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Long-term Pulmonary Outcomes in Pediatric Survivors of High-Risk Neuroblastoma

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Abstract

Background—Children with high-risk neuroblastoma (NB) are exposed to multimodality therapies early in life and survivors confront late therapy-related toxicities. This study assessed respiratory symptoms, pulmonary function tests (PFTs), and risk factors for abnormalities among survivors.

Methods—High-risk NB survivors followed in the Long-term Follow-up clinic at Memorial Sloan Kettering Cancer Center were enrolled. Self-administered symptom questionnaires were completed. Medical records were reviewed for treatment information and co-morbidities. PFTs included spirometry, plethysmography, and diffusion capacity of the lung for carbon monoxide (DLCO).

Results—Thirty nine survivors participated (median age at study: 11.4 years; median age at diagnosis: 2.3 years; median time since completion of therapy: 5.5 years). Chronic respiratory symptoms were reported for 33%. PFT abnormalities were identified in 79% and included low forced expiratory volume in 1 second (FEV1) (38%), decreased total lung capacity (TLC) (44%), and abnormal DLCO (67%). PFT abnormalities were mostly mild to moderate. Mean forced vital capacity, forced expiratory volume in 1 second, and total lung capacity were normal and mean DLCO was mildly abnormal. Risks included thoracic surgery, chest radiation therapy (RT), thoracic surgery plus chest RT, and shorter time since completion of therapy ($p<0.05$).

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Conclusions—While respiratory abnormalities were common, they were mostly mild or moderate. Continued pulmonary surveillance of this at-risk population is warranted.

Keywords

neuroblastoma; pulmonary function tests; risk factors; respiratory symptoms; survivors; antineoplastic therapy

Introduction

With advances in cancer therapies, there is a growing population of survivors of childhood cancer.^{1, 2} Data from the Childhood Cancer Survivor Study demonstrate that survivors have an increased risk of lung fibrosis, recurrent pneumonia, chronic cough, pleurisy, requirement for supplemental oxygen, and exercise-induced shortness of breath more than five years post-diagnosis.^{3, 4} Increased mortality due to pulmonary causes among cancer survivors has also been reported.⁵ Limited information is available on pulmonary outcomes in survivors of high-risk neuroblastoma (NB).^{6–8}

Studies investigating late effects of cancer therapies have linked specific chemotherapeutic agents, radiation therapy (RT), and hematopoietic stem cell transplant (HSCT) to late pulmonary toxicities.^{3, 9–27} Late respiratory complications of anti-neoplastic treatments have been described in children.^{8–23, 25} Additionally, studies have suggested that exposure to some cancer therapies very early in life may increase the risk for long-term sequelae.^{13, 28}

Children with high-risk NB are exposed to multimodality therapies very early in life, and may therefore have a higher risk for developing pulmonary complications including subclinical abnormalities in lung function. Pulmonary outcomes among high-risk NB survivors have not been well-described and results of pulmonary function testing (PFTs) in long-term survivors of NB are limited. This study aimed to examine late pulmonary outcomes and measure PFTs among a large group of high-risk NB survivors followed at a single institution with the hypothesis that chronic respiratory symptoms and abnormalities in lung function are common and specific risk factors may predict late respiratory abnormalities.

Materials and Methods

This was a cross sectional study that assessed respiratory conditions and PFTs among pediatric survivors of high-risk NB. Children aged 6–21 years who had survived high-risk NB (stage 3 or 4), were alive and disease free at least one year after completion of treatment, were evaluated at least once in the Long-term Follow-up (LTFU) clinic at Memorial Sloan Kettering Cancer Center (MSKCC) between 2012–2015, and were able to cooperate with the testing procedures were eligible for study participation.

Demographic data and therapeutic exposures were abstracted from the MSKCC medical record. Radiation therapy to the chest included the mediastinum, chest wall, thoracic spine, and whole lungs. Thoracic surgery was defined as thoracotomy for tumor or lymph node resection and/or resection of lung tissue, but did not include thoracoabdominal exploration

only. After providing informed consent, parents or guardians of study participants were asked to complete a self-administered questionnaire. Questions included assessments of (1) pulmonary conditions including chronic cough, shortness of breath, wheeze, bronchitis, pneumonia, and oxygen use, (2) history of allergy and asthma symptoms for the study participant and close family members, and (3) exposure to potential environmental triggers of respiratory disease. Questionnaires did not assess treatment exposures or therapies for lung disease other than use of supplemental oxygen. Chronic respiratory symptoms were defined as symptoms present with frequency ≥ 2 days per week or ≥ 2 nights per month for at least 3 months of the past year. Subjects who were 12 years or older completed an additional questionnaire regarding self-reported respiratory symptoms and/or environmental exposures in the month prior to the visit.

PFTs were assessed at the Pediatric PFT laboratory at Weill Cornell Medical College. Spirometry, plethysmography, and diffusion capacity of the lung for carbon monoxide (DLCO) were measured (Vmax Encore, Viasys, Yorba Linda, CA). DLCO was assessed using the single breath method. Airway responsiveness was tested by repeating spirometry 15 minutes after albuterol administration. National Health and Nutrition Examination Survey III reference equations by ethnic group were used to generate percent predicted values.²⁹ Normal PFT parameters were defined as percent predicted values ≥ 80 . Definitions of PFT abnormalities adhered to the American Thoracic Society (ATS)/European Respiratory Society guidelines.²⁹ Abnormalities in forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1) were defined by percent predicted values as follows: (1) mild: 70–79; (2) moderate: 60–69; (3) moderately severe: 50–59; (4) severe: 35–49; (5) very severe: <35 .²⁹ Abnormalities in total lung capacity (TLC) were defined by percent predicted values as follows: (1) mild: 70–79; (2) moderate: 60–69; (3) severe: <60 . Abnormalities in DLCO were defined by percent predicted values as follows: (1) mild: 61–79; (2) moderate: 40–60; (3) severe: <40 .²⁹ Obstructive disease was defined as $FEV1/FVC < 0.8$. Restrictive disease was defined by percent predicted $TLC < 80$.

Descriptive statistics were calculated for demographic and treatment variables and medical complications including PFT abnormalities. Bivariate analyses were employed to determine associations between potential risk factors, such as age at treatment and time since completion of therapy, and PFT abnormalities and/or respiratory symptoms using two-sample t-test, χ^2 or Fisher's exact tests as appropriate. All statistical tests were 2-sided, with a significance level of $P < 0.05$. Unadjusted odds ratios and 95% confidence intervals were not computed due to small or zero cell counts for a number of the bivariate analyses. Row percentages were calculated instead. All analyses were conducted with SAS version 9.3 (SAS Institute, Inc., Cary, NC).

The study was approved by the institutional review boards at Weill Cornell Medical College and MSKCC.

Results

A total of 214 neuroblastoma survivors aged 6–21 years are followed in the LTFU clinic; the majority of survivors were treated for high-risk NB. Thirty-nine survivors of high-risk NB

were enrolled in the study. No subjects were excluded from participation due to developmental delay or behavioral issues. Study participants were diagnosed between 1996 and 2009. Characteristics of study participants are shown in Table 1. Chronic respiratory symptoms were reported for 33% of the subjects and included exercise-induced respiratory symptoms (n=16), cough (n=10), congestion/phlegm (n=5), shortness of breath (n=5), and wheeze (n=4). A physician-diagnosed respiratory condition at any time was reported for 38% and included asthma (n=8), recurrent pneumonia (n=4), pulmonary fibrosis or “scarring” (n=2), and use of supplemental oxygen (n=4).

Among the 14 study participants 12 years old, 93% reported respiratory symptoms in the past month. The frequency of respiratory symptoms included every day (29%), several days in a week (21%), a few days of the month (29%), and only when sick with a cold (14%). Self-reported respiratory symptoms included cough (12/14), shortness of breath (7/14), congestion/phlegm (8/14), wheeze (2/14), and exercise-induced symptoms (2/14). While no adolescent survivors of NB reported that they smoke, 13% of all study participants had exposure to cigarette smoke in the home.

PFT abnormalities were noted in 79% of participants. Restriction was identified in 41%, obstruction in 8%, and mixed obstructive and restrictive defect in 3%. The most common abnormalities were low FEV1 (38%), decreased TLC (44%), and reduced DLCO (67%). The number of subjects with abnormal lung function parameters by severity can be seen in Table 2. There were no associations between chronic respiratory symptoms and abnormal PFT parameters.

In bivariate analysis, a number of risk factors were associated with PFT abnormalities as seen in Table 3. Significant associations were seen between subjects treated with thoracic surgery and decreased FVC (100.0% versus 39.4% for thoracic surgery vs. no thoracic surgery, respectively; $P=0.008$) and FEV1 (83.3% versus 30.3% for thoracic surgery vs. no thoracic surgery, respectively; $P=0.024$), chest RT and decreased FVC (85.7% versus 40.6% for chest RT vs. no chest RT, respectively; $P=0.044$), and thoracic surgery plus chest RT and decreased FVC (100.0% versus 42.9% for thoracic surgery plus chest RT vs. no thoracic surgery plus chest RT, respectively; $P=0.047$) and FEV1 (100.0% versus 31.4% for thoracic surgery plus chest RT vs. no thoracic surgery plus chest RT, respectively; $P=0.020$). There were no associations between thoracic surgery, chest RT, or thoracic surgery plus chest RT and abnormal TLC. There were weak associations between chest RT and decreased FEV1 (71.1% versus 31.3% for chest RT vs. no chest RT, respectively; $P=0.085$) and DLCO (100.0% versus 67.7% for chest RT vs. no chest RT, respectively; $P=0.157$), as well as HSCT and low FEV1 (50.0% vs. 23.5% for HSCT vs. no HSCT, respectively; $P=0.092$). Participants with normal DLCO had longer time intervals since completion of their cancer therapy compared to those with abnormal DLCO (8.34 compared to 5.73 years respectively; $P=0.033$).

As seen in Table 4, subjects exposed to thoracic surgery had decreased mean FVC compared to subjects with no thoracic surgery ($P=0.052$) and those treated with chest RT had lower mean TLC compared to subjects with no chest RT ($P=0.054$). Subjects exposed to each potential risk factor (compared to the absence of the risk factor), other than smoking, had

lower mean FVC and FEV1 (statistical trends indicated; $P = 0.200$). Subjects exposed to thoracic surgery (compared to no thoracic surgery) and thoracic surgery plus chest RT (compared to no thoracic surgery plus chest RT) had decreased mean TLC (statistical trends indicated; $P=0.060$ and $P=0.090$, respectively).

In addition, there were significant associations between treatment exposures and respiratory symptoms and conditions as seen in Table 5. Parents of subjects treated with HSCT were more likely to report chronic shortness of breath (23.8% vs. 0.0% for HSCT vs. no HSCT, respectively; $P=0.053$). Exposure to cigarette smoke in the home was associated with chronic respiratory symptoms (80.0% vs. 27.3% for cigarette smoke vs. no cigarette smoke, respectively; $P=0.038$), with a weaker association with a physician-diagnosed chronic respiratory condition (80.0% vs. 33.3% for cigarette smoke vs. no cigarette smoke, respectively; $P=0.063$). No associations between the age at diagnosis or cyclophosphamide dose and PFT abnormalities or reported chronic respiratory symptoms or conditions were seen.

Discussion

Here we report the late pulmonary toxicities among pediatric survivors of high-risk NB. Respiratory conditions and mild and moderate PFT abnormalities were common in this cohort. Risk factors for respiratory abnormalities included treatment with thoracic surgery, chest RT, thoracic surgery plus chest RT, and shorter time since completion of therapy.

Approximately one-third of subjects reported chronic respiratory symptoms in the past year and the presence of a physician-diagnosed respiratory condition ever. This differs from a prior study that described respiratory symptoms among two thirds of pediatric survivors of high-risk NB, with 3/18 reporting severe respiratory symptoms.⁸ These patients were treated in the late 1980s with high-dose chemotherapy, total body irradiation (TBI), and autologous HSCT.⁸ While the number of subjects in the earlier study is small, the higher prevalence of respiratory symptoms may suggest that newer treatment modalities are less likely to cause severe pulmonary toxicity. Notably, no subjects in our cohort received TBI and only one subject was treated with whole lung irradiation, both of which have been associated with late adverse pulmonary outcomes.^{16, 27, 30} While 93% of adolescent subjects in our cohort reported respiratory symptoms in the past month, only half (7/14) reported frequent symptoms (daily or several days of the week). Adolescent questionnaires did not ask about self-reported chronic respiratory symptoms, preventing a direct comparison with parental-reported data.

PFT abnormalities were common in our study, corresponding with long-term follow-up studies of adult survivors of childhood cancer.^{31, 32} Interestingly, in this cohort, PFT impairments were mostly mild to moderate in severity. The most common abnormality was decreased DLCO. Decreased DLCO was associated with shorter times since completion of therapy, which suggests that diffusion capacity may improve over time. This may reflect transient interstitial lung disease related to cancer therapies versus a transient reduction in lung volume, although a similar relationship between TLC and time since completion of therapy was not seen. A similar pattern of normalization of impaired DLCO from six months

to four years following treatment for stage 4 NB with high-dose chemotherapy, total body irradiation, and autologous HSCT was previously seen.⁸ Mild transient declines in DLCO have also been reported in children with other forms of neoplastic disease treated with HSCT.^{14, 18} Recent data from adult survivors of childhood cancer reveal a decline in DLCO over more extended time periods (median 17–22 years since diagnosis, respectively).^{32, 33}

Pulmonary toxicities have been associated with anti-neoplastic agents and HSCT in multiple populations with neoplastic disease. Chest RT as well as chemotherapeutic agents such as bleomycin, mitomycin-C, carmustine, busulfan, and cyclophosphamide can cause pneumonitis and interstitial lung injury acutely in addition to pulmonary fibrosis and other lung toxicities over time.^{3, 8–22} Multiple studies have reported late PFT abnormalities after HSCT,^{14–26} and lung function impairment has been described among pediatric patients.^{8–23, 25} Here we identified weak associations between HSCT and chronic shortness of breath as well as abnormal FVC and FEV1. Additionally, exposure to thoracic surgery, chest RT, and thoracic surgery plus chest RT were associated with abnormal lung function. There were weak associations between chest RT and PFT abnormalities. Chest RT was previously identified as a risk factor for developing pulmonary problems among advanced stage NB survivors⁶ and is a risk factor for abnormal PFTs among adult survivors of childhood cancer.^{31–33} The small number of subjects treated with chest RT in our cohort may have limited our power to detect any significant associations with PFT abnormalities.

We did not find an association between age at diagnosis and respiratory symptoms or PFT abnormalities. Earlier studies in other pediatric cancer populations have identified associations between age at treatment exposure and late pulmonary outcomes,³³ including associations between exposure to carmustine therapy at a young age and severe pulmonary fibrosis and increased mortality¹³ as well as chest RT at a young age and PFT abnormalities.¹⁰ In addition, studies of adult survivors of childhood cancer have revealed associations between age at diagnosis and PFT abnormalities.^{32, 33} The absence of similar findings in our cohort may again be related in part to the small number of subjects treated with chest RT.

It is reassuring that none of the adolescent survivors of high-risk NB in this study self-reported smoking cigarettes although this may not accurately reflect behavior patterns. We found chronic respiratory symptoms to be more common among children exposed to second hand smoke at home although the exposure group was small. Studies of adult survivors of childhood cancer reveal lower smoking rates than in the general population^{4, 34, 35} and minor differences in smoking prevalence based on exposure to cardiopulmonary toxic therapies; this suggests differences in behavior based on perceived risk.³⁴ Further studies are needed to determine if knowledge of subclinical decreases in PFT parameters prevent smoking initiation among adolescent or young adult survivors of high-risk NB.

Limitations to this study include the use of non-validated questionnaires. Additionally, 62% of subjects were enrolled in the summer months, perhaps leading to an under-reporting of chronic respiratory symptoms. Adolescent questionnaires collected data on respiratory symptoms present in the past month, thereby preventing a direct comparison to parental-reported chronic respiratory symptoms. The cross-sectional design of this study prevents any

conclusions regarding patterns in lung function over time. The small number of subjects in this cohort limited the risk factor analyses. The role of exposure to specific alkylating drugs could not be assessed because a large number of subjects were exposed to many of the same agents. Similarly, the role of immunotherapy on pulmonary outcomes could not be studied since all but two subjects were treated with either anti-GD2 antibody alone or in conjunction with GD2/GD3 vaccine. The significance of the association between thoracic surgery and chest RT and decreased forced flow rates is unclear given the absence of associations with decreased TLC. In addition, the small number of study subjects did not allow for multivariate analyses of potential confounders. Moreover, not all survivors are followed at the LTFU clinic and this small cohort of survivors may not be representative of survivors overall.

Late pulmonary sequelae in children following treatment for high-risk NB early in life are common. Almost all children in this study had abnormal PFTs and one-third reported chronic respiratory symptoms. Survivors of high-risk NB should be screened for respiratory symptoms and PFT abnormalities. Further studies, including longitudinal assessments of lung function and measurements of exercise capacity are needed to better characterize the true extent of pulmonary disabilities in this at-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol*. 2010; 28(15): 2625–2634. [PubMed: 20404250]
2. Hampton T. Cancer survivors need better care: new report makes recommendations. *JAMA*. 2005; 294(23):2959–2960. [PubMed: 16414936]
3. Mertens AC, Yasui Y, Liu Y, Stovall M, Hutchinson R, Ginsberg J, et al. Pulmonary complications in survivors of childhood and adolescent cancer. A report from the Childhood Cancer Survivor Study. *Cancer*. 2002; 95(11):2431–2441. [PubMed: 12436452]
4. Dietz AC, Chen Y, Yasui Y, Ness KK, Hagood JS, Chow EJ, et al. Risk and impact of pulmonary complications in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study. *Cancer*. 2016; 122(23):3687–3696. [PubMed: 27504874]
5. Mertens AC, Yasui Y, Neglia JP, Potter JD, Nesbit ME Jr, Ruccione K, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the Childhood Cancer Survivor Study. *J Clin Oncol*. 2001; 19(13):3163–3172. [PubMed: 11432882]
6. Laverdiere C, Cheung NK, Kushner BH, Kramer K, Modak S, LaQuaglia MP, et al. Long-term complications in survivors of advanced stage neuroblastoma. *Pediatr Blood Cancer*. 2005; 45(3): 324–332. [PubMed: 15714447]

7. Laverdiere C, Liu Q, Yasui Y, Nathan PC, Gurney JG, Stovall M, et al. Long-term outcomes in survivors of neuroblastoma: a report from the Childhood Cancer Survivor Study. *J Natl Cancer Inst.* 2009; 101(16):1131–1140. [PubMed: 19648511]
8. Neve V, Foot AB, Michon J, Fourquet A, Zucker JM, Boule M. Longitudinal clinical and functional pulmonary follow-up after megatherapy, fractionated total body irradiation, and autologous bone marrow transplantation for metastatic neuroblastoma. *Med Pediatr Oncol.* 1999; 32(3):170–176. [PubMed: 10064183]
9. Abid SH, Malhotra V, Perry MC. Radiation-induced and chemotherapy-induced pulmonary injury. *Curr Opin Oncol.* 2001; 13(4):242–248. [PubMed: 11429481]
10. Benoist MR, Lemerle J, Jean R, Rufin P, Scheinmann P, Paupe J. Effects of pulmonary function of whole lung irradiation for Wilm's tumour in children. *Thorax.* 1982; 37(3):175–180. [PubMed: 6285541]
11. Ginsberg SJ, Comis RL. The pulmonary toxicity of antineoplastic agents. *Semin Oncol.* 1982; 9(1):34–51. [PubMed: 6176027]
12. O'Driscoll BR, Hasleton PS, Taylor PM, Poulter LW, Gattamaneni HR, Woodcock AA. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. *N Engl J Med.* 1990; 323(6):378–382. [PubMed: 2370889]
13. O'Driscoll BR, Kalra S, Gattamaneni HR, Woodcock AA. Late carmustine lung fibrosis. Age at treatment may influence severity and survival. *Chest.* 1995; 107(5):1355–1357. [PubMed: 7750330]
14. Kaya Z, Weiner DJ, Yilmaz D, Rowan J, Goyal RK. Lung function, pulmonary complications, and mortality after allogeneic blood and marrow transplantation in children. *Biol Blood Marrow Transplant.* 2009; 15(7):817–826. [PubMed: 19539213]
15. Barisione G, Bacigalupo A, Crimi E, Van Lint MT, Lamparelli T, Brusasco V. Changes in lung volumes and airway responsiveness following haematopoietic stem cell transplantation. *Eur Respir J.* 2008; 32(6):1576–1582. [PubMed: 18684842]
16. Weiner DJ, Maity A, Carlson CA, Ginsberg JP. Pulmonary function abnormalities in children treated with whole lung irradiation. *Pediatr Blood Cancer.* 2006; 46(2):222–227. [PubMed: 15926160]
17. Cerveri I, Fulgoni P, Giorgiani G, Zoia MC, Beccaria M, Tinelli C, et al. Lung function abnormalities after bone marrow transplantation in children: has the trend recently changed? *Chest.* 2001; 120(6):1900–1906. [PubMed: 11742920]
18. Quigley PM, Yeager AM, Loughlin GM. The effects of bone marrow transplantation on pulmonary function in children. *Pediatr Pulmonol.* 1994; 18(6):361–367. [PubMed: 7892070]
19. Hoffmeister PA, Madtes DK, Storer BE, Sanders JE. Pulmonary function in long-term survivors of pediatric hematopoietic cell transplantation. *Pediatr Blood Cancer.* 2006; 47(5):594–606. [PubMed: 16086420]
20. Frisk P, Arvidson J, Bratteby LE, Hedenstrom H, Lonnerholm G. Pulmonary function after autologous bone marrow transplantation in children: a long-term prospective study. *Bone Marrow Transplant.* 2004; 33(6):645–650. [PubMed: 14688819]
21. Frisk P, Arvidson J, Hedenstrom H. A longitudinal study of pulmonary function after stem cell transplantation, from childhood to young adulthood. *Pediatr Blood Cancer.* 2012; 58(5):775–779. [PubMed: 21584939]
22. Efrati O, Toren A, Duskin H, Modan-Moses D, Bielora B, Goldstein G, et al. Pulmonary function studies in children treated by chemoradiotherapy and stem cell transplantation. *Pediatr Blood Cancer.* 2008; 51(5):684–688. [PubMed: 18698587]
23. Bruno B, Souillet G, Bertrand Y, Werck-Gallois MC, So Satta A, Bellon G. Effects of allogeneic bone marrow transplantation on pulmonary function in 80 children in a single paediatric centre. *Bone Marrow Transplant.* 2004; 34(2):143–147. [PubMed: 15170172]
24. Wieringa J, van Kralingen KW, Sont JK, Bresters D. Pulmonary function impairment in children following hematopoietic stem cell transplantation. *Pediatr Blood Cancer.* 2005; 45(3):318–323. [PubMed: 15747333]

25. Gower WA, Collaco JM, Mogayzel PJ Jr. Pulmonary dysfunction in pediatric hematopoietic stem cell transplant patients: non-infectious and long-term complications. *Pediatr Blood Cancer*. 2007; 49(3):225–233. [PubMed: 17029245]
26. Ferry C, Gemayel G, Rocha V, Labopin M, Esperou H, Robin M, et al. Long-term outcomes after allogeneic stem cell transplantation for children with hematological malignancies. *Bone Marrow Transplant*. 2007; 40(3):219–224. [PubMed: 17530002]
27. Venkatramani R, Kamath S, Wong K, Olch AJ, Malvar J, Sposto R, et al. Pulmonary outcomes in patients with Hodgkin lymphoma treated with involved field radiation. *Pediatr Blood Cancer*. 2014; 61(7):1277–1281. [PubMed: 24482138]
28. Oberfield SE, Chin D, Uli N, David R, Sklar C. Endocrine late effects of childhood cancers. *J Pediatr*. 1997; 131(1 Pt 2):S37–41. [PubMed: 9255226]
29. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005; 26(5):948–968. [PubMed: 16264058]
30. Armstrong GT, Stovall M, Robison LL. Long-term effects of radiation exposure among adult survivors of childhood cancer: results from the childhood cancer survivor study. *Radiat Res*. 2010; 174(6):840–850. [PubMed: 21128808]
31. Mulder RL, Thonissen NM, van der Pal HJ, Bresser P, Hanselaar W, Koning CC, et al. Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer. *Thorax*. 2011; 66(12):1065–1071. [PubMed: 21803931]
32. Green DM, Zhu L, Wang M, Ness KK, Krasin MJ, Bhakta NH, et al. Pulmonary function after treatment for childhood cancer. A report from the St. Jude Lifetime Cohort Study (SJLIFE). *Ann Am Thorac Soc*. 2016; 13(9):1575–1585. [PubMed: 27391297]
33. Armenian SH, Landier W, Francisco L, Herrera C, Mills G, Siyahian A, et al. Long-term pulmonary function in survivors of childhood cancer. *J Clin Oncol*. 2015; 33(14):1592–1600. [PubMed: 25847925]
34. Frobisher C, Winter DL, Lancashire ER, Reulen RC, Taylor AJ, Eiser C, et al. Extent of smoking and age at initiation of smoking among adult survivors of childhood cancer in Britain. *J Natl Cancer Inst*. 2008; 100(15):1068–1081. [PubMed: 18664655]
35. Emmons K, Li FP, Whitton J, Mertens AC, Hutchinson R, Diller L, et al. Predictors of smoking initiation and cessation among childhood cancer survivors: a report from the childhood cancer survivor study. *J Clin Oncol*. 2002; 20(6):1608–1616. [PubMed: 11896111]

Table 1

Characteristics of Pediatric Survivors of High-Risk Neuroblastoma (n=39).

Characteristics	Subjects
Male	24 (61.5%)
Median age	11.4 years (range 6.4–16.9)
Ethnicity ^a	
Asian American	5 (13%)
Caucasian	28 (72%)
Hispanic American	6 (15%)
Median age at diagnosis	2.3 years (range 0.7–6.9)
Median time since completion of therapy	5.5 years (range 1.3–15.2)
Treatments	
Chemotherapy ^b	39 (100%)
Cyclophosphamide	39 (100%)
Etoposide	39 (100%)
Vincristine	38 (97%)
Cisplatin	37 (95%)
Doxorubicin	33 (85%)
Isotretinoin	30 (77%)
Carboplatin	24 (62%)
Topotecan	22 (56%)
Irinotecan	12 (31%)
Melphalan	9 (23%)
Thiotepa	9 (23%)
Temozolomide	9 (23%)
Adriamycin	6 (15%)
Ifosfamide	6 (15%)
Beta-glucan	5 (13%)
Busulfan	2 (5%)
3 alkylating agents ^c	
Thoracic surgery	6 (15%)
Chest radiation therapy ^c	7 (18%)
Whole lungs	1 (3%)
Mediastinum	2 (5%)
Thoracic spine	2 (5%)
Chest wall	2 (5%)
Hematopoietic stem cell transplant	22 (56%)
Immunotherapy	

Characteristics	Subjects
Anti-GD2 antibody ^d	37 (95%)
GD2/GD3 vaccine	4 (18%)
Radioimmunotherapy ^{e,f}	2 (5%)

^a Ethnicity was self-reported at time of study participation.

^b Agents administered to only 1 subject are not listed and include: celebrex, cytarabine, dacarbazine, L-asparaginase, lenalidomide, octreotide, and thalidomide.

^c Median RT dose: 2100 cGy (range, 900 to 2160 cGy).

^d Anti-GD2 antibody included: 3F8, 03-077, and ch14.18.

^e IntraOmmaya compartmental radioimmunotherapy for CNS metastases included: ¹³¹I-8H9 (1, 2.5%), ¹³¹I-3F8 (1, 2.5%).

^f One of two patients who received radioimmunotherapy also received chest radiation therapy.

Table 2

Pulmonary Function Abnormalities.

PFT Parameter (mean, range) ^a	N (%)
FVC (81, 34–122)	39 (100)
Normal	20 (51)
Mild	9 (23)
Moderate	4 (11)
Moderately Severe	3 (8)
Severe	2 (5)
Very Severe	1 (3)
FEV1 (82, 40–119)	39 (100)
Normal	24 (62)
Mild	7 (20)
Moderate	3 (8)
Moderately Severe	2 (5)
Severe	3 (8)
Very Severe	0 (0)
TLC (84, 49–144)	39 (100)
Normal	22 (56)
Mild	9 (23)
Moderate	5 (13)
Severe	3 (8)
DLCO (71, 45–109)	36 (92)
Normal	10 (28)
Mild	17 (47)
Moderate	9 (27)
Severe	0 (0)

^aPercent predicted values.

Table 3

Association of Pulmonary Function Abnormalities and Potential Risk Factors.

Potential Risk Factor	Normal	Abnormal	P value
	FVC^a		
	Years	Years	
Mean age at diagnosis	2.63	2.73	0.83
Years since completion of therapy	5.85	6.71	0.421
	N (%)	N (%)	
Thoracic surgery	0 (0.0)	6 (100.0)	0.008
No thoracic surgery	20 (60.6)	13 (39.4)	
Chest radiation therapy	1 (14.3)	6 (85.7)	0.044
No chest radiation therapy	19 (59.4)	13 (40.6)	
Thoracic surgery + chest radiation therapy	0 (0.0)	4 (100.0)	0.047
No thoracic surgery + chest radiation therapy	20 (57.1)	15 (42.9)	
Hematopoietic stem cell transplant	9 (40.9)	13 (59.1)	0.14
No hematopoietic stem cell transplant	11 (64.7)	6 (35.3)	
Smoking exposure	3 (60.0)	2 (40.0)	>0.999
No smoking exposure	17 (51.5)	16 (48.5)	
	FEV1^a		
	Years	Years	
Mean age at diagnosis	2.53	2.91	0.431
Years since completion of therapy	6.36	6.12	0.821
	N (%)	N (%)	
Thoracic surgery	1 (16.7)	5 (83.3)	0.024
No thoracic surgery	23 (69.7)	10 (30.3)	
Chest radiation therapy	2 (28.6)	5 (71.4)	0.085
No chest radiation therapy	22 (68.8)	10 (31.3)	
Thoracic surgery + chest radiation therapy	0 (0.0)	4 (100.0)	0.020
No thoracic surgery + chest radiation therapy	24 (68.6)	11 (31.4)	
Hematopoietic stem cell transplant	11 (50.0)	11 (50.0)	0.092
No hematopoietic stem cell transplant	13 (76.5)	4 (23.5)	
Smoking exposure	3 (60.0)	2 (40.0)	>0.999

Potential Risk Factor	Normal	Abnormal	P value
	FVC^a		
	Years	Years	
No smoking exposure	21 (63.6)	12 (36.4)	
	TLC^a		
	Years	Years	
Mean age at diagnosis	3.04	2.4	0.175
Years since completion of therapy	6.27	6.27	>0.999
	N (%)	N (%)	
Thoracic surgery	2 (33.3)	4 (66.7)	0.374
No thoracic surgery	20 (60.6)	13 (39.4)	
Chest radiation therapy	2 (28.6)	5 (71.4)	0.206
No chest radiation therapy	20 (62.5)	12 (37.5)	
Thoracic surgery + chest radiation therapy	1 (25.0)	3 (75.0)	0.3
No thoracic surgery + chest radiation therapy	21 (60.0)	14 (40.0)	
Hematopoietic stem cell transplant	12 (54.5)	10 (45.5)	0.789
No hematopoietic stem cell transplant	10 (58.8)	7 (41.2)	
Smoking exposure	2 (40.0)	3 (60.0)	0.632
No smoking exposure	20 (60.1)	13 (39.4)	
	DLCO^a		
	Years	Years	
Mean age at diagnosis	2.33	2.87	0.314
Years since completion of therapy	8.34	5.73	0.033
	N (%)	N (%)	
Thoracic surgery	0 (0.0)	5 (100.0)	0.293
No thoracic surgery	10 (32.2)	21 (67.7)	
Chest radiation therapy	0 (0.0)	6 (100.0)	0.157
No chest radiation therapy	10 (33.3)	20 (66.7)	
Thoracic surgery + chest radiation therapy	0 (0.0)	3 (100.0)	0.54
No thoracic surgery + chest radiation therapy	10 (30.3)	23 (69.7)	
Hematopoietic stem cell transplant	6 (30.0)	14 (70.0)	>0.999
No hematopoietic stem cell transplant	4 (25.0)	12 (75.0)	

Potential Risk Factor	Normal	Abnormal	P value
	FVC ^a		
	Years	Years	
Smoking exposure	2 (40.0)	3 (60.0)	0.61
No smoking exposure	8 (26.7)	22 (73.3)	

^aPercent predicted values.

Table 4

Comparison of Pulmonary Function Parameters between Patients with and without Potential Risk Factors

Potential Risk Factor	FVC ^a	P value
Thoracic surgery	67	0.052
No thoracic surgery	83.9	
Chest radiation therapy	71.4	0.13
No chest radiation therapy	83.5	
Thoracic surgery + chest radiation therapy	66	0.1
No thoracic surgery + chest radiation therapy	83.1	
Hematopoietic stem cell transplant	77.5	0.17
No hematopoietic stem cell transplant	86.3	
Smoking exposure	75.6	0.47
No smoking exposure	82.6	
	FEV1^a	
Thoracic surgery	71.3	0.13
No thoracic surgery	83.4	
Chest radiation therapy	73	0.16
No chest radiation therapy	83.4	
Thoracic surgery + chest radiation therapy	68	0.11
No thoracic surgery + chest radiation therapy	83.1	
Hematopoietic stem cell transplant	77.2	0.08
No hematopoietic stem cell transplant	87.1	
Smoking exposure	79.2	0.74
No smoking exposure	82.1	
	TLC^a	
Thoracic surgery	70.5	0.06
No thoracic surgery	86.3	
Chest radiation therapy	71.3	0.054
No chest radiation therapy	86.6	
Thoracic surgery + chest radiation therapy	68.5	0.09
No thoracic surgery + chest radiation therapy	85.6	
Hematopoietic stem cell transplant	83	0.76
No hematopoietic stem cell transplant	84.9	

Potential Risk Factor	FVC ^a	P value
Smoking exposure	74.2	0.21
No smoking exposure	85.8	
	DLCO^a	
Thoracic surgery	62.4	0.16
No thoracic surgery	71.8	
Chest radiation therapy	61.2	0.07
No chest radiation therapy	72.4	
Thoracic surgery + chest radiation therapy	62	0.27
No thoracic surgery + chest radiation therapy	71.3	
Hematopoietic stem cell transplant	69.7	0.7
No hematopoietic stem cell transplant	71.5	
Smoking exposure	70	0.89
No smoking exposure	70.9	

^aMean percent predicted values.

Table 5

Association of Respiratory Symptoms and Conditions and Potential Risk Factors.

Potential Risk Factor	Symptom Not Present	Symptom Present	P value
	Cough		
	Years	Years	
Mean age at diagnosis	2.75	2.43	0.557
Years since completion of therapy	6.16	6.36	0.636
	N (%)	N (%)	
Thoracic surgery	3 (60.0)	2 (40.0)	0.592
No thoracic surgery	25 (75.8)	8 (24.2)	
Chest radiation therapy	5 (83.3)	1 (16.7)	>0.999
No chest radiation therapy	23 (71.9)	9 (28.1)	
Thoracic surgery + chest radiation therapy	3 (100.0)	0 (0.0)	0.55
No thoracic surgery + chest radiation therapy	25 (71.4)	10 (28.5)	
Hematopoietic stem cell transplant	16 (76.2)	5 (23.8)	0.727
No hematopoietic stem cell transplant	12 (70.6)	5 (29.4)	
Smoking exposure	2 (40.0)	3 (60.0)	0.103
No smoking exposure	26 (76.8)	7 (21.2)	
	Wheeze		
	Years	Years	
Mean age at diagnosis	2.66	2.74	0.917
Years since completion of therapy	6.35	5.09	0.483
	N (%)	N (%)	
Thoracic surgery	5 (100.0)	0 (0.0)	>0.999
No thoracic surgery	29 (87.9)	4 (12.1)	
Chest radiation therapy	5 (83.3)	1 (16.7)	0.513
No chest radiation therapy	29 (90.6)	3 (9.4)	
Thoracic surgery + chest radiation therapy	3 (100.0)	0 (0.0)	>0.999
No thoracic surgery + chest radiation therapy	31 (88.6)	4 (11.4)	
Hematopoietic stem cell transplant	20 (95.2)	1 (4.8)	0.307
No hematopoietic stem cell transplant	14 (82.4)	3 (17.7)	
Smoking exposure	4 (80.0)	1 (20.0)	0.446

Potential Risk Factor	Symptom Not Present	Symptom Present	P value
	Cough		
	Years	Years	
No smoking exposure	30 (90.9)	3 (9.1)	
	Congestion/Phlegm		
	Years	Years	
Mean age at diagnosis	2.61	3.02	0.567
Years since completion of therapy	6.16	6.55	0.81
	N (%)	N (%)	
Thoracic surgery	4 (80.0)	1 (20.0)	0.527
No thoracic surgery	29 (87.9)	4 (12.1)	
Chest radiation therapy	5 (83.3)	1 (16.7)	>0.999
No chest radiation therapy	28 (87.5)	4 (12.5)	
Thoracic surgery + chest radiation therapy	3 (100.0)	0 (0.0)	>0.999
No thoracic surgery + chest radiation therapy	30 (85.7)	5 (14.3)	
Hematopoietic stem cell transplant	19 (90.5)	2 (9.5)	0.64
No hematopoietic stem cell transplant	14 (82.4)	3 (17.7)	
Smoking exposure	4 (80.0)	1 (20.0)	0.527
No smoking exposure	29 (87.9)	4 (12.1)	
	Shortness of Breath		
	Years	Years	
Mean age at diagnosis	2.76	2.05	0.322
Years since completion of therapy	6.23	6.12	0.948
	N (%)	N (%)	
Thoracic surgery	5 (100.0)	0 (0.0)	>0.999
No thoracic surgery	28 (84.9)	5 (15.2)	
Chest radiation therapy	5 (83.3)	1 (16.7)	>0.999
No chest radiation therapy	28 (87.5)	4 (12.5)	
Thoracic surgery + chest radiation therapy	3 (100.0)	0 (0.0)	>0.999
No thoracic surgery + chest radiation therapy	30 (85.7)	5 (14.3)	
Hematopoietic stem cell transplant	16 (76.2)	5 (23.8)	0.053
No hematopoietic stem cell transplant	17 (100.0)	0 (0.0)	

Potential Risk Factor	Symptom Not Present	Symptom Present	P value
	Cough		
	Years	Years	
Smoking exposure	3 (60.0)	2 (40.0)	0.12
No smoking exposure	30 (90.9)	3 (9.1)	
	Any Symptom		
	Years	Years	
Mean age at diagnosis	2.71	2.59	0.82
Years since completion of therapy	6.15	6.33	0.882
	N (%)	N (%)	
Thoracic surgery	3 (60.0)	2 (40.0)	>0.999
No thoracic surgery	22 (66.7)	11 (33.3)	
Chest radiation therapy	5 (83.3)	1 (16.7)	0.643
No chest radiation therapy	20 (62.5)	12 (37.5)	
Thoracic surgery + chest radiation therapy	3 (100.0)	0 (0.0)	0.54
No thoracic surgery + chest radiation therapy	22 (62.9)	13 (37.1)	
Hematopoietic stem cell transplant	14 (66.7)	7 (33.3)	0.899
No hematopoietic stem cell transplant	11 (64.7)	6 (35.3)	
Smoking exposure	1 (20.0)	4 (80.0)	0.038
No smoking exposure	24 (72.7)	9 (27.3)	
	Symptoms with Exercise		
	Years	Years	
Mean age at diagnosis	2.76	2.54	0.656
Years since completion of therapy	6.4	5.96	0.692
	N (%)	N (%)	
Thoracic surgery	3 (60.0)	2 (40.0)	>0.999
No thoracic surgery	19 (57.6)	14 (42.4)	
Chest radiation therapy	3 (50.0)	3 (50.0)	0.682
No chest radiation therapy	19 (59.4)	13 (40.6)	
Thoracic surgery + chest radiation therapy	2 (66.7)	1 (33.3)	>0.999
No thoracic surgery + chest radiation therapy	20 (57.1)	15 (42.9)	
Hematopoietic stem cell transplant	11 (52.4)	10 (47.6)	0.521

Potential Risk Factor	Symptom Not Present	Symptom Present	P value
	Cough		
	Years	Years	
No hematopoietic stem cell transplant	11 (64.7)	6 (35.3)	
Smoking exposure	1 (20.0)	4 (80.0)	0.141
No smoking exposure	21 (63.6)	12 (36.4)	
	Physician-Diagnosed Condition		
	Years	Years	
Mean age at diagnosis	2.58	2.8	0.668
Years since completion of therapy	6.56	5.68	0.433
	N (%)	N (%)	
Thoracic surgery	4 (80.0)	1 (20.0)	0.396
No thoracic surgery	19 (57.6)	14 (42.4)	
Chest radiation therapy	3 (50.0)	3 (50.0)	0.663
No chest radiation therapy	20 (62.5)	12 (37.5)	
Thoracic surgery + chest radiation therapy	3 (100.0)	0 (0.0)	0.26
No thoracic surgery + chest radiation therapy	20 (57.1)	15 (42.9)	
Hematopoietic stem cell transplant	11 (52.4)	10 (47.6)	0.254
No hematopoietic stem cell transplant	12 (70.6)	5 (29.4)	
Smoking exposure	1 (20.0)	4 (80.0)	0.063
No smoking exposure	22 (66.7)	11 (33.3)	