

# Prognostic Factors and Secondary Malignancies in Childhood Medulloblastoma

Theodora Stavrou, M.D., M.P.H., Christina M. Bromley, Ph.D., H. Stacy Nicholson, M.D., M.P.H., Julianne Byrne, Ph.D., Roger J. Packer, M.D., Alisa M. Goldstein, Ph.D., and Gregory H. Reaman, M.D.

**Purpose:** Little is known of the outcome of long-term survivors of childhood medulloblastoma, one of the most common pediatric malignancies. To determine the potential for secondary malignancies, a retrospective outcome evaluation in 88 consecutive cases of childhood medulloblastoma was performed.

**Patients and Methods:** The records of all patients with childhood medulloblastoma diagnosed at Children's National Medical Center in Washington, DC from 1969 through 1997 were reviewed.

**Results:** The median follow-up time was 92 months (range 6–257 months). Overall survival was 59% at 5 years and 52% at 10 years. Univariate analysis showed that age at diagnosis, extent of surgical resection, presence of metastatic disease (M stage), ventriculoperitoneal shunt placement within 30 days from diagnosis, posterior fossa radiation therapy dose, and adjuvant chemotherapy significantly affected survival. Although based on small numbers, the risk of second neoplasms was significantly increased in this cohort. Multiple basal cell carcinomas developed in the areas of radiation therapy in two patients; these patients also had nevoid basal cell carcinoma syndrome (NBCCS) diagnosed. One other patient died of glioblastoma multiforme 8 years after treatment of medulloblastoma. A meningioma developed in another patient 10 years after radiation therapy.

**Conclusion:** As survival of medulloblastoma patients improves, increased surveillance regarding secondary malignancies is required, especially because radiation-induced tumors may occur many years after treatment. These two cases of NBCCS also illustrate the importance of considering the concomitant diagnosis of NBCCS in young patients with medulloblastoma. In those patients, alternative therapy should be considered to minimize radiation therapy-related sequelae.

**Key Words:** Medulloblastoma—Prognostic factors—Nevoid basal cell carcinoma syndrome—Secondary malignancies.

Medulloblastoma is the most common posterior fossa tumor and accounts for approximately 20% of all childhood brain tumors (1). The mean age at diagnosis is 6.3 years, and more males than females are affected (1,2). Approximately 60% to 80% of children with medulloblastoma live more than 5 years from diagnosis (3–7).

Several factors are known to influence overall survival (OS) and progression-free survival (PFS) in patients with

medulloblastoma (8–11). For example, children with less than complete resections or with presence of metastatic disease at diagnosis have lower survival rates when compared with children with complete resections without metastatic disease (11). Current treatment of medulloblastoma is based on initial surgical resection followed-up by radiation therapy with or without chemotherapy with agents such as cisplatin, vincristine, lomustine, or cyclophosphamide (4–6).

Survivors of childhood medulloblastoma experience long-term sequelae, most commonly caused by radiation therapy. Learning disabilities and poor growth are frequent side effects and radiation-induced cancers may occur many years after treatment (12–14). We retrospectively studied 88 cases of medulloblastoma in an attempt to define factors affecting survival and to investigate the occurrence of late relapses and secondary malignancies in this cohort of patients.

## PATIENTS AND METHODS

The records of all patients with childhood medulloblastoma diagnosed at Children's National Medical Center in Washington, DC from 1969 until 1997 were reviewed ( $n = 88$ ). These factors were examined for prognostic significance: age at diagnosis, sex, race, extent of surgical resection, M stage at diagnosis, risk, ventriculoperitoneal shunt placement within 30 days from diagnosis, adequacy of radiation therapy dose, and addition of chemotherapy as treatment modality.

The extent of surgical resection was based on the surgeon's operative impression for disease diagnosed before 1990 and on postoperative magnetic resonance imaging for disease diagnosed later. The extent of resection was classified as gross total, incomplete, and biopsy only. The M stage was classified according to Chang system (15). Myelograms, magnetic resonance imaging of the spine, and cerebrospinal fluid cytology were used to define the M stage.

Patients were defined as at poor risk if they were younger than age 3 years at diagnosis, had undergone other than gross total resections, or had evidence of metastatic disease at diagnosis (M1–4). Patients who did not meet the previously defined criteria were considered to be at average risk.

Risks of second neoplasms were evaluated using population-based data from the United States and Norway

Submitted for publication June 21, 1999; accepted December 29, 2000.  
From the Departments of Hematology-Oncology (T.S., H.S.N., J.B., G.H.R.), Neurology (R.J.P), Children's National Medical Center, Washington, DC, U.S.A.; and Genetic Epidemiology Branch (T.S., C.M.B., A.M.G), National Cancer Institute, Bethesda, Maryland, U.S.A.

(16–19). Data from the Surveillance, Epidemiology, and End Results (SEER) program of the United States National Cancer Institute was used to calculate risks of second malignant neoplasms. The SEER program collects histologic data on cancers diagnosed in the SEER population-based registries, which cover approximately 10% of the United States population. To estimate the risk of second cancers, we calculated numbers of person-years of observation according to gender, age, calendar year, and the interval from the date of medulloblastoma diagnosis to the date of diagnosis of second cancer, date of death, or date of last follow-up, whichever occurred first. The SEER incidence rates specific for gender, age, race, and 5-year calendar year intervals were multiplied by the total number of person-years to estimate the number of cancer cases expected. Because SEER does not include nonmelanoma skin cancers or nonmalignant meningiomas, we also used age-specific incidence rates from Norway (18,19). Because we did not have detailed incidence rates (i.e., rates by gender, age, race, and calendar-year intervals) available, we chose overall age-specific incidence rates to produce conservative estimates of the expected numbers of tumors. For meningiomas, the incidence rates per 100,000 were 1.5 for males and 2.8 for females (18). Comparison with data from Connecticut showed similar incidence rates (17). For basal cell carcinomas, we used age-specific incidence rates for individuals aged 0 to 29 years; the incidence rates per 100,000 were 0.7 for males and 1.2 for females (19). The incidence rates were multiplied by the number of person-years to estimate the number of these tumors expected. We summed the expected numbers of tumors from each evaluation to obtain an overall expected value. Statistical tests and 95% confidence intervals (CI) were calculated based on the assumption that the numbers of second cancers observed adhered to a Poisson distribution as implemented in the Eptome computer program (National Cancer Institute, Bethesda, MD, U.S.A.) (20).

Descriptive statistics were calculated using SAS (Version 6.12 for Windows; SAS Institute, Cary, NC, U.S.A.). Two measures of survival were estimated. Overall survival was calculated from date of diagnosis to date of death or last follow-up. Progression-free survival was calculated from date of diagnosis to date of failure or last follow-up. Failure was defined as relapse or progressive disease. Two patients were lost to follow-up and did not contribute to OS. Kaplan-Meier estimates were used for OS and PFS throughout this study. This method is most suitable for smaller data sets with precisely measured event times. To test for differences in survivor functions, the PROC LIFETEST program of SAS (Cary, NC, U.S.A.) was used. Two alternative statistics were calculated to test the null hypothesis: the log-rank test (also known as the Mantel-Haenszel test) and the Wilcoxon test. The Wilcoxon statistic differs from the log-rank statistic only by correcting for the total number of subjects at risk at each time point. The Wilcoxon test is more sensitive to differences between survivor functions at earlier points in

time, whereas the log-rank is more sensitive to differences between groups at later points in time (21). Because of the small number of patients available for this study, the power to detect differences at later time points was limited. Therefore, the Wilcoxon test was chosen instead of the more commonly used log-rank test. Significant prognostic factors based on the univariate survival analysis were also evaluated using stratified analysis to control for possible confounding effects that may influence the results. In addition, multivariate analysis was performed on these three risk factors: extent of surgical resection, M stage, and age at diagnosis (younger than 3 years vs. older patients). These three factors were each tested individually while adjusting for the other two factors.

## RESULTS

At the time of the analysis, 49 (55%) patients were alive and free of disease. Three patients died of causes unrelated to medulloblastoma, one of them because of secondary malignancy. Thirty-six patients (41%) died because of either disease recurrence (relapse) or progression.

The median age at diagnosis was 69 months (range 3–273 months). Twenty-three patients (26%) were younger than age 3 years at diagnosis. There were 54 males (61%) and 60 patients (68%) were white (Table 1).

Most children (69%) presented with signs of increased intracranial pressure. The mean duration of these symptoms was 1.6 months. Other symptoms at presentation included truncal ataxia, sixth nerve palsies, and increasing head circumference.

Gross total resection was achieved in 56 (63%) patients. Fifty-five (62%) patients had no evidence of metastatic disease at diagnosis. When using risk, as previously defined in

**TABLE 1.** Demographic data and prognostic factors

Factor	Cases
Age (y)	
3 or younger	23
Older than 3	65
Sex	
Male	54
Female	34
Race	
White	60
Black	20
Other	8
M stage	
M0	55
M1–4	23
Unknown	10
Extent of resection	
Gross total	56
Incomplete	28
Biopsy	3
None	1
Treatment modality	
Radiation only	44
Chemotherapy only	4
Radiation and chemotherapy	38
No treatment	2

the methods, the majority of the patients (61%) were classified as at poor risk. Twenty-nine (33%) patients required ventriculoperitoneal shunts placed within 30 days of diagnosis.

Thirty-eight (43%) patients were treated with surgery and radiation alone and 44 patients (50%) received adjuvant chemotherapy (Table 1). The median whole-brain radiation therapy dose was 36 Gy (range 23–45 Gy), the median dose to the spine was 32 Gy (range 19–46 Gy), and the median dose to the posterior fossa was 54 Gy (range 40–56 Gy).

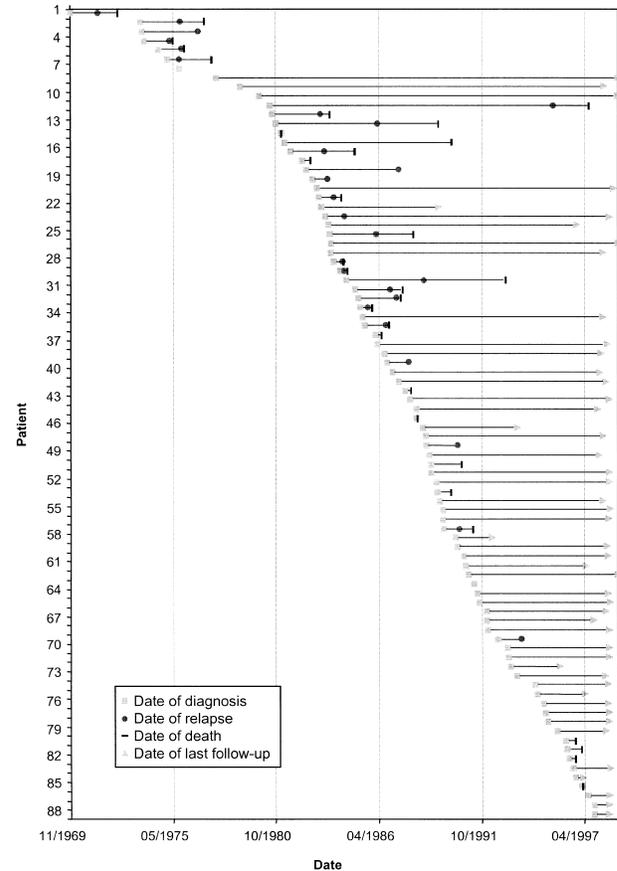
Twenty-two (58%) patients receiving adjuvant chemotherapy were treated with the vincristine, lomustine, cisplatin regimen (6), whereas the others received different types of chemotherapy based on their participation in Children's Cancer Group protocols. Two patients died before receiving any therapy. Of four patients treated with chemotherapy but not radiation therapy, two are alive and free of disease to date. Both were females, with disease diagnosed at the ages of 2 and 14 months; they both had gross total resections and no evidence of metastatic disease at presentation. The chemotherapeutic regimens used were vincristine, cisplatin, carboplatin, Cytosar, and etoposide for one patient, and vincristine, carmustine, cisplatin, Cytosar, and methotrexate for the other patient.

The median follow-up time was 92 months (range 6–257 months). The median OS was 109 months (range 0–257 months) and the median PFS was 37 months (range 0–257 months). The median time from date of diagnosis to date of failure (relapse or progressive disease) was 13 months (range 0–180 months) and the median time from date of relapse to date of death was 6.4 months (range 0–52 months). Figure 1 shows detailed follow-up for all patients.

All of the relapses ( $n = 26$ ) occurred within the time period described by Collins, i.e., age at diagnosis plus 9 months, except the longest relapse, which occurred 15 years after diagnosis (22,23). Twenty-two (84%) of the relapses occurred before 1990. Most relapses occurred in patients who were treated with surgery and radiation only (77%) and in the group of patients defined as at poor risk (80%). Seven of eight local relapses occurred in patients without presence of metastatic disease at diagnosis (M0). The two patients in whom extraneural relapses developed had unknown M stages and had not received any chemotherapy before their relapses. That is, they were initially treated with surgery and radiation therapy. Table 2 indicates the different relapse sites by M stage and treatment.

Secondary malignancies developed in a total of four patients (two patients with multiple basal cell carcinomas [BCCs], one with glioblastoma, one with meningioma). Medulloblastoma was diagnosed in three of these four patients before age 3 years. All four patients received radiation therapy; only one patient also received chemotherapy.

Multiple BCCs developed in two patients in the areas of radiation therapy. These patients also had nevoid basal cell carcinoma syndrome (NBCCS), an autosomal dominant multisystem disorder with variable expression (24). Both



**FIG. 1.** Detailed follow-up for all 88 patients. Dates of diagnosis, relapse, death, and last follow-up are presented. Forty-nine patients were alive and free of disease at the time of analysis. Patients for whom exact date of death was unknown or unavailable are presented with date of diagnosis or date of relapse as last date shown on graph.

patients presented with medulloblastoma at age 2 years; one had gross total resection and received radiation therapy (23 Gy craniospinal and 45 Gy in the posterior fossa). The second patient had an incomplete resection and was treated with radiation therapy (35 Gy craniospinal and 53 Gy in the posterior fossa) and chemotherapy. Biopsy confirmed BCCs were diagnosed 3 and 6 years subsequent to medulloblastoma diagnosis, respectively. The exact date of BCC development was, however, unknown because the patients may have had BCCs before seeking medical attention and subsequent biopsy. For both patients, BCCs occurred in both the craniospinal and posterior fossa fields. Both patients exhibited other manifestations of NBCCS, including the presence of palmar and plantar pits, calcification of the falx cerebri, and jaw cysts. One NBCCS patient also had bifid ribs.

A glioblastoma multiforme developed in another patient 8 years after treatment of medulloblastoma. His disease was initially diagnosed when he was age 5 and he received 39 Gy whole-brain radiation, 30 Gy spinal radiation, and 55 Gy in the posterior fossa. Meningioma developed in one other

**TABLE 2.** Sites of relapses by M stage and treatment

Site of relapse	Number of patients	M stage			Treatment	
		M0	M1-4	M unknown	XRT	XRT + Chemotherapy
Local (tumor bed)	8	7	0	1	4	4
Local and distant	6	1	4	1	5	1
Distant	12	4	1	7	11	1

patient at age 12, 10 years subsequent to his treatment of medulloblastoma. His medulloblastoma was diagnosed when he was age 2 and he received 23 Gy craniospinal radiation and 45 Gy in the posterior fossa.

The risk of second cancers was significantly increased in this cohort of patients. There was a 20-fold excess of second neoplasms (95% CI: 2-73) based on two observed and 0.1 expected cancers. Inclusion of the two cases of BCCs in the two NBCCS patients increased the risk to 39 (95% CI: 10-99).

### SURVIVAL ANALYSIS

Overall, the OS rate was 59% at 5 years and 52% at 10 years. Progression-free survival rate was 56% at 5 and 10 years. Sex, race, duration of symptoms before diagnosis and preirradiation chemotherapy were not significant prognostic factors for OS and PFS by univariate analysis. There were, however, significant differences in OS and PFS for patients with disease diagnosed before the magnetic resonance imaging compared with OS and PFS during the magnetic resonance imaging era (designated as starting in 1990). Before 1990, OS was 50% and PFS was 48% at 5 years. In contrast, for patients with disease diagnosed in 1990 or later, OS was 83% and PFS was 80% at 5 years.

The extent of surgical resection was a strong prognostic factor, with patients who underwent gross total resection faring better than patients who had incomplete resection or biopsy only. Patients without metastatic disease at diagnosis (M0) also fared significantly better than patients with M1-4 stages (Table 3).

There was a marginally significant difference ( $P = 0.09$ ) in the OS for children with disease diagnosed when they were younger than age 3 years. This difference was significant for PFS ( $P = 0.005$ ). The 5- and 10-year PFS for patients with disease diagnosed when they were younger than age 3 years were 45%, compared with 61% and 59%, respectively, for patients whose disease was diagnosed when they were older than age 3 years.

Ventriculoperitoneal shunt placement within 30 days from the date of diagnosis also had a negative impact on survival. The 5- and 10-year OS rates for this group of patients were 41% and 34%, compared with 67% and 60% for patients who either did not have shunts or had shunts placed more than 30 days from the date of diagnosis.

When patients were placed into groups based on risk status, the patients at average risk fared better than the patients at poor risk did (Table 3). The 5- and 10-year OS rates

for the patients at average risk were 75% and 57%, and for the patients at poor risk, rates were 49% and 46%. The 5- and 10-year PFS rates were 77% and 51% for the patients at average risk and 43% for the patients at poor risk.

A statistically significant difference was also observed for radiation therapy to the posterior fossa. Patients who received more than 54 Gy had better survival rates than patients who received  $\leq 54$  Gy.

Patients who received adjuvant chemotherapy had better outcomes compared with children treated with radiation alone, and one regimen (vincristine, lomustine, cisplatin) ( $n = 22$ ) gave better survival than all the other chemotherapy regimens ( $n = 20$ ) combined ( $P < 0.05$ ). However, further analysis of the data indicated that all the patients treated with this regimen had disease diagnosed after 1990, and the vincristine-lomustine-cisplatin treatment group included many more patients at average risk (68% vs.19%).

To further examine the significant prognostic factors, additional survival analysis stratified on risk status was conducted. No statistically significant differences were observed for timing of ventriculoperitoneal shunt placement, radiation therapy dose to the posterior fossa, and addition of chemotherapy. For several of these comparisons, the numbers of events were too small to be meaningful.

On multivariate analysis, a statistically significant difference was observed when the extent of resection was adjusted for metastatic disease and for age at diagnosis ( $P = 0.01$  for PFS). A similar observation was seen when M stage

**TABLE 3.** Results of univariate analysis

Prognostic factors	OS	PFS
Age ( <b>3 y or younger</b> , older than 3 y)	0.09	0.005*
Sex (male, female)	0.71	0.39
Race (white, black)	0.57	0.38
Extent of resection (gross total, <b>other</b> )	0.0006*	0.0001*
M stage (M0, <b>M1-4</b> )	0.0036*	0.0002*
Risk ( <b>poor</b> , average)	0.016*	0.0005*
Radiation dose to the brain ( $\leq 36$ GY, $>36$ GY)	0.56	0.91
Radiation dose to the spine ( $\leq 32$ GY, $>32$ GY)	0.64	0.85
Radiation dose to the posterior fossa ( $\leq 54$ GY, $>54$ GY)	0.015*	0.0002*
<b>Radiation vs. radiation and adjuvant chemotherapy</b>	0.06	0.03*
VCR, CCNU, cisplatin vs. <b>other chemotherapy regimens</b>	0.027*	0.002*
VP shunt placement ( $<30$ d, $\geq 30$ d)	0.012*	0.002*
Preirradiation chemotherapy	0.92	0.41

\*Indicates statistical significance. If comparison showed statistically significant difference, group with poorer survival is indicated with bold type.

Median values used to dichotomize radiation doses.

was adjusted for the extent of resection and the age at diagnosis ( $P = 0.02$  for PFS). Thus, in this study, the extent of surgical resection and M stage at diagnosis appear to be independent prognostic factors for PFS.

## DISCUSSION

Retrospective single institution studies have their limitations, which include small numbers of patients, different types of treatment used during different time periods, and variation in neurosurgical and radiation therapy techniques. Most of the patients treated at our institution were at poor risk, which could be attributed to the fact that it serves as a tertiary treatment center. The relatively small number and high proportion of patients at poor risk limited the assessment of several variables of interest. For example, several factors, such as tumor volume and age, have been associated with the need for a postoperative shunt in children with medulloblastoma (7,25). Because of our limited number of patients, we were unable to show that ventriculoperitoneal shunt placement within 30 days from diagnosis was an independent prognostic factor for survival on multivariate analysis.

Our data confirmed the extent of tumor resection and M stage as significant prognostic factors of survival (3,4,7,8, 11). However, the observed statistically significant differences in survival in the groups treated with different doses of radiation therapy and with adjuvant chemotherapy could be attributed to unequal distribution between the groups of patients at poor risk. For the same reason, we were unable to conclude that the regimen consisting of vincristine, lomustine, and cisplatin offered a significant survival advantage when compared with the other chemotherapy regimens.

Collins law states that the period of risk for recurrence of a tumor is the age at diagnosis plus 9 months. One patient with disease diagnosed at age 13 years had a recurrence 15 years after diagnosis. Other exceptions to this law have been previously reported (26,27), making it difficult to define the time period after which medulloblastoma is considered "cured." Twenty-six patients had recurrent medulloblastoma. Only one of these patients is alive and free of disease to date; this patient had an isolated spinal relapse and was treated with local irradiation and chemotherapy. This observation supports previous reports that found poor survival rates of children with medulloblastoma that relapses (28–31).

Secondary malignancies are a significant risk for long-term survivors of childhood medulloblastoma and include high-grade gliomas, cancers of the thyroid gland, cervix uteri, and salivary glands, and acute leukemias (14,32–33). Glioblastoma multiforme developed 8 years after radiation therapy in one of our patients. Review of the literature revealed two more cases of children in whom glioblastoma multiforme developed after treatment of medulloblastoma 6 and 13 years after radiation therapy (34,35). All three patients died of the secondary malignancy. There are at least

14 reported cases of radiation-induced meningiomas after treatment of medulloblastoma, with an average latency period of approximately 15 years (36,37). The earlier detection in our case (10 years) could have occurred because of increased surveillance (i.e., annual head magnetic resonance imaging as part of the routine follow-up), or it may reflect the different range in the latency period of the development of meningiomas.

Our study comprehensively evaluated medulloblastoma patients during long-term follow-up for the presence of secondary malignancies. Based on development of second malignancies in four of 88 patients, the relative risk of second cancers in this study was 39 (95% CI: 10–99); if the two cases of NBCCS were omitted, the relative risk was 20 (95% CI: 2–73). In a large, population-based, registry study from the United States and Sweden (14), the relative risk of second malignancies after medulloblastoma was 5.4 (95% CI: 3.3–8.4). In this registry study, the relative risk remained unchanged even 10 years after diagnosis, suggesting that long-term survivors should continue to be vigilant. The relative risk may be even higher for children with disease diagnosed at a young age. In a study of second malignancies after childhood intracranial tumors, Duffner et al. (38) noted a risk of 18.9% for second malignancy (8 years after diagnosis) if diagnosis occurred before age 24 months, compared with 4.8% for diagnoses that occurred between the ages of 24 and 36 months. Although our data are too sparse to allow this comparison, it may be relevant that the patient in our study in whom meningioma developed had medulloblastoma diagnosed at age 2. Whereas radiotherapy must be considered as a potential risk factor contributing to this high rate of second malignancies after childhood medulloblastoma, some authors also have implicated alkylating agent chemotherapy and etoposide (38). Accumulated experience of long-term survival after medulloblastoma is not yet sufficient to allow full evaluation of treatment effects.

The incidence of NBCCS in patients with medulloblastoma is estimated to be between 1% and 2% overall and between 4% and 5% in patients younger than age 5 years (39). Numerous BCCs often develop in the irradiated areas in patients with NBCCS with medulloblastoma, usually 6 months to 3 years after radiotherapy, which is substantially earlier than in patients without NBCCS (40). Reports have shown that these patients may also be at risk for other types of secondary malignancies (41).

Significant morbidity was observed in our two patients in whom NBCCS was diagnosed. They were both black, and one might expect some degree of protection from the development of BCCs in these patients because of increased skin pigmentation (42). However, many BCCs developed (and continue to develop) in the radiation field and they have required multiple surgeries for excision of these tumors.

One should consider the concomitant diagnosis of NBCCS in all medulloblastoma patients younger than age 3 years because the mean age at diagnosis of medulloblas-

toma in NBCCS is younger than in the general population, 2 years versus 6 years, respectively (39). Assessment of family history of other relatives and physical examination of the parents may help to establish the diagnosis. Because these patients are known to have many BCCs develop in the irradiated areas and will more likely present with medulloblastoma diagnosed at a young age (younger than 3 years), chemotherapy alone or alternatively focal radiation with chemotherapy should be considered to minimize treatment-related toxicity.

Given the intensive treatment regimen for medulloblastoma and the improved survival, screening/surveillance to minimize treatment-related side effects, including the development of second malignancies, needs to be evaluated. Surveillance should include adequate follow-up, careful physician examinations including magnetic resonance imaging scans, and patient education regarding early recognition of secondary malignancies, especially skin cancer. Additional studies are needed to assess the expected benefits relative to expended resources of increased surveillance.

## REFERENCES

- Heideman RL, Packer RJ, Albright LA, et al. Tumors of the central nervous system. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*, 3<sup>rd</sup> ed. Philadelphia: Lippincott-Raven, 1997:651-6.
- Davis FG, Freels S, Grutsch J, et al. Survival rates in patients with primary malignant brain tumors stratified by patient age and tumor histologic type: an analysis based on Surveillance, Epidemiology, and End Results (SEER) data, 1973-1991. *J Neurosurg* 1998;88:1-10.
- Hughes EN, Shillito J, Sallan SE, et al. Medulloblastoma at the Joint Center for Radiation Therapy between 1968 and 1984: The influence of radiation dose on the patterns of failure and survival. *Cancer* 1988;61:1992-8.
- Evans AE, Jenkin RDT, Spoto R, et al. The treatment of medulloblastoma: Results of a prospective randomized trial of radiation therapy with and without CCNU, vincristine, and prednisone. *J Neurosurg* 1990;72:572-82.
- Tait DM, Thornton-Jones H, Bloom HJG, et al. Adjuvant chemotherapy for medulloblastoma: The first multicenter control trial of the International Society of Pediatric Oncology (SIOP I). *Eur J Cancer* 1990;26:464-9.
- Packer RJ, Sutton LN, Elterman R, et al. Outcome for children with medulloblastoma treated with radiation and cisplatin, CCNU, vincristine chemotherapy. *J Neurosurg* 1994;81:690-8.
- David KM, Casey ATH, Hayward RD, et al. Medulloblastoma: is the 5 year survival rate improving? *J Neurosurg* 1997;86:13-21.
- Albright AL, Wisoff JH, Zeltzer PM, et al. Effects of medulloblastoma resections on outcome in children: A report from the Children's Cancer Group. *Neurosurgery* 1996;38:265-71.
- Weil MD, Lamborn K, Edwards MSB, et al. Influence of a child's sex on medulloblastoma outcome. *JAMA* 1998;279:1474-6.
- Zerbini C, Gelber RD, Weinberg D, et al. Prognostic factors in medulloblastoma, including DNA ploidy. *J Clin Oncol* 1993;11:616-22.
- Zeltzer PM, Boyett JM, Finlay JL, et al. 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. *J Clin Oncol* 1999;17:832-45.
- Jenkin D, Greenberg M, Hoffman H, et al. Brain tumors in children: long-term survival after radiation treatment. *Int J Radiat Oncol Biol Phys* 1995;31:445-51.
- Johnson DL, McCabe MA, Nicholson HS, et al. Quality of long-term survival in young children with medulloblastoma. *J Neurosurg* 1994;80:1004-10.
- Goldstein AM, Yuen J, Tucker MA. Second cancers after medulloblastoma: population-based results from the United States and Sweden. *Cancer Causes Control* 1997;8:865-71.
- Chang CH, Housepian EM, Herbert C Jr, et al. An operative staging system on megavoltage radiotherapeutic technique for cerebellar medulloblastoma. *Radiology* 1969;93:1351-9.
- Ries LAG, Kosary CL, Hankey BF, et al. SEER Cancer Statistics Review, 1973-1996, National Cancer Institute. Bethesda, MD, 1999.
- Muir CS, Storm HH, Polednak A. Brain and other nervous system tumors. In: Doll R, Fraumeni JF Jr, Muir CS, eds. *Trends in Cancer Incidence and Mortality*. Plainview, NY: Cold Spring Harbor Laboratory Press, 1994. Also cited in: *Cancer Surv* 1994;19/20:369-392.
- Helseth A. Incidence and survival of intracranial meningioma patients in Norway 1963-1992. *Neuroepidemiol* 1997;16:53-9.
- Magnus K. The Nordic profile of skin cancer incidence. A comparative epidemiological study of the three main types of skin cancer. *Int J Cancer* 1991;47:12-9.
- Boice JD Jr, Lubin JH, Preston DL. *Epidemiologic Analysis With a Personal Computer (EPITOME)*. Washington, DC: US Government Printing Office; 1991. NIH Publication 91-3180.
- Allison, Paul D. *Survival Analysis Using the SAS System: A Practical Guide*. Cary, NC: SAS Institute, 1995.
- Collins VP. Wilms' tumor: Its behavior and prognosis. *J La State Med Soc* 1955;107:474-80.
- Bloom HJG, Wallace ENK, Henk JM. The treatment and prognosis of medulloblastoma in children. *AJR Am J Roentgenol* 1969;105:43-62.
- Gorlin RJ. Nevoid basal cell carcinoma syndrome. *Medicine* 1987;66:98-113.
- Sutton LN, Phillips PC, Molloy PT. Surgical management of medulloblastoma. *J Neurooncol* 1996;29:9-21.
- Brown WD, Tavare JC, Sobel EL, et al. Medulloblastoma and Collins' Law: A critical review of the concept of a period of risk for tumor recurrence and patient survival. *Neurosurgery* 1995;36:691-7.
- Friedberg MH, David O, Adelman LS, et al. Recurrence of medulloblastoma: violation of Collins' law after two decades. *Surg Neurol* 1997;47:571-4.
- Lefkowitz IB, Packer RJ, Ryan SG, et al. Late recurrence of primitive neuroectodermal tumor/medulloblastoma. *Cancer* 1988;62:826-30.
- Lefkowitz IB, Packer RJ, Siegel KR, et al. Results of treatment of children with recurrent medulloblastoma/primitive neuroectodermal tumors with lomustine, cisplatin, and vincristine. *Cancer* 1990;65:412-7.
- Wara WM, Le QTX, Sneed PK, et al. Pattern of recurrence of medulloblastoma after low-dose craniospinal radiotherapy. *Int J Radiat Oncol Biol Phys* 1994;30:551-6.
- Bouffet E, Doz F, Demaille MC, et al. Improving survival in recurrent medulloblastoma: earlier detection, better treatment or still an impasse? *Br J Cancer* 1998;77:1321-6.
- Kiltie AE, Lashford LS, Gattamaneni HR. Survival and late effects in medulloblastoma patients treated with craniospinal irradiation under three years old. *Med Pediatr Oncol* 1997;28:348-54.
- Jenkin D. The radiation treatment of medulloblastoma. *J Neurooncol* 1996;29:45-54.
- Pearl GS, Mirra SS, Miles ML. Glioblastoma multiforme occurring 13 years after treatment of a medulloblastoma. *Neurosurgery* 1980;6:546-51.
- Schmidbauer M, Budka H, Bruckner R, et al. Glioblastoma developing at the site of a cerebellar medulloblastoma treated 6 years earlier. *J Neurosurg* 1987;67:915-8.
- Dweik A, Maheut-Lourmiere J, Lioret E, et al. Radiation-induced meningioma. *Childs Nerv Syst* 1995;11:661-3.
- Starshak RJ. Radiation-induced meningioma in children: report of two cases and review of the literature. *Pediatr Radiol* 1996;26:537-41.
- Duffner PK, Krischer JP, Horowitz ME, et al. Second malignancies in young children with primary brain tumors following treatment with prolonged postoperative chemotherapy and delayed irradiation: A Pediatric Oncology Group Study. *Ann Neurol* 1998;44:313-6.
- Evans DGR, Farndon PA, Burnell LD, et al. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. *Br J Cancer* 1991;64:959-61.
- Strong LC. Genetic and environmental interactions. *Cancer* 1977;40:1861-6.
- O' Malley S, Weitman D, Olding M, et al. Multiple neoplasms following craniospinal irradiation for medulloblastoma in a patient with nevoid basal cell carcinoma syndrome. *J Neurosurg* 1997;86:286-8.
- Korczak JF, Brahim JS, DiGiovanna JJ, et al. Nevoid basal cell carcinoma syndrome with medulloblastoma in an African-American boy: A rare case illustrating gene-environment interaction. *Am J Med Genet* 1997;69:309-14.