Advances in Radiation Oncology (2020) **5**, 426-433

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Impact of Respiratory Developmental Stage on Sensitivity to Late Effects of Radiation in Pediatric Cancer Survivors

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Received 23 September 2019; revised 19 November 2019; accepted 4 December 2019

Abstract

Purpose: Pulmonary dysfunction is a prevalent and potentially debilitating late effect of pediatric cancer treatment. We postulated that age, as a surrogate for respiratory developmental status, might be associated with vulnerability to pulmonary injury.

Materials and Methods: Sixty-one children treated with lung radiation at our institution who had undergone a pulmonary function test (PFT) between 1995 and 2016 were analyzed. Data collection included age at diagnosis and treatment, radiation dose and location, spirometry, and plethysmography results. PFTs were normalized according to age, sex, height, and ethnicity, and transformed into standardized z-scores. Obstructive disease was defined as forced expiratory volume in 1 second z score/forced vital capacity z score < -1.645, restrictive as total lung capacity z score < -1.645, and abnormal diffusion as diffusing capacity of the lung for carbon monoxide z score < -1.645. We determined the incidence of PFT abnormalities in our population and estimated the relative risk of developing pulmonary abnormalities using models adjusted for age.

Results: At a mean age of 24 years (range, 12-31) and time from radiation of 9 years (range, 1-20), the cumulative incidence of any pulmonary abnormality was 34.4%. Among patients with an abnormal PFT, diffusing and restrictive abnormalities were most common (57.1% and 52.4%). When stratified by age at radiation treatment, 66.7% of patients <5 years had a PFT abnormality, compared with 47.6% for aged 5 to 13 and 20.6% for patients >13. Compared with patients >13 years, those <5 years and 5 to 13 years at radiation treatment had a significantly increased risk of an abnormal PFT with an odds ratio of 7.71 (95% confidence interval, 1.17, 51.06) and 3.51 (95% confidence interval, 1.06, 11.57), respectively ($P < .035$). Furthermore, this association remained when examining each type of abnormality ($P > .05$).

Conclusions: PFT abnormalities were common among our cohort of childhood cancer survivors treated with lung radiation. Younger age at treatment is associated with an increased risk of developing pulmonary dysfunction, presumably owing to developmental immaturity.

Sources of support: This work had no specific funding.

Disclosures: Dr Constine received speakers fee from Proton Therapy Cooperative Group in November 2018.

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https://doi.org/10.1016/j.adro.2019.12.002

Introduction

Advances in cancer therapy translate into 5-year survival rates of more than 80% for pediatric cancers.[1,2] Unfortunately, these lifesaving therapies are also responsible for a host of adverse health outcomes that develop years or even decades after completion of therapy. Radiation therapy (RT) is an integral part of the treatment of pediatric cancers but can cause pulmonary damage. Exposure of lung tissue to RT depends on treatment approaches that include targeted or large volume RT to the lungs (eg, as treatment for primary and metastatic tumors in the thorax), total body irradiation (eg, conditioning for stem cell transplant), and incidental exposures (eg, from treatment for solid tumors in adjacent areas). Consequently, pulmonary late effects are highly prevalent among pediatric cancer survivors, with an estimated cumulative incidence of pulmonary dysfunction at 81.3% by age 50.[3] Therapy-associated pulmonary dysfunction can compromise quality of life, or terminate it, although the incidence and prevalence are controversial owing to the paucity of investigations and heterogeneity of endpoints (eg, pulmonary function test results, imaging abnormalities, impaired function, or death).

The causality of lung disease is multifactorial and relates to toxic effects of radiation on the pulmonary parenchyma, airways, and chest wall. Lung development continues throughout childhood, with alveoli increasing in number and size and airways elongating at various rates.[4-6] Thus, irradiation can stunt lung development and result in abnormal size, structure, and functioning of the lung. In addition, radiation can interfere with chest wall development and restrict lung function and growth. The adverse effects of pediatric lung radiation have been investigated in prior studies and can manifest as radiation pneumonitis, obstructive lung disease, restrictive disease, and diffusion defect.[7,8] It is unclear, however, how specific stages of lung and musculoskeletal development, using age as a surrogate, may contribute to the vulnerability for pulmonary late effects.

The aim of our study was to examine the association between age at RT and pulmonary abnormalities. We hypothesized that exposure to RT at younger ages may have more severe effects on lung development as assessed by pulmonary function testing. We also sought to further explore the relationship of dose and irradiated volume to the various specific pulmonary toxicities.

Methods

Patients who received a diagnosis of cancer before 21 years of age and received RT to the thorax, upper abdomen, total abdomen, or total body between 1995 and 2016 were identified in our institution's departmental database. Demographics, disease, and treatment information were retrospectively collected from medical records. Specific treatment parameters ascertained included the dosage and volume of radiation (partial or whole lung), along with administration of pulmonary toxic chemotherapeutic agents such as bleomycin. The study was approved by the institutional review board at our institution (RSRB00063202).

The most recent data from pulmonary function tests (PFT) performed at least 6 months posttreatment were extracted from medical records. Spirometry, body plethysmography, and diffusing capacity of the lung for carbon monoxide (DLCO) were performed by the Pulmonary Function Laboratory at our institution according to American Thoracic Society protocols.[9-11] PFTs were performed using the Body Box 5500 (Morgan Scientific, Haverhill, MA). Spirometry values were normalized according to sex, age, height, and ethnicity. Plethysmography and diffusing capacity were normalized according to sex and height according to reference equations.[12] Measurements were converted to standard deviation (Z) scores to allow for comparison between tests. Pulmonary function parameters within 1.645 standard deviations above or below the mean predicted value were considered normal.

Restrictive disease was defined as total lung capacity (TLC) z score < -1.645. Obstructive disease was defined as forced vital capacity z score > -1.645, forced expiratory volume in 1 second (FEV_1) z score < -1.645, and FEV_1/forced vital capacity ratio z score < -1.645. Hyperinflation was defined as residual volume/TLC ratio z score $> +1.645$. Diffusion defect was defined as DLCOadj z score < -1.645.

Patients were stratified categorically by age for statistical analysis. Age groupings were selected as a surrogate for approximate developmental stage with age <5 years representing early pulmonary development, age >5 or <13 representing prepuberty, and age >13 representing puberty. Prescribed radiation dose was used for analysis as dose distribution measurements were not available for all patients.

Statistical analysis

Patient characteristics were compared among those with normal and abnormal pulmonary function using 2-sided t tests for continuous variables and χ^2 tests for categorical variables. Logistic regression was used to determine association between abnormal pulmonary function and age, in addition to other factors of interest such as radiation dose, bleomycin, location of radiation, and cancer diagnosis. A P value <.05 was considered significant for all analyses. All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

Table 1 Characteristics of patients with and without PFT abnormality

Analysis of patients with PFT abnormality	No abnormality	Any abnormality	*P* value
	40	21	
Sex			
Male	19 (47.5)	11 (52.4)	.717
Female	21 (52.5)	10 (47.6)	
Race			
White	37 (92.5)	14 (66.7)	.067
Black	1 (2.5)	2 (9.5)	
Asian	0 (0)	1 (4.8)	
Other	2 (5)	4 (19)	
Ethnicity			
Hispanic	4 (10)	4 (19)	.319
Non-Hispanic	36 (90)	17 (81)	
Primary diagnosis			
HL	30 (75)	7 (33.3)	.008
Leukemia	4 (10)	6 (28.6)	
Wilms	2 (5)	2 (9.5)	
CNS tumor	1 (2.5)	0 (0)	
Rhabdomyosarcoma	0 (0)	1 (4.8)	
Neuroblastoma	0 (0)	2 (9.5)	
Ewing sarcoma	0 (0)	1 (4.8)	
Other	3 (7.5)	2 (9.5)	
Lung metastasis	7 (17.5)	4 (19)	.881
Average age at PFT (SD)	17.85 (4.64)	18.86 (4.75)	.427
Age at radiation			
Mean (SD)	13.48 (4.63)	11.48 (6.49)	.172
<5	2 (5)	4 (19.1)	.026
>5 or <13	11 (27.5)	10 (47.6)	
>13	27 (67.5)	7 (33.3)	
Average no. of years posttreatment at PFT (SD)	4.5 (3.67)	7.22 (6.34)	.037
Bleomycin exposure	29 (72.5)	7 (33.3)	.003
Location of lung radiation			
Whole	11 (27.5)	10 (47.6)	.116
Partial	29 (72.5)	11 (52.4)	
Prescribed dose of radiation (cGY)			
Mean (SD)	2,028.28 (538.05)	1,854.29 (995.73)	.378
<20 Gy	11 (27.5)	13 (61.9)	.008
>20 Gy	29 (72.5)	8 (38.1)	
Bone marrow transplant	7 (17.5)	10 (47.6)	.012

Abbreviations: CNS = central nervous system; HL = Hodgkin lymphoma; PFT = pulmonary function test; SD = standard deviation.

Results

Patient characteristics

A total of 136 patients treated with lung-exposing radiation were identified. Of these, 61 (44.9%) had PFT results available for review. Demographic, diagnosis, and treatment information were similar between patients with and without a PFT; however, patients with a PFT available more often received bleomycin ($P < .001$) or had a diagnosis of Hodgkin lymphoma ($P < .024$, Table E1, available at https://doi.org/10.1016/j.adro.2019.12.002). Only patients with at least one PFT were included in these analyses.

Mean age at RT was 12.7 years (range, 1.1-22.3 years), and mean age at most recent PFT was 18.2 years (range, 7-27 years). The most frequent diagnoses were Hodgkin lymphoma (60.7%) and leukemia (16.4%). The average prescribed dose of radiation was 19.7 ± 7.25 Gy (range, 10.5-50.4 Gy), and 36.1% of patients received radiation to the whole lung and 67.2% received partial lung radiation. Thirty-six (59%) children received bleomycin. Compared with those <5 years and 5 to 13 years, patients >13 years at treatment more often received a radiation dose >20 Gy ($P < .001$), more frequently received bleomycin ($P < .001$), and were more likely to have a primary diagnosis of Hodgkin lymphoma ($P < .001$). Patients >5 years at treatment more often received partial lung radiation compared with those <5 years (data not shown).

Table 2 Characteristics of patients by type of PFT abnormality

Analysis of patients with PFT abnormality	Diffusing abnormality	Restrictive	Obstructive	*P* value
	12	11	5	
Primary diagnosis				
HL	5 (41.7)	4 (36.3)	2 (40)	.856
Leukemia	4 (33.3)	2 (18.2)	1 (20)	
Other	3 (25)	5 (45.5)	2 (40)	
Average age at PFT (mean [SD])	17.2 (5.02)	17.4 (4.72)	19.6 (5.41)	.888
Age at radiation				
Mean (SD)	14.63 (6.24)	12.19 (7.38)	9.8 (5.66)	.851
<5	2 (16.7)	2 (18.2)	1 (20)	.997
>5 or <13	6 (50)	5 (45.5)	2 (40)	
>13	4 (33.3)	4 (36.3)	2 (40)	
Average no. of years posttreatment at PFT (mean [SD])	5.38 (5.73)	5.6 (7.08)	7.05 (5.6)	.874
Bleomycin exposure				
Yes	5 (41.7)	4 (36.3)	2 (40)	.996
No	7 (58.3)	7 (63.6)	3 (60)	
Location of lung radiation				
Whole	5 (41.7)	5 (45.5)	1 (20)	.611
Partial	7 (58.3)	6 (54.5)	4 (80)	
Prescribed dose to lung				
Mean (SD)	2,032.5 (1,188.21)	2,298 (1,609)	1,779.55 (603.82)	.923
<20 Gy	7 (58.3)	6 (54.5)	2 (40)	.785
>20 Gy	5 (41.7)	5 (45.5)	3 (60)	

Patients may have more than one PFT abnormality.
Abbreviations: HL = Hodgkin lymphoma; PFT = pulmonary function test; SD = standard deviation.

PFTs

Abnormal PFTs were found in 21 out of 61 (34.4%) patients, and 6 out of 61 (10%) had multiple PFT abnormalities (Table 1). Among patients with an abnormal PFT, diffusing and restrictive abnormalities were the most common (57.1% and 52.4%, respectively; Table 2). Obstructive disease was present in 23.8% of those with an abnormal PFT. The characteristics of survivors with abnormal PFTs are shown in Table 1. When stratified by age at treatment, 66.7% of patients <5 years had a PFT abnormality, compared with 47.6% for aged 5 to 13 and 20.6% for patients >13 at treatment (Fig 1). Among the 21 patients with PFT abnormalities, 19% were <5 years of age, whereas 5% of those without PFT abnormalities were <5 years old. In comparison, of the patients with abnormalities, 33% were >13 years old and 67.5% of those without PFT abnormalities were >13 years of age. In addition, patients with a PFT abnormality were more likely to have received whole lung radiation (47.6% vs 27.5%, $P = .116$), a bone marrow transplant incorporating total body irradiation (TBI; 47.6% vs 17.5%, $P = .012$), and received <20 Gy (61.9% vs 27.5%, $P = .008$),

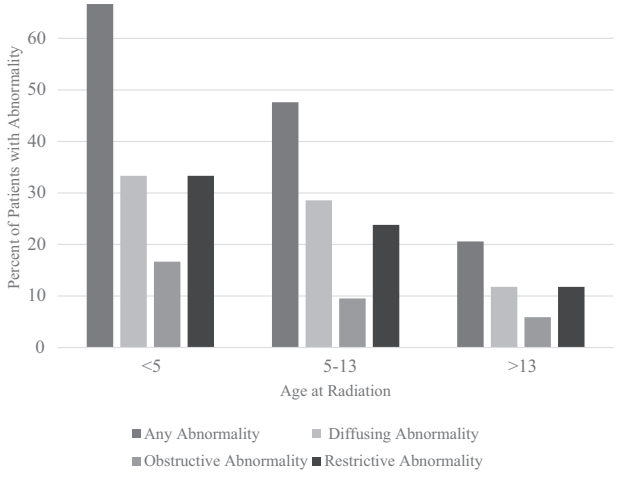

Figure 1 Prevalence of pulmonary function test abnormalities according to age at radiation treatment.

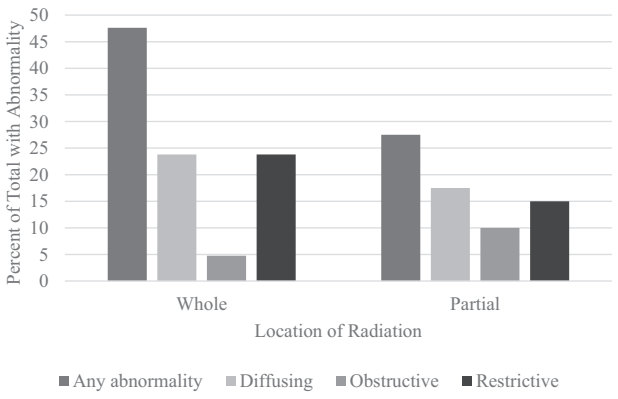

Figure 2 Prevalence of pulmonary function test abnormality by volume of lung radiation.

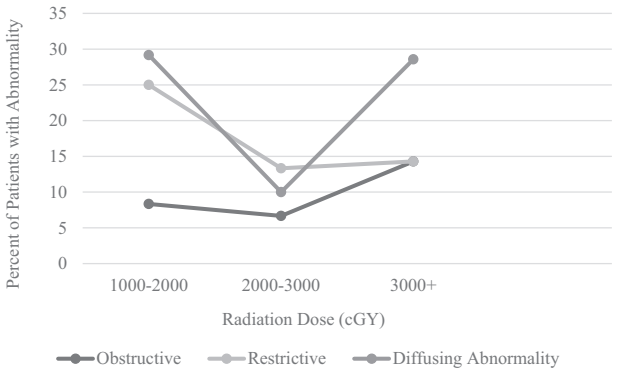

Figure 3 Prevalence of pulmonary function test abnormality according to radiation dose.

in large part owing to the lower doses used with whole lung RT/TBI compared with localized RT that included portions of the lungs. Patients with a PFT abnormality were less likely to have received bleomycin (33.3% vs 72.5%, $P = .003$).

There was no significant difference in the distribution of obstructive, restrictive, and diffusing abnormality according to age group. When stratified by whole and partial lung radiation, 47.6% of patients with whole lung radiation had a PFT abnormality compared with 27.5% of patients who received partial lung radiation (Fig 2). Notably, when we conducted sensitivity analyses restricted to survivors who received whole lung RT, the association between younger age and risk of pulmonary dysfunction was attenuated and no longer significant (likely owing to limited sample size, data not shown, $P = .95$). However, it does appear that patients most vulnerable to RT-associated pulmonary injury were those treated to relatively lower doses that generally included the whole lung, or to higher doses to a portion of the lungs (Fig 3).

Compared with patients >13 years, those <5 years and 5 to 13 years at RT had a significantly increased risk of an abnormal PFT as follows: odds ratio [OR] 7.71 (95% confidence interval [CI], 1.17-51.06) and 3.51 (95% CI, 1.06-11.57), respectively ($P < .035$ [Table 3]), although statistical significance was lost after adjustment for bleomycin use and time since RT. In exploratory analyses examining each type of abnormality, a similar trend was seen but not statistically significant (Table 3).

Discussion

Pulmonary dysfunction is prevalent among pediatric cancer survivors who receive radiation to the lung as part of their treatment regimen. In our cohort, more than a third of patients had pulmonary function abnormalities, which in several cases persisted for years (average time between treatment and PFT was 5.44 years). Diffusing capacity was the most common PFT abnormality, followed by restrictive disease. Pulmonary dysfunction more commonly afflicted children who were treated with lung radiation at a young age.

Our findings are consistent with several studies describing the high prevalence of pulmonary dysfunction in pediatric cancer survivors in which 20% to 100% of childhood cancer survivors treated with radiation demonstrate some pulmonary dysfunction.[3,13-16] Littman et al demonstrated that pediatric patients with Wilms tumor treated with whole lung irradiation had a lower VC, TLC, and FEV_1 compared with those who did not receive irradiation.[17] A reduction in FVC, FEV_1, TLC, and DLCO has previously been documented in pediatric patients who received whole lung irradiation for treatment of metastatic disease and solid malignancies.[18,19] These findings suggest a relationship between whole lung irradiation and the development of restrictive and diffusing abnormalities. Restrictive disease is likely a result of restricted chest wall growth and parenchymal changes, and radiation-induced changes in the lung parenchyma and exposure to pulmonary toxic chemotherapy can result in abnormal diffusing capacity.

In analyzing the contribution of age at lung radiation to the development of pulmonary dysfunction, we identified increased odds of developing pulmonary late effects in children <13 years at time of radiation. Our findings support previous studies reporting an increased risk for pulmonary dysfunction in patients treated at age <5 years.[20-22] Kaplan et al found that children treated at age >8 years had significantly more abnormalities compared with younger children.[23] However, this study had fewer patients and exclusively studied those treated for rhabdomyosarcoma. Our study further explored the age-related risk and found that children <5 years at time of lung radiation had about 7 times the odds of developing pulmonary dysfunction relative to those treated at age >1. However, this association was no longer statistically significant after adjustment for bleomycin exposure and time from RT. This trend remained for each type of abnormality but was not statistically significant, as we were likely underpowered to identify these associations. Of note, when age was analyzed as a continuous variable, the results were skewed owing to fewer patients at the higher end of the age spectrum.

Given that childhood is a period of rapid growth and development, the late effects of therapeutic radiation are likely related to the patient's developmental age. Airways are formed early in gestation, and during childhood they increase in length and radius.[24] Alveolar multiplication occurs most rapidly in the first few years of life, with slower growth in the number of alveoli into adolescence.[4]

Table 3 Multivariable logistic regression evaluating the association of age at radiation with PFT abnormality

	N	Any abnormality OR (95% CI)	Diffusing abnormality OR (95% CI)	Restrictive abnormality OR (95% CI)	Obstructive abnormality OR (95% CI)
N		21	12	11	5
Crude model					
Age at RT					
<5 y	6	7.71 (1.17-51.06)*	3.75 (0.51-27.50)	3.75 (0.51-27.50)	3.20 (0.24-42.19)
>5 or <13	21	3.51 (1.06-11.57)*	3.00 (0.73-12.27)	2.34 (0.55-9.97)	1.68 (0.22-12.96)
>13	34	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Model adjusted for time since treatment					
Age at RT					
<5 y	6	4.45 (0.38-51.79)	4.27 (0.28-64.08)	2.22 (0.15-33.44)	11.35 (0.20-634.6)
>5 or <13	21	3.09 (0.86-10.77)	3.09 (0.71-13.45)	2.06 (0.45-9.51)	2.10 (0.26-16.98)
>13	34	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Model adjusted for time since treatment and bleomycin exposure					
Age at RT					
<5 7	6	1.91 (0.13-29.04)	3.64 (0.18-72.86)	1.26 (0.06-25.63)	6.57 (0.08-571.7)
>5 or <13	21	1.63 (0.35-7.58)	2.74 (0.46-16.18)	1.30 (0.19-8.72)	1.44 (0.11-19.21)
>13	34	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)

Abbreviations: CI = confidence interval; OR = odds ratio; PFT = pulmonary function test; RT = radiation therapy; SD = standard deviation.
* Indicates statistical significance ($P < .05$).

After this period of rapid multiplication, lung volume increases primarily by increase in alveolar volume. Radiation can interfere with alveolar development by impairing cell proliferation or by interfering with vascular supply.[25] In addition, radiation can interfere with the skeletal, muscle, and cartilage growth of the thorax.[26] These alterations can affect the ultimate size and mechanics of the lung.

In addition to age-related susceptibility, differences in treatment and diagnosis likely explain some differences in PFTs. Hodgkin lymphoma was common in our older patients, and younger patients were more frequently diagnosed with sarcomas, Wilms tumor, and leukemia; these diagnoses dictated differences in dosimetric risk factors (volume, prescribed dose) and chemotherapy exposure. Previous studies have described the relationship between mean lung dose and pulmonary late effects, with increasing doses significantly associated with dysfunction.[27-29] In our study, total prescribed radiation dose was grouped into <20 Gy and >20 Gy bins in accordance with prior studies demonstrating increased development of pulmonary dysfunction in patients who received chest radiation at doses >20 Gy.[8,27,30] Older children were more commonly treated with partial lung RT that would typically involve doses greater than that to the whole lung (eg, for pulmonary metastases) or TBI; however, the whole lung doses are still typically 12 to 15 Gy, and this combination of large volume and moderate dose may partially explain the greater incidence of pulmonary toxicity in the younger patients in addition to the pulmonary or chest wall developmental immaturity. In addition, the pulmonary toxic effects of bleomycin are well documented.[21,31] The risk of pulmonary late effects was lower in children who received bleomycin. Patients who received bleomycin were more often older and received partial lung radiation, suggesting that the volume of RT was more relevant to impairment of PFTs than was bleomycin administration. This likely explains the apparent protective effect of bleomycin, which has been noted in previous studies.[21] Larger studies are needed to clarify the effect of age-related susceptibility and treatment. However, our study does parallel a finding in a recent study of cardiotoxicity in children: small doses to large volumes or large doses to small volumes are most relevant to subsequent toxicity.[32]

Conclusions

The limitations of our study are the limited number of postradiation PFTs and the retrospective study design. There may have been a selection bias for patients who underwent PFT, possibly related to hospitalization or symptoms resulting in overestimation of the prevalence of pulmonary dysfunction. However, many of the patients were treated on Children's Oncology Group protocols recommending screening PFTs posttreatment, regardless of symptoms. The strengths of this study include the inclusion of patients with all cancer diagnoses involving treatment with lung radiation. The broad study period

allowed for analysis of the long-term outcomes of pulmonary radiation over many years after radiation and identified the persistence of PFT abnormalities in our patients. Lastly, we were able to use age as a surrogate to analyze the contribution of lung developmental stage to the vulnerability for pulmonary late effects.

The significance of this study lies in recognizing the high prevalence of pulmonary dysfunction in pediatric cancer survivors, particularly those very young at diagnosis. As pediatric cancer survival rates increase, these pulmonary abnormalities may have long-term consequences as patients age. Early detection of pulmonary function abnormalities in this patient population may allow for more rapid and targeted intervention. Certainly, all efforts should be made to minimize radiation dose and volume, especially in younger children. Unanswered is the question of the relative toxicity of low doses to large lung volumes compared with high doses to small lung volumes in developing children. Additional study of the vulnerability of developing children to pulmonary toxic therapy is clearly warranted to inform therapeutic decision making.

Acknowledgments

The authors thank Mrs Laura Finger for editorial assistance.

Supplementary data

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2019.12.002.

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