**Brief Report**

**Influence of a Child’s Sex on Medulloblastoma Outcome**

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**Context.**—Aggressive treatment of medulloblastoma, the most common pediatric brain tumor, has not improved survival. Identifying better prognostic indicators may warrant less morbid therapy.

**Objective.**—To investigate the role of sex on outcome of medulloblastoma.

**Design.**—Retrospective study of significant factors for survival with a median follow-up of 82 months.

**Setting.**—University medical center.

**Patients.**—A total of 109 consecutive, pediatric patients treated for primary medulloblastoma from 1970 to 1995 with surgery and postoperative radiotherapy and, after 1979, chemotherapy.

**Main Outcome Measures.**—Factors independently associated with survival.

**Results.**—The final multivariate model predicting improved survival included sex (hazard ratio, 0.52; 95% confidence interval [CI], 0.29-0.92; P = .03; favoring female), metastases at presentation (hazard ratio, 2.01; 95% CI, 1.14-3.52; P = .02), and extent of surgical resection (hazard ratio, 0.60; 95% CI, 0.34-1.04; P = .07; favoring greater resection). The overall, 5-year freedom from progression was 40% and survival was 49%. Radiotherapy dose (P = .72), and chemotherapy (P = .90) did not significantly affect a disease outcome.

**Conclusions.**—The sex of the child was an important predictor for survival of medulloblastoma; girls had a much better outcome. The difference in survival between sexes should be evaluated in prospective, clinical trials.

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**MEDULLOBLASTOMA**, the most common brain tumor in children, is the only disease where postoperative irradiation of the entire craniospinal axis is considered standard of care. Children with the disease routinely undergo craniotomy followed by high doses of craniospinal radiotherapy and, in many cases, a year of intensive chemotherapy. Sadly, this aggressive approach is extremely morbid and yet has not improved survival over the past 2 decades.1 Therapy inevitably has serious adverse effects on the developing central nervous and skeletal systems, including marked learning disabilities, hormonal and hearing abnormalities, short stature, and induction of secondary tumors.2-5

In fact, it is difficult to demonstrate that variations in outcome are more than the result of variations in classification of the disease at presentation. Medulloblastoma has been staged as low risk or high risk.6-10 Most trials demonstrate a 5-year survival of approximately 70% for low-risk patients and 30% for high-risk patients. None of the staging or treatment protocols take sex into account. Based on earlier work,10 we investigated whether factors other than residual tumor volume and the patient’s age influence the outcome of the malignancy.

**Methods.**

We, retrospectively, evaluated all patients with primary medulloblastoma, 11 years or younger, treated with postoperative radiotherapy at the University of California, San Francisco, between 1970 and 1995. Most patients underwent spinal evaluation with examination of the cerebrospinal fluid, myelogram, magnetic resonance imaging, or a combination of these tests. Following standard clinical practice, patients were staged as low risk if they were older than 3 years, had undergone a gross total resection, and had negative evaluation of the craniospinal axis.10 High-risk patients were considered to be children 3 years old or younger, those who had undergone less than complete resection, or patients found to have evidence of disease beyond the posterior fossa.

Tumor volumes were localized with the aid of computed tomography (CT) beginning in the mid-1970s, and later with magnetic resonance imaging. All patients were treated with linear accelerators using 4-MV or 6-MV photons. Until 1989, and most recently, radiation was delivered to the posterior fossa in single daily fractions of 1.8 Gy to a total of 56 Gy or less. Between 1989 and 1992, patients were treated with 1 Gy twice daily to a total dose of 72 Gy to the posterior fossa.11 Patients treated once a day received an average dose of 36 Gy to the craniospinal axis and those treated twice daily received 24 to 40 Gy.

Combinations of chemotherapeutic agents changed over time. Prior to 1979, most patients received radiation only. Subsequently, procarbazine was given postoperatively, followed by hydroxyurea plus radiation at reduced craniospinal doses. After 1990 most high-risk patients older than 3 years were treated with hyperfractionated radiotherapy, followed by cisplatin, lomustine, and vincristine.

No patients were lost to follow-up. After treatment, patients were followed up with regular CT or magnetic resonance scans and cerebrospinal fluid cytology. Time to progression was measured from the start of radiotherapy until relapse, and patients who died without evidence of disease were censored for this analysis. Duration of survival was measured from the start of radiotherapy until last follow-up or death. Estimates of time to progression and survival were computed using the method of Kaplan and Meier.12 We used χ² or t test statistics (as appropriate to the data) to compare patient characteristics by sex. Univariate and multivariate analyses of survival were performed with the Cox proportional hazards regression model13 using statistical software (Stata Corporation, College Station, Tex). All variables in Table 1 were evaluated as potential prognostic factors by univariate analyses. For the purpose of these analyses, the extent of surgical resection was categorized as gross total resection or less than gross total resection. Multivariate analyses used forward stepwise selection with inclusion based on P=.05. We evaluated whether the hazard ratio for any factor,

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eg, sex, metastasis, or surgery, changed with time from diagnosis by graphing log (−log survival) vs log (time).

**Results**

From 1970 to 1995, 109 patients were treated (Table 1). 62 patients were males, and 47 females. The median age of the patients was 7 years (range, 5 months to 21 years), 25% were aged 3 years or younger. The spine was evaluated in 93%. Gross total resection was performed on 54%. There were 39 low-risk patients and 70 high-risk. There were 7 patients considered poor risk solely based on age younger than 3 years at diagnosis. Adjuvant chemotherapy was used in 17 low-risk and 59 high-risk patients. Standard radiotherapy was delivered to 80 patients and 29 patients received hyperfractionation. Seven infants received chemotherapy and posterior fossa irradiation only (6 of these patients are still alive without disease).

The median follow-up for living patients was 96 months (range, 3-275 months) and the median time to relapse was 24 months. The actuarial 5-year freedom from progression was 40% (64% for low-risk patients and 27% for high-risk patients). There were relapses in 61 patients; 15 low-risk and 46 high risk. Median overall survival was 59 months, and a total of 58 patients died. Five-year survival was 64% for the low-risk patients vs 41% for the high-risk patients, and 49% overall (Figure 1). The data for time to progression overall and by sex parallel these curves (Figure 2). There were 6 late deaths (5-7 years following therapy) from disease, and 4 girls died of therapy-related causes other than tumor recurrence. There was no significant difference in time to progression or survival detected over the varying diagnostic and treatment eras.

Prognostic factors that were significant for overall survival by univariate analysis included stage (low risk vs high risk) (P = 0.01), sex (P = 0.01), metastasis at presentation (P < 0.01), and extent of surgical resection (P < 0.01) (Table 2). For the purpose of the multivariate analysis of survival time, we chose to use the individual factors of stage; age, extent of surgical resection, and disseminated disease at presentation. Results using risk grouping provide a similar outcome with regard to the effect of sex and are not presented. Cox stepwise analysis yielded a final model with sex (hazard ratio, 0.52; 95% CI, 0.29-0.92; P = 0.03; favoring female), metastasis at presentation (hazard ratio, 2.01; 95% CI, 1.14-3.52; P = 0.02), and favoring increased extent of surgery (hazard ratio, 0.60; 95% CI, 0.34-1.04; P = 0.07). Extent of surgery was left in the model (although the P value was slightly above the 0.05 cutoff) to ensure that the apparent difference between the sexes was not due to a difference in extent of resection.

There was no indication that the hazard ratio changed over time for either extent of resection or presence of metastases. This supports the belief that use of the multivariate model adequately adjusted for any difference between the sexes in these risk factors. There was some indication that the hazard ratio for sex decreased with time (ie, the benefit for girls became more apparent). This trend can also be seen in Figure 1, where the separation of the survival curves only became apparent after 24 months of follow-up. To further confirm the result regarding sex, comparison between the sexes was done separately within the 2 risk groups. For the high-risk group, the hazard ratio was 0.47 favoring female (P = 0.03; 95% CI, 0.23-0.93). Results for the low-risk group were similar with a hazard ratio of 0.65. However, with the fewer events, this was not statistically significant. An overall test for interaction between risk group and sex was not statistically significant (P = 0.56).

These results indicate that females had a significant survival advantage compared with males. Males more often presented with high-risk disease, yet there were no significant differences in adverse prognosticators noted for males and males had poorer survival in both the low- and high-risk groups. Multivariate analysis showed sex to be a major prognostic indicator even when adjustment was made for standard risk factors. Radiotherapy dosage (P = 0.72), chemotherapy (P = 0.90), and treatment era (P = 0.13) did not affect outcome.

**Comment**

Medulloblastoma is treated postoperatively with craniospinal axis irradiation and, when indicated, with systemic chemotherapy. These nonspecific therapies include a large volume of normal tissue and are, therefore, extremely toxic. Acutely, patients suffer from fatigue, nausea, skin erythema, hair loss, and low blood cell counts. However, it is the chronic side effects of decreased intellect and stature, hearing, and hormonal deficits that can be devastating. Attempts to decrease toxic effects by using combined modality therapy have not demonstrated a survival benefit. Early reports of dramatic improvement in outcome after cisplatin chemotherapy have not been reproduced.10

Prediction of outcome remains dependent on the accuracy of pathology and staging. Thorough evaluation of the extent of disease at presentation is performed to gauge the required intensity of treatment. The assignment of patients to categories of low vs high risk of failure presently is predicted by postoperative residual disease in the craniospinal axis and patient age. Improved imaging with magnetic resonance imaging in addition to cytological examination has improved staging.26 Unfortunately, the advances in imaging have not yet produced longer survival. Our data suggest that sex may be an important determinant of medulloblastoma outcome: girls did remarkably better than boys.

Our results are from a retrospective analysis at a single institution.17,18 There were slightly more boys than girls in our
patient population, which is similar to other studies. Although boys generally presented with worse disease, both sexes presented with a range of risk factors. It is clear from the separation of the survival curves with time that without adequate follow-up the differences based on sex will not be observed. Patients were treated over 2 decades, on several different therapeutic regimens, and we cannot be certain what role physician bias may have played in treatment decisions. However, there were several advantages for this group. Children were aggressively studied prior to therapy; 93% had craniospinal axis evaluated (88% were evaluated with magnetic resonance imaging or CT). Patients were treated by a small group of physicians at a single institution. Al-
tients were treated by a small group of physicians at a single institution. Although difficult to quantify, improved outcome in many studies is associated with expertise acquired by treating a large number of patients.

There is a clinical axiom in oncology that “girls are good, boys are bad.” The effect of sex on the course of medulloblastoma has been previously shown to be significant in epidemiological study. We do not know the mechanism for a potential influence of sex on the biology of medulloblastoma. It might be that girls are more sensitive to therapy; 4 of the 3 patients who died of treatment-related causes were female. We hypothesize that the improved outcome for girls might be due to the result of therapy-induced precocious puberty. We have not documented the induction of precocious puberty in this group; however, others have demon-
strated early puberty following combined modality therapy. There is no reference in the literature regarding hormonal inter-
actions for this central nervous system tumor, nor do we know of studies demonstrating a beneficial effect of female hormones on medulloblastoma. However, estrogen and progesterone have been used to treat a 12-year-old boy with massive spinal recurrence with equivocal results (M.D.W., and Carol A. Diamond, MD, unpublished data, 1995).

The treatment of medulloblastoma is not satisfactory; the sequela of cranio-
spinal irradiation delivered to children are severe. To date, treatment is based on the extent of primary resection, dis-
ease outside of the primary area, and age of the patient. If in fact sex is sig-
ificant, then it might be justifiable to treat boys more aggressively and girls less extensively. The data suggest that the difference in survival between sexes following medulloblastoma should be evaluated in prospective, clinical trials.

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Table 2—Survival by Variable

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>P*</th>
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<tbody>
<tr>
<td>Stage, favoring low risk</td>
<td>2.21</td>
<td>1.30-3.74</td>
<td>.001</td>
</tr>
<tr>
<td>Sex, favoring female</td>
<td>0.47</td>
<td>0.27-0.82</td>
<td>.02</td>
</tr>
<tr>
<td>metastasis at presentation, favoring none</td>
<td>2.37</td>
<td>1.24-7.16</td>
<td>.19</td>
</tr>
<tr>
<td>Extent of surgical resection, favoring gross total</td>
<td>0.45</td>
<td>.18-1.03</td>
<td>.02</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td>0.97</td>
<td>0.92-1.02</td>
<td>.45</td>
</tr>
</tbody>
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*P value based on univariate Cox proportional haz-
ards model.

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