

Background: Treatment exposure-based risk-stratification of long-term cancer survivors is needed to allocate tailored health care in survivorship clinics. Investigators from the United Kingdom (UK) developed a treatment exposure-based algorithm that stratifies survivors into low, medium, and high risk groups. Because this algorithm has not been validated, we sought to use the large, diverse population of the Childhood Cancer Survivor Study (CCSS) to validate risk for poor outcomes.

Methods: Five-year survivors of childhood cancer (diagnosed between 1970-1999 at <21 years of age) were categorized into low, medium, and high risk groups based on treatment exposures and diagnoses (Table). Primary endpoints included cumulative health-related (i.e., non-recurrence, non-external) late mortality and cumulative incidence of grade 3-5 chronic conditions (CTCAEv4.03) conditional on reaching age 20 without the outcome. Siblings were a comparison group for chronic conditions. Cox proportional hazards models among survivors estimated hazard ratios (HRs) and 95% confidence intervals (CI) adjusted for sex and race.

Results: A total of 21,504 survivors were analyzed with a median follow-up of 22 years. Application of the risk stratification algorithm resulted in 3,152 low risk, 6,443 medium risk, and 11,909 high risk survivors. Among those who survived to age 20 without any grade 3-5 conditions, the risk of developing one by age 35 was 12.2% (95% CI 1.0-14.7%), 14.2% (12.8-15.7%) and 25.4% (24.2-26.6%) for low, medium, and high-risk patients, respectively, and 6.9% (6.1-7.9%) for siblings. HRs of grade 3-5 conditions for medium (HR 1.8, 95% CI 1.6-2.1) and high (HR 3.9, 95% CI 3.5-4.4) risk relative to low risk survivors, respectively, were elevated. Cumulative health-related mortality was similarly associated with risk categories; conditional on being alive at age 20, survivors within low, medium, and high risk groups had cumulative incidences of 2.3% (95% CI 1.7-3.1%), 3.3% (2.8-3.9%) and 6.1% (5.6-6.6%), respectively, by age 35.

Conclusions: Risk categorizations based on treatment exposures were effective at providing generalized risk stratification within the CCSS with respect to risk of grade 3-5 conditions and health related mortality, particularly for identifying high risk survivors. These risk groups may be useful to physicians in determining follow-up intervals and guiding management and long-term surveillance of these survivors.

Risk Stratum	Diagnosis	Treatments
Low	ALL	Chemo only with DED<100 mg/m ²
	Wilms Tumor	No RT & DED=0
	Non-CNS tumors	Surgery Only
Medium	Anyone not in Low or High Risk	
	CNS	No RT
High	Any	Auto or Allo Transplant
		Cranial RT >24Gy; direct RT to neck, chest, abdomen, or pelvis
		CED>= 10 g/m ² ; Cisplatin >400 mg/m ² , DED > 250
RT=Radiation Therapy; DED=Doxorubicin Equivalent Dose; CED=Cyclophosphamide Equivalent Dose		