Title: Improvements in Long-Term Outcomes from Reduced Radiation Exposure in Pediatric Hodgkin Lymphoma Survivors: A Lifespan Perspective

Authors: Jenna R. Rogers[1,2]; Zachary J. Ward[3]; Kayla L. Stratton[4]; Wendy M. Leisenring[4]; Chelsea Taylor[2]; Gregory T. Armstrong[5]; Eric J. Chow[4]; Melissa M. Hudson[6]; Mercedes McMahon[2]; Lindsay M. Morton[7]; Kevin C. Oeffinger[8]; Angela Feraco[9,10]; Lisa Diller[9,10]; Jennifer M. Yeh[2, 10]

[1]Harvard Kenneth C. Griffin Graduate School of Arts and Sciences; [2]Department of General Pediatrics, Boston Children's Hospital; [3]Center for Health Decision Science, Harvard T.H. Chan School of Public Health; [4]Fred Hutchinson Cancer Center; [5]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital; [6]Department of Oncology, St. Jude Children's Research Hospital; [7]Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health; [8]Duke Cancer Institute; [9]Dana-Farber/Boston Children's Cancer and Blood Disorders Center; [10]Department of Pediatrics, Harvard Medical School.

Purpose: Treatment protocols for pediatric Hodgkin lymphoma (HL) have evolved to reduce late effects from long-term toxicities by limiting radiation exposure. However, estimates of late effect reductions are unknown for survivors across their lifespan. We estimated long-term health outcomes among 5-year survivors of pediatric HL with and without chest-directed radiation (RT) exposure who reach middle and late adulthood.

Methods: We used the Cancer Outcomes Microsimulation: Pediatric and Adolescent SurvivorShip (COMPASS) model based on data from the Childhood Cancer Survivor Study cohort of 5-year survivors, along with national databases, to simulate the lifetime clinical course of survivorship, including multiple chronic conditions due to treatment exposures and age-related risks. Risks of breast cancer, heart failure (HF), and myocardial infarction/coronary artery disease (MI/CAD) were predicted across treatment subgroups defined by RT exposure: extended-field RT, chest RT ≥35 Gy, chest RT <35 Gy, and chemotherapy only. Outcomes included overall survival, cumulative incidence, and conditional outcomes upon reaching age 40, with comparisons to matched general population individuals.

Results: At age 65, overall survival among 5-year survivors ranged from 24.7% for extended-field RT to 70.6% for chemotherapy only, compared to 86.4% for the general population. Survivors who received RT had higher cumulative risks for breast cancer, HF, and MI/CAD, with lower risks associated with lower doses of chest RT. Survivors treated with chemotherapy only still faced high risks. For example, for chest RT ≥35 Gy, chest RT <35 Gy, and chemotherapy only, breast cancer risk was 59.5% (95% uncertainty interval [UI], 49.1-68.80), 49.0% (95% UI, 33.2-64.5), and 20.0% (95% UI, 10.0-33.5) compared to 6.1% (95% UI, 3.9-8.7) in the general population. HF risk was 33.4% (95% UI, 25.0-43.1), 28.1% (95% UI, 14.2-48.4), and 16.8% (95% UI, 8.8-28.9]), respectively, compared to 4.3% (95% UI, 1.9-7.0) in the general population. Among survivors reaching age 40, 10-year risks of these conditions were lower in those treated with reduced radiation but all survivors had higher risks than the general population.

Conclusions: Simulated lifetime risks suggest that radiation-related late toxicity contributes to increased morbidity in pediatric HL survivors through late adulthood. Importantly, all survivors, including those treated without RT, face considerably higher risks than the general population. Dissemination of these findings can facilitate survivorship planning and discussion of late effects for tailored risk communication and decision-making.

Figure 1. Projected cumulative incidence of late toxicities among 5-year HL survivors and the general population at age 65