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# Treatment Outcome and Prognostic Factors of Medulloblastoma

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*Medulloblastoma, once a tumor with a dismal prognosis, is one of the most common primary brain tumors of childhood. As the methods of treatment have been continuously refined, the outcome has improved remarkably during the last few decades. The outcome of 78 medulloblastoma patients, which were managed from 1972 to 1992 at the Department of Neurosurgery of Seoul National University Hospital, were analyzed to calculate the 3-year and 5-year survival rates (3yS and 5yS). Of those, 52 cases which were treated after July 1982 were studied 1) to calculate the 3yS and 5yS, 2) to figure out the prognostic factors of survival, and 3) to investigate the role of adjuvant chemotherapy ('8-drugs-in-a-day' protocol: CCNU, cisplatin, vincristine, hydroxyurea, procarbazine, cytosine arabinoside, methylprednisolone and cyclophosphamide).*

*The 3yS and 5yS of the 78 patients were 57.4% and 47.3%, respectively. Of the 52 patients treated after July 1982, the 3yS and 5yS were 67.8% and 64.1%, respectively. The latest recurrence was at 56 months after surgery. All the recurrences were within the risk period of Collins' rule. Of the prognostic factors studied by univariate analysis (age, sex, Chang's classification T- and M-stages, extent of surgical removal, and chemotherapy), Chang's classification M-stage and sex were the statistically significant factors ($p=0.028$ and 0.024 respectively). On multivariate analysis, only the M-stage was statistically significant ($p=0.004$). Adjuvant chemotherapy had different influences in different patient groups. Only in the 'poor risk' group, did adjuvant chemotherapy have a strong tendency to better outcome ($p=0.069$).*

*Further data collection and analysis will lead to better treatment modalities and better outcome for this most common primary malignant brain tumor in childhood.*

**Key Words**: *Medulloblastoma, Survival rate, Prognostic factor, Chemotherapy*

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## INTRODUCTION

Medulloblastoma makes up 3.1-3.7% of intracranial tumors of all ages (Choux et al., 1983; Helseth & Mork, 1989). It accounts for 14-18% of all intracranial tumors in children which corresponds to 24% of posterior fossa tumors in children (Choux et al., 1983 ; Hoffman et al., 1983 ; Sutton, 1991). Application of microsurgical technique and continuously refined methods of craniospinal irradiation improved the treatment outcome of this highly malignant tumor remarkably. Recently adjuvant chemotherapy has been tried to enhance the quality and length of survival.

In 1988, the authors reported the outcome of 49 medulloblastoma patients who were treated from 1972 to 1987 (Cho et al., 1988). In this study, 3-year survival rate and disease-free survival rate were 49.3% and 48.5%, respectively. Five-year survival rate was not reported due to the relatively small number of cases which were followed up for more than 5 years. All the recurrences were found within 2 years after surgery. The prognostic factors for better outcome were ; extent of surgical resection, radiation dose to the posterior fossa and the patient group (treated before July 1, 1982 vs. after July 1, 1982). The influences of age, T-stage and presence of desmoplasia on survival were not statistically significant. After the study, the authors made a management protocol which included postoperative staging (brain CT/MRI, lumbar CSF cytology and spine myelography/MRI) and posterior fossa irradiation of more than 50Gy (usually 54-55Gy) for all cases older than 2 years. The '8 in 1' chemotherapy (CCNU, cisplatin, vincristine, hydroxyurea, procarbazine, cytosine arabinoside, methylprednisolone, and cyclophosphamide) was applied in 'poor risk' cases (with brain stem involvement, with a definite residual mass, Chang's stage $M_{1-4}$, or age younger than 2 years). For the 'average risk' group, chemotherapy was done randomly.

In the present study, the authors analyzed the treatment outcome of 78 medulloblastoma patients which were managed from 1972 to 1992 1) to calculate the 3-year and 5-year survival rates, 2) to find out the prognostic factors of survival, and 3) to investigate the role of adjuvant chemotherapy.

## CLINICAL MATERIALS AND METHODS

### Patient population

From 1972 to 1992, 78 patients with medulloblastoma (male : female=49 : 29) were treated at the Department of Neurosurgery, Seoul National University Hospital. The mean age was 11.0 years (ranged from 3 months to 49 years). For the 78 patients, 3-year and 5-year survival rates (3yS and 5yS) were estimated. The period of recurrence was observed.

Since July, 1982, a relatively standardized treatment policy (prone position, dural closure, radical removal as much as possible, application of the advanced irradiation techniques, etc.) has been applied for 52 patients (male : female=30 : 22). The mean age was 11.1 years (ranged from 3 months to 49 years). The 52 patients were reviewed to figure out the 3yS, 5yS, the period of recurrence, prognostic factors for better/poor survival and the role of adjuvant chemotherapy.

### Radiation therapy

Since early 1982, radiation therapy of medulloblastoma patients has been done with a relatively uniform method. Radiotherapy to the whole neuraxis started within 3 weeks after operation or after preradiotherapy chemotherapy using a telecobalt unit. Radiotherapy technique was described previously (Kim et al., 1988 ; Kim et al., 1993). In short, whole brain irradiation was given through the bilateral ports and whole spinal irradiation was given through one or two posterior fields depending on the length of the spine. The lower margin of the whole brain field abutted on the divergent upper margin of the spine field and the abutted margin was shifted at every 10 Gy. Radiation dose was 50-55 Gy to the primary tumor site, 30-45 Gy (mainly 36-40 Gy) to the whole brain, and 24-36 Gy to the whole spine. Radiotherapy to the whole spine was not performed in two patients because of very poor performance status. In 4 cases radiotherapy was delayed (until postoperative day 61-81 ; mean : day 67) due to fever/infection or postoperative hemorrhage. All the 4 cases were alive at the latest follow-up.

### Chemotherapy

Chemotherapy was done according to the '8-drugs-in-a-day' protocol (Children's Cancer Study Group CCG 921 protocol). In 11 patients, preradiation chemotherapy started before postoperative day 14. Before the radiation therapy, two cycles of chemotherapy every 2 weeks were applied. After irradiation, eight cycles of chemotherapy were performed every 6 weeks. If a residual mass persists, additional treatments were given case by case.

Toxicity of '8-drugs-in-a-day' chemotherapy was reported in another article (Shin and Ahn, 1993). In brief, the toxicity was as follows ; low hemoglobulin (

< 8 g/dl) in 23.7% of tests, low polymorphonuclear leukocytes count (< 500/mm$^3$) in 40.7% of tests, low platelet count (< 100,000 mm$^3$) in 37.0% of tests, elevated blood urea nitrogen (BUN)/creatinine in 46.3% of tests, herpetic infection in 21% of patients, ototoxicity in 8% of patients, and syndrome of inappropriate secretion of antidiuretic hormone, fever with neutropenia, paralytic ileus in 4% of patients, each. Though doses of chemotherapeutic agents were modified in 38% of treatment cycles, all the planned chemotherapy schedules were finished. There were no mortalities related to the chemotherapy.

### Prognostic factors

The prognostic factors analyzed were 1) age (3 years or younger vs. older than 3 years), 2) sex, 3) Chang's T-stage ($T_{1-3a}$ vs. $T_{3b-4}$) and M-stage ($M_0$ vs. $M_{1-4}$) (Chang et al., 1969), 4) the extent of surgical removal of the tumor (95% or more vs. less than 95%) and the application of adjuvant chemotherapy (postoperative radiation therapy only vs. postoperative radiation plus chemotherapy).

### Role of adjuvant chemotherapy in each risk group

The role of adjuvant chemotherapy was studied in the 'average risk' and 'poor risk' groups. The survival outcome of patients who received irradiation and chemotherapy were compared with the results of patients who had irradiation only in each risk group. For the decision whether the chemotherapy should be given or not, the 'poor risk' was defined as brain stem involvement, a definite residual mass, Chang's stage $M_{1-4}$ and age younger than 2 years. However, for the statistical analysis, 'poor risk' was defined as the presence of a definite residual mass and Chang's M-stage. T-stage was not used as a criteria of risk because the brain stem involvement is strongly related to the extent of surgical removal and the significance of minimal brain stem involvement is questionable. Also age was excluded from the criteria of risk because no cases younger than 2 years were irradiated (patients not irradiated were excluded from this comparison).

### Statistical analysis

Data were analyzed statistically using PC-SAS (Strategic Application Software) interfaced with an IBM personal computer. The 3yS and 5yS were calculated by the Kaplan-Meier method. The log rank test was used to compare the differences of survival among subgroups of patients defined by each of the prognostic factors. Weibull's model was applied for the multivariate analysis of prognostic factors.

## RESULTS

### Survival rates and period of recurrence

For the 78 patients treated from 1972 to 1992, the 3yS and 5yS were 57.4% and 47.3%. At 3 years after surgery, 27 cases died of recurrence while 26 were followed up without evidence of disease (NED). At 5 years after surgery, 31 cases died of recurrence and 15 were followed up NED. The longest time from surgery to recurrence was 56 months (Fig. 1). All the recurrences were within the risk period of Collins' rule.

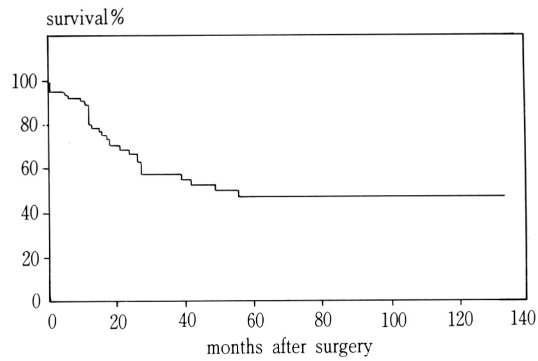


**Fig. 1.** Graph showing the survival rates of 78 patients who were treated during the period 1972-1992. The 3yS and 5yS were 57.4% and 47.3%, respectively.

For the 26 patients treated from 1972 to June 1982, the 3yS and 5yS were 36.3% and 18.2%. There were 2 postoperative mortalities (within one month after surgery ; table 1, the first and second cases). At 3 years after surgery, 10 died of recurrence while 7 were followed up NED. At 5 years after surgery, 14 died of recurrence and 3 were followed up NED. The latest recurrence was at 56 months after surgery. For the 52 patients treated from July 1982 to 1992, the 3yS and 5yS were 67.8% and 64.1%. There were 2 postoperative mortalities (Table 1, the third and fourth cases). At 3

**Table 1.** Postoperative mortalities (death within one month after surgery)

| Age/Sex | Stage | Extent of Removal | Cause of Death | Time of Death |
|---|---|---|---|---|
| 11/M | $T_2$? | PR | cerebellar swelling, hydrocephalus | POD 19 |
| 12/M | $T_{3a}M_2$ | PR | bone marrow suppression, acute renal failure | POD 30 |
| 3/M | $T_3$b? | GTR | tumor site hemorrhage, hydrocephalus | POD 1 |
| 13/M | $T_{3a}M_1$ | NTR | pneumonia | POD 28 |

abbreviations : PR=partial removal (≤ 50% removed), GTR=gross total removal (no evidence of residual mass on operative findings and postoperative imaging study), NTR=near total removal (95-99% removed), POD=postoperative day

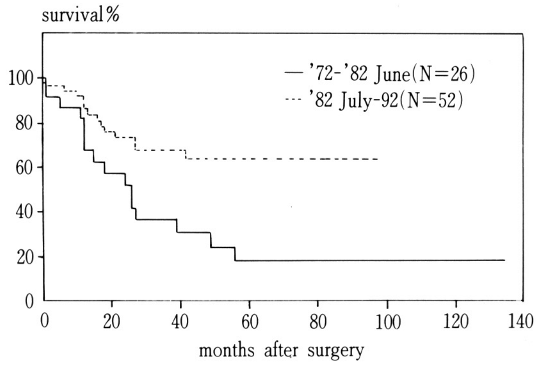


**Fig. 2.** Graph showing the survival rates of 26 patients who were treated during the period 1972-June 1982 (solid line) and of 52 patients who were treated during the period July 1982- 1992 (dotted line). The 3yS and 5yS of the former group were 36.3% and 18.2%, respectively, while those of the latter group were 67.8% and 64.1%, respectively.

years after surgery, 11 died of recurrence and 19 survived NED. At 5 years after surgery, 12 died of recurrence while 12 were followed up NED. The longest time from surgery to recurrence was 42 months (Fig. 2).

### Prognostic factors

The prognostic significance of age, sex, T- and M-stages of Chang's classification, the extent of surgical removal and chemotherapy were analyzed in the 52 patients treated after July 1982. Univariate analysis was done for each factor. Then multivariate analysis was performed.

The 5yS of patients 3 years old or younger was 83.3% and that of older patients (> 3 years) was 63.0%. The difference of survival between the two groups was not statistically significant (Fig. 3, p=0.888). The 5yS of female patients was 84.7% while that of male patients was 47.6%. The difference reached statistical significance (Fig. 4, p=0.024).

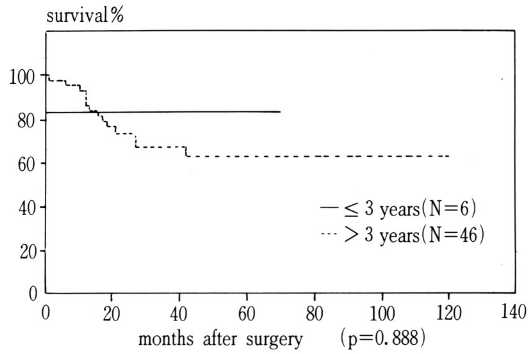


**Fig. 3.** Graph showing the survival rates of 6 patients who were 3 years old or younger (solid line) and of 46 patients who were older than 3 years (dotted line). The difference was not statistically significant.

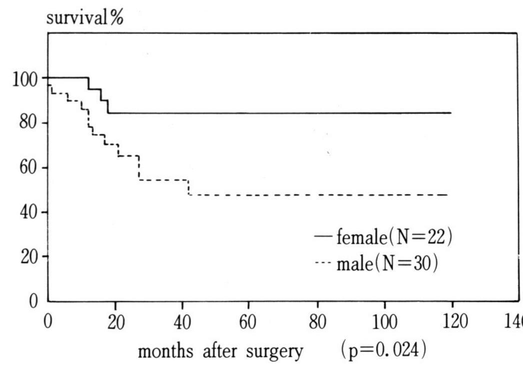


**Fig. 4.** Graph showing the survival rates of 22 female patients (solid line) and of 30 male patients (dotted line). The difference was statistically significant.

The 5yS of patients in which the extent of tumor involvement was $T_{3a}$ or less was 70.6% while the 5yS of those with the stage of $T_{3b}$ or more was 58.6%. The difference of survival between the two groups was not statistically significant (Fig. 5, p=0.554). The 5yS of patients of stage $M_0$ was 81.7% and that of patients with stage $M_1$ or more was 52.0%. The difference was statistically significant (Fig. 6, p=0.028). In 2 cases only biopsy was done. The tumor was removed less than 50% in 25 patients (partial removal), 50-95% in 13 patients (subtotal removal), and 95-99% in 24 cases (near total removal). In 14 cases gross total removal (the operative findings and the postoperative imaging study revealed no evidence of a residual mass) was possible. The 5yS of patients whose tumors were removed less than 95% was 59.8% and that of patients with more than 95% of tumor removed was 67.0%. The difference was not stastically significant (Fig. 7, p=0.289). When the groups were separated at 99% of surgical removal, the p value was 0.332. The 5yS of patients treated with postoperative radiation therapy only was 61.2% and that of patients with postoperative radiation and adjuvant chemotherapy was 83.7%. The difference was not statistically significant (Fig. 8, p=0.144).

Using Weibull's model, multivariate analysis was done for the prognostic significance of sex, T-stage ($\leq T_{3a}$ vs. $\geq T_{3b}$), M-stages ($M_0$ vs. $M_{1-4}$), and the extent of surgical removal ($\leq$ 95% vs. $>$95%). Patients who were not irradiated or of unknown stage were excluded. Thirty four patients were analyzed. Statistically only the M-stage had a prognostic sig-

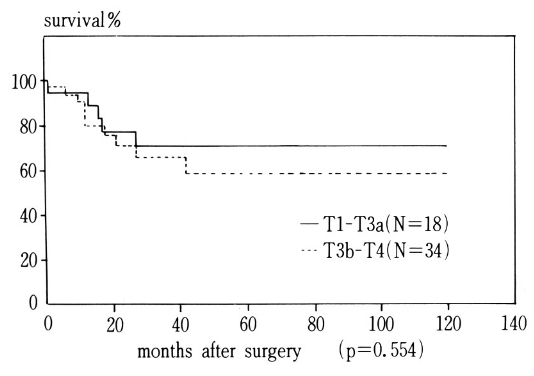


**Fig. 5.** Graph showing the survival rates of 18 patients with the stage $T_{1-3a}$ (solid line) and of 34 patients with the stage $T_{3b-4}$ (dotted line). The difference was not statistically significant.

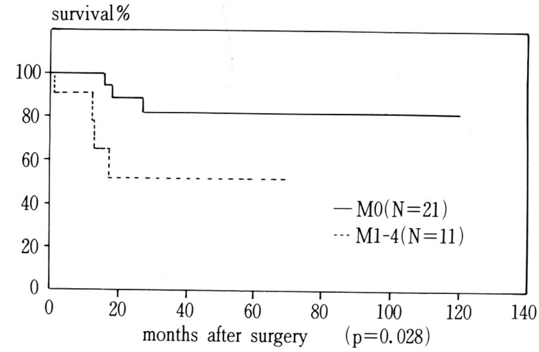


**Fig. 6.** Graph showing the survival rates of 21 patients with the stage $M_0$ (solid line) and of 11 patients with the stage $M_{1-4}$ (dotted line). The difference was statistically significant.

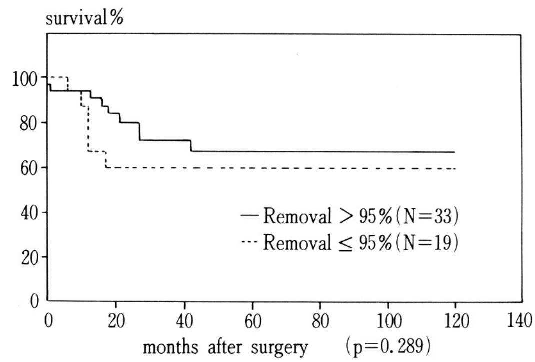


**Fig. 7.** Graph showing the survival rates of 33 patients in which the tumor was removed by more than 95% of initial volume (solid line) and of 19 patients in which the tumor was removed to a lesser degree. The difference did not reach statistical significance.

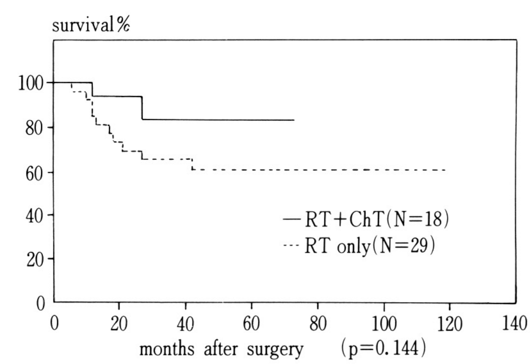


**Fig. 8.** Graph showing the survival rates of 18 patients who were treated with postoperative radiation therapy and chemotherapy (solid line) and of 29 patients treated with postoperative radiation therapy only (dotted line). The difference did not reach statistical significance.

nificance (p=0.004). T-stage (p=0.188), the extent of surgical removal (p=0.403), and sex (p=0.870) were not significant factors.

### Role of adjuvant chemotherapy in each risk group

The effect of adjuvant chemotherapy was investigated in two groups, 'average risk' group and 'poor risk' group. Patients of gross total removal and $M_0$ stage were included in the 'average risk' group. If gross total removal was not possible or M-stage was $M_{1-4}$, the patients were included in the 'poor risk' group.

Of 14 'average risk' group patients, 7 received radiation therapy only and 7 had radiation and chemotherapy. In each treatment subgroup, only 1 patient died. The 5ySs were 85.7% and 75.0%, respectively. The difference was not statistically significant (Fig. 9, p=0.792).

Of 16 'poor risk' group patients, 5 were treated with radiation therapy only (Before 1987, chemotherapy was not performed routinely even for the 'poor risk' group.) and 11 with radiation and chemotherapy. To test the balance of prognostic factors between the two subgroups, the distribution of cases with advanced M-stages (the only significant factor in multivariate analysis) were examined. Cases with advanced M-stages ($\geq 1$) were 3 out of 5 in 'radiation therapy only' subgroup and 8 out of 11 in 'chemotherapy' subgroup (p=1.000). The 5ySs of the two subgroups were 33.3% and 90.0%, respectively. There was a tendency of better survival in the subgroup of chemotherapy though the difference did not reach statistical significance (Fig. 10, p=0.069).

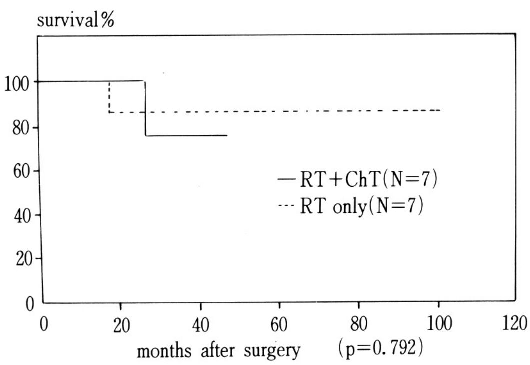


**Fig. 9.** Graph showing the impact of chemotherapy on survival in 'average risk' group revealed no beneficial effects of adjuvant chemotherapy.

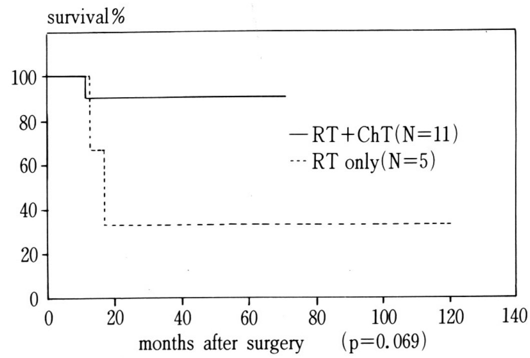


**Fig. 10.** Graph showing the impact of chemotherapy on survival in 'poor risk' group demonstrated a strong tendency to better survival in the group of adjuvant chemotherapy.

## DISCUSSION

### Survival rates and period of recurrence

In 1930 Cushing reported the operative mortality rate and the 3yS of medulloblastoma as 32% and 1.6%. Until the early 1950s, medulloblastoma was a disease of poor prognosis with the 5yS less than 10%. Since the introduction of craniospinal radiation by Paterson and Farr (1953) the treatment outcome of this tumor has remarkably improved. The advent of CT and MRI, the application of microsurgical technique, the improved methods of radiation therapy and the trial of adjuvant chemotherapy have increased the 5yS up to 50-60% by the 1980s. In Korea, Yoon et al reported the 1 year survival rate of 31 cases of this tumor as 61% in 1983. In our previous study reported in 1988, the 3yS of 49 patients treated after 1972 was 49.3% while the 3yS of 23 patients treated lately (after July 1982) was 77% (Cho et al., 1988).

According to the reports of the late 1980s and early 1990s, the 5ySs of the treated (with or without chemotherapy) medulloblastoma cases were 53% – 77% (Caputy et al., 1987 ; Deutsch, 1988 ; Halberg et al., 1991 ; Hoppe-Hirsch et al., 1990 ; Hughes et al., 1988 ; Jenkin et al., 1990 ; Lefkowitz et al., 1988 ; Levin et al., 1988 ; Tait et al., 1990). In the present study, the 5yS of 52 patients treated after July 1982 (including postoperative mortality cases) was 64.1% which is similar to the results of other studies. Comparing with the result of 26 patients treated before July 1982, the survival rates have much improved. Changes of surgical technique (such as the use of operating microscope, the shift from sitting position to prone position, better control of perioperative hydrocephalus and the water-tight closure of dura), refined methods of radiation therapy (such as the shift from anteroposterior : posteroanterior method to orthogonal method and the application of radiation dose more than 50 Gy, mainly around 55 Gy, both of which were proved to be significant prognostic factors by Kim et al in 1988) and probable beneficial effects of chemotherapy may have contributed to the improvements. Details of the recurred cases are presented in another article.

According to Deutsch (1988), 16 of 18 recurrences were within 3 years after surgery and Hughes et al. (1988) reported that the median time from surgery to recurrence in 18 cases was 19 months. In our previous report, all the 10 recurrences were detected within 2 years after surgery. However, in the present study, the longest interval from surgery to recurrence was 56 months. Though there was no case in which the tumor recurred beyond the risk period of Collins' rule, the recurrences do not seem to be limited to the early years after surgery. Belza et al. (1991) stated that a patient can not be regarded as 'cured' unless 8 years have passed without recurrence after surgery. Lefkowitz et al. (1988), Belza et al. (1991) and Latchaw et al. (1985) estimated the rate of recurrences beyond the risk period of Collins' rule (among all the recurrences) to be 43%, 17%, and 2%, respectively.

#### Prognostic factors

As the prognositic factors of medulloblastoma, the influences of age, sex, Chang's classification (T-stage and M-stage), desmosis and differentiation on the histopathological study, the extent of surgical removal, radiation dose, chemotherapy, the findings of immunohistochemical analysis and the results of flow cytometry have been investigated by many authors. In our previous study, the radiation dose was a significant prognostic factor. Thereafter the planned doses of radiation were more than 50 Gy. In the present analysis, the prognostic significances of age, sex, T-stage, M-stage, the extent of surgical removal and chemotherapy were observed. Multivariate analysis was done for those factors. However, the chemotherapy was excluded in the multivariate analysis because the influence of chemotherapy on the outcome was different in different subgroups of patients. The prognostic significances of the findings of immunohistochemistry for cellular differentiation and the results of flow cytometry are presented in another article.

Concerning the prognostic significance of patient age, many authors have reported that patients younger than 2 to 4 years did poorer than older patients (Allen et al., 1985 ; Choux et al., 1983 ; Evans et al., 1990 ; Hughes et al., 1988 ; Packer et al., 1984 ; Roberts et al., 1991) though Lefkowitz et al. (1988) denied its significance. In the present analysis, though the size of the young age group was too small to be compared, age was not a significant prognostic factor.

Tait et al. (1990) and Roberts et al. (1991) reported a better outcome in female patients while Caputy et al. (1987) and Lefkowitz et al. (1988) did not find any prognostic significance of sex. Our results revealed a significantly better outcome in female patients. As shown in multivariate analysis, the effect of sex was indirect and related to the other factors such as M-stage and T-stage.

Like the present study, the majority of authors agree to the idea that Chang's classification T-stage does not have a significant prognostic influence (Caputy et al., 1987 ; Cho et al., 1988 ; Choux et al., 1983 ; Evans et al., 1990). Though the T-stage was one of the major determinants of the clinical performance status, the extent of surgical removal and the pre-radiation tumor burden, the impact on the outcome did not reach statistical significance.

Except for the reports of Berry et al. (1981) and Caputy et al. (1987), all the studies regarding the influence of Chang's classification M-stage demonstrated the statistical significance on the outcome (Allen et al., 1985 ; Deutsch, 1988 ; Evans et al., 1990 ; Jenkin et al., 1990 ; Packer et al., 1984 ; Tait et al., 1990). It is not suprising that the disseminated tumors are more difficult to irradicate even with chemotherapy. Also in the present series, M-stage showed a strong prognostic influence on the survival outcome.

The role of surgical removal is still controversial. Though most neurosurgeons try to remove the tumor as much as possible, the radical approach was not unaminously supported by the statistical analysis of the treatment outcome. Caputy et al. (1987), Evans et al. (1990) and Lefkowitz et al. (1988) could not find any significant benefit of radical removal while Choux et al. (1983), Hughes et al.

(1988), Jenkin et al. (1990) and Tait et al. (1990) reported better outcomes in cases with radical removal. The results of the present study failed to show the prognostic significance of radical removal.

### Role of adjuvant chemotherapy

The role of adjuvant chemotherapy was investigated by the comparison of outcomes of patients treated with radiation therapy only and of patients treated with radiation therapy plus chemotherapy. To avoid selection bias, cases who were irradiated but not treated with chemotherapy due to poor performance scale were excluded from the statistical analysis. The influence of chemotherapy was different in different risk groups. Therefore chemotherapy was not included in the multivariate analysis. Our study revealed that the addition of chemotherapy had a strong tendency (p=0.069) to better outcome in the 'poor risk' group. In the 'average risk' group, the benefit of chemotherapy was not shown.

The impact of chemotherapy has been studied in various series. A majority of the reports agree 1) chemotherapy does not improve the outcome of medulloblastoma patients which include all risk groups, 2) though it has beneficial effects in the early postoperative period the effects in the late follow-up period are questionable, and 3) in selected patient groups, chemotherapy has significant beneficial effects on the outcome. Allen et al. (1985, CCNU, vincrinstine and prednisolone), Bloom (1982, the study of SIOP : CCNU and vincristine), Choux et al. (1983), Evans et al. (1990, the study of CCSG : CCNU, vincristine and prednisolone), Krischer et al. (1991, the study of POG : MOPP), Loeffler et al. (1988, cisplatin and vincristine), Packer et al. (1988, CCNU, cisplatin and vincristine) and Tait et al. (1990, the study of SIOP) reported the significant benefit in the 'poor risk' group which includes cases with any one of the following risk factors - young age, high T-stage, high M-stage and a significant amount of residual tumor. Though the size of each patient group should be larger for a better statistical analysis, our results were consistent with the view that chemotherapy is indicated at least in the 'poor risk' group. Recently Packer et al. (1991) reported a better outcome in the 'poor risk' group treated with chemotherapy compared with that of the 'average risk' group treated with postoperative radiation therapy only. They insisted chemotherapy should be applied to both risk groups. However, our data and other authors did not support the idea. Still we perform chemotherapy randomly in the 'average risk' group. Concerning the '8 in 1' chemotherapy in medulloblastoma, the response rate was reported as 76.5% by Chastagner et al. (1988).

In 1989 we introduced pre-radiation chemotherapy. According to Kovnar et al. (1990) and Kretschmar et al. (1989), pre-radiation chemotherapy has less myelosuppression and better drug delivery due to the tumor-induced blood brain barrier breakdown and the lack of radiation-induced vasculopathy. They reported good responses to this method.

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