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Pulmonary Function after Treatment for Embryonal Brain Tumors on SJMB03 that Included Craniospinal Irradiation

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Abstract

Purpose—Treatment of children with embryonal brain tumors (EBT) includes craniospinal irradiation (CSI). There are limited data regarding the effect of CSI on pulmonary function.

Methods—Protocol XXXXX enrolled patients 3 to 21 years of age with EBT. Pulmonary function tests (PFTs) [forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) by spirometry, total lung capacity (TLC) by nitrogen washout or plethysmography and diffusing capacity of the lung for carbon monoxide corrected for hemoglobin (DLCO_{corr})] were obtained. Differences between PFTs obtained immediately after the completion of CSI and 24 or 60 months after completion of treatment (ACT) were compared using exact Wilcoxon signed rank tests and repeated measures models.

Results—303 eligible patients (spine dose: 2345 cGy- 201; > 2345 cGy-102; proton beam, 20) were enrolled between June 24, 2003 and March 1, 2010, 260 of whom had at least one PFT. The median age at diagnosis was 8.9 years (range, 3.1–20.4 years). The median thoracic spinal RT dose was 23.4 Gy (Inter Quartile Range (IQR), 23.4–36.0 Gy). The median cyclophosphamide dose was 16.0 g/m² (IQR, 15.7–16.0 g/m²). 24 and 60 months ACT, DLCO_{corr} was <75% predicted in 23% (27/118) and 25% (21/84), FEV₁ <80% predicted in 20% (34/170) and 29% (32/109), FVC < 80% predicted in 27% (46/172) and 28% (30/108) and TLC <75% predicted in 9% (13/138) and 11% (10/92) of patients. DLCO_{corr} was significantly decreased 24 (median difference (MD) in % predicted, – 3.00%; p=0.028) and 60 months ACT (MD in % predicted, – 6.00%; p=0.033) compared to the end of RT. These significant decreases in DLCO_{corr} were also observed in repeated measures models (p=0.011 and p=0.032 at 24 and 60 months ACT, respectively).

Conclusions—A significant minority of EBT survivors experience PFT deficits following CSI. Continued monitoring of this cohort is planned.

Introduction

Improved rates of survival among children diagnosed with medulloblastoma are largely due to advances in treatment regimens, most of which feature craniospinal irradiation (CSI). Five-year survival rates following a diagnosis of medulloblastoma have improved from 52% among children diagnosed in 1975–1984¹ to 61.2% among children diagnosed in 2004–2010.² The outcome for children with other embryonal central nervous system tumors, such as, primitive neuroectodermal tumor (PNET), PNET variants (e.g., ependymoblastoma, pineoblastoma, central nervous system (CNS) neuroblastoma) or atypical teratoid rhabdoid tumor (ATRT) has not improved as dramatically, but their treatment also generally includes CSI.

Curative treatment for these individuals has not come without cost. Normal central nervous system (CNS) tissue damage is possible either because of its proximity to the original tumor site or because it is located in the region or path exposed to a radiation exit dose. Newer protocols use conformal techniques and proton beam technology for some patients in order to minimize normal tissue exposure and decrease the potential for adverse medical late-effects.^{3–5} Well documented impairments include neurocognitive deficits, neuroendocrine dysfunction and musculoskeletal deformity. These impairments often emerge during

childhood, but can be progressive or have a delayed onset. The severity of the functional loss is typically worse among those who received higher doses and volumes of irradiation when younger than five years of age.⁶

Less is known about the specific effects of childhood exposure to CSI on other organs, including the lungs. Some evidence of long-term pulmonary toxicity has been reported in single institution case series limited to a total of 21 patients treated during childhood for medulloblastoma with CSI and no chemotherapy.^{7,8} We undertook the present study to evaluate the impact of CSI at 24 and 60 months after diagnosis in a large cohort of children who received uniform treatment on the XXXXX protocol, which included CSI, myeloablative multiagent chemotherapy and hematopoietic stem cell support.⁹

Patients and Methods

Patients

XXXXXXXXXXXXXXXXXXXXX enrolled patients aged 3–21 years with medulloblastoma, primitive neuroectodermal tumor (PNET), PNET variants (e.g., ependyoblastoma, pineoblastoma, central nervous system (CNS) neuroblastoma) or atypical teratoid rhabdoid tumor (ATRT) starting in June 2003. Patients were stratified as either average risk (AR) (< 1.5 cm² residual tumor; no metastatic disease) or high risk (HR) (≥ 1.5 cm² residual disease or metastatic disease) based on postoperative tumor volume and modified Chang staging for metastatic disease¹⁰.

To insure a minimum of 24 months of follow-up when this project was initiated, we evaluated patients enrolled prior to March 1, 2010. Two of the 305 enrolled before March 1, 2010 were ineligible, leaving 303 patients in the study cohort. XXXXXX was approved by the XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX Institutional Review Board IRB) and the IRB or Ethical Review Committee (ERC) at each participating institution, and all patients or their parents/legal guardians signed an Informed Consent document prior to participation in the study. Continuing Review was obtained and IRB/ERC approval was renewed annually at each participating institution. The retrospective review of pulmonary function test (PFT) data was approved by the XXXXX IRB.

Radiation Therapy and Chemotherapy

All patients underwent maximal surgical resection of their tumor followed by riskadapted radiation therapy (RT). Patients with average-risk disease received 23.4 Gy CSI followed by primary site irradiation (55.8 Gy) using a 1-cm clinical target volume (CTV) margin surrounding the post-operative tumor bed. Similarly, patients stratified to the high-risk arm received primary site irradiation (55.8 Gy) using a 1-cm CTV margin, but the CSI dose ranged from 36 to 39.6 Gy. Additional macroscopic metastatic sites in the brain and spine were irradiated to a total dose 50.4 to 54.0 Gy. Treatment was administered using 1.8 Gy fractions per day, five days per week. The dose-volume histograms for the right and left lungs treated with 23.4 Gy or 36.0 Gy are shown in Figure 1. The thoracic spinal radiation dose was the nominal spinal treatment dose if no boost treatments had been given. If five or

more of the thoracic vertebral bodies received a boost dose, the thoracic spinal radiation dose was estimated to have been the nominal spinal treatment dose plus the boost dose.

After completion of CSI and a 6-week rest period, all patients received four courses of high-dose cyclophosphamide, cisplatin, and vincristine with peripheral blood stem cell (PBSC) support⁹.

Pulmonary Function Testing

Pulmonary function tests were to be obtained, per protocol, at the completion of CSI, prior to each course of high-dose chemotherapy, and 24 and 60 months after the completion of chemotherapy. There was no baseline/pre-treatment evaluation of PFTs. PFTs were performed predominantly in children 6 years of age and older. All tests were performed by experienced pediatric pulmonary function technicians, and according to the guidelines of the American Thoracic Society^{11–15}. PFTs included spirometry and single-breath carbon monoxide diffusion capacity. Spirometry, performed by using a pneumotachograph, measured forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV₁). Diffusion capacity for carbon monoxide was measured by the single breath method and corrected for hemoglobin (DLCO_{corr}). Total lung capacity (TLC) was determined by the nitrogen wash-out method¹⁶ prior to 2008 and, thereafter, by body plethysmography at XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX¹⁷. The observed values of each patient were standardized to % predicted for the patient's age, race, sex, and height on the basis of reference equations^{17–27}. PFTs were classified as abnormal for FVC < 80% predicted, FEV₁ < 80% predicted, TLC < 75% predicted, and DLCO_{corr} < 75% predicted.

Statistical Methods

Descriptive statistics were calculated using standard methods. Fisher's exact test and the chi square test were used to examine associations between categorical variables. Differences between time 1 (post-RT, prior to first course of high-dose chemotherapy) and time 5 (24 months after the end of chemotherapy), and time 6 (60 months after the end of chemotherapy) PFT outcomes were examined using exact Wilcoxon signed rank tests. In addition, pulmonary function measures were estimated using repeated measures models as implemented in SAS using proc mixed with an unstructured covariance structure. Repeated measures models were used to examine predictors of pulmonary outcomes. Comparisons of pulmonary function values collected at different time points were performed for each variable (DLCO_{corr} % predicted, FEV₁ % predicted, TLC % predicted and FVC % predicted) separately.

Results

At least one evaluation of pulmonary function was obtained on 260 of 303 (85.8%) eligible patients. PFTs were more likely to be performed on patients who were > 5 years of age, average risk, and M0 (Table 1). The median age at diagnosis was 8.9 years (range, 3.1 to 20.4 years). The majority were male, non-Hispanic white with M0 stage, average risk, and were diagnosed with medulloblastoma. The majority received the protocol specified cumulative dose of cyclophosphamide (median, 16.0 g/m²; Inter Quartile Range (IQR), 15.7

to 16.0 g/m²), and the median spinal radiation dose was 23.4 Gy (IQR, 23.4 to 36.0 Gy) (Table 1). Compliance with protocol specified PFTs was very good (approximately 70%) with the exception of 60 months after completion of treatment, when it was 51% (Table 2).

The majority of patients retained normal PFTs throughout the period of study. The mean estimates for the four PFTs decline prior to each course of chemotherapy following completion of CSI, demonstrate recovery at the 24 month after completion of therapy evaluation, but then decline slightly at the 60 month, compared to the 24 month, after completion of therapy evaluation (Figure 2). Both TLC % predicted ($p = 0.006$) and DLCO_{corr} % predicted ($p = 0.032$) were significantly lower at the 60 month time point compared to the evaluation prior to the first course of high dose chemotherapy (Table 3).

Sex, race, age at diagnosis, radiation dose, use of proton beam RT, M-stage, risk group, and cumulative cyclophosphamide dose were evaluated in univariable models with time (as a categorical variable) for each PFT percent of predicted outcome separately. M-stage, RT dose and risk group were extremely highly correlated with each other ($p < 0.00001$), and were not included in models together. Each covariate was first examined in a model with time (as a categorical variable) for each pulmonary outcome separately. The interaction between time and each covariate was also included in the model. Variables significant at the 0.10 level were then included in a multivariable model.

In a model which included covariates marginally significant in the exploratory analyses above [time point, sex, age at diagnosis (categorical variable), CSI dose group and use of proton beam CSI], we found males had higher DLCO_{corr} % predicted than females ($p < 0.001$). Patients who were younger at diagnosis had higher DLCO_{corr} % predicted ($p = 0.007$ for age as a categorical variable), and those treated with photon CSI had a larger DLCO_{corr} % predicted ($p = 0.006$). Time point remained a significant predictor of DLCO_{corr} % predicted ($p < 0.001$). All of these factors remained significant adjusted for race. In additional repeated measures models that included patients with at least two DLCO measurements ($n = 174$), results were similar. We found that males had higher DLCO_{corr} % predicted than females ($p = 0.002$). Younger patients had higher DLCO_{corr} % predicted ($p = 0.001$ for age as a categorical variable). Patients treated with photon CSI had a larger DLCO_{corr} % predicted ($p = 0.024$). In addition, patients who received lower RT doses (2345 cGy) had larger DLCO_{corr} % predicted than those treated with higher doses ($p = 0.032$). All of these factors remained significant adjusted for race.

Sex was the only significant predictor of FEV₁ % predicted ($p = 0.025$) in addition to elapsed time from diagnosis ($p < 0.001$), with males having a higher FEV₁ % predicted than females. Sex remained a significant predictor after adjusting for race and age. In univariable models none of the other factors investigated [race, age (continuous or categorical), CSI dose group, proton beam CSI, M-stage, risk group, cyclophosphamide dose] was found to be a significant predictor of FEV₁ % predicted. In additional repeated measures models that included patients with at least two FEV₁ measurements ($n = 236$), results were similar. Sex was the only significant predictor of FEV₁ % predicted ($p = 0.007$) in addition to elapsed time from diagnosis ($p < 0.001$), with males having a higher FEV₁ % predicted than females.

In a model which included variables significant in univariable models (time, sex, race, photon versus proton beam CSI and age at diagnosis), the factors that remained significant predictors of larger TLC % predicted were decreased elapsed time from diagnosis ($p<0.001$), male sex ($p=0.009$), white, non-Hispanic race group ($p=0.004$), photon beam ($p=0.002$) and younger age ($p=0.003$). In repeated measures models that included patients with at least two TLC measurements ($n=192$), results were similar. Significant predictors of larger TLC % predicted were male sex ($p=0.015$), white, non-Hispanic race group ($p=0.001$), photon beam ($p<0.001$) and younger age group ($p=0.003$).

In a model that included time, sex, CSI dose group, M-stage, CSI dose group*time interaction and M-stage*time interaction, male sex ($p=0.003$) and shorter elapsed time from diagnosis ($p<0.001$) remained as significant predictors of larger FVC % predicted. The main effect of CSI dose group was not significant ($p=0.27$). The result was consistent adjusted for race and sex at diagnosis. In additional repeated measures models that included patients with at least two FVC measurements ($n=237$), results were similar. Male sex ($p<0.001$) and shorter elapsed time from diagnosis ($p<0.001$) were significant predictors of FVC % predicted. In addition, the CSI dose group*time interaction was significant ($p=0.016$). The main effect of CSI dose group was not significant ($p=0.17$). The result was consistent adjusted for race and age at diagnosis.

Discussion

We have demonstrated that PFTs remain in the normal range for the majority of patients enrolled on XXXXXX, an intensive treatment protocol that included CSI followed by four courses of myeloablative multiagent chemotherapy and hematopoietic stem cell support, when evaluated 24 and 60 months after the completion of treatment. However average values for TLC % predicted and $DLCO_{corr}$ % predicted were significantly decreased at the 60 month evaluation when compared to the initial evaluation obtained following CSI but prior to the first course of high-dose chemotherapy. In this young population with still limited follow-up, the identification of mildly impaired pulmonary function in a subset is a concern.

Previous publications describing pulmonary function deficits following CSI in CNS tumor survivors are limited by evaluation of cohorts of very small sample size, inclusion of pediatric and adult patients, inconsistency in pulmonary evaluations with regard to elapsed time from exposure to evaluation and confounding by concurrent treatment with pulmonary toxic chemotherapeutic agents such as nitrosoureas. Restrictive lung defects were identified in only 9.2% of XXXXXX patients who have completed the 60 month evaluation. Jakacki et al. reported such defects in one of the seven treated with CSI and chemotherapy and two of eight treated with CSI only⁸, and Endicott et al. reported such defects in three of the seven treated with CSI and nitrosourea containing chemotherapy and none of the 13 treated with only CSI⁷.

All patients in the current study were treated with cyclophosphamide. Reports of unequivocal cyclophosphamide-related pulmonary toxicity are uncommon²⁸. There are rare reports of possible cyclophosphamide-related pulmonary toxicity in pediatric patients^{29,30}.

Cumulative doses in two of the three possible pediatric cases were 60 grams and 42 grams³⁰. Surface areas were not reported, but the two patients were 4 ½ years and 3 ½ years of age at diagnosis³⁰. Mulder et al. did not identify treatment with high-dose cyclophosphamide as a significant predictor of restrictive pulmonary function impairment or diffusion capacity impairment among 193 adult survivors of childhood cancer who received bleomycin, pulmonary radiation therapy and/or pulmonary surgery³¹. Similarly, Venkatramani et al. reported that treatment with cyclophosphamide was not a significant risk factor for either pneumonitis or adverse late pulmonary outcomes among 109 patients who received radiation therapy that included the lungs³². The design of the current study precluded analyses of the independent contributions of treatment with cyclophosphamide and craniospinal irradiation to the pulmonary toxicity observed.

Restrictive lung defects following spinal irradiation may be related to direct injury of lung tissue, damage to the chest wall and/or the spine. Spinal irradiation may impair subsequent linear growth in survivors of medulloblastoma^{33,34}, and may be more common following higher doses of spinal irradiation³⁵. The strengths of this study are the evaluation of a pulmonary function in a large number of patients at protocol specified time points following treatment with CSI and high-dose, combination chemotherapy for pediatric embryonal central nervous system malignancies. A weakness of this study was the inability to obtain pulmonary function testing on all patients prior to initiation of radiation therapy, which was attributable, in part, to the difficulty of obtaining valid PFTs on patients less than six years of age, enrollment of a larger percentage of patients with average risk and M0 disease, and the lack of data regarding the prevalence of scoliosis in this cohort. Restrictive pulmonary defects measured as reduced lung volumes may also be produced by muscle weakness and/or poor effort. We cannot exclude that the changes we observed were produced in part by residual neurological deficits or muscle weakness.

In summary we have demonstrated that, although most XXXXX patients have normal pulmonary function following CSI, average values for TLC and DLCO_{corr} were significantly decreased at the 60 month evaluation when compared to the initial evaluation. In this young population, the identification of mildly impaired pulmonary function in a subset is a concern and supports the need for continued observation and documentation of potential confounding abnormalities such as scoliosis.

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References

1. Ries, LAG.; Smith, MA.; Gurney, JG., et al., editors. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995. Bethesda, MD: National Cancer Institute; 1999.
2. Howlader, N.; Noone, AM.; Krapcho, M., et al. Bethesda, MD: National Cancer Institute; 2014. SEER Cancer Statistics Review, 1975–2011, based on November 2013 SEER data submission, posted to the SEER web site, April 2014.

3. Merchant TE. Three-dimensional conformal radiation therapy for ependymoma. *Childs Nerv Syst.* 2009; 25:1261–1268. [PubMed: 19373477]
4. Merchant TE, Hua CH, Shukla H, Ying X, Nill S, Oelfke U. Proton versus photon radiotherapy for common pediatric brain tumors: comparison of models of dose characteristics and their relationship to cognitive function. *Pediatr Blood Cancer.* 2008; 51:110–117. [PubMed: 18306274]
5. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. *Lancet Oncol.* 2009; 10:258–266. [PubMed: 19274783]
6. Merchant TE, Pollack IF, Loeffler JS. Brain tumors across the age spectrum: biology, therapy, and late effects. *Semin Radiat Oncol.* 2010; 20:58–66. [PubMed: 19959032]
7. Endicott TJ, Fisher BJ, Wong E, Paterson NA, Gaspar LE, Bauman M. Pulmonary sequelae after electron spinal irradiation. *Radiother Oncol.* 2001; 60:267–272. [PubMed: 11514006]
8. Jakacki RI, Schramm CM, Donahue BR, Haas F, Allen JC. Restrictive lung disease following treatment for malignant brain tumors: a potential late effect of craniospinal irradiation. *J Clin Oncol.* 1995; 13:1478–1485. [PubMed: 7751895]
9. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St. Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *Lancet Oncol.* 2006; 7:813–820. [PubMed: 17012043]
10. Chang C, Housepian EM, Herbert C Jr. An operative staging system and a megavoltage radiotherapeutic technic for cerebellar medulloblastomas. *Radiology.* 1969; 93:1351–1359. [PubMed: 4983156]
11. American Thoracic Society. Standardization of Spirometry, 1994 Update. *Am J Respir Crit Care Med.* 1995; 152:1107–1136. [PubMed: 7663792]
12. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J.* 2005; 26:720–735. [PubMed: 16204605]
13. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005; 26:319–338. [PubMed: 16055882]
14. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. *Eur Respir J.* 2005; 26:153–161. [PubMed: 15994402]
15. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. *Eur Respir J.* 2005; 26:511–522. [PubMed: 16135736]
16. Newth CJ, Enright P, Johnson RLJ. Multiple breath nitrogen washout techniques: including measurements with patients on ventilators. *Eur Respir J.* 1997; 10:2174–2185. [PubMed: 9311523]
17. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. *Eur Respir J.* 1995; 8:492–506. [PubMed: 7789503]
18. Paoletti P, Viegi G, Pistelli G, et al. Reference equations for the single-breath diffusing capacity. A cross-sectional analysis and effect of body size and age. *Am Rev Respir Dis.* 1985; 132:806–813. [PubMed: 3876793]
19. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999; 159:179–187. [PubMed: 9872837]
20. Wang X, Dockery DW, Wypij D, Fay ME, Ferris BGJ. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol.* 1993; 15:75–88. [PubMed: 8474788]
21. Knudson RJ, Lebowitz MD, Holberg CJ, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. *Am Rev Respir Dis.* 1983; 127:725–734. [PubMed: 6859656]
22. Eigen H, Bieler H, Grant D, et al. Spirometric pulmonary function in healthy preschool children. *Am J Respir Crit Care Med.* 2001; 163:619–623. [PubMed: 11254514]
23. *Pulmonary Function Testing in Children: Techniques and Standards.* Philadelphia: W.B. Saunders Co; 1971.
24. Kim YJ, Hall GL, Christoph K, et al. Pulmonary diffusing capacity in healthy Caucasian children. *Pediatr Pulmonol.* 2012; 47:469–475. [PubMed: 22081537]

25. Zapletal, A.; Samanek, M.; Paul, T. *Methods, Reference Values*. Basel: S. Karger, AG; 1987. Lung Function in Children and Adolescents.
26. Hibbert ME, Lannigan A, Landau LI, Phelan PD. Lung function values from a longitudinal study of healthy children and adolescents. *Pediatr Pulmonol*. 1989; 7:101–109. [Erratum appears in *Pediatr Pulmonol* 1990;8(1):68]. [PubMed: 2797918]
27. Stanojevic S, Wade A, Stocks J, et al. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med*. 2008; 177:253–260. [PubMed: 18006882]
28. Myers JL, DeRemee RA, Specks U. Lung toxicity associated with cyclophosphamide use. Two distinct patterns. *Am J Respir Crit Care Med*. 1996; 154:1851–1856. [PubMed: 8970380]
29. Rodin AE, Haggard ME, Travis LB. Lung changes and chemotherapeutic agents in childhood. Report of a case associated with cyclophosphamide therapy. *Am J Dis Child*. 1970; 120:337–340. [PubMed: 5537047]
30. Alvarado CS, Boat TF, Newman AJ. Late-onset pulmonary fibrosis and chest deformity in two children treated with cyclophosphamide. *J Pediatr*. 1978; 92:443–446. [PubMed: 273085]
31. Mulder RL, Thonissen NM, van der Pal HJ, et al. Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer. *Thorax*. 2011; 66:1065–1071. [PubMed: 21803931]
32. Venkatramani R, Kamath S, Wong K, et al. Correlation of clinical and dosimetric factors with adverse pulmonary outcomes in children after lung irradiation. *Int J Radiat Oncol Biol Phys*. 2013; 86:942–948. [PubMed: 23726005]
33. Gaspar LE, Dawson DJ, Tilley-Guillford SA, Banerjee P. Medulloblastoma: Long-term follow-up of patients treated with electron irradiation of the spinal field. *Radiology*. 1991; 180:867–870. [PubMed: 1871308]
34. Gerosa MA, di Stefano E, Olivi A, Carteri A. Multidisciplinary treatment of medulloblastoma: a 5-year experience with the SIOP trial. *Childs Brain*. 1981; 8:107–118. [PubMed: 7018855]
35. Probert JC, Parker BR. The effects of radiation therapy on bone growth. *Radiology*. 1975; 114:155–162. [PubMed: 813276]

Figure 1.

– Dose-volume histogram (DVH) for the right and left lungs for spinal radiation doses of 23.4 Gy and 36.0 Gy using photons (Red – left lung, Green – Right lung, Solid line – 23.4 Gy, Dashed line – 36.0 Gy). The figure includes a cumulative DVH from a single patient estimating dose to both lungs.

Figure 2.

– Estimated mean pulmonary function values by time point (FEV₁ - forced expiratory volume in one second; FVC - forced vital capacity; TLC - total lung capacity; DLCO_{corr} - diffusing capacity of the lung for carbon monoxide corrected for hemoglobin; ACT – after completion of treatment)

Table 1

Demographic and tumor characteristics by presence of PFT data

	Any PFT data?		P-value
	Yes (n=260)	No (n=43)	
Sex			
Male	158 (61%)	25 (58%)	0.740
Female	102 (39%)	18 (42%)	
Race Category			
White, non-Hispanic	196 (75%)	29 (67%)	0.191
Black, non-Hispanic	19 (7%)	6 (14%)	
Hispanic	22 (8%)	6 (14%)	
Cannot classify as one of the above	23 (9%)	2 (5%)	
Age at Diagnosis (years)			
5	49 (19%)	30 (70%)	<0.001
>5	211 (81%)	13 (30%)	
Median	8.9	4.3	<0.001
Range	3.1 – 20.4	3.1 – 14.8	
Institution			
St. Jude	135 (52%)	17 (40%)	0.142
Other	125 (48%)	26 (60%)	
Diagnosis			
Atypical Teratoid Rhabdoid Tumor	18 (6.9%)	3 (7.0%)	0.771
Medulloblastoma	208 (80.0%)	33 (76.7%)	
Medulloblastoma	1 (0.4%)	0	
Pineoblastoma	12 (4.6%)	4 (9.3%)	
Primitive Neuroectodermal Tumor	21 (8.1%)	3 (7.0%)	
Risk Group			
Average	178 (68%)	22 (51%)	0.036
High	82 (32%)	21 (49%)	
M stage			
0	192 (74%)	24 (56%)	0.019
1/2/3	68 (26%)	19 (44%)	
Cumulative Cyclophosphamide Dose (g/m²)			
< 12 g/m ²	14 (5.4%)	13 (30.2%)	<0.001
12 to < 16 g/m ²	130 (50.0%)	19 (44.2%)	
16 g/m ²	116 (44.6%)	11 (25.6%)	
Median	16	15.9	<0.001

	Any PFT data?		P-value
	Yes (n=260)	No (n=43)	
Inter Quartile Range	15.7 to 16.0	8.0 to 16.0	
Spine RT dose (Gy)			
Median	23.4	23.5	0.009
Inter Quartile Range	23.4 – 36.0	23.4 – 39.6	

PFT – Pulmonary Function Test; RT – Radiation Therapy; Gy - Gray

Table 2

Numbers of Patients with PFT Data by Time Point

	Any PFT data (Number obtained/number eligible) [^]	DLCO _{corr}	FEV ₁	TLC	FVC
T1	213/295 (72%)	146	212	157	212
T2	199/294 (68%)	147	198	158	198
T3	205/289 (71%)	158	205	170	205
T4	196/288 (68%)	144	196	158	195
T5	172/235 (73%)	118	170	138	172
T6	109/214 (51%)	84	109	92	108

PFT – Pulmonary Function Test; FEV₁ - forced expiratory volume in one second; FVC - forced vital capacity; TLC - total lung capacity; DLCO_{corr} - diffusing capacity of the lung for carbon monoxide corrected for hemoglobin

[^] Denominator excludes patients who died or had relapsed or progressive disease prior to the planned PFT assessment time point.

Table 3

Estimates of mean percent predicted (standard error) for individual PFTs derived from repeated measures models

Time Point	DLCO _{corr}	FEV ₁	TLC	FVC
T1	90.80 (1.60)	91.18 (0.98)	97.08 (1.29)	89.74 (0.95)
T2	85.18 (1.81)	91.99 (0.96)	97.22 (1.25)	91.20 (0.92)
T3	81.51 (1.67)	90.83 (0.98)	92.50 (1.15)	89.76 (0.92)
T4	78.93 (1.69)	87.38 (1.02)	92.33 (1.32)	86.15 (1.10)
T5	86.28 (1.70)	90.59 (1.08)	94.89 (1.31)	88.94 (1.09)
T6	85.62 (2.14)	89.47 (1.30)	92.66 (1.39)	87.86 (1.28)

PFT – Pulmonary Function Test; FEV₁ - forced expiratory volume in one second; FVC - forced vital capacity; TLC - total lung capacity; DLCO_{corr} - diffusing capacity of the lung for carbon monoxide corrected for hemoglobin