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The treatment of medulloblastoma

Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone

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✓ In a prospective randomized trial designed to study the effectiveness of adjuvant chemotherapy following standard surgical treatment and radiation therapy, 233 eligible patients with medulloblastoma were treated by members of the Childrens Cancer Study Group and the Radiation Therapy Oncology Group. Eligible patients were randomly assigned to receive radiation therapy with or without adjuvant chemotherapy consisting of 1-(2-chloroethyl)-3-cyclohexyl-nitrosourea (CCNU), vincristine, and prednisone. The estimated 5-year event-free survival probability was 59% for patients treated with radiation therapy and chemotherapy and 50% for patients treated with radiation therapy alone, a difference which is not statistically significant. The 5-year survival probability was 65% for both groups. Although the treatment difference was not statistically significant when all patients were combined, in the small number of patients with more extensive tumors, event-free survival was better in the group receiving chemotherapy (48% vs. 0%, $p = 0.006$). In these latter patients the survival time is also significantly prolonged. Extent of disease (as measured by the M staging criteria described by Chang) and age at diagnosis were significantly associated with outcome; advanced disease and young age had a worse prognosis. The extent of tumor resection was not an independent prognostic factor. It is concluded that chemotherapy does not benefit patients with low-stage medulloblastoma, but may benefit those with more advanced stages of disease.

KEY WORDS • **brain neoplasm** • **medulloblastoma** • **radiation therapy** • **chemotherapy** • **CCNU** • **vincristine** • **prednisone**

In 1974, members of the Childrens Cancer Study Group (CCSG) and the Radiation Therapy Oncology Group (RTOG) proposed a study to determine if adjuvant chemotherapy would increase the survival rate of children with medulloblastoma and malignant infratentorial ependymomas. Secondary objectives of the study were to document the toxicity attendant upon combined treatment and to examine the effect of prognostic factors on recurrence.

Primary malignant intracranial neoplasms account for approximately 20% of malignant disease in children. Medulloblastoma constitutes 18% of the intracranial tumors. During the third National Cancer Survey, 79 medulloblastomas were seen in 6.77 million children under 15 years of age which, on extrapolation to the total United States population, suggests that there are approximately 250 medulloblastoma patients diagnosed annually.[5] Eighty percent of such patients are diagnosed in the first 15 years of life, with a median age

This article is a report from the Childrens Cancer Study Group (CCSG) and the Radiation Therapy Oncology Group. Contributing CCSG investigators, institutions, and grant numbers are given in the Appendix.

of 5 years. Because of the primary site and local infiltration, curative surgical excision is rarely possible. Since this tumor disseminates malignant cells throughout the subarachnoid space via the cerebrospinal fluid (CSF), surgical treatment is followed by radiation therapy (RT) to the entire central nervous system (CNS) axis.

With the combination of surgical resection and maximally tolerated CNS axis radiation therapy, an increasing number of patients survived. Five- and 10-year survival rates varied widely depending in part on two factors: 1) the time period covered by the report, and 2) whether the survival rate quoted included all patients with medulloblastoma seen at the institution, only those referred for RT, or just those who completed the RT course. The report by Chatty and Earle[4] in 1971 includes 201 patients with medulloblastoma seen in their own institution and those reviewed by the Armed Forces Institute of Pathology, with a 5-year survival rate of 12%; however, details of the time period covered or the patients included were not given. In 1969, Bloom, *et al.*,[1] reported a 32% survival rate of patients referred for RT between 1950 and 1964, with the survival rate increasing to 38% for those who completed the course. They mentioned a 25% operative mortality rate. Smith, *et al.*,[12] reporting the University of Minnesota's experience in 1973, gave results of patients treated between 1960 and 1972 with an overall 5-year survival rate of 25%, or 32% if patients with incomplete removal or early deaths were excluded. The most promising results were those by Jenkin,[8] who discussed the result of treatment during two time periods: 1940 to 1952 in which only the cranium received RT, and 1953 to 1965 when total CNS irradiation was introduced. There were no 5-year survivors during the first period and 50% in the second (eight of 15 completing RT). Thus, in the late 1960's and early 1970's, reports varied from 12% to 50% for 5-year survivors with medulloblastoma, with the majority of series reporting 30% to 35% for patients referred to RT departments.

Recurrent medulloblastoma had responded to several chemotherapeutic agents at the time CCSG-942 was conceived. Diverse early reports of chemotherapy for brain tumors included a few children with medulloblastoma, and the response rates were quite high. Lassman, *et al.*,[11] in 1965 and Lampkin, *et al.*,[10] in 1967 each reported cases of recurrent medulloblastoma having significant improvement following treatment with vincristine (VCR), and by the early 1970's review articles suggested response rates on the order of 50% or better.[2] Phase I and II studies of the more recently developed nitrosoureas also included an occasional child with recurrent medulloblastoma who achieved a clinical response to 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU).[7,13] Two pilot studies, employing VCR and CCNU as adjuvant treatment following RT for medulloblastoma, showed that the combination could be tolerated. Preliminary data suggested that the disease-free survival period was improved compared with historical controls (HJG Bloom and J Lemerle: personal communication, 1974).

The agents selected for this study were VCR, CCNU, and prednisone. The first two were chosen since each had a different mechanism of action, and published reports suggested that they were associated with the highest response rate in the treatment of recurrent medulloblastoma. Although VCR was not considered to cross the blood-brain barrier, it was thought to be possibly active against much of the tumor which has no such barrier. The lipid solubility of CCNU made it attractive as an antineoplastic agent for intracranial tumors. Prednisone was proposed for two reasons: 1) to minimize possible undesirable neurological reactions following initiation or withdrawal of drug therapy; and 2) for the theoretical possibility of chemotherapy enhancement. Also, it was hoped that its inclusion in each chemotherapy course would alleviate the need for haphazard administration of corticosteroids for symptoms relating to cerebral edema. It was decided (arbitrarily) to administer chemotherapy for 1 year in the belief that, if disease was not eradicated during this period, further chemotherapy would not likely be effective.

A randomized trial with a "no chemotherapy arm" was considered ethical, since the 5-year survival rate with RT alone was 30% or better and the toxic effect of the proposed combination could be significant. Increasing numbers of patients were developing complications of hematological toxicity and immune suppression as a result of intensive multimodal therapy. It was thought conceivable that the gains made by suppression of disease could be matched by losses from complications.

Study Design

Patient Eligibility

To be eligible for the study, patients had to be between 2 and 16 years of age, inclusive, with histologically proven medulloblastoma (or infratentorial malignant ependymoma). They were to be entered into the study within 3 weeks following the primary surgical treatment and could not have received RT or antitumor chemotherapy other than corticosteroids. They were to be considered past any immediate life-threatening operative or postoperative complications.

Pre-Study Evaluation

Neuroradiological investigations were undertaken as required to establish the presence of a posterior fossa mass. In the early years of the study these normally included an air encephalogram and/or ventriculogram. By the end of the study, as increasing experience was obtained with computerized tomography (CT), preoperative investigations usually included a CT scan. The patients were staged according to the extent of the primary tumor, employing the criteria of Chang, *et al.*[3] (Table 1). Patients with metastases outside the cerebrospinal axis (Chang stage M_4) were not eligible for the study.

TABLE 1

Staging system according to Chang, et al.[3]

Stage	Description
T_1	tumor < 3 cm in diameter and limited to the classic midline position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres
T_2	tumor ≥ 3 cm in diameter, further invading one adjacent structure or partially filling the fourth ventricle
T_{3a}	tumor further invading two adjacent structures or completely filling the fourth ventricle with extension into the aqueduct of Sylvius, foramen of Magendie, or foramen of Luschka, thus producing marked internal hydrocephalus
T_{3b}	tumor arising from the floor of the fourth ventricle or brain stem and filling the fourth ventricle
T_4	tumor further spreading through the aqueduct of Sylvius to involve the third ventricle or midbrain, or tumor extending to the upper cervical cord
M_0	no evidence of gross subarachnoid or hematogenous metastasis
M_1	Microscopic tumor cells found in cerebrospinal fluid
M_2	gross nodular seedings demonstrated in the cerebellar, cerebral subarachnoid space, or in the third or lateral ventricles
M_3	gross nodular seeding in spinal subarachnoid space
M_4	metastasis outside the cerebrospinal axis

Surgery

All patients were to undergo as extensive a resection as was compatible with subsequent good neurological function. The extent of the surgical procedure could depend upon the prevailing practice at the individual institutions, but it was recommended that as much tumor should be removed as possible. Ventriculoperitoneal shunts were to be avoided and, if such a shunt was placed, it was recommended that a Millipore filter should be installed in the system. Although discouraged, shunt procedures did not exclude a patient from entering the study. A copy of the operative report and a comprehensive surgical check sheet with diagram were submitted to the data center. The surgeon stated the extent of the tumor (Chang T-stage), the presence or absence of metastases (Chang M-stage), and the extent of resection: grossly total; subtotal (50% to 99%); partial (< 50%); or biopsy only. A postoperative CT scan was not required; therefore, the extent of removal was a surgical impression only. These records were reviewed by members of the Study Committee and, when necessary, were corrected according to the study definitions. The final T-stage, M-stage, and extent of surgical resection were used for analysis.

Pathology Review

Histological sections of the tumors were sent for central review. Patients were entered into the study initially according to the institution's pathology report. Changes were made following the central pathology review, and the analyses were performed according to the review of the study pathologist.

Radiation Therapy

While standard methods of delivering whole brain and CNS axis RT were allowed, it was required that the primary tumor be given the maximum tolerable dose and that elective irradiation of the neuraxis be undertaken. The following doses were recommended: 3500 to 4000 cGy to the entire CNS axis and 5000 to 5500 cGy to the posterior fossa at a rate of 800 to 1000 cGy in five fractions per week. Additional treatment to a cumulative dose of 5000 cGy was to be given to localized spinal metastases. A reduction of 500 cGy could be used for children aged 3 years or less. The RT records were reviewed by a member of the study committee (R.D.T.J.).

Chemotherapy

One-half of the patients were randomly assigned to receive adjuvant chemotherapy in addition to RT (Regimen I) whereas the other half received RT only and served as controls (Regimen II). The agents selected for primary therapy were VCR, CCNU, and prednisone. Single-agent chemotherapy consisting of VCR was given concurrently with the RT and was followed by 1 year of multiagent chemotherapy starting at 3 months (Fig. 1). Vincristine was prescribed weekly, 1.5 mg/sq m for eight injections during the postoperative period concurrent with RT, then VCR was restarted 4 weeks following the completion of RT together with CCNU and prednisone in cycles lasting 6 weeks. Vincristine was given on Days 1, 8, and 15 of each 6-week cycle for a total of eight cycles over a period of 1 year (or longer, if interruptions had occurred). Oral CCNU, 100 mg/sq m, was given on Day 1 of each 6-week cycle concurrently with VCR and prednisone. It was initiated 4 weeks following the completion of RT and was continued for eight cycles. Prednisone, 40 mg/sq m in three divided oral doses, was given daily for 14 days concurrently with the 6-week VCR and CCNU cycles for 12 months. In those patients still requiring steroid support, an effort was made to reduce the maintenance dose until it was discontinued. Guidelines for dose modification following toxicity were given but no escalations were planned.

Definition of Relapse

Since the study was designed to measure both the time to relapse and survival time, efforts were made to document the time and site of relapse. Investigators were urged to keep the patients in the study as long as possible until recurrent disease was indisputable. To be indicative of relapse, abnormal symptoms had to be accompanied by new or deteriorating neurological signs or be documented by changes in CT, CSF cytology, or myelogram.

Statistical Considerations

The randomization was stratified to balance the two treatment groups for Chang T-stage and M-stage. Kap-

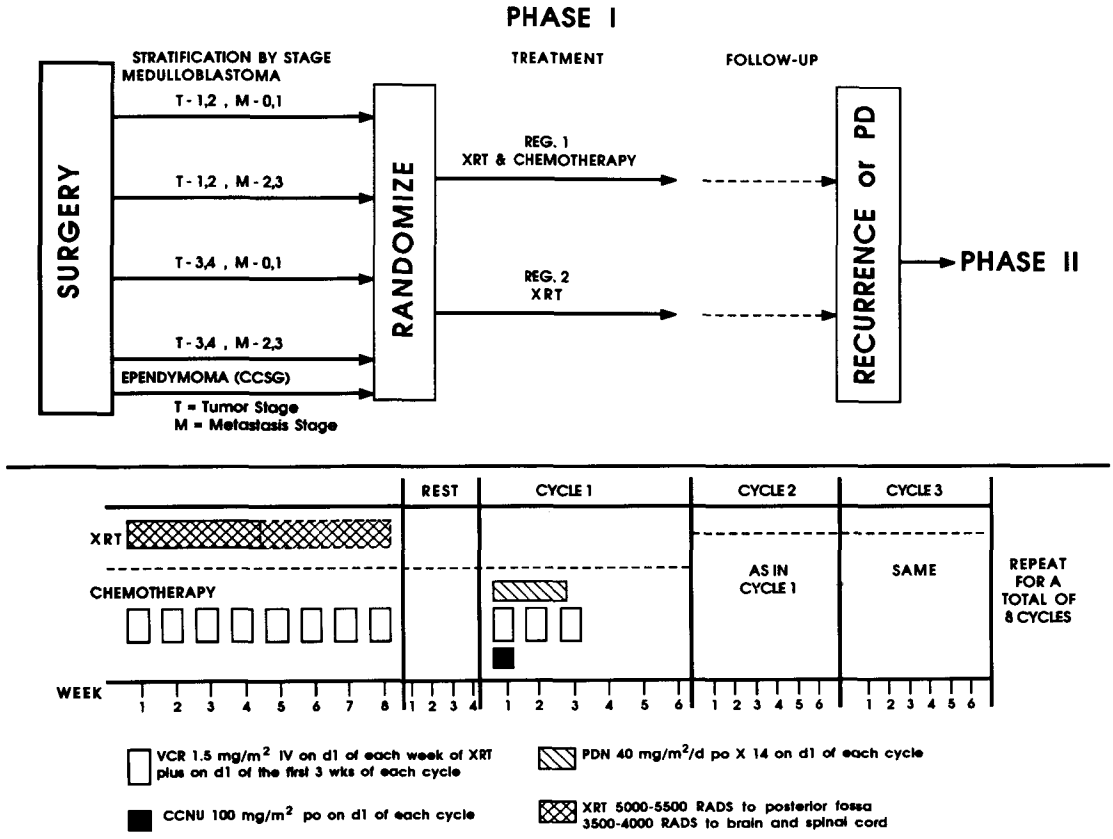

FIG. 1. Randomization schema and the dose and schedule of chemotherapy. XRT = radiotherapy; PD = progressive disease; VCR = vincristine; PDN = prednisone; IV = intravenous; po = oral.

lan-Meier (life-table) estimates of survival and event-free survival were used throughout the analysis. In this paper the term "survival" will be used in the statistical sense to denote the percentage of patients who are still alive at a specified time. "Event-free survival" will be used to denote the percentage who are alive without sepsis or disease recurrence or progression. Test of treatment effects and prognostic variables were based on the log-rank statistic and on the likelihood-ratio test based on Cox's multivariate regression model.[9] The follow-up period for all patients was terminated at June, 1985, 10 years after the beginning of the study.

Results

Between June, 1975, and June, 1981, 311 patients with medulloblastoma or ependymoma were entered into the study. Upon review, 36 patients were declared not evaluable for the primary study comparing chemotherapy versus no chemotherapy for the following reasons: 12 had a recurrence or had been previously treated; 10 were ineligible because the lesion was outside the posterior fossa or had metastasized outside the CNS; 10 were declared ineligible after histological review; two were ineligible because of severe postoperative complications; one because of bacterial meningitis; and one because of an unacceptable (2-month) delay between surgery and the start of therapy. Several patients (two under 2 years and five over 16 years) outside the nominal range of eligible age were retained in the analysis. Of the remaining 275 patients, central pathology review established that 179 had medulloblastoma, 36 had ependymoma, and three had other primitive neuroectodermal tumors; 57 lacked formal histological review by the study pathologist. The institution's pathologist classified 54 of the last group as having medulloblastoma and three as having ependymoma. The 233 patients who were classified as having medulloblastoma by either the institution's or review pathologist will be the subject of this paper. The results for treatment of patients with ependymoma will be reported elsewhere.

Of the 233 medulloblastoma patients in the study, 179 were randomized and followed their treatment assignments (88 to receive RT + chemotherapy and 91 to receive RT alone). Treatment of 12 patients was switched after randomization (six to RT + chemotherapy and six to RT alone) and, in 42 patients, treatment was nonrandomly chosen (21 RT + chemotherapy and 21 RT alone). The demographic and staging characteristics of the sample are shown in Table 2.

TABLE 2

*Demographic and prognostic characteristics**

Factor	Cases	
	No.	Percent
regimen		
randomized to treatment (88 CRX, 91 RT)	179	76.8
randomized but switched (6 CRX, 6 RT)	12	5.1
nonrandomized (21 CRX, 21 RT)	42	18.0
total CRX	115	
total RT	118	
M stage		
M_0	191†	82.0
M_1	19‡	8.2
M_2	15	6.4
M_3	8	3.4
T stage		
T_1-T_2	79	33.9
T_3-T_4	154	66.1
extent of resection		
partial	33	14.3
subtotal	105	45.5
total	93	40.3
not known	2	
age (nominal (yrs)		
< 2	24	10.3
3–5	75	32.2
6–10	80	34.3
11–15	46	19.7
≥ 16	8	3.4
sex		
male	154	66.1
female	79	33.9
pathology		
reviewed	179	76.8
not reviewed	54	23.2
group		
Childrens Cancer Study Group	211	90.6
Radiation Therapy Oncology Group	22	9.4

* CRX = patients receiving radiation therapy and chemotherapy; RT = patients receiving radiation therapy alone.

† No reported cytology or myelogram in 85 cases, no reported myelogram in 86 cases.

‡ No reported myelogram in 16 cases.

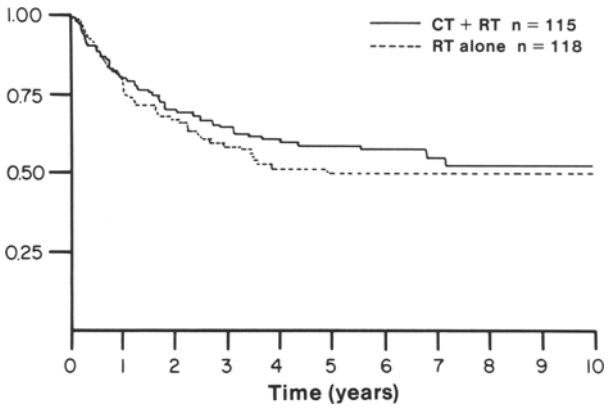

FIG. 2. Five-year event-free survival rate of all eligible patients according to treatment regimen. The 5-year rate for the 115 receiving chemotherapy (CT) and radiation therapy (RT) was 59%, and that for the 118 with RT alone was 50%, a nonsignificant difference.

Chemotherapy Trial

The event-free survival rate at 5 years for all 233 eligible medulloblastoma patients was 55%, and the 5-year survival rate was 65%. The event-free survival rate for all eligible patients was 59% for the group receiving chemotherapy and 50% for those not so treated (Fig. 2). Five-year survival rates in the chemotherapy and no-chemotherapy groups were 65% and 65%, respectively. Corresponding 5-year event-free survival rates and survival rates based on 191 randomized patients were, respectively, 57% and 64% for the chemotherapy group, and 52% and 68% for the no-chemotherapy group. The differences between chemotherapy and no-chemotherapy groups were not significant in a log-rank test stratified on M-stage, T-stage, and patient age. Although there was no significant difference overall between the patients who did and did not receive chemotherapy, there was one subset where chemotherapy improved event-free survival. This will be discussed further after the analysis of prognostic factors.

Adequacy of Chemotherapy

The chemotherapy regimen was divided into two phases: 8 weeks of VCR initially combined with RT and, following a rest period of 4 weeks, VCR was restarted in combination with CCNU and prednisone every 6 weeks for eight courses. In general, the chemotherapy schedule was correctly followed, although in some patients the combined courses had to be postponed because of prior hematological or neurological toxicity. Guidelines for dose reductions were included in the protocol, but no drug escalations were planned. The adequacy of chemotherapy was calculated as the proportion of drug a patient received in each course for which he was eligible (that is, to the end of the study or until he relapsed). Sixty percent of reviewed patients received 75% or more of the recommended dose in every therapy course received. The reductions in dose were usually appropriate because of prior hematological toxicity. All patients receiving any chemotherapy have been included in the analysis. Table 3 gives the number and percent of patients with dose reductions for initiation of therapy and each course during maintenance together with the incidence of toxicity.

Toxicity

During the initial 3 months of treatment, patients who received VCR concurrently with RT had increased toxicity compared to those receiving RT alone, and developed a larger number of serious infections. Grade III hematological toxicity (white blood cells (WBC) < 2000/cu mm, absolute neutrophil count (ANC) < 500/cu mm, or platelets < 75,000/cu mm) occurred at least once in 38% of patients, and Grade IV toxicity (WBC < 1000/cu mm, ANC < 250/cu mm, or platelets < 25,000/cu mm) occurred in 12%. During the complete

TABLE 3

*Adequacy of chemotherapy and toxicity report for 115 patients receiving irradiation plus chemotherapy**

Dose No.	Reported Courses	Evaluable Courses	Significant Dose Reduction†	Serious to Life-Threatening Toxicity
initiation	105	92	13 (14.1)	29 (31.5)
maintenance doses				
1	96	85	6 (7.1)	10 (11.8)
2	91	85	12 (14.1)	7 (8.2)
3	85	79	15 (19.0)	9 (11.4)
4	80	75	13 (17.3)	3 (4.0)
5	77	73	16 (21.9)	9 (12.3)
6	73	71	20 (28.2)	7 (9.9)
7	67	65	17 (26.2)	4 (6.2)
8	59	57	16 (28.1)	4 (7.0)
totals	733	682	128 (18.8)	82 (12.0)

* Numbers in parentheses indicate percentages of evaluable courses.

† Significant dose reduction was classified as amounts less than 75% of the protocol dose.

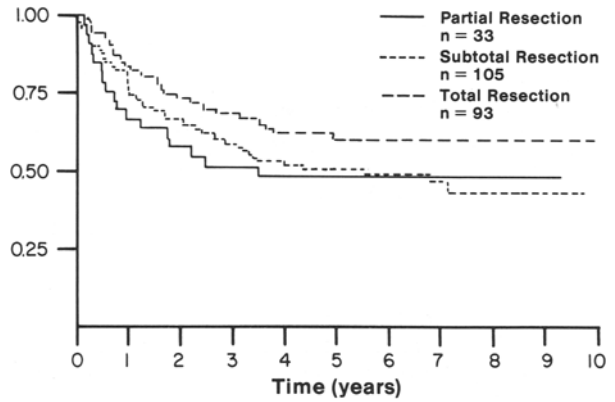

FIG. 3. Five-year event-free survival rates by the extent of surgical resection. The rate was 48% for 33 patients with partial resection (see text), 51% for the 105 patients with subtotal resection, and 61% for the 93 with total resection ($p = 0.07$).

treatment course there were 11 severe infections among patients treated with RT + chemotherapy (four fatal) and two among patients treated with RT alone (both nonfatal). Four of the infections in the chemotherapy-treated group were not associated with severe neutropenia, Two occurred during the RT period when, by error, the patients received VCR, CCNU, and prednisone. One patient died of chicken pox at age 14 months and one fatal case of meningitis occurred 15 months after initiation of treatment, 2 and 3 months following completion of chemotherapy. Grade III or IV toxicity occurred during the first 3 months in 10 (18%) of 57 patients randomly assigned to receive RT alone. The one patient with Grade IV toxicity with < 20,000 platelets/cu mm developed a fatal gastrointestinal bleed after the count had returned to 90,000/cu mm. Treatment was interrupted in three patients.

TABLE 4

*Radiotherapy dose in this series**

Dose (rad)	Cases	
	No.	Percent
to posterior fossa		
< 4500	12	5.5
4500–4999	19	8.6
5000–5500	163	74.1
5501–6050	23	10.5
> 6050	3	1.4
total cases	220	
to brain		
< 3150	13	6.0
3150–3499	20	9.2
3500–4000	136	62.4
4001–4400	22	10.1
> 4400	27	12.4
total cases	218	
to spine		
< 3150	28	12.9
3150–3499	29	13.4
3500–4000	143	65.9
4001–4400	16	7.4
> 4400	1	0.5
total cases	217	

* Includes patients with incomplete irradiation due to recurrence or other causes. Patients for whom data was not available were excluded.

Radiation Therapy

A more detailed report regarding RT will be published separately. However, the results can be summarized as follows. The RT protocol guidelines included two suggested methods of delivery and a range of total dose: 3500 to 4000 cGy to both the cranium and the spinal cord and between 5000 and 5500 cGy to the posterior fossa. Of 220 patients for whom posterior fossa data were reviewed, 74% received the protocol dose, 14% less, and 12% more than 5000 to 5500 cGy (Table 4). Thirty-three (15%) patients received less than 3500 cGy to the brain, and 57 (26%) received less than 3500 cGy to the spine. There is a significant difference in the event-free survival rate for patients receiving different doses of radiation. A multivariate analysis of dose to the posterior fossa, whole brain, and spine resulted in a significant relationship between decreased dose and poor event-free survival data ($p < 0.001$). However, in this analysis, no account is taken of the fact that some of the patients received a lower RT dose because of advancing disease when RT was electively discontinued, so that in these patients the relapse was the cause rather than the result of the lower dose. This aspect is dealt with more fully in the Discussion.

Surgery and Extent of Surgical Resection

No statistical difference was found in the event-free survival rates between patients who had gross complete removal of tumor and those whose resections were less than complete, although there was a trend that patients with incomplete resections did less well (Fig. 3, p =

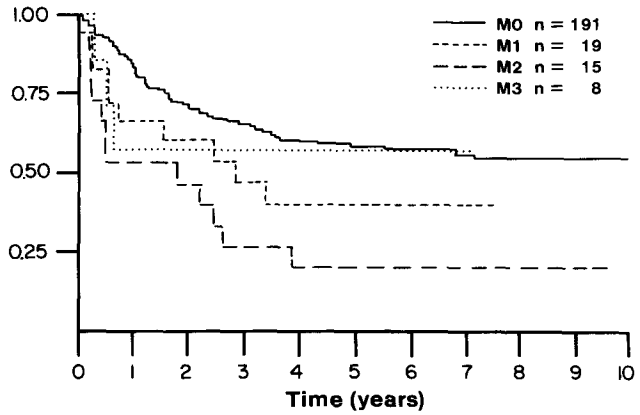

FIG. 4. Five-year event-free survival rates according to the presence or absence of intracranial metastases. The rate was 59% for 191 patients classified as M_0, 40% for 19 patients classified as M_1 (see text), 20% for 15 patients classified as M_2, and 57% for eight patients classified as M_3 ($p < 0.003$).

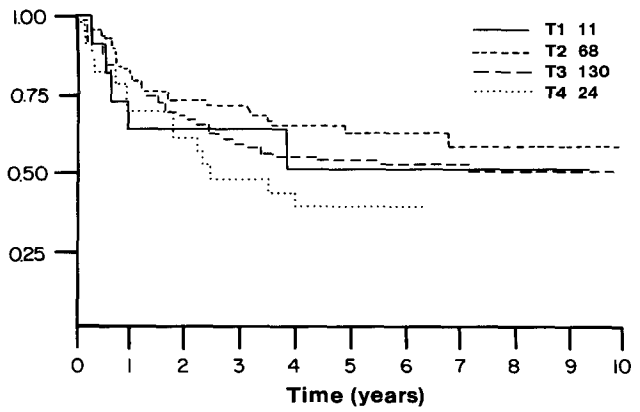

FIG. 5. Five-year event-free survival rates by tumor stage (see text). The rate was 51% for 11 patients with T_1 tumors, 63% for 68 patients with T_2 tumors, 54% for 130 with T_3 tumors patients, and 39% for 24 patients with T_4 tumors. The difference is not significant.

0.07). There is an association between the extent of surgical resection, T-stage, and M-stage, since it is not possible to achieve a complete surgical resection in patients who have local spread and, in general, it is less likely to be successful in patients with more advanced T-stages. No difference due to extent of resection was found after controlling for T-stage and M-stage.

Stage of Disease

Efforts were made to study the staging criteria proposed by Chang, *et al.*[3] (Table 1). Of the 233 patients, 191 (82%) were classified as M_0 (no spinal or brain metastasis, no cells in the CSF, Table 2). This is higher than is generally reported. It is likely that the M_0 group included patients with stages M_1 to M_3, since cytology data were reported in only 56% of the M_0 patients and an initial myelogram was performed in only 11% of

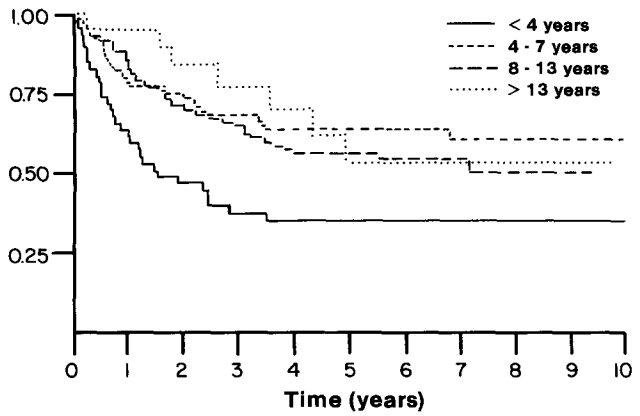

FIG. 6. Five-year event-free survival rates by age at diagnosis. The rate at 5 years for the 47 children aged less than 4 years was 32%, the 77 children between 4 and 7 years old had a rate of 64%, the rate was 56% for the 88 between 8 and 13 years, and 53% for those aged 14 years or older. The difference is significant ($p = 0.003$).

M_0 patients. However, the surgical check sheet classified the patients as M_0. The subcategories of M_1, M_2, and M_3 are not reliably separable; therefore, these categories were collapsed in most analyses. Nonetheless, the influence of M-stage is striking. The event-free survival rate for patients grouped by M-stage criteria is given in Fig. 4. The 5-year event-free survival rate for M_0 patients was 59% as compared with 36% for M_1 to M_3 patients; this difference is significant ($p < 0.003$). There was no significant difference between the data for M_1, M_2, and M_3 patients.

The event-free survival rate by T-stage is seen in Fig. 5. There was no significant difference in the event-free survival rates between T-stages, although there is a trend that the most advanced stages did less well. When stages T_1 and T_2 are aggregated and compared to stages T_3 and T_4, the event-free survival rates at 5 years were 61% and 52%, respectively.

Age, Sex, and Race

There was a significant trend in 5-year event-free survival rate according to age at diagnosis, with children less than 4 years old doing least well (32%, $p = 0.003$) (Fig. 6). This can be partially explained by the higher proportion of M_1 to M_3 patients among the younger children. Sixteen (34%) of the 47 children under 4 years had M_1 to M_3 tumor, as compared with 26 (14%) of the 186 children over 4 years ($p = 0.003$). However, after controlling for M-stage, the age difference is still significant ($p = 0.014$).

There is no significant difference in event-free survival rate on the basis of sex. The 5-year rate for males was 56% and for females was 51%.

There was a difference in the event-free survival rate by race, in that black children did better than white, and other races did least well. Event-free survival rates at 5 years were 78%, 55%, and 42%, respectively, with

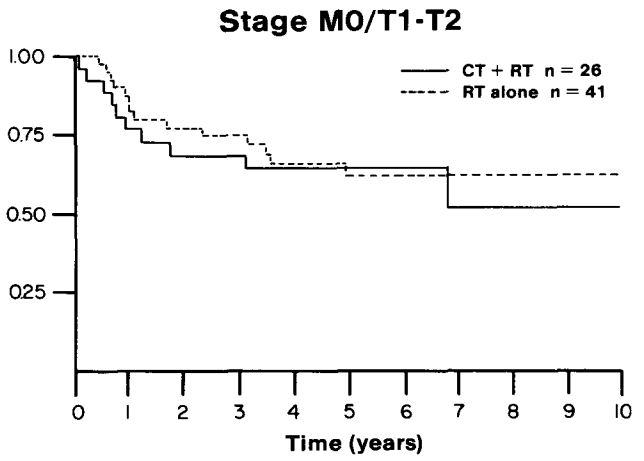

FIG. 7. Five-year event-free survival rates by regimen for patients with M_0 and T_1 or T_2 tumors. The rate for 26 patients with chemotherapy (CT) and radiation therapy (RT) was 65%, and for the 41 with RT alone was 62%.

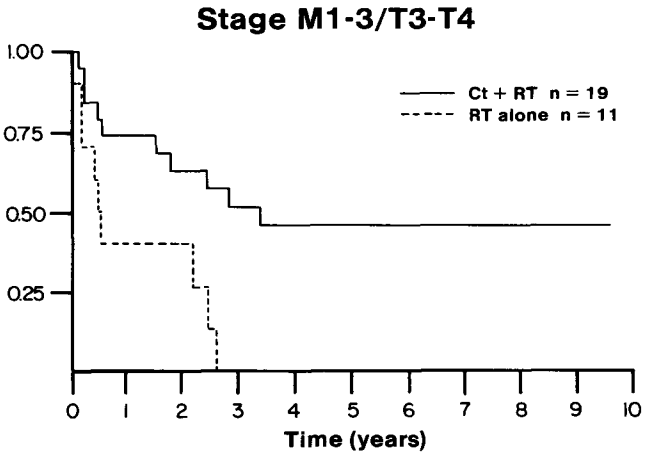

FIG. 8. Event-free survival rates by regimen for patients with M_1 to M_3 and T_3 or T_4 tumors. The rate was 46% for the 19 patients with chemotherapy (CT) and radiation therapy (RT), and 0% for the 11 with RT alone.

a borderline significance ($p = 0.06$). There is no significant difference between whites and the combined group of blacks and other races.

Pathology and Treating Group (CCSG or RTOG)

In 54 patients there was no central review of the pathology. Thirty-two of these were CCSG registrations for whom pathology material could not be obtained for central review. The remaining 22 patients were RTOG patients, whose material was not requested for review by the CCSG pathology center. The 5-year event-free survival rate was 53% for CCSG patients with review pathology, 51% for CCSG patients without review pathology, and 72% for RTOG patients ($p = 0.31$). The apparent difference in event-free survival rates between RTOG and CCSG patients is most likely due to a higher proportion of M_0 patients (21 of 22 cases) in the RTOG sample.

Interaction Between Disease Stage and Treatment Regimen

No benefit from chemotherapy was seen in the 67 patients who had tumor stage T_1 and T_2 and no metastasis (M_0) (Fig. 7). In the group of 124 M_0 patients who also had a more advanced T-stage (T_3 or T_4), the event-free survival rate was 61% in those receiving RT + chemotherapy and 51% in those receiving RT alone, a difference that is not significant ($p = 0.27$). There were too few patients (12) with low T-stage and advanced M-stage (T_1 or T_2, M_1 to M_3) for analysis, but the group with advanced T-stage and M-stage (T_3 or T_4, M_1 to M_3) showed a striking effect of chemotherapy. Here the event-free survival rate was 46% vs. 0% ($p = 0.006$) (Fig. 8). When five nonrandomized patients (three receiving RT + chemotherapy and two RT alone) were excluded, event-free survival rates were 46% and 0%, respectively ($p = 0.003$). Five-year survival rates were, respectively, 57% and 19% for all patients, and 61% and 19% when nonrandomized patients were excluded ($p = 0.06$ and $p = 0.04$, respectively).

Multivariate Analysis of Treatment Effect and Prognostic Factors

A Cox stepwise multivariate analysis was performed to determine which factors significantly affected outcome. All potential prognostic factors were included in this analysis regardless of their univariate significance. These consisted of age categories (< 4, 4 to 7, 8 to 13, or > 13 years), sex, race (white or other), M-stage (M_0 vs. M_1 to M_3), T-stage (T_1 or T_2 vs. T_3 or T_4), extent of resection (partial, subtotal, or total), pathology (reviewed, or not reviewed), and treating group (CCSG or RTOG). Because we had observed apparent interactions between treatment and stage of disease, all first-order interactions of treatment regimen with the prognostic factors listed above were also included. Interactions reflect the degree to which the effect of treatment varies in different prognostic subgroups (for example, if the addition of chemotherapy were advantageous for some stages but not others).

The results of the stepwise analysis are shown in Table 5. The entries in the table are the p values at which a particular factor was entered into the model. Sex, race, and extent of resection are not listed because none was significant at the $p = 0.10$ level in any analysis. One should note that since 15 different tests (eight main effects and seven interactions) were performed, one could expect one or two values of $p < 0.10$ in each column of the table by chance alone.

In the stepwise analysis of event-free survival rates with nonrandomized patients and with only randomized patients, the interaction between treatment and M-stage was very significant and entered first at $p < 0.001$ and $p = 0.004$, respectively. This was followed by age, t-stage or the treatment/T-stage interaction, and the treatment/group interaction at less significant levels.

TABLE 5

Stepwise multivariate analysis of event-free survivors (EFS)

Variable*	Randomized Patients† (190 cases)		All Patients‡ (231 cases)	
	EFS	Surv	EFS	Surv
main effects				
age	0.050 (3)	0.034 (1)	0.015 (2)	0.002 (1)
T stage	0.081 (4)	—	—	—
interactions with treatment				
M stage	0.004 (1)	—	<0.001 (1)	0.065 (3)
T stage	—	—	0.031 (4)	—
group	0.056 (2)	0.040 (2)	0.039 (3)	0.007 (2)

* Expressed as p values for Cox Likelihood Ratio Test. Only $p < 0.1$ values are listed; a — indicates that variable was not significant at $p < 0.1$ in stepwise analysis. Numbers in parentheses indicate the order in which the variables entered.

† One case was excluded because of missing covariates.

‡ Two cases were excluded because of missing covariates.

The order of entry of these differed in the two analyses.

In the stepwise analysis of survival for all patients and for randomized patients, age was the first significant entrant ($p = 0.002$ and $p = 0.034$, respectively). This was followed by the treatment/group interaction and, when nonrandomized patients were included, the treatment/M-stage interaction.

An additional Cox analysis was performed which tested treatment plus treatment/T-stage interaction plus treatment/M-stage interaction after adjusting for age, T-stage, and M-stage. This test yielded $p = 0.025$ for event-free survival rates in all patients and $p = 0.054$ in randomized patients. This test was not significant for overall survival rates.

Initial treatment, therefore, does not have as pronounced an effect upon survival time as it does upon event-free survival time in this study. This observation can be explained in large part by the longer post-recurrence survival times among patients treated initially with RT alone. For example, the median survival time after recurrence was 3.9 months for all patients who were treated initially with chemotherapy and RT, but 10.4 months for those treated initially with RT alone. The difference is much more pronounced in patients who suffered a recurrence after 18 months. Median post-recurrence survival times in these patients was 5.2 months for the RT + chemotherapy group and 28.3 months for those with RT alone ($p = 0.004$). It is probable that patients who suffered a recurrence after RT alone and received subsequent chemotherapy derived benefit from it.

Patterns of Relapse

Table 6 summarizes the sites of first relapse and Table 7 lists the other reasons patients were removed from the study. In the 81 patients whose site of recurrent disease could be determined, 43 (53%) had recurrence in the posterior fossa, alone or combined with other sites. The remaining patients first developed disease outside the posterior fossa, although many had a subsequent recurrence at the primary site. Eight patients had skeletal or bone marrow metastases without intracranial recurrence, and this could not be related to the presence or absence of an extracranial CSF shunt. The category of progressive disease in the 22 additional patients includes those who failed to respond to initial treatment.

TABLE 6

Sites of first relapse in 81 patients

Site*	Cases	
	No.	Percent
posterior fossa		
alone	29	36
+brain	6	7
+cord + CSF	4	5
+CSF	4	5
totals	43	53
other sites		
brain ± CSF	11	14
cord ± CSF	10	12
brain + cord ± CSF	3	4
CSF	6	7
bone	8	10
totals	38	47

* CSF = cerebrospinal fluid.

TABLE 7

Reasons for removal from study other than relapse

Reason for Removal	No. of Cases
progressive disease/unknown site of recurrence	13
infection	4
death, other, or unknown cause	6
total	23

Discussion

This study was designed to determine the benefit of adjuvant chemotherapy on the recurrence and survival rates of children with medulloblastoma treated with standard surgery and RT. Additional objectives of the study were to assess the toxicity attendant on adjuvant chemotherapy and the staging system proposed by Chang, *et al.*,[3] and to analyze other prognostic factors.

At the time the study was designed, 5-year survival rates were between 30% and 35%. In the ensuing years, small studies from individual institutions have reported survival rates up to 75%. Patients were entered from 26 institutions and the number of cases contributed from each institution varied from one to 33. The overall survival rate of patients in this study was 65% at 5 years, which was much better than the original projection.

The study showed a benefit from chemotherapy, as measured by event-free survival rates, which depended on disease stage. In particular, patients with metastatic tumors (Chang M-stage M_1 to M_3) and larger or more

invasive tumors (Chang T-stage T_3 or T_4) realized the greatest benefit from chemotherapy, whereas patients apparently without metastasis or with smaller tumors (stages M_0 and T_1 or T_2) realized no benefit. The higher toxicity and death rate due to infections in the chemotherapy arm probably offset any advantage this therapy had in the latter group of patients. One must be cautious about significant treatment interactions, because the act of examining many treatment interactions increases the chance of observing a spuriously significant result. It was reassuring in our analysis that the treatment/M-stage interaction was very significant in the stepwise analysis, and that the treatment/stage interaction was significant in a multivariate analysis after adjusting for age and stage.

An association was seen between a reduced dose of RT and a worse outcome. However, the low-dose group included patients with no response or progressive disease in whom treatment was abandoned and those who died early. These factors account for almost half of the relapses in the low-dose group. Low-dose irradiation was also associated with young patients who had a worse prognosis (see below).

The toxicity of the regimens was considerable. Although in the postoperative period bacterial meningitis can be seen in any patient with medulloblastoma, the number of infections in the two arms was different, a much larger number being seen in the patients receiving chemotherapy. Two of the three toxicity-related deaths were associated with an incorrect schedule of chemotherapy when the patients received the three maintenance drugs during the initial period of RT. There were also more interruptions in the RT schedule in patients on chemotherapy. During the study planning it was not expected that the 8 weeks of VCR therapy would be so myelosuppressive but, given concurrently with RT, it did increase the hematological toxicity compared to the group receiving RT alone. Two deaths occurred due to late infections, one with chicken pox and one with meningitis, 2 to 3 months following the completion of chemotherapy. By and large, the maintenance period of the study was better tolerated and most of the serious side effects occurred early.

The separation of the patients by the staging system proposed did have an effect on prognosis. The influence of the M-stage was much stronger than that of the T-stage and the presence of any metastasis adversely affected the event-free survival rate. M-stage M_1 is defined as tumor cells in the CSF, but the study did not state at what time the CSF should be sampled. For example, CSF collected in the immediate postoperative period might show cells which had been dislodged by the surgical procedure and their presence would not be as significant as cells detected prior to any surgical intervention or some weeks thereafter. If M_1 is to be used as an important variable in treatment planning, the time when the CSF is sampled should be designated and should probably be at the craniotomy during the initial procedure or at least 2 weeks after the surgical exploration. The study records did not include details of the CSF findings in 45% of patients listed as M_0; however, we believe that in most cases the CSF was examined for tumor cells, since it is standard practice in the majority of neurosurgical services and the surgical check sheet classified the patient as having an M_0 disease. In a much higher proportion of patients (73%) the findings of a myelogram were not reported, and it is probable that this study was not performed. Only 3% of patients were reported as having an M_3 disease, a much smaller number than the 43% reported by Deutsch and Reigel.[6]

The effect of T-stage alone was not so marked as M-stage, although the T- and M-staging identified patients with more advanced disease who appeared to benefit from chemotherapy as measured by event-free survival time.

The known adverse influence of young age was confirmed and the children less than 4 years old formed a group that did least well. Young children had more advanced disease in that a higher proportion had M-stage M_1 to M_3, which adversely affected the prognosis. There was also a tendency that they received a lower dose of RT. At variance with previously reported findings was the lack of significant benefit of older age. Although there was a trend of improved event-free survival time accompanying older age, there was not a marked difference in the children who were aged 10 years or older. Sex did not influence outcome either; the previously seen benefit of female sex did not emerge in this study. A better outcome was seen in Black children, but there was no obvious explanation for this unexpected finding.

The results of this study closely parallel those conducted by members of the International Society of Paediatric Oncology (SIOP). The larger numbers in that study (285 patients with medulloblastoma) led to a significant difference being seen in the total group between those who received chemotherapy and those who did not. By and large, the trend in results of analyses for the subgroups is the same in both studies, in that the benefit from chemotherapy is seen in the patients with the worse prognoses. In the SIOP study a significant benefit is seen for chemotherapy in patients with brain-stem involvement, but the extent of disease was not a prognostic factor in the study reported here (HJG Bloom: personal communication, 1974). In the SIOP study, the benefit of chemotherapy has translated into a significant improvement in survival time.

Conclusions

This study has shown that at 5 years the overall event-free survival rate of 55% and total survival rate of 65% in children with medulloblastoma are better than that predicted in 1974 when the study was initiated. The addition of chemotherapy did not benefit the majority of children with low-stage disease, but did improve both the event-free survival rate and total survival rate of the group with advanced disease Chang T-stage T_3 or T_4 and M-stage M_1 to M_3. Patients with M-stage M_0 and T-stage T_3 or T_4 may benefit from

chemotherapy although the difference in this study was not significant. With better documentation of M status (CSF cytology and myelography) so that occult disease is excluded, a larger difference could emerge between those receiving chemotherapy and those who do not in a group with more advanced T-stage. Significant prognostic factors were the presence of metastases, advanced T-stage, and young age. The extent of surgical resection did not affect outcome.

From these results, we conclude that patients with medulloblastoma may consist of two prognostic groups. Those without metastasis (M-stage M_0), those with smaller tumors (T-stage T_1 or T_2), and those aged over 4 years have a favorable outcome without benefit of chemotherapy. Those with any evidence of metastasis (M-stage M_1 to M_3), young age, and probable advanced local disease (T-stage T_3 or T_4) have a worse prognosis and do benefit from adjuvant chemotherapy as prescribed. The study was unable to detect a benefit of chemotherapy for those with an intermediate prognosis (T_1 or T_2 and M_1 to M_3, T_3 or T_4 and M_0). Careful workup in future studies, including CSF cytology, myelography, and postoperative CT scans, should help to determine the correct treatment for those intermediate patients.

APPENDIX

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