preserve hearing, we focused on avoiding high-dose irradiation to the acoustic and/or cochlear nerve during dose planning.

Our analyses suggested that high-dose treatments (≥ 3.5 Gy/min) apparently carry the greatest risk of transient tumor expansion ($p = 0.877$), but the difference was not statistically significant. Additional follow-up of patients with VS will allow us to draw a more definitive conclusion regarding risk factors associated with transient tumor expansion after GKS.

Conclusions

Transient expansion after GKS for VS was found to be much more frequent than previously reported, strongly suggesting a correlation with deterioration of facial and trigeminal nerve functions. However, the present study revealed neither prognostic factors influencing this phenomenon nor the underlying mechanisms.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Low-dose Craniospinal Irradiation and Ifosfamide, Cisplatin and Etoposide for Non-metastatic Embryonal Tumors in the Central Nervous System

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Objective: The current study was conducted to evaluate the effects of low-dose craniospinal irradiation (CSI) combined with chemotherapy on non-metastatic embryonal tumors in the central nervous system (CNS), including medulloblastoma and supra-tentorial primitive neuroectodermal tumors (ST-PNET).

Methods: All patients were treated according to the following protocol. After surgery, the patients ≤5 years old received 18 Gy and the patients >5 years old received 24 Gy CSI. The dose to the primary tumor bed was 39.6–54 Gy. Chemotherapy consisted of ifosfamide, cisplatin and etoposide (ICE chemotherapy).

Results: Sixteen patients aged 0.5–20.4 (median 6.1) years were enrolled and followed for 11–165 (median 112) months. Both 5-year actuarial overall survival (OAS) and progression-free survival (PFS) were 81% (95% confidence interval (CI): 62–100%) for the 16 patients. Both 5-year OAS and PFS were 82% (CI: 59–100%) for the patients with medulloblastoma and 80% (CI: 45–100%) for the patients with ST-PNET. Both 5-year OAS and PFS were 75% for the eight patients ≤5 years old and 88% for the eight patients >5 years old. Both 5-year OAS and PFS were 100% for six average-risk patients (3 years or older, total resection and posterior fossa) and 70% for 10 poor-risk patients (others). The median total intellectual quotient at the last follow-up was 85 (ranging from 48 to 103) in 12 patients who were followed for 3–145 (median 49) months. Eight patients received hormone replacement therapy.

Conclusion: Low-dose CSI and ICE chemotherapy may have a role as a treatment option for a subset of patients with non-metastatic embryonal tumors in the CNS.

Key words: medulloblastoma – primitive neuroectodermal tumor – chemotherapy – radiotherapy – late effect

INTRODUCTION

The standard therapy for medulloblastoma has been 35–36 Gy craniospinal irradiation (CSI) and 54–55.8 Gy to the tumor bed after surgical resection (1). A recent randomized trial has shown that a combination of pre-radiotherapy intensive chemotherapy and 35 Gy CSI was significantly better in outcome than 35 Gy CSI alone for non-metastatic medulloblastoma in terms of event-free survival and possibly overall survival (OAS) (2). However, since CSI has produced neuro-cognitive dysfunction and endocrine deficiency in young children and infants (3), dose reduction in CSI with or without chemotherapy has been tested. A total of 25 Gy of CSI was associated with the poorer outcomes in multi-institutional phase III trials with or without chemotherapy (4,5). Subset analysis, however, showed that for patients treated with radiotherapy alone, event-free survival at

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5 years was identical between 25 and 35 Gy CSI (4). Pilot studies and a multi-institutional phase II study suggested that 23.4–30 Gy CSI with pre- or post-radiation chemotherapy could achieve similar results with standard-dose CSI for average-risk medulloblastoma (6–8). Important questions remain with respect to the radiotherapy dose in CSI for medulloblastoma. To reduce the incidence of the late adverse effects of CSI, we performed a prospective protocol study using reduced-dose CSI sandwiched between chemotherapy that consisted of an ifosfamide, cisplatin and etoposide (ICE) regimen.

Patients with supra-tentorial primitive neuroectodermal tumors (ST-PNET) have clinical features different from those with medulloblastoma (9–12). However, these two diseases were categorized as the embryonal tumors in the WHO classification of brain tumor (9). Because of the similarity in pathological features, these two diseases have been often treated similarly (13,14). We have also determined the treatment strategy for ST-PNET to be similar to that of medulloblastoma with regard to maximal surgical resection, intensive chemotherapy and radiotherapy. Patients with ST-PNET were also entered and evaluated in this study.

In this study, we have evaluated long-term outcome, both in survival and adverse effect of patients with non-metastatic medulloblastoma and ST-PNET, or embryonal tumors in the central nervous system (CNS).

MATERIALS AND METHODS

Selection Criteria

Entry criteria for patients were as follows: the age between 6 months and 30 years, and with histologically proven medulloblastoma or ST-PNET. The patients or guardians had to give informed consent prior to surgery and again prior to adjuvant therapy.

Treatment

The flow chart of the treatment strategy is shown in Fig. 1.

Total surgical resections were attempted in patients with medulloblastoma who had Chang's Stage T1, T2 or T3a without evidence of metastasis (Stage M0) (15). Brainstem origin tumors were biopsied or partially removed. Patients with ST-PNET without evidence of metastasis were also treated at first with maximum surgical resection. Ventriculostomy, but not venticuloperitoneal shunting, was performed at tumor removal in patients with hydrocephalus.

Patients with either medulloblastoma or ST-PNET received ICE chemotherapy and CSI with a generous local boost to the tumor site (16). The ICE regimen consisted of three agents; ifosfamide at 900 mg/m^2 (Days 1–5), cisplatin at 20 mg/m^2 (Days 1–5) and etoposide at 60 mg/m^2 (Days 1–5) every 4 weeks. To prevent hemorrhagic cystitis and to suppress emesis, sodium 2-mercaptoethane sulfonate (810 mg/m^2/day) and granisetron hydrochloride (40 or 80 mg/kg/day), a 5-hydroxy-tryptamine receptor antagonist, were intravenously administered from Day 1 to 5. Hydration, including the infusion of mannitol, was done routinely.

In principle, the ICE chemotherapy regimen should have begun within 2 weeks of the surgery. The intent was for the ICE chemotherapy regimen to begin within 2 weeks of the surgery, but this did not always occur, as the timing of the chemotherapy and radiotherapy varied. Patients <2.5 years old received eight cycles of chemotherapy every 4 weeks and then received 18 Gy CSI and a local boost of 30–36 Gy when they became 2.5 years old. For patients between 2.5 and 5 years old, one course of ICE followed by 18 Gy CSI and a local boost of 30–36 Gy were scheduled. For patients <5 years old, one course of ICE followed by 24 Gy CSI and a local boost of 30 Gy were scheduled. Thus, the irradiation dose to the hypophysis and hypothalamus was 18 Gy for patients 5 years old or younger and 24 Gy (20–30) for patients >5 years in medulloblastoma. For patients with ST-PNET, the dose to the hypophysis and hypothalamus was distributed from 18 to 38 Gy.

After the radiotherapy, up to six cycles of ICE was administered to the patients 2.5 years old or older. The intent was for patients to receive CSI immediately followed by the local tumor boost, but if myelosuppression had been prolonged by the ICE before radiotherapy, they received local irradiation first, followed by CSI.

Whole-brain irradiation was performed using nearly parallel-opposed lateral fields with multi-leaf collimators to block the lenses of both eyes and including all cerebrospinal fluid space. Whole-spinal irradiation was performed using posterior single or two serially arranged posterior fields including all cerebro-spinal fluid space leaving the patient in the same position on the table. Dose distribution was calculated using a three-dimensional radiotherapy planning

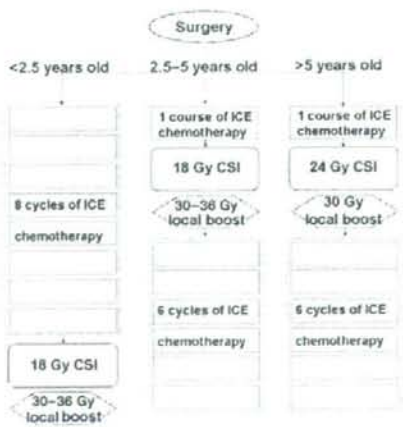

Figure 1. Flow chart of the treatment strategy. ICE chemotherapy, ifosfamide, cisplatin and etoposide; CSI, craniospinal irradiation

system. The radiotherapy dose was prescribed at the center of the midline for the whole brain and at the mean depth of the spinal canal. The boost to the posterior fossa in medulloblastoma and to the tumor bed in ST-PNET was performed using two angled and wedged fields to reduce the dose to the ear structures, temporal and posterior lobes for medulloblastoma. In patients treated in the latter half of the study period, three or more non-coplanar fields were used to reduce unnecessary dose to the surrounding structures. Daily fractions of 1.8–2.0 Gy were used at the isocenter.

Toxicity-related Dose Adjustment for the ICE Regimen

All patients underwent urological and audiological examination and renal monitoring before each cycle of chemotherapy. The chemotherapy doses were modified if there was any evidence of hematological, renal or audiological toxicity according to the dose-reduction criteria (16). If the creatinine clearance was <70%, cisplatin was omitted for that cycle and only given thereafter if renal or hearing function improved. Routine urological examination was performed from Day 1 to 5 in each cycle. Ifosfamide was omitted if macrohematuria was observed and was begun again when microscopic hematuria disappeared. Etoposide and ifosfamide were reduced according to the myelosuppression score consisting of the blood count nadir and symptoms related to the previous course of ICE (16). The score was cumulative overall courses. When using this method, the next cycle would be omitted if the score was higher than anticipated for a long time without recovery.

Follow-up

Patients were followed-up by regular clinical examination. The follow-up intervals after the end of the treatment were every month in the first year, every 3 months in the second year, every 4 months in the third year and subsequently every 6 months. Repeat cranial MRIs with or without spinal MRI were performed every 3 months in the first year and every 6 months in the second to fifth years. After that, the follow-up was performed annually at our institution or at local hospitals.

Statistical Methods

The final analysis was performed in March 2007. OAS and PFS were analyzed. OAS was calculated as the time from the date of surgical diagnosis to the date of death. Patients still alive were censored at date last seen. Subjects with average risk included children >3 years of age with posterior fossas and those with tumors that were totally or 'nearly totally' (≤1.5 cc of residual disease) resected. Subjects with poor risk included children <3 years of age and/or those with subtotal resection (>1.5 cc's residual disease) and/or a non-posterior fossa location, including supra-tentorial location (10,11,12,17,18).

PFS was calculated as the time from the date of surgery to the date of recurrence or death. In those cases where death followed recurrence, the date of recurrence was used. Kaplan–Meier survival curves were produced, and log-rank tests were performed to compare OAS. Greenwood's formula was used to calculate the standard errors, which were then used to calculate the CI. The *t*-test was used to compare the interval between surgery and radiotherapy between groups.

RESULTS

Sixteen patients aged 0.5–20.4 (median 6.1) years were enrolled and followed for 11–165 months with a median of 112 months. The characteristics of the patients are listed in Table 1. In total, both the 5-year actuarial OAS and PFS were 81% (95% confidence interval, CI: 62–100%) for the 16 patients (Fig. 2). Both 5-year OAS and PFS were 82% (CI: 59–100%) for patients with medulloblastoma and 80% (CI: 45–100%) for patients with ST-PNET. The 5-year OAS and PFS were both 100% (CI: 100–100%) for the six average-risk patients and 70% (CI: 42–98%) for the 10 high-risk patients (Fig. 3). There was no statistical difference between the two groups (OAS: $P = 0.35$; PFS: $P = 0.26$). OAS and PFS were 81% (CI: 62–100%) and 68% (CI: 44–99), respectively, at 7 years, and were 74% (CI: 53–96%) and 68% (CI: 44–99%), respectively, at 9 years.

All eight patients ≤5 years of age received 18 Gy CSI. One of these eight patients (No. 10) experienced dissemination of the disease at 11 months after surgery and died at 16 months after surgery. Another patient (No. 11) who underwent a biopsy followed by three courses of chemotherapy and radiotherapy died at 11 months after biopsy without disappearance of the disease. The other six patients are alive at 117–months after surgery without evidence of disease. The 5-year OAS and PFS for the eight patients were both 75% (CI: 45–100%).

In the eight patients >5 years old, 24 Gy CSI was given to six patients. The CSI was stopped at 20 Gy due to severe myelosuppression in one patient (No. 4), and an additional 6 Gy (i.e. 30 Gy CSI) was given to another patient (No. 7) because of a strong fear that surgery would disseminate the disease. The 5-year OAS and PFS for the eight patients were both 88% (CI: 65–100%). Local relapse was observed in two patients, and dissemination disease was observed in one patient. All patients received 24 Gy CSI. One of them was rescued by high-dose chemotherapy with stem cell transplantation and lived for 44 months after the diagnosis of relapse. There was no statistical difference between patients ≤5 years and patients >5 years of age (OAS: $P = 0.51$; PFS: $P = 0.69$).

The total amounts of chemotherapeutic agents are listed in Table 2. Because we used reduction criteria for each agent in each cycle of the treatment, the total amount of chemotherapeutic agent varied. Two patients experienced relapse of the local tumor during chemotherapy, and the treatment was

Table 1. The characteristics of patients

No.	Sex	Age (years)	Primary	T	Risk	Surgery	Interval (days)	CSI (Gy)	Local (Gy)	TTT (days)	Relapse (months × 1)	Survival (months × 1)	Status	Adverse effects (months × 2)	IQ(initial) × 3	IQ (last follow-up) × 4
1	M	0.5	Cerebellum	T2	High	Partial	584	18	39.6	63		127	Alive	Growth hormone deficiency (38) Thyroid hormone deficiency (18) Radiation-induced hemangioma (53)	92	100
2	M	1	Cerebellum	T3b	High	NT	275	18	48	125		165	Alive		98	74
3	F	5	Cerebellum	T2	Low	NT	45	18	48	245		143	Alive		101	92
4	M	7.2	Cerebellum	T2	Low	NT	21	20	50	53		103	Alive	Thyroid hormone deficiency (31)	103	—
5	M	7.6	Cerebellum	T2	Low	NT	40	24	50	43	Local (76)	120	Dead	Corticosteroid deficiency (82) Thyroid hormone deficiency (49)	85	78
6	F	8.8	Cerebellum	T2	Low	Total	6	24	54	45		95	Alive	Thyroid hormone deficiency (12)	94	96
7	F	12.6	Cerebellum	T3a	Low	Total	37	30	54	49		113	Alive	Thyroid hormone deficiency (33)	68	73
8	M	20.4	Cerebellum	T2	Low	Total	7	24	50	255		111	Alive		—	—
9	F	1.2	4th ventricle	T3a	High	Total	22	18	46	40		134	Alive	Growth hormone deficiency (38) Antidiuretic hormone (ADH) deficiency (36)	79	—
10	M	1.9	4th ventricle	T3a	High	NT	262	18	50	52	Dissemin. (11)	16	Dead		—	—
11	F	2.5	pons	T3b	High	Biopsy	64	18	54	47	Local (0)	11	Dead		—	—
12	M	1.6	lt. parietal	—	High	NT	47	18	48	42		117	Alive		103	86
13	F	2.5	lt. parietal	—	High	NT	64	18	50	64		134	Alive	Corticosteroid deficiency (57) Thyroid hormone deficiency (63) Gonadotropin deficiency (115)	58	48
14	F	10.5	rt occipital	—	High	NT	22	24	54	45	Dissemin. (72)	88	Dead	Thyroid hormone deficiency (35)	—	—
15	F	12.3	rt. temporal	—	High	NT	28	24	54	49	Local (22)	28	Dead		85	—
16	M	14.3	rt occipital	—	High	NT	33	24	54	55		70	Alive		85	—

T, T stage; Interval, interval between surgery and radiotherapy; NT, nearly total resection; CSI, cerebrospinal irradiation dose; Local, local total irradiation dose; TTT, total treatment time; dissemin., dissemination; months × 1, months from surgical diagnosis; months × 2, months from the completion of all therapy at the onset of the disease or the start of hormonal supplement; IQ(initial) × 3, IQ score for the first time; IQ(last follow-up) × 4, IQ score at the last follow-up if IQ test was conducted more than once.

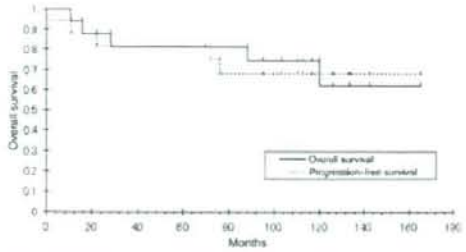

Figure 2. Overall and progression-free survival curves for 16 patients with non-metastatic embryonal tumors in the central nervous system.

stopped after three courses. The regimen of chemotherapy was changed in one patient after relapse, and a salvage operation was performed in another patient for the relapsed tumor.

Total intellectual quotient (IQ) was measured in 12 patients with the follow-up period ranging from 3 to 145 months with a median of 49 months (Fig. 4, Table 1). The median total IQ at the last follow-up was 85 (ranging from 48 to 103). In nine patients who were able to undergo the examination for verbal IQ (VIQ) and performance IQ (PIQ), there was no apparent discrepancy between VIQ (median 82, 95%CI: 48–119%) and PIQ (92, 58–113%) ($P = 0.75$). In eight patients whose total IQ was measured more than twice during the follow-up (median follow-up 78, 19–145%), two patients, whose latest IQ scores were 74 and 86, respectively, showed apparent deterioration in total IQ of >10 points (−24 and −17 points).

Eight patients received hormone replacement therapy because of deficiencies in thyroid hormone, corticosteroid hormone, growth hormone, antidiuretic hormone or gonadotropin (seven, two, two, one and one patients, respectively). Irradiated dose to the hypophysis and hypothalamus of the eight patients were 18–32 Gy (median 22 Gy). Two of the eight patients had ST-PNET.

No patients suffered from symptomatic hearing deficiency or required hearing aids. One patient experienced hemangioma in the skull in the irradiated region 4.4 years at the region which received 18 Gy and underwent surgical removal of the tumor.

Table 2. The nominal cycles of chemotherapy and the actual amount of chemotherapeutic agents

No.	Nominal cycles	Ifosfamide	Cisplatin	Etoposide
1	8	6.7	8	6.25
2	7	6.66	7	7
3	8	8	8	8
4	7	1.75	6	5.4
5	8	2	8	8
6	6	1	6	6
7	6	2.35	5.25	4.95
8	6	6	5	6
9	8	6.05	7	6.05
10	7	5.85	6	6
11	3[1]	3	3	3
12	8	4.45	5.45	6
13	8	3.95	7.2	7.2
14	6	1.75	5	4.75
15	3[1]	2.35	2.75	2.35
16	6	2.95	6	6

The dose of each agent is shown in respect of the dose for one cycle.
[1]Stopped due to relapse during the treatment.

DISCUSSION

For medulloblastoma, the results of a multi-institutional study confirmed that low-dose CSI cannot be justified with or without chemotherapy (4,5). However, the possibility of serious late complications related to radiotherapy after standard-dose CSI suggests that we should investigate better treatment options with less morbidity. Packer et al. (6) have shown that reduced-dose craniospinal radiation therapy (23.4 Gy) followed by adjuvant chemotherapy of lomustine 75 mg/m^2, vincristine 1.5 mg/m^2 and cisplatin 75 mg/m^2 for average-risk patients can achieve PFS of 79 ± 7% at 5 years for average-risk medulloblastoma. Recently, Packer et al. have conducted a phase III trial for average-risk patients in which they compared the adjuvant chemotherapy described above

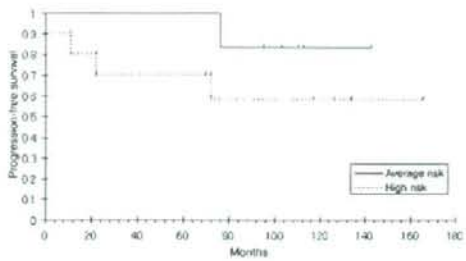

Figure 3. Progression-free survival curves for six patients with average risk and 10 patients with high risk of non-metastatic embryonal tumors in CNS.

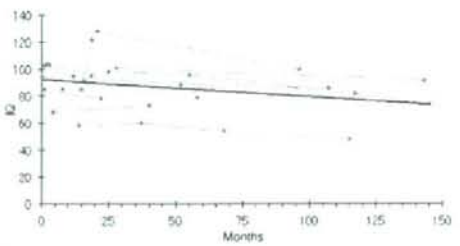

Figure 4. Temporal change of total intellectual quotient for 12 measurable patients with the regression line.

with a therapy in which cyclophosphamide was substituted for lomustine with the same low-dose craniospinal radiation therapy (23.4 Gy). They found that either choice of chemotherapy resulted in similar event-free survival rates: 82 ± 2.8% for chemotherapy with lomustine and 80% ± 3.1% for that with cyclophosphamide (19). Gajjar et al. (20) performed a prospective study of risk-adapted radiotherapy followed by chemotherapy in children with average-risk and high-risk medulloblastoma. In their analysis, 5-year event-free survival was 83% (73–93%) for the average-risk group, which received 23.4 Gy craniospinal radiotherapy, and 70% (55–85%) for the high-risk group, which received a conventional dose of 36–39.6Gy. They compared decreases in IQ and found that the difference between the low-dose craniospinal radiotherapy group and the conventional dose group was not statistically significant ($P = 0.097$) (21). The present study was consistent with their studies, showing similar survival rates and a moderate decrease in IQ. The reduced-dose CSI and chemotherapy may be as effective as standard CSI in terms of tumor control and neuro-cognitive function in long-term follow-up.

The combination of 18 Gy CSI and chemotherapy has been tested in 10 patients in a previous clinical trial, and seven of the 10 patients survived >5 years (22). Six out of eight patients ≤ 5 years old received 18 Gy CSI and survived >9 years in the present study. If we combine our results involving eight patients with these 10 patients in the literature, 13/18 survived longer than 5 years. The 5-year survival rate is not inferior to the previous results obtained with a higher CSI dose. However, Jakacki et al. (23) have reported that the administration of 1800 cGy CSI with chemotherapy to seven patients aged from 20 to 64 months was not advisable because of the high recurrence rate. Again, the number of patients was too small to exclude the possibility of a bias.

The superiority of low-dose CSI to conventional CSI for the purpose of reducing the late adverse effects remains a subject of debate (24,25). A full-scale IQ <80 was reported to be observed even in children with brain tumors who received irradiation only at the posterior fossa (26). Oyharcabal-Bourden et al. (27) have shown that the median total IQ in the follow-up was reported to be 83, and hormone replacement therapy was required in 41.9% of the patients who received adjuvant chemotherapy followed by 25 Gy craniospinal radiation therapy. Our results, which included a median total IQ of 85 and a requirement of hormone replacement therapy in 50% of the patients, were highly consistent with their study.

Treatment outcome of patients with ST-PNET has been reported to be poorer than that of those with medulloblastoma (10–11), and thus patients with ST-PNET are now treated with intensive chemotherapy in clinical trials (12). Because of the cerebral location of ST-PNET, the neuro-cognitive function is usually much poorer in these patients than in those with medulloblastoma. Our series is too small to be compared with the previous larger series, but the treatment outcome was comparable to other poor-risk patients with medulloblastoma. Careful evaluation of the long-term outcome of recent high-dose chemotherapy studies with low-dose radiotherapy for ST-PNET are warranted.

It has recently been suggested that three-dimensional conformal radiotherapy is useful for reducing the dose to the ear structures (28). Intensity-modulated radiotherapy (IMRT) was reported to reduce the dose more, but we must be careful about inducing secondary cancer due to increased whole-body irradiation by IMRT (29). The fact that one patient developed radiation-induced hemangioma in our study showed the importance of reducing unnecessary irradiation in children.

Remarkable advances in molecular biology have led us to routinely use molecular markers to select patients who would be cured with low-dose CSI and those who would respond to chemotherapy. Promeroy et al. have reported that micro-array analysis may be effective for dividing patients with medulloblastoma into favorable and unfavorable groups (30). Gajjar et al. (31) have found a possible relationship between the expression of erbB2 and PFS. Rutkowski et al. (32) have shown that the definitions of favorable and unfavorable risk groups can be improved by the determination of c-myc and trkC mRNA expression. A combined clinical and molecular staging system may well be the breakthrough to accurately predicting disease risk for patients with embryonal tumors in CNS.

The greatest shortcoming of this paper is the small number of patients. Also, combining patients with medulloblastoma and ST-PNET makes it difficult to compare our study with the previous literatures. However, the long-term follow-up of the patients in a single institution has added some potentially important findings. Our experience can be added as supplemental data suggesting a possible role for reduced-dose CSI and chemotherapy in patients with non-metastatic medulloblastoma and ST-PNET.

In conclusion, the combination of surgical resection, ICE chemotherapy and low-dose CSI may have a role in the treatment of a subset of patients with embryonal tumors in the CNS. The possibility of reducing the risk of late neuro-cognitive damage through reduction of the CSI dose is to be further evaluated.

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Conflict of interest statement

None declared.

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CLINICAL STUDY - PATIENT STUDY

Late recurrence and salvage therapy of CNS germinomas

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Abstract Central nervous system (CNS) germinoma is a curable tumor and its recurrence rate after initial therapy may be approximately 10% or higher. This study elucidates the time-course of recurrence and results of salvage therapy. Twenty-five patients with recurrent germinoma treated at Hokkaido University Hospital were retrospectively reviewed. The median age at initial treatment was 12 years (range: 8–37). All patients had been tumor-free for at least 6 months after the initial treatment. The median follow-up period was 134 months (range: 44–338). The median age at first recurrence was 18 years and the median time to the first recurrence was 50 months. Among the patients, 9 (36%) had the first recurrence at 60 months or later. The latest recurrence in a patient occurred 230 months after the initial treatment. The results of salvage therapy were estimated in all 25 patients. Seventeen patients (68%) were salvaged and were tumor-free at the final observation. The remaining 8 patients died of disease. At first recurrence, 11 patients were treated using radiation therapy with or without surgery and 7 out of the 11 patients died due to the recurrent tumor. On the other hand, 13 patients who received salvage chemotherapy and radiotherapy were tumor-free at the last follow-up. In conclusion, late recurrence is not a rare event in patients with CNS germinoma. To identify a true cure rate of this disease, a 10-year or longer observation period may be required. As a salvage therapy, platinum-based chemotherapy followed by wide-field low-dose radiation therapy appears to be effective.

Keywords Central nervous system · Germinoma · Intracranial · Recurrence · Salvage therapy

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Introduction

It has been reported in large series that in patients with gonadal germinoma (seminomas), a counterpart of central nervous system (CNS) germinomas, late recurrences are relatively rare [7, 14, 29], and thus, follow-up for detecting recurrence may not be needed after 5 years [17, 18, 24, 32]. CNS germinoma, as well as gonadal germinoma, is sensitive to both radiotherapy and platinum-based chemotherapy, and patients have a good prognosis with overall survival of approximately 90% at 5 years [2, 10, 15, 16, 19, 21, 25, 26]. Therefore, late recurrence of germinoma may be an exceptional event similar to that of gonadal germinoma.

CNS germinoma is a rare malignancy in childhood accounting for only 1–2% of primary CNS tumors. Although the overall survival rates of patients with germinoma treated with various therapeutic methods have been reported in the literature, reports focusing on its recurrence rate and time-course of recurrence are scarce due to its rarity and the short follow-up periods of the previous studies [1–4, 9–12, 15, 16, 19, 21, 25, 26, 28, 31].

In particular, late recurrence of germinoma beyond 5 years is unknown. Elucidation of the time-course of recurrence may provide insight on the necessary duration of observation in outpatient clinics. We assessed 25 patients with recurrent germinoma after a complete remission induced by various initial therapies. In addition, to determine the optimal therapy for recurrent CNS

germinomas, the results of salvage therapies in 23 patients with adequate follow-up periods were estimated. It should be noted that we reported the preliminary results of 13 patients in this series in 1999 [23].

Materials and methods

Clinical materials

A series of 25 patients who had recurrent CNS germinoma were retrospectively assessed from a review of clinical records over the past 33 years, since 1973 when computed tomography scans became routinely available at Hokkaido University Hospital. The tumor recurrence was found either by routine follow-up CT or MRI, or appearance of clinical symptoms. Three patients were referred to our institute at the time of recurrence. The other 22 patients received initial therapy at our institution; during this period 133 patients with primary CNS germinoma were treated. The median age of the 25 patients at initial treatment was 12 years (range: 8–37). There were 23 male and 2 female patients. Primary tumors were localized in the pineal region in 8 cases, the suprasellar (neurohypophyseal) region in 5 cases, hypothalamus region in 3 cases, basal ganglia in 3 cases, and multiple regions in 6 cases. The median age at first recurrence was 18 years (range: 10–43). The median follow-up period from the initial treatment to the final observation was 126 months (range: 44–303).

All patients had achieved a complete remission after initial therapy that varied for each patient, and had been tumor-free for at least 6 months. The level of serum human chorionic gonadotropin (hCG) or hCG-beta was recorded as positive in 13 patients at their onset of disease. However, using current methods to measure hCG, it has been determined that almost all germinomas produce hCG. In this study, therefore, hCG-producing germinoma was not distinguished from non-secreting germinoma precisely at recurrence.

The levels of hCG-beta of all 25 cases were either low or negative at the time of recurrence and the levels of AFP were within the normal range in all cases.

Initial therapy at the onset of disease

Ten patients were treated with conventional high-dose (>45 Gy) radiation therapy and one patient underwent radiosurgery alone using Gamma Knife. The other patients received non-platinum based chemotherapy followed by conventional high-dose radiation therapy. Since 1992, 12 patients have been treated with platinum-based chemotherapy followed by reduced-dose (24 Gy) fractionated radiation therapy as initial treatment at our institution [5]. All of the 12 patients received involved-field irradiation that caused a relatively high recurrence rate, and the results of this treatment strategy have been reported elsewhere in detail [2, 22, 27]. According to our management policy for CNS germinoma at that time, 7 patients treated preceding surgically removal for definitive diagnosis and treatment [20].There are not any reported cases in which chemotherapy alone was performed as the first treatment [8].

Salvage therapy

At the time of recurrence, 8 patients underwent surgical biopsy or partial removal of the tumor for tissue diagnosis according to our management policy at that time. Among them, one patient (case 16) received subtotal tumor removal after undergoing salvage ICE chemotherapy that was not effective. Histopathological diagnosis of this tumor was a mixed germ cell tumor including mature teratoma and germinoma. Histological examination of the remaining 9 patients revealed recurrent germinoma. Fifteen patients did not receive surgery and therefore the histology of their recurrent tumor was not verified.

Including 2 patients (case 16 and 25) whose follow-up period after salvage therapy was less than 12 months, the outcomes of the 25 patients treated with various salvage therapies were assessed. Twenty-two patients received radiation therapy as part of the salvage therapy. Chemotherapy has been utilized as a mode of salvage therapy at our institution since 1989. Although the regimens of chemotherapy varied, platinum-based regimens were most frequently used at our institute. The PE regimen consisted of cisplatin (20 mg/m^2/day) and etoposide (100 mg/m^2/day) administered for five successive days at 4-week intervals. The CARE regimen used carboplatin (450 mg/m^2/day) on day 1 and etoposide (100 mg/m^2/day) administered for five successive days at 4-week intervals. The ICE regimen consisted of ifosfamide (900 mg/m^2/day), cisplatin (20 mg/m^2/day) and etoposide (60 mg/m^2/day) administered for five successive days at 4-week intervals.

Evaluation of response to salvage therapy

A complete response to adjuvant therapy was defined as complete disappearance of the recurrent tumor either on MRI in recent cases or on CT in cases before 1988. The time from completion of initial treatment to the date of the first recurrence was measured and the progression-free survival (PFS) rate was calculated according to the Kaplan–Meier method. The overall survival after the first recurrence was defined as the interval in months from the date of completion of salvage therapy to the date of the final observation or death of the patient, and was calculated using the Kaplan–Meier method.

Results

The time-course of recurrence of CNS germinoma

Figure 1 shows the progression-free survival curve after the initial therapy in 25 patients with recurrent germinoma. The median PFS was 50 months (range: 6–230). Among the patients, 9 (36%) had the first recurrence at 60 months or later. The latest recurrence occurred 230 months after initial treatment in a patient with basal ganglia germinoma who underwent partial surgical removal and received 40.5 Gy of radiation therapy to the whole ventricle field. Nineteen of the 25 patients presented intracranial recurrence. Thirteen of the 19 recurrent tumors recurred out of the initial irradiation field of the intracranial region. The remaining 6 patients had independent spinal recurrences without an intracranial lesion.

Including one patient treated initially with Gamma Knife alone, the median PFS of 12 patients who received conventional high-dose radiation therapy was 58 months (range: 6–230) and that of 12 patients who were treated with induction chemotherapy followed by low-dose irradiation was 34 months (range: 13–142). There was no significant difference in the PFS periods ($P > 0.05$, Wilcoxon test).

The median PFS of 11 patients who received surgical treatment including stereotactic biopsy as the initial treatment was 56.5 months (range: 20–230), and that of 14 patients who were treated with non-surgical modalities was 48 months (range: 6–77). There was no significant difference in the PFS periods ($P > 0.05$, Wilcoxon test).

There was no significant impact upon outcome of interval from initial diagnosis to first recurrence. Nine patients suffered from recurrence 5 years after the initial treatment, and among them 3 patients died. Of the remaining 16 patients, 5 of them died. In addition, there was no significance of the period from initial diagnosis to first relapse comparing 15 long-term survivors vs. 8 non-survivors ($P > 0.05$, Wilcoxon test).

Assessments of salvage therapy in 25 patients

Although 24 patients achieved a complete remission after various salvage therapies, one patient's recurrent tumor was resistant to salvage chemotherapy. Surgical removal of this tumor revealed a mixed germinoma. Among the 25 patients, 8 patients died of the disease and 17 patients were alive and tumor-free at the final observation. Figure 2 shows the overall survival curve after the initiation of salvage therapy for the first recurrence. The calculated 5-year overall survival rate after the recurrence was 70% (95% confidence interval: 50–90).

Recurrent tumors of 12 patients were detected at a scheduled routine follow-up examination and those of 13 patients were found due to worsening of clinical symptoms. The recurrence-free survival after the initial treatment of the 12 patients without symptomatic progression was 43 months and that of the 13 symptomatic patients was 58 months ($P > 0.1$, Wilcoxon test). After salvage therapy, only one of the 12 patients (10%) died of recurrent disease, whereas 7 of 13 patients (54%) with symptomatic recurrence died. Seven of 9 patients who experienced a second recurrence died.

Seven of 11 patients who were treated with reirradiation alone for their first recurrence died due to further recurrences. Most of the cases in which reirradiation resulted in failure were described in our previous report in detail [23]. A patient treated solely with platinum-based chemotherapy deceased from further relapses. Ten patients whose primary tumor was treated with platinum-based chemotherapy and 24 Gy or 25.2 Gy irradiation were salvaged with platinum-based chemotherapy followed by reirradiation (Table 1).

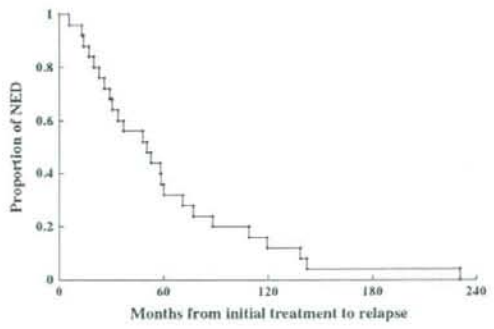

Fig. 1 Kaplan–Meier plots of progression-free survival after the initiation of primary therapy in 25 patients with recurrent CNS germinoma. NED: no evidence of disease

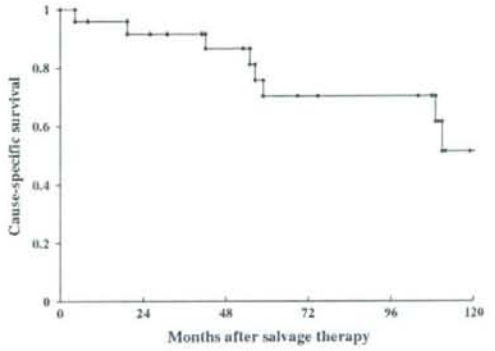

Fig. 2 Kaplan–Meier plots of overall survival after the initiation of salvage therapy for the first recurrence

Table 1 Details of all 25 patients with recurrent germinoma

Case no. (onset year)	Diagnosis	Location	Initial radiation	Initial chemotherapy	RFS (months)	Location of 1st recurrence	HCG/ HCG-β	Surgery at recurrence	Salvage therapy for 1st recurrence	Survival (months/status at final observation)
1. (1967)	Germinoma	Pineal	51 Gy/24fr local	None	77	Frontal lobe with dissemination	Positive	Partial removal	30 Gy/12fr WB, 30 Gy local	81 Dead
2. (1968)	Germinoma	Pineal	45 Gy local	None	60	Pineal	Negative	None	30 Gy/15fr local	253 Alive
3. (1976)	Germinoma	Hypothalamus	44.8 Gy/16fr local	None	14	Pineal	Unknown	None	40 Gy/16fr local	56 Dead
4. (1976)	Germinoma	Pineal	50.4 Gy/16fr WV	None	37	Lumbar spine	Positive	Partial removal	40 Gy/16fr for spine	56 Dead
5. (1977)	Germinoma	Pineal	50 Gy/25fr local	None	119	Neurohypophysis	Negative	None	35 Gy/14fr local	174 Dead
6. (1979)	Germinoma	Hypothalamus, Basal ganglia	45 Gy/15fr WV	None	6	Whole spine	Positive	Biopsy	30 Gy/15fr local	117 Dead
7. (1979)	Germinoma	Basal ganglia	40 Gy/16fr local	None	23	Cervical spine	Negative	Partial removal	30 Gy/20fr local	82 Dead
8. (1980)	Germinoma	Hypothalamus, Basal ganglia	40.5 Gy/18fr WV	None	230	Neurohypophysis	Negative	None	ICE, 24 Gy/ 12fr local	338 Alive
9. (1982)	Germinoma	Neurohypophysis	45 Gy/15fr WV	None	58	Corpus callosum	Negative	None	CDDP, VP-16	114 Dead
10. (1932)	Germinoma	Basal ganglia	50 Gy/20fr local	ACNU	71	Cervical spine	Positive	None	45 Gy/18fr local	180 Dead
11. (1983)	Germinoma	Pineal	40 Gy/20fr WV	None	48	Lumbar spine	Positive	Partial removal	40 Gy/16fr local	152 Alive
12. (1987)	Germinoma	Pineal	24 Gy/12fr local	ICE	142	Neurohypophysis	Positive	Biopsy	ICE, 24 Gy/ 12fr local	150 Alive
13. (1989)	Germinoma	Neurohypophysis, Germinoma	30 Gy/15fr WB	None	50	Lateral ventricle	Negative	Biopsy	ICE 24 Gy/12fr local	229 Alive
14. (1989)	Germinoma	Pineal, Posterior 3rd ventricle	24 Gy/12fr WV	ICE	29	Basal ganglia	Positive	None	ICE, 25.2 Gy/ 14fr CS	82 Alive
15. (1992)	Germinoma	Hypothalamus, Basal ganglia	24 Gy/12fr local	ICE	88	Lateral ventricle	Negative	None	ICE, 24 Gy/ 12fr CS	163 Alive
16. (1994)	Germinoma	Hypothalamus	24 Gy/12fr local	ICE	138	Corpus callosum	Negative	Partial removal	ICE, 18 Gy/ 10fr CS plus local boost	164 Alive
17. (1992)	Germinoma	Pineal, Neurohypophysis	24 Gy/12fr local	ICE	34	Hypothalamus, Lateral ventricle	Positive	None	ICE, 24 Gy/ 12fr CS	189 Alive
18. (1994)	Germinoma	Hypothalamus	24 Gy/12fr local	ICE	13	Lateral ventricle	Negative	None	ICE, 24 Gy/ 12fr WV	44 Alive

Table 1 continued

Case no. (onset year)	Diagnosis	Location	Initial radiation	Initial chemotherapy	RFS (months)	Location of 1st recurrence	HCG/ HCG-β	Surgery at recurrence	Salvage therapy for 1st recurrence	Survival (months/status at final observation)
19. (1995)	Germinoma	Neurohypophysis	24 Gy/12fr local	CDDP, VP-16	31	Pineal, Cerebellopontine angle	Positive	None	CBDCA, VP-16, 24 Gy/12fr CS	150 Alive
20. (1995)	Germinoma	Basal ganglia	24 Gy/12fr local	CDDP, VP-16	109	Lumbar spine	Negative	None	ICE, 36 Gy/ 18fr local	150 Alive
21. (1995)	Germinoma	Neurohypophysis	24 Gy/12fr local	ICE	20	Lateral ventricle	Positive	None	24 Gy/12fr CS plus local boost 6 Gy	132 Alive
22. (1997)	Germinoma	Hypothalamus, Basal ganglia	24 Gy/12fr local	ICE	26	Pineal	Positive	None	ICE, gemcitabine, taxotel, 46 Gy/23fr local	134 Alive
23. (1997)	Germinoma	Hypothalamus, Pineal	24 Gy/12fr local	ICE	17	Lateral ventricle	Positive	None	24 Gy/12fr CS	127 Alive
24. (1998)	Germinoma	Pineal	24 Gy/12fr local	ICE	53	Temporal lobe	Negative	None	ICE, 24 Gy/12fr CS	122 Alive
25. (2002)	Germinoma	Neurohypophysis, Germinoma	Gamma knife	CBDCA, VP-16	58	Frontal lobe	Positive	None	ICE, 25.2 Gy/14fr CS	67 Alive

ICE: Ifosfamide, cisplatin, etoposide, CDDP: Cisplatin, CBDCA: Carboplatin, VP-16: Etoposide CS: Craniospinal, WB: Whole brain, WS: Whole spinal, WV: Whole ventricle; RFS: Recurrent free survival

In case 16, a recurrent tumor showed no response to the ICE chemotherapy and was then surgically removed

The pathological diagnosis of the tumor was a mixed germinoma

All of them were alive without further recurrence at the final observation.

Discussion

Recurrence rates of approximately 10–15% after initial therapy for CNS germinomas have been reported in the literature [10, 21, 30]. Concerning the short periods of follow-up of the reported cases and the number of late recurrences presented here, the actual recurrence rate of CNS germinoma might be much higher than the reported incidence. The method of follow-up has been a subject of debate in terms of frequency, duration, and technique. Earlier detection of recurrent disease will produce a better outcome after salvage therapy. To detect a recurrence without progression of symptoms, regular whole-neuraxis MRI follow-up is required. Regarding the time-course of recurrence as shown in Fig. 1, MRI observation beyond 10 years may be necessary, although it may be practically difficult. In addition, a secondary neoplasm may also occur years after initial chemoradiation therapy [21]. We suggest a regular follow-up MRI once a year for 10 years.

It has been suggested that PFS might be influenced by the mode of primary therapy, particularly the dose of radiation therapy. In the present series, however, there was no significant difference in PFS among the patients who received either high- or low-dose irradiation.

Since 1992, we have treated recurrent germinomas with platinum-based chemotherapy and additional radiation therapy. In the present series, 17 patients with recurrent CNS germinoma were successfully salvaged. Ten of them received low-dose (18–25.2 Gy) re-irradiation in whole ventricle or larger fields. Douglas et al. [6] and Nakamura et al. [15] also reported the efficacy of combination therapy using platinum-based chemotherapy and low-dose radiotherapy for recurrent CNS germinoma. Of course, if high-dose wide-field irradiation is utilized as the initial therapy, reirradiation as salvage therapy may be harmful.

In our review of patients with CNS germinoma, recurrent germinomas were consistently susceptible to platinum-based salvage chemotherapy. Some investigators used high-dose chemotherapy followed by autologous stem-cell rescue in patients with recurrent or progressive CNS malignant germ cell tumors [13]. This approach may be useful in patients with recurrent germinoma as intensification of salvage therapy. The long-term results of this approach, however, remain unknown.

In conclusion, late recurrence is not a rare event in patients with CNS germinoma. To identify a true cure rate of this disease, a 10-year or longer observation period may be required. As a salvage therapy, platinum-based chemotherapy followed by wide-field low-dose radiation therapy appears to be effective.

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Role of surgery for optic pathway/ hypothalamic astrocytomas in children

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Optic pathway/hypothalamic pilocytic astrocytomas in children are usually treated with chemotherapy following a surgical biopsy. In this report, we retrospectively considered the role of surgical intervention. In a series of 25 patients without neurofibromatosis type 1, the median age at initial treatment was 3.1 years (range, 0–15 years). Twenty cases were verified by histology, and five cases were diagnosed by MRI findings. Twenty-three patients received chemotherapy. All patients were alive at median follow-up of 66 months. Aims of surgery at the initiation of treatment were biopsy in 12 cases (1 stereotactic and 11 craniotomies) and debulking in 7 cases. The 11 open biopsies revealed pilocytic astrocytoma; however, noticeable complications occurred in five children after the biopsies. Review of preoperative MRIs showed that all had typical findings indicating pilocytic astrocytoma. The open biopsy offered no noteworthy benefit for the patients despite surgical risk and delay of chemotherapy. The extent of the seven resection surgeries was 70% or less removal, and postoperative adjuvant therapy was needed for six of the seven patients. The remaining six children who did not undergo surgery obtained remission with chemotherapy alone. After relapse in nine patients, 15 bulk-reduction surgeries were performed. Surgical resection was not curative in any patient. In five patients, mostly older children, cystic expansion of tumor was partially resected, resulting in additional remission. In conclusion, considering the risk of open surgery and the effectiveness of chemotherapy, the role of surgical intervention is restricted to bulk-reduction surgery only when it is inevitable, especially at relapse after chemotherapy.
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Optic pathway/hypothalamic glioma is a rare brain tumor that occurs mostly in young children. Initial manifestations are usually serious visual disturbance, hypothalamic dysfunction including diencephalic syndrome, or both. Although in general this tumor is WHO grade I pilocytic astrocytoma, in some patients, particularly in very young populations, the optic pathway/hypothalamic pilocytic astrocytoma (OPHPA) may show an aggressive clinical course, including dissemination through the cerebrospinal fluid pathway, and these are a variant type known as pilomyxoid astrocytoma.[1,2]

The literature contains a number of discussions concerning notable progress in the treatment of OPHPA, especially focusing on chemotherapy and radiation therapy.[2–15] Neurosurgical management, which seems even now to offer major contributions to control of the tumor, has rarely been given attention.[14,16,17]

In the young population with neurofibromatosis type 1 (NF-1)–associated OPHPA, decisions to initiate chemotherapy are generally made without biopsy and are guided by ophthalmological and imaging examinations.[18,19] In cases of sporadic OPHPA in non-NF-1 patients, a biopsy or a partial resection by craniotomy to confirm histology remains the first mode of treatment.[3,14]

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In addition to cases requiring the histopathological diagnosis, certain cases refractory to chemotherapy, cases with a large mass causing obstructive hydrocephalus, or cases with cystic expansion compressing the optic pathway occasionally require surgical debulking during the long clinical course. This report reconsiders the role of surgical interventions for various stages of OPHPAs, excluding NF-1–associated tumors.

Materials and Methods

We retrospectively assessed a series of 25 consecutive patients who had a clinical diagnosis of a sporadic OPHPA from a review of clinical records since 1992, when high-resolution MRI became routinely available. We excluded NF-1–associated gliomas, single optic nerve gliomas, unilateral hypothalamic gliomas, and quiescent cases found in patients older than 15 years because these tumors have different natural histories and require dissimilar treatment strategies.[8,18]

Histology (pilocytic astrocytoma, including pilomyxoid type) was verified in 20 of the 25 patients, with 19 patients undergoing surgery at the initiation of therapy and another at relapse. The remaining five patients were diagnosed by pathognomonic radiological appearance and typical clinical manifestations. Fifteen of the 25 patients had newly diagnosed disease; the remaining 10 patients were referred to our hospital after a biopsy or at the time of relapse. The median ages of symptom onset and initial treatment were 1 year (range, 0–14 years) and 3.1 years (range, 0–15 years), respectively.

At the time of initial diagnosis of brain tumor, all cases, in retrospect, had a typical appearance suggestive of pilocytic astrocytoma on high-resolution MRI (Fig. 1A,B) and CT, located in the midline involving the optic pathway and hypothalamus. Although the majority of the 25 tumors appeared as apparently well-demarcated masses on MRI, two had a predominantly infiltrative pattern involving the whole optic pathway, including the bilateral optic nerves, chiasm, tracts, geniculate ganglions, internal capsules, and optic radiations. Contrast enhancement on MRI was present for the most part in all but one case; in this latter case, a large tumor (involving the chiasm, right optic tract, and bilateral hypothalamus and occupying the third ventricle) exhibited a scarce enhancement pattern. To resolve obstructive hydrocephalus, the tumor was subtotally resected and found to be pilocytic astrocytoma upon histological examination. The maximum diameters of the 25 tumors, encompassing globular masses but excluding the infiltrating part to the surrounding brain, ranged from 34 to 65 mm. No cases had dissemination at the time of diagnosis.

Initial manifestations and reasons for initiation of therapy were diverse. Fifteen (60%) of the 25 children had their initial symptom before 2 years of age. Twenty children had visual impairment at the time of correct diagnosis. The interval between onset of initial manifestation and diagnosis of brain tumor was longer than 2 years for seven children. Among them, five children who were younger than 3 years at diagnosis showed a long-term history of visual impairment without hypothalamic dysfunction that had not been recognized by their parents. In contrast, 9 of 10 infants presenting recognizable symptoms, including either pendular/fixation nystagmus or diencephalic syndrome such as emaciation, anorexia, and weight loss, had diagnosis without delay. Others were found with headache due to obstructive hydrocephalus, dwarfism, or precocious puberty or had tumors that were found incidentally. An 8-year-old patient whose tumor was found incidentally was initially asymptomatic, but the tumor grew during a 3-year observation period and caused obstructive hydrocephalus and a slight visual field defect. All the patients were therefore symptomatic at the time of initial treatment.

The aims of surgery, at the initiation of treatment, were biopsy (very limited resection) in 12 cases (1 stereotactic surgery and 11 craniotomies) and tumor debulking in 7 cases. If a typical low-grade astrocytoma was encountered during craniotomy and limited resec-

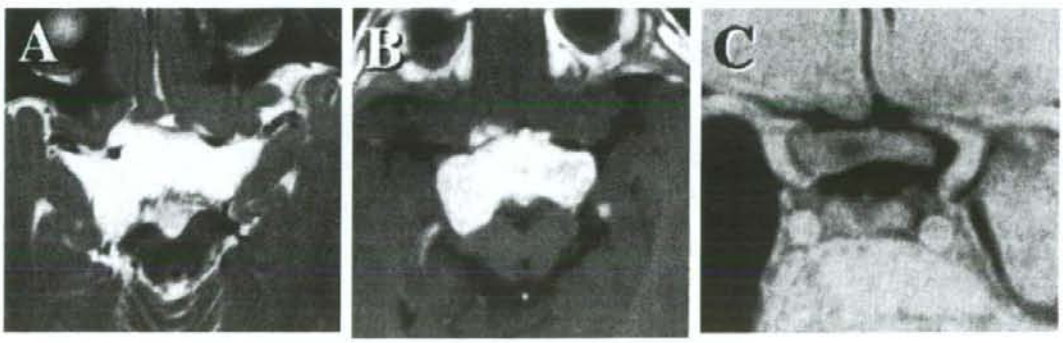

Fig. 1. MR images of a 1-year-old patient demonstrate typical appearance of pilocytic astrocytoma. T2-weighted axial image (A) shows a high-signal intensity suprasellar mass that is homogeneously enhanced with gadolinium contrast on T1-weighted image (B). After six cycles of chemotherapy, the tumor almost completely disappeared on usual MR images; however, a coronal image of three-dimensional MR cisternography (C) depicted a tiny residual tumor within the right side of the chiasm.

tion was then performed, it was evaluated as a "biopsy" case in this report. Partial removal was defined as less than 90% resection. These 19 patients underwent surgery for progressive symptoms or progressive tumor growth. In six patients, the decision to initiate chemotherapy was made without biopsy and was guided by serial MRI examinations. In nine patients with relapse, a total of 15 salvage surgeries were performed. In the present series, 21 (62%) of 34 various craniotomies were performed by the senior author (Y.S.). The surgical procedures applied were pterional frontobasal transsylvian, transcallosal interseptal, transcallosal trans-foramen of Monro, frontal transcortical, and interhemispheric trans-lamina terminalis approaches.

Twenty-three (92%) patients were treated with chemotherapy, and six patients (24%) with a relapsing tumor after chemotherapy received radiation therapy. The remaining two patients underwent surgical resection alone without adjuvant therapy. Generally, three chemotherapeutic regimens were used: cisplatin with vincristine,[5] carboplatin with vincristine, and temozolomide.

Neurological and radiological examinations were performed before and after surgery. Assessment of overall response was based on tumor evaluation by MRI and interpreted according to the Response Evaluation Criteria in Solid Tumors (RECIST).[20] Complete surgical resection was defined as no visible tumor found on high-resolution postsurgical MRI and was not based on surgical record.

Results

Outcome of Patients

All 25 children tolerated the various therapies well and were alive at median follow-up of 66 months. Among them, only one patient achieved a completely tumor-free status of 9-year duration, after spontaneous complete involution on serial MRI observation. Final outcome of the remaining 24 patients could not be determined due to the short period of observation. At the final observation, Karnofsky performance status was better than or equal to 70% in 20 patients. All children, except one who was completely blind at birth, retained functional vision in at least one eye.

Initial Therapy in Cases with Surgical Biopsy or Resection

At the initiation of treatment, 19 patients underwent surgery, including stereotactic biopsy in 1 case, craniotomy biopsy (limited resection) in 11 cases, and debulking surgery in 7 cases. No endoscopic biopsy was applied in this series. Five children received a ventriculoperitoneal shunt for obstructive hydrocephalus. Because of the location of a tumor at the bottom of the third ventricle, endoscopic third ventriculostomy was not available for any patient.

Eight of 12 biopsies were performed at a previous hospital, with these children then referred to our institution. The 12 biopsies revealed a histological diagnosis of WHO grade I pilocytic astrocytoma, including pilomyxoid type in seven patients. There were no cases of anaplastic tumor. One tumor was initially diagnosed as fibrillary astrocytoma, but pathology review confirmed pilocytic astrocytoma. Because 7 of these 11 children were younger than 4 years, precise assessments of their visual function (including visual field evaluation and minimal change of cognitive function) were not possible. Noticeable postsurgical symptomatic complications were observed in five patients. One patient had deterioration of cognition after consciousness disturbance for 2 weeks. One had worsened bitemporal hemianopsia. One had postsurgical epileptic seizures. One had moderate, but transient, hemiparesis. In two infants who underwent a frontal interhemispheric approach, postsurgical MRI examinations showed medial frontal malacia in the rectal and cingulate gyri on T2-weighted images; one was symptomatic (consciousness disturbance for 2 weeks), and the other was asymptomatic. In another child, a small cerebral infarction was found due to a perforating artery injury originating from the middle cerebral artery, although this child seemed asymptomatic.

For initial treatment, bulk-reduction surgery by craniotomy was performed in seven children with large-volume tumors (Table 1). The senior author (Y.S.) performed two of these craniotomies. Although obstructive hydrocephalus in two children resolved after craniotomy, the extent of resection surgeries appeared to be insufficient, resulting in removal of 70% or less of the tumor volume. Following the surgery, six patients received adjuvant chemotherapy. One child received radiation therapy at 6 years of age, 4 years after initial surgery, due to an aggressive relapse after cycles of chemotherapy with carboplatin and vincristine. As a result, benefits of the first resection surgery were obscure for the seven children; nevertheless, postsurgical complications were considerable, as shown in Table 1.

Initial Therapy in Cases without Biopsy

Given patient age, initial manifestations, location of tumor, and preoperative radiological appearance, the decision to initiate chemotherapy was made without biopsy and was guided by serial MRI in six patients with typical features of OPHPA at initial diagnosis. All these patients had their disease newly diagnosed at Hokkaido University Hospital. They successfully obtained a durable remission after either six or eight cycles of chemotherapy using cisplatin and vincristine, although no patients achieved a complete response. One patient underwent unilateral optic nerve decompression during first-line chemotherapy. Two patients who had a large mass after completion of initial chemotherapy continually received second-line chemotherapy using either carboplatin/vincristine or temozolomide. Two of the six patients showed relapse: one patient, after a 34-month remission, was treated with temozolomide; the second patient, after a 65-month remission, required subsequent irradiation and then salvage surgery for bulk reduction.

Table 1. Results of bulk-reduction surgery at initial treatment

Patient Age	Route (Approach)	Postsurgical Complications	Brain Tissue Damage	Extent of Surgery (Volume)
2 years	Frontal interhemispheric	Epilepsy	Mesial frontal lobe	<50%
1 year	Anterior transcallosal	Cerebral salt wasting syndrome, slight right hemiparesis, possible cognitive deterioration	Fornix, anterior commissure, right deep frontal, hypothalamus	<50%
3 years	Right frontal transcortical	Hypothalamic dysfunction, body temperature dysregulation, mental deterioration, worsened vision	Right frontal lobe, hypothalamus, visual pathway	~70%
3 years	Frontal interhemispheric	Panhypopituitarism, epilepsy, right visual loss	Optic nerve, chiasm, hypothalamus, stalk, mesial frontal lobe	<50%
3 years	Anterior transcallosal through foramen of Monro	None	None	<50%
7 months	Frontobasal transsylvian	None (total blindness prior to surgery)	Resection of right optic nerve	<50%
5 months	Frontobasal transsylvian	Right visual loss	Right optic nerve and chiasm	<50%

At median follow-up of 47 months, all six of these children were alive with stabilized residual mass on MRI.

Fig. 1 shows representative MR images for a 1-year-old patient who presented with diencephalic syndrome, progressive emaciation, and severe visual impairment. This child was given chemotherapy without biopsy. During the period of chemotherapy, the tumor had gradually shrunk toward the optic chiasm and finally disappeared almost completely on usual MR images. However, a coronal image of three-dimensional MR cisternography (three-dimensional constructive interference in steady-state MRI) showed a tiny residual tumor in the right side of the chiasm. The patient's disease had been stable for 73 months with slightly improved visual acuity. For this child, either biopsy or partial resection would have resulted in additional visual impairment.

OPHPA occasionally infiltrates the optic nerve in the optic canal and orbit. In our series, only 3 of the 25 cases presented with optic nerve invasion in remarkably expanded optic canal(s). Fig. 2 shows a coronal image of a swollen optic nerve in the right optic canal. This patient had count-finger visual acuity on the right and 2/200 on the left. The right vision occasionally deteriorated to the level of light perception, especially when the patient had a high fever. Because of the deterioration of visual acuity during first-line chemotherapy, the optic canal was unroofed by an emergent craniotomy to decompress the affected nerve without tumor resection. Postoperatively, the patient's visual acuity was preserved and 3 years later was 4/200 on the right and hand movement to 2/200 on the left. After cycles of chemotherapy, the swollen optic nerve gradually shrank.

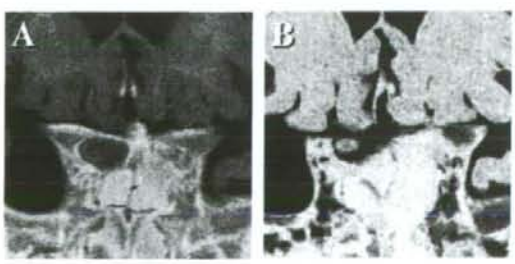

Fig. 2. A coronal image shows a swollen optic nerve in the right optic canal (A; multiple planner reconstruction image). Due to deterioration of visual acuity, the optic canal was unroofed to decompress the affected nerve. After cycles of chemotherapy, the optic nerve gradually shrank (B; three-dimensional MR cisternography).

Salvage Surgery for Relapse

Nine children underwent salvage surgery for relapse: 12 partial resections, 2 gross total removals, and 1 cyst puncture by image-guided stereotactic method. The salvage bulk-reduction surgery was performed to partially remove a relapsing tumor after prolonged chemotherapy and prior to second-line chemotherapy, to reduce a large mass prior to planned radiation therapy to solve obstructive hydrocephalus, or to remove the wall of the expanding cyst(s). Five patients underwent salvage surgery once, and three patients underwent such surgery twice. Another child, who had previously received various chemotherapies and radiation, underwent partial removal twice and then gross total removal twice.

Regarding postsurgical quality of life, complete surgical resection could not be achieved in any patient due to the invasive nature of the tumor into the optic pathway and the bilateral hypothalamus. Median follow-up for the nine patients was 128 months (range, 42–174 months), and all were alive at the final observation.

Fig. 3 shows a large pilocytic astrocytoma in a 33-month-old patient who had been given cycles of chemotherapy following initial biopsy when she was 6 months old. Because the second partial removal was insufficient, the patient was referred to our institution. To further reduce the large volume, a radical resection was performed, leaving the tumor margin intact to preserve the residual hypothalamic function and very poor

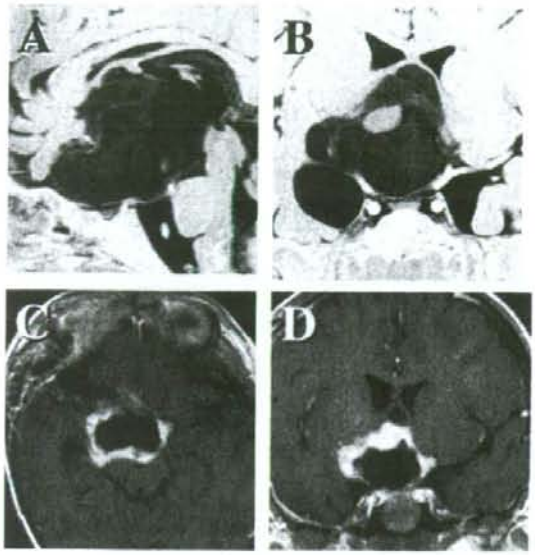

Fig. 3. A progressively growing pilocytic astrocytoma in a 2-year-old child who underwent long-term chemotherapy and partial tumor removal twice (A and B). Through the frontobasal transsylvian route, a radical third resection was performed, leaving the tumor margin intact (C and D). Tumors of this size involve the circle of Willis, including its numerous perforators.

vision of the left eye. Maintenance chemotherapy using temozolomide is ongoing at the time of this writing. Relapsing tumor of a similar size was seen in three children, and all involved the circle of Willis, including its numerous perforators, as well as the optic pathway and the hypothalamus. In these cases, the risk posed by sufficient bulk-reduction surgery that was required prior to either alternative chemotherapy or radiation therapy was extremely high, although we fortunately did not observe any unacceptable postsurgical sequelae.

Spontaneous involution after partial resection was observed in three patients. In the case shown in Fig. 4, the mass filling in the third ventricle was selectively removed, leaving a part of the tumor infiltrating the chiasm and the hypothalamus, because the patient still retained good vision and pituitary function without diabetes insipidus. Although the selective excision was technically hard, intraoperative observation revealed that the proliferating part of a relapsing tumor was very soft and easily resectable, while the tumor infiltrating the brain tissue was relatively firm, probably due to a mixed gliofibrous component.

For one child who had received chemotherapy, radiation therapy, and partial resections with transection of the left optic nerve over a period of 8 years, a radical total resection of a relapsing tiny tumor adherent on the chiasm was attempted. The result of surgery was evaluated as a gross total removal on MRI. Three years later, the tumor eventually recurred on the left optic tract and was radically resected again. This patient had been receiving maintenance chemotherapy using temozolomide, and he was tumor free on MRI for an additional 2 years, maintaining half nasal-side vision of the right eye. Whether this final surgery could lead to a disease cure is not clear because of the short observation period.

Multi- or single-cystic expansion of the tumor was observed in five older patients after a long disease course, with enlargement of tumor cyst(s) occurring at 4, 8, 10, 15, and 18 years of age. Four of the five patients underwent partial resection of the cyst wall by craniotomy, and the fifth patient underwent an image-guided stereotactic puncture of a subcutaneous reservoir. Only one experienced a further relapse of multiple cysts and was treated by craniotomy again. These surgical treatments resulted in further remission in all five patients, and three resulted in improvement of deteriorating vision. Among them, a spontaneous complete involution of the residual enhancing mass was observed in the child who received stereotactic puncture of the cyst. Pathological examinations showed predominantly degenerative changes of pilocytic astrocytoma, in which the index for Ki-67 staining was less than 1%. Fig. 5 shows a multicystic expansion of a pilocytic astrocytoma. The volume of tumor parenchyma enhanced with gadolinium contrast

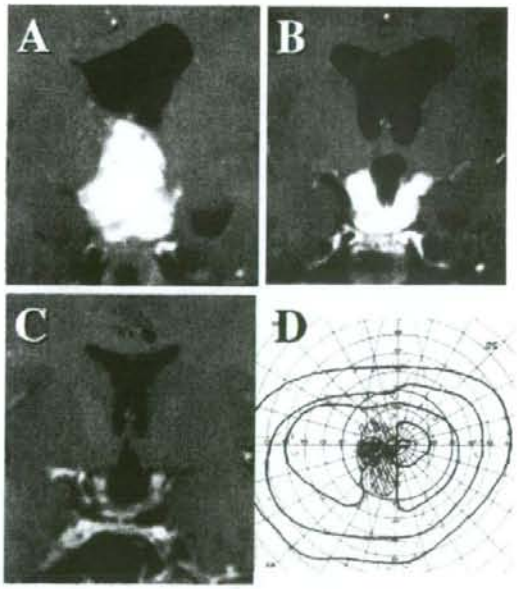

Fig. 4. A relapsing tumor (A) in a 7-year-old boy, who had received chemotherapy for 7 years following a partial resection. MR image shows a homogeneous tumor, but the tumor infiltrating the chiasm and the hypothalamus was relatively firm, and only the soft mass filling in the third ventricle was selectively resected (B). Five years later, when the patient was 13 years old, the residual tumor had spontaneously shrunk, and visual function was preserved (C and D).