Treatment intensity and risk of chronic health conditions and late mortality among long-term survivors of Wilms: A report from the Childhood Cancer Survivor Study

Background. Wilms tumor (WT) therapy continues to evolve, with refinements in risk stratification leading to intensification of therapy for patients with adverse prognostic factors, and deintensification for others. Development of chronic health conditions (CHCs) including cardiac conditions, subsequent malignant neoplasms (SMNs), and mortality are of concern for the large cohort of WT survivors, however the impact of specific treatment regimens on late morbidity and mortality in WT survivors is largely unknown.

Methods. Late mortality (all-cause and non-recurrence death > 5 years from diagnosis), SMNs, and severity-graded CHCs (2=moderate, 3=severe, 4=life-threatening, 5=fatal) were assessed in 5-year WT survivors diagnosed from 1970-99. Survivors were categorized according to therapy received (Table). Cumulative incidence of mortality and standard mortality ratios (SMR) were estimated. Piecewise exponential models estimated rate ratios (RR) with 95% confidence intervals (CI).

Results. Among 1507 survivors (median age at follow-up 26.7 yrs; range 6.0-55.4), 35-year cumulative incidence of all-cause mortality was 7.9% (SMR 2.9, CI 2.3-3.6) and 5.1% (SMR 1.9, CI 1.4-2.4) for mortality not due to recurrence. RRs for development of any grade 2-5 CHC, grade 3-5 SMN, and grade 2-5 cardiac CHCs were higher for survivors compared to sibling controls (2.0, CI 1.8-2.3; 7.4, CI 5.0-10.8; and 2.6, CI 2.2-3.1, respectively). Compared with VA and no RT, RR for non-recurrence late mortality and CHCs among survivors were higher for VAD + any RT, and for ≥ 4 drugs + any RT (Table).

Table. Multivariable RRs (95% CI) of mortality and CHCs among WT survivors by treatment*

Treatment	N	All-cause late mortality	Non-recurrence late mortality	Chronic Health Conditions		
				Any grade 2-5	SMN grade 3-5	Cardiac grade 2-5
Surgery only	32	1.1 (0.1-9.0)	1.5 (0.2-12.4)	0.8 (0.4-1.6)	3.0 (0.4-24.8)	1.0 (0.3-3.0)
VA no RT	677	1.0	1.0	1.0	1.0	1.0
VAD no RT	96	1.6 (0.5-4.7)	1.5 (0.4-5.3)	0.8 (0.5-1.2)	0.8 (0.1-6.9)	1.1 (0.6-2.0)
VAD + ART, no LRT	437	3.0 (1.7-5.4)	2.6 (1.3-5.1)	1.5 (1.3-1.9)	2.5 (1.0-6.1)	1.8 (1.3-2.5)
VAD + ART + LRT	95	3.0 (1.2-7.2)	2.7 (1.0-7.6)	1.7 (1.2-2.5)	8.4 (3.0-23.4)	2.2 (1.4-3.7)
≥ 4 drugs + RT (any)	170	6.5 (3.5-12.2)	3.8 (1.7-8.6)	2.0 (1.5-2.6)	4.2 (1.5-12.1)	2.6 (1.8-3.8)

*adjusted for sex, race, attained age as cubic splines.
V, vincristine; A, actinomycin-D; D, doxorubicin; ART, abdominal radiotherapy; LRT, lung radiotherapy

Conclusions. Administering increased-intensity therapy for WT is associated with increased late health consequences and non-recurrence late mortality, necessitating strategies to monitor and improve long-term health among survivors.

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Authors. Brent R. Weil, Daniel M. Green, Andrew J. Murphy, Qi Liu, Rebecca M. Howell, Christopher B. Weldon, Elizabeth A. Mullen, Arin L. Madenci, Wendy M. Leisenring, Joseph P. Neglia, Kevin C. Oeffinger, Amanda M. Termuhlen, Sogol Mostoufi-Moab, Jennifer M. Levine, Kevin R. Krull, Yutaka Yasui, Leslie L. Robison, Gregory T. Armstrong, Eric J. Chow, Saro Armenian