

Figure 1. Overall survival of childhood ALL patients treated at St. Jude Children's Research Hospital trials between 1962 and 2007.

diagnosis have a remarkably low risk of recurrence and death due to their initial ALL, and with the rare exception, are cured.

Table 1. Characteristics of 5-year survivors of childhood ALL in the CCSS cohort

Characteristic	n	%
Total	4151	100
Sex		
Male	2212	53.3
Female	1939	46.7
Race		
White, non-Hispanic	3383	81.5
Black, non-Hispanic	167	4.0
Hispanic, Latino	269	6.5
Other	332	8.0
Age at diagnosis of ALL, y		
0-4	2254	54.3
5-9	1140	27.5
10-14	532	12.8
15-21	225	5.4
Age at study, y		
0-9	58	1.4
10-19	628	15.1
20-29	2084	50.2
30-39	1215	29.3
40 and older	166	4.0
Survival time, y		
5-14	337	8.1
15-24	2633	63.4
25-34	1181	28.5
Treatment era		
1970-1974	650	15.7
1975-1979	1089	26.2
1980-1986	2412	58.1
Chemotherapy		
Anthracyclines	1782	48.7
Alkylating agents	2006	54.9
Both anthracyclines and alkylating agents	1444	39.5
Radiation therapy		
Cranial/craniospinal	2266	92.2
Total body irradiation	134	5.5
Other sites	62	2.3
Bone marrow transplantation	205	4.9

Late mortality among ALL survivors differed significantly for those treated with radiation (87.3%) compared with those who did not receive radiation as part of their treatment for ALL (96.1%). The CCSS results are similar to those reported from the Nordic countries,¹⁴ but are in contrast to those more recently reported by the British CCSS for ALL patients diagnosed and treated between 1940 and 1991, in whom a standardized mortality ratio of 21.5 (95% CI: 20.0-23.0) was found for this older cohort of childhood ALL survivors.¹⁵

Second neoplasms

For more than 4 decades, it has been well-recognized that survivors of pediatric and adolescent ALL are at increased risk of developing subsequent neoplasms.¹⁶⁻¹⁹ Second and subsequent neoplasms are predominantly in the skin (43%) and CNS (31%). The majority of secondary skin cancers are basal cell carcinoma, whereas 70% of the CNS neoplasms consist of meningioma. Beyond skin and CNS, there are an increasing number of solid tumors consisting of breast, bone, soft tissue, and thyroid malignancies. Results from cohorts with long-term follow-up are now providing a more detailed description of the incidence and risk factors for second and subsequent malignancies.^{12,20-22} Provided in Figure 2 are recent data from the CCSS cohort of ALL survivors for the cumulative incidence of second neoplasms, in which the estimated cumulative incidence at 30 years is 14.6% (95% CI: 12.9-16.4). Whereas the risk of second neoplasms in ALL survivors is strongly associated with radiation therapy, they are also observed among nonirradiated survivors (Figure 2). With the elimination of cranial radiation as standard therapy for ALL, it is anticipated that the occurrence of second neoplasms will markedly decline in future cohorts of ALL survivors. Because of these risks, recommendations are made for enhanced screening for breast and skin cancer among specific exposed populations (www.childrensoncologygroup.org/disc/le/), which may include ALL survivors.

Chronic medical conditions

With longer follow-up from ALL diagnosis, survivors are at increasing risk for the development of a wide range of chronic medical problems, including neurologic, neurosensory, endocrine, pulmonary, cardiac, musculoskeletal, neoplasia, gastrointestinal,

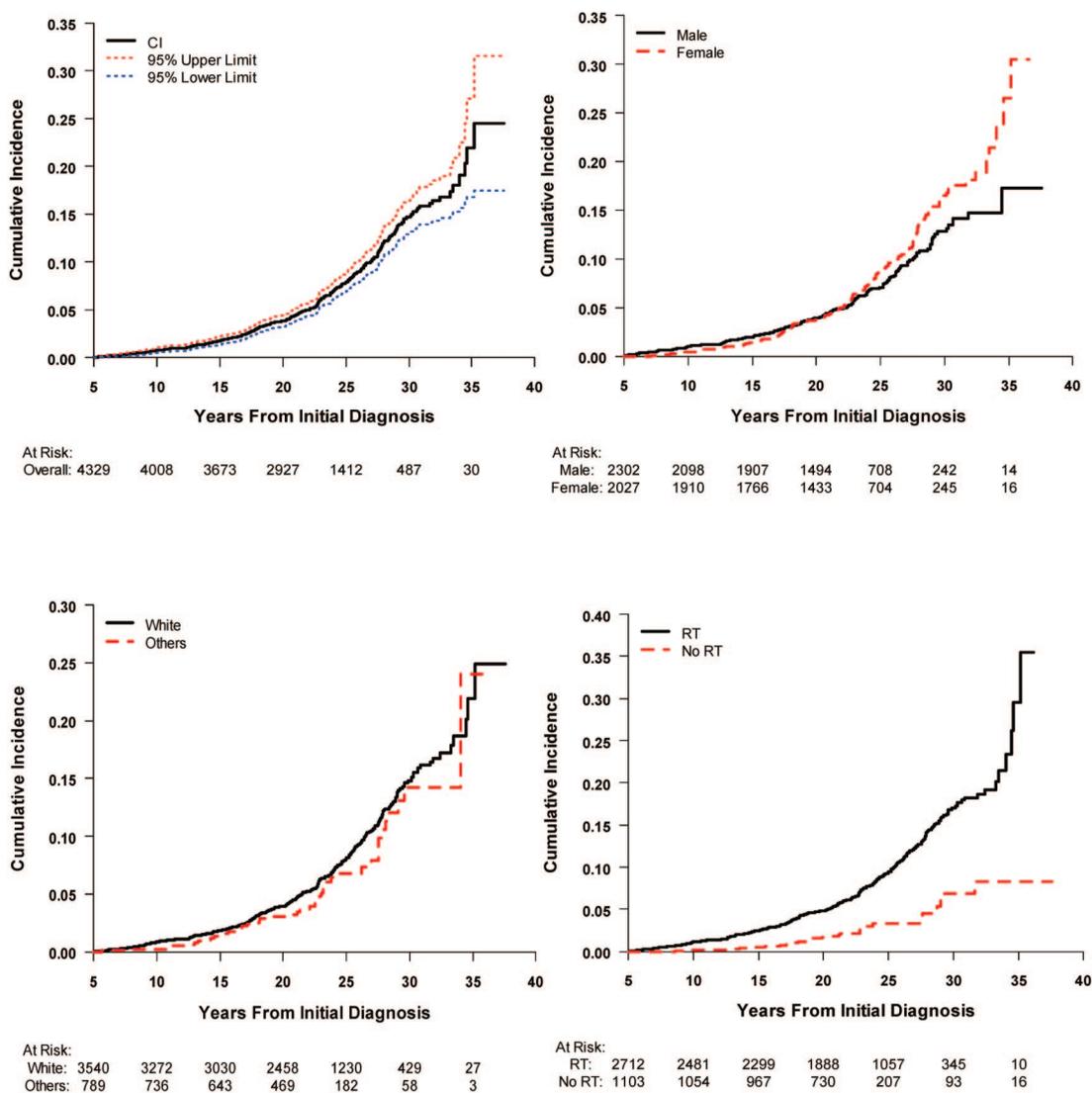


Figure 2. Cumulative incidence of second neoplasms among 5-year survivors of childhood ALL in the CCSS cohort. Shown are the overall incidence and 95% confidence limits (top left panel); by sex (top right panel); by race (bottom left panel); and by radiation treatment (bottom right panel).

and genitourinary conditions.²³ These chronic health conditions can, to varying degrees, be associated with increased morbidity and mortality. Applying the Common Terminology Criteria for Adverse Events (version 3) from the National Cancer Institute, it was determined that 50% of the ALL survivors followed in the CCSS cohort reported one or more chronic medical conditions.¹² This incidence is statistically significantly higher than the rate of 38% reported by siblings. Compared with siblings, ALL survivors were 3.7 times more likely to report a severe or life-threatening (grade 3 or 4) chronic health condition (95% CI: 3.0-4.5) and 2.8 times (95% CI: 2.4-3.2) more likely to report multiple chronic health conditions. ALL survivors were at highest risk for developing musculoskeletal, cardiac and neurological conditions, with relative risks of 7.7, 6.9, and 5.3, respectively. The 25-year cumulative incidence of any chronic health condition was 64.9%. When considering chronic health conditions graded as severe or life-threatening, the cumulative incidence at 25 years was 21.3% (95% CI: 18.2-24.4). Radiation therapy, for the treatment or prevention of CNS leukemia was significantly associated with a 4.1-fold increased risk of an endocrinologic chronic health condition and a 1.7-fold increased

risk for having a grade 3 or 4 (severe or life-threatening) chronic health condition. Moreover, when considering self-reported health status, exposure to radiation therapy was associated with a 2.2-fold increased risk of severe functional impairment. For survivors of all forms of childhood and adolescent cancers, long-term risk of serious chronic health conditions was significantly associated with radiation therapy, surgery, and chemotherapy, particularly exposure to alkylating agents and anthracyclines. Although combinations of these therapeutic exposures were not assessed specifically within the ALL survivor population, it is anticipated that comparable levels of risks would apply.

Treatment of ALL, particularly glucocorticoid therapy and radiation, is known to be associated with an increased occurrence of osteonecrosis. Among long-term survivors of childhood and adolescent ALL, the cumulative incidence of osteonecrosis at 20 years has been found to be low (0.43%), but significantly higher than expected (6.2-fold higher than that observed in siblings). The risk of osteonecrosis is highest in long-term survivors of ALL who received a stem-cell transplant.²⁴

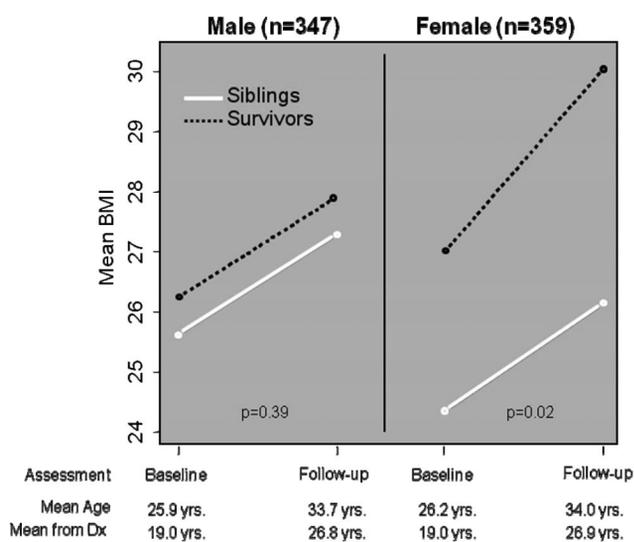


Figure 3. Mean BMI among 706 long-term survivors of childhood ALL treated with ≥ 20 Gy cranial radiation. (Adapted from Garmey et al.²⁶)

Obesity

Increased adiposity is a significant public health problem in the general population. Survivors of childhood ALL treated with cranial radiation have been found to be at substantially increased risk of obesity.²⁵ In the original report from the CCSS cohort, it was found that ALL survivors treated with > 20 Gy cranial radiation were significantly more likely to be obese (BMI > 30) compared with siblings. Whereas this was true for both male and female ALL survivors, it was found that the risk was higher among females (odds ratio of 2.59, $P < .001$) than in males (odds ratio of 1.86, $P < .001$). Beyond the risk associated with cranial radiation dose, it was also found that younger age at cranial radiation was a significant risk factor, with female ALL survivors treated with > 20 Gy cranial radiation before the age of 4 years having a 3.8-fold increased risk (95% CI: 2.3-6.0) of obesity as an adult. Subsequent follow-up of the ALL survivors demonstrated the increased risk of obesity continued for both males and females, but the proportion of obese female survivors increased at a greater pace (Figure 3). Among those females treated with > 20 Gy cranial radiation, the mean BMI was 29.3 (SD 7.3), with 40% being obese as defined by a BMI of > 30 .²⁶ To further define the risk profile for obesity among childhood ALL survivors, CCSS investigators assessed the potential role of the leptin receptor gene (Gln223Arg). Female ALL survivors who were overweight or obese were significantly more likely to be homozygous for the arginine allele, and a statistically significant interaction was found between genotype and radiation exposure.²⁷

Social and psychological outcomes

The diagnosis and treatment of ALL during childhood has the potential to disrupt the social development, emotional health, and academic progress of survivors. Investigations of survivors of childhood ALL have documented that diagnosis and treatment can increase the risk for adverse psychological outcomes including lower cognitive functioning, executive function, depression and somatic distress.²⁸⁻³⁰ CNS-directed therapy, including radiation and/or chemotherapy, for the prevention or treatment of CNS leukemia is well-recognized to be associated with decreased cognitive function, and particularly vulnerable are the youngest patients (eg, those of preschool ages).³¹ In the CCSS cohort, treatment-related impairment resulted in decreased educational attainment and

greater utilization of special education services.³² It was found that those ALL survivors who were provided with special educational services had comparable educational attainment to siblings, whereas those not reporting use of special education had lower educational attainment. With extended follow-up, ALL survivors have been found to have a higher frequency of impairment in task efficiency ($P < .001$), memory ($P = .004$), and emotional regulation ($P < .001$), as well as lower executive functioning.³⁰ Survivors of childhood ALL have also been extensively evaluated relative to marriage, employment, education, and access to health insurance.^{12,29,33-35} Within the CCSS cohort, leukemia survivors were significantly more likely to report being unemployed compared with siblings (relative risk 1.26, 95% CI: 1.11-1.41). Moreover, analyses stratified for sex, rates of college graduation, marriage, and having health insurance were significantly lower among ALL survivors than their sibling counterparts. Lower rates of marriage, educational attainment, and having health insurance are associated with history of cranial radiation.

Summary

With $> 90\%$ of childhood ALL patients achieving survival beyond 5 years, efforts need to be focused not only on innovative approaches for treating and curing those who continue to have a poor prognosis, but also on further refinement of ALL treatments with the objective of maintaining a high cure rate but minimizing long-term adverse effects. The population of more than 50 000 survivors of childhood ALL in the United States will continue to grow and age. Long-term surveillance of this population is important to better understand the incidence of late-occurring events and defining high-risk features. Moreover, long-term follow-up efforts should integrate intervention strategies for early detection and prevention. The Children's Oncology Group has developed comprehensive guidelines for clinical follow-up on survivors of cancer diagnosed and treated during the pediatric and adolescent period.³⁶ The guidelines (www.childrensoncologygroup.org/disc/le/pdf/) use the available literature to formulate exposure-based recommendations that are the clinical consensus of experts in the field. With continued research, it is anticipated that a larger proportion of recommendations will transition to evidence-based recommendations.

Disclosures

Conflict-of-interest disclosure: The author declares no competing financial interests. Off-label drug use: None disclosed.

Correspondence

L. L. Robison, Department of Epidemiology and Cancer Control, St Jude Children's Research Hospital, 262 Danny Thomas Pl, Memphis, TN 38105; phone: (901) 595-5817; fax: (901) 595-5845; e-mail: les.robison@stjude.org.

References

- Howlander N, Noone AM, Krapcho M, et al, eds. *SEER Cancer Statistics Review, 1975-2008*. Bethesda, MD: National Cancer Institute. Available online at: http://seer.cancer.gov/csr/1975_2008/. Accessed May 4, 2011 (November 2010 SEER data).
- Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBAL-CAN 2008. *Int J Cancer*. 2010;127(12):2893-2917.
- Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol*. 2010;28(15):2625-2634.
- Mariotto AB, Rowland JH, Yabroff KR, et al. Long-term

