, six and one, respectively (Table 2). Thus good functional status

was maintained at follow-up in 50% of survived patients for Group a, 14% for Group b, 57% for Group c and 86% for Group d.

After reoperation, visual function deteriorated in 25% and 10.5% of the patients in Groups a and b respectively (Table 3), whereas there was no deterioration in Groups c and d. All patients required hormone replacement therapy after recurrence (Table 4). Finally 100% of the patients in Group a, 95% in Group b, 100% in Group c and 71% in Group d developed diabetes insipidus.

Second recurrence was seen in eight, third in three and fourth in two patients in spite of additional treatment. The Kaplan-Meier graph demonstrated that 5-year recurrence-free survival for Group a was 50%, for Group b 16%, for Group c 80% and for Group d 83.3% (Figure 2). The 10-year recurrence-free survival for Group c was 60%. Comparison of Groups a and b showed a p-value of 0.35 which was not significant. It was significant for Groups b and c (p = 0.004) and for Groups b and d (p = 0.001).

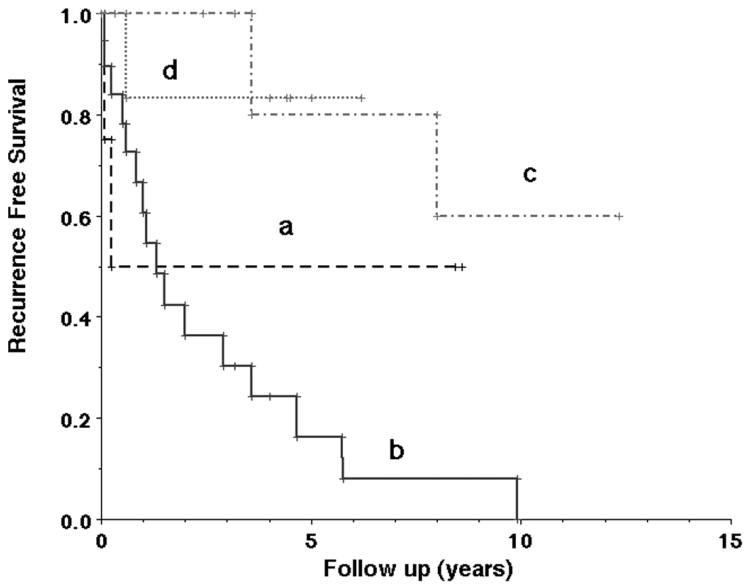

Figure 2. The recurrence-free survival rate after recurrence calculated with the Kaplan Meyer method. Group a represents those who underwent total surgical resection at reoperation, Group b patients treated with subtotal surgical resection only, Group c those treated with subtotal surgical resection followed by radiotherapy and Group d, those treated with radiosurgery. The recurrence-free survival was 50% for Group a, 16% for Group b, 80% for Group c and 83.3% for Group d at 5 years. The *P* value, estimated by log rank test, for the relationship between Groups a and b is 0.35, which is not significant.
Correlations between Groups b and c, (*P* = 0.004) and between Groups b and d, (*P* = 0.001), are statistically significant.

DISCUSSION

The close proximity and strong attachment of craniopharyngiomas to the adjacent nervous and vascular structures prevent the surgeon from total excision for fear of damaging these structures. The capsule of a craniopharyngioma is so closely attached to the hypothalamus and other neurovascular structures that complete excision of the tumor is not easy in all cases and sometimes impossible (32). Van Effenterre and Boch reviewing large surgical series reported in the literature on craniopharyngioma found that total removal has ranged from 6% to 90% (10). In the report by the Brain Tumor Registry of Japan it was seen that from 1981-1993 only 20.1% patients with craniopharyngioma underwent total surgical resection (22). The recurrence rate ranged between 30 and 50% (5, 7, 13, 23, 25, 26) according to some reports published before 80's, with only a few authors reporting better results. However, recent publications show a tendency for the recurrence rate to decrease (4, 8, 13, 17, 18, 27, 28, 30, 31, 32), mainly due to the development of microsurgical and neuroimaging studies.

The optimal treatment of recurrent craniopharyngioma is still controversial. Surgery should be considered as the first choice of treatment among therapeutic modalities for recurrent craniopharyngiomas although it is more difficult than primary operation (6, 24). Some surgeons have advocated selective surgical treatment of recurrent craniopharyngiomas (8, 13, 21, 31) but others have opted for surgical treatment of all such cases (6, 11, 32). However previous manipulation of a tumor either surgically or by irradiation can produce such strong adhesion that the tumor capsule becomes firmly adherent to the contagious structures so that curative surgery is not possible for all cases. Some surgeons (5, 12, 23, 29) reported higher mortality, morbidity and failure to achieve a total tumor resection than for surgery of virgin tumors. Yasargil et al.'s series showed a dramatic difference in mortality and serious morbidity rates between patients who underwent only primary complete microsurgical excision and those who underwent a second or subsequent craniotomy (32).

In our series, recurrent tumors could be totally removed only in 11.4%. Furthermore, the surgical mortality of recurrent cases was 11.4% while it was 4.8% for initial cases. Fahlbusch et al., reported, an operative mortality rate of 1.1% for patients who underwent primary resection and of 10.5% for tumor recurrence (11). Our results are thus in agreement with the literature, which demonstrates a higher mortality and morbidity rate associated with surgery for tumor recurrence. Fahlbusch (11) reported 77.7% of their patients were independent following primary transcranial surgery compared to 57.9% of those who underwent transcranial surgery for recurrence. Yasargil et al (32) reported that among children, 72.5% showed a good outcome following primary surgery and 61.4%, after reoperation, and among adults, the corresponding rates were 80.3% and 73%. Long-term survival was 59.4% after secondary microsurgery compared to 90% for primary tumors. In our data in Table 2, the functional outcomes were worse in recurrent tumors. There were nearly 10% of poor outcomes in the patients with initial operations. However, 30% in those with recurrent patients, it may be due to the previous manipulation either surgically or by irradiation produced strong adhesions with the surrounding structures such as hypothalamus and other neurovascular structures.

Of the patients with primary tumors with normal visual function 13% suffered a post operative deficit, whereas 75% of those with recurrent tumors had permanent visual deficits (8). Our data showed worsening of visual function following surgery of recurrent tumors whether total or subtotal removal. After recurrence, all patients in our series required hormone replacement therapy. Postoperative endocrinological replacement was required for 100% of all groups of recurrent patients, while 90% of Group A, 79% of Group B, and 96%

patients of Group C required hormone replacement after initial surgery. After recurrence, diabetes insipidus developed among the 100% of the patients of Groups a and c, 95% of those in Group b and 71% of those in Group d.

Radiotherapy is generally regarded as beneficial for patients with residual or recurrent craniopharyngioma and has a very high salvage rate after local recurrence following surgery (14, 19). Reoperation after tumor recurrence or after radiation therapy is considerably more difficult than after a primary operation and carries a higher mortality and morbidity (11, 23, 27, 32), so that this modality is reserved for cases where it is thought that the tumor can not be removed completely by surgery (11, 23, 27). Amacher et al. reported the actual destruction of residual tumors by radiotherapy (3). In one series the 10-year progression-free survival and survival from the time of recurrence were 72% and 77%, respectively (15) while in another series of recurrent craniopharyngioma treated with radiotherapy, the 10 and 15 year progression free survival were 72% and 72% respectively (14). After radiotherapeutic treatment of recurrent tumors in our series, the recurrence free survival rate for Group c was 80% at 5 years and 60% at 10 years. Richmond et al. (23) recommended minimum surgery plus radiotherapy for the cystic or mixed type tumors. Seven of our patients with recurrent craniopharyngioma were treated with subtotal removal followed by radiotherapy, resulting in a mean of 6.3-year (range 3-12 year's) follow-up and tumor-free survival 71.4%. Visual dysfunction improved in 71.4% of the patients and remained unchanged in 28.6%. All required hormone replacement therapy and all had diabetes insipidus. In case of the fractionated radiation therapy, optic nerve is relatively resistant to irradiation and rate of deterioration of visual function was negligible as mentioned by Jose CC et al (14). Our data indicate that radiotherapy had a beneficial effect after recurrence on survival time whether the tumor was cystic or solid, and in addition current technology minimizes radiation damage to adjacent neural structures.

Gamma knife surgery is effective for achieving long-term control of tumors without compromising the quality of patient survival. Mokry (20) reported that radiosurgery achieved reduction in the volume of the residual tumor in 74% of the patients. Chung et al. (9) reported that in their series of 31 patients, gamma knife radiosurgery was used as the initial treatment for six patients and for recurrent tumors in 25 patients. Tumor control was achieved in 87% of patients, while 84% showed fair to excellent clinical outcomes in an average follow-up period of 36 months. Their treatment resulted in failure for four patients. Kobayashi et al. (16) reported that after treatment with radiosurgery with a mean follow-up of 13.9 months, 70% of their patients showed marked shrinkage and 30% central necrosis within 6 months after the treatment and regression continued more than 2 years without significant deterioration of clinical signs and symptoms. In our series, seven patients with recurrent craniopharyngioma were treated with radiosurgery. With a mean follow-up of 4.2 years, tumor control was seen in 85.7% while visual dysfunction improved in 85.7%. All patients required hormone replacement and five (71%) patients had diabetes insipidus. Since conventional radiotherapy carries the risk of damaging the hypothalamus and the optic pathway, it would appear that gamma knife surgery may be superior to in this respect if this treatment modality is applicable (9).

CONCLUSIONS

Surgery aiming at total removal should be the therapeutic option for treatment of recurrent as well as primary craniopharyngiomas provided that the patient's clinical condition does not preclude such a procedure. For recurrent craniopharyngiomas, the recurrence-free survival time was longer for patients who were treated with subtotal resection followed by radiotherapy or radiosurgery with better functional outcome.

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