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● *Original Contribution*

MEDULLOBLASTOMA IN CHILDREN: A CORRELATION BETWEEN STAGING AND RESULTS OF TREATMENT†

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Fifty-nine children with cerebellar medulloblastoma were followed prospectively after they were staged and treated consistently with postoperative megavoltage radiotherapy to the entire neural axis. The probabilities of surviving 5 and 10 years were 40.4% and 30.9% respectively; a gradual reduction of the survival rates was observed as the T-category of the tumor increased: i.e. 5 year survival rate was 75% for T_1, 50.5% for T_2, 32.3% for T_3 and 0 for T_4. Children without gross nodular seeding in the subarachnoid space ($M_0 - M_1$) had better survival rates than children with gross nodular seeding ($M_2 - M_3$). Improved survival rates were observed by increasing the dose of radiation to the posterior fossa. Among children who had similar surgery, those who had $T_1 - T_2$ tumors fared better than those with $T_3 - T_4$ tumors. The short term (up to 4.5 years) survival rates were better for older children but younger children had better long term survival rates. The posterior fossa was involved in 59% of children who developed recurrent tumor; however, in 75% of the recurrent cases either the posterior fossa was not involved or concomitant involvement of another site also was present.

Brain tumors, Medulloblastoma, Radiotherapy, Tumor staging.

INTRODUCTION

Primary intracranial neoplasms account for about one fifth of all childhood neoplasms; medulloblastoma represents approximately one fifth of all intracranial neoplasms in children.

Following the introduction of the irradiation of the whole neuro-axial system[13] in the post-operative treatment of medulloblastoma, the previously hopeless outlook of children with this tumor has changed markedly. In several more recent reports, long-term survival has been achieved in more than one third of the children who were treated with the whole neuro-axial radiotherapy. However, there is considerable variation on the survival rates reported from various centers.[1-3,8,10-13,15,16]

Staging systems now are available for tumors of most anatomic sites and convincing differences in survival have been demonstrated in various tumors according to their stage. Unfortunately, because of its relative inaccessibility, much difficulty has been encountered in developing staging systems for tumors of the central nervous system (CNS). However, one exception is an operative staging system for medulloblastoma[3] which was developed in the 1960s at our center; this system has been adopted by the Radiation Therapy Oncology Group and Children's Cancer Study Group for their Phase III study of this tumor. This operative staging system is detailed in Table 1. Our preliminary results in 24 children with medulloblastoma staged according to this system and followed prospectively had shown good correlation between stage of the tumor and survival.[3] In this report we have added 35 new patients to the previous series and provided long term follow-up in all children followed prospectively after their staging and treatment.

METHODS AND MATERIALS

During the period from January 1963 to December 1975, 72 patients with a histologically-proven diagnosis of cerebellar medulloblastoma received postoperative radiotherapy at the Division of Radiotherapy, Columbia-Presbyterian Medical Center. Nine patients were older than 16 years of age, and were excluded from this report. Four children treated in 1975 were excluded because of the short follow-up

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Table 1. Operative staging system for cerebellar medulloblastoma[3]

T_1	Tumor less than 3 cm dia. and limited to the classic mid-line position in the vermis, the roof of the fourth ventricle, and less frequently to the cerebellar hemispheres.
T_2	Tumor 3 cm or greater in dia., further invading one adjacent structure or partially filling the fourth ventricle.
T_3	This stage is subdivided into T_{3a} and T_{3b}. 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 4th ventricle.
T_4	Tumor further spreading through the aqueduct of Sylvious 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.

period. The remaining 59 children constituted the basis of this report. Forty-three children were treated prior to January 1970 and were at risk of surviving at least 5 years. Eleven children were treated prior to January 1966 and were at risk of surviving 10 years. No patient was lost to follow-up. All 23 living children in this series were seen and evaluated as of 31 December 1975, the date at which the status of each patient was recorded. Survival was measured from the date the tissue diagnosis was established, i.e. the date of operation. Four children who failed to complete their radiotherapy course were included in the calculation of survival. Life tables were used throughout this study to compute the probability of surviving. Tests of significance were performed using Gehan's generalized Wilcoxon test.[6]

The following clinical data were observed among the 59 children.

Age and sex. The mean age of all children was 7.03 years and the median 6.25 years. The mean age of 20 girls was 7.04 years, ranging from 14 to 192 months. The mean age of 39 boys was 7.03 years, ranging from 16 to 203 months.

Symptomatology. The symptoms recorded most often were gait disturbance, headache and vomiting.

Laboratory work-up

Plain skull film. Diastasis (a sign of increased intracranial pressure) was noted in 28 children, who had a mean age of 4.67 years. Nine children without diastasis had a mean age of 10.83 years. In 4 children the findings were equivocal; no mention of diastasis was made in the X-ray report of the remaining 18 children.

Echoencephalogram. This was interpreted as abnormal in 15 children because of dilated and/or shifted third ventricle; it was equivocal in 3 children and normal in 12. No data were available for 29 patients.

Pneumoencephaglogram (PEG) *and/or ventriculogram.* These were performed in 47 children. In 21, a mass was demonstrated in the fourth ventricle; this often was associated with other indirect signs of a posterior fossa mass. In the remaining 26 only indirect signs were seen. Tumor nodules in the third or lateral ventricles were observed in 3 patients. Hydrocephalus was described in 18 children; it was graded as marked in 7 of these.

Myelogram. Only one patient had myelogram in initial evaluation because of signs of cervical cord compression. It demonstrated tumor seeding and blockage in the cervical cord.

Arteriographic studies. Seventeen children had arteriographic study and 11 of them also had PEG and/or ventriculogram. The arteriogram was suggestive of a posterior fossa mass in 16 children and was associated with evidence of hydrocephalus in 19. The study was inconclusive in 1.

Radionuclide brain scan. Ten children had positive findings on a ^{197}Hg brain scan; 7 had suspicious results and 4 had negative results.

Computerized axial tomography (CAT Scan). This new diagnostic tool became available to us in late 1974; results were positive for 1 patient. Our subsequent experience confirms the superior value of this method in demonstrating posterior fossa tumor; it is especially helpful with contrast enhancement in assessing the size and stage of tumor preoperatively.

Cerebrospinal fluid (CSF) *cytology.* It was negative in 20 children; and was suspicious in 3. In other 7 children, medulloblasts were recovered from the CSF. In 3 of these 7 children, gross tumor seeding in the spinal canal was documented by clinical and/or radiographic criteria. However, 4 of the 20 children who had negative CSF cytology did have evidence of gross involvement of the cord.

Staging

Fifty-eight children were staged according to the operative staging system. The remaining one child was operated elsewhere and the available information was not sufficient for accurate staging. The distribution of the 58 children according to *T* and *M*

Table 2. Distribution of 58 patients with medulloblastoma according to T and M category

	T_1	T_2	T_{3a}	T_{3b}	T_4	Total
M_0	3	6	3	7	1	20
M_x	2	7	2	5	1	17
M_1	0	3	2	1	0	6
M_2	0	3	4	2	0	9
M_3	0	1	1	2	2	6
Total	5	20	12	17	4	58

category is shown in Table 2. Patients were classified as M_x (new designation) when they did not have evidence of gross nodular seeding, but the lack of CSF cytologic study prevented their classification either as M_0 or as M_1. In one third (11/33) of children with T_3 and T_4 tumors, there was evidence of gross nodular seeding; only in 16% (4/25) of children with T_1 and T_2 tumors, was gross nodular seeding present.

Treatment

Surgery. The type of surgery as listed in the operative record was: gross total removal of the tumor in 5 patients, subtotal removal in 34 and partial removal in 8 patients. Only biopsy of the tumor was performed in the remaining 11 patients. Restoration of the CSF circulation was achieved in the majority of the patients. Subtotal of gross total removal was performed in 76% (19/29) of those children who had T_1 and T_2 tumors, and in 65.5 (19/29) of those children who had T_3 and T_4 tumors.

Radiotherapy. All children were treated consistently by a ^{60}Co unit according to our reported technique.[3] In brief, the radiotherapy usually commenced 7–9 days post-operatively. The whole brain was irradiated through two parallel opposed lateral ports. Following the completion of the prescribed dose to the whole brain, 3600–4000 rad in 4 weeks, irradiation of the spinal axis with a single or two adjoining vertical ports began and continued until a prescribed dose of 3500 rad in 4.5 weeks was reached. One week after the completion of the whole brain irradiation, the posterior fossa received a boost dose of an additional 1000 rad in 1 week through two smaller parallel opposed lateral posterior fossa ports. The adjoining cranial and spinal fields in the cervical region were interlaced at two different levels at 3–4 cm apart, so that hot spot dose at this adjoining zone was reduced by about 50%. The daily dose of 200 rad was given to the whole brain and posterior fossa fields and was calculated at the midline with a weekly dose of 1000 rad. A daily dose of 150 rad was given to the spinal port and was calculated at various depths depending on the child's size; usually, this depth was determined to be about 3–4 cm. A weekly dose of 750 rad was given to the spinal ports.

Four children died prior to completion of the radiotherapy course, of causes not related to radiotherapy. All four had far-advanced tumors. The first child, a 10 year old boy with T_4M_3 tumor, died of massive gastrointestinal hemorrhage after he received 1600 rad to the whole brain. The duodenal ulcer which caused his demise was identified on autopsy. Both cerebellar and spinal subarachnoid spaces were involved by tumor. The second child, a 22 month old girl with a T_4M_0 tumor, had a postoperative course complicated by focal and generalized seizures, bronchopneumonia, paralytic ileus and hyponatremia. At autopsy the tumor was seen to extend through the tentorium into the right thalamus. The third child, a 16 month old boy with T_4M_3 tumor, died after he received only one treatment to the whole brain. On autopsy the third and lateral ventricles, the cerebral and cerebellar leptomeninges and the spinal cord all were covered by tumor. The fourth child, an 18 month old girl with $T_{3a}M_x$ tumor, had received 3800 rad to the whole brain prior to her death. On autopsy suppurative meningitis was identified as the cause of death; the tumor had been completely eliminated.

Radiotherapy was started on the average 8.7 days postoperatively (range 5–20 days) and lasted 69.2 days. Mean time-dose factors recorded among 55 children who completed their radiotherapy course were: (a) Whole brain, 3710 rad in 18.6 fractions over 30.2 days. (b) Posterior fossa, 4956 rad in 24.8 fractions over 50.8 days. (c) Spinal cord, 3496 rad in 23.2 fractions over 37.7 days. The time–dose factors for the posterior fossa listed above are associated with a nominal standard dose (NSD) of 1488.7 ret. The highest NSD (1703 ret) was observed in a child who received a posterior fossa dose of 6000 rad in 30 fractions over 56 days. The posterior fossa dose was raised to 6000 rad by necessity, to compensate for 2 week interruption of treatment. He was alive with osseous metastases at 5.5 years after the diagnosis. The other children who received doses more than 5500 rad also had interruption of treatment and additional dose was given to compensate for longer elapsed interval.

Chemotherapy. In this series, chemotherapy was used in children with recurrent tumors only.

RESULTS

Survival rates

Stage of tumor and survival. Figure 1(A) shows the survival according to stage of T-category. The 5-year surivival rate was 75% for children with T_1 tumors, 50.5% for those with T_2, 32.3% for those with T_3 and

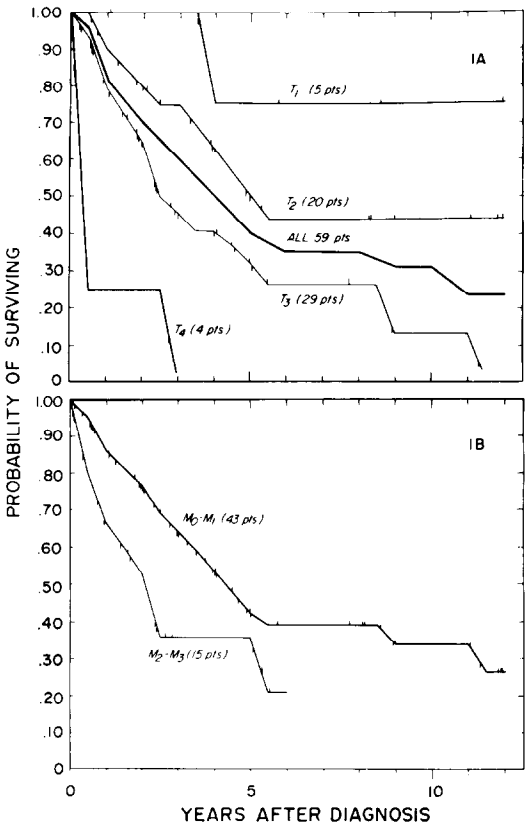

Fig. 1. The probability of survival according to T-category (IA) and M-category (IB). Individual children are identified in this figure. Bars above the survival curve identify children living at the time of the study. Bars below the survival curve represent children dead at the time of study. No stage was assigned to one child (see text). $T_1 + T_2$ vs $T_3 + T_4$ gives $p = 0.013$; T_2 vs T_3, $p = 0.14$.

0% for those with T_4 tumors. The 10 year survival rate was 75% for T_1, 43.7% for T_2 and 13.2% for T_3. The overall 5 and 10 year survival rates were 40.4% and 30.9% respectively for all stages as calculated by life tables. The minimum 5-year survival rate computed by the direct method was 39.53% (17/43) thus being in good agreement with the 5-year survival rate computed by the actuarial method. Because 4 of 11 children at risk survived at least 10 years, the 10 year survival rate as calculated by the direct method was 36.4%.

Figure 1(B) shows the survival according to stage of M-category. An initial wide separation of the two survival curves is noted. The survival of 15 children with gross nodular seeding in the subarachnoid space (M_2, M_3) is much poorer compared to that of 43 children who were staged as M_0 to M_1.

Collins first observed that children with Wilms tumor who survived without evidence of recurrence, past a period of risk (being equal to their age at the time of diagnosis plus 9 months of gestation period) may be considered cured.[4] Bloom *et al.* have extended Collins' rule to medulloblastoma.[2] We also

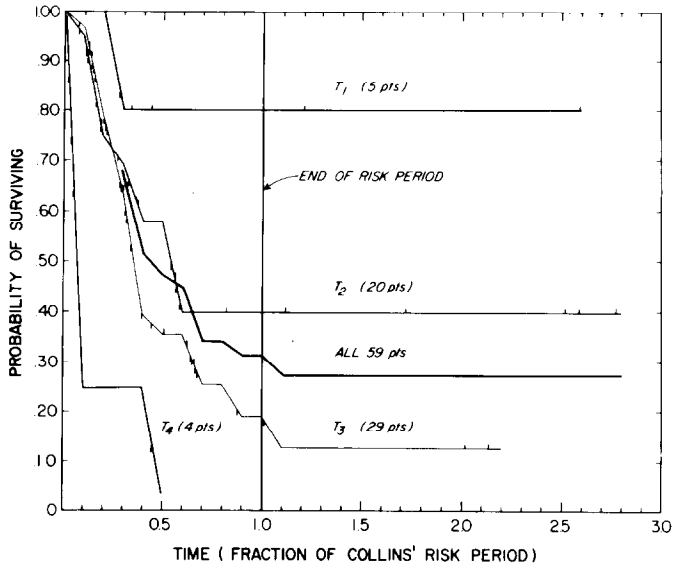

Fig. 2. The probability of survival according to T-category measured on a time scale representing fractions of the Collins[4] period of risk. If a child survived after the diagnosis for a period equal to his/her age at diagnosis plus nine months, then the surviving time in this scale will equal 1.0. The longest survivor in this figure has surpassed 2.8 times (or 280%) the risk period. Children living at the time of the study are identified with bars above the survival curve; dead children are represented with bars below the survival curve. $T_1 + T_2$ vs $T_3 + T_4$, $p = 0.08$; T_2 vs T_3, $p = 0.49$.

examined the survival rates of our patients over a time scale that represented fractions of Collins period of risk. As seen in Fig. 2, the probability of surviving the Collins period of risk was 80% for T_1 tumors, 39.7% for T_2, 19% for T_3 and 0 for T_4. For the entire group this probability was 31.1% with only one child dying after having exceeded the Collins' period of risk; however, he had evidence of recurrent tumor prior to reaching the end of this risk period.

Type of operation and survival. Figure 3 shows that the survival rates varied according to the type of operations. The 5-year survival rate was 25% among those 16 children who had partial excision or biopsy only of the tumor and was 44% among the 38 children who had subtotal or gross total removal of the tumor. Half of these latter 38 children had T_1 and T_2 tumors and their 5-year survival rate was 46.4%. The 5-year survival rate for the remaining 19 children with T_3 and T_4 tumors was 39.9%. Of the 5 children who had gross total removal of the tumor, 3 died at 5, 24 and 25 months respectively; 1 was alive with recurrent tumor at 32 months; and 1 was alive and well at 12 years.

Radiation dose and survival. Figure 4 shows the influence of dose to the posterior fossa on survival. The 5-year survival rate was 35.3% when a dose of 4000–4700 rad was delivered to the posterior fossa (17 patients); it was 45% when the dose was 4700–

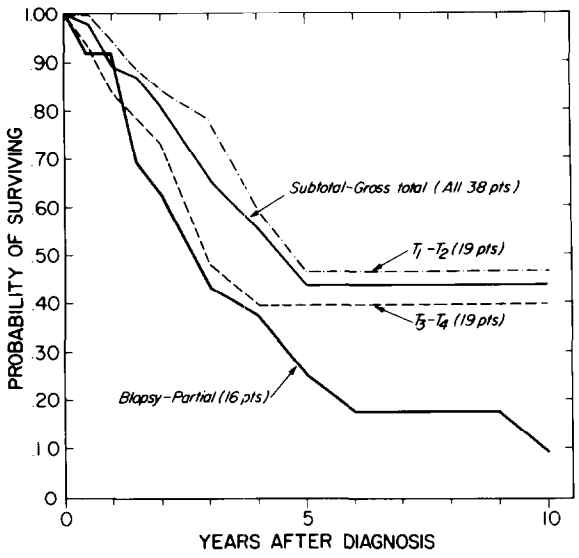

Fig. 3. Survival rates according to type of surgery for children who completed the radiotherapy course. The 38 children with subtotal or gross total removal of the tumor had better survival rates than the 16 children who had biopsy or partial removal of the tumor ($p = 0.08$). Half of the children who underwent subtotal or gross total removal had $T_1 - T_2$ tumors and their survival rates were better than the survival rates or the remaining 19 children who underwent the same type of surgery but had $T_3 - T_4$ tumors.

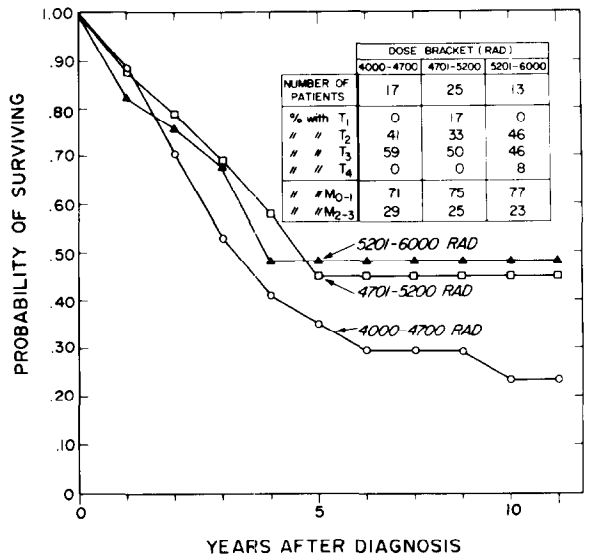

Fig. 4. Posterior fossa dose and survival rates. The inset shows the distribution of patients in each dose bracket according to the T and M category. Low vs medium, $p = 0.40$; medium vs high, $p = 0.80$.

5200 rad (25 patients). A further small increase in the survival rate (to 48.25%) was noted when the dose was 5400 rad or in its N.S.D. equivalent range of 5200–6000 rad (13 patients).

Age, sex and survival. Figure 5(A) shows the survival of 39 males which was compared to that of 20 females. The two curves run close to each other except for the interval between 5 and 8 years where they separate in favor of the males. Figure 5(B), shows the survival of children older than 75 months, (the age that represented the median of all 59 patients) as compared to the survival of children younger than 75 months. The survival appears to be higher for older children in the first 4.5 years. However, the two curves cross over at 4.5 years with the younger age group faring better thereafter.

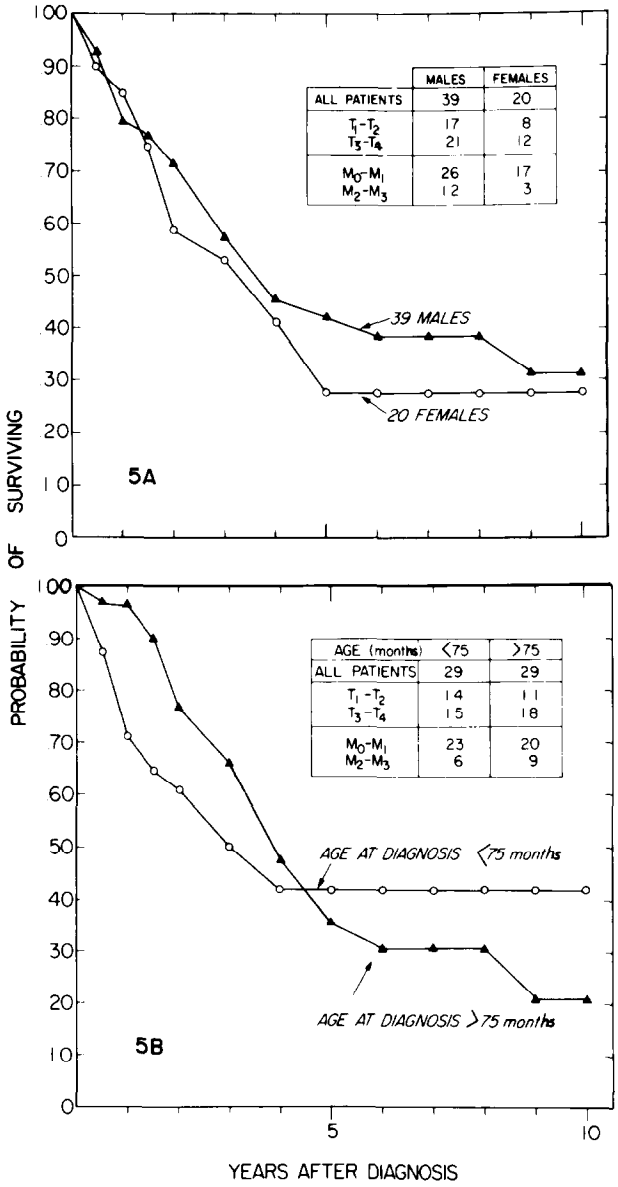

Fig. 5. The influence of age and sex on the survival rates. The insets show the number of patients according to T and M category. The median age was 75 months. Older children had better survival rates initially, but the long term survival was better in the younger children ($p = 0.21$). The male patients appear to have slightly better survival rates ($p = 0.20$).

Tumor recurrence

Thirty-two patients were diagnosed as having tumor recurrence. Three of them manifested blastic-lytic metastases with positive bone marrow biopsy 7 months, 8 months and 4 years after the initial treatment respectively. One child had reexploration and biopsy of the recurrence in the posterior fossa. In the remaining 28 patients the diagnosis was based on a combination of deteriorating neurological signs and symptoms with at least one of the following laboratory findings: positive CSF cytology in 7, positive radionuclide brain scan in 11, positive CAT scan in 1, positive pneumoencephaglogram or arteriogram in 7 and abnormal echoencephalogram in 5.

The time of recurrence. Twelve developed recurrence in first year, 11 in 2nd, 1 in 3rd, 5 in 4th, 1 in 6th, and remaining 2 during the 8th year after the initial treatment.

The sites of recurrence. These are given in Table 3. It is noted that the single most common site of recurrence was the posterior fossa (8 of 32 patients or 25%) which was overall involved in 59% (19/32) of patients with recurrence. However, in 24 of 32 patients with recurrence (or 75%), the posterior fossa either was not involved or it was not the only involved site.

Initial stage of disease. Tumor recurrence was diagnosed in 48% (12/25) of those children who had T_1 and T_2 tumor originally and in 69% (20/29) of those with T_3 and T_4 tumors originally and who completed their radiotherapy course.

Tumor dose. Children who received a dose of less than 4700 rad to the posterior fossa had a recurrence rate of 76.5% (13/17). The recurrence rate was 52% (13/25) among children who were treated to a posterior fossa dose of 4700–5200 rad, and it was 46.2% (6/13) when the posterior fossa dose was 5200–6000 rad.

Therapy for recurrence. Twenty-eight children received radiotherapy and/or chemotherapy after the diagnosis of recurrent tumor was made, whereas 4 received only supportive treatment. Of the 28 who received specific therapy, 16 were retreated with radiotherapy alone, 9 with radiotherapy and chemotherapy, and 3 with chemotherapy alone. Radiotherapy for recurrent tumor consisted of irradiation of the entire neuro-axis with posterior fossa boost. Twelve children received single agent or combination chemotherapy. Vincristine alone was used in 5 children; vincristine and cyclophosphamide in one child; vincristine, methyl-CCNU and procarbazine in 2; methyl CCNU in 2; CCNU in 1, and intrathecal methotrexate in 1. Children with recurrent tumor who were treated with radiotherapy and/or chemotherapy did better initially than those who were treated with radiotherapy alone (Fig. 6). After the first year however, the survival curves approached each other and at 16 months they crossed over with the radiotherapy only curve remaining slightly higher thereafter.

The mean survival after diagnosis of recurrence was made, was about 14 months. The longest survival was observed in a 6 year old boy who was retreated with radiotherapy alone, 14 months following the initial neuro-axial irradiation, after he developed cerebellar signs consistent with early recurrence and a positive radionuclide brain scan. The retreatment technique for this boy was 4000 rad to the posterior fossa only and 2000 to the spine. He was alive and well now 10 years after retreatment.

Table 3. Recurrent medulloblastoma

Site(s) involved	No. of patients
Posterior fossa (P.F.) alone	8
PF and CSF	4
PF and cerebral structures†	4
PF and spinal structures‡	3
Cerebral structures† alone	2
Cerebral† and spinal structures‡	3
Spinal structures‡ alone	5
Bones alone	2
Bones and CSF	1
Total	32

†Meninges and/or third and/or lateral ventricles.
‡Meninges and/or nerve roots.

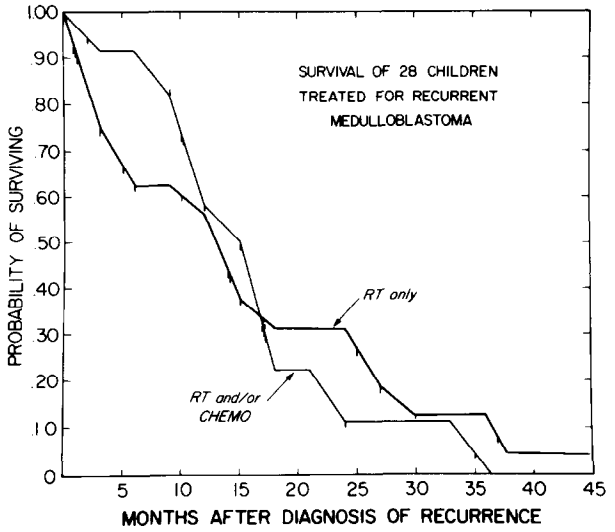

Fig. 6. Survival after the diagnosis of recurrence. Sixteen children were treated with radiotherapy alone (*RT* only) after the diagnosis of recurrence was made, whereas, 9 children received chemotherapy in additon to radiotherapy and 3 children were treated with chemotherapy alone. Bars above the survival curves identifying children living at time of study; bars below the survival curve represent dead children ($p = 0.40$).

Complications of treatment

During the radiotherapy course blood-count changes are related to extensive bone marrow irradiation and are manifested mainly by leukopenia when the vertebral column is irradiated. During the irradiation to the whole brain ports, lymphopenia has been observed. The kinetics of development of leukopenia and its recovery will be reported separately.[7]

Delayed effects also have been observed. Short stature secondary to loss of height of the vertebral column has been reported[14] and was observed in the majority of our long-term survivors. However, radiographic appearance of the vertebral column is not otherwise abnormal. One patient developed hypothyroidism and a thyroid nodule which was histologically a benign adenoma. Also, another patient developed a benign tumor in the irradiated area. This was an osteochondroma of the L_2 spinous process.

Brain stem necrosis was seen at autopsy on a patient who was retreated twice with radiotherapy following recurrences of the tumor. An estimated dose of 12,100 rad was delivered to the posterior fossa in three courses over a 10 month period.

Gross mental changes have not been observed as a consequence of whole brain irradiation. However, these patients did not undergo psychologic evaluation as a group. Table 4 shows the performance of patients surviving for 5 years or more without evidence of recurrent tumor.

Although, the spinal field ends at the sacral bone (S_2) the gonads are apparently not impaired. One of our patients had an induced abortion performed at the age of 14, 5 years after the radiotherapy course. Autopsy of the aborted fetus, showed no abnormalities. One year later this patient gave birth to a normal child.

DISCUSSION

In this series of patients, it is shown that surgical staging of a primary medulloblastoma in the posterior fossa is feasible and that the stage of the tumor correlates well with the survival rates. In most instances the observed differences did not reach conventional levels of statistical significance. This

Table 4. Performance of patients surviving for 5 or more years with no evidence of disease

Patient's hospital No.	Age at last follow-up (years)	Sex	Tumor stage	Years after radiotherapy	Karnofsky performance status	Comments
162 64 41	15	F	T_1M_x	13	90	Doing well at school at normal grade level; average student
165 76 92	16	M	T_2M_x	12	90	Doing well at school; in top third of class. Particularly good in mathematics
167 23 31	17	M	T_2M_1	12	90	Graduated from high school recently; mid third of class. Will attend trade school
171 25 18	15	M	T_2M_0	11	90	Doing well at school; one grade behind normal
182 34 52	12	M	T_2M_x	9	80	Attending special school. Deficient verbal function
183 88 16	25	M	T_1M_x	9	90	Works regularly at a printing shop. Requires hearing aid, right ear
188 93 72	11	M	T_3M_0	8	80	Attending special classes at school. Decreased hearing left ear. Significant deficit, especially in learning
186 06 30	17	F	T_1M_0	8	90	Doing well at school at normal grade level. Caring for her infant son at home
201 84 61	10	M	T_1M_0	6	80	Attending special classes at school; recently failed school screening hearing test
202 99 50	13	F	T_3M_2	$5\frac{1}{2}$	60	Attending school for children with learning disabilities functioning at a satisfactory level. Severe aphasia
206 58 39	14	F	T_3M_1	5	90	Doing well at school at normal grade level. Participates actively in sports

however, was to be expected because the size of a sample that can be accumulated at any individual institution is restricted.

It is unfortunate that most children have advanced disease at the time of diagnosis with stage T_3 representing the largest group of patients (about 50%). The continuing decline in survival rates even beyond the fifth year after the initial diagnosis and treatment, in our patients, was the result of continuing death occurring exclusively among children who had T_3 tumors. On the other hand, the survival curves of children with T_1 and T_2 tumors entered a plateau phase with no deaths observed beyond the 5th year. Brain stem involvement by tumor, classified here as T_{3b}, is a grave omen for prognosis. Bloom *et al.*[(2)] also have observed that the influence of brain stem invasion on the survival rate became more evident after the passage of more than 5 years following initial treatment.

The treatment results of patients with T_1 and T_2 tumors are more encouraging. In the small number of our patients with T_1 tumor, the death of one child (whose staging was in the border line of T_1 and T_2) caused the drop of the 5-year survival to 75%. It is possible that with larger numbers of patients, the long term survival of children with T_1 tumors could approach 90%. In the most recent years, there has been a tendency for patients to be diagnosed at a somewhat earlier T stage. Thus T_1–T_2 tumors were diagnosed in 8/15 or 53% and M_0–M_1 tumors in 11/15 or 73% of those children treated in the last 5 years. Among patients treated prior to the last 5 year period the corresponding proportions were 17/43 or 40% for T_1–T_2 and 32/43 or 74% for M_0–M_1. It is likely therefore that the pattern of survival rates will be maintained and in fact it may improve for those children treated in the last 5 years. If Collins' rule[4] holds true for medulloblastoma as it has been proposed,[2] then the probability of cure (i.e. the probability of exceeding Collins' period of risk) would be 31% for all 59 children; It would be 80% for children with T_1, 40% for those with T_2, and 20% for those with T_3 tumors. Although, exceptions to this rule have been reported,[9] the children we studied generally followed the rule. In fact, 75% (27/36) of the deaths occurred prior to lapse of one half of the risk period.

In an attempt to identify sources of bias, we have investigated various factors that may have influenced the results in favor of early stages of disease. It was found that children with T_1 and T_2 tumors were on the average one year older than children with T_3 and T_4 tumors in our series. Because it is generally believed that older patients carry a better prognosis, one could attribute the better survival of children with T_1 and T_2 tumors to their older age. This is, however, an unlikely interpretation because the age difference of one year between the two groups is rather small to account for the observed differences in survival. Also, when the survival was measured as a fraction of Collins period of risk (rather than in absolute survival years), it was shown again that earlier stage tumors were associated with better survival rates. Finally, in the patients we studied, the long term survival (beyond 5 years) was better in the younger age group. In the data reported by Bloom *et al.*[2] a similar cross over of the survival curves was seen at 5 years with older children having inferior survival rates afterward.

Because a greater percentage of our patients with early tumors underwent more complete tumor removal and because more substantial tumor mass reduction was associated with better survival rates, the extent of surgery may have been another factor influencing the survival rates in favor of earlier stages. To what extent this bias may have occurred is not clear. The value of the staging nevertheless can be tested within a group of patients who underwent the same type of surgery. Indeed, it was shown that the survival rates of patients with T_1–T_2 tumors who underwent subtotal or gross total tumor removal were superior to the survival rates of those patients who had the same type of surgery performed but who had T_3–T_4 tumors.

Subtotal tumor removal with good restoration of cerebral-spinal fluid flow from the aqueduct of Sylvius to the fourth ventricle represented the optimal surgery in the patients we studied. Surgery of lesser extent (including biopsy only) was associated with inferior survival rates, whereas, over-enthusiastic and too extensive surgery, i.e. gross total removal, in 5 children in our series resulted in only one long term survivor.

Increased radiation dose to the posterior fossa, (within the dose range we studied), was associated with improved survival rates and reduction of the overall recurrence rate from 76.5% to 46.2%. If further increase of dose is attempted it may entail potential risk of radiation necrosis and achieve only a small gain of increased survival rate. Our current policy is to deliver a tumor dose of 5500 rad in 6.5 weeks to the posterior fossa for T_2, T_3, T_4 and 5000 rad in 6 weeks for T_1 lesions, whereas, the remainder of the brain is irradiated to 4000 rad in 4 weeks. The dose to the spinal axis is 3600 rad in 5 weeks for M_0–M_x lesions and 5000 rad in 6.5 weeks for grossly seeded spine (M_3).

In agreement with other series[2,5,8] using whole neuro-axial irradiation technique, the most common site of recurrence (about 60%) was the posterior fossa, but in 75% of the recurrence the tumor either was not confined to the posterior fossa or it was

located elsewhere. This latter finding justifies our policy to irradiate the entire neural axis in cases of recurrent medulloblastoma.

A higher percentage of recurrences occurred among those children who originally had higher-staged tumors and who had received lower radiation doses to the posterior fossa.

Recurrences in the subfrontal and temporoparietal region have been reported[5,10] and also were noted in two of our patients who were found on autopsy to have, larger tumor collections on the temporal lobe in addition to more wide-spread leptomeningeal involvement. This is an interesting site of recurrence because it may be the result of inappropriate shielding of the middle cranial fossa during radiotherapy. Tayloring of whole brain irradiation ports can be intriguing;[3] portions of low temporal lobe can be shielded inadvertently or situated in the penumbra portion of the radiation field. Special attention is urged whenever shields are placed by the base of the skull especially in cases of neoplasms that seed cells into the CSF and involve the meninges such as acute leukemia, medulloblastoma, ependymoma and pinealomas.

An early recognition of the symptoms and signs of recurrence and prompt reinstitution of radiotherapy is worthwhile. Unfortunately, early death after recurrence is the rule, with sporadic exceptions only being cited in the literature.[10] One such exception is the long term survivor included in this report. The addition of various chemotherapeutic agents and regimens to the radiotherapeutic management of recurrent tumors initially showed an encouraging elevation of the survival curve. Unfortunately, in our limited experience this improvement was not sustained beyond the first year after recurrence.

Despite the dramatic increase in survival rates following the introduction of whole neuro-axial irradiation in the treatment of medulloblastoma, further improvement of the survival rates and especially the survival rates of children with more advanced stage tumors is desired. Several national collaborative groups now are studying combined therapeutic approaches, including the addition of chemotherapeutic agents as part of the initial management, in an effort to determine whether such a combination would reduce the recurrence and increase the survival rates.

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