Result of Radiation Therapy of Cerebellar Medulloblastoma
—with Emphasis on the Neuraxis Dose—

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Treatment of cerebellar medulloblastoma has been much improved with modern surgical technique for gross total tumor removal and adequate radiation therapy for the whole craniospinal axis. Questions have been arosen about the optimal radiation dose for the preventive treatment of whole cranium and whole spinal axis. Recently, many authors have reported their treatment results as comparable to older data, using lower than conventional dose of 3,600 cGy~4,000 cGy. For 50 patients treated between 1981 and 1990 at the Department of Radiation Therapy of SNUH, retrospective analysis was done for the treatment result, especially the neuraxis control, by radiation dose for the presymptomatic area of the disease. Analysis only by total spinal dose did not give any significant difference. But further analysis by following patient group; 3,600 cGy/150 cGy (n=6), 3,000 cGy/150 cGy (n=10), 2,400 cGy/150 cGy (n=17) and 2,400 cGy/100-120 cGy (n=11) showed significant improvement of neuraxis control by decreasing order (p=0.003). There was no significant difference in overall survival between the groups. For the 19 patients who had been confirmed initially as having no neuraxis disease, TDF 30 was the cur-off value that could prevent neuraxis failure (p=0.004). We couldn't define any TDF value that give reasonable control for the patient group with positive CSF study at initial diagnosis.

Key Words: Medulloblastoma, Radiation therapy, Neuraxis control, Dose, TDF

INTRODUCTION

The treatment result of cerebellar medulloblastoma, has been markedly improved since Cushing[1], over fifty years ago, demonstrated that only one of sixty one patient treated by operation and reoperation without adequate XRT were alive 3 years later. Acknowledgement of the nature of the disease of frequent dissemination through the CSF pathway and prophylactic treatment of that area by craniospinal radiation therapy (CSRT) was the turning point of the treatment of this disease. Accurate assessment to the disease extent by post-surgical staging and neuraxis evaluation by repeated cytologic examination and myelogram, aggressive resection with less operative morbidity, delivery of higher radiation dose to the posterior fossa all have contributed to the improved disease free survival rates. Many institutions reported their overall and disease free survival rates as high as 60-70%. Multi-institutional trial resulted in 50-60% of 5 year overall survival rate for group of patients both with low and high risk factors. It is well known that high dose over 5,000 cGy to the posterior fossa is essential for local control and better survival rates[2], but there have been much debates in the optimal radiation dose for the control of neuraxis. Best results have been obtained with doses between 3,600-4,000 cGy to the whole brain and 3,000-3,600 cGy to the whole spinal axis historically. As there comes to be many long-term survivors, recent literature has stressed the potential hazards of irradiation upon the growing central nervous system. Of particular concern are the radiation effects upon the intellectual and physical development of younger children. Growth retardation due to irradiation to the growing spine and/or hypopituitarism secondary to irradiation to the hypothalamo-pituitary axis is another common problem of CSRT[3~6]. These observation prompted us to lower the dosage of CSRT step by step to the current dose 2,400 cGy to the spinal axis and 3,600 cGy to the cranium while delivering higher dose up to 5,580 cGy to the posterior fossa. In previous paper[7], we have analysed our treatment result with emphasis on the radiation technique and dose to the posterior fossa. Now, We are presenting our treatment result by the varying dose of radiation to the craniospinal axis.

MATERIALS AND METHODS

Records of fifty patients with histologically proven medulloblastoma were reviewed, who was treated between July 1981 and July 1990 at the

Department of Therapeutic Radiology of SNUH (Table 1). Patients characteristics are summarized in Table 2. Age ranged 3 to 55 years with median age of 13 years. Twelve patients (23%) were older than 16 years and nine patients (18%) were younger than 5 years. All had classical medulloblastoma as their pathological finding except six patients with desmoplastic variant. After operation, routine postoperative CT were done for 42 patients (84%) within one week of operative day. Extent of tumor resection was evaluated by this postoperative CT finding if there was residual tumor or not. CSF analysis was done for 33 patients (66%), in most cases at 10 to 14 postoperative days. We used the last cytologic result that was done immediately before starting CSRT when multiple examinations had been done. Routine myelogram was not checked until recent days but was done only for the patients who had shown positive cytologic result.

1. Extent of Surgery

It is unclear whether the extent of resection is best defined by the intraoperative observations of the surgeons or by the postoperative CT. We mainly depended upon the CT findings whether there was residual enhancing lesion or not (Table 3). Shunt procedure was done in 16 patients (32%). V-P shunt was the most common procedure.

Table 1. Patient Entry (1981-1990)　　SNUH

No registered	50
No analyzed	50
Follow-up period (months)	
range	1~134
median	66

Table 2. Patient Characteristics

Characteristic	No of patients (%)
Sex	
Male	31 (62)
Female	19 (38)
Age (year)	
3~ 5	9 (18)
6~10	18 (36)
11~15	11 (22)
16~20	5 (10)
21~55	7 (14)
ECOG status	
0~2	36 (72)
3~4	14 (28)
Histology	
classical	44 (88)
desmoplastic	6 (12)
Total	50 (100)

Table 3. Extent of Surgery

Surgery	No of patients (%)
Biopsy only	1 (2)
Subtotal resection	34 (68)
Total resection	15 (30)
Total	50 (100)
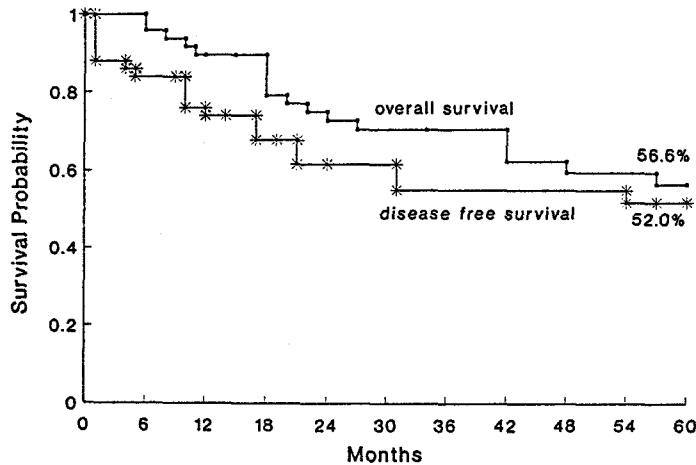
Fig. 1. Survival.

Table 4. Radiation Dose		
Area	Dose (cGy)	No of patients (%)
Posterior fossa	4,000	1 (2)
	5,000	6 (12)
	5,500	43 (86)
Whole brain	3,000	4 (8)
	3,600	15 (30)
	4,000	26 (52)
	4,500	3 (6)
	5,000	2 (4)
Whole spine	None	1 (2)
	2,400	29 (56)
	3,000	14 (28)
	3,600	7 (14)

2. Radiation Therapy

Radiation therapy was usually started within 3 weeks of operative day using orthogonal technique for CSRT. Whole brain field extending to C3 or C4 was treated by lateral ports and the whole spine was treated by one or two ports according to the length of spine. Lower margin of brain field abutted on the divergent upper margin of spine field at C3 or C4 level initially and was shifted up 1 to 2 cm at accumlated dose of 1,080 cGy. All patients were treated by Cobalt 60 Teletherapy Unit. Posterior fossa was treated up to 5,580 cGy in 43 patients (86%). Whole brain dose ranged from 3,000 to 5,
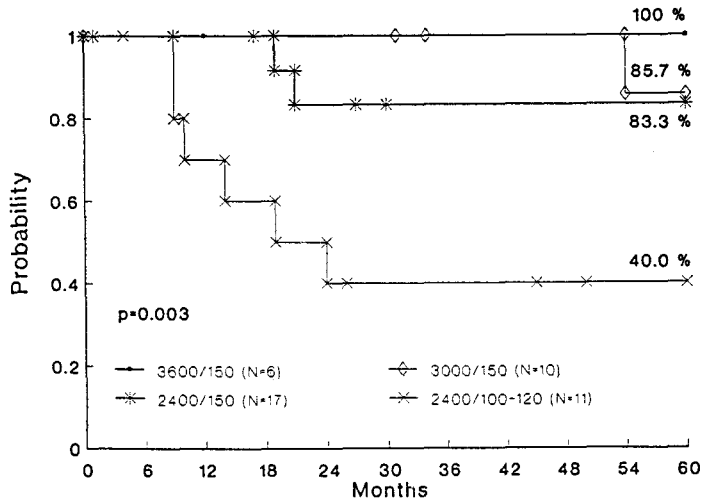
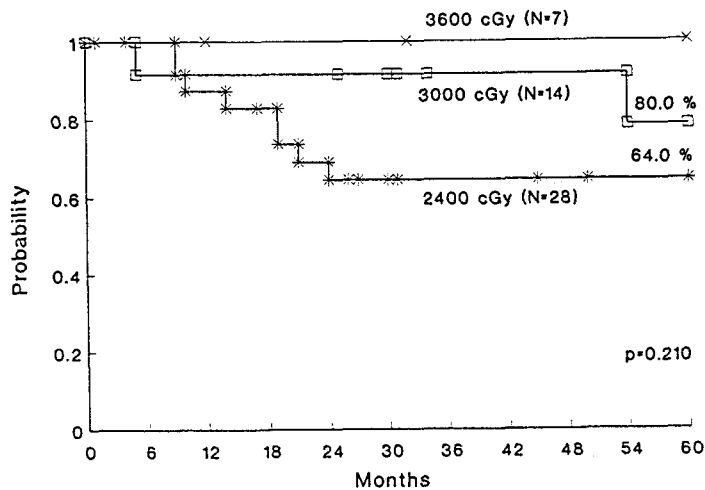Fig. 2. Neuraxis control by total spinal dose.

Fig. 3. Neuraxis control by Radiation dose.

000 cGy. Most patients received 3,600 (30%) or 4, 000 cGy (52%) with 150 to 180 cGy daily fraction size. Whole spinal axis was treated with total dose ranging from 2,400 cGy to 3,600 cGy. Dose was calculated at the point of anterior margin of spinal cord. Most patients received 2,400 cGy (29/50, 58%) or 3,000 cGy (14/50, 28%) with 100 to 150 cGy daily tumor dose. For seven patients, 3,600 cGy was given. One patient didn't receive spinal RT for deterioration of general condition. There was no significant difference in the distribution of patients for each dose group whether there was initial neuraxis disease or not. Routine blood count was checked at least once and in most cases twice a week during CSRT. Distribution of the patients according to the radiation dose is shown in Table 4.

3. Chemotherapy

Chemotherapy was given to thirteen patients; for seven patients with recurrence and for six patients with postoperative adjuvant intent. For latter six patients treated in late 1980, two cycles of pre-RT "eight in one" combination drug therapy was done before the initiation of CSRT. They had at least one of bad prognostic factors such as initial T3, T4 primary tumor, subtotally resected tumor, presence of initial neuraxis disease.

4. Analyses

There have been no exclusion of entered patients in the analysis of overall and disease free survival. But there was one patient excluded in the analysis of neuraxis control who had not received spinal radiation therapy. Survival rates were calculated by Kaplan-Meier method. The day of operation was used as the base of follow up.

RESULTS

1. Survival

Overall and disease free survival rates were 67%, 56% at 3 years and 56%, 53% at 5 year respectively (Fig 1). Follow up period ranged from 1 to 134 months with median of 66 month. Twenty one patients died and twenty nine patients were censored at the time of this analyses. Twenty six patients were known to be fee of disease.

2. Patterns of Failure and Neuraxis Control

Twenty three patients have failed after completion of all treatment. Among them, initial failure sites were identifiable for twenty two patients (Table 5). Except one patient with multiple bone metastasis, all initial relapses occured within central nervous system. All failures were found within 3 years after completion of treatment. Eleven of 23 patients (47. 8%) have relapsed only at their primary site. Another two patients had a component of neuraxis failure with their posterior fossa recurrence; at periventricular space and spinal cord respectively. Seven patients (14%) developed recurrent disease only on their CSF pathway. It included 3 isolated spinal failures, 2 disseminated CSF failures with clinical signs of multi-level neurologic deficits and one periventricular seeding. Another one patient developed frontal lobe mass at 19 month of follow up. He had received 4,000 cGy to the brain but

Table 5. Patterns of Falulre

Failure site	No of patients (%)
PF* only	11 (47.8)
Neuraxis only	7 (30.4)
Extraneural	1 (4.3)
Combined	3 (13)
PF+PVS**	1
PF+spinal SAS+	1
Spinal SAS+BM++	1
Unknown	1 (4.3)
Total	23 (100)

*PF: Posterior fossa   **PVS: Periventricular space
+SAS: Subarachnoid space   **BM: Bone marrow

Table 6. Analyses of Neuraxis Failures by Radiation Dose

| Total dose (cGy) | Fraction size (cGy) | No of pts | Initial neuraxis disease | | | Total |
			Neg	Pos	Unknown	
3,600	150	6	0/5	0/1	0/0	0/6
	100~120	1	0/0	0/1	0/0	0/1
3,000	150	10	0/2	0/2	1/6	1/10
	100~120	4	0/2	1/2	0/0	1/4
2,400	150	17	0/5	2/5	0/7	2/17
	100~120	11	4/5	1/4	1/2	6/11

treatment had been stopped for 2 months during CSRT for meningitis and wound infection. Long rest period and inadvertent eye block both seem to be contributing factors for the recurrence. A patient with clinical signs of disseminated CSF seeding at 9 month of follow up had initial spinal metastatic deposit at the level of lumber spinal cord.

3. Neuraxis Control by Spinal Axis Dose

Neuraxis control rate seemed to be improved as total spinal dose goes up from 2,400 cGy to 3,600 cGy but analyses by total dose did not give statistically significant value (p=0.210) (Fig. 2). When total spinal axis doses were further divided by daily faction size, statistically significant improvement in the neuraxis control was found as higher spinal doses were used with larger fraction size (p=0. 003) (Fig. 3).

Treatment scheme of patients with neuraxis failure are seen at table 6. Patients who had no neuraxis disease at diagnosis did well with spinal axis dose of 2,400 cGy only when it was given by not too small fraction size. There was no neuraxis failure in the patient group who was given 2,400 cGy with 150 cGy fraction size but four of five failures who was given the same total dose with traction size of 120 cGy or less. For patients with positive neuraxis disease initially, 2,400 cGy appears to be obviously less optimal dose regardless of daily fraction size. There was no neuraxis failures among four patients who were treated by 3, 000 cGy with fraction size 150 cGy or more. On the contrary, one out of two patients who had been given 3,000 cGy with fraction size less than 120 cGy have failed in the neuraxis.

4. Neuraxis Control by TDF Value for Spinal Dose

For heterogeneity and variability of the patients in the duration of interruption during treatment days, TDF factors were calculated for each spinal dose. TDF ranged from 22.7 to 50.8 for whole patients group. Median TDF value for patients with negative and positive neuraxis disease was 31.6 and 35.9. Mean TDF value was 33.9 and 36.7 respectively. TDF 40 was the most consistent value that neuraxis failure developed among all patients who received CSRT regardless of initial neuraxis disease although it was not statistically significant. (Nine of thirty four in patients with TDF below 40 and one of fourteen patients with TDF below 40 had neuraxis failure.) When only those patients with no initial neuraxis disease were considered, TDF 30 was revealed as statistically significant value that

control neuraxis of cytology-negative patients (p= 0.004). For patients with positive neuraxis disease at diagnosis, definitive TDF value above which neuraxis failure can be controlled could not be drawn.

DISCUSSION

Recently reported series of results of treatment of medulloblastoma from major centers indicate 5 year disease free survival of 60-65% following surgery and CSRT[2,8]. Multi-instiliutional trials conducted between 1975 and 1980 have shown 50 -55% disease free survival at 5 years[9~11].

The operating microscope, laser, ultrasonic aspirator and other new components of the surgical armamentarium have made more complete resection possible[3,12]. Uncontrolled, nonrandomized retrospective reports primarily from single institution, have concluded that the extent of surgical resection impacts greatly on the probability of long-term survival of patients with medulloblastoma[13,14]. However, there is no agreement regarding what constitiutes a complete excision. It is unclear whether the extent of resection is best defined by the intraoperative observations by the surgeon or postoperative CT or a combination of both measures. Most observers would now agree that possibly the latter assumes major importance[15]. It has been suggested that any enhancement in the surgical bed on CT within the first 48 hours after operation represents tumor, while enhancement in the next few days may represent either tumor or postoperative changes although there is still controversies[16,17]. We have routinely checked postoperative CT 1-2 days after operation for most patients with medulloblastoma. The term "total resection" used here indicates that there is no residual enhancing area in postoperative CT. Serveral cases which showed invasion of structures such as floor of fouth ventricle, middle cerebellar peduncle or posterior cerebellar artery during operation that might have been left were included in the totally resected group because there was no enhancing area in postoperative CT. There was no difference in 5 year overall and disease free survival between the "totally resected" and "residual" group in this study.

The dose of radiotherapy needed for effective control of subclinical disease has not been well established. Neuropsychologic and endocrinologic sequalae of treatment and retarded spinal growth, which are believed primarily due to

whole brain and whole spine irradiation, have led to some recently to question the validity of conventionally used dose of radiation. It seems unlikely that the volume of radiation can be significantly decreased without increasing the incidence of disease recurrences. As an example, a recent report has documented isolated tumor recurrence in the cribriform plate when this area was inadvertently shielded during treatment[18]. There were five frontal lobe failure in Halberg's series which seemed to be due to too generous eye block[19]. There was one patient in this study who developed frontal lobe mass 19 months after completion of radiation therapy. 4,000 cGy was given to the whole brain and review of the simulation film revealed likelihood that disease would be missed at the area of cribriform plate. We used anterior electron beam boost to the area of cribriform plate for six patients treated in later time.

The best survival rates have been obtained after delivery of doses between 3,600 and 4,000 cGy to the entire craniospinal axis, supplemented to a total dose of 5,500 cGy to the primary site[20]. These dosages are rather arbitrally chosen and have not been determined by careful comparative studies. It has been suggested, but not proven, that patients who are carefully staged and found to have localized disease (standard or low-risk patients) could equally well be treated with a reduced dose of CSRT[18]. A recent uncontrolled study of 22 patients, by Tomita and Mclone[3], has shown good short-term survival in chidren with totally resected tumors after treatment with 2,500 cGy of CSRT. In that study, among 8 patients with relapses, 6 had evidence of seeding along the CSF pathway. Three of them showed diffuse CSF seeding and 3 had posterior fossa recurrence associated with cord or CSF disease. Edward et al of JCRT (Joint Center for Radiation Therapy)[8] reported result of 60 patients who were treated either by low dose below 2,700 cGy or higher dose above 2,700 cGy for CSRT. There was no statistically significant difference in survival rates between patient group by dose. There was only one isolated spinal subarachnoid space seeding in a patient who was given 2,950 cGy. Another one who had been given 2,400 cGy showed concurrent failure in the posterior fossa. Halberg et all at UCSF (University of California, San Francisco)[19] reported the result of comparison of 2,400-2,600 cGy CSRT for 26 patients and 3,600-4,000 cGy for 39 patients. In that study, procarbazine and hydroxyurea was given prior to and during RT. Isolated spinal failure was seen in two patients, one

in the low dose group and the other in the high dose gorup. Spinal subarachnoidal failue was a component of failure in five patients and four of them belonged to high risk group and received low dose of CSRT. Brand et al[21] reported their result of pilot study for 38 patients. Of 14 patients among 19 failures in patients with high risk factors, 10 (71%) failed in the primary site and 8 of them showed concurrent spinal subarachnoid seeding. Another one patient who developed supratentorial and spinal failure had extraneural metastasis. In this pilot study, there was no significant difference in failure pattern between low dose and high dose group. The results of nonprospective trials sited above shows no significant difference in survival rates among the patients treated with low dose and high dose CSRT. They report lower survival rate in the patients with high risk factors but not depending on the CSRT dose used. They say that their main portion of treatment failure has continued to be the one in the posterior fossa and low dose CSRT did not increase the failures in CSF pathway. But on reviewing above results, one should speculate that there were considerable number of failures in the cranial and spinal subarachnoidal space, as the only site or as a component of failure. Also, it should not be missed that there were only small number of patients who were fully staged with repeated CSF cytology and myelography as initial diagnostic procedures. In Tomita's series, it is criticized that follow up period was relatively short. In our series, failures only in the posterior fossa (11/23, 48%) consisted rather smaller proportion compared to the other single institution experiences. Isolated relapse in the spinal subarachnoid space counted three (13%). Eight patients failed only in the CSF pathway (34.8%) and 3 of them had an isolated relapse in the spinal subarachnoid space. Another two patients developed CSF disease as a component of failure during the course of disease. These figures show relatively low proportion of primary site failure and higher proportion of neuraxis failure compared to other seires. We have applied low dose below 3,000 cGy to spinal axis since April 1987. Dose for the whole brain was also lowered but not below 3,600 cGy as there would be more tumor burden in the cranial subarachnoid space and ventricles although many authors says that there is no reason to use higher dose to the cranical subarachnoid space if there is microscopic disease except the fact that radiation tolerance dose is slightly higher for brain than that of spine. Since many recurrences have been still in the

primary site, there seems to be no difference in the overall and disease free survival whether patients had low or standard spinal axis doses. Neuraxis control rates showed some trend that higher total spinal dose gives better control rates than lower spinal doses. Small fraction size we have adopted to avoid treatment rest period affected neuraxis control rates badly. In this study, patients who were given higher total spinal axis dose by proper fraction size did much better in the view of neuraxis control. No patients with higher total spinal dose (3, 600 cGy) failed in neuraxis whether they were given by small or larger fraction size although the number of patients was small. Two of those who were given 3,600 cGy spinal dose were found to have primary site failure at 12 and 15 month respectively and one died of trafffic accident. As seen at table 5, for those patients with negative neuraxis disease on diagnosis, reduced spinal dose as low as 2,400 cGy seems to give reasonable neuraxis control only if the dose was given by not too small fraction size. TDF value 30 is considered optimal for the patients with negative initial neuraxis disease. On the other hand, for patients who had positive neuraxis disease initially, we couldn't find optimal TDF value in this analysis. Dose below 3,0u0 cGy with less than 120 cGy fraction size appears to be inadequate. At least 3,000 cGy with fraction size not less than 150 cGy, and more safely, 3,600 cGy which had been given conventionally would be needed for the patients whc had positive CSF cytology without gross neuraxis disease. For the patients who had a gross metastatic deposits within their CSF pathway, a boost dose would be needed up to curative level. In this retrospective study, accurate comparison between each group of patients with different spinal axis dose could not be done. First, there were small and uneven number of patients to each group. Second, cranial and spinal radiation dose were not matched as same low or high dose range. Whole brain dose were kept to be high until April 1987 whereas spinal dose had been lowered as early as July 1984. So, many patients receiving 2, 400 cGy to their spinal axis still received 4,000 cGy to their brain. Uncontrolled spinal subarachnoidal disease might have affected cells reside in the cranical subarachnoid space and ventricle. Cells which had been initially killed at cranial subarachnoid space might have been contaminated by travelling cells in the spinal subarachnoid space and presented recurrent disease within the cranial or spinal neuraxis.

A prospective randomized trial jointly conducted by the POG and CCSG which was begun in 1986 to test the efficacy and relative toxicities of reduced-dose neuraxis irradiation (2,340 cGy/21F) compared to 3,600 cGy standard CSRT in favorable subset children with medulloblastoma[23]. This study is said to be halted in Dec. 1990, followed by interim analysis which showed an excess of both isolated neuraxis failures and overall treatment failures in the reduced-arm. The result was reported in 1991 Astro meeting and has not yet published in article, so we couldn't see the detail of radiation therapy and characteristics of the patients entered.

It is quite uncertain that failures in the neuraxis is due entirely to low spinal axis dose. Good treatment technique in CSRT to avoid cold spots in neuraxis, accuracy in daily set-up and interruption during te treatment days; these are all to be considered and controlled for proper comparison and analsyses of the treatment result among the centers. But to achieve maximum effect of CSRT in medulloblastoma, it is thought to be too early to decrease the dose of whole brain or whc'e spine until there is more clear definement of favorable patient group to which we can apply lower dose of CSRT or improved survival is demonstrated with the addition of chemotherapy. Less morbidity and neurologic sequalae might be expected with electron beam spinal RT as Moshe et al the MDAH have tried. Gasper et al[25] says that they could reduce the dose to normal tissues anterior to spinal cord (i.e., bone, bone marrow, thyroid gland, esophagus, ovaries and testes) by using electron beam spinal irradiation. It is another point that we shouldn't miss that posterior fossa disease is still to be better controlled. Giving higher dose to the posterior fossa by multiple daily frctionation is another concern in this view.

In this study, there were different observation compared to the results of other centers for the patients above 16 years of age. Many reports tend to show somewhat better survival rates in adult patients with medulloblastoma[26~28] but it was not the case of ours. They showed worse disease free survival although it was not statistically significant. Mean and median age of our adult patients was older than that of other reports. Some explain their better survival rates as higher proportion of laterally placed tumor, higher incidence of desmoplastic variant among adult patients and more indolent nature of their disease. Hughes et al[26] reported that posterior fossa failure was the most common failure pattern as we have seen in the children group but all failures were observed beyond 3 years after

completion of treatment in adult group. In our cases, 6 of 12 adult patients failed and only 2 of them showed primary site failure as their cause of death.

We have been trying systemic chemotherapy in postoperative adjuvant setting in recent years. Current reports of multi-institiutional trial for chemotherapy for patients with high risk factors[10] encouraged us to use adjuvant systemic therapy for the patients whose tumors were subtotally resected, or having initial T3b and T4 tumors by Chang's postoperative staging and for patients with established CSF disease initially. The "eight in one" regimen we use is expected to minimize myelosuppression by limiting the exposure to myelotoxic agents to less than 24 hours without compromizing antineoplastic effect. It includes drugs that is both lipid-soluble and water-soluble drug and cycle-active and cycle-independent agent. We expect cytoreductive effect by two cycles of chemotherapy done prior to XRT and better control of microscopic disease within the entire craniospinal axis by the drugs. The result would come later.

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═ 국문초록 ═

전중추신경계 조사선량을 중심으로 한 수아세포종의 방사선치료성적

서울대학교 의과대학 치료방사선과학교실

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후두와에서 발생하는 수아세포종은 육안적 전 종양적출술후 전 중추신경계와 원발부위에 적절한 양의 방사선을 조사 함으로써 50~60%의 장기생존율을 보이는 종양이다. 일반적으로는 후두와에 5,000 cGy 이상의 고선량을, 그리고 전중추신경계에는 3,600~4,000 cGy의 방사선 조사량을 사용하므로써 가장 좋은 결과를 보였으나 최근 장기무병 생존율이 높아짐에 따라 방사선치료로 인한 신경학적 합병증 및 성장, 지능장애의 문제들이 대두되어 많은 저자들이 예전보다 적은량의 방사선을 사용하여 그와 비슷한 결과를 얻을 수 있음을 주장하고 있다. 서울대학교병원 치료방사선과에서는 1981년부터 1990년도 까지의 50명의 환자들을 대상으로 후향적 분석을 실시하여 전중추신경계의 조사선량에 따른 치료성적을 분석해 보았다. 50명 환자중 분석 당시 NED 상태였던 21명에서의 관찰기간은 12개월에서 134개월이었고 그 중앙값은 71개월이었다. 한명을 제외한 모든환자에서 예방적 중추신경계조사가 실시되었으며 척추조사선량은 7명에서 3,600 cGy, 14명에서 3,000 cGy, 그리고 29명에서 2,400 cGy가 조사되었다. 2,400 cGy 조사군을 다시 fraction size로 세분하여 보았을 때 네 치료군 사이에서 생존율의 차이는 없었으나 Neuraxis control에 있어서는 의미있는 향상을 보여주었다(p=0.003). 치료중 휴식기간과 fraction size를 동시에 고려하기 위하여 척추조사선량을 TDF 값으로 환산하였을 때 진단당시 neuraxis disease가 없었던 환자에서는 TDF 30 이 통계학 적으로 의미있게 (p=0.004) neuraxis control을 좌우하는 값으로 보였다. 진단당시 neuraxis disease가 있었던 군에서는 neuraxis control을 하는데 기준이 될 수 있는 정확한 TDF 값을 발견할 수 없었다.