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ORIGINAL ARTICLE

Obstructive and restrictive pulmonary dysfunction in long-term lymphoma survivors after high-dose therapy with autologous stem cell transplantation

Jo S. Stenehjem[a,b], Knut B. Smeland[a], Klaus Murbraech[c], Harald Holte[d], Stein Olav Kvaløy[a,e], Torgeir Wethal[f], Cecilie E. Kiserud[a]* and May Brit Samersaw-Lund[e,g]*

[a]National Advisory Unit for Late Effects after Cancer Treatment, Oslo University Hospital, Oslo, Norway; [b]Department of Research, Cancer Registry of Norway, Oslo, Norway; [c]Department of Cardiology, Oslo University Hospital, Rikshospitalet, Oslo, Norway; [d]Department of Oncology, Oslo University Hospital, Oslo, Norway; [e]Faculty of Medicine, University of Oslo, Oslo, Norway; [f]Department of Cardiology, St. Olavs University Hospital, Trondheim, Norway; [g]Department of Respiratory Medicine, Oslo University Hospital, Oslo, Norway

ABSTRACT

Background: Obstructive and restrictive dysfunction in long-term lymphoma survivors (LSs) after high-dose therapy with autologous stem-cell transplantation (HDT-ASCT) has not been addressed systematically previously.

Material and methods: LSs treated in Norway 1987–2008 with HDT-ASCT who performed spirometry, measurement of static lung volumes and echocardiography 2012–2014 at either Oslo or St. Olavs University Hospitals was eligible. Smoking data were recorded by questionnaire. Treatment data were collected from medical records or hospital databases. Factors associated with obstructive and restrictive impairments (dichotomous outcomes) were examined by Poisson regression. Linear regression with the margins post-estimation command was used to derive adjusted mean values of forced expiratory volume in 1 s (FEV_1). We used the normative reference data recommended by the European Respiratory Society for calculating percent predicted values.

Results: A total of 226 LSs were studied, of whom 11.5 and 5.8% had obstructive and restrictive impairment, respectively. For women and men, mean FEV_1 was 2.31 and 3.34 l corresponding to 11.4%- and 11.1%-points below that predicted from norms, respectively. In multivariable regression analyses, cumulative doxorubicin dose (400–775 mg/m^2) and current smoking were associated with increased risk of obstructive impairment, and chest RT (>13–66 Gy) was associated with increased risk of restrictive impairment. Currently smoking LSs within the highest doxorubicin category (400–775 mg/m^2), had the lowest adjusted mean FEV_1.

Conclusions: Despite intensive cancer treatment, our analysis showed modest reductions in obstructive parameters among long-term LSs after HDT-ASCT compared to normative reference data. To limit obstructive impairments in LSs after HDT-ASCT, we suggest that targeted smoking-cessation advice is directed towards patients who have received high cumulative doses of doxorubicin.

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Introduction

The past three decades, high-dose chemotherapy with autologous stem cell transplantation (HDT-ASCT) has been a treatment option for relapsed or refractory Hodgkin (HL) and non-Hodgkin lymphomas (NHL), or as consolidation of first remission in selected patients with NHL with particularly high risk of relapse [1,2]. With improvements in diagnosis and treatment, the number of lymphoma survivors (LSs) post-HDT-ASCT has increased, and 5-year survival up to 73% and 62% have been reported for HL and NHL, respectively [3–5].

Chest radiotherapy (RT) and chemotherapy such as bleomycin are recognized risk factors of pulmonary toxicity among LSs [6–8]. Further, alkylating agents such as cyclophosphamide and busulfan have also been linked to pulmonary late-effects in LSs [9,10], while the role of anthracyclines is sparsely documented in relation to pulmotoxicity [11]. Smoking has been shown to induce pulmonary function impairment in adult LSs and may potentiate toxic effects from RT and chemotherapy [7]. Risk of lung cancer after HL has been demonstrated to increase in a multiplicative manner among smoking patients compared to the non-smoking [12].

Treatment-induced pulmonary dysfunction include both obstructive, restrictive and gas diffusing capacity impairments, which in turn may reduce exercise capacity, physical functioning and quality of life [6,12–14]. Together with exercise and diet, smoking cessation has been highlighted as a modifiable factor that may improve the length and quality of life among cancer survivors [15].

CONTACT Jo S. Stenehjem jo.stenehjem@kreftregisteret.no National Advisory Unit for Late Effects after Cancer Treatment, Oslo University Hospital, Oslo, Box 4950 Nydalen, 0424 Oslo, Norway
*Co-senior authors.

Supplemental data for this article can be accessed here.

Pulmonary function impairments and how they relate to treatment and smoking among LSs after HDT-ASCT have been scarcely described previously [16]. We recently examined gas diffusing capacity in LSs after HDT-ASCT, and found that over 37% suffered from impairment (DLCO or DLCO/VA <75%-predicted) [17].

In the present study, we address obstructive and restrictive parameters in adult LSs compared with normative reference data after an average follow-up of 10.4 years post-HDT-ASCT. We assessed the prevalence of pulmonary function impairments, and examined the association with cancer treatment, smoking and other clinical factors.

Material and methods

Study population

The study population was recruited from a national cohort of all adult HL and NHL survivors treated with HDT-ASCT in Norway between 1987 and 2008 [18,19]. A total of 399 LSs aged ≥18 years at treatment, resident in Norway by March 2012 and not currently undergoing active treatment for relapsed disease were considered eligible and invited to a follow-up examination. Participants were recruited from Oslo ($n = 186$) and St. Olavs University Hospitals ($n = 40$). Between March 2012 and March 2014, the study participants attended an outpatient visit undergoing thorough medical exams including pulmonary function testing, echocardiography and blood sampling. Comorbidities were registered by a physician. Smoking data were recorded by questionnaire. Height and weight were measured and body mass index (BMI) was calculated as kg/m^2.

The study was approved by the South East Regional Committee for Medical and Health Research Ethics. Written informed consent was obtained from all participants.

Treatment

Treatment data were collected from medical records and databases at Oslo and St. Olavs University Hospitals. The total number of treatment lines of chemotherapy given prior to HDT-ASCT was registered (1, 2 or ≥3). During 1987–1995, total body irradiation (TBI, 1.3 Gy twice daily for 5 consecutive days with lung shielding for two doses) followed by high dose cyclophosphamide (60 mg/kg for 2 days) constituted the high-dose regimen. From 1995 onwards, the conditioning regimen was constrained to chemotherapy only, including carmustine, etoposide, cytarabine and melphalan (BEAM) [18]. Cumulative doses of chest RT and selected chemotherapies were calculated and divided into approximately equally sized categories of exposed LSs: chest RT (unexposed, 1–13 Gy, >13–65 Gy), bleomycin (unexposed, 1–12 international units (IU) $\cdot 10^4/m^2$, >12–21 IU $\cdot 10^4/m^2$), cyclophosphamide (0–3.49, 3.50–5.99 and 6.00–12.30 g/m^2) and doxorubicin (<300 mg/m^2, 300–399 mg/m^2, 400–775 mg/m^2). Daunorubicin doses were converted to doxorubicin isotoxic doses using a conversion factor of 0.83 [20].

Assessment of spirometry and static lung volumes

Pulmonary function testing was performed on a Sensor Medics Vmax Pulmonary Function Unit (VIASYS Respiratory Care Inc., Yorba Linda, CA), and was carried out according to the guidelines recommended by the American Thoracic Society-European Respiratory Society (ATS-ERS) task force [21,22]. Recorded spirometric variables were forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and FEV_1/FVC. Static lung volume was recorded as total lung capacity (TLC). Normal lung function values, specific to sex, age and height, were calculated based on the reference data (general population) recommended by the ERS and expressed as percent predicted (100% = general population) [21,22].

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria obstructive impairment severity was graded as: Grade 0 'no impairment' = FEV_1/FVC >0.70; grade 1 'mild impairment' = FEV_1/FVC <0.70 and FEV_1 ≥ 80%-predicted; grade 2 'moderate impairment' = FEV_1/FVC <0.70 and FEV_1<80–50%-predicted. Obstructive impairment used as dichotomous outcome in the regression models was defined as grade 2 [23].

Restrictive impairment was defined and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 [24]. Impairment severity was graded as: Grade 0 'no impairment' = TLC >90%-predicted; grade 1 'mild impairment' = ≤90–75%-predicted; grade 2 'moderate impairment' = TLC <75–50%-predicted; grade 3 'severe and undesirable impairment' = TLC <50–25%-predicted. Restrictive impairment was defined as grade 2 or higher (or FVC <75%-predicted and FEV1/FVC >0.70 if missing TLC %-predicted).

Smoking

Smoking status was categorized as 'never', 'former' and 'current'. 'Former smoking' was defined as cessation minimum 1 year before examination. 'Current smoking' was defined as daily smoking or cessation less than a year ago. Smoking history was quantified as pack-years calculated from smoking duration (years) multiplied by number of cigarette-packs a day (1 pack equaling 20 cigarettes).

Echocardiography

Heart failure (HF) was defined as recommended by the American College of Cardiology and the American Heart Association corresponding to patients with current or prior symptoms of HF [25]. Simpson's biplane rule was used to assess left ventricular ejection fraction (LVEF) [26]. Left ventricular systolic dysfunction (LVSD) was defined as a LVEF <50% [27]. The echocardiographic examination has been described in detail elsewhere [19].

Blood sampling

Blood samples were collected at approximately 8 am the same day pulmonary function testing was performed.

Hb concentration was measured and anemia was defined as Hb-levels <11.7 g/dl (women) and <13.4 g/dl (men) [28].

Data analysis

Data are presented as mean ± SD, median (ranges) or numbers (%). Paired sample *t*-tests were used for mean comparisons with the reference population. Poisson regression with robust variance was used to estimate risk ratios (RRs) with corresponding 95% confidence intervals (CIs) and *p*-values [29]. RRs of obstructive and restrictive impairments (dichotomous outcomes) were examined in univariable and multivariable Poisson regression analyses according to relevant explanatory variables (specified in Table 2). Risk of pulmonary function impairment was also evaluated after excluding 22 patients presenting at examination with airway infection, physician diagnosed asthma or chronic obstructive pulmonary disease (COPD) or prior thoracotomy. Linear regression was used together with the post-estimation command -margins- of Stata 15 to derive adjusted means of FEV_1 (L) according to combinations of cumulative doxorubicin dose and smoking status (covariates specified in Figure 3) [30]. Tests for significance were two-sided and *p*-values of <.05 were considered to represent statistical significance. For the linear regressions, variables with $p < .05$ in the univariable models or variables that were considered clinically relevant were included in the multivariable models. For the Poisson regressions, we only included variables in the multivariable models with $p < .05$ from the univariable models due to the low number of events (i.e., LSs with impairments). Tests for trend (denoted as 'P_{trend}') across categories were performed by entering categorical variables as continuous in the models. Data analyses were conducted using Stata version 15 (StataCorp, College Station, TX).

Results

After mean follow-up periods of 13 and 10 years since diagnosis and HDT-ASCT, respectively, 226 LSs who underwent pulmonary function testing were included in the present study (Figure 1). Primary diagnosis, gender, age at examination, time from HDT-ASCT to examination and chemotherapy doses (doxorubicin and cyclophosphamide) did not differ between participants and non-participants (results not shown). Forty percent of the participants had received chest RT, compared to 28% of the non-participants ($p = .013$).

Among the participants, 11.5 and 5.8% had obstructive and restrictive impairments, respectively. Over 43% reported former smoking, while around 17% were current smokers. Over 11% of the patients were diagnosed with heart failure or anemia (Table 1).

Figure 2 shows significant reductions in obstructive parameters in both male and female LSs compared to the general population (reference 100%). The %-predicted mean FEV_1 was 88.6% (CI 95%: 84.8–92.3%) in females and 88.9% (CI 95%: 86.4–91.4%) in males, while the %-predicted mean FEV_1/FVC in females was 90.9 (CI 95%: 88.9–92.9) and 94.6 (CI 95%: 93.1.1–96.1) in males. The %-predicted means of FEV_1

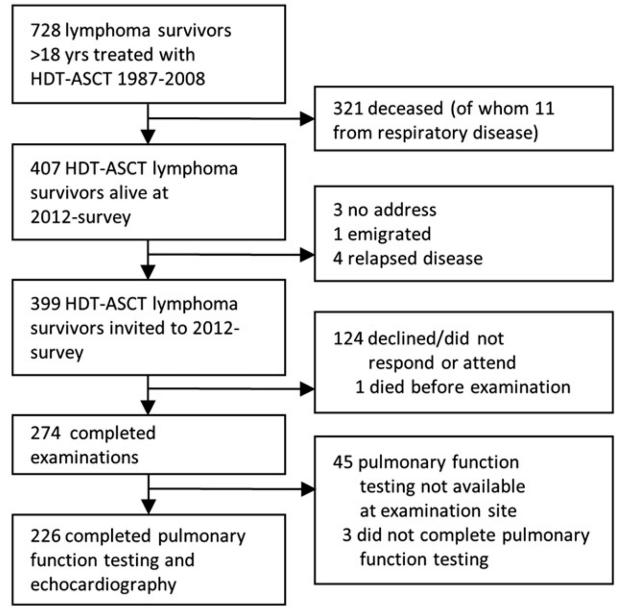

Figure 1. Overview of study design and exclusions.

and FEV_1/FVC were further reduced when examined among currently smoking LSs (Supplementary Figure S1).

Table 2 shows uni- and multi-variable models of factors associated with impaired pulmonary function. In the multivariable analyses, increased risk of obstructive impairment was associated with infection or asthma or COPD or prior thoracotomy (combined) at examination (RR 4.10, 95% CI: 2.13–7.91), cumulative doxorubicin dose (P_{trend} 0.004) and smoking (P_{trend} 0.008). No association was seen between RT (chest or TBI) and obstructive impairment. Chest RT was significantly associated with restrictive impairment in the multivariable analyses (P_{trend} 0.033). Exclusion of the 22 patients with airway infections, physician diagnosed asthma or COPD or prior thoracotomy at examination did not alter the results materially (results not shown).

Figure 3 shows adjusted mean FEV_1 (l) according to smoking status within groups of cumulative doxorubicin dose. The highest doxorubicin category (400–775 mg/m^2), showed statistically significant lower means of FEV_1 compared to the lowest dose-group (<300 mg/m^2). Currently smoking LSs had a lower, although not statistically significant, mean FEV_1 compared to never or former smokers within each category of doxorubicin exposure. The lowest mean FEV1 (ca. 2.50 l) was seen among currently smoking LSs within the highest doxorubicin category (400–775 mg/m^2).

The prevalence of obstructive and restrictive impairments according to treatment and smoking variables were included as supplementary material (Supplementary Table S1), and show the distribution of LSs with impairments across categories of these variables.

Discussion

After an average follow-up of 10.4 years since HDT-ASCT, we detected relatively small proportions of LSs with obstructive (11.5%) and restrictive (5.8%) impairments. The reduction in the patients' FEV_1 was modest and on average 11.4%-points

Table 1. Participant characteristics at time of examination by gender.

Variables	Total	Females	Males
Participants, *N* (%)	226 (100)	81 (36)	145 (64)
Age at primary lymphoma diagnosis, median years (range)	42 (10–66)	42 (18–66)	43 (10–66)
Age at examination, median years (range)	56 (24–77)	56 (24–75)	56 (26–77)
Time (years) since primary lymphoma diagnosis, mean (SD)	13.2 (6.5)	12.6 (5.9)	13.6 (6.7)
Time (years) since HDT-ASCT, mean (SD)	10.4 (5.7)	10.3 (5.5)	10.4 (5.9)
Lymphoma subtypes, *N* (%)			
Hodgkin lymphoma (HL)	49 (21.7)	20 (24.7)	29 (20)
Non-Hodgkin lymphoma (NHL)	177 (78.3)	61 (75.3)	116 (80)
BMI, mean kg/m^2 (SD)	26.2 (4.3)	25.4 (5)	26.6 (3.8)
Infection/Asthma/COPD/Thoracotomy at exam, *N* (%)[a]	22 (9.7)	11 (13.6)	11 (7.6)
Airway infection	3 (1.3)	2 (2.5)	1 (0.7)
Asthma[a]	13 (5.8)	6 (7.4)	7 (4.8)
COPD[a]	6 (2.7)	3 (3.7)	3 (2.1)
Thoracotomy	1 (0.4)	–	1 (0.7)
Cancer treatment			
Lines of chemotherapy pre HDT-ASCT, *N* (%)			
1	64 (28.3)	19 (23.5)	45 (31.1)
2	126 (55.8)	53 (65.4)	73 (50.3)
≥3	36 (15.9)	9 (11.1)	27 (18.6)
Type of HDT-ASCT, *N* (%)			
TBI + high-dose cyclophosphamide	39 (17.3)	12 (14.8)	27 (18.6)
BEAM-treatment	187 (82.7)	69 (85.2)	118 (81.4)
Relapse post-HDT-ASCT, *N* (%)	51 (22.6)	37 (25.5)	14 (17.3)
RIC allogeneic SCT post-HDT-ASCT, *N* (%)	15 (6.6)	4 (4.9)	11 (7.6)
Chest-RT incl. TBI, mean Gy among exposed (SD)	25.9 (12.9)	26.2 (12.7)	25.8 (13)
Chest-RT excl. TBI, mean Gy among exposed (SD)	35.4 (8.5)	34.1 (9.4)	36.2 (7.9)
Bleomycin, mean IU · 10^4/m^2 among exposed (SD)	11.8 (5.2)	12.9 (4.8)	10.5 (5.4)
Cyclophosphamide, mean g/m^2 (SD)	4.6 (2.8)	4.3 (2.8)	4.8 (2.8)
Doxorubicin, mg/m^2 (SD)	323 (110)	321 (99)	323 (117)
Pulmonary function			
FEV$_1$, mean L (SD)	2.97 (0.81)	2.31 (0.52)	3.34 (0.69)
FVC, mean L (SD)	3.91(1.04)	2.99 (0.62)	4.43 (0.84)
FEV$_1$/FVC, mean ratio-value (SD)	0.76 (0.08)	0.77 (0.08)	0.75 (0.07)
TLC (*N* = 213), mean L (SD)	6.45 (1.39)	5.27 (0.84)	7.13 (1.17)
Obstructive pulmonary dysfunction, *N* (%)			
Grade 0 – No	176 (77.9)	62 (76.6)	114 (78.6)
Grade 1 – Mild	24 (10.6)	7 (8.6)	17 (11.7)
Grade 2 – Moderate	26 (11.5)	12 (14.8)	14 (9.7)
Obstructive impairment[b]	26 (11.5)	12 (14.8)	14 (9.7)
Restrictive pulmonary dysfunction, *N* (%)			
Grade 0 – No	163 (72.1)	65 (80.2)	98 (67.6)
Grade 1 – Mild	36 (15.9)	9 (11.2)	27 (18.6)
Grade 2 – Moderate	11 (4.9)	1 (1.2)	10 (6.9)
Grade 3 – Severe and undesirable	1 (0.5)	1 (1.2)	–
Missing TLC %-predicted value	15 (6.6)	5 (6.2)	10 (6.9)
Restrictive impairment[c]	13 (5.8)	3 (3.7)	10 (6.9)
Smoking			
Status at examination, *N* (%)			
Never	90 (39.8)	33 (40.7)	57 (39.3)
Former	98 (43.4)	31 (38.3)	67 (46.2)
Current	38 (16.8)	17 (21)	21 (14.5)
Pack-years (*N* = 120), mean (SD)	17.3 (18.2)	17.2 (23.5)	17.4 (14.5)
Years since cessation (*N* = 91), mean (SD)	20.3 (13.1)	20.7 (13.9)	20.1 (12.8)
Cardiac function			
Heart failure	26 (11.5)	8 (9.9)	18 (12.4)
LVEF (total *N* = 223), mean percentage (SD)	54.1 (6.6)	55.2 (5.5)	53.5 (7.1)
LVSD (total *N* = 223), *N* (%)	38 (17)	11 (13.6)	27 (19)
Blood sample (N = 225)			
Hemoglobin, mean g/dl (SD)	14.0 (1.2)	13.2 (1)	14.4 (1.1)
Anemia, *N* (%)	25 (11.1)	5 (6.2)	20 (13.8)

[a]One patient was diagnosed with both asthma and COPD.

[b]FEV$_1$<80%-predicted and FEV$_1$/FVC <0.70 according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for obstructive pulmonary function impairment.

[c]Restrictive impairment (TLC <75%-predicted or FVC <75%-predicted and FEV$_1$/FVC >0.70 if missing TLC) according to Common Terminology Criteria for Adverse Events v3.0.

BEAM: carmustine, etoposide, cytarabine and melphalan; BMI: body mass index; COPD: chronic obstructive pulmonary disease; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; Gy: gray; HDT-ASCT: high dose therapy with autologous stem cell transplantation; IU: international units; LVEF: left ventricular ejection fraction; LVSD: left ventricular systolic dysfunction; RIC: reduced intensity conditioning; RT: radiotherapy; SCT: stem cell transplantation; SD: standard deviation; TBI: total body irradiation; TLC: total lung capacity; VA: alveolar volume.

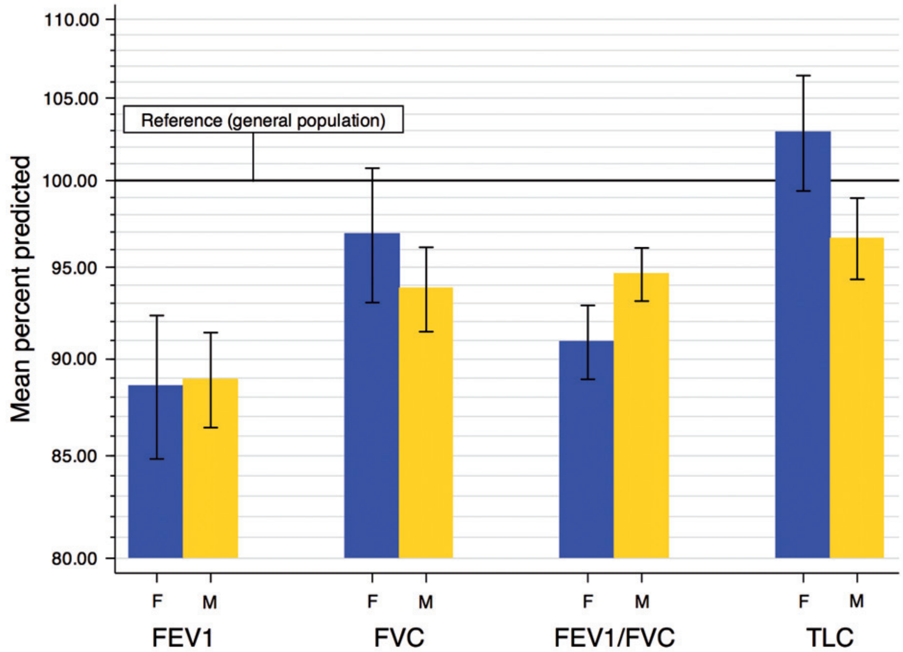

Figure 2. Mean percent predicted obstructive and restrictive parameters with 95% confidence intervals among lymphoma survivors after HDT-ASCT compared with normative reference data. F: female; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; M: male; TLC: total lung capacity.

(females) and 11.1%-points (males) lower than that predicted from normative reference data. Risk of obstructive impairment was independently associated with increasing cumulative doxorubicin dose and smoking status.

The proportion of current smokers in our patient group 2012–2014 (16.8%) was over 2%-points higher than the Norwegian population average (14.7% for all ages combined) [31]. In a sample of the Norwegian general population from 2005, the prevalence of obstructive impairment was around 6% in women and 9% in men, with smoking and age above 65 as the strongest predictors [32]. The relatively large proportion of current smokers and the close relation between current smoking and obstructive impairment seen in our data, underline the need for increased focus on smoking cessation in this patient group. Although cancer survivors do not appear to be more likely to quit smoking than the general population [33], oncology care providers who intervene early after diagnosis may benefit from the so-called 'teachable moment' to encourage cessation and lifestyle-change [15].

Gandola et al. reported on pulmonary function in 24 LSs (and three breast cancer survivors) after a median follow-up of 20 months post HDT-ASCT [16]. However, the present study is, to the best of our knowledge, the first to address the long-term pulmonary function after HDT-ASCT in LSs. In line with our results after 10 years of follow-up, Gandola et al. found FEV_1/FVC and TLC after 2 years of follow-up to be close to that predicted [16]. The modest reduction in obstructive and restrictive parameters after HDT-ASCT differ from the marked reduction in diffusing capacity, which we recently found to be impaired in 37% in this group of LSs [17].

Our finding that risk of obstructive impairment increased with increasing cumulative doxorubicin doses was somewhat unexpected, and has, to the best of our knowledge, not been reported previously in LSs after HDT-ASCT. Ellis et al. reported that chest RT and doxorubicin treatment in osteogenic sarcoma patients ($n = 28$) did not cause any significant obstructive sequelae after a mean follow-up of 42 months, but did not evaluate risk of impairment by treatment using regression techniques [11]. Apart from the longer follow-up time, our patient group differ from that of Ellis et al., by being larger and having received higher maximum cumulative doxorubicin doses (450 versus 775 mg/m^2), which might explain why the elevated risk of obstructive impairment was seen most clearly in the highest dose-group of our patients. A possible underlying mechanism of this observation might be doxorubicin-induced impairment of the endothelial function measured by brachial artery reactivity [34], which in turn has been associated with lower FEV_1 early in COPD [35].

Current smoking has also been associated with endothelial dysfunction in a dose-related manner [36]. Thus, smoking has likely contributed in conjunction with doxorubicin with deteriorative effects on the endothelial function, which in turn has resulted in the reduction in FEV_1 and FEV_1/FVC seen in our patients. However, the predominant mechanisms of smoking-induced reduction in spirometric parameters are likely related to airway abnormalities such as alveolar wall destruction in emphysema [37]. An increased risk of obstructive impairment was most clearly seen in current smokers, and no statistically significant difference was found between never and former smokers. We also checked for an association between smoking history (quantified as pack-years) and obstructive impairment, but found no relationship (results not shown). This indicates that obstructive impairment might be partially reversed upon smoking cessation among LSs after HDT-ASCT, and corresponds well with the findings of Scanlon et al. [38], who reported that COPD patients who stopped smoking experienced an improvement in FEV_1 in the year after quitting.

Table 2. Risk ratios with 95% confidence intervals of impaired pulmonary function associated with treatment exposures and other characteristics.

	Obstructive impairment ($N=26$)[a]		Restrictive impairment ($N=13$)[b]	
	Uni RR	Multivariable RR (95% CI)	Uni RR	Multivariable RR (95% CI)
Female gender	1.53	–	0.54	–
Age at examination (years.)	1.02	–	**0.97**	0.94 (0.84–1.06)
Body mass index (kg/m^2)	0.96	–	1.08	–
Infection/Asthma/COPD/Thoracotomy at examination (ref. none)	**4.91**	**4.10 (2.13–7.91)**	0.77	
Years since diagnosis	1.03	–	1.00	–
Years since HDT	1.02	–	0.99	–
Lines of chemotherapy pre HDT-ASCT		–		–
1	1.00	–	1.00	–
2	1.63	–	2.29	–
≥3	1.78	–	1.78	–
P-trend		–		–
Type of HDT-ASCT		–		–
TBI + high-dose cyclophosphamide	0.88	–	1.15	–
BEAM-treatment	1.00	–	1.00	–
Relapse post-HDT-ASCT (ref. no relapse)	1.53	–	1.03	–
Chest RT (N)		–		
Unexposed	1.00	–	1.00	1.00 (reference)
1–13 Gy	1.12	–	1.43	3.03 (0.30–34)
>13–66 Gy	0.82	–	**3.14**	**3.63 (1.11–12)**
P-trend		–		**0.033**
Bleomycin[c]		–		–
Unexposed	1.00	–	1.00	–
1–12 IU · 10^4	2.68	–	NA	–
>12–21 IU · 10^4	NA	–	4.55	–
P-trend		–		–
Cyclophosphamide		–		–
0–3.49 g/m^2	1.00	–	1.00	–
3.50–5.99 g/m^2	1.19	–	0.24	–
6.00–12.30 g/m^2	2.06	–	0.42	–
P-trend		–		–
Doxorubicin				–
<300 mg/m^2	1.00	1.00 (reference)	1.00	–
300–399 mg/m^2	1.25	1.47 (0.48–4.50)	0.83	–
400–775 mg/m^2	**2.73**	**3.37 (1.44–7.88)**	2.28	–
P-trend		**0.004**		–
Smoking status				–
Never	1.00	1.00 (reference)	1.00	–
Former	2.02	2.17 (0.79–5.98)	0.61	–
Current	**4.74**	**3.77 (1.33–11)**	1.18	–
P-trend		**0.008**		–
Heart failure	1.40	–	2.31	–
Anemia	1.45	–	1.45	–

[a]FEV_1<80%-predicted and FEV_1/FVC <0.70 according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for obstructive pulmonary function impairment.
[b]Restrictive impairment (TLC <75%-predicted or FVC <75%-predicted and FEV_1/FVC >0.70 if missing TLC) and diffusion capacity impairment (DLCO or DLCO/VA <75%-predicted) according to Common Terminology Criteria for Adverse Events v3.0.
[c]Unexposed group split into NHL and HL patients, using unexposed HL patients as reference (coefficient for unexposed NHL patients ($N=176$) not shown).
BEAM: carmustine, etoposide, cytarabine and melphalan; DLCO: carbon monoxide transfer factor corrected for hemoglobin; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; Gy: gray; HDT-ASCT: high dose therapy with autologous stem cell transplantation; IU: international units; NA: not applicable; RR: risk ratio; RT: radiotherapy; TBI: total body irradiation; TLC: total lung capacity; VA: alveolar volume. **Bold** RRs, CIs and P-trends represent statistical significance at a 0.05 level.

When cumulative doxorubicin dose and smoking status were combined and plotted against adjusted mean FEV_1 (Figure 3), we found a statistically significant difference of around 0.6 l between never/former smoking LSs who received <300 mg/m^2 of doxorubicin and currently smoking LSs who received 400–775 mg/m^2 of doxorubicin, which highlight the large difference in pulmonary late-effects between subgroups of LSs after HDT-ASCT. Although we did not find any statistically significant differences in FEV_1 (l) between never/former and currently smoking LSs within each group of cumulative doxorubicin dose, the mean FEV_1 values were consistently lower among current compared to never/former smokers. These findings may help to target smoking cessation advice towards subgroups of LSs who are particularly vulnerable to further pulmonary compromise.

No associations were found between RT (chest or TBI) and obstructive impairment. For TBI, this is likely to be due to the use of low single doses and lung shielding [39]. In contrast to what have been reported from studies in childhood cancer survivors [13,40], a restrictive impairment was found in only 13 (5.8%) of our patients. Two of the 13 LSs with restrictive impairment received HDT-ASCT before 1998, and none of these two received mantle field or mediastinal RT. However, a statistically significant association was detected in the multivariable regression model with chest RT. The low prevalence of restrictive impairments might be explained by the fact

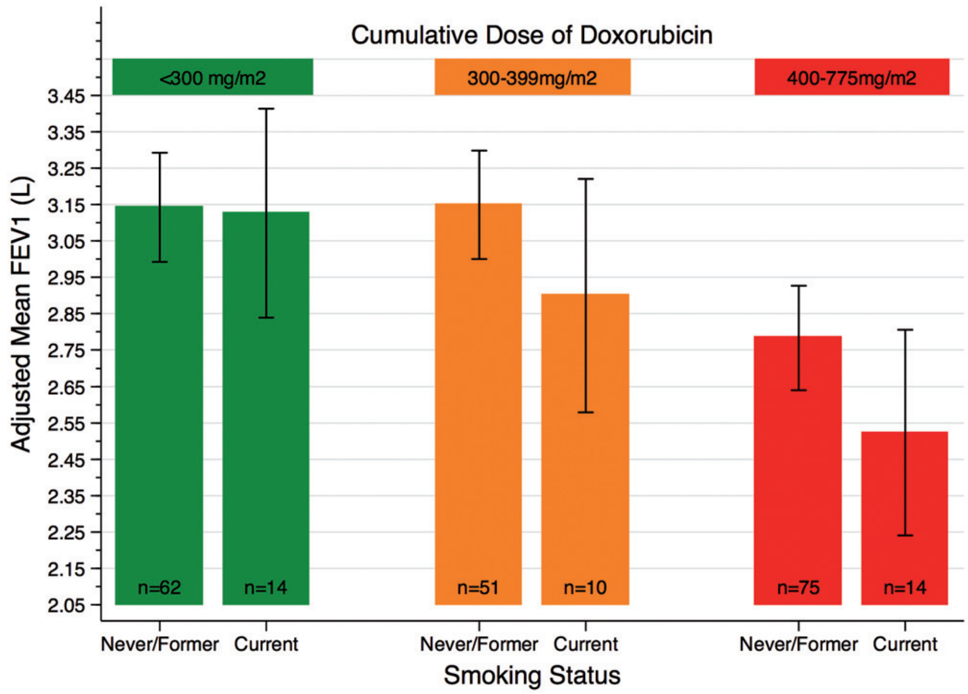

Figure 3. Adjusted mean forced expiratory values in 1s (FEV_1, l) with 95% confidence intervals by smoking status over groups of cumulative doxorubicin exposure, adjusted for height (continuous; age (continuous); sex; infection/asthma/COPD/thoracotomy (yes, no); lines of chemotherapy pre HDT-ASCT (1, 2, ≥3); cyclophosphamide (0–3.49, 3.50–5.99 and 6.00–12.30 g/m^2). Adjusted means were predicted by using Stata's post-estimation command margins after linear regression. Non-overlapping CIs represent statistically significant differences between groups.

that we only studied LSs who received RT as adults, and thereby excluding development impairments of the lung induced by chest RT, which is typically seen in childhood cancer survivors [41]. Also, the low number of LSs with restrictive impairment reduced the statistical power and yielded imprecise risk estimates for each of the chest RT dose-groups.

Pulmonary impairment has been associated with reduction in exercise capacity, physical functioning and quality of life among cancer survivors [6,14,15]. Therefore, it is particularly important to preserve cardiopulmonary function by smoking cessation in this patient group. Also, Travis et al. [12] reported that smoking HL patients have a 20-fold increased risk of secondary lung cancer compared to their non-smoking peers, as risks from smoking appeared to multiply risks from treatment.

Strengths of the present study include the large, homogenous study population of LSs after HDT-ASCT, in which long-term obstructive and restrictive pulmonary dysfunction have not been addressed previously. Further strengths include the high-quality data on spirometry, lung volume, echocardiography, blood sampling, treatment history and smoking, which enabled a well-controlled analysis. Apart from a larger proportion of participants receiving chest RT, no differences in treatment where found between participants and non-participants, which strengthen the generalizability of the results. Still, we cannot rule out that other factors, not assessed in the attrition analysis, might indicate that participants were healthier than non-participants.

As we lacked complete pre-diagnostic or pre-transplant measurements of spirometry and lung volume, our analysis was limited to address factors associated with long-term obstructive and restrictive impairments, and could not identify change in pulmonary function caused by treatment, smoking or other clinical factors. It is important to note that very few patients treated today will exceed a cumulative doxorubicin dose of 400 mg/m^2. Therefore, possible doxorubicin-induced obstructive impairment might be less relevant for today's lymphoma patients compared to what was observed in our study participants, although the majority of our participants did not exceed 400 mg/m^2. The numbers of LSs with obstructive ($n = 26$) or restrictive ($n = 13$) impairments were low, resulting in few cases in each category of the covariates included in the multivariable analyses, and hence yielded wide confidence intervals. The results from the multivariable analyses should therefore be interpreted cautiously. Also, the low number of current smokers, yielded wide confidence intervals and detection of statistically significant differences between never/former and current smokers within doxorubicin dose-groups might have been hampered by insufficient statistical power. Nevertheless, we believe that the present cross-sectional analysis offers new and important clinical insights into the long-term pulmonary function of this patient group.

In summary, our analysis showed modest reductions in FEV_1 and FEV_1/FVC among long-term LSs after HDT-ASCT compared to normative reference data despite intensive cancer treatment. Risk of obstructive impairment was linked to cumulative doxorubicin exposure and current smoking, and risk of restrictive impairment was linked to chest RT. Currently smoking patients who received the highest doxorubicin doses had the lowest adjusted mean FEV_1. To limit obstructive impairments in LSs after HDT-ASCT, we suggest that targeted smoking-cessation advice is directed towards patients who have received high cumulative doses of doxorubicin.

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Disclosure statement

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ORCID

Jo S. Stenehjem http://orcid.org/0000-0002-1964-5410

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