Early aging in adult survivors of childhood medulloblastoma: long-term neurocognitive, functional, and physical outcomes


Psychosocial Oncology and Palliative Care (K.E., N.J., N.M.D.), Biostatistics (S.F., T.P.), Haematology Oncology (W.P.M.), and Radiation Oncology (N.L., D.C.H.), Ontario Cancer Institute, Princess Margaret Hospital; Psychology (B.J.S., D.J.M.), and Haematology Oncology (B.J.S., D.J.M., E.B., U.T.), Hospital for Sick Children; Dalla Lana School of Public Health, (T.P.) Neurology (W.P.M.), Psychiatry (K.E., N.M.D.), Psychology (D.J.M.), Radiation Oncology (N.L., D.C.H.), and Pediatrics, (B.J.S., D.J.M., E.B., U.T.) University of Toronto; Toronto, Canada

Treatment for medulloblastoma during childhood impairs neurocognitive function in survivors. While those diagnosed at younger ages are most vulnerable, little is known about the long-term neurocognitive, functional, and physical outcomes in survivors as they approach middle age. In this retrospective cohort study, we assessed 20 adults who were treated with surgery and radiotherapy for medulloblastoma during childhood (median age at assessment, 21.9 years [range, 18–47 years]; median time since diagnosis, 15.5 years [range, 6.5–42.2 years]). Nine patients also underwent chemotherapy. Cross-sectional analyses of current neurocognitive, functional, and physical status were conducted. Data from prior neuropsychological assessments were available for 18 subjects; longitudinal analyses were used to model individual change over time for those subjects. The group was well below average across multiple neurocognitive domains, and 90% had required accommodations at school for learning disorders. Longer time since diagnosis, but not age at diagnosis, was associated with continued decline in working memory, a common sign of aging. Younger age at diagnosis was associated with lower intelligence quotient and academic achievement scores, even many years after treatment had been completed. The most common health complications in survivors were hearing impairment, second cancers, diabetes, hypertension, and endocrine deficiencies. Adult survivors of childhood medulloblastoma exhibit signs of early aging regardless of how young they were at diagnosis. As survival rates for brain tumors continue to improve, these neurocognitive and physical sequelae may become evident in survivors diagnosed at different ages across the lifespan. It will become increasingly important to identify factors that contribute to risk and resilience in this growing population.

Keywords: brain tumor, late effects, neuropsychology, pediatric cancer, radiation.

Medulloblastomas are the most common malignancy of the central nervous system in children, accounting for 10%–20% of all pediatric cancers. With the advent of craniospinal radiation therapy in the 1950s, 5-year survival rates improved dramatically and currently approach 80% for average-risk disease. However, survival comes at a significant cost that impacts physical and mental health. These late effects develop and progress for years after treatment has been completed and, in addition to neurocognitive deficits, include second tumors, cardiac and endocrine complications, and hearing loss. Changes to brain structure affecting white matter, vasculature, and cortical thickness are thought to underlie the documented progressive cognitive impairment affecting processing speed, attention, and working memory. In contrast to the cognitive decline seen in aging adults with dementia, the
changes noted in these survivors are not associated with a loss of previously acquired skills, but rather, with a slower-than-expected rate of development; for example, medulloblastoma survivors acquire knowledge at 50% to 60% of the expected rate relative to population norms. This results in a 10 to 20-point decline in age-adjusted intelligence quotient (IQ) scores compared to the population norms within the first 5 to 10 years after treatment and a leveling off thereafter, with younger children most at risk for adverse outcomes. Very little is known about how these developmental challenges evolve as survivors approach midlife. In this retrospective study we examined the long-term outcomes in adult survivors of childhood medulloblastoma, providing a cross-sectional analysis of current neurocognitive, functional, and physical status. In addition, we conducted longitudinal analyses to examine change over time for a subset with serial assessments.

**Methods**

**Participants**

Adult survivors of childhood medulloblastoma routinely undergo comprehensive neuropsychological assessments as part of their long-term follow-up care at Princess Margaret Hospital, the largest cancer hospital in Canada and the designated aftercare site for survivors of childhood cancers in Toronto. During the period from 2005 through 2009, 31 medulloblastoma survivors were seen in the long-term follow-up clinic, and 20 of them (14 of whom were male) were referred for assessments. Neurocognitive, functional, and physical data from all 20 were included in this retrospective analysis. Demographic and treatment details are provided in Table 1.

**Procedure**

All procedures were conducted according to the guidelines of the University Health Network Research Ethics Board. To explore neuropsychological outcomes, raw neuropsychological assessment data were transformed to age-corrected scaled scores for each participant according to the normative data for each test. We then converted scaled scores to z scores and clustered subtest scores into 8 neurocognitive domains (Table 2). We also computed a clinical impairment index, which we defined as the percentage of subtest scores from each assessment that were at least 2 standard deviations below the mean (ie, $z \leq -2$, as described in Schretlen et al.49). To address concerns about different tests or test versions used across multiple assessments, we chose domains in which analogous measures were available (eg, Memory: California Verbal Learning Test5 and Children’s Auditory Verbal Learning Test;6,31 Children’s Memory Scale29 and Wechsler Memory Scale).32,33 Estimates of 3 of the 4 domains that comprise the current Wechsler IQ model (ie, verbal comprehension, perceptual organization, and working memory) were obtained according to previously published standards.25,28,30–54 We defined speed, memory, academics, executive function, and motor dexterity as the mean of the test scores within each domain.

**Neurocognitive data were analyzed in two ways. First, a cross-sectional analysis of participants’ most recent assessment results was conducted using Wilcoxon signed-rank tests to compare medulloblastoma survivors with population norms. Second, because 18 of the 20 survivors had undergone previous neuropsychological assessments (Fig. 1), we used multivariate longitudinal analyses to model individual change over time in the 8 neurocognitive domain scores and clinical impairment scores, using age at diagnosis, time since diagnosis, and radiation dose as predictors. The sample size is based on all available cases of the study time frame. Preliminary analyses revealed that linear models provided the best fit for our data and that there was no effect of radiation dose on any of the outcomes measured in either multivariate or univariate models; results for radiation dose are therefore not reported. Linear mixed modeling was used to explore the association between the other 2 clinically meaningful predictors (time since diagnosis and age at diagnosis) and the neurocognitive domains over time. The model used random effects on the intercept and fixed effects on the 2 predictors. Correlation between the 2 predictors was investigated before they were included in the multivariate analysis. An investigation of the residuals did not reveal major departures from normality. All analyses were performed using SAS software, version 9.1 for Windows (SAS Institute), and all reported $P$ values were 2-sided. Because multiple comparisons were conducted, $P$ values $<.01$ were considered to be statistically significant. Nonetheless, there are differences in opinion regarding the appropriate $\alpha$ level correction,55,56 and results should be interpreted with caution.

Details of medical history and current functional and physical status were obtained through chart review.

**Results**

**Neurocognitive Outcomes**

Cross-sectional analyses of the most recent neuropsychological test scores revealed below average Wechsler Abbreviated Scale of Intelligence (WASI) IQ scores relative to population norms, although the difference in performance IQ scores did not meet our criterion for statistical significance; verbal IQ $= -0.863$ [$P = .001$]; performance IQ $= -0.657$ [$P = .023$] (Fig. 2). All other neurocognitive domain scores were impaired, compared with population norms (working memory $= -1.207$ [$P = .001$]; speed $= -2.401$ [$P < .001$]; memory $= -1.034$ [$P < .001$]; executive function $= -3.387$ [$P = .001$]; academic achievement $= -1.161$ [$P = .001$]; and motor dexterity $= -2.536$ [$P = .001$]).

For the longitudinal analyses, we considered age at diagnosis and time since diagnosis as predictors. Our
results demonstrate an association between younger age at diagnosis and poorer IQ and academic achievement scores, even many years after treatment has been completed (Table 3). Moreover, longer time since diagnosis was associated with progressive decline in working memory, regardless of age at diagnosis (Fig. 3A and Table 3). It is worth noting that 2 of the oldest survivors, who had received diagnoses before the age of 5 years, were functioning at or close to the average range across multiple neurocognitive domains (Fig. 3A). These 2 survivors received relatively lower doses of cranial radiation (CSI + PF boost: 31.9 + 12 Gy; 30 + 20 Gy) and did not receive chemotherapy or treatment for hydrocephalus.

Age at diagnosis and time since diagnosis were not associated with any of the other neurocognitive domains assessed (Table 3). However, we note that the intercepts for all models with the exception of that for the memory domain were below average (Table 3). Furthermore, overall level of impairment tended to increase over time in survivors regardless of age at diagnosis (Table 3 and Fig. 3B).

To explore the possibility that potentially important findings were lost by combining predictors, we examined the effects of age at diagnosis and time since diagnosis separately for each of the domains. The results obtained from univariate analyses did not differ from the results of multivariate analyses described above. The only additional relationship was a trend between younger age at diagnosis and more impaired working memory (intercept = −2.07 [95% confidence interval (CI), −2.95 to −1.18]; age at diagnosis = 0.12 [95% CI, 0.01 to 0.23], P = .03). We were also interested in exploring the contributions of literacy (reading and spelling) and numeracy (arithmetic computations) to the academic achievement model, and we performed

Table 1. Participant demographic characteristics and medulloblastoma treatment history

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age at diagnosis, years</th>
<th>Age at first assessment, years</th>
<th>Age at last assessment, years</th>
<th>Surgery</th>
<th>Extent of resection</th>
<th>Shunt/EVD/Ventriculostomy</th>
<th>Hydrocephalus</th>
<th>Chemotherapy</th>
<th>CSI dose (fractions)</th>
<th>PF boost (fractions)</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>7.62</td>
<td>13.02</td>
<td>17.94</td>
<td>Gross total</td>
<td>No</td>
<td></td>
<td></td>
<td>CCNU</td>
<td>45 (n/a)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1.84</td>
<td>27.00</td>
<td>27.00</td>
<td>Subtotal</td>
<td>Yes</td>
<td></td>
<td></td>
<td>None</td>
<td>0</td>
<td>50 (25)</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>3.03</td>
<td>6.77</td>
<td>21.40</td>
<td>Gross total</td>
<td>No</td>
<td></td>
<td></td>
<td>None</td>
<td>25.2 (14)</td>
<td>28.8 (16)</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>4.71</td>
<td>36.03</td>
<td>45.69</td>
<td>Biopsy</td>
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<td></td>
<td></td>
<td>None</td>
<td>31.92 (24)</td>
<td>12 (6)</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>1.98</td>
<td>16.43</td>
<td>19.64</td>
<td>Subtotal</td>
<td>No</td>
<td></td>
<td></td>
<td>Vincristine, Cytochalasin B, Cisplatin, Etoposide</td>
<td>25.2 (14)</td>
<td>27 (15)</td>
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<td>6</td>
<td>F</td>
<td>7.73</td>
<td>14.90</td>
<td>41.45</td>
<td>Subtotal</td>
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<td></td>
<td></td>
<td>None</td>
<td>37.5 (20)</td>
<td>15 (9)</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>8.19</td>
<td>21.56</td>
<td>21.56</td>
<td>Subtotal</td>
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<td></td>
<td></td>
<td>Vincristine, Cytochalasin B, Cisplatin, Etoposide</td>
<td>39.6 (24)</td>
<td>16.2 (9)</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>8.08</td>
<td>16.44</td>
<td>18.89</td>
<td>Subtotal</td>
<td>No</td>
<td></td>
<td></td>
<td>None</td>
<td>36 (20)</td>
<td>18 (10)</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>12.88</td>
<td>13.06</td>
<td>24.17</td>
<td>Subtotal</td>
<td>No</td>
<td></td>
<td></td>
<td>CCNU, Vincristine</td>
<td>23.4 (13)</td>
<td>32.4 (18)</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>12.36</td>
<td>12.73</td>
<td>18.84</td>
<td>Gross total</td>
<td>No</td>
<td></td>
<td></td>
<td>CCNU, Cisplatin, Vincristine</td>
<td>23.4 (13)</td>
<td>30.6 (17)</td>
</tr>
<tr>
<td>11</td>
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<td>13.75</td>
<td>36.63</td>
<td>39.99</td>
<td>Gross total</td>
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<td></td>
<td></td>
<td>None</td>
<td>35 (17)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>12</td>
<td>F</td>
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<td>15.26</td>
<td>24.57</td>
<td>Gross total</td>
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<td></td>
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<td>15 (7)</td>
</tr>
<tr>
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<td>10.46</td>
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<td>Subtotal</td>
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</tr>
<tr>
<td>14</td>
<td>M</td>
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<td>34.41</td>
<td>47.24</td>
<td>Gross total</td>
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<td></td>
<td></td>
<td>None</td>
<td>30 (18)</td>
<td>20 (12)</td>
</tr>
<tr>
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<td>19.74</td>
<td>Subtotal</td>
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<td>Etoposide, Ifosfamide, Carboplatin</td>
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<td>18 (10)</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>11.26</td>
<td>17.91</td>
<td>20.14</td>
<td>Subtotal</td>
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<td></td>
<td></td>
<td>Etoposide, Ifosfamide, Carboplatin/CCNU, Vincristine</td>
<td>36 (20)</td>
<td>18 (10)</td>
</tr>
<tr>
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<td>15.38</td>
<td>22.15</td>
<td>Subtotal</td>
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<td>Etoposide, Ifosfamide, Carboplatin</td>
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</tr>
<tr>
<td>18</td>
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<td>35 (17)</td>
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<tr>
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<td>6.62</td>
<td>9.51</td>
<td>19.27</td>
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<td>Etoposide, Ifosfamide, Carboplatin</td>
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<td>16.2 (9)</td>
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<td>Subtotal</td>
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<td></td>
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<td>36 (n/a)</td>
<td>18 (n/a)</td>
</tr>
</tbody>
</table>

n/a, indicates that fractionation details were not available, because treatment had been completed abroad.

aCisplatin was switched to Cytochalasin B due to toxicity.
bICE chemotherapy was switched to CCNU and Vincristine due to toxicity.

EVD: external ventricular drain; CSI: craniospinal irradiation; PF: posterior fossa.
separate multivariate analyses for those variables. Results of those post-hoc analyses revealed that younger age at diagnosis was associated with weaker literacy skills (intercept \( = -2.24 \) [95% CI, -3.22 to -1.25]; age at diagnosis = 0.154 [95% CI, 0.04 to 0.26], \( P = .01 \)), whereas longer time since diagnosis was associated with weaker numeracy skills (intercept = -1.03 [95% CI, -2.37 to 0.31]; time since diagnosis = -0.06 [95% CI, -0.08 to -0.03], \( P < .001 \)).

**Functional Outcomes**

Information about participants’ living arrangements, education, and employment is provided in Table 4.

Data from the 2006 Canadian Census for adult residents of the province of Ontario aged 18–39 years old, provided for comparison purposes, highlight the poorer functioning in this group of survivors. For example, 17 participants (85%) were living with and supported by their parents. Although all but 1 of the survivors in our sample completed high school, 90% of them reported receiving modified programming or accommodations at school for learning disabilities. Eleven participants (55%) were either competitively employed or attending school full time, the other 9 (45%) were not competitive in the work force; 5 (25%) survivors were dependent on parents or other caregivers for their daily care, and the other 4 (20%) were employed in supported settings by family members. In contrast, the majority of
same-age peers who live in this province were married, employed, and had at least some college- or university-level education.57

Physical Outcomes

All 20 participants developed health complications over the years since completing treatment. Endocrine deficiencies were most common in our sample, and 60% were hypothyroid. Fifty-five percent of the group had documented high frequency hearing loss (25%) and/or use of hearing aids (in both ears, 30%; in 1 ear, 5%), a median of 26 years after diagnosis in those treated with radiation only and 4 years after diagnosis in those who also received chemotherapy. Information about body mass index was available for 45% of the group and ranged from 20 to 37 (median, 27). Second tumors were diagnosed in 25% of survivors 8–27 years after the initial medulloblastoma diagnosis. These included 4 patients with multiple meningiomas, 1 of whom also had metastatic thyroid carcinoma and ovarian tumor, and 1 patient with recurrent basal cell carcinoma. In terms of the meningiomas, 2 survivors received no treatment, and the other 2 underwent surgical resections but did not receive any additional therapy. Three of these survivors underwent multiple neuropsychological assessments, the last of which occurred 2–6 years after the meningioma diagnosis. Qualitative inspection of their neurocognitive profiles revealed no obvious relation between tumor location and decline in neurocognitive performance. Finally, clinic notes also documented hypertension that was controlled with medication in 20% of the group of survivors. Ten percent of them also developed diabetes, 28 and 38 years after diagnosis.

Discussion

In this study, we examined neurocognitive, functional, and physical outcomes of a group of adults who were treated for medulloblastoma in childhood. Strengths of this work include the longitudinal design, very long duration of follow-up and older age of participants, and the use of validated, objective measures to assess neurocognitive functioning. Novel findings include the stability of IQ scores 20–40 years after diagnosis and the continued decline in working memory regardless of age at diagnosis in survivors.

The pattern of educational and occupational attainment and social independence in this group of survivors was below that of same-age peers, suggesting that the altered developmental trajectory that is known to
follow treatment for medulloblastoma is permanent rather than a delay that recovers over time. Our findings confirm previous research demonstrating the vulnerability of the very young brain to the neurotoxic effects of radiotherapy, as evidenced by the relationship between age at diagnosis and IQ and academic achievement scores in our sample. By contrast, there was no relationship between age at diagnosis and working memory, speed, executive function, memory, or motor dexterity, nor was there a relationship with overall level of impairment. However, it is notable that processing speed and executive functioning scores were well below average, even at the initial assessment, for many survivors in our cohort. This was evident by the intercepts that were 2 standard deviations less than the mean for both domains. Because most of our data were collected 10 years after treatment, we were unable to characterize the initial decline in performance in those domains that likely occurred during that time period.

Our results extend previous longitudinal data demonstrating an initial decline in IQ 2–5 years after diagnosis and an attenuation of that decline 5–10 years afterwards. Here, we show that although estimates of
verbal and performance IQ scores were less than those of the population average, they do not continue to decline many years after diagnosis. Similarly, we demonstrate that there is no longer a statistically significant relationship between time since diagnosis and overall academic achievement scores at very long-term follow-up. This finding may be consistent with the model put forth by Mabbott et al., showing a rapid decline in academics during the first 5–10 years after diagnosis and a plateau in the slope of the curve thereafter. Our post-hoc analyses of academic achievement data, however, revealed a different pattern for literacy and numeracy—that is, age at diagnosis was the critical factor in determining basic literacy skills, but math skills continued to deteriorate with increasing time after diagnosis.

Survivors face progressive physical and neurocognitive challenges decades after treatment is complete, most notably in terms of continuing decline in working memory, regardless of age at diagnosis. Our finding of continued decline in numeracy is of interest in this regard, given that mathematics has a strong working memory component as well. These results extend the findings in pediatric brain tumor survivors showing an early effect of cranial radiation on processing speed and delayed emergence of working memory deficits, and they are consistent with self-reported deficits in processing speed and working memory that were unrelated to age at diagnosis in the large cohort of adult brain tumor survivors followed in the Childhood Cancer Survivor Study. This pattern of neurocognitive decline resembles other frontal subcortical neurodegenerative diseases, which are characterized by deficits in executive functions, working memory, and psychomotor speed and likely reflect the impact of radiation treatment on cerebral white matter and vasculature. Indeed, cranial radiation is associated with elevated rates of hypertension, central obesity, and dyslipidemia among brain tumor survivors, placing them at increased risk of cardiovascular disease and diabetes. In our sample, the rates of hypertension and diabetes also appear to be higher than expected relative to published prevalence rates, with 14% of Canadians aged 35–44 years requiring medication for hypertension and 3.5% of residents in the province of Ontario aged 20–49 years diagnosed with diabetes. These data underscore the need for routine screening and education about cardiovascular risk factors and healthy lifestyle practices as part of long-term follow-up care in an attempt to attenuate this process, the efficacy of which should be assessed in future generations of survivors.

Taken together, the progressive deterioration in working memory, persistent very slow processing speed, and the development of multiple physical late effects, including diabetes and hypertension, are consistent with premature aging in this population. Although the nature and course of aging in this population is not yet understood, it is unlikely to be typical given diminished physical and cognitive reserve, and evidence of changes in white matter integrity over the course of development in survivors. Use of novel imaging techniques and other biomarkers sensitive to healthy and pathological aging will be helpful to characterize this process in survivors as they continue to age. Regardless of underlying mechanisms, these deficits are likely to continue to progress, producing middle-aged adults whose needs are similar to the elderly. These findings raise concerns about the physical and cognitive supportive care needs that this growing population of early-aging adults will require, particularly as their parents are no longer able to care for them.

Our results are relevant to questions about the long-term impact of cranial radiation if treatment is given later in development, during adolescence or adulthood. Despite inconsistencies in the literature on neurocognitive effects of radiation in young or middle-aged adults, our data raise the possibility that adults may be vulnerable to radiation-induced decline in working memory at whatever age the radiation is given, if the patients are examined many years after treatment is completed. As newer treatment protocols for adult brain tumor patients continue to increase length of survival, monitoring for treatment-related neurotoxicities will become increasingly important.

Limitations of this study include the retrospective study design, resulting in differences in numbers of assessments, tests administered, and timing of test administration.

Table 4. Functional outcomes in medulloblastoma survivors

<table>
<thead>
<tr>
<th>Marital status/living arrangements</th>
<th>Medulloblastoma survivors, %</th>
<th>Census data, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single/with parent(s)</td>
<td>85</td>
<td>35.6</td>
</tr>
<tr>
<td>Single/living independently</td>
<td>10</td>
<td>17.8</td>
</tr>
<tr>
<td>Married or common law</td>
<td>5</td>
<td>46.6</td>
</tr>
<tr>
<td>Highest level education^a</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 10</td>
<td>5</td>
<td>11.5^b</td>
</tr>
<tr>
<td>High school diploma</td>
<td>75</td>
<td>38.2^c</td>
</tr>
<tr>
<td>Community college/university</td>
<td>20</td>
<td>50.3</td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Competitively employed</td>
<td>15</td>
<td>76.3^d</td>
</tr>
<tr>
<td>Employed by family</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>25</td>
<td>23.9</td>
</tr>
</tbody>
</table>

Census data for residents of the province of Ontario aged 18–39 years are provided for comparison. ^a90% of medulloblastoma survivors reported receiving academic accommodations for learning disorders. ^bNo degree. ^cIncludes trades, registered apprenticeships, and other diplomas. ^dThe Census does not distinguish between those who are competitively employed or employed by family.
relative to chronological age and age at diagnosis. We did not have sufficient power in our sample to examine the impact of other factors such as chemotherapy agents, extent of surgical resection, interventions for hydrocephalus, or primary or secondary tumor size and location. The use of a small clinical sample raises questions about bias, and the generalizability of our findings to the larger community of medulloblastoma survivors or other brain tumor survivors. However, the majority of adult survivors of childhood medulloblastoma followed at a tertiary cancer center in Paris, France were unable to live independently or obtain competitive employment, suggesting that outcomes across major urban centers are similar. In North America, 20% of central nervous system tumor survivors from the Childhood Cancer Survivor Study reported having work difficulties due to their health, and 40% of them were unemployed, a rate similar to that found in our study. The higher rate of chronic health conditions in childhood cancer survivors followed in cancer centers, compared with those who are followed in their communities, raises the possibility of selection bias in our sample as well. Although the authors of that study conclude that prevalence of chronic health conditions is overestimated as a result of selection bias, it is also possible that the lower rate of reported problems in childhood cancer survivors followed in the community is due to less attentive screening and follow-up. Whether individuals who do not attend long-term follow-up clinics are better or worse off than those who do in terms of neurocognitive status is unknown.

Summary and Significance

Although adult survivors of medulloblastoma diagnosed early in life are at risk for poorer neurocognitive, functional, and physical outcomes than are those diagnosed at older ages, here we show that working memory continues to decline decades after treatment is completed, regardless of age at diagnosis. As survival rates continue to improve, our results suggest that the sequelae associated with improved treatment protocols may become increasingly evident not only in pediatric brain tumor survivors, but possibly also in brain tumor survivors diagnosed at different ages across the lifespan. These people will have limited resources to withstand the challenge of aging in the face of diminished cognitive, physical, and neural reserve. It will become increasingly important to identify factors that contribute to risk and resilience in this growing population.

Acknowledgments

We thank Dr Jason Pole for providing the Canadian Census data. Preliminary results of this study were presented at the annual meeting of the American Society for Clinical Oncology.

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References


