

Title: Treatment and sex-specific exposure-based risk-stratification for care of survivors of childhood Hodgkin Lymphoma: A report from the Childhood Cancer Survivor Study.

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. However, for children treated for Hodgkin Lymphoma, long term risks are also influenced by sex, which is not incorporated into this risk model. We sought to use the large, diverse population of the Childhood Cancer Survivor Study (CCSS) to validate risk for poor outcomes in children treated for Hodgkin Lymphoma with an emphasis on the impact of sex on long term outcomes.

Methods: Five-year survivors of childhood cancer (diagnosed between 1970-1999 at <21 years of age) were categorized into medium and high-risk groups based on treatment exposures and diagnoses (Table). The primary endpoint included cumulative incidence of grade 3-5 chronic conditions (CTCAEv4.03) conditional on reaching age 25 without the outcome. Patients were censored at age 40 due to a lack of follow-up. 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 2,131 survivors of Hodgkin Lymphoma met study criteria and were analyzed with a median follow-up of 22 years, with a median age of 36 at last follow-up. Application of the risk stratification algorithm resulted in 241 medium risk and 1,890 high risk survivors, with high risk patients having received transplant, doxorubicin equivalent dose ≥ 250 , or direct radiation to the neck, chest, abdomen, or pelvis. Among those who survived to age 25 without any grade 3-5 conditions, the risk of developing one by age 40 was 39.8% (95% CI 37.2- 42.5%) for high risk patients and 27.2% (19.8 – 37.2%) medium risk patients, respectively, and 8.5% (7.5 – 9.7%) for siblings. The risk of grade 3-5 condition by age 40 in high risk patients was substantially higher for females at 50.6% (46.9 – 54.6) than for males at 29.7% (26.6 – 33.3%). The same pattern was observed for medium risk patients, with females having 35.9% (25.4 – 50.6) and males having 17.7% (9.2 – 34.2) cumulative incidence. In multivariable analysis that included risk, race/ethnicity, and sex, the strongest predictor of HR of grade 3-5 conditions was females vs. male sex (HR 1.9, 95% CI 1.6 – 2.3). High vs. medium risk remained associated with increased rates of grade 3-5 toxicity (HR 1.7, 95% CI 1.2 – 2.4), whereas toxicity did not vary by race (HR 1.0, 95% CI 0.8 – 1.3).

Conclusions: Risk categorizations of medium and high risk based on treatment exposures were effective at providing generalized risk stratification within the CCSS with respect to risk of grade 3-5 conditions in both males and females. However, females treated for childhood Hodgkin Lymphoma remained at nearly double the risk of toxicity after adjusting for treatment exposure. 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	Treatments
Medium	No Radiation Therapy No Transplant Chemotherapy not meeting High Risk criteria
High	Auto or Allogeneic Transplant Cranial RT >24Gy; Direct radiation therapy to neck, chest, abdomen, or pelvis Cyclophosphamide Equivalent Dose ≥ 10 g/m ² Cisplatin >400 mg/m ² Doxorubicin Equivalent Dose ≥ 250