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# Long term effects of therapy among childhood cancer survivors treated in the last two decades

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ABSTRACT

Chemotherapy regimens have been modified over the last two decades to minimize the late effects of therapy. This study was designed to evaluate neurocognitive deficits, cardiovascular events, obesity, sexual development and bone disease among survivors of childhood cancer treated after 1990.

Patient and parent questionnaires were used to prospectively collect data from childhood cancer survivors who were at least 2 years after completion of therapy or 5 years from diagnosis. Medical records were reviewed to collect data regarding diagnosis and treatment. The participants were evaluated in the clinic for physical and psychosocial late effects. Univariate and multivariate analyses were performed to identify risk factors for long-term effects of therapy.

A total of 129 survivors participated in the study; 64 (50%) were females. Seventy-eight patients and 98 parents completed questionnaires. The median age at diagnosis was 4.3 years. Median time from completion of therapy to the study participation was 5.7 years. Acute lymphoblastic leukemia was the most common diagnosis (50%). Median cumulative dose of cyclophosphamide was 1,000 mg/m$^2$ and that of anthracyclines was 123 mg/m$^2$. A fourth of the survivors received radiation therapy. Six percent of participants were obese and 6 (4.6%) had abnormalities on echocardiogram. Thirty-six (28%) required additional resources at school. Twenty-two participants (17%) had a fracture, 18 (64%) were in patients with ALL. The diagnosis, age at diagnosis and time since completion of therapy were not associated with the outcomes of interest.

Larger sample size and longer follow-up is needed to confirm these results.



## 1. Introduction

Over last few decades survival rates have continued to improve among children with cancer. Over 80% of children with cancer are expected to become long-term survivors and one in every 530 adults, between the ages of 20 and 39, is a childhood cancer survivor [1]. Studies have shown that by the age 50, survivors have a higher rate of all-cause mortality and a high incidence (44%) of high grade chronic health conditions [2]. Subsequent neoplasms, cardiac and pulmonary disease have been seen in survivors as a function of treatment decade and treatment dose and lowering of therapeutic exposure has contributed to decline in late mortality among childhood cancer survivors [3,4]. This study aims to evaluate the burden of significant long term complications related to cancer therapy in survivors of childhood cancer diagnosed and treated after 1990. Specifically, the study focuses on the prevalence of neurocognitive deficits, cardiovascular events, obesity and bone disease.

## 2. Materials and methods

This was a prospective study conducted from July 1, 2014 to June 30, 2015 in the multidisciplinary long term follow-up clinic for childhood cancer survivors at the Center for Cancer and Blood Disorders of Northern Virginia, Pediatric Specialists of Virginia. The study was approved by the Institutional Review Board of Inova Fairfax Hospital. Childhood cancer survivors were eligible to participate in the study if they were at least 2 years after

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completion of therapy or 5 years from diagnosis and had received treatment after 1990. Patient and parent questionnaires were used to collect information regarding the outcomes of interest. Parent questionnaire alone was used for children under 12 years while both parent and patient questionnaires were utilized for children between 12 and 18 years of age. Patient questionnaire alone was used for participants 18 years of age or older at time of the study. Patient and parent questionnaires assessed for the presence of symptoms related to neurocognitive deficits, cardiovascular disease and bone disease during the clinic visits in addition to questions about their perception of overall health and wellbeing. 'Infrequent symptoms' were defined subjectively as symptoms experienced "little of the time" or none of the time" in a given week. Symptoms that were 'frequent' were reported to occur 'most of the time' or 'all the time' in a given week. Results from laboratory evaluation and findings on physical examination from the visit were also collected to assess the outcomes of interest. The primary outcomes were measured based on clinical and laboratory assessments as follows:

1. Neurocognitive deficits: evaluation of overall school performance, grades, need for special education and additional help at school.
2. Cardiovascular disease: presence of cardiovascular symptoms including shortness of breath, palpitations, chest pain and syncope; risk factors for heart disease such as smoking, exercise, hypertension and family history of heart disease; systolic and diastolic blood pressure; fasting lipid profile; echocardiogram to assess cardiac function
3. Obesity: height, weight and BMI; fasting lipid profile and fasting glucose values to evaluate for metabolic syndrome
4. Sexual development in girls: age at menarche, laboratory assessments for endocrine evaluation performed as clinically indicated.
5. Bone Health: history of bone and joint pain, fractures and avascular necrosis; vitamin D and calcium levels; radiological assessments performed as clinically indicated in symptomatic patients

Medical records of all participants were reviewed to obtain information regarding demographics and treatment details, specifically, information regarding age at diagnosis, gender and ethnicity, details of diagnosis, date of starting and stopping therapy, and doses of chemotherapeutic agents and radiation therapy. Cumulative doses of drugs known to have associations with long term adverse effects, including anthracyclines and alkylating agents, were calculated. Details about the dose, field and fractionation of radiation were also collected. Medical records were reviewed for any acute neurological or cardiovascular adverse events and history of second malignant neoplasms.

Parents and participants response to questions regarding school performance was used as a measure of neurocognitive deficits. Prevalence of obesity was assessed by using body mass index (BMI). Center for Disease Control guidelines were used to label participants as overweight or obese [5]. The Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents were used to assess the results of the lipid profile [6]. Descriptive statistics were used for this study. Prevalence of the outcomes was calculated for the cohort. Statistical significance for risk factors was calculated by using T-test for continuous variables and Chi-square for categorical variables. Univariate and multivariate analyses were performed to evaluate associations of adverse events with age at diagnosis, time since diagnosis, gender and therapeutic exposure.

## 3. Results

A total of 129 childhood cancer survivors participated in this study. The demographics of the participants are described Table 1. Half of the participants were females. Median age at diagnosis was 4.3 years and median time from completion of therapy to study participation was 5.7 years. Twenty-six participants (20%) were adults (eighteen years or older) and answered individual questionnaires. The three commonest primary cancer diagnoses were acute lymphoblastic leukemia (ALL) (50%), lymphoma (12%) and sarcoma (11%).

Table 2 shows the details of treatment for all subjects obtained by review of medical records. Two thirds of the participants

**Table 1**
Patient characteristics.

| | |
|---|---|
| Number of survivors | 129 |
| Parent-completed questionnaires | 98 |
| Patient completed questionnaires | 78 |
| Gender | |
| Female | 64 (50%) |
| Male | 65 (50%) |
| Race/ethnicity | |
| Caucasian | 69 (53%) |
| African-American | 6 (5%) |
| Hispanic | 25 (19%) |
| Asian & Filipino | 16 (12%) |
| Other | 9 (10%) |
| Median age at diagnosis (years) | 4.3 (range 0 −20) |
| Median age at time of study entry (years) | 13 (range 13 −29) |
| Median time from completion of therapy to study participation (years) | 5.7 (range 2 −19) |
| Primary diagnosis | |
| Acute lymphoblastic leukemia | 66 (50%) |
| Lymphoma | 16 (12%) |
| Sarcoma | 14 (11%) |
| Renal tumor | 10 (8%) |
| Neuroblastoma | 8 (6%) |
| Acute myeloid leukemia | 7 (5%) |
| Primitive neuroectodermal tumor | 4 (3%) |
| Other[a] | 7 (6%) |

[a] 'Other' includes germ cell tumors, hepatoblastoma, Langerhans cell histiocytosis, histiocytic sarcoma and reticular dysgenesis.

**Table 2**
Treatment characteristics.

| | |
|---|---|
| Received stem cell transplant | 21 (16%) |
| Received chemotherapy & radiation | 32 (25%) |
| Received chemotherapy alone | 85 (66%) |
| Median Cumulative Dose of cyclophosphamide ($mg/m^2$) | 1,000 |
| Cumulative Dose of cyclophosphamide | |
| < 3,000 | 83 (64%) |
| 3,000–6,000 | 24 (18%) |
| > 6,000 | 22 (17%) |
| Median Cumulative Dose of anthracyclines ($mg/m^2$) | 123 |
| Cumulative Dose of anthracyclines | |
| < 250 | 99 (77%) |
| 250 - 400 | 20 (15%) |
| > 400 | 10 (8%) |
| Radiation dose (max received to any area of body) | |
| None | 97 (75%) |
| 12–24 Gy | 16 (12.5%) |
| 24–36 Gy | 1 (0.8%) |
| > 36 Gy | 12 (11.7%) |
| Received total body irradiation | 4 (3%) |
| Received cranial radiation | 14 (11%) |
| Received mediastinal radiation | 4 (3%) |

received chemotherapy only while 25% received a combination of chemotherapy and radiation. The median cumulative dose of cyclophosphamide was 1,000mg/m$^2$. Approximately a third of the participants received a cumulative dose of 3,000 mg/m$^2$ or greater. The median cumulative anthracycline dose was 123 mg/m$^2$. Twenty three percent of the participants received a cumulative anthracycline dose of 250 mg/m$^2$ or greater. Eleven percent of the participants received cranial radiation and 3% received mediastinal radiation. Thirty one (47%) of children with ALL received high dose methotrexate as part of their therapy. Cumulative dose of intrathecal methotrexate ranged from 192 mg to 312 mg among survivors of ALL. Survivors of ALL also received prednisone or dexamethasone during maintenance therapy. Children with average risk ALL were prescribed dexamethasone during maintenance therapy at a cumulative dose of 600 mg/m$^2$ in girls and 960 mg/m$^2$ in boys. Prednisone was prescribed for children with high risk ALL during maintenance and varied from 4000 mg/m$^2$ in girls to 6400 mg/m$^2$ in boys.

Majority (92%) of survivors and their parents reported that the survivors were asymptomatic or only mildly symptomatic in the 12 months prior to study entry (Appendix 1). Ten participants (8%) had experienced frequent symptoms in the preceding 12 months. One each had frequent chest pain and shortness of breath while 4 complained of fatigue and 4 of joint pain.

Clinical and laboratory data from clinic visit is reported in Table 3. Approximately a fifth of the participants (19%) were considered obese or overweight. Fasting lipid profiles were obtained in 113 participants. Total cholesterol was abnormally elevated in 12 (13%), LDL levels were elevated in 11 (10%) and HDL was abnormally decreased in 17 participants (15%). Echocardiography was performed in 97 participants. Six participants had an abnormal echocardiogram showing a decreased ejection fraction (EF) and/or shortening fraction (SF). Fifteen (12%) reported having a chronic cardiovascular comorbidity on questionnaire, including diabetes, hypertension, high cholesterol and heart disease. One participant was a self-reported current smoker.

Twenty-eight (22%) survivors experienced bone fractures and 12 survivors (9%) developed avascular necrosis. Eighteen of 28 (64%) fractures occurred in patients with a primary diagnosis of acute lymphoblastic leukemia. Low serum vitamin D was recorded in 62 (54%) patients and low serum calcium was noted in 2 (2%) patients.

Female participants of pubertal age, 10 years and older (N = 50), answered questions regarding menarche. Eighty one percent had achieved menarche at the time of the study with a median age of 11.6 years for onset of menarche.

Majority of parents and participants reported good performance at school. Seventy percent of survivors had 'excellent' or 'very good' grades, 28% had 'good' or 'fair' grades and only 2% reported grades as being 'poor' (Table 3). About one third (30%) required additional school resources, which included an Individualized Education Program (IEP), an educational plan developed for every child attending public school or special education/resources. Medications for attention deficit hyperactivity disorder (ADHD) were used by 13 survivors (10%). Fifty five percent of survivors requiring additional resources were survivors of ALL.

**Table 3**
Incidence of outcomes in the 12 months prior to the study based on clinical examination and laboratory evaluation.

| | |
|---|---|
| **Obesity (N = 129)** | |
| Overweight (BMI 25–29.9) | 16 (13%) |
| Obese (BMI 30+) | 8 (6%) |
| **Cardiovascular Disease (N = 129)** | |
| Elevated blood pressure | 40 (31%) |
| *Fasting lipid profile abnormalities (N=113)* | |
| Total cholesterol | High (≥200 mg/dL): 12 (13%)<br>Borderline (170–199 mg/dL): 29 (26%) |
| HDL | Low (<40 mg/dL): 17 (15%)<br>Borderline (40–45 mg/dL): 12 (11%) |
| LDL | High (≥130 mg/dL): 11 (10%)<br>Borderline (110–129 mg/dL): 17 (15%) |
| Cardiovascular comorbidity[a] | 15 (12%) |
| *Echocardiogram results (N = 97)* | |
| Abnormal[b] | 6 (7%) |
| **Bone health (N = 129)** | |
| Fractures | 28 (22%) |
| Avascular necrosis and/or joint replacement | 12 (9%) |
| Low Serum Vitamin D (<30 ng/mL) | 62 (54%) |
| Low Serum Calcium (<8.8 mg/dL) | 2 (2%) |
| **Sexual development in girls (N = 50)** | |
| Achieved menarche | 40 (81%) |
| **Neurocognitive deficits (N = 117)** | |
| Grades | |
| Excellent/very good | 82 (70%) |
| Good/fair | 33 (28%) |
| Poor | 2 (2%) |
| Require IEP/additional school resources | 36 (31%) |
| ADHD medications | 13 (11%) |

[a] Cardiovascular comorbidity was defined as history of diabetes, hypertension, high cholesterol and heart disease as assessed by the questionnaire.
[b] Abnormal echocardiogram result was defined as a decreased shortening fraction (SF) or ejection fraction (EF).

## 4. Discussion

Improvement in survival from childhood cancer has been associated with increased rate of long term complications and increased risk of non-cancer related deaths among survivors [3]. Among five year survivors of childhood cancer, there is an increase in absolute risk of excess death compared to the general population, largely due to subsequent neoplasms and cardiac and/or pulmonary causes. Subsequent neoplasms are the most common cause of death among twenty year survivors of childhood cancer [3,7]. However, the majority of these observations are based on studies of patients treated on older chemotherapy regimens used prior to 1990.

This study used information from parent and patient questionnaires and medical records to evaluate overall wellbeing as well as neurocognitive deficits, cardiovascular disease, bone health, obesity and sexual maturation of childhood cancer survivors. Approximately 2/3rd of the participants were survivors of ALL and lymphoma.

Overall, a vast majority of participants (92%) were reported to be well in the twelve months prior to study entry. However, 30% of the participants required additional school resources. Of these, 2/3rd were treated with chemotherapy alone. Over half of them were survivors of ALL and received high dose methotrexate. Additionally, survivors of ALL also received prednisone or dexamethasone during maintenance therapy which can have detrimental neurocognitive effects [8]. Ten percent of the participants required prescription medications for ADHD which is double of the national average of 5% reported by CDC for children between 2 and 17 years of age in 2016 [9]. Neurotoxicity from cranial radiation and chemotherapy, coupled with the psychological stress of childhood cancer are responsible for the increased burden of neurocognitive deficits in childhood cancer survivors. Survivors lack further educational attainment compared to population controls and are more likely to experience early retirement; when the year of treatment initiation was considered, there was a lower risk of early retirement in patients treated after 1992, suggesting a temporal relationship

between cancer treatment and risk of long-term neurocognitive sequelae. Additionally, learning disabilities, inattention-hyperactivity and social withdrawal are more prevalent in survivors compared with siblings [10].

Obesity was found in 6% of participants and an additional 13% were overweight in this study (Table 3). Abnormal lipid profile was seen in upto 15% of participants. Obesity and metabolic syndrome (obesity, abnormal glucose metabolism and dyslipidemia) are common in survivors of childhood cancer [11]. Injury to the hypothalamus from tumors or from cranial radiation increases risk of obesity and metabolic syndrome. Cranial radiation and high dose corticosteroids for treatment of ALL increase risk of obesity in survivors of childhood ALL. Forty six percent of survivors have been reported to be obese at 10 year follow up [12]. This is higher than the prevalence in the current study and could be because of differences in the intensity of treatment over time. It is possible that the prevalence of obesity in this cohort may increase with longer follow up.

Decrease in shortening fraction or ejection fraction was seen in 6 of 97 patients who had echocardiogram. Survivors of childhood cancer are at increased risk of developing cardiovascular disease. Exposure to anthracyclines and chest radiation are most important risk factors for development of cardiovascular disease [13]. The risk is significantly increased with a cumulative dose of 250 mg/m$^2$ or greater. The median dose of anthracycline in this study was only 123 mg/m$^2$ and only 3% of participants received mediastinal radiation. The six patients who had abnormal echocardiograms had an anthracycline dose that ranged from 60 to 450 mg/m$^2$ and none received mediastinal radiation. It is possible that the prevalence of echocardiogram abnormalities would increase with longer follow up. Hypertension was seen in 31% of the participants in this study. Hypertension has been reported in up to 70% of adult survivors of childhood cancer [14]. The prevalence of hypertension increases over longitudinal follow up and no specific associations with treatment other than nephrectomy have been found.

Twenty eight participants reported fractures and 18 (64%) of those fractures were in patients with a primary diagnosis of ALL. Survivors of childhood ALL, brain tumors and hematopoietic stem cell transplantation are at increased risk of poor bone mineral density and a greater risk of fractures [11]. Treatment-induced endocrine and hypothalamic dysfunction responsible for obesity also contribute to bone disease. Chemotherapy and radiation treatment have been shown to alter bone metabolism, increasing the risk of low bone mineral density and fractures among survivors [15]. Survivors of ALL in this study received prednisone or dexamethasone during maintenance therapy which could also contribute to poor bone health.

Vitamin D was abnormally low in 54% of patients. It is difficult to assess whether this is specific for survivors since vitamin D levels tend to be low among Americans in general as well. Sixty one percent of American children have vitamin D insufficiency [16]. While an increased rate of fractures has been reported during treatment of ALL, the occurrence of fractures in survivors is not well characterized [17]. In the childhood cancer survivor study there was no significant difference in the prevalence of self-reported fractures among survivors and their siblings [18].

Female sexual development, measured by onset and age of menarche, was not delayed in this cohort. Female survivors had onset of menarche at an age similar to the national average of 12.8 years [19]. Sperm count to assess male fertility could not be assessed as part of this study.

There are several limitations to this study. This is not a longitudinal study and it is likely that there may be under reporting of the late effects as the prevalence increases over time. The sample size is small and may not accurately reflect the prevalence of these outcomes in the general population of childhood cancer survivors. The data was predominantly obtained from questionnaires and medical records. No objective neurocognitive testing was performed to assess neurocognitive outcomes in this cohort. While the data was prospectively collected there was no control group within the study. Despite the limitations, this study is representative of the burden of the long term complications amongst childhood cancer survivors treated with more recent treatment regimens. Over 90% of the survivors and their parents felt that they were in good health. However, 10–30% of participants reported having ADHD, fractures, need for additional school resources and hypertension. While the frequency of severe effects may have decreased with modified therapy in the more recent decades, we continue to observe long term effects of therapy in a significant proportion of survivors. Larger sample size and longer follow up is needed to confirm these results.

## Impact statement

Our study suggests that survivors of childhood cancer may require additional resources at school even in absence of exposure to cranial radiation, and that survivors of ALL may have higher frequency of fractures.

## Disclosure statement

The authors have no disclosures.

## APPENDIX 1

Incidence of symptoms in the 12 months prior to the study based on data collected on parent and patient questionnaires.

| | Parent responses (n = 98) | Patient responses (n = 78) |
|---|---|---|
| **Shortness of breath** | | |
| No symptoms | 67 (68%) | 49 (63%) |
| Infrequent symptoms | 30 (31%) | 28 (35%) |
| Frequent symptoms | 1 (1%) | 1 (1%) |
| **Chest pain** | | |
| No symptoms | 82 (84%) | 57 (73%) |
| Infrequent symptoms | 15 (15%) | 20 (26%) |
| Frequent symptoms | 1 (1%) | 1 (1%) |
| **Heart racing** | | |
| No symptoms | 85 (87%) | 56 (72%) |
| Infrequent symptoms | 13 (13%) | 22 (28%) |
| Frequent symptoms | 0 | 0 |
| **Lightheadedness/dizziness** | | |
| No symptoms | 72 (73%) | 43 (55%) |
| Infrequent symptoms | 26 (27%) | 35 (45%) |
| Frequent symptoms | 0 | 0 |
| **Fatigue** | | |
| No symptoms | 50 (51%) | 40 (51%) |
| Infrequent symptoms | 44 (45%) | 34 (43%) |
| Frequent symptoms | 4 (4%) | 4 (5%) |
| **Joint or bone pain** | | |
| No symptoms | 58 (59%) | 44 (56%) |
| Infrequent symptoms | 36 (37%) | 31 (40%) |
| Frequent symptoms | 4 (4%) | 3 (4%) |

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