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Second primary malignancies among childhood medulloblastoma survivors: a population-based competing risk analysis

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Abstract

Purpose: Childhood medulloblastoma (MB) survivors face elevated second primary malignancy (SPM) risk because of multimodal treatment. Prior studies were limited by small samples, older data, and methods that ignored competing risks. We aimed to quantify SPM risk using contemporary SEER data and competing risk methodology.

Methods: Using the SEER 17 registries database (2000-2023), we identified 1806 patients diagnosed with MB at ages 0-19 years. Standardized incidence ratios (SIRs) were calculated using the MP-SIR module. Cumulative incidence functions (CIFs) were estimated within a competing risk framework, with non-SPM death as the competing event. Fine-Gray regression was fitted to identify independent predictors of SPM, yielding subdistribution hazard ratios (sHRs).

Results: Of 1806 MB patients, 104 (5.8%) developed SPMs over a mean follow-up of 111 months. The overall SIR was 21.87 (males) and 20.78 (females). The most frequent SPM types were brain/central nervous system tumors (n = 26; SIR = 63.64), thyroid cancer (n = 23; SIR = 75.17 in males), and leukemia (n = 19; SIR = 25.60), with acute myeloid leukemia exhibiting SIRs of 99.41-100.95. On Fine-Gray regression, more recent diagnosis era was the only factor statistically associated with SPM occurrence; compared with 2000-2005, sHRs were 1.72 (95% CI 1.05-2.83; P = 0.031) for 2012-2017 and 2.28 (95% CI 1.04-5.01; P = 0.039) for 2018-2023. This era association should be interpreted cautiously, as it is likely driven by longer follow-up, more intensive surveillance, and declining competing mortality in recently diagnosed cohorts rather than a true increase in the underlying biologic risk of SPM; similarly, the null associations for radiation therapy and chemotherapy do not exclude a true effect, given the limited treatment detail available in SEER. Among 5-year survivors, cumulative SPM incidence surpassed non-SPM death beyond 15 years. Mortality after SPM diagnosis was 51.9%.

Conclusion: Childhood MB survivors face a substantially elevated SPM risk persisting beyond two decades. Brain tumors, thyroid cancer, and therapy-related leukemia predominate. These findings support lifelong surveillance incorporating thyroid screening, neuroimaging, and hematologic monitoring for MB survivors.

Keywords: Childhood cancer survivors; Competing risk analysis; Medulloblastoma; SEER database; Second primary malignancy.