**Metastasis Stage, Adjuvant Treatment, and Residual Tumor Are Prognostic Factors for Medulloblastoma in Children: Conclusions From the Children’s Cancer Group 921 Randomized Phase III Study**


**Purpose:** From 1986 to 1992, “eight-drugs-in-one-day” (8-in-1) chemotherapy both before and after radiation therapy (XRT) (54 Gy tumor/36 Gy neuraxis) was compared with vincristine, lomustine (CCNU), and prednisone (VCP) after XRT in children with untreated, high-stage medulloblastoma (MB).

**Patients and Methods:** Two hundred three eligible patients with an institutional diagnosis of MB were stratified by local invasion and metastatic stage (Chang T/M) and randomized to therapy. Median time at risk from study entry was 7.0 years.

**Results:** Survival and progression-free survival (PFS) ± SE at 7 years were 55% ± 5% and 54% ± 5%, respectively. VCP was superior to 8-in-1 chemotherapy, with 5-year PFS rates of 63% ± 5% versus 45% ± 5%, respectively (P = .006). Upon central neuropathology review, 188 patients were confirmed as having MB and were the subjects for analyses of prognostic factors.

Children aged 1.5 to younger than 3 years had inferior 5-year estimates of PFS, compared with children 3 years old or older (P = .0014; 32% ± 10% v 58% ± 4%, respectively). For MB patients 3 years of age or older, the prognostic effect of tumor spread (M0 v M1 v M2+) on PFS was powerful (P = .0006); 5-year PFS rates were 70% ± 5%, 57% ± 10%, and 40% ± 8%, respectively. PFS distributions at 5 years for patients with M0 tumors with less than 1.5 cm² of residual tumor, versus ≥ 1.5 cm² of residual tumor by scan, were significantly different (P = .023; 78% ± 6% v 54% ± 11%, respectively).

**Conclusion:** VCP plus XRT is a superior adjuvant combination compared with 8-in-1 chemotherapy plus XRT. For patients with M0 tumors, residual tumor bulk (not extent of resection) is a predictor for PFS. Patients with M0 tumors, ≥ 3 years with ≤ 1.5 cm² residual tumor, had a 78% ± 6% 5-year PFS rate. Children younger than 3 years old who received a reduced XRT dosage had the lowest survival rate.


**MEDULLOBLASTOMA** (MB) was first reported in 1925 by Bailey and Cushing, who described 25 patients with densely cellular brain tumors of the posterior fossa that were fatal if radiation therapy (XRT) was not administered after surgery. MB was named after a still-unidentified “indifferent” cell thought to be a precursor for both glia and neurons. In 1973, Hart and Earle described a series of mostly adult patients who had small, round, blue cell tumors of the supratentorial fossa that did not fit into the current classification; they were called primitive neuroectodermal tumors (PNETs). This controversy in nosology was later extended by the combining of the histopathologically similar supratentorial PNETs with MB into the revised World Health Organization childhood brain tumor classification of all intracranial childhood embryonal brain tumors.

On the basis of that World Health Organization revision, the term posterior fossa PNET was formally introduced, although MB has continued in use.

Five-year survival rates of 50% to 80% have been reported with different treatment approaches over the past 25 years. These results occurred after the introduction of craniospinal radiotherapy with local boost and, later, chemotherapy. Clinical trials and reports, however, used different definitions of high- and low-risk patients. Thus, conclusions are difficult to draw in regard to relative efficacy of newer treatments, such as lower neuraxis XRT, or the risk/benefit of intensive chemotherapy for “high-risk” patients.
PROGNOSTIC FACTORS FOR MEDULLOBLASTOMA IN CHILDREN

Prospective clinical trials by the Children’s Cancer Group (CCG; CCG-942) and the International Society for Pediatric Oncology (SIOP; SIOP I) concluded that young age and advanced tumor stage were associated with inferior survival and that vincristine (VCR), lomustine (CCNU), and prednisone (VCP) chemotherapy in addition to XRT could improve survival in higher-stage patients. However, there was no clear benefit of three-drug chemotherapy in improving survival for all patients. The reasons for inferior survival, biologic or therapy-related, were not established. These data, however, were confounded: (a) Chang metastasis (M) staging was not universally performed; (b) treatment was not stratified for all “risk” groups; (c) few M1 + patients were studied; (d) the lower-stage, “better-risk” group could have been contaminated with higher-stage patients; and (e) the risk groups were created retrospectively.

Between 1986 and 1992, the CCG undertook a series of treatment trials for all patients with intracranial PNETs. In contrast to previous multi-institutional group trials, eligibility for study entry required stratification for the known probable risk factors, ie, tumor size and extension, site (Chang tumor [T] stage), M stage, age, and complete postoperative assessment of residual tumor. Patients with “low-stage” T1/2 M0 MB with less than 1.5 cm² of residual tumor (and stage T3a between 1988 and 1992) were enrolled onto a different study, CCG-923, and were randomized to receive either 23.4 Gy or 36 Gy neuraxis XRT plus 54 Gy to the tumor and no chemotherapy. CCG-921 included patients with “higher-stage” and/or residual disease MB, all other PNETs, and malignant ependymal tumors. Patients who were 1.5 years of age or older were randomized to receive either the VCP regimen or the “eight-drugs-in-one-day regimen” (8-in-1) in addition to XRT to the primary tumor site and neuraxis. The 8-in-1 regimen was chosen on the basis of encouraging phase II response and survival data. Infants younger than 1.5 years of age were not randomized and were assigned to receive 8-in-1 chemotherapy and delayed XRT. The major study question was a comparison of survival between the two therapy regimens. Subsidiary study aims were to evaluate (a) the impact of therapy on patterns of relapse in MB (posterior fossa PNET), (b) the role of M and T stage on prognosis in MB, (c) the effect of (chemotherapy) toxicities before and after XRT on delivery of XRT, and (d) early disease control and survival in infants who received chemotherapy alone.

The survival, treatment, and prognostic factors for infants with PNET and ependymoma and for older randomized patients with supratentorial PNET have been reported. Clinical variables associated with XRT, patterns of relapse in MB, and selected survival-related interactions with neurosurgical treatment variables also were reported for MB and supratentorial PNET. We report here the patient, tumor, and treatment-related factors that influenced tumor progression and survival for patients on CCG-921 with MB.

PATIENTS AND METHODS

Between 1986 and 1992, 203 patients with institutional diagnoses of MB or “posterior fossa PNET” were eligible for and randomized onto CCG-921. Eligibility criteria for randomization included the following: (a) age 1.5 to less than 21 years, (b) Chang M stages 1 to 4 or Chang T stage T3b-T4 (and stage T3a from 1986 to 1988), and (c) more than 1.5 cm² of residual tumor on postoperative computed tomography (CT)/magnetic resonance imaging (MRI).

Surgical Treatment and Staging

Surgical resection or biopsy was performed on all patients. Staging criteria were derived from the following items: (a) the neurosurgeon’s report; (b) the postoperative CT or MRI scan with or without enhancement [the scan was to be obtained before the sixth postoperative day to avoid the enhancement artifact simulating residual tumor at the operative site]; (c) postoperative myelography (or spinal CT/MRI); (d) CSF cytology for evidence of metastatic disease; and (e) morphologic examination of bone marrow. These latter studies were to be performed within 6 weeks of surgery, before the start of XRT and chemotherapy. The neurosurgeons’ reports were reviewed (A.L.A., J.H.W.) with the above data to confirm the diagnosis of posterior fossa tumor and T/M staging. Estimation of resection used gross total, near total, partial, etc, as described. Scans were reviewed (P.S.) to evaluate residual tumor bulk more than, equal to, or less than 1.5 cm². Chang T/M staging (Table 1) was performed at the patient’s institution using a combination of the neurosurgical report and scans.

Table 1. Chang Classification of Tumor and Metastasis Stage for Medulloblastoma

<table>
<thead>
<tr>
<th>T stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Tumor less than 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</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor greater than 3 cm and invading one adjacent structure or partially filling fourth ventricle</td>
</tr>
<tr>
<td>T3a</td>
<td>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</td>
</tr>
<tr>
<td>T3b</td>
<td>Tumor arising from floor of fourth ventricle and filling fourth ventricle</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor spread through aqueduct of Sylvius to involve third ventricle, midbrain, or down into upper cervical cord</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>M stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No gross subarachnoid or hematogenous metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Microscopic tumor cells found in CSF</td>
</tr>
<tr>
<td>M2</td>
<td>Gross nodular seeding in cerebellum, cerebral subarachnoid space, or in third or fourth ventricles</td>
</tr>
<tr>
<td>M3</td>
<td>Gross nodular seeding in spinal subarachnoid space</td>
</tr>
<tr>
<td>M4</td>
<td>Extraneuraxial metastasis</td>
</tr>
</tbody>
</table>
Therapy

Therapy consisted of surgery followed by randomization to one of two chemotherapy regimens and standard XRT, as described below. Regimen A included an "induction" period of eight weekly VCR 1.5 mg/m² injections during XRT. This was followed by "maintenance" therapy (VCP) consisting of eight 6-week cycles of VCR 1.5 mg/m² weekly for 3 weeks, lomustine 100 mg/m² for 1 day, and prednisone 40 mg/m² for 14 days. Regimen B included induction therapy of two courses of 8-in-1 chemotherapy, which consisted of VCR 1.5 mg/m², methylprednisolone 300 mg/m² three times, lomustine 75 mg/m², hydroxyurea 1,500 mg/m², procarbazine 75 mg/m², cisplatin 60 mg/m², cyclophosphamide 300 mg/m², and cytarabine 300 mg/m², 14 days apart, followed by XRT. This was followed by maintenance therapy of eight cycles of 8-in-1 chemotherapy every 6 weeks (Fig 1).

Radiation Therapy Guidelines

The primary site was treated before craniospinal axis XRT on both regimens to provide time for bone marrow recovery for children treated on regimen B. For children 3 years of age and older, the XRT dose was 54 Gy (1.8 Gy per fraction, five fractions per week) to the primary tumor and 36 Gy to the craniospinal axis. For children ages 1.5 to 2.9 years, the XRT dose was 45 Gy to the primary tumor and 23.4 Gy to the craniospinal axis. Children with spinal cord metastases defined at the treating institution by CT/MRI were to receive an additional 14.4 Gy to 18 Gy to the area of bulky disease with 1- to 2-cm margins. For interruptions in treatment of more than 5 days, the total dose was to be modified to achieve an equivalent time dose factor value.

The posterior fossa volume extended from the C₁-C₂ interspace to 1 cm superior to the midpoint between the foramen magnum and the cranial vertex. For other primary sites, the tumor volume as defined on the preoperative CT scan was to be treated with a minimum margin of 2 cm. The craniospinal axis volume comprised the whole brain, spinal cord, and theca to the inferior border of S2.

Divergent, individually shaped blocks were recommended to shape the cranial field at the base of the skull and eyes. Specific attention was paid to ensure that the cribriform plate was not blocked. The large cranial field was to be rotated so that the inferior border was parallel to and was matched with the diverging superior edge of the spinal field. This junction was to be moved 1 cm after each 12.6 Gy, to smooth out any dose inhomogeneity occurring at the junction. Inferiorly, the spinal field was flared to include the cauda equina nerve roots.

Treatment records and diagnostic scans and myelograms used to establish XRT fields were centrally reviewed and evaluated by radiation oncologists (K.R.S. and J. Cherlow, MD). Compliance with XRT protocol guidelines (volume and dose) was evaluated for the primary tumor, brain, and spinal cord treatment for each patient.

Statistical Considerations and Methods

The randomization was stratified by histology, site, and MB versus non-MB, and the patients with MB were further stratified by T stage (T1/2 v T3/4) and M stage (M0 v M1 v M2/4). Sample size estimates in the statistical design of the protocol overestimated the annual accrual rate by more than 50%, and no specific guidance was provided for interim analyses. Six years of accrual of patients with MB, at 34 patients per year, and 3 years of follow-up before this analysis, provide approximately 84% power for detecting a survival difference of 20% (40% v 60%) at 4 years, even when it is assumed that the hazard rates after 4 years are approximately zero. No adjustment was made for interim analyses, and at no time during accrual was consideration ever given to terminating the study. All patients were analyzed as randomized.

Durations of progression-free survival (PFS) and survival were measured from the date of randomization to the first date of progressive...
disease or death for children who failed or to the date of last contact for children who survived without failure. The Kaplan-Meier method was used to estimate the distributions of PFS and survival. SEs of the Kaplan-Meier estimates were calculated as suggested by Peto et al and appear in the text following estimates for specific points in time (estimates ± SE). Comparisons of PFS distributions were made using the stratified Mantel-Haenszel statistic. The Cox life-table regression model was used to generate estimates of relative risk. The traditional and exact \( \chi^2 \) tests were used to assess imbalance in potential risk factors between the two treatment arms. The median follow-up period of patients remaining at risk for failure was 7.0 years.

**Table 2. Demographics by Treatment Regimen for All Patients With Confirmed Medulloblastoma**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>VCP (n = 96)</th>
<th>8-in-1 Chemotherapy (n = 92)</th>
<th>Total (n = 188)</th>
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</thead>
<tbody>
<tr>
<td>No. %</td>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>65 (58%)</td>
<td>58 (65%)</td>
<td>123 (65%)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (34%)</td>
<td>34 (65%)</td>
<td>65 (65%)</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5-2.9 years</td>
<td>8 (11%)</td>
<td>11 (10%)</td>
<td>19 (10%)</td>
</tr>
<tr>
<td>3-4 years</td>
<td>23 (23%)</td>
<td>23 (46%)</td>
<td>46 (24%)</td>
</tr>
<tr>
<td>5-9 years</td>
<td>43 (33%)</td>
<td>33 (76%)</td>
<td>76 (40%)</td>
</tr>
<tr>
<td>≥ 10 years</td>
<td>22 (25%)</td>
<td>25 (47%)</td>
<td>47 (25%)</td>
</tr>
<tr>
<td>CCG membership</td>
<td></td>
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<tr>
<td>Full member</td>
<td>38 (46%)</td>
<td>46 (84%)</td>
<td>84 (45%)</td>
</tr>
<tr>
<td>Affiliate</td>
<td>42 (38%)</td>
<td>38 (80%)</td>
<td>80 (43%)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (8%)</td>
<td>8 (23%)</td>
<td>23 (12%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (0%)</td>
<td>0 (1%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

**NOTE.** These patients had similar distribution of characteristics with the entire patient set (n = 203).

*P values are for distribution of characteristics between treatment regimens.

**Study Population**

Two hundred twelve patients with an institutional diagnosis of MB and who were at least 1.5 years of age were registered and randomized. Nine (4.2%) were found to have inadequate documentation of eligibility or staging criteria. Thus, 203 met eligibility criteria, ie, had “high-stage” posterior fossa PNET and MB (T3b-T4, or M1+ or > 1.5 cm$^2$ of residual tumor). Of these, 155 were registered as having MB and 48 as having posterior fossa PNET. The latter group, on neurosurgical review, had primary tumors in the posterior fossa, were diagnosed as having MB upon histopathologic review (described below), and were similarly distributed on both treatment regimens; they are included in the total MB group in this article.

Sixty-five percent of patients with MB were male. Other demographics are summarized in Table 2. All patients received either three-drug (VCP) or 8-in-1 chemotherapy in addition to XRT. Patients were evenly distributed between the two treatment regimens.

**Survival and PFS**

All 203 eligible, randomized patients with MB, diagnosed by institution type, were included in the initial survival and PFS analyses. Five-year estimates of survival and PFS were 55% ± 5% and 54% ± 5%, respectively (Fig 2).

The major question of this therapeutic study was whether 8-in-1 chemotherapy was superior to VCP chemotherapy for MB. There is a clear survival advantage for VCP over 8-in-1 therapy (stratified as randomized, \( P = .006 \)). Five-
year estimates of PFS were 63% ± 5% compared with 45% ± 5% for VCP and 8-in-1 chemotherapy, respectively (Fig 3).

**Analyses of Patients With Centrally Reviewed Neuropathology**

The central pathology review was performed (by L.B.R.) and confirmed for 181 (89%) of 203 patients with MB: nine patients had discordant diagnoses, two had other eligible diagnoses, and 11 were not available for review. In addition, seven patients registered as having non-MB posterior fossa tumors were determined to have MB on central review. These 188 patients with confirmed MB comprise the study population on whom the survival analyses were performed (described below). Seven-year estimates of survival and PFS were 56% ± 5% and 55% ± 5%, respectively. VCP was superior to 8-in-1 chemotherapy (stratified as randomized, \( P = .032 \)), with 5-year PFS estimates of 64% ± 5% and 47% ± 6%, respectively (data not shown). After first relapse or progression, 50% of patients were dead within 6 months and the 2-year estimate of survival was 9% ± 3% (Fig 4).
Histomorphologic evidence of cellular differentiation (performed at the institution of diagnosis) was found in 53 (28%) of 188 patients. No specific differentiation was observed in 135 patients; astrocytic differentiation was seen in 20 patients, neuronal in 17, ependymal in eight, oligodendrogial in five, and mixed in three. No correlation between absence or presence of cellular differentiation and PFS was found ($P > .9$; data not shown). The use of and variation in staining techniques precludes firm conclusions.

**Analyses of Prognostic Factors**

By protocol, children aged 1.5 to younger than 3 years old received 9 Gy less XRT (tumor dose) and they had an inferior PFS compared with children 3 years of age and older ($P = .0014$) and even with 3- to 4-year-old children ($P = .0012$) (Fig 5). Nonetheless, there was no significant difference in outcome for the 1.5- to 2.0-year-old group versus the 2.1- to 2.99-year-old group ($P > .8$; data not shown). In children 3 years of age or older, there was no statistical evidence ($P > .5$) that age group was prognostic. Thus, only children 3 years or older ($n = 169$) were included in subsequent analyses of prognostic factors. There also was no correlation between sex and PFS ($P > .32$).

**Chang T/M Stage**

The distribution of Chang T/M stages for CCG-921 MB patients at least 3 years of age demonstrated that most were at stage T3b (46%) or T3a (38%), and 82 (49%) of 169 patients had M1+ tumors (Table 3). Patients at the M1+ stage were distributed among all T stages and age groups.
Only two of 169 assessable patients had M4 extra-axial bone marrow disease at diagnosis.

An ordered effect of lower M stage and improved PFS for patients with confirmed MB who were $\geq 3$ years old was demonstrated (Fig 6; $M_0$, $M_1$, $M_2$, $M_4$, $Unknown$). The differences were statistically significant ($P = .0006$). Five-year estimates of PFS for patients with $M_0$, $M_1$, and $M_2$ tumors were $70\% \pm 5\%$, $57\% \pm 10\%$, and $40\% \pm 8\%$, respectively. The presence of a positive CSF cytology alone, $M_1$ stage, was not a statistically significant factor in PFS compared with $M_0$ ($P = .15$) or $M_2+$ stage ($P = .103$); this was possibly due to the small number of patients with $M_1$ tumors.

For evaluation of T stage and pre-entry residual disease, CT/MRI scans and neurosurgical reports were submitted for 167 (99%) of 169 patients. There was no statistical evidence of a relationship between T stage and PFS (Fig 7): Neither $T_1/2$ versus $T_3/4$ (stratified by treatment and M stage; $P > .4$) nor $T_1/2$ versus $T_3a$ versus $T_3b$ comparisons (stratified by treatment and M stage; $P > .6$) were significant.

Surgical Resection

Neurosurgeons reported gross or near total resection in 134 (79%) of 169 patients. When a “total” resection was reported, scans demonstrated $\geq 1.5$ cm$^2$ of residual tumor in only four of 61 patients. Thus the neurosurgeons’ estimates of resection were generally accurate.

**Confirmation of Residual Tumor**

The correlation of PFS with residual tumor was assessed in two ways: (a) the neurosurgeons’ reports of extent of resection and (b) postoperative CT/MRI scans, measuring volume of residual disease (see below). The neurosurgeons’ estimates of resection did not correlate with PFS for patients of all stages ($P = .7$, data not shown). For patients with $M_0$ tumors, however, the data suggested a trend of improved PFS for patients with near total or total resection ($P = .077$). Five-year PFS estimates were $74\% \pm 6\%$ and $56\% \pm 12\%$ for patients with more than $90\%$ resection versus those with $\leq 90\%$ resection, respectively (data not shown). Because

### Table 4. Age and T Stages by M Stage in Patients 3 Years or Older With Confirmed Medulloblastoma

<table>
<thead>
<tr>
<th>M Stage</th>
<th>$M_0$ (n = 86)</th>
<th>$M_1$ (n = 31)</th>
<th>$M_2-M_4$ (n = 51)</th>
<th>Unknown (n = 1)</th>
<th>Total (n = 169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T stage</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>$T_1-T_2$</td>
<td>3</td>
<td>7</td>
<td>9</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>$T_3a$</td>
<td>12</td>
<td>10</td>
<td>22</td>
<td>64</td>
<td>38</td>
</tr>
<tr>
<td>$T_3b$</td>
<td>46</td>
<td>12</td>
<td>19</td>
<td>1</td>
<td>78</td>
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<td>$T_4$</td>
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<tr>
<td>Age</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>$3-4$ years</td>
<td>17</td>
<td>10</td>
<td>19</td>
<td>46</td>
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</tr>
<tr>
<td>$5-9$ years</td>
<td>43</td>
<td>13</td>
<td>19</td>
<td>76</td>
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</tr>
<tr>
<td>$\geq 10$ years</td>
<td>26</td>
<td>8</td>
<td>13</td>
<td>47</td>
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</tbody>
</table>

*The P values represent significance for distribution of characteristics of M stages among the T stages and age groups. Sixteen of 19 $T_1/2$ patients were $M_1+$ compared with 63 of 142 $T_3a$ and $T_3b$ patients ($P = .03$). This is an artifact of the inclusion criteria for low-T stage patients. The subset of patients had similar distribution of characteristics compared with the entire eligible patient set (n = 203).
most patients had more than 90% resection, this comparison had limited statistical power.

The neurosurgical assessment of residual tumor mass could be confirmed by CT/MRI scan in 162 (96%) of 169 patients, and 121 (75%) of 162 patients ≥ 3 years of age (all M stages) had less than 1.5 cm² of residual tumor. For these patients, residual disease bulk did not correlate significantly with PFS ($P = .089$, data not shown). However, for the M0 subset of patients who had less than 1.5 cm² of residual tumor, the correlation with improved PFS was significant ($P = .023$). Five-year PFS was 78% ± 6% and 54% ± 11% for children with less than 1.5 cm² and ≥ 1.5 cm² of residual tumor, respectively (Fig 8). Children 3 years or older who were M1+ stage at diagnosis showed no difference in PFS based on residual tumor volume ($P > .6$; data not shown).

**Toxicity Data**

As expected, 8-in-1 chemotherapy was associated with more grade 3/4 toxic episodes than VCP (Table 5, courses are grouped in pairs). The hematologic toxicity for each course of 8-in-1 chemotherapy was two- to three-fold that of...
VCP chemotherapy: gastrointestinal, electrolyte, magnesium, and renal toxicity (decreased creatinine clearance, calcium/magnesium levels) and ototoxicity were the most frequently reported nonhematologic side effects. Only peripheral neurotoxicity (peripheral nervous system) (presumably caused by VCR) was noted with greater frequency in the VCP arm.

Effect of Chemotherapy on Delivery of XRT and Outcomes

Both chemotherapy regimens were analyzed to assess their effects on delivery of XRT. By design, 8-in-1 patients had a 28-day longer interval between surgery and initiation of XRT than did the VCP patients. For those who received VCP therapy, 32 of 100 patients required more than 5 days of interruption, compared with 24 of 103 8-in-1 recipients ($P > .1$, not significant). Patients who received 8-in-1 chemotherapy also started XRT a median of 4.5 days later than scheduled, as compared with the scheduled timing for the VCP group ($P = .01$). More than 96% of patients received the specified total radiation dose; thus, subgroup analysis by decreased dose would not be informative. For those patients who experienced a delay in initiation of XRT beyond the time prescribed by the protocol, there was no evidence of an effect on PFS ($P > .9$; data not shown). Within treatment regimens, there was no adverse effect of delay of XRT. Thus, the causative role of the 28-day delay in XRT on decreased survival in the 8-in-1 group cannot be ascertained from this study.

DISCUSSION

Our results demonstrate the superiority of XRT and standard VCP over 8-in-1 chemotherapy plus XRT for high-stage patients with MB. The latter therapy, previously thought to be very aggressive, produced significant and promising results in phase II trials for recurrent childhood brain tumors and other selected brain tumors. These data again confirm the important role for prospective, adequately controlled, randomized clinical trials using appropriate statistical methods to evaluate the efficacy of new treatments.

Table 5. Grade 3 and 4 Toxicities of Chemotherapy by Course and Regimen for Medulloblastoma Patients on CCG-921

<table>
<thead>
<tr>
<th>Toxicity Type</th>
<th>VCP* (n = 96)</th>
<th>8-in-1 Regimen* (n = 92)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-2</td>
<td>3-4</td>
</tr>
<tr>
<td>WBC</td>
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<td>16</td>
<td>10</td>
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<tr>
<td>Cr/Clear</td>
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<td>1</td>
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<tr>
<td>N&amp;V</td>
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<td>Pulmon</td>
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*Induction, first therapy after surgery; for regimen A (VCP) consisted of XRT plus VCR for 8 weeks; for regimen B (8-in-1 chemotherapy), induction consisted of two courses of 8-in-1 chemotherapy plus XRT.

Patient courses with any toxicity, n

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<th>VCP* (n = 96)</th>
<th>8-in-1 Regimen* (n = 92)</th>
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NOTE. An entry in this table represents eligible patients with one or more episodes of the same toxicity in a phase/course(s) (grade 1-4 for renal, pulmonary, and electrolyte; grade 3 and 4 for all others). Maintenance courses are grouped by two courses and the toxicities are for two courses. The CCG toxicity scale was adapted from NCI toxicity scale. Abbreviations: IND, induction; ANC, absolute neutrophil count; PLTS, platelet count; HGB, hemoglobin; Cr/Clear, serum creatinine or creatinine clearance; N&V, nausea and vomiting; Pulmon, pulmonary as vital capacity, PAO 2, CO diffusion; PNS, peripheral nervous system; Na/K, sodium/potassium; Ca, calcium; Mg, magnesium.

*Induction, first therapy after surgery; for regimen A (VCP) consisted of XRT plus VCR for 8 weeks; for regimen B (8-in-1 chemotherapy), induction consisted of two courses of 8-in-1 chemotherapy plus XRT.
given in standard VCP therapy); 8-in-1 chemotherapy had one third of the VCR total dose during maintenance therapy. Thus, the decreased dose-intensity of both proven-effective agents for MB, VCR and lomustine in the 8-in-1 regimen, could have been responsible for the decreased survival rate. The lack of peripheral neurotoxicity in the 8-in-1 group corroborates the lack of VCR dose-intensity. The children on 8-in-1 chemotherapy received cisplatin, which is effective against MB,13 yet its addition in the 8-in-1 regimen did not affect a better survival. Reasons for this are speculative and are not easy to dissect. As well, the 1-month delay in initiating XRT could have had a role in the decreased survival of the 8-in-1 group. Future clinical trials using more intensive chemotherapy for MB need to assess true improvement in survival against VCP and XRT; the latter represents the best-studied treatment regimen to date.

Over the last 30 years, there has been variability in assigning risk and prognostic factors to patients with MB. Both tumor11,12,17,23,45 and treatment-related factors2,10,13,18,20,31,46 have been proposed (T stage, tumor size, location and invasion47; metastasis stage in the neuraxis11,21; extent of surgical resection10,19,47,48; histopathology45,49; age4,18,23,30,51; treatment/hospital site20,46,52; and a combination of the above53). These inconsistent conclusions most likely resulted from multiple factors, including patient selection bias, small patient populations, surgical philosophy, tumor detection methods, changes in imaging techniques, extent of residual tumor evaluation, and variation in XRT dosage. Prospective risk factor assignment was a methodologic feature of this study.

The CCG-921 study confirmed prospectively the unequivocal impact of neuraxis dissemination at diagnosis (M1+ stages) on early tumor progression or relapse for both MB (this study and in Cohen and Duffner52) and related supratentorial PNET.27,28 Even patients with small primary posterior fossa tumors, if accompanied by dissemination at diagnosis, experienced relapse earlier, and these relapses were often extraparenchymal recurrences.32 Of 16 patients with small primary T1/2 tumors and M1+ disease, 10 had cranial or spinal lesions requiring boosts that would have been missed without staging. Although the presence of a positive CSF cytology alone (M1) lacked statistical power, the progression from M1 to M2 and M3 was an ordered one for PFS, and M0 versus M1+ comparisons were significant. Extraxial spread to the bone marrow at diagnosis was rare, as we documented only two patients with M4 disease in our study. For this reason, the role of routine marrow assessment at diagnosis is probably unwarranted as a staging strategy for MB.

The role of residual tumor mass vis-à-vis the neurosurgeons’ reports of extent of resection also has been clarified. A residual tumor mass of less than 1.5 cm² is statistically associated with improved survival only in the subset of CT/MRI scan-confirmed M0 patients 3 years of age or older at diagnosis. Why would CT/MRI scan-detectable disease be related to survival, while neurosurgeons’ observations were not? The absolute residual tumor burden, most likely in the range of 10⁶ cells (1 cm³), is critical for the chemotherapy/XRT effect rather than the percentage of tumor removed. We favor this explanation, because generally the neurosurgeons’ reports and scans correlated well; there was no correlation between residual tumor and PFS in patients with M1+ disease (who had more bulk disease remaining before XRT and chemotherapy). Recently, Ayan et al54 reported that patients with M0 stage who had local subarachnoid invasion at the time of resection, ie, more residual disease, also had decreased PFS compared with those without invasion. This advantage in PFS of about 25% for patients with “total-body” minimal residual tumor is an association also reported for ependymoma55 and supratentorial PNET.56 These results suggest a future strategy to improve survival: suspected or proven PNET and MB brain tumors should have pretherapy extent-of-disease staging, including neuraxis evaluation,27-30 so as to offer tailored neurosurgical treatment with maximal tumor cytoreduction when possible.

This trial has clarified the relationship between age as a prognostic factor and outcome. Children aged 1.5 to 2.9 years had inferior survival compared with older age groups, yet we do not consider age a prognostic factor in this context. It is tempting to conclude that PNETs in these younger children are somehow different. Recent molecular and cytogenetic analyses of PNETs demonstrating higher frequencies of specific chromosomal abnormalities in younger patients support this conclusion.57,58 The caveat is that planned reductions in neuraxis and posterior fossa XRT dosages were administered to all these young children and there is a known dose response with “shoulder” effect at 50 Gy.59 Previous reports of reduced survival in young children did not emphasize the effect of lower XRT dosage on survival.12,18,23,49,50

Our evidence for this conclusion is that there were no demonstrable differences in PFS between the 1.5- to 2-year-old group versus the 2- to 3-year old group (all received reduced XRT), nor between the 3- to 4-year-olds and the older patients, all of whom received optimal tumor and neuraxis XRT dosage and surface-area proportional chemotherapy.31 The clear cutoff in PFS was between groups who received less than 50 (45) Gy tumor dose and 36 (23.4) Gy neuraxis dose. Even older children who had decreased tumor XRT volume or 5% to 15% dose reduction or more than 120% time to administer XRT did not have a statistically different survival outcome.31 These latter differences were smaller than the planned 30% reduction in dosage received
by 1.5- to 2.9-year-olds on study. Hence, the probable explanation for the poorer survival of these young children is that they received a lower therapeutic XRT dosage rather than that their tumors possessed different biologic characteristics.

The importance of T stage has been clarified by our study design, using complete pretherapy T/M staging, which previously was correlated with survival when XRT was the sole therapy.\textsuperscript{21,47} In the group clinical trials that tested the association of T stage and adjuvant chemotherapy and XRT, the CCG found only a weak correlation,\textsuperscript{11} whereas the SIOP study found a significant survival advantage with low T stage.\textsuperscript{12} Up to one half of patients on previous CCG and SIOP trials did not have CSF cytology or myelography,\textsuperscript{11,12} so the T3/4 group was composed of both M0 and M1+ patients. These data again underscore the necessity of prospective staging as the diagnostic standard for all PNETs and stratification in planning of randomized trials.

It was our hypothesis that patients with tumors involving the floor of the fourth ventricle or invading the brainstem (T3b by Chang staging) would fare worse.\textsuperscript{21} In fact, when data were corrected for M stage, we found no independent effect of any T stage or interaction of extent of surgical resection with T3a/3b stage on PFS. Additionally, no significant association with PFS was noted in T1/2/3a–stage patients with no residual tumor on the CCG-923 study, which did not use chemotherapy.\textsuperscript{24} We conclude that when patients are completely staged and stratified, there is no univariate effect of T stage on PFS.

The use of XRT and VCP chemotherapy in high-stage patients was based on the CCG-942 study of 19 M1+ patients in which there were no stage T3/4 M1+ survivors who received XRT alone, compared with 46% 5-year PFS in patients who received XRT and chemotherapy.\textsuperscript{11} Our data confirm this result but do not indicate whether chemotherapy was additionally helpful for patients with M0 disease and more than 1.5 cm\textsuperscript{2} of residual tumor.

An important conclusion from our data relates to the survival implications of more complete tumor resections. Five-year survival for one fourth of the children with MB on this study (stage M0 and residual mass > 1.5 cm\textsuperscript{2}) could be enhanced by about 25% solely by application of a neurosurgical philosophy/technique designed to increase near total and total resections; this survival enhancement would occur independently of any improvements in adjuvant therapies. This strategy should be generally applicable, as there were no differences in amount of residual tumor between patients operated upon at affiliate versus full-member institutions (data not shown).

The optimal, least toxic therapy for high-stage MB remains to be determined. Future therapy trials need to be constructed with the idea of uniform risk assignment as proposed by ourselves, Laurent and Cheek,\textsuperscript{53} and Jenkin et al.\textsuperscript{60} The conclusion that patients 3 years of age or older who are stage M0 with less than 1.5 cm\textsuperscript{2} of residual tumor can achieve a 78% PFS was based on a retrospective statistical construct. This finding suggests future testing of a lessening-of-toxicity hypothesis with lower neuraxis XRT dosage and increased intensity of chemotherapy.\textsuperscript{13} It is hoped that this treatment will spare the long-term neuropsychologic\textsuperscript{61,62} and endocrine costs\textsuperscript{62,63} of therapy without compromising PFS.

\begin{table}[h]
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Institution & Investigators & Grant No. \\
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Group Operations Center & W. Archie Bleyer, MD & CA 13539 \\
Arcadia, CA & Anita Khayat, PhD & \\
& Harland Sather, PhD & \\
& Mark Krailo, PhD & \\
& Jonathan Buckley, MBBS, PhD & \\
& Daniel Stram, PhD & \\
& Richard Sposto, PhD & \\
University of Michigan Medical Center & Raymond Hutchinson, MD & CA 02971 \\
Ann Arbor, MI & & \\
University of California Medical Center & Katherine Matthay, MD & CA 17829 \\
San Francisco, CA & & \\
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Madison, WI & & \\
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& & \\
Seattle, WA & Susan Shurin, MD & CA 20320 \\
Rainbow Babies & Gregory Reaman, MD & CA 03888 \\
Children's Hospital & Jorge Ortega, MD & CA 02649 \\
Cleveland, OH & & \\
Children's National Medical Center & & \\
Washington, DC & & \\
Children's Hospital of Los Angeles & & \\
Los Angeles, CA & & 
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\caption{Participating Principal Investigators of the Children's Cancer Group}
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REFERENCES


17. Halperin EC, Friedman HS: Is there a correlation between duration of presenting symptoms and stage of medulloblastoma at the time of diagnosis? Cancer 78:874-880, 1996
