Late recurrence in survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study (CCSS)

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Abstract:
Background: An increasing percentage of childhood cancer patients are surviving their disease, but limited research suggests that late recurrences may impact overall survival. The goal of this study is to estimate late recurrence rates for the most common pediatric cancers and to determine additional risk factors for late recurrence. **Methods**: CCSS is a retrospective cohort study of five-year survivors of childhood cancer diagnosed before 21 years of age, between 1970 and 1986 at one of 26 consortium centers. Late recurrence was defined as first recurrence occurring > five years post-diagnosis. Recurrences were determined by self-report questionnaire or by confirmation through medical record, death certificate or pathologic review. Probability of late recurrence was calculated using cumulative incidence. Adjusted hazard ratios (HR) were obtained using Cox proportional hazards regression. **Results**: In 12,948 survivors with no recurrence ≤ five years from diagnosis, 670 (5.2%) subjects had a first recurrence > five years after their primary diagnosis. Late recurrences ranged from 5 to 28.9 years from diagnosis (median 7.9 years). Cumulative incidence varied by diagnosis (table). In multivariate analysis, significant risk factors for increased late recurrence included a primary diagnosis of Ewing's sarcoma or CNS tumors (HR of 2.3 and 2.7 respectively vs. leukemia survivors), age ≥ 10 years at diagnosis (HR 1.4 vs. age < 10 years), chemotherapy exposure (HR 1.5 vs. none), and radiation exposure (HR 1.4 vs. none) ($p < 0.001$ for all). At the time of last follow-up, 51.6% of subjects with a late recurrence had died versus 6.4% of those with no history of recurrence. **Conclusions**: Late recurrences occur in survivors of childhood cancers with a significant risk of mortality. This emphasizes the importance of long-term survivor follow-up into adulthood, particularly for adolescents and patients with Ewing's sarcoma and CNS tumors.

Cumulative Incidence of a First Late Recurrence in Childhood Cancer Survivors

Diagnosis	20-year cumulative incidence (%)	95% confidence intervals
Leukemia	4.9	4.3-5.6
CNS tumors	10.8	9.4-12.5
Lymphoma	4.0	3.3-4.8
Wilms' tumor	0.9	0.5-1.7
Neuroblastoma	2.4	1.6-3.6
Ewing's sarcoma	13.2	10.1-17.3
Other sarcomas	4.8	3.9-5.9