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# Improved survival with the use of adjuvant chemotherapy in the treatment of medulloblastoma

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✓ Between 1975 and 1989, 108 children with newly diagnosed medulloblastoma/primitive neuroectodermal tumor (MB/PNET) of the posterior fossa were treated at the authors' institution. The patients were managed uniformly, and treatment included aggressive surgical resections, postoperative staging evaluations for extent of disease, and craniospinal radiation therapy with a local boost.

Beginning in 1983, children with MB/PNET were prospectively assigned to risk groups; those with "standard-risk" MB/PNET were treated with radiation therapy alone, while those in the "poor-risk" group received similar radiation therapy plus adjuvant chemotherapy with 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), vincristine, and cisplatin. The 5-year actuarial disease-free survival rate for all patients treated between 1975 and 1982 was 68%, and 73% when patients who died within 2 weeks after operation were excluded. This survival rate was statistically better for patients treated after 1982 (82%) compared to those treated between 1975 and 1982 (49%) ($p < 0.004$). There was no difference in disease-free survival rates over time for children with standard-risk factors; however, there was a significant difference in the 5-year survival rate for poor-risk patients treated prior to 1982 (35%) compared to those treated later (87%) ($p < 0.001$). For the group as a whole, a younger age at diagnosis correlated with a poorer survival rate; however, this relationship between age and outcome was significant only for children treated before 1983 ($p < 0.001$). These results demonstrated an encouraging survival rate for children with MB/PNET, especially those treated with aggressive surgical resection followed by both radiation therapy and chemotherapy. The results strongly suggest that chemotherapy has a role for some, and possibly all, children with MB/PNET.

KEY WORDS • **medulloblastoma** • **primitive neuroectodermal tumor** • **radiation therapy** • **chemotherapy** • **children**

MEDULLOBLASTOMA/PRIMITIVE neuroectodermal tumor (MB/PNET) is the most common malignant central nervous system (CNS) tumor of childhood.[7] The survival rate for patients with MB/PNET arising in the posterior fossa has slowly risen over the past four decades.[4,5] Improvement in outcome has been due to multiple factors including refinements in surgical techniques, advances in postoperative care, and the routine use of presymptomatic craniospinal radiation therapy (RT).[4,5,15] Prior to the mid-1970's, diagnosis was often difficult and required arteriography or pneumoencephalography.[22] The introduction of computerized tomography (CT) has simplified diagnosis and has likely resulted in earlier diagnosis in many cases.[22] It also, for the first time, provided a sensitive measure of the extent of tumor at diagnosis, the amount of residual disease present following surgery, and tumor recurrence.[15,22]

The majority of large reviews of patients with MB/PNET summarize the outcome of patients treated over many decades.[4,5,7] Several variables are now believed to have an impact on the outcome of these patients including: size of the tumor at the time of diagnosis, the extent of tumor resection, and the amount of disease outside the primary site after surgery; these variables are difficult to evaluate in longitudinal studies.[15] Since 1975, all patients with MB/PNET treated at the Children's Hospital of Philadelphia have undergone CT scanning with and without contrast enhancement or, more recently, magnetic resonance (MR) imaging prior to and following surgery. In addition, beginning in 1975 cerebrospinal fluid (CSF) cytological studies have been

performed for all patients within 3 weeks after surgery to test for the presence of free-floating tumor cells and, since 1979, all have undergone myelography following surgery. The amount and volume of RT given to patients with MB/PNET following surgery have been relatively standardized during this time period. The only major variable in management has been the use of chemotherapy.

Since early 1983, patients with MB/PNET at our institution were prospectively assigned after surgery to one of two major risk groups based on the extent of tumor at the time of diagnosis and the degree of surgical resection. Children with standard-risk disease were treated with RT alone. Patients who were considered to be at highest risk for disease relapse following standard craniospinal and local boost RT were offered treatment with adjuvant chemotherapy consisting of vincristine during RT followed by 6-week cycles of 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), vincristine, and cisplatin. The preliminary results of this treatment regimen have been published and a disease-free survival rate of greater than 90% at a median of 20 months from diagnosis was reported.[13] This review will update this experience and compare results in patients treated with RT and chemotherapy to patients treated with RT alone between 1983 and 1989. Evaluation of the 108 patients treated since 1975 should also supply up-to-date survival information for children with MB/PNET.

TABLE 1

*Chang staging system for posterior fossa medulloblastoma**

| Stage | Definition |
|---|---|
| tumor | |
| $T_1$ | tumor < 3 cm in diameter & limited to the midline position in the vermis, 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 |
| $T_3$: | |
| $T_{3a}$ | tumor invading 2 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 |
| metastasis | |
| $M_0$ | no evidence of gross subarachnoid or hematogeneous 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 seedings in the spinal subarachnoid space |
| $M_4$ | extraneural metastasis |

* Derived from classification system of Chang, *et al.*[3]

## Clinical Material and Methods

Between January, 1975, and December, 1989, 108 newly diagnosed patients with MB/PNET were treated at the Children's Hospital of Philadelphia. All patients had tumors which arose in the posterior fossa. Patients with histologically identical tumors arising in other parts of the neuraxis were excluded from this analysis. The majority (91%) of children underwent surgical resection at our institution. Ten patients were referred elsewhere after surgical resection but prior to receiving further therapy.

At the time of diagnosis, those patients with posterior fossa MB/PNET who had surgery at the Children's Hospital of Philadelphia were managed uniformly. A course of dexamethasone (1 to 2 mg/kg/day) was begun, and posterior fossa decompression and exploration were performed, whenever possible, within 48 hours of diagnosis. A ventriculostomy was placed at the time of operation in patients with hydrocephalus, and total surgical resections were attempted in all cases. At surgery, the size of the tumor was graded by the surgeon on a scale of 1 to 4 according to the classification of Chang and associates[3] (Table 1). Within 72 hours of completion of surgery, CT was performed with and without dye. Since early 1989, MR imaging, with and without gadolinium, has been substituted for CT in some patients.

Based on the surgeon's impression at the time of surgery and the postoperative CT or MR study, tumor resections were graded as follows: total or near-total resection (no areas of residual lump disease or only residual tumor rim enhancement); partial resection (residual lump disease > 50% resection); or biopsy (< 50% resection). Seven to 14 days after surgery, a myelogram and lumbar CSF cytological examination were performed to assess the extent of dissemination. Based on these results, a metastasis stage was designated for each patient ($M_0$ through $M_3$)[3] (Table 1). If, at evaluation, myelography was normal but free-floating tumor cells were found in the CSF, a repeat spinal tap was performed 21 days after operation and results from this analysis were used for designation of the metastasis stage.

The tumor removed at the time of original operation was evaluated by examination of paraffin-embedded material and immunoperoxidase techniques. Tumors were classified as outlined by Rorke, *et al.*[18,19] Immunoperoxidase techniques were introduced at different times during the study, so the decision concerning cellular differentiation varied depending on the stains used.

### *Treatment Protocol, 1975 to 1982*

Between January, 1975, and December, 1982, following the evaluation methods mentioned previously, patients older than 1 year were treated with craniospinal RT plus a local tumor boost. The RT doses routinely used are outlined in Table 2. The majority of patients

TABLE 2

*Prescribed radiation therapy dose schedule*

| Study & Age Group | Local Boost Dose (cGy) | Craniospinal Dose (cGy)* |
|---|---|---|
| 1975–1988 treatment group | | |
| < 1 yr | 0 | 0 |
| 1–3 yrs | 5400 | 2400–3600*† |
| > 3 yrs | 5580 | 3600* |
| 1988–1990 treatment group | | |
| < 1½ yrs | 0 | 0 |
| 1½–5 yrs | 5400 | 1800*‡ |
| 5–9 yrs | 5580 | 2400* |

* Patients with metastatic lump disease received an additional 1000 to 2000 cGy to the metastatic lesion.

† Specific dose determined at discretion of managing physician.

‡ All patients received adjuvant chemotherapy.

TABLE 3

*Factors in the stratification of children with MB/PNET**

| Factor | Standard Risk | Poor Risk† |
|---|---|---|
| extent of dissemination | $M_0$ | $M_1$–$M_3$ |
| extent of resection | total or near-total resection | partial resection or biopsy |
| extent of local disease | $T_1$, $T_2$, $T_{3a}$ | $T_{3b}$–$T_4$ |

* MB/PNET = medulloblastoma/primitive neuroectodermal tumor. For definition of T and M stages see Table 1.

† Factors indicating poor-risk disease.

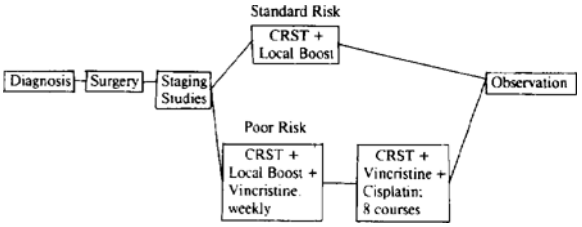


FIG. 1. Protocol for treatment of children with medulloblastoma/primitive neuroectodermal tumor. CRST = craniospinal radiation therapy.

received the craniospinal portion of RT first, followed by the local tumor boost. Daily fractions of 180 cGy were used. The entire tentorium was treated, with the anterior aspect of the field extending to the posterior clinoid process. Ten patients treated within the time period were given adjuvant chemotherapy with vincristine during RT, then received CCNU and vincristine following RT (as part of a treatment trial performed in collaboration with the Childrens Cancer Study Group).[1] No preselection criteria were used to determine which patients would be treated with RT alone and which would also receive adjuvant chemotherapy. Children younger than 1 year initially received chemotherapy without RT. The type of drug therapy used for infants varied over this time period.

Retrospectively, based on the criteria used since 1983 to assign patients to risk groups, 23 of the patients treated between 1975 and 1983 would fall into the poor-risk group and 18 into the standard-risk group. All 18 standard-risk children went on to receive RT with or without chemotherapy. Three of the poor-risk patients died postoperatively, two were treated with chemotherapy alone, and 18 received RT with or without chemotherapy.

### *Treatment Protocol, 1983 to 1989*

Between 1983 and 1989, patients were prospectively assigned to two major risk groups. Patients considered to have a poor-risk MB/PNET had one or more of the following: tumors that were partially resected or biopsied; brain-stem tumor infiltration at the time of surgery; and/or tumors that were disseminated at the time of diagnosis (Chang stage $M_1$ through $M_3$, Table 3). Histological findings and age were not used as criteria to determine risk status.

Children less than 1½ years of age were treated with chemotherapy alone (Table 2). Children aged 1½ years or older who were in the poor-risk group received RT plus adjuvant chemotherapy with CCNU, vincristine, and cisplatin. This treatment protocol is described below. Patients between 1½ and 3 years of age were initially given reduced craniospinal RT (2400 cGy as compared to 3600 cGy for older patients) and the same dosage of local boost RT. Beginning in June, 1988, however, a further reduction in the dosage of craniospinal RT was made; children between 1½ and 5 years of age were treated with 1800 cGy of craniospinal radiation and those between 5 and 9 years of age were treated with 2400 cGy (Table 2).

Children with standard-risk disease diagnosed since 1983 (Table 3) were treated with RT alone. The only exception to this were children less than 5 years of age, diagnosed since 1988; these patients were treated with a further reduced dose of craniospinal radiation in addition to the adjuvant chemotherapy given to poor-risk patients.

During the treatment period from 1983 to 1989, 20 children were considered to have standard-risk criteria and 47 had poor-risk parameters. One of the standard-risk patients died and the remainder either received RT alone (10 cases) or a reduced RT dose plus chemotherapy (nine cases). Of the poor-risk patients, two died postoperatively, three received chemotherapy alone, and 42 received both RT and chemotherapy.

### *Chemotherapy Protocol*

Therapy used since 1983 is outlined in Fig. 1. Weekly vincristine administration at a dose of 1.5 mg/sq m (up to a maximum dose of 2 mg/sq m) was begun during RT. Six weeks after completion of RT, patients were begun on a regimen of CCNU at 75 mg/sq m, cisplatin at 68 mg/sq m every 6 weeks, and vincristine at 1.5 mg/sq m (up to a maximum dose of 2 mg/sq m) weekly

for 3 consecutive weeks. Eight 6-week cycles of drugs were planned.

All patients underwent formal audiological examination and renal monitoring (glomerular filtration rate or creatine clearance) before each cycle of chemotherapy. A CT scan, with and without contrast enhancement, was performed every 3 months (after every two cycles of therapy) while the patient was receiving treatment and at 6-month intervals thereafter for the first 3 years after treatment. The chemotherapy dosage was modified if there was any evidence of significant audiological, renal, or hematological toxicity. The cisplatin dosage was reduced by 25% if hearing loss was greater than 40 dB in the 4000- to 8000-Hz range or if renal function was reduced by 25%. The cisplatin dosage was reduced by 50% if there was a 20-dB hearing loss in the 50- to 2000-Hz range or a 25% to 49% reduction in renal function. If hearing loss was greater than 20 dB in the 50- to 2000-Hz range or if loss of renal function was greater than 50%, the cisplatin was omitted for that cycle and only given thereafter if renal or hearing function improved. The CCNU dosage was reduced by 50% if there was marked thrombocytopenia (platelet count < 50,000/cu mm) or symptomatic neutropenia (absolute neutrophil count < 500/cu mm with associated fever or evidence of infection requiring hospitalization). The vincristine dosage was reduced by 50% if severe symptomatic paresthesia developed and was omitted for at least one dose for ileus or significant weakness (and begun again when weakness improved or ileus resolved).

### *Statistical Analysis*

Disease-free survival was estimated by the Kaplan-Meier product limit method.[8] The log rank test was used to compare differences in survival among subgroups of patients defined by era of treatment and clinical factors.[17] Mean age and radiation dose between eras of treatment were compared using t-tests. Chi-square tests were used to evaluate the distribution of sex, metastasis stage, tumor stage, and extent of resection among groups.

## Results

### *All Patients*

The 108 patients treated between 1975 and 1989 had a mean age of 7.0 years at diagnosis (Table 4). The tumor stage, metastasis stage, and extent of resection for these patients were as shown in Table 4. Seven children died within 1 month of diagnosis and received no therapy after surgery. Of the remaining 101 patients, five were less than $1\frac{1}{2}$ years of age at diagnosis and received chemotherapy alone; three remain alive at $\frac{1}{2}$, 18, and 66 months after diagnosis. The 96 patients treated with postoperative RT received a mean dose of 5303 cGy to the local tumor site and 3036 cGy to the remainder of the craniospinal axis.

The 5-year actuarial disease-free survival rate for all patients was 68%; 75 (69%) of 108 remain free of progressive disease. The 5-year disease-free survival rate for patients receiving some form of postoperative therapy (either chemotherapy alone or RT with or without adjuvant chemotherapy) was 73% and for those receiving only RT was 74%. Children in the standard-risk group had a 5-year disease-free survival rate of 61%, as 17 of 28 remain alive and in continuous remission. In comparison, 48 (80%) of 60 patients with poor-risk criteria who received RT remain in remission with a 5-year disease-free survival rate of 71%.

Of the 26 patients for whom evaluation could adequately determine the extent of disease at time of first relapse, 13 were found to have disease only at the local site, six had disease locally with dissemination to distant CNS sites, and seven had dissemination to distant sites (including two metastases to bone alone, without subarachnoid or intraparenchymal evidence of relapse).

TABLE 4
*Clinical characteristics in 108 patients*

| Factor | 1975–1982 Group | 1983–1989 Group | Total Series |
|---|---|---|---|
| no. of cases | 41 | 67 | 108 |
| mean age (yrs) | 7.5 | 6.7 | 7.0 |
| age range (yrs) | 0.1–18 | 0.5–21 | 0.1–21 |
| sex (M/F) | 20/21 | 47/20 | 67/41 |
| T stage | | | |
| $T_1$–$T_2$–$T_{3a}$ | 26 (63%) | 28 (42%) | 54 (50%) |
| $T_{3b}$–$T_4$ | 15 (37%) | 39 (58%) | 54 (50%) |
| M stage | | | |
| $M_0$ | 30* (73%) | 54 (81%) | 74* (69%) |
| $M_{1-3}$ | 8 (20%) | 13 (19%) | 21 (20%) |
| extent of resection | | | |
| total | 28 (68%) | 49 (73%) | 77 (71%) |
| subtotal/partial | 13 (32%) | 16 (24%) | 29 (27%) |
| biopsy | 0 | 2 (3%) | 2 (2%) |
| poor risk† | 23 (56%) | 47 (70%) | 70 (65%) |
| standard risk† | 18 (44%) | 20 (30%) | 38 (35%) |
| mean local RT dose (cGy)‡ | 5186 | 5370 | 5303 |
| mean craniospinal RT dose (cGy)‡ | 3157 | 2962 | 3036 |

* Three patients did not have metastasis staging.
† See text for definitions of standard-risk and poor-risk disease.
‡ Patients not treated with radiation therapy (RT) are excluded.

### *Patients Treated Between 1975 and 1982*

The 41 patients treated between 1975 and 1982 had a mean age of 7.5 years at diagnosis. Their tumor stage, metastasis stage, and extent of resection were as shown in Table 4. Four children died within 1 month of surgery, having received no further treatment. Two children, less than 1 year of age at diagnosis, were treated with chemotherapy alone and both died within 6 months of diagnosis. One child died of autopsy-confirmed radiation vasculitis 21 months following completion of RT. This child is excluded from analysis of disease-free survival, so a total of 35 patients were

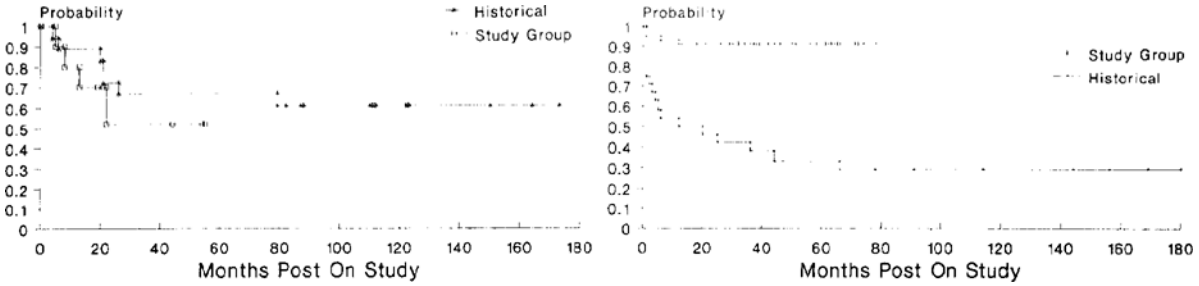


FIG. 2. Five-year actuarial disease-free survival rate for children with medulloblastoma/primitive neuroectodermal tumor (MB/PNET) treated between 1983 and 1989. *Left:* Rate for children with standard-risk disease. The historical group (18 cases) includes those treated between 1975 and 1982 and the study group (10 cases) includes those treated with radiation therapy alone. *Right:* Rate for children with poor-risk MB/PNET. The historical group (18 cases) includes those treated between 1975 and 1982 and the study group (42 patients) includes all poor-risk patients treated with both radiation therapy and chemotherapy.

evaluated. The mean doses of local and neuraxis RT received were as outlined in Table 4.

Nineteen (54%) of 35 who received RT remain alive and free of disease at a median of 108 months after diagnosis. The 5-year actuarial disease-free survival rate for all of these patients was 49%. The 5-year disease-free survival rate was 67% for the 18 patients retrospectively determined to have standard-risk criteria and 44% for the 18 patients considered to be in the poor-risk category who received RT (Fig. 2). Six of 10 children who received adjuvant chemotherapy are alive, compared to 13 of 25 treated with RT alone. The site of first relapse was local in 12 patients, local with dissemination to the leptomeninges in three, leptomeningeal alone in one, and extraneural alone in two patients.

### *Patients Treated Between 1983 and 1989*

The 67 children treated between 1983 and 1989 had a mean age of 6.7 years at diagnosis (Table 4). The tumor stage, metastasis stage, and extent of resection were as shown in Table 4. Three children died within 1 month of diagnosis without receiving postoperative therapy. Three were aged less than $1\frac{1}{2}$ years at diagnosis and were treated with chemotherapy alone; all remain alive and in continuous disease-free remission.

Fifty-three of 61 patients who received RT (mean doses given in Table 2) remain alive and free of disease, a median of 40 months after diagnosis. The 5-year actuarial disease-free survival rate for this group as a whole was 82%, and 88% if postoperative deaths were excluded from analysis. The 5-year disease-free survival rate for children with standard-risk disease who were treated with RT alone (10 cases) was 52% because four of 10 patients have relapsed (Fig. 2 *left*). Forty-seven (92%) of 51 patients treated with both RT and chemotherapy remain in continuous disease-free remission, having a 5-year disease-free survival rate of 88%. This group of 51 children included 42 who met the poor-risk criteria based on one or more of the following: extent of resection, brain-stem involvement, and/or leptomeningeal dissemination; 40 of those 42 patients are alive for an actuarial 5-year disease-free survival rate of 92% (Fig. 2 *right*). The remaining nine children were considered standard-risk patients by these criteria, but were less than 5 years of age at diagnosis and were treated with reduced RT and chemotherapy; seven of these patients are alive and in continuous disease-free remission since initiation of treatment.

In the eight patients who have relapsed, the sites of relapse were local in one, local with dissemination in three, and disseminated alone in four. Of the children who received chemotherapy, two had local and disseminated relapse and two had disseminated relapse alone.

### *Toxicity of Chemotherapeutic Regimen*

The chemotherapeutic regimen used since 1983 did have significant toxicity. Some degree of ototoxicity was seen in more than 90% of the patients with cumulative doses of cisplatin. Hearing loss was initially demonstrable at 4000 and 8000 Hz, and more than 50% of the patients required some modification of their cisplatin dose by the sixth therapy cycle. Upon completion of therapy, one patient (the second child treated on the protocol) required a hearing aid. Nephrotoxicity (as documented by falling glomerular filtration rates) was likewise seen with cumulative doses of cisplatin. Dose modification was required in approximately 25% of the patients by the sixth therapy cycle. There were no cases of acute renal failure or permanent symptomatic kidney damage. Admissions for fever and neutropenia were infrequent and sporadic. No life-threatening infections were encountered during the period of study.

### *Comparison of Patients Treated in 1975 to 1982 and 1983 to 1989*

There was no difference between the patients in the two treatment periods in regard to age, extent of dissemination, or degree of resection (Table 4). A greater number of male patients were treated after 1983 ($p = 0.03$). The doses of local and craniospinal RT used were similar in the two groups, although children treated

since 1983 received a slightly lower mean dose of craniospinal RT because younger children treated from 1988 received 1800 cGy of craniospinal RT. More patients evaluated since 1983 were considered to have brain-stem involvement ($T_{3b}$) or larger tumors ($T_4$) at diagnosis: 39 (58%) of 67 patients as compared to 15 (37%) of 41 patients. For this reason, a higher percentage of children had poor-risk tumors in the period between 1983 and 1989 ($p = 0.04$).

Five-year actuarial disease-free survival rates were statistically different for patients treated after 1983 (82% vs. 49%; $p = 0.001$). This difference remained highly significant independent of whether postoperative deaths or children receiving chemotherapy alone were excluded from the analysis. There was no difference in disease-free survival rates over time for those children with standard-risk factors; 5-year disease-free survival was 67% for children treated between 1975 and 1982 compared to 52% for children treated between 1983 and 1989 ($p = 0.45$, Fig. 2 *left*). There was a significant difference in 5-year disease-free survival rates, however, for poor-risk children treated prior to 1983 compared to those treated later ($p < 0.001$). This difference in poor-risk patients remained if children who were considered a poor risk based on age alone and who received chemotherapy (a selection criterion for children between $1\frac{1}{2}$ and 5 years of age who were diagnosed since 1988) were excluded from analysis ($p < 0.001$; Fig. 2 *right*).

For the group as a whole, age at diagnosis was related to outcome, as younger children were less likely to survive ($p = 0.02$). However, this relationship between age and outcome, which was highly significant in children treated before 1983 ($p = 0.001$), did not hold true for children treated after 1983 ($p = 0.24$). The tumor stage did not predict outcome when all 108 patients were considered but was of borderline significance for patients treated between 1975 and 1982 (5-year disease-free survival rate of 58% for children with $T_1$, $T_2$, and $T_{3a}$ tumors compared to 33% for those with $T_{3b}$ and $T_4$ lesions; $p = 0.08$). Survival did not differ significantly according to the metastatic stage although, of those treated before 1983, there was a trend toward a poorer survival rate for patients with $M_1$ to $M_3$ disease (38%) compared to those with $M_0$ disease (52%). The extent of resection did not influence outcome.

Children who received less than 3000 cGy of craniospinal radiation (three cases) or less than 5000 cGy of local radiation (five cases) and no chemotherapy had a statistically higher rate of relapse, but since so few children were available in these categories, the significance of these findings is questionable.

## Discussion

### *Comparison to Previous Experience*

The probability of survival for children with MB/PNET has risen over the past decades. In 1984, Farwell, *et al.*,[4] reported a 22% survival rate at 5 years for the 143 cases of Connecticut children diagnosed since 1950; however, patients treated between 1968 and 1977 had a statistically better survival probability because nearly 50% of the patients were alive 5 years later. A similar rise in the survival rate was seen for patients treated at Duke University between 1940 and 1983.[5] The Joint Center for Radiation Therapy and the University of California at San Francisco have reported that studies of patients treated more recently have disease-free survival rates ranging between 55% and 68% at 5 years after diagnosis.[6,11] Factors associated with the improving survival rate for children with MB/PNET in these studies include a decrease in autopsy diagnosis, a lower operative morbidity, and changes in RT protocol such as the use of craniospinal radiation and higher doses of local radiation. Earlier diagnosis, although not evaluated as an independent variable in any of these studies, may also have an impact on outcome. Our results in 108 newly diagnosed patients treated since 1975 compare favorably to those outlined above. The 5-year actuarial disease-free survival rate for all patients was 68% and if we exclude from diagnosis patients who died within 1 month of diagnosis or who received chemotherapy alone, 75 (69%) of 108 remained free of progressive disease at the time of analysis. During the period of observation, the only improvement in survival over time at our institution has been seen in the children with so-called poor-risk MB/PNET.

### *Rationale for Use of Chemotherapy*

In the late 1970's, two independent large randomized treatment trials of similar design were undertaken by the Childrens Cancer Study Group/Radiation Therapy Oncology Group (CCSG/RTOG), and the International Society of Pediatric Oncology (SIOP).[1] The estimated 5-year disease-free survival rate for patients treated in the CCSG/RTOG study was 65%, which is similar to the overall survival rate for patients in our study. In these two randomized studies, patients were treated with either craniospinal and local RT or similar RT plus concomitant adjuvant chemotherapy with vincristine followed by CCNU and vincristine. The addition of chemotherapy did not improve the survival rate when all patients were analyzed; however, for those patients in the CCSG/RTOG study who had large tumors ($T_3$ and $T_4$) and metastatic disease ($M_1$ through $M_3$ lesions), event-free survival rates were better for the group receiving chemotherapy. A similar trend toward improved survival for patients with extensive lesions (those with brain-stem involvement or metastatic disease) receiving chemotherapy was seen in the SIOP study. Neither the CCSG/RIOG or the SIOP study could show an improvement in survival data for patients with smaller lesions or those without metastatic disease at the time of diagnosis.

Given these reasons, a study was begun at our institution in 1983 prospectively separating patients into risk groups based on their tumor and metastasis stages.

In addition, prior to the study, it was suggested that patients with less-aggressively resected tumors fared more poorly,[9] and this criterion was added to the assigned parameters. We decided that patients who had both localized disease at time of diagnosis and total or nearly total resections would be treated with RT alone, while those with poor-risk parameters would be treated with the same dose and volume of RT plus adjuvant chemotherapy. Cisplatin was added to the CCNU and vincristine regimen based on data demonstrating that at the time of relapse, approximately one-half of the children with MB/PNET responded to cisplatin therapy.[20] The combination of cisplatin, CCNU, and vincristine had been tested in a pilot study at our institution for children with relapsed MB/PNET and resulted in complete disappearance of tumor in six of the seven children.[10]

*Significance of the Results*

The overall survival rate for patients treated at our institution prior to the initiation of this protocol in 1983 was similar to that reported by other groups. For those patients who were considered to have standard-risk MB/PNET, there was no improvement in 5-year disease-free survival rates over time; this survival rate was 67% for patients treated prior to 1983 compared to 52% for those treated since 1983. The major change in the rate of survival has been seen in children treated with adjuvant chemotherapy. The 5-year actuarial disease-free survival rate of patients treated before 1982 was 44% compared to 88% for those treated identically, except for the addition of chemotherapy; no other factors clearly changed during this study period. The treatment groups were similar in regard to age, extent of dissemination at the time of diagnosis, and the degree of surgical resection. One possible bias is that, since 1983, a higher percentage of patients have been considered to have poor-risk disease on the basis of brainstem involvement ($T_{3b}$). Possible reasons for this include: 1) a greater awareness by our surgeons of the staging criteria and the need to look carefully for brainstem involvement at surgery; 2) the introduction of improved neuroimaging techniques; and 3) changing referral patterns so that children with large or infiltrating tumors were more likely to be referred to our institution. However, this possible selection bias does not explain why children treated with chemotherapy in the poor-risk group fared better than those with standard-risk tumors treated with RT alone. The dose and extent of RT did not differ over this time period, and it seems that the best explanation for the improvement in survival was the addition of chemotherapy. Interestingly, the only other study reporting a disease-free survival as favorable as ours was that by McIntosh and coworkers,[12] who found an 81% 6-year disease-free survival rate in children with MB/PNET treated similarly with RT and adjuvant cyclophosphamide and vincristine.

During the period of this study, criteria used to prospectively assign patients to risk groups did not change. The only alteration in treatment since 1983 was the decision in 1988 for a pilot study using reduced-dose RT plus chemotherapy for all children between $1\frac{1}{2}$ and 5 years of age at diagnosis. Fourteen patients meeting this age criterion have been treated to date. Nine of these had standard-risk tumors as evaluated by the other risk parameters but received adjuvant chemotherapy due to their age. Even if these nine patients are deleted from the analysis of outcome, the actuarial disease-free survival rate of 92% was strikingly better for the 42 poor-risk patients treated with RT and the new chemotherapy protocol than the 44% rate for children with poor-risk disease treated between 1975 and 1982.

The results of our study bring into question the utility of postoperative staging studies to determine which patients should receive adjuvant chemotherapy. There is ample evidence that evaluation for the extent of disease confirms a significant incidence of subarachnoid tumor spread in children with MB/PNET.[2,15] Anywhere between 10% to 30% of patients, possibly even a higher portion in children less than 3 years of age at diagnosis, will have disseminated disease at the time of diagnosis.[2,15] Evaluation for lump disease outside the primary tumor site is mandatory for the determination of appropriate RT because areas of lump disease on myelography are conventionally given additional local radiation boosts. Because poor-risk patients treated with chemotherapy are faring better than standard-risk patients, the use of tumor and metastasis staging and extent of resection to determine which patient should receive chemotherapy seems questionable.

One factor we did not analyze regarding outcome was the effect of histological differentiation along identifiable cell lines. In a previous report, our group found cellular differentiation to correlate with a poorer outcome for children with MB/PNET.[16] But since histological techniques varied during the period of analysis, primarily due to the introduction of immunoperoxidase staining for glial and neuronal intermediate filaments, we could not analyze the relationship between cellular differentiation and disease-free survival.

*Future Directions*

The morbidity rate resulting from the use of both RT and chemotherapy in children with MB/PNET is considerable. This becomes an increasing concern as survival rates rise. In a previous study, children under 5 years of age at diagnosis treated at our institution with between 2400 and 3600 cGy of whole-brain radiation suffered a significant drop in overall intelligence.[14] The detrimental effects of similar doses of cranial irradiation on endocrine function have been well documented.[15] For these reasons, and because of preliminary evidence that 2400 cGy of RT was successful in controlling leptomeningeal disease relapse in patients with

MB/PNET and the encouraging results of patients treated in our study with RT and chemotherapy,[6,21] we decided in 1988 to attempt to further reduce the radiation dose from 2400 to 1800 cGy for children less than 5 years of age. At the present time, there is no evidence that this decrease in radiation has resulted in an increase in disease relapse; however, this study is still in its infancy and results are too preliminary for conclusions. Other children in our study were treated with a relatively standard dose of RT, allowing no conclusions to be drawn between the amount of radiation given and disease control in patients with MB/PNET. Extraneural relapse was only seen in patients who had not received chemotherapy.

Different drug combinations, with or without cisplatin, are presently being evaluated by others either before or after RT for children with MB/PNET. Only time will tell which chemotherapeutic regimen is the most efficacious and least toxic for children with this disease. The cisplatin utilized in our protocol may cause significant ototoxicity and nephrotoxicity; however, side effects have to date been primarily transient, with the exception of one child who requires a hearing aid. Which therapy is best is unknown; however, our results strongly suggest that chemotherapy has a role for at least some and possibly for all children with MB/PNET.[15] The use of chemotherapy coupled with RT and aggressive surgical resection has resulted in encouraging overall 5-year disease-free survival rates for patients treated in the era of CT and MR imaging.

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