Long-term outcomes of survivors of Ewing sarcoma diagnosed between 1970 and 1999: a report from the Childhood Cancer Survivor Study

Duncan C Ramsey MD MPH – Oregon Health and Science University; Portland, OR (co-first)
David S. Shulman, MD – Boston Children's Hospital; Boston, MA (co-first)
Erik Geiger – University of Miami; Miami, FL
Andrew Murphy MD – St. Jude's Children's Research Hospital; Memphis, TN
Danielle Cameron MD MPH – Boston Children's Hospital; Boston, MA
Grace C Zhou MS – Fred Hutch Cancer Center; Seattle, WA
Deo Kumar Srivastava, PhD – St. Jude's Children's Research Hospital; Memphis, TN
Yutaka Yasui, PhD – St. Jude's Children's Research Hospital; Memphis, TN
Rebecca Howell MD – MD Anderson Cancer Center; Houston, TX
Kiri Ness PhD – St. Jude's Children's Research Hospital; Memphis, TN
Joseph Neglia MD – University of Minnesota; Minneapolis, MD
Lucie M Turcotte MD, MPH, MS – University of Minnesota; Minneapolis, MD
Kevin Krull PhD – St. Jude's Children's Research Hospital; Memphis, TN
Kevin Raskin MD – Harvard Medical School; Boston, MA
Eric Chow MD MPH – Fred Hutch Cancer Center; Seattle, WA
Gregory T. Armstrong MD MSCE – St. Jude's Children's Research Hospital; Memphis, TN
Brent Weil – Boston Children's Hospital; Boston, MA
Steven Dubois, MD – Boston Children's Hospital; Boston, MA (co-senior)
Christopher Weldon MD PhD – Boston Children's Hospital; Boston, MA (co-senior)

Purpose
Survivors of Ewing sarcoma (EWS) are at long-term risk of treatment- and disease-related complications. It is not known whether these complications are affected by advances in chemotherapy, radiotherapy, and surgery treatment such as the addition of ifosfamide and etoposide (IE) to the previous standard chemotherapy regimen of vincristine, doxorubicin, and cyclophosphamide (VDC). The purpose of this study is to characterize outcomes including survival, late complications, and functional status in survivors of EWS, by treatment strategy.

Methods
Five-year survivors of EWS diagnosed 1970-1999 from the Childhood Cancer Survivor Study (CCSS) were included. Chemotherapy regimen (VDC and VDC+IE), diagnosis era (1970-1988 and 1989-1999), and local control method (surgery and radiotherapy) were used as independent variables. We analyzed cumulative incidence (CI) of cause-specific late (death >5 years from diagnosis) mortality, subsequent malignant neoplasms (SMNs), and chronic health conditions (CHCs). An age-matched sibling cohort was used as a comparator group for SMN and CHCs outcomes.

Results
At 30 years of follow-up, with 142 deaths the cumulative incidence of mortality among all 740 EWS survivors was XX%. Among 683 survivors with chemotherapy data available, there were 408 and 275 survivors in the VDC and VDC+IE groups, respectively. Compared to the general population, the standardized mortality ratios were significantly increased for late mortality due to any cause (8.3; 95%CI 7.27-9.56), SMNs (13.10; 95%CI 9.81-17.13), and cardiac causes (6.64; 95%CI 4.11-10.16.). Survivors of EWS had significantly increased risk of SMN, and any grade 3-5 CHC and death (HR 6.47 95%CI 4.97-8.43; 5.78 95%CI 4.79-6.96).

When comparing the VDC+IE group to the VDC group, there was no increased risk for all-cause (HR 1.11; p=0.50; 95%CI 0.79-1.56), EWS-specific (HR 1.13; p=0.60; 95%CI 0.72-1.78), or

SMN-related (HR 1.63; p=0.20; 95%CI 0.77-3.43) mortality. There was no increased risk for the development of any Grade 3-5 CHC (HR 1.12; 95%CI 0.81-1.54) after VDC+IE vs. VDC, specifically with no difference in grade 3-5 cardiovascular (HR 1; 95%CI 0.65-1.54), neurological (HR 1.03; 95%CI 0.38-2.74]), or respiratory (HR 1.21; 95%CI 0.43-3.42) CHCs. There was a statistically significant increased risk of grade 3-5 renal CHCs (HR 3.55; 95%CI 1.07-11.70), although the overall absolute risk was low [2.8% incidence at ** years (VDC+IE) vs 1.6% (VDC)]. [Any SMN results to report comparing VDC+IE vs VDC?]

Conclusion

EWS survivors face an increased risk of mortality that continues at least 35 years after diagnosis. The addition of IE to the standard of care for Ewing sarcoma patients was not associated with increased all-cause late mortality, SMNs, or the development of Grade 3-5 CHCs overall, demonstrating no clear increase in long-term morbidity as a trade-off for the improved 5-year survival conferred by the addition of IE to VDC in EWS.