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Title: Subsequent CNS Malignancy Among Survivors of Childhood Cancer: a Report from the Childhood Cancer Survivor Study (CCSS)

Abstract

Subsequent malignant neoplasms (SMNs) of the central nervous system (CNS) following childhood cancer are a frequently fatal late effect of cancer therapy. We used the CCSS (5-year childhood cancer survivors, diagnosed 1970-1999) to assess whether temporal changes in therapy have reduced CNS SMN risk. Twenty-year cumulative incidence rates (95% confidence interval) were estimated, and standardized incidence ratios (SIR, 95% CI) were calculated comparing observed to expected rates from SEER. Multivariable models assessed demographic and treatment-related risk factors for CNS SMN. Among survivors diagnosed between 1970-1979 (N=6223), 1980-1989 (N=9680), and 1990–1999 (N=8999) with median follow-up of 40.5, 32.2, and 22.6 years, respectively, 157 CNS SMNs (1970s, 52; 1980s, 63; 1990s, 42) were identified, excluding meningiomas. Malignant gliomas (N=131) were the most common SMNs. Cranial radiotherapy (CRT) exposure decreased by treatment decade, with the proportion of survivors receiving no CRT increasing from 23.0% (1970s), to 45.7% (1980s), and 66% (1990s). Decreases in >0–10Gy exposure (39.0% to 14.1%) and 20.1–30Gy (19.2% to 2.4%) were observed while those receiving >30Gy CRT has not substantially changed (12%, 11.1%, and 8.8%, respectively). Twenty-year cumulative incidence and SIR for development of SMN were 0.32% (0.18-0.46%) and 6.6 (5.0–8.7); 0.55% (0.41-0.70%) and 8.3 (6.6-10.4); and 0.43% (0.31-0.55%) and 9.2 (7.0–12.0), respectively, with no statistically significant differences between treatment eras, including when stratified by attained age. Multivariate analysis showed increased risk for all CRT dose levels >10Gy and for primary diagnoses of medulloblastoma/PNET (HR 3.6, 2.0-6.6) and astrocytoma (HR 2.4, 1.4-3.9). Three-year cumulative incidences of death after SMN, by treatment decade, were 70%, 73%, and 69%, respectively. In conclusion, CNS SMN incidence has not decreased despite fewer survivors being treated with CRT, and CNS SMNs remain a significant source of mortality for affected patients.