

Subsequent malignant neoplasm, chronic medical conditions and late mortality in survivors of pediatric soft tissue sarcoma: A report from the Childhood Cancer Survivor Study (CCSS)

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Background:

Approximately 67% of children with soft tissue sarcoma (STS) survive 5+ years. Late mortality, subsequent malignant neoplasms (SMN), and frequency or severity of chronic medical conditions (CMC) have not been extensively assessed.

Methods:

The CCSS, a multi-institutional retrospective cohort study of 5+ year survivors of childhood cancer, assessed outcomes for 1246 STS survivors and 4023 siblings with up to 5 questionnaires over 14 years. Self-reported CMCs were graded using CTCAE v4.03. Cox proportional hazards models provided hazard ratios (HR) and associated 95% confidence intervals (CI) for CMC. SMNs ≥ 5 years from primary cancer diagnosis were confirmed by pathology report, medical record, or death certificate. Standardized incidence ratios (SIR) and standardized mortality ratios (SMR) were generated using SEER and US mortality rates, respectively.

Results:

Median age at diagnosis was 8 years (range 0-20); median follow-up was 20 years (1.5-33.9). 243 survivors died, with SMR 5.3 (95% CI 4.7-6.0) and cumulative incidence 17.1% at 35 years from diagnosis. Compared with siblings, 42% of survivors reported ≥ 1 severe, disabling or life-threatening (grade 3-4) CMC (HR 3.5; 95% CI 2.9-4.2). Hearing, vision and/or speech were the most prevalent severe chronic morbidities at 35 years post diagnosis (cumulative incidence at 35 years 17.0%, CI 14.7-19.3%), with survivors 2.6 times more likely to have experienced this CMC as compared to siblings (CI 1.8-3.8). Survivors who received radiation to the brain, head or neck (HR=3.3, CI 1.8-6.4), pelvis (HR=4.2, CI 2.2-7.8), or extremities (HR=4.2, CI 2.2-8.1) were at particular risk for multiple (≥ 2) severe to life-threatening CMCs. The SIR of SMN was 5.6 (CI 4.6-7.0). The most frequent SMN was new (non-recurrent) soft tissue sarcoma (n=22, SIR 22.6, CI

14.9-34.3), but risk was highest for the development of a secondary osteosarcoma (n=12, SIR = 55.0, CI. 31.3-96.9).

Conclusion: Survivors of pediatric STS, especially those exposed to radiation, experience significant long-term sequelae. This observation should guide long-term surveillance and inform the evolution of new therapies.