

Reduction in late mortality among five-year survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS)

Background: Over the past four decades, treatment of many childhood cancers has been modified with the aim of achieving high survival rates while reducing the risk of life-threatening late-effects, and promoting risk-based follow-up care of survivors.

Methods: Late mortality was evaluated in 34,033 5-year survivors (diagnosed <21 years of age from 1970-1999, median follow-up 21 years, range 5-38) using cumulative incidence and Poisson regression models adjusted for demographic and disease factors to calculate relative risk (RR) and 95% confidence intervals (CI). Mortality due to non-recurrence/non-external (NR/NE) causes, which includes deaths that reflect late-effects of cancer therapy, was evaluated.

Results: 1,622 (41%) of the 3,958 deaths were attributable to NR/NE causes, including 751 subsequent neoplasm (SN), 243 cardiac, and 136 pulmonary deaths. Changes in therapy by decade included reduced rates of: cranial radiotherapy (RT) for acute lymphoblastic leukemia (ALL, 86%, 54%, 22%), RT for Wilms tumor (WT, 77%, 54%, 49%) and RT for Hodgkin lymphoma (HL, 96%, 88%, 77%).

Cumulative incidence (%) of death at 15 years from diagnosis:

Treatment era	All-Cause	NR/NE Causes	SN	Cardiac	Pulmonary
1970-74	12.4	3.5	1.8	0.5	0.4
1975-79	9.7	2.8	1.5	0.4	0.2
1980-84	8.8	2.7	1.4	0.3	0.3
1985-89	6.9	2.2	1.3	0.2	0.2
1990-94	6.0	2.1	1.0	0.1	0.1
P-value	<0.001	<0.001	<0.001	0.001	0.02

Reductions in 15 year cumulative NR/NE mortality were observed across treatment eras for ALL ($p<.001$), HL ($p=.005$), and WT ($p=.005$). Cardiac deaths decreased in ALL ($p=.002$), HL ($p=.06$), and WT ($p=.04$), and SN deaths decreased in WT ($p<.001$). Year of diagnosis (adjusted for age, sex, diagnosis, follow-up time) was significantly associated with a reduced risk of all-cause mortality (RR=0.85, CI 0.83-0.87), NR/NE death (RR= 0.87, CI 0.84-0.91), death from SN (RR=0.84, CI 0.80-0.89), cardiac death (RR=0.78, CI 0.69-0.87) and pulmonary death (RR=0.79, CI 0.68-0.91).

Conclusion: The CCSS cohort provides evidence that the strategy of modifying therapy to reduce the occurrence of late-effects, and promotion of early detection, is successfully translating into a significant reduction in observed late mortality.

Gregory T. Armstrong, MD, MSCE, Yutaka Yasui, Yan Chen, Wendy Leisenring, Todd M. Gibson, Ann Mertens, Marilyn Stovall, Melissa Hudson, Kevin Oeffinger, Smita Bhatia, Kevin Krull, Paul C. Nathan, MD, MSc, Joe Neglia, Dan Green, Leslie L. Robison, PhD

Corresponding Author: Gregory T. Armstrong, Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Mail Stop 735, Memphis, TN; Phone: 901-595-5892, Fax: 901-595-5845, Email: greg.armtrong@stjude.org