Pulmonary Function after Treatment for Childhood Cancer

A Report from the St. Jude Lifetime Cohort Study (SJLIFE)

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Abstract

Rationale: The relationship between treatment-related impairment of pulmonary function in adult survivors of childhood cancer and subsequent physical function has not been studied.

Objectives: In this prospective evaluation of 606 adult survivors of childhood cancer, we sought to determine the risk factors for, as well as the functional impact of, clinically ascertained pulmonary function impairment.

Methods: We measured FEV₁, FVC, total lung capacity (TLC), and single-breath diffusing capacity of the lung for carbon monoxide corrected for hemoglobin (DL_{COcorr}), expressing the results as percent predicted and lower limit of normal (LLN) values, and we also assessed functional exercise capacity (6-minute-walk distance). Lung radiation exposure was expressed as the estimated percentage of lung tissue that received at least 10 Gy (V10). Associations of clinical and treatment factors with pulmonary function measures were assessed using log-binomial regression to calculate relative risks and 95% confidence intervals.

Measurements and Main Results: The participants' median age at evaluation was 34.2 years, and the median elapsed time from diagnosis was 21.9 years. Among the sample population, 50.7% had an FEV₁ percent predicted less than 80%, 47.2% had an FVC percent

predicted less than 80%, 31.2% had a TLC percent predicted less than 75%, and 44.6% had DL_{COcorr} percent predicted less than 75%. Also, 49.0% had FEV₁ less than the LLN on the basis of the Global Lung Function Initiative (GLI) criteria, and 45.4% had FVC less than LLN. Obstructive lung defects (FEV₁/FVC, <0.7) were found in 0.8%, but none had obstructive lung defects on the basis of the GLI criterion of FEV₁/FVC less than the LLN. Restrictive lung defects (TLC, <75%) were found in 31.2% of participants. V10 and elapsed time since diagnosis were associated with abnormal FEV₁ and FVC based on the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 criteria, and with abnormal FEV₁ using the GLI criterion. Age at diagnosis was an additional risk factor for abnormal FVC based on the GLI criteria. Age at diagnosis and V10 were associated with abnormal TLC. Increased body mass index, V10, and elapsed time since diagnosis were risk factors for abnormal DL_{COcorr}. Abnormal pulmonary function tests were associated with decreased 6-minute walk distance.

Conclusions: Impaired pulmonary function in adult survivors of childhood cancer is associated with decreased physical function. These patients may benefit from interventions designed to preserve and/or improve pulmonary function.

Keywords: lung injury; radiation pneumonitis; metastasectomy; thoracic surgical procedures

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Table 1. Distribution of demographics and treatment exposures among all St. Jude Lifetime Cohort Study nonparticipants, those who underwent on-campus evaluation, and those who underwent pulmonary function testing

Variable	Received Pulmonary Toxic Therapy			Pairwise Comparison	
	SJLIFE On-Campus Evaluation and PFTs Performed (n = 606) (%)	SJLIFE On-Campus Evaluation (n = 42) (%)	SJLIFE Nonparticipants (n = 383) (%)	SJLIFE PFTs Performed vs. SJLIFE Participants without PFTs*	SJLIFE PFTs Performed vs. SJLIFE Nonparticipants*
Sex					
Male	51.0	38.1	56.4	0.11	0.10
Female	49.0	61.9	43.6		
Race/ethnicity					
Non-Hispanic white	81.2	81.0	80.7	0.46	0.21
Non-Hispanic black	14.9	11.9	13.1		
Hispanic	2.0	4.8	2.1		
Other	2.0	2.4	4.2		
Age at diagnosis, yr					
0–4	15.0	26.2	15.4	0.04	0.60
5–9	20.0	23.8	22.7		
10–14	31.5	35.7	27.9		
15–22	33.5	14.3	33.9		
Diagnosis					
Acute lymphoblastic leukemia	5.0	31.0	7.8	<0.001	<0.001
Acute myeloid leukemia	5.8	14.3	9.4		
Other leukemia/myelodysplastic syndrome	3.5	4.8	5.7		
Central nervous system tumor	1.3	0.0	0.8		
Hodgkin lymphoma	49.3	16.7	42.0		
Non-Hodgkin lymphoma	4.0	2.4	6.3		
Neuroblastoma	2.3	0.0	1.0		
Wilms tumor	5.8	7.1	6.0		
Osteosarcoma	5.8	2.4	5.0		
Ewing sarcoma family of tumors	4.6	7.1	2.9		
Germ cell tumor	5.1	7.1	6.5		
Rhabdomyosarcoma	2.3	2.4	2.6		
Nonrhabdomyosarcoma soft tissue sarcoma	2.6	4.8	1.6		
Other malignancy	2.7	0.0	2.3		
Lung radiation therapy	76.7	40.5	69.5	<0.001	0.01
Cyclophosphamide	64.5	61.9	61.6	0.73	0.36
High-dose cyclophosphamide [†]	31.5	28.6	25.8	0.69	0.06
BCNU	1.8	0.0	1.3	0.38	0.54
Bleomycin	21.3	11.9	21.9	0.15	0.81
Busulfan	2.6	11.9	6.0	0.01	0.01
CCNU	2.0	0.0	0.8	0.36	0.13
Lung surgery [‡]	19.7	42.9	19.6	<0.001	0.93
Other chest surgery [§]	3.0	2.4	1.6	1	0.17
Dactinomycin	16.7	19.0	14.9	0.69	0.46
Anthracycline	64.5	64.3	63.2	0.98	0.67
Cardiomyopathy					
Lower than grade 3	95.0	92.9	—	0.65	—
Grade 3 or higher	5.0	7.1	—	—	—
Hematopoietic stem cell transplant (HSCT)					
Autologous HSCT	1.7	7.1	5.2	0.04	0.01
Allogeneic HSCT	6.6	11.9	7.8		
Autologous and allogeneic HSCT	0.3	0.0	0.8		

(Continued)

Table 1. (Continued)

Variable	Received Pulmonary Toxic Therapy			Pairwise Comparison	
	SJLIFE On-Campus Evaluation and PFTs Performed (n = 606) (%)	SJLIFE On-Campus Evaluation (n = 42) (%)	SJLIFE Nonparticipants (n = 383) (%)	SJLIFE PFTs Performed vs. SJLIFE Participants without PFTs*	SJLIFE PFTs Performed vs. SJLIFE Nonparticipants*
Age at evaluation, yr					
18–25	15.5	23.8	—		0.01
26–35	42.7	54.8	—		
36–45	31.2	14.3	—		
46–55	10.1	2.4	—		
>55	0.5	2.4	—		
Body mass index, kg/m ²					
<25	45.9	45.2	—		0.75
≥25 and <30	30.2	28.6	—		
≥30 and <35	12.4	11.9	—		
≥35 and <40	6.2	4.8	—		
≥40	5.4	0.0	—		
Smoking status					
Current smoker	23.9	29.0	—		0.64
Former smoker	14.6	15.9			
Never smoker	61.5	55.3			

Definition of abbreviations: BCNU = 1,3-bis(2-chloro-ethyl)-1-nitrosourea or carmustine; CCNU = 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea or lomustine; PFTs = pulmonary function tests; SJLIFE = St. Jude Lifetime Cohort Study.

*Chi-square test.

†High-dose cyclophosphamide greater than or equal to 1,000 mg/m²/course or cumulative dose greater than or equal to 10,000 mg/m².

‡Lobectomy, metastasectomy, wedge resection.

§Thoracotomy, rib resection, chest wall resection.

||Sixty-seven with missing cardiomyopathy grade.

Five-year survival rates following a diagnosis of childhood cancer have improved dramatically, with more than 80% of affected patients now expected to reach this milestone (1). As a result, over 420,000 survivors of childhood cancer were estimated to be living in the United States in 2013, with anticipated growth of this population to 500,000 by 2020 (2). This progress has resulted largely from improvements in treatment regimens, some of which predispose patients to chronic pulmonary dysfunction and contribute to a significantly increased risk of death due to respiratory causes among adult childhood cancer survivors (3–5).

Therapeutic interventions that may impair pulmonary function include surgical procedures in which lung tissue is removed or the structure of the bony thorax and/or respiratory muscles is modified; radiation therapy that includes part or all of the lungs and chest wall; and/or chemotherapeutic agents such as 1,3-bis(2-chloro-ethyl)-1-nitrosourea (carmustine, BCNU), bleomycin, busulfan (6, 7), or 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea (lomustine, CCNU) (8) that may cause parenchymal lung damage. In addition, patients who undergo hematopoietic stem cell transplants

may develop pulmonary dysfunction following graft-versus-host disease, which is strongly associated with restrictive and obstructive lung disease (9, 10).

The reported prevalence of pulmonary dysfunction among adult childhood cancer survivors has varied, depending on cohort composition, treatment diversity, time from exposure, and method of ascertainment (11–13). Studies of larger childhood cancer survivor cohorts have been limited by self-reported ascertainment of outcomes (14). Formal pulmonary function tests (PFTs) may identify childhood cancer survivors with undiagnosed deficits who may be at increased risk of death due to respiratory causes (15, 16). Notably, researchers in previous studies have not evaluated the functional impact of pulmonary dysfunction among childhood cancer survivors.

To address these deficits, we undertook the present analysis to describe the prevalence of clinically ascertained abnormal pulmonary function in a large, well-characterized cohort of adult childhood cancer survivors, identify factors associated with pulmonary dysfunction, and evaluate the relationship of pulmonary function deficits to exercise capacity. We

hypothesized that exposure of larger volumes of lung to radiation therapy would produce greater impairment of pulmonary function and that impaired pulmonary function would be associated with impaired functional capacity. Some of the results of these studies were reported previously in the form of an abstract (17).

Methods

Patients eligible for our study were identified from the St. Jude Lifetime Cohort Study (SJLIFE), which comprises individuals treated for a childhood malignancy at St. Jude Children's Research Hospital who survived at least 10 years from diagnosis and were aged 18 years or older. The detailed methods used for ascertainment, recruitment, and evaluation of this cohort were reported previously (18). Body mass index was calculated and categorized using the National Heart, Lung, and Blood Institute methods (19). Nonpulmonary toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

(20). This investigation was approved by the institutional review board of St. Jude Children's Research Hospital, and all participants and/or their legal guardians provided informed consent.

Cancer Treatment

Cumulative doses for 32 specific chemotherapeutic agents, as well as all surgical procedures performed, were abstracted from the medical records (21). High-dose cyclophosphamide was defined as treatment with greater than 1 g/m²/course or a total cumulative dose greater than or equal to 10 g/m² (11). Pulmonary toxic therapy as defined by the Children's Oncology Group (22) included (1) bleomycin, busulfan, BCNU, or CCNU; (2) radiation therapy to the chest (thorax), whole lung, mediastinum, axilla, mini-mantle, mantle, extended mantle, total lymphoid irradiation, subtotal lymphoid irradiation, or total body irradiation (22); and/or (3) surgical procedures, including pulmonary lobectomy, pulmonary metastasectomy, or pulmonary wedge resection (22). Other thoracic surgical procedures considered in the analyses included chest wall surgeries (e.g., rib and chest wall resection) and thoracotomies performed for purposes

other than removal of lung metastases (e.g., resection of a mediastinal mass).

Radiation Dosimetry

Radiation dosimetry was estimated for the total lung volume by recreating 65 treatment plans using data from 51 patients. These patients represented the spectrum of survivors who received chest radiation. For each of these 65 treatment plans, the mean lung dose and volume of lung receiving 10 Gy (V10), 20 Gy (V20), and 24 Gy (V24) were calculated (*see METHODS* in the online supplement). Radiation dosimetry was not evaluable for 15 patients (5 treated at an outside institution, 4 treated with chest radiation for secondary breast cancer, and 6 for whom an appropriate dose model for radiation therapy was not available).

Pulmonary Function Testing

Pulmonary function testing was performed at the initial SJLIFE on-campus clinical evaluation for all participants who had received pulmonary toxic therapy. Prebronchodilator spirometry, performed according to the American Thoracic Society (ATS)/European Respiratory Society standards (23, 24), was used to

measure FEV₁ (25), FVC, and single-breath diffusing capacity of the lung for carbon monoxide corrected for hemoglobin (DL_{COcorr}). Total lung capacity (TLC) was determined by performing body plethysmography (26). The results for FEV₁ and FVC were analyzed using race- and sex-specific equations (25), and the results for TLC (27, 28) and DL_{COcorr} (29) were evaluated by using sex-specific equations. In addition, FEV₁ and FVC were estimated using the race- and sex-specific equations developed by the Global Lung Function Initiative (GLI) (30, 31).

FEV₁ percent predicted less than 80% and FVC percent predicted less than 80% were classified as abnormal on the basis of CTCAE v4.03 (20), and DL_{COcorr} percent predicted less than 75% was classified as abnormal on the basis of CTCAE v3.0 (32). TLC percent predicted less than 75% was considered abnormal to facilitate cross-study comparisons (11).

Interpretation of PFTs was based on ATS/European Respiratory Society recommendations, and results were classified as obstructive, restrictive, or mixed ventilatory defects (33). TLC percent

Figure 1. Flow diagram showing the St. Jude Lifetime Cohort Study (SJLIFE) study population from which the pulmonary function participants were derived. PFTs = pulmonary function tests.

Table 2. Pulmonary function test results and American Medical Association disability classification

	Number with Test Performed	Mean ± SD	Median	Range	Percent Predicted <80%	Percent Predicted Less than LLN	AMA Class 1* (>75% to ≤90%)	AMA Class 2* (>50% to ≤75%)	AMA Class 3* (>25% to ≤50%)	AMA Class 4* (<25%)
FEV ₁	606	78.1 ± 16.7	79.0	28.0–133.0	50.7%	49.0%	35.8%	32.0%	7.3%	0%
6MWD	539	78.9 ± 16.4								
No 6MWD	67	72.4 ± 17.9								
FVC	606	78.8 ± 16.9	81.0	30.0–127.0	47.2%	45.4%	34.5%	32.5%	6.4%	0%
6MWD	539	79.5 ± 16.6								
No 6MWD	67	73.8 ± 18.8								
TLC	597	81.6 ± 15.4	82.0	36.0–128.0	Percent Predicted <75% 31.2%	—	35.7%	31.2%	2.9%	0%
6MWD	535	81.8 ± 15.1								
No 6MWD	62	79.8 ± 18.1								
DL _{COcorr}	597	76.2 ± 16.8	77.0	16.0–138.0	44.6%	—	36.7%	40.7%	5.7%	0.3%
6MWD	535	76.3 ± 16.6								
No 6MWD	62	75.3 ± 18.5								
FEV ₁ /FVC					<0.7 0.8%	Less than LLN 0%				

Definition of abbreviations: 6MWD = 6-minute-walk distance; AMA = American Medical Association; DL_{COcorr} = single-breath diffusing capacity of the lung for carbon monoxide corrected for hemoglobin; LLN = lower limit of normal; TLC = total lung capacity.

*American Medical Association disability classification published in *AMA Guides to the Evaluation of Permanent Impairment* (36).

predicted less than 75% (13) or the combination of FEV₁/FVC greater than or equal to the lower limit of normal (LLN) and FVC less than the LLN (34) were classified as restrictive lung defects. Obstructive lung defects were defined by either prebronchodilator FEV₁/FVC less than 0.70 (35) or prebronchodilator FEV₁/FVC less than the LLN (34). Mixed ventilatory defects were defined by FEV₁/FVC less than the LLN and FVC less than the LLN (34). Severity of lung impairment was classified using the system published in the *AMA Guides to the Evaluation of Permanent Impairment* (36).

Functional Assessment

Functional exercise capacity was evaluated with the 6-minute-walk (6MW) test using guidelines established by the ATS. Participants were asked to walk as fast as possible without running on a flat, hard surface for 6 minutes, using customary walking aids (i.e., canes, walkers, crutches). The distance was recorded in meters. Individuals who had undergone a lower extremity amputation were assigned a missing 6MW distance for the purposes of the present analyses (37).

Statistical Methods

Descriptive statistics were provided for demographic, treatment, and other variables for all SJLIFE eligible survivors who received pulmonary toxic therapy, as well as for participants in this study who completed an on-campus visit that included PFTs, and for continuous and categorical PFT variables. Inclusion of exposure to dactinomycin and doxorubicin/daunorubicin was based on these drugs' modification of the acute toxic effects of radiation (38), and to cyclophosphamide to facilitate cross-study comparisons (11). The relationships between each PFT outcome (FEV₁ percent predicted, <80%; FEV₁ percent predicted less than the LLN; FVC percent predicted, <80%; FVC less than the LLN; TLC percent predicted, <75%; DL_{COcorr} percent predicted <75%) and exposures of interest (all those listed in Table 1) were modeled independently using log-binomial regression models because the abnormal PFT outcomes were common.

Given little *a priori* justification for including a particular set of covariates in the model to adjust for confounding bias, we used Bayesian Model Averaging (BMA) (39), which accounts for model uncertainty

by averaging over all possible models, as well as least absolute shrinkage and selection operator (LASSO) for generalized linear models (39, 40). However, because of the large number of covariates with a relatively smaller number of events, we first used Occam's principle (41) and chose the variables that were significant at an α -level of 0.20 in univariate regression models for the selection process. This still resulted in a large number of independent variables to be included in the selection process with all interactions.

To identify a smaller group of variables, we applied LASSO and BMA approaches to

all the selected variables from univariate analysis. We reran LASSO and BMA for the selected variables along with all two-way interactions to determine the final model. The BMA approach, which incorporates model uncertainty, usually returns a parsimonious model with the most conservative results in terms of covariates' significance (42). In addition, the performance of LASSO may be very poor when there are highly correlated variables in the predictor set (43). In light of the above-described reasons and the fact that models chosen using the BMA approach were more stable and more clinically

meaningful, we chose to report the results of the BMA approach.

The model with the smallest Bayesian Information Criterion and the largest posterior probability was chosen as the "final" or "most appropriate" model. The procedure was implemented using the BMA package in R (44). The association between 6MW distance (continuous variable) and each PFT outcome (continuous variable) was evaluated using linear regression models adjusted for age, height, and sex. These analyses were conducted using SAS 9.3 software (SAS Institute, Cary, NC).

Figure 2. (A) Distribution of FEV₁ percent predicted values. (B) Distribution of FVC percent predicted values. (C) Distribution of total lung capacity (TLC) percent predicted values. (D) Distribution of single-breath diffusing capacity of the lung for carbon monoxide corrected for hemoglobin (DLCO_{corr}) percent predicted values. MIN = minimum value; Q1 = first quartile value; Q3 = third quartile value; MAX = maximum value; Pleth = plethysmography.

Results

Nine hundred eighty-nine SJLIFE eligible patients received pulmonary toxic therapy, 648 of whom completed a SJLIFE on-campus evaluation and 606 (61.3% of eligible) of whom completed PFTs (Figure 1). The most frequent diagnosis among those who underwent PFTs was Hodgkin lymphoma (Table 1). SJLIFE participants who received pulmonary toxic therapy and had PFTs performed were more likely to have been treated with lung radiation therapy, less likely to have received busulfan, and less likely to have received a hematopoietic stem cell transplant (Table 1). The median age at diagnosis was 13.0 years, and the median age at pulmonary function testing was 34.2 years. The participants were a median of 21.9 years from diagnosis. SJLIFE participants who received pulmonary toxic therapy and had PFTs performed received higher cumulative doses of cyclophosphamide, busulfan, and anthracyclines than SJLIFE nonparticipants (see Table E2 in the online supplement).

Among the 450 patients with evaluable radiation therapy records, the mean proportions of the lungs that received 10 Gy, 20 Gy, and 24 Gy were ($\pm$ SD) 0.58 ($\pm$ 0.27),

0.23 ($\pm$ 0.19), and 0.15 ($\pm$ 0.17), respectively (see Table E2). Pertinent chemotherapy exposures included cyclophosphamide in 391 (64.5%), an anthracycline in 391 (64.5%), bleomycin in 129 (21.3%), and dactinomycin in 101 (16.7%). BCNU, CCNU, and busulfan were infrequently administered (Table 1).

At least one PFT was abnormal in 65.0% (392 of 603) of the patients. Approximately one-half (50.7%; 307 of 606) of the patients had a FEV₁ percent predicted less than 80%, and one-third (31.2%; 186 of 597) had a TLC percent predicted less than 75% (Table 2). The distributions of FEV₁, FVC, TLC, and DL_{CO}corr are presented in Figures 2A–2D. Using the criteria of the GLI, we found that no participant had an obstructive lung defect or a mixed obstructive and restrictive lung defect. Approximately one-half (49.9%; 297 of 606) of the patients had a restrictive lung defect. Approximately one-third of patients were in AMA class 2 for pulmonary disability, but less than 10% were in AMA class 3 or 4 (Table 2).

In multivariable models selected by BMA, all PFT results except TLC were worse with increasing elapsed time after diagnosis and increasing percentages of the lungs that received 10 Gy or more

(Table 3). Using the GLI criteria, we found that age at diagnosis was an additional significant risk factor for abnormal FVC and that body mass index was an additional risk factor for impaired DL_{CO}corr. V10 and age at diagnosis were associated with impaired TLC (Table 3). Prior treatment with dactinomycin, an anthracycline and/or cyclophosphamide, evaluated as high dose versus not high dose or increasing cumulative dose, other thoracic surgical procedures, and current smoking were not significant variables in the selected BMA model with the smallest Bayesian Information Criterion and the largest posterior probability.

FEV₁ percent predicted ($P < 0.001$), FVC percent predicted ($P < 0.001$), TLC percent predicted ($P = 0.004$), and DL_{CO}corr percent predicted ($P < 0.001$) were significant risk factors for decreased 6MW distance among the 539 participants who completed the 6MW test (Table 4). The distribution of 6MW distances is shown in Figure 3. Sixty-seven patients were not included in the analysis of 6MW test data (see Table E3). The mean FEV₁ percent predicted ($P = 0.008$) and FVC percent predicted ($P = 0.02$) were significantly lower among those with a missing 6MW test

Table 3. Multivariable log-binomial regression models

Dependent Variable	Independent Variable	Relative Risk	95% Confidence Interval	P Value
FEV ₁ percent predicted <80%	Elapsed time after diagnosis (per yr)	1.04	1.03–1.05	<0.001
	V10 (per 10% increase)	1.07	1.04–1.09	<0.001
FEV ₁ less than LLN	Elapsed time after diagnosis (per yr)	1.04	1.03–1.05	<0.001
	V10 (per 10% increase)	1.06	1.04–1.09	<0.001
FVC percent predicted <80%	Elapsed time after diagnosis (per yr)	1.05	1.04–1.06	<0.001
	V10 (per 10% increase)	1.08	1.05–1.11	<0.001
FVC less than LLN	Elapsed time after diagnosis (per yr)	1.05	1.04–1.06	<0.001
	Age at diagnosis (yr)	0.97	0.95–0.98	<0.001
	V10 (per 10% increase)	1.07	1.04–1.10	<0.001
TLC percent predicted <75%	Age at diagnosis (yr)	0.86	0.79–0.95	0.002
	Race/ethnicity other than non-Hispanic white	2.09	0.98–4.45	0.055
	Elapsed time after diagnosis (per yr)	1.02	0.99–1.05	0.231
	V10 (per 10% increase)	1.07	1.01–1.13	0.019
	Elapsed time after diagnosis $\times$ race/ethnicity	0.99	0.97–1.02	0.534
	Elapsed time after diagnosis $\times$ age at diagnosis (yr)	1.003	1.001–1.006	0.019
	Age at diagnosis (yr) $\times$ V10 (per 10% increase)	1.002	1.00–1.01	0.488
DL _{CO} corr percent predicted <75%	Elapsed time after diagnosis (per yr)	1.03	1.02–1.04	<0.001
	V10 (per 10% increase)	1.07	1.04–1.10	<0.001
	Body mass index (per kg/m ²)	0.97	0.95–0.99	<0.001

Definition of abbreviations: DL_{CO}corr = single-breath diffusing capacity of the lung for carbon monoxide corrected for hemoglobin; LLN = lower limit of normal; TLC = total lung capacity; V10 = estimated percentage of lung tissue that received at least 10 Gy.

Table 4. Linear regression models with factors predicting 6-minute walk distance

	β -Value*	SE	P Value
FEV ₁ percent predicted	1.06	0.27	<0.001
FVC percent predicted	1.15	0.27	<0.001
TLC percent predicted	0.85	0.29	0.004
DL _{CO} corr percent predicted	1.26	0.28	<0.001

Definition of abbreviations: DL_{CO}corr = single-breath diffusing capacity of the lung for carbon monoxide corrected for hemoglobin; TLC = total lung capacity.

*Adjusted for age, sex, and height. β -value is interpreted as follows: For FEV₁, for example, each 1% absolute increment in FEV₁ is associated with a 6-m increase in 6-minute walk distance.

distance (see Table 2). Scatterplots of 6MW distance for each PFT are shown in Figures 4A–4D.

Discussion

Surgical procedures, chest radiation, and specific chemotherapeutic agents may impair pulmonary function among childhood cancer survivors, but the severity of long-term pulmonary dysfunction among adult childhood cancer survivors, its association with host factors or treatment intensity, and the implications of impaired pulmonary function for physical activity and subsequent survival have not been well studied. Using the SJLIFE study, the largest cohort of clinically well-characterized childhood cancer survivors evaluated by pulmonary function testing, we observed abnormal pulmonary function in the majority of childhood

cancer survivors exposed to potentially pulmonary toxic treatment. Novel findings of the present study include quantification of the dose–response relationship between risk of pulmonary dysfunction and chest radiation therapy. In addition, we demonstrate that impaired pulmonary function adversely impacts exercise capacity.

The prevalence of restrictive pulmonary deficits in our cohort differs from previous investigations of pulmonary outcomes among childhood cancer survivors who underwent clinical assessments. We identified restrictive pulmonary impairment in 31.2% (186 of 597) of SJLIFE childhood cancer survivors, compared with 18.7% (28 of 150) of Dutch childhood cancer survivors (11) and 21.5% (26 of 121) of North American childhood cancer survivors (13). This difference may be related, in part, to the higher proportions of survivors with Hodgkin lymphoma and of those who had

undergone pulmonary metastasectomy in the SJLIFE cohort than in the Dutch and North American studies (11, 13). In contrast to restrictive pulmonary deficits, we observed a low prevalence of obstructive pulmonary deficits (0.8%; 5 of 606), similar to that previously reported (11, 13).

In recent studies, independent predictive factors for pulmonary impairment identified by multivariable analyses have included pulmonary radiation and thoracic surgery. Pulmonary radiation therapy (evaluated as yes or no) in the Dutch study and chest radiation dose greater than 20 Gy in a recent North American cohort were significant in multivariable models for both restrictive pulmonary deficits and impaired diffusion capacity. In the present study, we have demonstrated, using more precise dose-volume estimates, that inclusion of larger volumes of lung in the treatment plan predicts greater impairment.

Researchers in previous studies have reported conflicting results related to age at diagnosis (11, 13). In the present study, younger age at diagnosis was associated with a greater risk of restrictive pulmonary deficits, whereas in the North American cohort age at diagnosis older than 16 years was a risk factor for restrictive pulmonary deficits. Surprisingly, bleomycin exposure was not associated with restrictive pulmonary deficits or impaired diffusion capacity in either the Dutch or North American multivariable models, and none was identified in the present study. This finding may be related to the low cumulative drug exposures in these contemporary cohorts.

Pulmonary toxicity is a well-established complication of treatment with BCNU, bleomycin, busulfan, and CCNU. The failure to identify an independent effect of treatment with one of these drugs in the present study may be related to the small number of participants exposed to each, limiting the statistical power of analyses to evaluate the impact of such treatments.

The evidence supporting chronic pulmonary injury following treatment with cyclophosphamide is limited (45–47). Mulder and colleagues (11) did not identify treatment with high-dose cyclophosphamide as a significant

Figure 3. Histogram of 6-minute-walk distances.

Figure 4. (A) Scatterplot of 6-minute-walk (6MW) distance and FEV₁ percent predicted. (B) Scatterplot of 6MW distance and FVC percent predicted. (C) Scatterplot of 6MW distance and total lung capacity (TLC) percent predicted. (D) Scatterplot of 6MW distance and single-breath diffusing capacity of the lung for carbon monoxide corrected for hemoglobin (DL_{COcorr}) percent predicted.

predictor of restrictive pulmonary or diffusion capacity deficits among 193 adult childhood cancer survivors who received bleomycin, pulmonary radiation therapy, and/or pulmonary surgery. In the present study, treatment with neither high-dose cyclophosphamide nor an increasing cumulative cyclophosphamide dose was identified as a risk factor for pulmonary function impairment.

Impairments identified in PFTs were associated with decreased functional capacity as measured by the 6MW distance. This finding is significant, as 6MW test performance has been correlated with

risk of mortality in other vulnerable populations. 6MW distance less than 475 m was predictive of death or lung transplant in a cohort of adults with cystic fibrosis (48), and desaturation during the 6MW test was predictive of mortality among patients with idiopathic interstitial pneumonia (49).

Strengths and Limitations

The present study has significant strengths, including uniform evaluation of a large cohort of childhood cancer survivors with detailed treatment exposure data. The use of dose-volume estimates, compared with estimates based on nominal thoracic dose

(11–13), provides a more precise estimate of the dose–response relationship between radiation exposure and pulmonary dysfunction. In our study, we also used established criteria to categorize the severity of pulmonary function deficits (11, 13, 20, 32).

Limitations of our study include the lack of pretreatment PFT results, the inability to obtain PFTs from all eligible individuals who received pulmonary toxic treatment, and the inability of a number of patients with clear impairment of pulmonary function and/or functional capacity to complete the 6MW test. These individuals were thus excluded from

the analyses, which may have led to underestimation of the prevalence of impaired functional capacity.

In addition, because the cohort consists of 10-year survivors alive at the time SJLIFE was initiated, our results can be generalized only to individuals who continue to survive following childhood cancer, as data for individuals who died due to pulmonary disease or other causes prior to study inception were not captured. A prior analysis suggested minimal differences in sociodemographic and cancer-related clinical characteristics between SJLIFE participants and nonparticipants (50). The comparisons between those who did undergo pulmonary function testing and those who were not SJLIFE participants demonstrated small differences in the proportions of those with Hodgkin lymphoma, those treated with lung radiation therapy, and those treated with busulfan and hematopoietic stem cell transplants (consistent with the busulfan data).

We do not feel that the small differences in proportions between those

who had pulmonary function testing and those who did not have an SJLIFE on-campus evaluation would significantly change the results of this study. Had more of the nonparticipants been participants, the overall population might have included a smaller percentage that had undergone chest radiation therapy, possibly improving the overall pulmonary function of the study population, but would have included a larger percentage who had undergone hematopoietic stem cell transplants, possibly worsening the pulmonary function of the overall population. Because radiation exposure was extrapolated from a dosimetric assessment of a sample of the study population, some degree of misclassification of radiation dose to the lungs may have occurred.

Finally, we lack data regarding spine mobility in our population, a factor that has been related to restrictive pulmonary defects in patients with ankylosing spondylitis (51, 52). Radiation-related impairment of spinal mobility and scoliosis (53) may represent additional factors producing or exacerbating

pulmonary function impairments in childhood cancer survivors.

Conclusions

In summary, we report that restrictive lung defects are present in approximately one-third, and diffusion defects in almost one-half, of childhood cancer survivors who receive pulmonary toxic therapy. These defects adversely impact functional capacity. Treatment of an increasing percentage of the lung with 10 Gy or more of radiation therapy is a significant risk factor. In future research, investigators should evaluate the impact of modifications aimed at restricting exposure to pulmonary toxic treatment modalities. Interventions designed to reduce the exposure of childhood cancer survivors to other pulmonary toxins, as well as the efficacy of increased aerobic exercise and decreased caloric intake for improving pulmonary function in childhood cancer survivors, should be evaluated. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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