Included studies pulmonary dysfunction surveillance

Evidence in CAYA cancer survivors

Year	Bibliography
2021	Mittal et al. Late effects in pediatric Hodgkin lymphoma survivors after uniform treatment with ABVD with or without radiotherapy. Pediatr Blood Cancer. 2021 Nov;68(11):e29293.
2021	Otth et al. Longitudinal lung function in childhood cancer survivors after hematopoietic stem cell transplantation. Bone Marrow Transplant. 2022 Feb;57(2):207-214.
2020	Khan et al. Impact of Respiratory Developmental Stage on Sensitivity to Late Effects of Radiation in Pediatric Cancer Survivors. Advances in Radiation Oncology 2020; 5: 426-433
2020	Stone et al. Assessment of Pulmonary Outcomes, Exercise Capacity, and Longitudinal Changes in Lung Function in Pediatric Survivors of High-Risk Neuroblastoma. 2020, PBC, 2019; 66(11): e27960
2018	Myrdal et al. Risk factor for impaired pulmonary function and cardiorespiratory fitness in very long-term adult survivors of childhood acute lymphoblastic leukemia after treatment with chemotherapy only. (2018). Acta Oncologica, 57:5, 658-664
2016	Record et al. Analysis of Risk Factors for Abnormal Pulmonary Function in Pediatric Cancer Survivors. 2016; 63:1264-71.
2016	Green, et al. Pulmonary Function after Treatment for Childhood Cancer. A Report from the St. Jude Lifetime Cohort Study (SJLIFE). 2016;13:1575-85.
2015	Armenian et al. Long-term pulmonary function in survivors of childhood cancer. 2015;33:1592-600.
2015	Green et al. Pulmonary Function After Treatment for Embryonal Brain Tumors on SJMB03 That Included Craniospinal Irradiation. 2015;93:47-53. 10.1016/j.ijrobp.2015.05.019
2015	De et al. Correlation of pulmonary function abnormalities with dose volume histograms in children treated with lung irradiation. 2015;50:596-603.
2015	Zorzi, et al. Bleomycin-associated Lung Toxicity in Childhood Cancer Survivors. 2015;37:e447-52.
2014	Madanat-Harjuoja et al. Pulmonary function following allogeneic stem cell transplantation in childhood: a retrospective cohort study of 51 patients. 2014;18:617-24.
2014	Denbo et al. Long-term pulmonary function after metastasectomy for childhood osteosarcoma: a report from the St Jude lifetime cohort study. 2014;219:265-71.
2014	Oancea et al. Cigarette smoking and pulmonary function in adult survivors of childhood cancer exposed to pulmonary-toxic therapy: results from the St. Jude lifetime cohort study. 2014;23:1938-43
2011	Mulder et al. Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer. 2011;66:1065-71.
2010	Ginsberg et al. Pre-transplant lung function is predictive of survival following pediatric bone marrow transplantation. 2010;54:454-60.
2010	Inaba et al. Pulmonary dysfunction in survivors of childhood hematologic malignancies after allogeneic hematopoietic stem cell transplantation. 2010;116:2020-30.

2007	Leung et al. A prospective cohort study of late sequelae of pediatric allogeneic hematopoietic stem cell transplantation. 2007;86:215-24. 10.1097/MD.0b013e31812f864d
2007	Oguz et al. Long-term pulmonary function in survivors of childhood Hodgkin disease and non-Hodgkin lymphoma. 2007;49:699-703. 10.1002/pbc.21175
2006	Hoffmeister et al. Pulmonary function in long-term survivors of pediatric hematopoietic cell transplantation. 2006;47:594-606.
2006	Weiner et al. Pulmonary function abnormalities in children treated with whole lung irradiation. 2006;46:222-7.
2005	Wieringa, et al. Pulmonary function impairment in children following hematopoietic stem cell transplantation. 2005;45:318-23
1998	Nysom et al. Pulmonary function after treatment for acute lymphoblastic leukaemia in childhood. 1998;78:21-7.
1998	Nysom et al. Risk factors for reduced pulmonary function after malignant lymphoma in childhood. 1998;30:240-8.
1995	Marina, et al. Serial pulmonary function studies in children treated for newly diagnosed Hodgkin's disease with mantle radiotherapy plus cycles of cyclophosphamide, vincristine, and procarbazine alternating with cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine. 1995;75:1706-11.
1995	Jenney et al. Lung function and exercise capacity in survivors of childhood leukaemia. 1995;24:222-30.

Evidence summary tables of included studies on "Who needs surveillance for pulmonary dysfunction?"

Main findings/message:
In univariate analysis hyperinflation significantly more frequent in pediatric cancer survivors in BMT versus no BMT (52.2% vs. 31.6%, P=0.01).
In univariate analysis any pulmonary abnormality, obstructive and hyperinflation are significantly more frequent in pediatric cancer survivors in not exposed to bleomycin versus exposed (72% vs 52%, p=0.02; 33% vs 12% p=0.01; 52% vs 21% p=<0.01).
In univariate analysis any pulmonary abnormality and obstructive disease are significantly more frequent in pediatric cancer survivors exposed to lung surgery versus no lung surgery (83.3% versus 61.3%, P=0.03).
In univariate analysis the prevalence of any pulmonary abnormality, obstructive, restrictive, and hyperinflation were not significantly different between exposed and non-exposed.

Record, et al. Analysis of Risk Factors for Abnormal Pulmonary Function in Pediatric Cancer Survivors. 2016; 63:1264-71. 10.1002/pbc.25969

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment** (= treatment analyzed in the paper)	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: NA ➢ Eligible cohort: 226 ➢ Analyzed cohort:143	☒ 1 **HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☒ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☒ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☒ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☐ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** Wang, Hankinson ☐ **Quality check performed** ☒ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☒ **Person who analyzed PFT was blinded to the exposure**
Centres: Single center (Atlanta survivor clinic) Country: USA Treatment era: 2000-2009 (7 pat dx. in late 1990) Years of Follow-up: Mean age: 14.1 ±4.8 yrs 2002-2012	Study population: Eligible (N): 226 Analysis (N): 143 (response rate 63.3%) Inclusion criteria: therapy after 2000 with at least one pulmonary toxic treatment Except children < 5 years and brain tumor Cancer diagnosis: Leukemia 28% Hodgkin 28% Non-hodgkin lymphoma 7% Neuroblastoma: 9.8% Renal tumor 10.5% Sarcoma 0.1% Other: 7.7%	Chemotherapy: Bleomycine 33.6% Busulfan, Carnustine (BCNU), Lomustine (CCNU): 11.9% Radiotherapy: 67.8% Surgery: 16.8% Bone Marrow Transplantation: 46.9%	Definition of outcome 1. Prevalence of pulmonary function abnormalities 2. Risk factors with these PF abnormalities (proportion) PFT: spirometry, body plethysmography, DLco Abnormal PFT if %-predicted pathological: **Restrictive =** TLC <80% **Obstructive =**FVC <80%, FEV1<80% or FEV1/FVC<80%, or FEF25-75% <68% **Hyperinflation** = RV>120% or RV/TLC >28% **Pulmonary vascular disease** =DLco/VAadj <4ml/mmHg **Symptoms:** medical record abstraction Results: **Any abnormal PFT in n=93 (65%),** 21% having multiple abnormalities, **80% being asymptomatic**	Analysis: univariate comparison of treatment characteristics by PFT abnormality Limitations: - Only univariate analysis performed - BMT not stratified into allo & auto, but most probably all allo BMT as GvHD reported - Patients without RV or TLC classified as normal if no other abnormality

	<u>Age at diagnosis:</u> Median 9 yr (0-21.8) <u>Age at follow-up:</u> Mean age at evaluation: 14.1 ± 4.8 yr		Hyperinflation n=59/129 (41.3%) Restrictive disease n=19/129 (13.3%) Obstructive disease n=37/143 (25.9%) Pulmonary vascular disease n=6/110 (5.5%) **Risk factors**: **BMT versus no BMT**: Hyperinflation 52.2% vs. 31.6% (P=0.01) **Bleomycin versus no Bleomycin:** Bleomycin has sign. lower percentages of any abnormality, obstructive and hyperinflation compared to no Bleomycin **Thoracic RT versus no thoracic RT:** No sig. difference **Lung surgery versus no lung surgery:** Any abnormality 83.3% versus 61.3% (P=0.03) Obstructive 50% versus 21% (P=0.01) **Exact results available from publication, TABLE III:** **"**Univariate Comparison of Demographis, Diagnosis and Treatment Characteristics by PFT Abnormality to Those without the PFT Abnormality Among Pediatric Cancer Survivors at Risk for Pulmonary Late Effects"	

Main findings/message:
In univariate analysis no significant association between bleomycin exposure and restrictive disease (OR 0.7, 95%CI 0.3-1.6) and DLco abnormalities (OR 0.8, 95%CI 0.4-1.7)
In univariate analysis no significant association between busulfan exposure and restrictive disease (OR 0.8, 95%CI 0.2-2.9) and DLco abnormalities (OR 0.4, 95%CI 0.1-1.6)
In univariate analysis no significant association between CCNU or BCNU exposure and restrictive disease (OR 1.1, 95%CI 0.3-4.2) and DLco abnormalities (OR 1.4, 95%CI 0.6-4.7)
In multivariable analysis significant association between increasing doses of chest radiation and restrictive disease (20 Gy: OR 5.6 (95%CI 1.5-21.0), p<0.05). Significant association between increasing doses of chest radiation and DLCO abnormality (≤20 Gy: OR 6.4 (95%CI 1.7-24.4), p<0.01; 20 Gy: OR 11.3 (95%CI 2.6-49.5). p<0.01). Increasing chest radiation doses are significant predictors of decline in DLco longitudinally (20 Gy: OR 24.4 (95%CI 5.7-38.3), p<0.01).
In univariate analysis no significant association between history of smoking and restrictive disease (OR 0.9, 95%CI 0.7-1.9) and DLco abnormalities (OR 0.9, 95%CI 0.2-5.3)

S. H. Armenian, et al. Long-term pulmonary function in survivors of childhood cancer. 2015;33:1592-600. 10.1200/jco.2014.59.8318

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment** (= treatment analyzed in the paper)	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	Study population (N) ➢ Original cohort: NA ➢ Eligible cohort: 155 Analysed cohort: 121	☐ 1 **HSCT a, b** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☒ **5 Bleomycin** ☒ **6 Busulfan** ☒ **7 Lomustin (CCNU)** ☒ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung, 9a** ☐ **10 Surgery** ☐ **11 Combinations** ☒ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☒ **Longitudinal data available** ☒ **Control group mentioned** ☐ **Reference values stated** ☐ **Quality check performed** ☒ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☒ **Person who analyzed PFT was blinded to the exposure**
Centres: Single center, City of Hope Survivorship Clinic Country: USA Treatment era: 1972-2007 Years of Follow-up: Time dx to t2: 17.1 yrs (range 6.3-40.1 yrs) Time t1 to t2: median of 5 yrs (1-10.3 yrs)	Study population: Eligible at t1 (N): 155 Analysis at t2 (N): 121 Response rate=78.1% Controls: General population, age- and sex-matched Inclusion criteria: Survivors diagnosed <age 22, with ≥2 yrs post diagnosis, treated with pulmonary-toxic chemotherapy and/or radiation and/or allogeneic HCT with cGVHD or pulmonary and/or surgery Cancer diagnoses: HL 34%	Chemotherapy (median doses) and %any Bleomycin (60 IU/m2), 35% Busulfan (436 mg/m2), 12% BCNU/CCNU (450 mg/m2), 10% Radiotherapy (median doses, range) chest (13.2 Gy, 2-76): 26% no radiotherapy 50% ≤20 Gy 24% >20 Gy Surgery 6% lobectomy, wedge resection or metastasectomy HSCT (53%) Autologous 17% Allogeneic 36%	Pulmonary function assessment: - PFT at baseline (t1) and at follow-up (t2) - Compared with healthy controls (at t2) - PFTs performed according to ATS protocols - PFT parameters measured: TLC, FVC, FEV1, FEV1/FVC, DLco, DLco/Va - %-predicted calculated by using established reference values (reference not stated) - cut-offs: obstructive FEV1/FVC<0.7, FEV1<80% predicted; restrictive TLC<75%, FEV1≥80% predicted diffusion DLco<75% predicted **Comparison survivors – survivors with risk factor analysis** (univariable analysis, if sig -> multivariable regression analysis) **Bleomycin**:	**Analysis:** - Cross-sectional and longitudinal analysis - Univariable logistic regression - Multivariable logistic regression, adjusted for race, health insurance status, smoking, heart failure Limitations: - Single center - Data collection not clearly prospective/retrospective - Selection bias – only survivors at follow-up at a tertiary center - No lung function quality checks reported, no missing values reported - Healthy control group not well characterized - Time between t1 and t2 highly variable Strength: - Longitudinal PFT assessment

	NHL 6% Leukemia 36% Sarcoma 11% Other 14% (not specified) <u>Age at diagnosis (yrs):</u> Median (range): 16.5 (0.2-21.9) <u>Age at follow-up (t2) (yrs):</u> Median (range): 32.2 (14.6-58.9)		- no significant association between bleomycin exposure and restrictive disease: univariable OR 0.7, 95%CI 0.3-1.6 - no significant association between bleomycin exposure and DLCO abnormality: univariable OR 0.8, 95%CI 0.4-1.7 (no multivariable anaylsis performed because not significant!) **<u>Busulfan</u>**: - no significant association between busulfan exposure and restrictive disease: univariable OR 0.8, 95%CI 0.2-2.9 - no significant association between busulfan exposure and DLCO abnormality: univariable OR 0.4, 95%CI 0.1-1.6 (no multivariable anaylsis performed because not significant!) **<u>BCNU or CCNU</u>**: - no significant association between BCNU or CCNU exposure and restrictive disease: univariable OR 1.1, 95%CI 0.3-4.2 - no significant association between BCNU or CCNU exposure and DLCO abnormality: univariable OR 1.4, 95%CI 0.6-4.7 (no multivariable anaylsis performed because not significant!) **<u>Smoking</u>** - no significant association between smoking history and restrictive disease: univariable OR 0.9, 95%CI 0.7-1.9 - no significant association between smoking history and DLCO abnormality: univariable OR 0.9, 95%CI 0.2-5.3 (no multivariable anaylsis performed because not significant!) **<u>Chest radiation</u>**: - significant association (multivariable) between increasing doses of chest radiation and restrictive disease: - ≤20 Gy: OR 1.6 (95%CI 0.5-5.7), not sign. - >20 Gy: OR 5.6 (95%CI 1.5-21.0), p<0.05 - significant association (multivariable) between increasing doses of chest radiation and DLCO abnormality: - ≤20 Gy: OR 6.4 (95%CI 1.7-24.4), p<0.01 - >20 Gy: OR 11.3 (95%CI 2.6-49.5). p<0.01	- PFT assessment blinded to exposure

			Longitudinal comparison t1 – t2 for DLco: - t1: 89 normal DLco patients - t2: 23/89 (25.8%) abnormal DLco test -> predictors for decline in DLco: - ≤20 Gy: OR 6.4 (95%CI not stated), not sign. - >20 Gy: OR 24.4 (95%CI 5.7-38.3), p<0.01	

Main findings/message:
Hodgkin and NHL survivors treated with thoracic radiation and chemo have significantly lower FEV1 and FEV1/FVC compared to survivors treated with chemo-only.

K. Nysom, et al. Risk factors for reduced pulmonary function after malignant lymphoma in childhood. 1998;30:240-8.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: 118 ➢ Eligible cohort: 63 Analysed cohort: 41	☐ 1 **HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung:** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☒ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☒ **Z-scores** ☐ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated:** Quanjer, Rosenthal ☒ **Quality check performed** ☒ **Lung function procedure stated** ERS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Danish Cancer Registry (Juliane Marie Centre, Rigshospitalet) Country: Denmark Treatment era: 1970 to 1992	Study population: Patients diagnosed with HD & NHL < age 15yr Reference values based on 348 healthy, non-smoking controls (age 13-24yr in a local population) ➔ 47 HD, 71 NHL (total 118) Eligible & Analysis: 32 with HD, 31 with NHL; **41** patients [22 with HD & 19 with NHL] were analysed Inclusion criteria: Alive and completed therapy; Informed consent Cancer diagnosis: Lymphoma (HD & NHL) Age at diagnosis: Median 11yr (3.9-15yr) Age at follow-up: Median 21.3yr (10.6-38.1yr)	Name of protocol: Various protocols (not all patients received all drugs in combinations) Stratification in 2 exposure groups: - **TI: Chemotherapy & thoracic RT** (can include RT to other sites) [21 patients] - **noTI: Chemotherapy only** (included RT to other sites but not thoracic) [20 patients] Chemotherapy (doses): 1. Bleomycin Median 113mg/m^2 (111-147) in Chemo only group; Median 115mg/m^2 (20-116) in Chemo & RT group 2. BCNU Median 702mg/m^2 (180-1064) in chemo only group; Median 231mg/m^2 (83-671) in chemo & RT group 3. CCNU 430 & 460mg/m^2 in chemo only group;	How was outcome assessed? Lung function (FEV1, FVC, TLC, DLCO) & heights were measured. Results of lung function values were analysed as **standard residuals** (observed minus predicted values/residual standard deviation), **equivalent to SD (Z-scores)**. These were expressed as mean values with 95% CI & ranges, and compared with reference data and between treatment groups (chemotherapy & thoracic RT versus chemotherapy only). Lung function results were considered **abnormal** if they were **>1.645 residual SD from predicted mean values**. Information on respiratory symptoms, self-directed physical work capacity, & smoking were collected. Main **descriptive results:** **Comparing all patients with reference values:** **- mean FEV1, FVC, TLC** significantly reduced when compared with reference values (-0.9 to -1.1 standard residual). **- mean DLCO was significantly reduced** when compared with reference value (-1.3 standard residual)	Analysis: Student's t-test, Chi-square & Mann-Whitney's unpaired tests were used to evaluate any significant difference between: • Patients and reference values; • TI/Chemo & RT group and noTI/chemo-only group; • Smokers and non-smokers (smaller N!) Multiple linear regression models were used to evaluate possible predictive variables of lung function Limitations and Potential bias/methodological problems: Some differences in demographic data between chemo & RT and chemo only groups: • More intrathoracic disease with HD (18 vs 4) in chemo & RT group • More smokers in chemo & RT group (9 vs 3) • Longer follow-up period from completion of therapy in chemo & RT group (11.3 vs 3yr)

	Time since diagnosis: Median 10.5yr (2.3- 23.7yr) Smoking: 10 smokers, 4 ex-smokers	Median 384mg/m^2 (67-525) in chemo & RT group 4. Cyclophosphamide 7g/m^2 in chemo only group; 7.2 & 7.8g/m^2 in chemo & RT; 5. Doxorubicin Median 421mg/m^2 (113-528) in chemo only group; Median 265mg/m^2 (50-446) in chemo & RT group 6. Methotrexate (IV) Median 24g/m^2 (1-80) in chemo only group 7. Other drugs include: Procarbazine, Dacarbazine, Mechlorethamine, Methotrexate intrathecal & oral Radiotherapy (doses): 1. Mantle & thoracic Median 37Gy (37-40) 2. Inverted Y/ Abdominal Median 37Gy (20-40) 3. CNS Median 24Gy (18-24)	**Comparing TI versus noTI:** **- mean FEV1, FVC, FEV1/FVC, TLC** lower in TI versus noTI. FEV1 and FEV1/FVC significantly lower in TI versus noTI; FVC and TLC not significant. Main results **multiple linear regression**: - Lung volumes (FVC, FEV1, TLC) were significantly related to age at diagnosis when adjusted for treatment group and smoking status.	

Main findings/message:
Lung function (FVC, DLCO, and DLCO/VA) decreased during first 6 months and improved thereafter. FVC and TLC were back to normal (>80% predicted) at 12 months, DLCO was normalized at 24 months, but DLCO/VA remained reduced. There is no sign. effect on lung function of cumualtive Bleomycine dose (DLCO, P=0.98; DLCO/VA, p=0.92), additional lung irradiation (bilateral full radiation, p>0.4) or smoking (p>0.25).

N. M. Marina, et al. Serial pulmonary function studies in children treated for newly diagnosed Hodgkin's disease with mantle radiotherapy plus cycles of cyclophosphamide, vincristine, and procarbazine alternating with cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine. 1995;75:1706-11.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	**Study population (N)** ➢ Original cohort: 85 Hodgkin patients ➢ Eligible cohort: 52 with mantle RT and COP/ABVD ➢ Analyzed cohort: 37	☐ **1 HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☒ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations:** ☒ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☒ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☒ **Longitudinal data available** ☐ **Control group mentioned** ☐ **Reference values stated** ☐ **Quality check performed** ☐ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single-centre: St. Jude's Children's Research Hospital, Departments of Pediatrics and Radiology University Country: USA Treatment era: 1983-1988 Years of Follow-up: Median (range) 93 (56-126) months Pulmonary function follow-up: Median 19 (3-79) months after end of therapy	Inclusion criteria: Biopsy-proven Hodgkin's disease Pulmonary functions measured before, during and after treatment Cancer diagnosis: Hodgkin's disease Age at diagnosis: Median 15 (range 6-20) years Time since diagnosis Lung functions from DX to 2 yrs after DX (all), up to 4 yrs after DX (some)	Name of protocol COP/ABVD Chemotherapy (doses) **COP**: cyclophosphamide (200mg/m2 i.v. weeklyx4), vincristine (1.0mg/m2 i.v. weeklyx4, procarbazine (100mg/m2 orally daily for 2 weeks) **ABVD** on days 1 and 14: doxorubicin (25mg/m2 i.v.), bleomycin (10mg/m2 i.v.), vinblastine (6.0mg/m2 i.v.), dacarbazine (250mg/m2 i.v.) Radiotherapy (doses) Absent pulmonary parenchymal disease: low dose mantle radiotherapy, when 18-20 Gy Nodular parenchymal involvement: mantle radiotherapy plus 14- 16 Gy bilateral whole lung radiation	How was outcome assessed? Medical history, physical examination, laboratory, diagnostic imaging, clinical staging (Ann Arbor), measurement of: DLCO, Spirometry, body plethysmography **Assessed parameters:** FVC, TLC, diffusing capacity (DLCO), diffusing capacity per unit of alveolar volume (DLCO/VA). All parameters presented as % predicted **Time points of PFT:** before 1st Bleomycin dose (Baseline lung function), after end of radiotherapy, after end of therapy, and in general also before each cycle of ABVD. Average 7 PFT per patient, range 3 to 12 Prevalence **FVC and TLC** decreased slightly at 1 yr post Dx (n.s.), back to baseline at 2 yrs post Dx.	Analysis: Repeated-measures mixed-effects model Limitations: Small study population, 30% drop-out PFT as % predicted Follow-up for only 2 (to 4) years Strength: Carefully conducted and reported study Longitudinal PFT Baseline PFT before treatment Homogeneous group (1 DX, 1 Treatment scheme) Analysis fine (change from baseline) Potential bias/methodological problems: NA

		<u>Surgery (kind of surgery)</u> NA	**DLCO and DLCO/VA**: declined during first 6 months of therapy, gradual improvement over time. Both remained decreased at one year post-diagnosis, DLCO/VA remained also decreased at 2 yrs after Dx (= 1 yr after end of tt) <u>Risk factors</u> No sign. effect on lung function of: - Cumualtive Bleomycine dose (but: bleomycin was omitted when DLCO/VA <50%): DLCO, P=0.98; DLCO/VA, p=0.92 - Additional lung irradiation (bilateral full radiation): p>0.4 - smoking: p>0.25	

Main findings/message:
Multiple thoracotomies in osteosarcoma patients predicted greater impairment of TLC. Prevalence of abnormal values not significantly different those exposed to Bleomycin or not.

J. W. Denbo, et al. Long-term pulmonary function after metastasectomy for childhood osteosarcoma: a report from the St Jude lifetime cohort study. 2014;219:265-71. 10.1016/j.jamcollsurg.2013.12.064

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	**Study population (N)** ➢ Original cohort: NA ➢ Eligible cohort: 26 ➢ Analyzed cohort: 21	☐ **1 HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☒ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☒ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** ATS guidelines ☐ **Quality check performed** ☐ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single centre: SJLIFE Country: USA Treatment era: 1968-1998 Years of Follow-up: Mean 20 years (±9 yesr SD)	Study population: Eligible (N): 26 Analysis (N): 21 Inclusion criteria: metastasectomy for osteosarcoma and available PFT results Cancer diagnosis: Osteosarcoma Age at diagnosis: Mean 13yeasr (± 5 years SD) Age at follow-up: Mean 35 years (±11 SD)	Chemotherapy (doses) Bleomycin in n=6 (mean 107mg/m2; range 45-150mg/m2) BCNU n=0 Radiotherapy (doses) NA Surgery (kind of surgery) Thoracotomy 100% HSCT NA	How was outcome assessed? Medical records, prospective measurements Spirometry, body plethysmography, DLCO measurement Abnormal PFT: FVC <80%; FEV1 <80%; TLC <75%; DLCOcorr <75% Incidence, Prevalence: - Abnormal TLC: 29% - Abnormal DLCOcorr: 47% - Abnormal FVC 40% - Abnormal FEV1 48% - None with obstructive disease - 29% (6/21) with restrictive disease Risk factors (RR, OR…): - After multiple thoracotomies higher prevalence of abnormal values for TLC, FVC, and FEV1 (only TLC statistically significant: p=0.031) - Prevalence of abnormal values not significantly different when comparing ≤2 resected lesions vs >2 resected lesions - Prevalence of abnormal values not significantly different those exposed to Bleomycin or not.	Analysis: Fisher's exact test Limitations: Small sample Sample size too small for risk factor analysis Strength: Homogeneous cohort No missing outcome data Potential bias/methodological problems: Confounding not assessed

Main findings/message:
Long-term cancer survivors treated with potentially pulmonary-toxic therapy screened decades after treatment have a high prevalence of restrictive dysfunction (17.6%) and decreased DLCO (40%); Compared Bleomycin exposure, pulmonary radiotherapy and pulmonary surgery are all associated with pulm function impairment. Pulm RT, in combination with bleomycin or surgery is the most important risk factor.

R. L. Mulder, et al. Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer. 2011;66:1065-71. 10.1136/thoraxjnl-2011-200618

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	**Study population (N)** ➢ Original cohort: 248 ➢ Eligible cohort: 220 ➢ Analyzed cohort: 193	☐ **1 HSCT** ☒ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☒ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☒ **10 Surgery** ☒ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☐ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☐ **Reference values stated** ☐ **Quality check performed** ☐ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**

Centres:
Single centre, Emma Children's Hospital /academic medical center
 	
Country:
Netherlands
 	
Treatment era:
1966-1996
 	
Years of Follow-up:
1996 to 2009
Median 17.9 years
(range 5.6-36.8)
	Inclusion criteria:
	1) Diagnosed between 1966 and 1996
	2) aged <18 years at dx
	3) treated mainly at EKZ/AMC
	4) survived ≥5 years after diagnosis at January 2007
	5) Received pulmonary toxic therapy (Bleomycin, pulmonary radiation, pulmonary surgery)
	6) ≥18 at PFT evaluation
	
	Cancer diagnosis:
	All cancers where pulmonary toxic therapy was used
	
	Age at diagnosis:
	Median 10 years (range 0-17)
	
	Age at follow-up:
	Median 27.3 years (range 18.2-47.0)
	
	Time since diagnosis
	Median 17.9 years (range 5.6-36.8)
		Name of protocol: NA
		
		Chemotherapy (doses)
		Bleomycin (**57%**; dose: 60 [10-594/m2])
		Not details on other chemotherapeutics
		
		Radiotherapy(doses)
		Any (40.9%)
		Complete thorax (6.7%)
		Part of thorax (13.5%)
		Mediastinum (13.5%)
		TBI (6.8%)
		
		Surgery (kind of surgery)
		Any (16.6%)
		Metastectomy uni (4.7%)
		Metastectomy bilat (5.7%)
		Lobectomy (0)
		Pneumonectomy (0)
		Thoracic wall resection (2.6%)
		Other (3.1%)
			How was outcome assessed?
			One-time assessment, at variable interval after Dx. First "complete" pulmonary function test performed at least 5 yrs after Dx included.
			- Diagnoses, graded per CTCAE and other standardized definitions
			- Pulmonary function test:
			  - Spirometry: FVC, FEV1, FEV1%
			  - Unclear how TLC was measured. (Plethysmography?)
			  - DLCO and DLCO/AV
			
			Prevalence at time of investigation (5 to 37 years after DX)
			Overall,
			- 21% with FEV1<80%
			- 3.1% with FEV1/FEV <70%
			- 2.1% with both parameters pathological (=obstructive)
			- 17.6% with TLC or FVC<75% predicted (=restrictive)
			- 39.9% with DLCO<75% pred
			- 4.3% with DLCO/AV <75%
			
			- **Total 44% had ≥Grade 2 pulmonary impairment**
				Analysis:
				Cross-sectional design
				Multivariable analysis
				
				Limitations:
				- Retrospective study
				- No description of lung function testing and validation, likely heterogeneous data quality; no quality control described.
				- No description of normal values used for lung function tests
				- Lung RT info not dose-specific (any).
				- Variable length of Follow-up (5 - 37 years)
				- No original lung function data described, only the proportion with pathological results based on definitions.
				
				Strength:
				- good participation rate (>85%)
				- Long-term outcomes, but at very variable distance from Dx (5 to 37 years)
				- clearly defined severity grading
				
				Potential bias/methodological problems:
				- retrospective study
				- Limited informaiton on lung function

			- 73% had one or more mild pulmonary function impairments (grade 1) - 14.5% had both restrictive lung function and decreased DLCO Risk factors (OR): **Restrictive disease (≥Grade 2)** Model 1: Pulmonary radiotherapy (OR 12.87; 3.37-49.08); vs. no RT Surgery yes vs. no (OR 3.79; 1.25-5.79) High-dose cyclophosphamide and bleomycin not associated with restrictive disease Multivariable Model 2 (ref: bleomycin alone): Radiotherapy only (OR 6.99; 2.27-21.54) Bleomycin + RT (OR 9.42; 1.71-51.86) RT + surgery (OR 33.44; 7.81-143.09) Surgery only not associated **DLCO impairment (≥Grade 2)** Model 1: Pulmonary radiotherapy (OR 5.84; 1.88-18.14); vs. no RT High-dose cyclophosphamide, bleomycin, and surgery not associated with DLCO impairment Multivariable Model 2 (ref: bleomycin alone): Radiotherapy only (OR 2.85; 1.32-6.19) Bleomycin + RT (OR 6.17; 1.37-27.84) RT + surgery (OR 5.98; 1.64-21.81) Surgery only and bleomycin with surgery not associated with DLCO impairment If longitudinal data available: NA **Exact results available from publication, Table 3**: "Risk factors for pulmonary function impairment (grade 2 or higher)	testing - Limited information on chemotherapy and radiation dosimetry - No information on smoking and lifestyle - Limited to survivors with known pulmonary toxic agents

Main findings/message:
Median 23 years after treatment for ALL with chemotherapy only, mean pulmonary function is within the lower predicted range for the whole group. Impaired DLCO (<80% predicted) was found in 22%. Smoking is a risk factor for impaired DLCO. No association found between cumulative dose of methotrexate and cyclophosphamide and impaired DLCO (only in text, no data shown).

O. Myrdal, et al. Risk factor for impaired pulmonary function and cardiorespiratory fitness in very long-term adult survivors of childhood acute lymphoblastic leukemia after treatment with chemotherapy only. (2018). Acta Oncologica, 57:5, 658-664

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☐ **Cohort** ☒ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	**Study population survivors (N)** ➢ Original cohort: NA ➢ Eligible cohort: 210 ➢ Analyzed cohort: 116	☐ **1 HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung: a** ☐ **10 Surgery** ☐ **11 Combinations** ☒ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☒ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated:** Pellegrino ☐ **Quality check performed** ☒ **Lung function procedure stated** According to ERS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Design Prospective cross-sectional Centres: Oslo University Hospital Country: Norway Treatment era: 1970 - 2002 Years of Follow-up from diagnosis: Median 23.2 years Range 7.4 – 40.0 years	Study population: Survivors of acute lymphoblastic leukemia (ALL) treated with chemotherapy only Inclusion criteria: Diagnosed before age 16 years with ALL, treated with chemotherapy only (no CSI, no BMT), diagnosed 1970 to 2002, age >18 years and alive in 2009 Cancer diagnoses: Acute lymphoblastic leukemia 100% Age at diagnosis: Median 5.4 years Range 0.3 – 16 years Age at follow-up: Median 28.5 years Range 18.6 – 46.5 years	Name of protocol Different protocols Chemotherapy (dose) median (range): 95% Methotrexate: 21g/m^2 (1-64) 77% Anthracyclines: 120mg/m^2 (40 – 510) 33% Cyclophosphamid: 3g/m^2 (0.3 – 10) Radiotherapy (dose): NA Surgery NA Smoking: 19%	How was outcome assessed? - Spirometry: FVC, FEV1, FE1/FVC - Lung volumes: TLC, RV - Gas diffusion capacity: DLCO, DLCO/VA - PFT results as absolute values and percentage of predicted normal values Prevalence: - Mean value for all lung function variables >80% predicted - 3% with restrictive impairment - 6% with obstructive impairment - 22% impaired DLCO Risk factor analysis: - No significant correlation between DLCO% predicted and cumulative dose of methotrexate or cyclophosphamide (only in text, no data shown) - Multiple linear regression analysis: smoking associated with reduced DLCO% predicted: β -9.8; 95%CI -16.0, -3.6; p-value 0.002	Analysis: - Students t-test or Mann-Whitney-U test: comparison of group mean - Chi-squared: comparison of categorical data - Multiple linear regression analysis: to detect associations between pulmonary function and explanatory variables - PFT according to ERS guidelines - All measurements on same machine - Reference values for PFT: Pellegrino et al - Obstructive= FEV1/FVC <0.7 (GOLD criteria) - Restrictive and DLCO impairment= <80% predicted (corresponds to lower 5th percentiles acc. to Pellegrino et al) Limitations: - No control group Strength: - long follow-up period - homogeneous population - accurate treatment data - all PFT performed with the same criteria

	<u>Time since treatment:</u> Median 23.2 years Range 7.4 – 40.0 years			- high response rate <u>Potential bias/methodological problems:</u> - PFT values compared to normal values from 2005

Main findings/message:
Treatment of childhood ALL causes mild pulmonary toxicity on the long term (61% normal lung function pattern). Age at treatment and intensity of treatment protocols are risk factors for reduced total lung capacity (TLC). Higher cumulative doses of cyclophosphamide are related with changes in TLC (simple regression model: R^2 =0.04, p=0.07; multiple regression model: R^2 =0.1, p=0.02). Change in TLC is not associated with the number of high-dose methotrexate cycles (simple regression model: R^2 =0.00, p=0.9). No increased pulmonary toxicity of tobacco smoking in survivors of childhood ALL compared with background population (simple regression model: R^2 =0.02, p=0.2); CAVE: small sample size and mild tobacco exposure.

6402. K. Nysom, et al. Pulmonary function after treatment for acute lymphoblastic leukaemia in childhood. 1998;78:21-7.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	**Study population (N)** ➢ Original cohort: 304 ➢ Eligible cohort: 162 ➢ Analyzed cohort: 94	☐ **1 HSCT** ☒ **2 Cyclophosphamid** ☒ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☒ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☒ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☒ **Z-scores** ☐ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** reference values form own laboratory by adjusting published reference values ☐ **Quality check performed** ☒ **Lung function procedure stated:** ERS ☐ **Cleaning of lung function data described** ☒ **Person who analyzed PFT was blinded to the exposure**
Design: Cross-sectional, retrospective Centres: Multicentre: Data from population-based Danish Cancer Registry Lung function test: Rigis hospital Country: Denmark Treatment era: 1970-1990 Years of Follow-up from diagnosis: Median: 10.6 years Range: 3.4-23.4 years	Study population: After acute lymphoblastic leukemia Inclusion criteria: Diagnosis of ALL, alive, in first remission, treatment finished, not treated with HSCT Cancer diagnosis: Acute lymphoblastic leukemia Age at diagnosis: Median: 3.9 years Range: 0.5-14.8 years Age at follow-up: Median: 16.2 years Range: 5.3-34.2 years Time since diagnosis Median: 10.6 years Range: 3.4-23.4 years	Name of protocol Several NOPHO protocols Chemotherapy (doses) AraC, CYC, DNR, DOX, L-ASP, MTX, PRED, VM26, 6TG, VCR CYC: 600 – 6700mg/m2 Radiotherapy (doses): Cranial irradiation 15-18 Gy or 24 Gy in 39 children	How was outcome assessed? Pulmonary function testing: - pneumotachograph: FEV1, FVC, flow-volume curves - Helium dilution technique: TLC - Single breath technique: transfer factor for carbon monoxide - comparison of values with reference values from laboratory, generated by adjusting published reference values (Quanjer and Tammeling et al) - data as standardized residuals; abnormal if >1.645 residual standard deviation from the predicted mean value PFT: - For every parameter at least one patient showed significantly reduced results (standardized residuals <1.645): see “additional data” Table 2 Aggregated data: - 26% (25/94) restrictive pattern - 11% (10/94) reduced TLCO - 2% (2/94) obstructive pattern - 61% normal pattern	Analysis: PFT results analyzed as standardized residuals (Z-scores) Pearson, spearman Simple and multiple linear regression models (step-down procedure) Chi-square test and Mann-Whitney test to compare baseline characteristics Limitations: Strongly correlated risk factors, for which they applied a complex statistical work around Small sample size of smokers Assessed only change in TLC in simple and multiple regression Strength: Large and homogeneous cohort All tests performed in same laboratory Evaluation of PFT result without knowledge of treatment protocol Potential bias/methodological problems:

			<u>Risk factors (RR, OR…):</u> Simple regression model - Cyclophosphamid: p=0.07 - High-dose MTX: p=0.9 - Smoking: p=0.2 - Younger age at treatment: p=0.045 - Younger age at follow-up: p=0.01 - Cranial irradiation: p=0.04 Multiple regression model - Cyclophosphamid: p=0.02 **Exact results available from publication, Table 2**: "Pulmonary function test results" and **Table 3** "Regression models for total tlung capacity"	Selection in study: 25% of eligible patients declined to participate; their characteristics are not described Long period of time and therefore many changes in treatment protocols

Main findings/message:
Significant PFT deficits in this population. Lower doses of radiotherapy (<23,45Gy) had larger DLCOcorr% predicted than those with higher dose (p=0.032) (univariable analysis). Cyclophosphamid dose is not significantly associated with change in FEV1% predicted (univariable analysis).

D. M. Green, et al. Pulmonary Function After Treatment for Embryonal Brain Tumors on SJMB03 That Included Craniospinal Irradiation. 2015;93:47-53. 10.1016/j.ijrobp.2015.05.019

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	**Study population (N)** ➢ Original cohort: 305 ➢ Eligible cohort: 303 ➢ Analyzed cohort: 260	☐ **1 HSCT** ☒ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung:** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☒ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** 10 different references for standardization ☐ **Quality check performed** ☒ **Lung function procedure stated:** ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Desgin Prospective cohort Centres: Multicentric Country: USA, Canada, Australia Treatment era: June 2003 - March 2010 Years of Follow-up from diagnosis: minimum 2 years	Study population: Embryonal brain tumors Inclusion criteria: Patients 3-21 years with embryonal brain tumors, treated on SJMB03 including CSI, minimum follow-up of 24 month, PFT data available Cancer diagnosis patients with PFT yes: Medulloblastoma 80% PNET 8% ATRT 7% Pineoblastoma 5% Medullomyoblastoma n=1 Age at diagnosis: Median 8,9 years Range 3,1-20,4 years Age at follow-up: NA	Name of protocol SJMB03 protocol Chemotherapy (dose): High-dose chemotherapy: CYC, Cisplatin, VCR, and peripheral blood stem cell support Median cumulative dose of CYC: 16,0 g/m2 (IQR: 15,7-16) Radiotherapy (dose): Median dose spinal radiation: 23,4 Gy IQR (23,4-36) Spinal dose ≤2345 cGy: 66,3 % Spinal dose >2345 cGy: 33,6% Proton beam: 0,07%	How was outcome assessed? Pulmonary function test after CSI, before each course of high-dose chemotherapy and 24 and 60 months after the completions of chemotherapy - PFT predominantly in children 6 years and older - Spirometry: FVC, FEV1 - Nitrogen washout method and body plethysmography: TLC - Single breath method: DLCO - values standardized to % predicted - abnormal values if: FEV1<80% pred., FVC <80% pred., DLCO<75% pred, TLC<75% pred Incidence, Prevalence: - DLCO corr < 75% predicted: 23% and 25% - FEV1 <80%: 20% and 29% - FVC <80%: 27% and 28% - TLC < 75%: 9%and 11% Risk factor analysis: - Higher **DLCO% predicted** in male (p<0.001), younger age at diagnosis (p=0.007), and treated with photon CSI (p=0.006)	Analysis: - Associations between categorical variables: Fisher exact test and X^2 - Differences between different time points: exact Wilcoxon signed-rank test - Repeated measures models were used to examine predictors of pulmonary outcomes Limitations: No PFT in young children No evaluation of scoliosis No baseline PFT/before CSI Many different references to standardize PFT results Strength: Large cohort with prospective and longitudinal data Homogenous cohort, one treatment protocol only Potential bias/methodological problems: Selection bias: PFTs more likely to be performed in those >5 years of age and with M0 stage disease

	Time since treatment: minimum 2 years		- Time point is significant predictor of DLCO% predicted (p>0.001) - Treatment with lower RT doses (≤2345 cGy) had larger DLCO (p=0.032) - Significant predictors of higher **FEV1% predicted**: male sex (p=0.025) and time from diagnosis (p<0.001). - Significant predictors of larger **TLC% predicted**: decreased time from diagnosis (p>0.001), male sex (p=0.009), white, non Hispanic race group (p=0.003), photon beam (p=0.002) and younger age (p=0.003) - Significant predictors of larger **FVC% predicted**: male sex (p=0.003) and shorter elapsed time from diagnosis (p<0.001) - No analysis of cyclophosphamide possible because all received CYC	Unclear how T1 and T6 are compared because number of eligible decreases from 295 to 214

ATRT=atypical teratoid rhabdoid tumor; CSI=craniospinal irradiation; PNET=primitive neuroectodermal tumor

Main findings/message:
In a cohort of 10-year survivors of childhood cancer, current and former smokers had lower FEV1/ FVC and DLCOcorr compared to non-smoker.

S. C. Oancea, et al. Cigarette smoking and pulmonary function in adult survivors of childhood cancer exposed to pulmonary-toxic therapy: results from the St. Jude lifetime cohort study. 2014;23:1938-43. 10.1158/1055-9965.epi-14-0266

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: NA ➢ Eligible cohort: 433 ➢ Analyzed cohort: 433	☐ 1 **HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☒ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1	☐ **Longitudinal data available** ☐ **Control group mentioned** ☐ **Reference values stated** ☐ **Quality check performed** ☐ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single, St. Jude (SJLIFE) Country: US Treatment era: unspecified Years of Follow-up: Not specified	Inclusion criteria: >10 years from diagnosis, >18 years of age at assessment; risk-based assessment of pulmonary function acc. to COG guidelines Cancer diagnosis: not specified Age at diagnosis: Median (range) yr 0-4: n= 60 5-9: n=88 10-14: n=139 15-22: n=146 Age at follow-up: Median (range) yr 35 (IQR 30-41) Time since diagnosis Median (range) yr 23 years IQR 18-29 years	Name of protocol not specified Chemotherapy (doses) bleomycin, busulfan, lomustine (BCNU), carmustine (CCNU), doses not provided Radiotherapy(doses): radiotherapy to the chest (thorax), whole lung, mediastinum, axilla, mini-mantle, mantle, extended mantle, total lymphoid irradiation, subtotal lymphoid irradiation, or total body irradiation, doses not provided Surgery (kind of surgery) pulmonary lobectomy, pulmonary metastasectomy or pulmonary wedge resection, HSCT (allo/auto) NA	How was outcome assessed? - Single breath diffusion capacity for carbon monoxide corrected for haemoglobin (DLCOcorr) - Spirometry: FEV1, FVC - Body plethysmography: TLC Definitions - Obstructive: FEV1/FVC < 0.70; acc. to GOLD criteria - Restrictive: TLC < 75% predicted; acc. to Guide to the Evaluation of Permanent Impairment - Smoker: smoked >100 cigarettes in their life Incidence, Prevalence: - 1 former smoker, 1 never smoker met criteria for obstructive lung disease (FEV1/ FVC <0.7) - Restrictive lung disease (TLC <75%) in 25.3% of current, 30.4% in former, 34.6% in never smokers. - Median TLC, FEV1, and FVC values not significantly different between never, former, and current smoker and between those who ever smoked more of less than 6 pack years (py) - Median DLCOcorr only significantly only different between never and current smoker (p=0.02) and those who ever smoked >6 py (p=0.03)	Analysis: - Kruskal wallis test - Dwass, Steel, Critchlow-Flinger multiple comparison procedure (DSCF) for pairwise comparisons between the groups - Chisq tests or Exact chisq tests for associations for categorical variables Limitations: Smoking assessed by self-report, no control group (used normative values) Strength: Large number, treatment exposure (although doses not provided) PFT performed according to ATS standards Potential bias/methodological problems: Critical risk of bias in classification of intervention due to self-reported outcome

			- FEV1/FVC median values among current (p=0.03) and former smoker (p=0.01) significantly lower compared to median values of never smoker <u>If longitudinal data available:</u> None **Exact results available from publication, Table 2**: "Pulmonary function among adult survivors of childhood cancer"	

Main findings/message: Comparing lung function parameters of leukemia survivors with age- and sex-matched controls a median of 4 years since diagnosis, FEV1, FVC, FRC, TLC, DLCO and VA are significantly lower in survivors than in controls. Risk factors for reduced parameters is cyclophosphamide.

6698. M. E. Jenney, et al. Lung function and exercise capacity in survivors of childhood leukaemia. 1995;24:222-30.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☐ **Cohort** ☒ **Cross-sectional** ☒ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	Study population (N) ➢ Original cohort: NA ➢ Eligible cohort: 178 ➢ Analyzed cohort: 70 69 with PFT	☐ 1 **HSCT** ☒ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☒ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☒ **Control group mentioned** ☐ **Reference values stated** ☐ **Quality check performed** ☐ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Multi-Centre Country: UK Treatment era: 1954-1988 Years of Follow-up: Median (range) yr Follow-up: August 1992	Inclusion criteria: Children with ALL or ANLL, diagnosed in the North West Region since 1953, completed treatment > 6 months without relapse, and age at study 6-30 years Cancer diagnosis: Acute lymphoblastic and non-lymphoblastic leukaemia (ALL, ANLL) Age at diagnosis: Median 5.8 (range 1.6-14.9) years Age at follow-up: Median 14.6 (range 13.3 – 15.9) years Time since diagnosis Median 4.2 (range 0.60 – 18.5) years	Name of protocol ALL: MRC UKALL protocol, prior to 1980: UKALL II, III, V, VII; after 1980: UKALL 8 and UKALL 10 ANLL: UKALL AML 9 or 10 trials Allogenic and autologous bone marrow transplantation was introduced for treatment of higher risk ALL and ANLL Chemotherapy (doses) Not specified Radiotherapy(doses) Cranial RT: n=45; dose 1800-2400cGy Craniospinal RT: n=10; dose 1200-2400cGy TBI: n=14; dose 1100-1440cGy Surgery (kind of surgery): NA HSCT: unclear if allogeneic or autologous HSCT, unclear number of patients with HSCT → not included as PICO	How was outcome assessed? Medical record: age at diagnosis, age at completion of therapy, details of cytotoxic chemotherapy and radiotherapy received, incidence of lower respiratory tract infections requiring hospitalisation Examination: cardiorespiratory system, resting BP and HR, height, weight and arm span Pulmonary function tests: FEV1, FVC, RV, FRC, ITGV, RAW, SGAW, TLC, DLCO Risk factor analysis - Cyclophposphamid leads to reduction in FEV1, FVC, TLC: p<0.001 - Craniospinal irradiation leads in reduction in FEV1, FVC, TLC: p<0.001 and DLCO=0.03 **Exact results available from publication, Table Va**: "Lung Function Results of Survivors of Leukemia" and **Table VI** "Independent Variables Which Led to a Reducation in Indices of Lung Function"	Analysis: - Multiple regression analysis on lung function data from control group to obtain predictive equations - Comparison survivors vs controls by student's unpaired t-tests - Interrelationships between variables examined by Pearson correlation coefficient and stepwise multiple regression Statistical significance was set at 5% 146 age- and sex-matched controls; close friend or siblings Limitations: No longitudinal data No pretreatment Pulmonary function Strength: Control group Potential bias/methodological problems: Table VI ("Independent variables which lead to a reduction in indices of lung function") shows significant results only

Main findings/message:
Lung function test results of survivors treated with bleomycin after a median of 2.3 years after treatment, bleomycin dose is associated with abnormal spirometry and smoking is associated with reduced DLCO.

A. P. Zorzi, et al. Bleomycin-associated Lung Toxicity in Childhood Cancer Survivors. 2015;37:e447-52. 10.1097/mph.0000000000000424

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☐ **Cohort** ☒ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: NA ➢ Eligible cohort: 195 ➢ Analyzed cohort 143	☐ 1 **HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☒ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☒ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** Stanojevic, Weng and Levison, reference equations from Sick Children, Pellegrino et al ☐ **Quality check performed** ☒ **Lung function procedure stated:** ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single center, Hospital for Sick Children, Toronto Country: Canada Treatment era: 1997-2010 Years of Follow-up: Median (range) yr 4,4 y (2,-7,4)	Inclusion criteria: Bleomycin containing regimen Cancer diagnosis: Hodgkin's disease 86% Extracranial germ cell tumor: 14% Age at diagnosis: Median (range) yr All < 18 years 63% aged between 11-15 years Age at follow-up: Median (range) yr 4,4 y (2,2-7,4) Time since treatment PFT median 2,3 years (1,4-4,9) after treatment	Name of protocol Median cumulative bleomycin dose= 60 U/m2 (20-180) MOPP/ABV 18% COPP/ABV 17% COPE/ABV 14% ABVD 1% AHOD0031 28% CCG59704 7% AHOD0831 1% PEB 14% Radiotehrapy Chest radiation 60% Dose median (range): 2100 cGy (1500-3000)	How was outcome assessed? - Medical records - Most recent post-treatment PFT (spirometry, body plethysmography, DLCO) - PFT performed according to ATS criteria - References: Stanojevic (spirometry); Weng and Levison (body plethysmography); unpublished reference equations from data collected at Sick Children (DLCO) Outcome definitions: Percent predicted for abnormal - TLC <80% - FVC <80% - DLCO <80% - Obstructive if: abnormal FVC, normal TLC and RV/TLC >=30% and scooped flow volume loop. - Restrictive: acc. to Pellegrino et al Prevalence: - Abnormal spirometry: 41% (n=58)	Analysis: Chi-squared, Fishers exact test Univariate analysis No multivariable model due to low event rates Limitations: Retrospective study PFT was performed with a median of 2,3 years (1,4-4,9) Strength: Homogeneous cohort Well defined PFTs Potential bias/methodological problems: Serious risk of confounding due to unadjusted analysis

			- obstructive: 70% (n=42) - restrictive: 18% (n=11) - mixed: 9% (n=5) - Abnormal DLCO: 19% (n=27) <u>Risk factors</u> No association between ventilator defects (obstr., restr., or mixed) and smoking (p=0.8) or lung radiation (p=0.13) OR for developing abnormal spirometry for each 1 U/m2 increase of bleomycin was 1.01 (95%CI 1.00-1.02) Association between being a smoker and abnormal DLCO (p=0.04). Cumulative bleomycin dose (p=0.07) and radiation (p=0.83) were not associated with reduced DLCO	

Main findings/message:
With longer follow-up time, the proportion of survivors after HSCT having a lung disease increases. Risk factors for restrictive lung disease in multivariate analysis were single fraction TBI (OR 22, 95%-CI 3.9-120), fractionated TBI 1.2Gy (OR 2.5, 95%-CI 0.4-16), fractionated TBI 2.0-2.25Gy (OR 2.8, 95%-CI 0.6-13) with no-TBI as reference. Risk factors for obstructive disease in univariate analysis were prior cyclophosphamide (p=0.05) and chronic GvHD (p=0.02). Risk factors for obstructive disease in multivariate analysis were cGvHD (OR 4.4, 95%-CI 1.6-12); SFTBI (OR 0.1, 95%-CI 0.5-0.5) seemed negatively associated, FTBI 1.2Gy (OR 0.1, 95%-CI 0.0-1.4) and FTBI 2.0-2.25Gy (OR 0.9, 95%-CI 0.3-2.8) were not associated.

P. A. Hoffmeister, et al. Pulmonary function in long-term survivors of pediatric hematopoietic cell transplantation. 2006;47:594-606.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☐ **Cohort** ☒ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: 472 ➢ Eligible cohort: 260 ➢ Analyzed cohort: 215	☒ 1 **HSCT b, d** ☒ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung a** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☒ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☐ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** reference equations of Rosenthal for children <18 years old and of Crapo for adults 18 years and older ☐ **Quality check performed** ☒ **Lung function procedure stated** ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single center Institution: Fred Hutchinson Cancer Research Center (FHCRC) Country: USA Treatment era: 1969-1995	Inclusion criteria: Myeloablative HSCT at FHCRC, at least 5 years survival after HSCT and at least 6y old Cancer diagnosis: ALL 36% AML 21% CML 10% MDS 6% JMML 1.5% Non-malignant 19% Age at diagnosis: Median (range) yr At HSCT 8.3y (0.3-18) Age at follow-up: Median (range) yr 19y (6.5-40.5)	Name of protocol Chemotherapy (doses)/ Radiotherapy(doses) a) 9.2 – 10.0 Gy single-fraction TBI (SFTBI) (13%) b) fractionated TBI (FTBI) with exposures of 2.0 – 2.75 Gy for 6 to 7 consecutive days or hyperfractionated exposures of 1.2 Gy 2 to 3 times daily for 4 consecutive days (62%). Between 1986 and 1990, some patients received 14.4 Gy TBI from a linear accelerator with lung shielding. Overall median dose not stated. Most TBI regimens included CY 60 mg/kg/day for 2 days. Most chemotherapy-only regimens utilized CY 50 mg/kg/day for 4 days for aplastic anemia (AA) patients and CY	How was outcome assessed? Medical records, prospective measurements, clinical examination, pulmonary function tests Incidence, prevalence: Obstruction (O)/ restriction (R), resp.: After 5-10 years FU: 8% (O)/ 20% (R); After 10-15 years: 12% (O)/ 36% (R); After 15-20 years: 9% (O)/ 43% (R); After >20 years: 38% (O)/ 50% (R) Risk factors: Univariate analysis: Restrictive: no PICO-relevant variable analyzed Obstructive: prior cyclophosphamide (p=0.05), chronic GvHD (p=0.02) Multivariate analysis: Restrictive: SFTBI (OR 22, 95%-CI 3.9-120), FTBI 1.2 Gy (OR 2.5, 95%-CI 0.4-16), FTBI 2.0-2.25Gy (OR 2.8, 95%-CI 0.6-13) versus non-TBI	Analysis: Multivariate analysis for restrictive and obstructive lung disease Limitations: Different exposures and cross-sectional design limit the strength of the study Strength: For HSCT studies, large number of participants. Potential bias/methodological problems: Follow-up data is aggregate data and not follow-up information of specific patients.

	Time since diagnosis Median (range) yr After HSCT: 10.5y (5-27.5)	(50 mg/kg/day for 4 days or 60 mg/kg/day for 2 days) combined with BU 4 mg/kg/day for 4 days for patients with a hematologic malignancy and some patients with non-malignant hematologic disorders. Non-TBI regimens: Cyclophosphamide (CY) with/ without procarbazine (n=24, 10%), busulfan with CY or CY dimethylmyleran (12%) Surgery (kind of surgery): NA HSCT (allo/auto/donor specifics/Conditioning): 5% autologous 95% allogeneic	Obstructive: cGvHD (OR 4.4, 95%-CI 1.6-12); SFTBI (OR 0.1, 95%-CI 0.5-0.5) seemed negatively associated, FTBI 1.2Gy (OR 0.1, 95%-CI 0.0-1.4) and FTBI 2.0-2.25Gy (OR 0.9, 95%-CI 0.3-2.8) were not associated. If longitudinal data available: Mean/Median duration until pulmonary disease develops: NA **Exact results available from publication, TABLE VI**: "Univariate Analysis of Risk Factors Associated With Restrictive Lung Disease and Obstructive Lung Disease" and **TABLE VII** "Multivariate Risk Factors for Restrictive Lung Disease" and **TABLE VIII** "Multivariate Risk Factors for Obstructive Lung Disease"	

Main findings/message:
Long-term follow-up of lung function after bone marrow transplantation frequently remains abnormal. Post-transplant survival is related to pre-transplant DLCO. Older age at transplantation is associated with significant decrease of FVC z-score (p=0.026) and DLCO z-score (p=0.039) from pre-transplant to post-transplant.

J. P. Ginsberg, et al. Pre-transplant lung function is predictive of survival following pediatric bone marrow transplantation. 2010;54:454-60. http://dx.doi.org/10.1002/pbc.22337

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: 457 ➢ Eligible cohort: not mentioned ➢ Analyzed cohort: 317 (post-HSCT) 273 (pre-HSCT) 133 (both pre- and post-HSCT)	☒ 1 **HSCT: 1a** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☒ **Z-scores** ☐ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☒ **Longitudinal data available** Only aggregate, not single patient ☐ **Control group mentioned** ☒ **Reference values stated** Rosenthal, Hankinson ☐ **Quality check performed** ☒ **Lung function procedure stated:** ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded 28yclop exposure**
Centres: Multicentre: Children's Hospital of Philadelphia; Hospital for Sick Children (Toronto) Country: USA/Canada Treatment era: 1978-2005 Years of Follow-up: Only time point of last lung function measurement available	Inclusion criteria: Treatment with stem cell transplant, at least one lung function test result available Exclusion: >1 transplantation Cancer diagnosis: Those with post-HSCT PFTs: ALL 84 (26%) AML 83 (26%) Immune 7 (2%) Other leukemia 14 (5%) Lymphoma 34 (11%) Non-malignant 47(15%) Other 1 (0%) Solid 37 (12%) Age at diagnosis: Categories only: < 6 years: 45 (14%) 6–12 years: 129 (41%) 12–18 years: 122 (38%)	Name of protocol: NA Chemotherapy (doses) no dose Radiotherapy(doses): no dose Surgery (kind of surgery): no further information Type of transplantation: For those with post-HSCT PFTs: Allogeneic 76% Autologous 24% Conditioning Busulfan/ CYC 74 (23%) TBI/ CYC 127 (40%) CTX+ other 49 (15%) TBI+ other 47 (15%) Other 16 (5%)	How was outcome assessed? Medical databases of transplanted patients and of the respiratory department for PFTs Lung Function Score (LFS) calculated with pre-transplant values: - FEV1 % and DLCO >80% predicted=1, 70 – 80% predicted=2, 60–70% predicted=3, <60% predicted=4. - FEV1 and DLCO scores were summed (maximum value of 8) - Sum assigned to one of four categories as the pre-transplant lung function score (LFS): LFS=2: Category I, LFS=3–4: Category II, LFS=5–6: Category III, LFS=7–8: Category IV Risk factors (RR, OR…): Predictors of post-HSCT PFTs (at the last time of measurement): - Older age at transplantation is associated with decrease of: - FVC z-score (p=0.026) - DLCO z-score (p=0.039) - FEV1 z-score (p=0.079) - TLC z-score (p=0.432)	Analysis: - One-way analysis of variance: for differences in pulmonary function by type of transplant, diagnosis, conditioning, and age at transplant - Kaplan–Meier curves and proportional hazards model: relationships between post-transplant survival and LFS, age, diagnosis, study site, race, and sex. - standard errors: differences between pre- and post-transplant populations - P-values Limitations: Retrospective data PFTs at different intervals Incomplete data on pre- and post-treatment PFTs Strength: Relatively large cohort Longitudinal data Results as percentage predicted and z-scores Potential bias/methodological problems:

	18+ years: 21 (7%) Age at follow-up: NA Time since diagnosis NA	Duration of protocol: PFTs at the following time points in post-transplant analysis: Pre-transplant: 133 (42%); 0–6 months post: 44 (14%); 6–12 months post: 107 (34%); 1–2 years post: 142 (45%); 2–5 years post: 156 (49%); 5+ years post: 98 (31%)	from pre-transplant to post-transplant (ANOVA). If longitudinal data available: 2-5 years post-transplant compared to pre-transplant (156 patients) FVC z-scores: mean -1.55 FEV1 z-scores: mean -1.56 TLC z-scores mean -0.70 DLCO z-scores mean -1.71 >5 years post-transplant compared to pre-transplant (98 patients) FVC z-scores: mean -1.68 FEV1 z-scores: mean -1.70 TLC z-scores mean -1.12 DLCO z-scores mean -1.54 Mean/Median duration until pulmonary disease develops NA **Exact results available from publication, TABLE III**: "Correlates of Last Post-Transplant Pulmonary Function"	Not all the patients have PFTs >2 years after transplantation Unknown if patients without post-PFT differ significantly than the ones with post-PFT, e.g. had better lung function

Main findings/message: **59% of pulmonary dysfunction after allogeneic HSCT with most events occurring during the first year post-HSCT. Risk factors were extensive chronic GVHD and abnormal pre-treatment PFTs. Limited chronic GvHD and age at HSCT were not risk factors.**				
L. M. Madanat-Harjuoja, et al. Pulmonary function following allogeneic stem cell transplantation in childhood: a retrospective cohort study of 51 patients. 2014;18:617-24. 10.1111/petr.12313				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: 163 ➢ Eligible cohort: 96 ➢ Analyzed cohort: 51	☒ 1 **HSCT 1a, 1b** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☒ **Pulmonary symptoms** ☐ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☒ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** Quanjer (ERS) ☒ **Quality check performed** ☒ **Lung function procedure stated** ATS ☒ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
<u>Centres:</u> Single center: Children's Hospital, Helsinki University Central Hospital <u>Country:</u> Finland <u>Treatment era:</u> 1993-2005	<u>Inclusion criteria:</u> Allogeneic HSCT. Final cohort (n=51) had at least one visit >1 yr post-HSCT and a baseline PFT. No metabolic disease, >6 mts post-HSCT, age >6 yrs <u>Cancer diagnosis:</u> ALL 55% AML or MDS 28% Non-malignant 8% CML 6% CGD 4% Lymphoma 2% <u>Age at HSCT:</u> Median (range) yr: 11.2 (6.2-19) <u>Age at follow-up:</u> Median (range) yr <u>Time since HSCT:</u> Median (range) yr: 4.1	<u>Name of protocol</u> NA <u>Chemotherapy (doses)</u> Cyclophosphamide 47% Cytarabine 47% Other 6% <u>Radiotherapy(doses)</u> Fractionated TBI 10-14 Gy 98% Total nodal irradiation 6 Gy 2% <u>HSCT:</u> Cyclophosphamide or cytarabine-based conditioning 94% + TBI 98%, Total nodal irradiation 2%	<u>How was outcome assessed?</u> Medical records. PFTs performed at baseline (pre-HSCT) and at follow-up visits starting at 6 month post-HSCT. RLD= FVC<80% + FEV1/FVC>80% OLD=FEV1<80% + FEV1/FVC<80% Patients with FVC<60% underwent lung biopsy. <u>Incidence, Prevalence:</u> 15.7% (8/51) had an abnormal pre-treatment PFT (5 restrictive, 3 mild obstructive) 59% developed abnormal PFT; 73% restrictive, 26% obstructive <u>PFT at baseline, 1-yr post HSCT, 5-yr post-HSCT</u> FVC: mean 93%, 75%, 77% FVC: median 92%, 82%, 83% FEV1: mean 95%, 75%, 75% FEV1: median 95%, 87%, 83% FEV1/FVC: mean 0.98, 0.90, 0.84 Significant reduction within 12 months in FEV1 and FVC in patients with normal baseline. After 12 months reduction not significant. <u>Risk factors:</u>	<u>Analysis:</u> Fisher exact test for evaluation of risk factors. Cox proportional hazards model for analysis of risk factors on pulmonary function. Longitudinal models for repeated measurements. <u>Limitations:</u> Retrospective analysis, small cohort, Only about half of eligible population had PFT; single center No data regarding doses of chemotherapy. <u>Strength:</u> Longitudinal data regarding timing of abnormal PFT. PFTs were reviewed according to ATS protocol. <u>Potential bias/methodological problems:</u> Selection bias – only patients with PFTs after treatment were included.

			Extensive chronic GVHD associated with a decline in FVC and FEV1. → Chronic GVHD (none=reference) Extensive: HR=10.20 (CI 2.42-43.03); p=0.002 Limited: HR=0.42 (CI 0.10-1.83); p=0.247 → Age at HSCT (6-11 years= reference): HR=1.14 (CI 0.40-3.26); p=0.804 (12-19yr) 12/51pts had FVC<60%, of which 8 had lung biopsies. 11/12 had extensive GVHD including lung involvement, as verified on lung biopsy. 4/12 (33%) died of pulmonary complications. **Exact results available from publication, Table 3**: "Risk factors for pulmonary dysfunction in survivors of allogeneic stem cell transplantation in childhood"	

Main findings/message:
Abnormal pulmonary function test results are present in up to 64% of survivors of pediatric allo-HSCT (DLCO). Older age (continuous) at allogeneic HSCT is associated with obstructive dysfunction measured by FEF 25-75% (HR 1.1; p=0.038) and impaired diffusion capacity (HR 1.1; p=0.005).

H. Inaba, et al. Pulmonary dysfunction in survivors of childhood hematologic malignancies after allogeneic hematopoietic stem cell transplantation. 2010;116:2020-30. 10.1002/cncr.24897

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: NA ➢ Eligible cohort: 208 ➢ Analyzed cohort: 89	☒ 1 **HSCT 1a** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☒ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** Hankinson ☐ **Quality check performed** ☒ **Lung function procedure stated** ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single Country: USA Treatment era: 1990-2005 Years of Follow-up: Median 8.9 (range 1.7-16.4) years	Inclusion criteria: Allo-HSCT at St. Jude, at least 6 years old, available pre-HSCT PFT for comparison Cancer diagnosis: ALL, AML, MDS, CML Age at HSCT: Median 12.7 (range 6.6-21.3) years Age at follow-up: Not stated Time since diagnosis Not stated	Name of protocol: Not stated Chemotherapy (doses): Mostly cyclophophamide, no pre-HSCT details known Radiotherapy(doses): Mostly TBI of 12 or 14 Gy Surgery (kind of surgery): N/A HSCT (allo/auto/donor specifics/Conditioning): all allo-HSCT patients, 46.1% unrelated, 41.6% matched sibling, 12.3% parent, 88.8% bone marrow, 11.2% PBSC, 78.6% fully matched, mostly Cy/TBI +/- other additions	How was outcome assessed? PFT per American Thoracic Society guidelines Incidence, Prevalence: Respiratory dysfunction in up to 64%, FEV1/FVC – 22.5%, FEV1 – 36%, FEF25-75 – 49.4%, RRV/TLC – 38.2%, FVC – 39.3%, TLC 43.8%, DLCO – 64% Risk factors (HR): Obstructive: male (2.1), respiratory event within 1 year of HSCT (2.7-3.2) PBSC (2.5), High risk disease (1.8), older age (1.1; p=0.038) Restrictive: PBSC (2.7), respiratory event <1 year of HSCT (2.3), acute GVHD (1.9) DLCO: high risk disease (2.6), CMV positive (1.7), older age (1.1) If longitudinal data available: Gradual decline over time	Analysis: Longitudinal methods, Cox proportional hazards models, Fisher's exact test, Cumulative incidences accounting for competitive risks; Independent analyses were performed for the 9 response variables Limitations: Restricted to ages 6 and above, restricted to those with good PFT results pre-HSCT Strength: Medium size, long follow-up, longitudinal data Potential bias/methodological problems: survivor bias, participation bias, testing bias

Main findings/message:
More than 1 year after allogeneic SCT 62% show impaired diffusion capacity (TLCO), 41% restrictive, and 11% obstructive disorder. Restrictive disease > 1 year after SCT associated with female sex (p=0.002) and younger age at SCT (p=0.08). Neither radiotherapy (TBI/TAI) nor donor-type were identified as risk factors for restrictive and/or obstructive disease. Significant reduction >1year after SCT compared to baseline only for TLCO. Significant reduction in FVC, FEV1 and TLC <1 year improve but not to normal again.

J. Wieringa, et al. Pulmonary function impairment in children following hematopoietic stem cell transplantation. 2005;45:318-23. 10.1002/pbc.20304

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	**Study population (N)** ➢ Original cohort: NA ➢ Eligible cohort: 106 ➢ Analysed cohort: 39	☒ **1 HSCT a, d** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☒ **Longitudinal data available** ☒ **Control group mentioned** ☒ **Reference values stated** Polgar and Weng ☐ **Quality check performed** ☐ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Design Prospective cohort Centres: Single centre, Leiden Country: Netherlands Treatment era: seen in late effects clinic 2001-2003 Years of Follow-up: Median 4.5 years Range 0.5-10 years	Study population: After allogeneic SCT Inclusion criteria: Allogenic SCT, visit outpatient late effect clinic, PFT before and at least twice after SCT Cancer diagnosis: Malignant: 30/39 (77%) - ALL 39% - AML 18% - CML 2% - MDS 16% - JMML 2% Benign: (23%) - SAA 14% - Thalassemia 2% - Fanconi anemia 2% - X-linked Adrenoleuko-dystrophy 5% Age at SCT: Median (range) 10 years (4-18)	Name of protocol According to disease: DCLSG protocols ALL-6, 7 and 8, relapse ALL 90 and 98 and ANLL 87, 92, 94 and 97 Chemotherapy (doses) CYC 120 – 200 mg/m2 and TBI or thoracoabdominal irradiation in 31 patients Busulfan (6.20 mg/kg) and CYC in 6 patients CYC only in 2 patients Radiotherapy dose: TBI: 7 - 12Gy Thoracoabdominal: 4 - 5Gy GvHD prophylaxis: NA HSCT Graft type: allogeneic, not specified	How was outcome assessed? PFT: spirometry (FVC, FEV1), helium dilution method (FRC, RV), single breath method using helium (TLCO) Parameters recorded as percentage predicted Reference for PFT: age, sex, length matched; paper Polgar and Weng Pathological when <80% predicted Prevalence: Significant reduction >1year after SCT compared to baseline only for TLCO Significant reduction in FVC, FEV1 and TLC <1 year improve but not to normal again Risk factors: -Restrictive lung disease > 1 year after SCT associated with female sex (p=0.002) and younger age (p=0.004) -Decrease in TLCO < 1 year after SCT more pronounced in boys and in those with malignant disease (p=0.009) - Decrease in TLCO > 1 year after SCT more in patients with malignant disease (p=0.05) - age at HSCT: trend towards a higher TLC at SCTpost2 for patients older than 10 years (P=0.08), w Longitudinal data:	Analysis: Changes in lung function values between pre-SCT, < 1 year post SCT and > 1 year post SCT: student paired t-test Risk factor analysis: linear regression Limitations: Small cohort Heterogeneous exposure before SCT which can influence "baseline" PFT Strength: Assessment via pulmonary function test Longitudinal data Potential bias/methodological problems: Bias due to confounding No information on 67 patients who had SCT in the study period and visited the outpatient clinic but did not have PFT at the given time points. PFT procedure not mentioned

	Time since SCT Median 4.5 years Range 0.5-10 years		See table III in additional information Mean/Median duration until pulmonary disease develops NA	

Main findings/message:
Cumulative incidence of pulmonary dysfunction at 10 years is 63.2%. TBI, age at HSCT (per year), and chronic GvHD are associated with reduced DLCO% predicted. TBI is associated with reduced TLC% predicted and FEV1/FVC predicted.

W. Leung, et al. A prospective cohort study of late sequelae of pediatric allogeneic hematopoietic stem cell transplantation. 2007;86:215-24. 10.1097/MD.0b013e31812f864d

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	Study population (N) ➢ Original cohort: NA ➢ Eligible cohort: 204 ➢ Analyzed cohort: 155	☒ 1 **HSCT: 1a, 1b, 1d** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☐ **Reference values stated** ☐ **Quality check performed** ☐ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single; St. Jude Children's Research Hospital (Memphis, TN) Country: USA Treatment era: 1990-2003 Years of Follow-up: Median (range) yr 9 (3.1-15.9)	Inclusion criteria: Surviving 1 or more year after allogeneic HSCT Cancer diagnosis: Myeloid malignancy 84 (54%), lymphoid malignancy 40 (26%), non-malignant 31 (20%) Age at diagnosis: Median (range) yr 9.7 (0.5 – 21.4) Age at follow-up: Median (range) yr 18.5 (4.6 – 36.1) Time since HSCT Median (range) 9 (3.1-15.9)	Name of protocol: NA Radiotherapy (doses) TBI 123 (79%) Dose of TBI 14.4Gy in n=59 Dose of TBI 8-12Gy in n=64 Dose of TBI none in n=32 Surgery (kind of surgery) HSCT (allo/auto/donor specifics/Conditioning) Alkylator-based conditioning 32 (21%)	How was outcome assessed? Prospective pulmonary function test Incidence, Prevalence: At least 1 parameter abnormal /77 survivors Cumulative incidence at 10 years 63.2% Risk factors: DLCO <80% predicted: - TBI: HR=2.2 (95%CI 1.07-5.09) p=0.026 - Age, per year: 1.1 (95%CI 1.04-1.17) p=<0.001 - chronic GVHD: HR=1.96 (95%CI 1.12-3.44) p=0.025 TLC <80% predicted: - TBI: HR=2.4 (95%CI 1.04-4.95) p=0.03 FEV1/ FVC predicted: - TBI: HR=2.4 (95%CI 1.1-5.74) ü=0.02 Longitudinal data available: No **Exact results available from publication, TABLE 4**: "Risk Factors for Late Sequelae"	Analysis: Cumulative incidence function of each late event was estimated Comparison by Kalbfleisch and Prentice and Gray. Limitations: Exposure data very limited, unclear how outcomes were assessed, procedures not clearly described. Only associations described that were found to be significant. Strength: Prospective cohort of exclusively childhood cancer survivors Potential bias/methodological problems: NA Recommendations: - if age > 8 at HSCT, TBI: → PFTs biennilally started 3 years after HSCT – pulmonary referral, flue shot, counselling for smoking, job, relocation

Main findings/message:
The odds of developing restrictive and hyperinflation defects increased with increasing mean and maximum lung dose but also with lung volume receiving at least 10Gy and 20Gy of irradiation. Thoracic surgery prior to radiation increased the odds of reduced FEV1 and RV/TLC. Bleomycin was found to have a protective effect but those patients also had less radiation why this finding was questioned.

A. De, et al. Correlation of pulmonary function abnormalities with dose volume histograms in children treated with lung irradiation. 2015;50:596-603.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: 170 ➢ Eligible cohort: 139 ➢ Analyzed cohort: 49	☐ 1 **HSCT:** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☒ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung: 9, 9ai** ☒ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☒ **Pulmonary diseases** ☒ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** Hankinson, Wang ☐ **Quality check performed:** ☒ **Lung function procedure stated:** ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: monocentric: Children's Hospital Los Angeles (CHLA), USA Country: Los Angeles Treatment era: 1999 - 2009 Years of Follow-up: Median: 2,91 Range: 0,01-8,28	Inclusion criteria: - Radiotherapy to the lungs. - One PFT post irradiation - Exclusion: TBI or palliative radiation Cancer diagnosis: Hodgkin Lymphoma (78%) Wilms tumor (2%) Ewing sarcoma (8%) Rhabdomyosarcoma (4%) Non-Hodgkin lymphoma (2%) Neuroblastoma (2%) Thymoma (2%) Synovial sarcoma (2%) Age at radiotherapy Median: 13,8 Range: 4,02-20,98 Age of pulmonary function test after irradiation Median: 2,91 Range: 0,01-8,28	Name of protocol: not specified, doses not specified Bleomycin in 78% of patients, Cyclophosphamide in 82% Doxorubicin in 94% Dosimetric parameter Median (range) Prescribed dose of radiation (Gy) 21 (10.5–1) Mean lung dose (Gy) 8.95 (1.1–1.1) Maximum lung dose (Gy) 23.04 (12–8.2) Surgery (kind of surgery) 18% of chest surgery (chest wall surgery, thoracoscopic biopsy of mediastinal or lung mass, incisional biopsy, and lung parenchymal resection) Duration of protocol: Not specified	How was outcome assessed? Retrospective review of medical records, functional tests Last pulmonary function test selected for the study % abnormal; Median value (range) FVC %pred: 24% - 94 (22–144) FEV1 %pred: 29%- 91 (24–131) FEV1/FVC %pred: 14% - 86 (67–105) FEF25–5% %pred: 20% - 87 (19–142) RV %pred: 21%- 98 (17–246) TLC %pred: 15%- 99 (28–165) RV/TLC: 21% - 21 (5–49) Phase II N2 %N 2/L: 27% 1.7 (0–7.2) DLCO adj %pred: 9% - 92.7 (28–157) DLCO adj/VA ml/mmHg/min/L: 5% - 5.5 (3.7-9) Risk factors: Abnormal FVC: - Thoracic surgery: OR 8.0; p = <0.01 - Bleomycin: OR 0.15; p=<0.05 - Age at radiation: OR1.13; p=NS - Mean dose (in Gy): OR 1.22; p=<0.01 - Max dose (on Gy): OR 1.10; p=<0.01 Abnormal FEV1:	Analysis: Univariate analysis/ logistic regression Limitations: Only patients who underwent pulmonary function testing were included in the study: 49/170 28,8% The majority of patients received radiotherapy because they are treated for lymphoma Only univariate (unadjusted) analyses were done Different timepoints assessed (last test available) with a wide range. Strength: NA Potential bias/methodological problems: only patients who have functional testing are included

			- Thoracic surgery: OR 3.2; p=NS - Bleomycin: OR 0.07; p=<0.01 - Age at radiation: OR 1.03; p=NS - Mean dose (in Gy): OR 1.20; p=<0.01 - Max dose (on Gy): OR 1.12; p=<0.01 Abnormal FEF25-75%: - Thoracic surgery: OR 2.35; p=NS - Bleomycin: OR 0.18; p=<0.05 - Age at radiation: OR 1.09; p=NS - Mean dose (in Gy): OR 1.18; p=<0.01 - Max dose (on Gy): OR 1.06; p=<0.05 Abnormal TLC: - Thoracic surgery: OR 1.94; p=NS - Bleomycin: OR 0.27; p=NS - Age at radiation: OR 1.14; p=NS - Mean dose (in Gy): OR 1.30; p=<0.01 - Max dose (on Gy): OR 1.07; p=<0.05 Abnormal RV/TLC - Thoracic surgery: OR 8.5; p=<0.01 - Bleomycin: OR 0.15; p=<0.05 - Age at radiation: OR 1.05; p=NS - Mean dose (in Gy): OR 1.30; p=<0.01 - Max dose (on Gy): OR 1.26; p=<0.05 Abnormal DLCO adj: - Thoracic surgery: OR 1.89; p=NS - Bleomycin: OR 0.06; p=<0.05 - Age at radiation: OR 1.01; p=NS - Mean dose (in Gy): OR 1.27; p=<0.01 - Max dose (on Gy): OR 1.07; p=<0.05 *mean dose = mean lung dose The odds of developing restrictive and hyperinflation defects increased with increasing Vdose beginning at V10 and V20 Obstructive disease - Thoracic surgery: OR 5.89; p<0.05 - Bleomycin: OR 0.27; p=NS - Mean dose (in Gy): OR 0.99; p=NS - Max dose (on Gy): OR 1.03; p=NS - Prescribed dose (in Gy): OR 1.05; p=NS	

			Restrictive disease - Thoracic surgery: OR 1.94; p=NS - Bleomycin: OR 0.27; p=NS - Mean dose (in Gy): OR 1.30; p<0.01 - Max dose (on Gy): OR 1.07; p<0.05 - Prescribed dose (in Gy): OR 1.04; p=NS Hyperinflation - Thoracic surgery: OR 8.5; p<0.01 - Bleomycin: OR 0.15; p<0.05 - Mean dose (in Gy): OR 1.29; p<0.01 - Max dose (on Gy): OR 1.26; p<0.01 - Prescribed dose (in Gy): OR 1.27; p<0.01 Diffusion defect - Thoracic surgery: OR 1.07; p=NS - Bleomycin: OR 0.08; p<0.01 - Mean dose (in Gy): OR 1.16; p<0.05 - Max dose (on Gy): OR 1.05; p=NS - Prescribed dose (in Gy): OR 1.05; p=NS	

Main findings/message: **Clinical and functional signs of pulmonary dysfunction in survivors of HL and NHL. None of the patients has subjective symptoms and signs of pulmonary dysfunction. FEV1, RV, RV/TLC, DLCO were significantly lower in the group treated with chemotherapy and radiotherapy to the chest compared to chemotherapy only.**				
A. Oguz, et al. Long-term pulmonary function in survivors of childhood Hodgkin disease and non-Hodgkin lymphoma. 2007;49:699-703. 10.1002/pbc.21175				
Study design Treatment era Years of follow-up	Participants	Treatment (= treatment analyzed in the paper)	Main outcomes	Additional remarks
☐ **Cohort** ☒ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	**Study population (N)** **Original cohort:** NA **Eligible cohort:** **Analyzed cohort:** 75	☐ **1 HSCT a, b** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☒ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☐ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests (e.g. 24% with reduced FEV1)**	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** reference equations recommended by the European Coal and Steel Community Severity scoring in accordance with ATS pulmonary function laboratory guidelines ☐ **Quality check performed** ☒ **Lung function procedure stated** ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single centre Country: Turkey Treatment era: 1992-2003	Cancer diagnosis: Hodgkin Lymphoma Non-Hodgkin Lymphoma Group 1: N=23 chemotherapy and thoracic chemotherapy Group 2: N=52 chemotherapy only Age at diagnosis median (range): 8 years (1.8-15.0) Age at end of therapy Median (range): 8.25 years (2.3-16) Age at follow-up Median (range):	Name of protocol BFM 90 n=19 BFM 95 n=8 LSA2L2 n=3 LMT89 n=7 COMP n=1 COPP n=13 ABVD n=5 COPP/ABVD n=18 MOPP n=1 Radiotherapy (doses) Hodgkin Lymphoma: n=34/37 Non-Hodgkin Lymphoma: n=7/38 Doses: 2400cGY (range 1500-4000cGy) 17/75 other than thoracic radiotherapy	How was outcome assessed? Lung function: spirometry, lung volumes, and diffusion capacity measurements in all patients using the Sensor Medics Vmax22 spirometry and gas dilution system. Definition pulmonary toxicity: - obstructive disorder by FEV1, FVC, FEV1/FVC - restrictive disorder by TLC, RV, RV/TLC ratio - interstitial involvement: diffusion capacity for carbon monoxide (DLCO) Incidence, Prevalence: Abnormal PFT: n=10/75 (13%) Group 1: - 5/23 low DLCO - 1/23 restrictive lung disease (low RV) - 1/23 restrictive lung disease (low TLC) - No obstructive disease Group 2: -4/52 low DLCO	Analysis: Student t-test to compare percent predicted of lung function in group 1 and group 2 Limitations: No data on long-term outcome of these patients No cut offs for pathological disease Did not take other risk factors between group1 and group2 into account, such as smoking or lung toxic chemotherapy Strength: Prospective design Potential bias/methodological problems: Reporting bias (retrospective) Did not take chemotherapy and other risk factors into account

	13 (7.5-25) <u>Time since diagnosis</u> Median (range): 5 years (2-13)	 Radiotherapy field: Mantle/minimantle n=16 Mediasten n=3 Paraaortic/Abdomen n=5 Cervical n=13 Cranial n=2 Liver n=1	- 2/52 restrictive lung disease (low RV) - 1/52 restrictive lung disease (low TLC) - No obstructive disease Percent predicted values, compared by student t-test - FVC Group 1: 101.17 +- 19.93 Group 2: 102.94 +- 18.11 p=0.706 - FEV1 Group 1: 95.43 +-16.47 Group 2: 105.09 +- 19.01 p=0.038 - FEV1/FVC Group 1: 96.43+-9.15 Group 2: 99.88 +- 11.93 p=0.221 - TLC Group 1: 102.74 +- 15.63 Group 2: 106.73 +- 17.46 p=0.349 - RV Group 1: 113.35 +-28.53 Group 2: 126.71 +- 24.63 p=0.043 - RV/TLC Group 1: 25.39 +- 5.31 Group 2: 27.71 +- 4.92 p=0.062 - DLCO Group 1: 101.35+-22.17 Group 2: 112.65 +- 4.92 p=0.025 **Exact results available from publication, TABLE II: "**Pulmonary Function Tests of the Patients"	

Main findings/message: **In a cohort of children nearly 3 years after treatment with whole lung irradiation, the severity of the most recent pulmonary function abnormality (Z-scores for FEV1, TLC, and DLCO) did not correlate with age at the time of radiation (r2<0.001, r2=0.08, and r2=0.08 respectively) and total radiation dose (r2=0.002, r2=0.06, and r2=0.13, respectively)**				
D. J. Weiner, et al. Pulmonary function abnormalities in children treated with whole lung irradiation. 2006;46:222-7.				
Study design Treatment era Years of follow-up	Participants	Treatment (= treatment analyzed in the paper)	Main outcomes	Additional remarks
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	**Study population (N)** **Original cohort:** NA **Eligible cohort:** 63 **Analyzed cohort:** 30 with PFT	☐ **1 HSCT a, b** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☒ **Pulmonary symptoms** ☐ **Pulmonary function test** ☐ **Absolute values** ☒ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests (e.g. 24% with reduced FEV1)**	☐ **Longitudinal data available** ☐ **Control group mentioned** ☐ **Reference values stated** ☐ **Quality check performed** ☒ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single center Country: USA, Department of Radiation Oncology at the Hospital of the University of Pennsylvania Treatment era: 1988 – 2003 Years of Follow-up median (range): 2.79 years (0–13.7)	Inclusion criteria: - pediatric oncology patients - whole lung irradiation - pulmonary function testing during follow-up Cancer diagnosis: Wilms tumor (n=15), Hodgkin disease (n= 3), Sarcoma (n=11) Hepatoblastoma (n=1) Age at radiation median (range): 7.6 (1.8 – 18) Age at follow-up (most recent PFT) median (range): 12.1 (range 5.3–19) Time since diagnosis Median (range) yr NA	Name of protocol not mentioned Chemotherapy, doses, median (range): Bleomycin: N=3 received Bleomycin; 20–40 U/m2 Radiotherapy, median (range): Whole lung irradiation 1,200 cGy (1,050 - 1,760) median fraction of 150cGy	How was outcome assessed? Medical records and PFT database Spirometry, body plethysmography, and diffusing capacity performed according to ATS protocols Equipment used: Sensormedics 6200 Body Plethysmograph and Sensormedics Vmax22 spirometer and gas dilution system (Sensormedics,Yorba Linda, CA). Definition of pulmonary function impairment: normal: -2<Z<2 mildly reduced -4<Z<-2 moderately reduced -6<Z<-4 severely reduced Z<-6 Assessed values: FVC, FEV1, FEV1/FVC, TLC, DLCO, MIP (maximum inspiratory pressure), MEP (maximum expiratory pressure) Incidence, Prevalence: Pulmonary function Test Standard Deviation z-scores: Mean, Median, (range): FVC (Z) n=30: -2.82, -2.37, (-13.3, 1.72) FEV1 (Z) n=30: -2.47, -1.79, (-14.2, 0.72) FEV1/FVC (%): 92, 93, (76, 100)	Analysis: - One-way analysis of variance: Differences in pulmonary function according to diagnostic groups - Spearman correlation: correlation of pulmonary function abnormalities and continuous variables including radiation dose and age at radiation exposure - Fisher exact test: presence of symptoms and pulmonary function Limitation: - Retrospective analysis - Small heterogenous group Strength: Longitudinal data with Z-scores. Potential bias/methodological problems: Participation rate

			TLC (Z) n=23: -3.95, -3.25, (-25.3, 9.31) DLCO (Z) n=21: -3.59, 3.32, (-10.32, 2.39) MIP (%pred), n=23: 96.2, 88.8 MEP (%pred): 90.9, 92.3 FVC (N=30) Normal n=14 (47%) ; mildly reduced n=10 (33%) moderately reduced n=3 (10%) ; severely reduced n=3 (10%) FEV1 (N=30) Normal n=15 (50%) ; mildly reduced n=9 (30%) moderately reduced n=3 (10%) ; severely reduced n=3 (10%) TLC (N=23) Normal n=9 (40%) ; mildly reduced n=4 (17%) moderately reduced n=3 (13%) ; severely reduced n=7 (30%) DLCO Normal n=15 (50%) ; mildly reduced n=9 (30%) moderately reduced n=3 (10%) ; severely reduced n=3 (10%) <u>Risk Factors</u> - Severity of the most recent pulmonary function abnormality (Z-scores for FEV1, TLC, and DLCO) did not correlate with: age at the time of radiation (r^2<0.001, r^2=0.08, and r^2=0.08 respectively) total radiation dose (r^2=0.002, r^2=0.06, and r^2=0.13, respectively) - Severity of the most recent pulmonary function abnormality did not correlate with radiation dose/body length : (r^2=0.002, r^2=0.027, and r^2=0.03, respectively) <u>If longitudinal data available:</u> N=15 with two or more tests (too small to answer PICO)	

Main findings/message:
In survivors exposed to potential lung toxic treatment modalities according to COG guidelines, only irradiation of an increasing percentage of the lung with 10 Gy or more increases the risk for reduced FEV1, FVC, TLC, and DLCOcorr percentage predicted

D. M. Green, et al. Pulmonary Function after Treatment for Childhood Cancer. A Report from the St. Jude Lifetime Cohort Study (SJLIFE). 2016;13:1575-85. 10.1513/AnnalsATS.201601-022OC

Study design Treatment era Years of follow-up	Participants	Treatment (= treatment analyzed in the paper)	Main outcomes	Additional remarks
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	**Study population (N)** **Original cohort:** 4421 **Eligible cohort:** 989 **Analyzed cohort:** 606 (FEV1, FVC), 597 (TLC, $DLco_{corr}$)	☐ **1 HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☒ **Percentage pathological tests (e.g. 24% with reduced FEV1)**	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** Hakinson, Goldman, Boren, Miller, GLI ☒ **Quality check performed** ☒ **Lung function procedure stated**: ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single centre, St Jude Lifetime Cohort Country: USA Treatment era: Not mentioned Years of Follow-up, median (range): Not mentioned Time since diagnosis median (range): 21.9 years	Inclusion criteria: - >10 years from diagnosis - age >=18 years - pulmonary toxic treatment acc. to COG Guidelines (Bleomycin, Busulfan, CCNU, BCNU, Radiation therapy to the chest [including whole lung, mediastinum, axilla, mini-mantle, mantle, extended mantle, total lymphoid irradiation, subtotal lymphoid irradiation]) complete PFT Cancer diagnosis: ALL 5% AML 3,5% Other leukemia 3,5% CNS tumor 1,3% Hodgkin's disease 49,3% NHL 4% Neuroblastoma 2,3% Wilms tumor 5,8% Osteosarcoma 5,8%	Name of protocol: Not mentioned Chemotherapy, %, doses Cyclophosphamide: n=391 (64,5%) Bleomycin: n=129 (21,3%) Busulfan: n=16 (2,6%) BCNU: n=11 (1,8%) CCNU: n=12 (2%) Chemotherapy, mean (SD) Cyclophosphamide: 7,1g/m2 (5.3) Bleomycin: 69.9mg/m2 (41.3) Busulfan: 442.9 mg/m2 (406) BCNU: 213.1 mg/m2 (159.99 CCNU: 459.7 mg/m2 (224.7) Chemotherapy median (IQR) Cyclophosphamide: 5.1g/m2 (3.6 – 9.2) Bleomycin: 60.1mg/m2 (4.1 – 79.5) Busulfan: 406.0mg/m2 (374.1 – 529.7) BCNU: 147.6mg/m2 (100.0 – 300.0) CCNU: 437.9mg/m2 (325.3 – 597.2) Radiotherapy to chest, doses	How was outcome assessed? Spirometry: FEV1, FVC, FEV1/FVC Body plethysmography: TLC, DLcocorr Definition of pulmonary function impairment: - FEV1%predicted < 80% (GLI, race and sex specific by Wanger et al, 2005, EurRespirJ) - FVC%predicted < 80% (GLI, race and sex specific by Wanger et al, 2005, EurRespirJ) - TLC%predicted < 75% (sex specific equations (Goldman et al., 1959, AmRevTuberc, Boren et al1966, AmJMed) - $DLco_{corr}$ %predicted < 75% (sex specific equations Miller et al, 1983, AmRevRespirDis) - FEV1/FVC: 0.8% percent predicted less than 0.7 Prevalence of abnormal parameters: - FEV1: 50.7% - FVC: 47.2% - TLC: 31.2% - $DLco_{corr:}$ 44.6% Risk factors (RR) *(here: parameters listed only for %predicted and not LLN)*: FEV1%predicted <80%	Analysis: Relation between each PFT outcome and treatment modeled by using multivariable log-binomial regression Limitations: No data on long-term outcome of these patients Strength: High participation rate All tests performed with same standards Prospective evaluation Potential bias/methodological problems: NA

	Ewing tumor 4,6% Germ cell tumor 5,1% Rhabdomyosarcoma 2,6% Non rhabdomyosarcoma 2,6% Other cancer 2,7% <u>Age at diagnosis</u> median (range): 13.0 years <u>Age at follow-up</u> median (range): 34.2 years	n=450 (76,7%) Lung radiation doses were estimated for the total lung and reported as the volume of lung receiving 10 Gy (V10), 20 Gy (V20), and 24 Gy (V24), reported as a percentage of the total lung volume Mean (SD) proportions (%) of the lungs that received: 10 Gy: 0.58 (0.27) 20 Gy: 0.23 (0.19), 24 Gy: 0.15 (0.17) <u>Surgery</u>: 19,7% (Thoracotomy, rib resection, chest wall resection) <u>HSCT</u>: Allo: 6,6%, auto: 1,7%, both: 0,3%	V10 (per 10% increase) RR= 1.07 (1.04–1.09); p<0.001 FVC%predicted <80% and V10 (per 10% increase) RR=1.08 (1.05–1.11); p<0.001 TLC% predicted <75% and V10 (per 10% increase) 1.07 (1.01–1.13); p0.019 DLCOcorr%predicted <75% and V10 (per 10% increase) 1.07 (1.04–1.10); p<0.001 In multivariable models selected by BMA, all PFT results except TLC were worse with increasing percentages of the lungs that received 10 Gy or more **Exact results available from publication, Table 3: "**Multivariable log-binominal regression models"	

Main findings/message:
Younger age at treatment is associated with an increased risk of developing pulmonary dysfunction (age categorical).

F. Khan, et al. Impact of Respiratory Developmental Stage on Sensitivity to Late Effects of Radiation in Pediatric Cancer Survivors. Advances in Radiation Oncology 2020; 5: 426-433

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☒ **Cross-sectional**: last PFT ☐ **Case-control** ☐ **Other:** _____ ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: 136 with RT ➢ Eligible cohort: 61 with PFT ➢ Analysed cohort: 61	☐ 1 **HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☒ **Z-scores** ☐ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** Rosenthal ☐ **Quality check performed** ☒ **Lung function procedure stated:** ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: single centre Country: USA Treatment era: 1995-2016 Years of Follow-up: Mean 9 years (range, 1-20)	Study population: Eligible (N): 61 Analysis (N): 61 Diagnoses: All childhood cancer diagnoses Age at radiation: Mean 12.7 years (range 1.1-22.3) Age at most recent PFT: Mean 18.2 (range 7-27)	Name of protocol: NA Chemotherapy: unknown except for bleomycin Radiotherapy (doses): Average dose 19.7±7.25 Gy (range 10.5-50.4Gy) 34% RT to whole lung (n=21) 66% partial RT to lung (n=40) RT field included: thorax, upper and total abdomen, total body irradiation Surgery: NA HSCT: Not stratified into auto/allo (n=17)	How was outcome assessed: Pulmonary function test (PFT) results; spirometry, body plethysmography, DLCO Pulmonary function parameters normal if within 1.645 standard deviations above or below the mean predicted value. Pulmonary outcomes: - obstructive: FVC z-score >-1.645, FEV1 z-score <-1.645, FEV1/FVC ratio z-score <-1.645 - restrictive: TLC z-score <-1.645 - hyperinflation: RV/TLC ratio z-score >+1.645 - DLCO z-score <-1.645 Results - Any abnormality: n=21 - Diffusion abnormality: n=12 - Restrictive abnormality: n=11 - Obstructive abnormality: n=5 Risk factor analysis for age at radiotherapy (multivariable logistic regression, crude model, OR (95%CI)): - Any abnormality - <5 years: 7.71 (1.17-51.06) - >5 or <13 years: 3.51 (1.06-11.57)	Analysis: Risk-factor analysis for age at RT (<5 years, 5-13 years, >13 years) using multivariable regression model, crude model and model adjusted for time since treatment and additional bleomycin exposure Limitations: - retrospective design - Few suervivors with pulmonary function abnormalities Strength: - z-scores - use of ATS guidelines, single center (one PFT laboratory only) - multivariate analysis Potential bias/methodological problems: - only 45% of initial cohort with PFT

			- >13 years: 1.0 (ref) - Diffusing abnormality - <5 years: 3.75 (0.51-27.5) - >5 or <13 years: 3.00 (0.73-12.27) - >13 years: 1.0 (ref) - Restrictive abnormality - <5 years: 3.75 (0.51-27.50) - >5 or <13 years: 2.34 (0.55-9.97) - >13 years: 1.0 (ref) - Obstructive abnormality - <5 years: 3.20 (0.24-42.19) - >5 or <13 years: 1.68 (0.22-12.96) - >13 years: 1.0 (ref) <u>Risk factor analysis for age at radiotherapy (multivariable logistic regression, adjusted for time since treatment, OR (95%CI)):</u> - Any abnormality - <5 years: 4.45 (0.38-51.79) - >5 or <13 years: 3.09 (0.86-10.77) - >13 years: 1.0 (ref) - Diffusing abnormality - <5 years: 4.27 (0.28-64.08) - >5 or <13 years: 3.09(0.71-13.45) - >13 years: 1.0 (ref) - Restrictive abnormality - <5 years: 2.22 (0.15-33.44) - >5 or <13 years: 2.06 (0.45-9.51) - >13 years: 1.0 (ref) - Obstructive abnormality - <5 years: 11.35 (0.20-634.6) - >5 or <13 years: 2.10 (0.26-16.98) - >13 years: 1.0 (ref) <u>Risk factor analysis for age at radiotherapy (multivariable logistic regression, adjusted for time since treatment and bleomycin exposure, OR (95%CI)):</u> - Any abnormality - <5 years: 1.91 (0.13-29.04) - >5 or <13 years: 1.63 (0.35-7.58) - >13 years: 1.0 (ref) - Diffusing abnormality	

			- <5 years: 3.64 (0.18-72.86) - >5 or <13 years: 2.74 (0.46-16.18) - >13 years: 1.0 (ref) - Restrictive abnormality - <5 years: 1.26 (0.06-25.63) - >5 or <13 years: 1.30 (0.19-8.72) - >13 years: 1.0 (ref) - Obstructive abnormality - <5 years: 6.57 (0.08-571.7) - >5 or <13 years: 1.44 (0.11-19.21) - >13 years: 1.0 (ref)	

Main findings/message:
Radiotherapy: exposure to thoracic radiotherapy associated with significant higher odds for abnormal FVC and FEV1 and trend for TLC and DLCO (large CI).
Surgery: exposure to thoracic surgery associated with significant higher odds for abnormal FVC, FEV1 and TLC, and trend for DLCO (large CI).
Combinations (radio PLUS surgery versus no radio and surgery): exposure to combination associated with significant higher odds for abnormal FVC, FEV1, and TLC and trend for DLCO (large CI)
Smoking with trend to lower odds for FVC, FEV1, TLC and DLCO (large CI)

A. Stone, et al. Assessment of Pulmonary Outcomes, Exercise Capacity, and Longitudinal Changes in Lung Function in Pediatric Survivors of High-Risk Neuroblastoma. 2020, PBC, 2019 November ; 66(11): e27960. doi:10.1002/pbc.27960.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☒ **Cross-sectional**: ☐ **Case-control** ☒ **Other: longitudinal** ☐ **Retrospective** ☒ **Prospective**	Study population (N) ➢ Original cohort: NA ➢ Eligible cohort: 62 ➢ Analysed cohort: 62; 23 for longitudinal analysis (2 PFT)	☐ 1 **HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung** ☒ **10 Surgery** ☒ **11 Combinations** ☒ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☒ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** NHANES III (Pellegrino) ☐ **Quality check performed** ☒ **Lung function procedure stated:** ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: single centre, long-term follow-up clinic Country: USA Treatment era: 1996-2013 Years of Follow-up: Median 5.29 years (range 0.24 – 15.24)	Study population: Eligible (N): 62 Analysis (N): 62; 23 for longitudinal analysis (2 PFT) Diagnoses: High-risk neuroblastoma (stage 3 or 4) Age at diagnosis: Median 2.75 years (range 0.03 – 10.86) Age at study: Median 10.92 years (range 6.37 – 17.53)	Name of protocol: NA Chemotherapy: Cyclophosphamide 100% Busulfan 6.5% Radiotherapy (doses): 34% chest radiation therapy: radiation fields mentioned, no doses Surgery: 23% thoracic surgery HSCT: 50% received autologous HSCT	How was outcome assessed: Pulmonary function test (PFT) results; spirometry, body plethysmography, DLCO Pulmonary outcomes: Abnormalities in FVC and FEV1: (1) mild: 70 –79%pred; (2) moderate: 60–69%pred; (3) moderately severe: 50–59%pred; (4) severe: 35–49%pred; (5) very severe: <35%pred Abnormalities TLC: (1) mild: 70–79%pred; (2) moderate: 60–69%pred; (3) severe: <60%pred Abnormalities in DLCO: (1) mild: 61–79%pred; (2) moderate: 40–60%pred; (3) severe: <40%pred Obstructive disease: FEV1/FVC<0.8 Restrictive disease: TLC<80 %pred Results - 77% with PFT abnormalities - Restriction in 35%, obstruction in 6%, and mixed in 6% - Decreased FVC in 53%, FEV1 in 47%, TLC in 42%, DLCO in 71%	Analysis: Descriptive (t-test, chi-squared, Fisher's exact test). Unadjusted logistic regression modelling. Limitations: - univariable analysis - 37% with longitudinal assessment - %predicted with fix cutoff values - very large 95%CI for some outcomes Strength: - results of single PFT parameters reported Potential bias/methodological problems: - size of original cohort unclear

			- longitudinal analyses: 2nd PFT median 2.97 years (range 1.07-5.55) after enrollment - decline from t1 to t2 in FVC: 79.9%pred to 70.0%pred, p<0.05 - decline from t1 to t2 in FEV1: 81.6%pred to 69.9%pred, p<0.05 <u>Results of univariable logistic analysis:</u> FVC (OR, 95%CI) - Thoracic surgery yes/no and normal/abnormal parameter: 18.20 (2.20 – 150.58), p=0.001 - Radiotherapy yes/no and normal/abnormal parameter: 4.40 (1.34 – 14.51) p=0.010 - Thoracic surgery + radiotherapy yes/no and normal/abnormal parameter: 14.00 (1.68 – 116.85), p=0.003 - Smoking yes/no and normal/abnormal parameter: 0.69 (0.19 – 2.53), p=0.569 FEV1 (OR, 95%CI) - Thoracic surgery yes/no and normal/abnormal parameter: 10.94 (2.19 – 54.71), p=0.001 - Radiotherapy yes/no and normal/abnormal parameter: 4.29 (1.35 – 13.58), p=0.005 - Thoracic surgery + radiotherapy yes/no and normal/abnormal parameter: 19.56 (2.33 – 164.05), p=0.001 - Smoking yes/no and normal/abnormal parameter: 0.59 (0.16 – 2.28), p=0.446 TLC (OR, 95%CI) - Thoracic surgery yes/no and normal/abnormal parameter: 3.28 (0.95 – 11.38), p=0.054 - Radiotherapy yes/no and normal/abnormal parameter: 4.33 (1.39 – 13.50), p=0.005 - Thoracic surgery + radiotherapy yes/no and normal/abnormal parameter: 5.82 (1.39 – 24.38), p=0.010 - Smoking yes/no and normal/abnormal parameter: 0.75 (0.20 – 2.90), p=0.748	

			DLCO (OR, 95%CI) - Thoracic surgery yes/no and normal/abnormal parameter: 2.33 (0.45 – 12.09), p=0.475 - Radiotherapy yes/no and normal/abnormal parameter: 2.05 (0.49 – 8.62), p=0.339 - Thoracic surgery + radiotherapy yes/no and normal/abnormal parameter: 1.75 (0.33 – 9.31), p=0.70 - Smoking yes/no and normal/abnormal parameter: 0.39 (0.10 – 1.52), p=0.263	

Main findings/message:
Higher cumulative dose of bleomycin (>80mg/m2) is associated with reduced DLCO (<80% predicted; OR 2.12 (95%CI 0.99 – 4.49))

A. Mittal, et al. Late effects in pediatric Hodgkin lymphoma survivors after uniform treatmentwith ABVD with orwithout radiotherapy. 2021, PBC, March2021; DOI: 10.1002/pbc.29293

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional**: ☐ **Case-control** ☐ **Other:** **longitudinal** ☐ **Retrospective** ☒ **Prospective**	Study population (N) ➢ Original cohort: 223 ➢ Eligible cohort: 154 ➢ Analysed cohort: 125 with PFT ➢ Analysed cohort: 119 with DLCO	☐ 1 **HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☒ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** Quanjer, Pellegrino ☐ **Quality check performed** ☒ **Lung function procedure stated:** ERS/ATS ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Single center Country: India Treatment era: 2003 – 2013 Years of Follow-up: Median 10.3yr (6.04-16.8)	Study population: Eligible (N): Analysis (N): 154 Diagnoses: Hodgkin lymphoma Age at diagnosis: Median 10 years	Name of protocol: ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) Chemotherapy: Bleomycin 100% Radiotherapy (doses): Radiotherapy total: 107 (69.5%) Radiotherapy to mediastinum/chest: 12 (7.8%) Radiotherapy to neck: 91 (59.1%) Radiotehrapy to other sites: 7 (4.5%) Surgery: Not stated HSCT: Not stated	How was outcome assessed: Spirometry (FEV1, FVC) best of three efforts, DLCO Pulmonary outcomes: FEV1: Normal (>80 % pred), mild decrease (70-79% pred), moderate decrease (60-69% pred), moderate severe decrease (50-59% pred), severe decrease (35-49% pred), very severe decrease (<35% pred) FVC: normal (≥80 % pred), decreased (<80% pred) Restrictive pattern: FVC<80%, FEV1/FVC≥85 Mixed pattern: FVC<80%, FEV1/FVC<85 DLCO: normal (>80 % pred), mild decrease (60-79% pred), moderate decr. (40-59% pred), severe decr. (<40% pred) Results - Restrictive: 36 (28.8%) - Mixed pattern: 18 (14.4%) - Moderate DLCO impairment: 7 (5.9%) - Severe DLCO impairment: 1 (0.8%) Risk factor analysis Cumulative bleomycin dose ≤80mg/m2 vs >80mg/m2: OR 2.12 (95%CI 0.99 – 4.49), p=0.051	Analysis: Multivariate analysis to estimate the effect of higher bleomyinc dose (>80mg/m2) on DLCO Limitations: - Impact of radiotherapy not taken into account - only categories of percentage of predicted used Strength: - homogeneous cohort - prospective design Potential bias/methodological problems: - 53% of cohort had DLCO assessed

Main findings/message:
Exposure to radiotherapy was associated with a significantly lower FEV1 and FVC and a trend towards lower MME, TLC and DLCO in a cohort of transplanted survivors

M. Otth, et al. Longitudinal lung function in childhood cancer survivors after hematopoietic stem cell transplantation. 2021, Bone Marrow Transplantation, November 2021; DOI: 10.1038/s41409-021-01509-1

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional**: ☐ **Case-control** ☒ **Other:** **longitudinal** ☒ **Retrospective** ☐ **Prospective**	Study population (N) ➢ Original cohort: 142 ➢ Eligible cohort: ➢ Analysed cohort: 72 with 2 PFT of good quality	☒ 1 **HSCT** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☐ **5 Bleomycin** ☐ **6 Busulfan** ☐ **7 Lomustin (CCNU)** ☐ **8 Carmustin (BCNU)** ☐ **9 Radiotherapy lung** ☐ **10 Surgery** ☐ **11 Combinations** ☐ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☒ **Z-scores** ☐ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☐ **Longitudinal data available** ☐ **Control group mentioned** ☒ **Reference values stated** GLI 2021, Zapletal, ECCS ☐ **Quality check performed** ☐ **Lung function procedure stated:** ☐ **Cleaning of lung function data described** ☐ **Person who analyzed PFT was blinded to the exposure**
Centres: Multicenter, national Country: Switzerland Treatment era: 1976 – 2010 Years of Follow-up: 9.4 years (6.1 – 12.3)	Study population Eligible (N): 142 Analysis (N): 72 with 2 PFT of good quality Diagnoses: Leukemia: 69% Lymphoma: 16% Other: 15% Age at diagnosis: 7.4 years (3.5 – 12.2) Age at last PFT: 16.2 years (14.2 – 20.0)	Name of protocol: Not mentioned, different Chemotherapy: Busulfan: n=25; median 422mg/m2 (324-470) Bleomycin: n=4; median 41mg/m2 (30-46) Carmustine: n=5; median 300mg/m2 (300-300) Lomustine: n=1; median 190mg/m2 Radiotherapy (doses): RT to thorax, n=52 (70%) Surgery: Thoracic surgery: n=10 (14%) HSCT: Allogeneic: 50 (68%) Autologous: 24 (32%)	How was outcome assessed: Spirometry (FEV1, FVC, MMEF), body plethysmography (RV. TLC), DLCO Pulmonary outcomes: Pulmonary function test results: FEV1, FVC, MMEF, RV, TLC, DLCO Results for radiotherapy (exposure yes/no) on intercept: FEV1 - Coefficient -1.306; 95%CI -2.055 - -0.558; p=0.001 FVC - Coefficient -1.473; 95%CI -2.207 - -0.739; p=<0.001 MMEF - Coefficient -0.664; 95%CI -1.583 – 0.253; p=0.156 TLC - Coefficient -0.717; 95%CI -2.051 – 0.616; p=0.292 RV - Coefficient 0.663; 95%CI -0.307 – 1.634; p=0.181 DLCO - Coefficient -1.279; 95%CI -2.773 - 0.213; p=0.093	Analysis: Mixed effect multivariable linear regression analysis with random intercept and slope Limitations: - retrospective - Lung function procedures not stated Strength: - z-scores - GLI 2021 references for FEV1, FVC, DLCO Potential bias/methodological problems: - 52% of initially eligible population with PFT results