

Temporal changes in treatment exposures across three decades, and long-term chronic health conditions and neurocognitive outcomes in adult survivors of pediatric medulloblastoma: A report from the Childhood Cancer Survivor Study (CCSS)

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Objective: Survivors of pediatric medulloblastoma are at significant risk of long-term physical, neurocognitive, and psychosocial sequelae. Over the past several decades, treatment protocols have aimed to reduce morbidity by reducing craniospinal radiation (CSI) dose. The impact of these changes in treatment exposures and of chronic health conditions on neurocognitive outcomes in medulloblastoma survivors is largely unknown.

Participants and Methods: 505 medulloblastoma survivors (58% male, median [min-max] 29 [18-46] years of age, 7 [0-20] years at diagnosis) diagnosed between 1970-99, and 727 siblings (44% males, 32 [18-58] years of age) completed the CCSS Neurocognitive Questionnaire assessing domains of task efficiency, emotional regulation, organization, and memory. Impairment was defined as a score greater than the 90th percentile of normative data. Treatment exposures were categorized to reflect temporal changes in therapeutic approaches: historical (surgery + CSI \geq 30Gy, no chemotherapy), high-risk (surgery + CSI \geq 30Gy + chemotherapy), standard-risk (surgery + CSI < 30Gy). Self-reported chronic health conditions were reviewed and graded by the organ system using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.3 as Grades 1 (mild), 2 (moderate), 3 (severe/disabling) or, 4 (life-threatening). Generalized estimating equations were used to calculate the risk of impairment in survivors compared to siblings, adjusting for age, sex, and race. Among survivors, multivariable modified Poisson regression was used to evaluate the risk of impairment associated with treatment groups and presence of Grade 2+ chronic health conditions (separate models), adjusting for sex, race, age at assessment, age at diagnosis and relapse/second neoplasms.

Results: Compared to siblings, survivors in all three treatment groups were at elevated risk of impaired task efficiency, emotional regulation, organization, and memory (e.g., impaired memory: historical therapy relative risk [RR] 4.3, 95% confidence interval [CI] 3.1-5.9; high-risk therapy RR 5.2, 95%CI 4.0-6.8; standard-risk therapy RR 4.5, 95%CI 3.4-6.1). Among survivors, high-risk therapy was associated with elevated impairment in organization (RR 1.5, 95%CI 1.1-2.2), but no other domains, compared to standard-risk therapy. Sensory motor conditions were associated with elevated risk of impaired task efficiency (RR 1.3, 95%CI 1.1-1.5), emotional regulation (RR 1.9, 95%CI 1.4-2.8), organization (RR 1.9, 95%CI 1.4-2.5) and memory (RR 1.3, 95%CI 1.1-1.6). The onset of seizures following diagnosis was associated with higher risk of impaired task efficiency (RR 1.2, 95%CI 1.0-1.4) and memory (RR 1.4, 95%CI 1.1-1.8)]. Respiratory disorders were associated with higher risk of impaired emotional regulation (RR 1.8, 95%CI 1.2-2.7). Auditory deficits were associated with higher risk of impaired task efficiency (RR 1.3, 95%CI 1.1-1.4) and memory (RR 1.3, 95%CI 1.0-1.5).

Conclusions: Despite reduced CSI intensity, long-term adult survivors of pediatric medulloblastoma continue to be at elevated risk for neurocognitive impairment. Treatment-related chronic health conditions are associated with this risk, and may provide intervention targets to mitigate or prevent long-term neurocognitive problems. Future studies should consider the impact of contemporary

molecular risk stratification and related changes in CSI dose and modality as well as chemotherapeutic regimens on neurocognitive outcomes.