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Influence of age and duration of follow-up on lung function after combined chemotherapy for Hodgkin's disease

B.V. Jensen, N.L.T. Carlsen, N.I. Nissen

Influence of age and duration of follow-up on lung function after combined chemotherapy for Hodgkin's disease. B.V. Jensen, N.L.T. Carlsen, N.I. Nissen.
ABSTRACT: Pulmonary function was studied in 48 patients 4–13 yrs after treatment for Hodgkin's disease with mantle-field irradiation followed by standard mechlorethamine, Oncovin, procarbazine and prednisone (MOPP) chemotherapy. The patients were found to have a restrictive lung disease suggestive of pulmonary fibrosis. Low age at therapy (≤30 yrs, median 24 yrs) was associated with a significantly more pronounced restrictive lung function impairment than older age (>30 yrs, median 40 yrs) suggesting a higher susceptibility to the pulmonary side-effects of therapy. In addition younger smokers had a significantly greater reduction in diffusion capacity and forced expiratory volume in one second than older smokers, suggesting a higher suseptibility to the additional adverse effect of smoking. With longer follow-up nonsmokers had an increase in static lung volumes. It is suggested that this may be the result of more frequent pulmonary infections in such patients as compared with the general population. However, the duration of follow-up was not associated with changes in other indices of lung function.
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Dept of Internal Medicine, the Finsen Institute, Copenhagen, Denmark.

Correspondence: B.V. Jensen, Dept of Internal Medicine and Hematology, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark.

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The optimal and curative management of Hodgkin's disease involves two treatment modalities (chemotherapy and radiotherapy) which are used in a more or less intensive treatment programme selected partly on the basis of prognostic factors in order to minimize the risk of late complications. With improvement in cure rates a detailed knowledge of the late side-effects of therapy is becoming increasingly important. A subject of considerable concern is the risk of late complications in young patients who have the likelihood of long-term survival [1].

Treatment with irradiation and chemotherapy may cause both short-term and long-term pulmonary pathological changes [2–6]. The few reports on long-term follow-up studies of respiratory function following combined modality therapy for Hodgkin's disease have demonstrated a minor reduction in lung volumes [7–9], and an unaffected [8], or moderate decrease [7–9] in, diffusion capacity. It is not known whether intensive therapy, potentially toxic to the lungs, is tolerated equally well in young and older patients. It is likewise unknown how the changes in lung function will develop during a longer follow-up.

The aim of the present investigation was to study the relationship between pulmonary function in long-term survivors of Hodgkin's disease and age at initial treatment, tobacco smoking and lengths of follow-up after aggressive therapy with mantle-field irradiation followed by mechlorethamine, Oncovin, procarbazine and prednisone (MOPP)-chemotherapy.

Material and methods

The study population consisted of 48 patients treated for Hodgkin's disease with mantle-field irradiation followed by standard MOPP-chemotherapy. All the patients had participated in randomized trials (Danish Hodgkin Study Group (LYGRA) [10] (n=42) or Cancer and Leukaemia Group B (CALGB) protocols [11] (n=6)) and had been treated in a uniform manner. We included only patients in first remission at least 3 yrs after therapy and excluded patients who had received irradiation to the lungs outside the mantle-field, who had received other treatment regimes, who had lung parenchymal Hodgkin involvement or had a history of chronic lung disease or congestive heart failure prior to the treatment.

A preliminary analysis of the influence of age at therapy and duration of follow-up on lung function with various subgroups yielded the same mean results. Accordingly the patients were arbitrarily grouped according to the mean values in the study group as follows:

1) Young patients: patients≤30 yrs old at therapy.
2) Older patients: patients >30 yrs old at therapy.

3) Short-term follow-up: patients with a follow-up period≤ 8 yrs after completion of the mantle-field.
4) Long-term follow-up: patients with a follow-up period >8 yrs.

The clinical characteristics of the patients are shown in table 1.

The radiotherapy was given as a standard mantle-field using the same irradiation technique in all 48 patients. The technical details of the treatment policy are described elsewhere [13]. The radiotherapy was delivered by a 6 MeV linear accelerator with median daily doses (5 days·wk^{-1}) of 1.75 GY to a median central dose of 37 Gy.

A median period of 38 days after completion of the mantle-field irradiation the 48 patients were randomized to six cycles of MOPP chemotherapy. Each cycle consisted of mechlorethamine (nitrogen mustard) 6 mg·m^{-2} body surface *i.v.* on days 1 and 8, Oncovine (vincristine) 2 mg *i.v.* on days 1 and 8, procarbazine 100 mg·m^{-2} daily for 14 days and, in cycle 1 and 4 only, prednisone 40 mg·m^{-2} orally, daily for 14 days. Following each 14 day treatment cycle the patients had a 14 day period without treatment. In the presence of toxicity standard dose reduction schemata were used.

The patients were re-examined between 10 and 12 a.m. after a 12 h fast, including nonsmoking. They underwent a physical examination and electrocardiogram (ECG) and haemoglobin levels were obtained. The patients were classified as nonsmokers (n=23, including 9 ex-smokers) or current smokers (n=25). Median smoking abstinence before the follow-up examination among the 9 ex-smokers was 12 yrs (3–30 yrs).

Pulmonary function testing was performed on a computerized Jaeger lung function equipment (Transfer Screen®). The inspiratory vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were calculated from the best of three flow-volume curves. The total lung capacity (TLC), residual volume (RV) and the transfer factor (carbon monoxide (CO) diffusing capacity) (T_{LCO}) were calculated from the same single-breath manoeuvre. TLC and RV were measured using a helium dilution technique where RV was calculated from the equation RV= TLC-VC. T_{LCO} was calculated according to OGILVIE *et al.* [14]. The results were expressed as percentages of predicted (*i.e.* adjusted for sex, age, height and weight) of 120 healthy sex- and age-matched, life-term nonsmokers living in the same area as the patients, examined with the same equipment and by the same technicians as the study group. A detailed description of the reference group has been published elsewhere [15].

Statistical analysis

The Student's t-test for unpaired data (two-tailed) was used to compare the mean values of the lung function results of the subgroups with that of the 120 healthy life-term nonsmokers [15]. The assumption of normality was tested graphically by normal probability plots [16]. The numbers of pack-years did not follow a normal distribution and were compared by a Mann-Whitney test. The influences of the age of the patients at initiation of therapy, the duration of the follow-up and the smoking habits on the lung function tests (LFT) at follow-up (percentage predicted values) were analysed using a stepwise regression model [16]:

$$LFT = Constant + K1 \cdot (\text{age at therapy in yrs}) + K2 \cdot (\text{yrs of follow-up}) + K3 \cdot (\text{nonsmoking=0, smoking=1})$$

Table 1. – Clinical characteristics of 48 long-term survivors of Hodgkin's disease

Subgroup:	Age at therapy		Follow-up period		Total
	Younger patients (≤30 yrs)	Older patients (>30 yrs)	Short-term (≤8 yrs)	Long-term (>8 yrs)	
Total number	27	21	22	26	48
Male/female ratio	14/13	12/9	9/13	17/9	26/22
Stage I	9	9	8	10	18
II	16	8	12	12	24
III	2	4	2	4	6
Median age at therapy	24	40	27	30	29
Median age at follow-up	33	46	33	40	38
Median yrs of follow-up	8.4	9.0	6.2	10.4	8.6
Nonsmokers n	12	11	12	11	23
Smokers n	15	10	10	15	25
Median pack-years for smokers	11	24*	9.5	20*	19

Prior to treatment patients were staged according to Ann Arbor classification [12]. Pack-year: number of packs of cigarettes smoked per day multiplied by the number of years smoking. Except for pack-years there were no significant differences between the subgroups. *: significant difference ($p<0.05$, Mann-Whitney test); n=number.

Table 2. – Results of stepwise regression for prediction of various lung function tests (percentage predicted) in 48 long-term survivors of Hodgkin's disease

Lung function test = constant + K1·(age at therapy in yrs) + K2·(yrs of follow-up) + K3·(nonsmoking=0, smoking=1)

Lung function test	Constant: K0	SE	Age at therapy: K1	SE	p	Years of follow-up: K2	SE	p	Smoking habits: K3	SE	p	SD
TLC	73	7	0.3	0.1	<0.02	1.5	0.6	<0.01	-	-	NS	11
VC	74	8	0.5	0.2	<0.01	1.3	0.7	<0.06	-	-	NS	13
RV	71	9	-	-	NS	1.8	0.9	<0.05	16	5	<0.003	17
RV/TLC	91	3	-	-	NS	-	-	NS	12	4	<0.01	15
FVC	63	6	0.7	0.2	<0.0005	-	-	NS	-	-	NS	13
FEV_1	69	6	0.7	0.2	<0.0005	-	-	NS	-	-	NS	13
TLCO Total	78	5	0.4	0.1	<0.005	-	-	NS	-7	3	<0.04	11
Nonsmokers	91	3	-	-	NS	-	-	NS	*	*	*	13
Smokers	66	6	0.6	0.2	<0.003	-	-	NS	*	*	*	9
TLCO/TLC	97	2	-	-	NS	-	-	NS	-9	3	<0.01	12

The model fitting results include the estimates of the model coefficient (K) for each independent variable, the standard error (SE) and the two-tailed significance level of the coefficient (p). For TLCO a separate analysis was performed for nonsmokers (n=23) and smokers (n=25). SD: estimated standard deviation about the regression line; NS: not significant; TLC: total lung capacity; VC: vital capacity; RV: residual volume; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; TLCO: transfer factor of the lungs for carbon monoxide.

Table. 3. – The influence of age at therapy on lung function (percentage predicted) in 48 long-term survivors of Hodgkin's disease

Age at therapy:		Young patients (≤30 yrs)			Older patients (>30 yrs)				Total		
Number	Total	27			21				48		
	Nonsmokers	12			11			Difference	23		
	Smokers	15			10			between the groups	25		
Lung function test		Mean±SD			Mean±SD			p-value	Mean±SD		
TLC	Total	93	11 *		100	12		<0.04	96	11	
	Nonsmokers	89	11 **		99	13		<0.05	94	12	
	Smokers	96	10		101	11		NS	98	10	
VC	Total	95	12		105	14		<0.02	99	14	
	Nonsmokers	94	12		106	14		<0.04	100	13	
	Smokers	96	13		103	15		NS	99	14	
RV	Total	95	22		95	16		NS	95	19	
	Nonsmokers	86	23 **		87	17 *		NS	87	21 ***	
	Smokers	102	18	$	103	9	$$	NS	103	15	$$$
RV/TLC	Total	100	18		93	14 *		NS	97	17	
	Nonsmokers	95	18		86	12 ***		NS	91	16 ***	
	Smokers	104	17		101	13	$$	NS	103	16	$$$
FVC	Total	77	12 ****		90	16 ***		<0.002	83	14 ****	
	Nonsmokers	75	13 ****		93	15		<0.006	84	14 ****	
	Smokers	78	11 ****		87	16 ***		NS	82	13 ****	
FEV_1	Total	83	13 ****		96	15		<0.003	89	14 ****	
	Nonsmokers	84	14 ****		96	14		<0.05	89	14 ****	
	Smokers	83	11 ****		97	17		<0.03	89	15 ****	
FEV_1/FVC	Total	109	7 ****		108	10 ****		NS	108	8 ****	
	Nonsmokers	111	7 ****		104	9		<0.04	108	9 ****	
	Smokers	106	6 ***		112	8 ****	$	NS	108	7 ****	
TLCO:	Total	84	12 ****		92	10 *		<0.02	88	12 ****	
	Nonsmokers	88	15 **		94	10		NS	91	13 **	
	Smokers	81	9 ****		91	11		<0.02	85	10 ****	
TLCO/TLC	Total	92	13 ****		93	11 ****		NS	92	12 ****	
	Nonsmokers	98	14		96	10		NS	97	12	
	Smokers	87	11 ****	$	90	11 ****		NS	88	11 ****	$$$

The significance levels for difference between mean values in the patients and predicted normal values [15] are indicated by: *: p<0.05; **: p<0.02; ***: p<0.01; ****: p<0.001 and for differences between nonsmoking and smoking patients by: $: p<0.05; $$: p<0.02; $$$: p<0.01. The Student's t-test is used. SD: standard deviation; NS: not significant. For further abbreviations see legend to table 2.

where LFT is the dependent variable, and age at therapy, years of follow-up and smoking habit are the independent variables. The K's are constants. The regression coefficients (K), the standard error of the coefficients (SE) and the significance level for the variables (p) are given in table 2.

Results

The subgroups of patients (younger *versus* older, short-term *versus* long-term follow-up) were comparable as regards male/female ratio and proportion of smokers (table 1). The physical examination of all patients, their ECG's and haemoglobin levels were normal.

The 48 patients had overall lung function measurements compatible with restrictive impairment (table 3). Compared to predicted normal values they had a reduction of FVC, FEV_1 and TLCO and an increase of FEV_1/FVC and the nonsmokers had reduced RV and RV/TLC but only a slight reduction in TLC ($p<0.08$).

Influence of age at therapy

At initiation of therapy the median age of the group of young patients was 24 yrs and that of the group of older patients 40 yrs. The two groups were comparable as regards the duration of follow-up (table 1). The younger patients had a more pronounced restrictive lung function impairment than the older patients, with lower TLC, VC, FVC, FEV_1 and TLCO values (table 3). Compared to predicted normal values the younger patients had reduced TLC, FVC, FEV_1 and TLCO values and increased FEV_1/FVC values (table 3). The young and older patients had comparable values of RV, RV/TLC and TLCO/TLC.

Influence of smoking

On average the smokers had higher RV, RV/TLC, lower TLCO/TLC but only slightly lower TLCO values ($p<0.09$) than nonsmokers (table 3). The group of young smokers had significantly lower FEV_1 and TLCO values than the group of older smokers (table 3). This despite the fact that the group of young smokers had smoked significantly less, with a lower number of pack-years than the group of older smokers (table 1). Among smokers the follow-up period was not associated with differences in lung function (table 4).

Influence of duration of follow-up

The median follow-up period from the end of mantle-field irradiation was 8.6 yrs (3.6–13.5 yrs). In the subgroup of patients with short-term follow-up it was 6 yrs and in the subgroup of patients with long-term follow-up 11 yrs. The two groups were comparable as regards age at therapy and at follow-up (table 1). Differences in lung function associated with the duration of follow-up of were observed only for nonsmokers. Nonsmokers with long-term follow-up had higher TLC and RV and lower TLCO/TLC than nonsmokers with short-term follow-up (table 4). Nonsmokers with short-term follow-up had TLC, RV and RV/TLC values below predicted normal values whilst

Table 4. – Influence of duration of follow-up on lung function (percentage predicted) in 48 long-term survivors of Hodgkin's disease

Follow-up period:		Short-term (≤8 yrs)			Long-term (>8 yrs)		Difference between groups p-value
Number	Nonsmokers	12			11		
	Smokers	10			15		
Lung function test		Mean±SD			Mean±SD		
TLC	Nonsmokers	87	11 ***		101	10	<0.005
	Smokers	97	13		99	9	NS
RV	Nonsmokers	75	19 ****		99	13	<0.003
	Smokers	101	14	$$$	104	16	NS
RV/TLC	Nonsmokers	86	18 ***		96	12	NS
	Smokers	103	16	$	103	15	NS
TLCO	Nonsmokers	90	16 *		92	10	NS
	Smokers	82	14 ****		87	8 ***	NS
TLCO/TLC	Nonsmokers	102	12		91	10 ***	<0.04
	Smokers	85	11 ****	$$$	90	10 ****	NS

The two groups of patients had comparable values of VC, FVC and FEV_1. The significance levels for differences between mean values in the patients and predicted normal values [15] are indicated by: *: $p<0.05$; **: $p<0.02$; ***: $p<0.01$; ****: $p<0.001$, and for differences between smokers and nonsmokers by: $: $p<0.05$; $$$: $p<0.01$. The Student's t-test is used. NS: not significant. For further abbreviations see legend to table 2.

these indices were within normal limits in nonsmokers with long-term follow-up, and the latter group had TLCO/TLC values below normal (table 4). In general, nonsmokers with long-term follow-up had a lung function very similar to that of the smokers (table 4). The duration of follow-up was not associated with differences in RV/TLC, VC, FVC, FEV_1, FEV_1/FVC or TLCO values.

Table 2 summarizes these relationships. It shows the results of regression analysis including the influence of age at therapy, years of follow-up and smoking habits on the lung function (percentage predicted values) at follow-up. Low age at therapy was associated with lower values of TLC, VC, FVC, FEV_1 and TLCO. The association between low age at therapy and low values of TLCO was only reflected in smokers and was not found in nonsmokers. Longer follow-up was associated with higher values of TLC, VC and RV. Tobacco smoking was associated with higher values of RV and RV/TLC and lower values of TLCO and TLCO/TLC.

Discussion

This long-term follow-up study demonstrates that mantle-field irradiation followed by standard MOPP chemotherapy is associated with a restrictive lung function impairment suggestive of diffuse pulmonary fibrosis. Younger patients appeared to be more susceptible to the pulmonary side-effects of therapy than older patients as they had developed a more pronounced restrictive lung function impairment. Damage to the capillaries has been considered to be the major factor in the causation of the pulmonary pathology after lung-toxic agents [4]. Assuming a higher capillary density per unit lung volume in the younger than the older patients [17] this may in part account for the higher sensitivity to therapy. However, the marked effect of lung toxic agents on type II pneumocytes [4] may also have contributed significantly to the late changes, especially in view of their important stem cell and secretory functions. The failure of alveolar multiplication may explain the reduced lung volumes.

In smokers the higher RV and RV/TLC and lower diffusion capacity relative to volume compared to nonsmokers may suggest a superimposed emphysema. Young smokers had significantly lower FEV_1 and TLCO values than older smokers despite the fact that they had smoked significantly less. The observed decrease in TLCO associated with tobacco smoking has been attributed to alteration of the pulmonary membrane by anatomical lesions probably of emphysematous nature [18–20]. In addition to being more susceptible to the pulmonary side-effects of therapy, younger patients seemed to be more susceptible to the additional adverse effects of tobacco smoke than older patients.

With increasing duration of follow-up an increase in the TLC and RV and a decrease in TLCO/TLC were observed among the nonsmokers. The pulmonary changes were very similar to those observed among smokers and the functional changes could only be observed in nonsmokers. The reason for this increase in static lung volumes with longer follow-up period is uncertain and the duration of follow-up was not associated with changes in TLCO, FVC or FEV_1. However, a high proportion of patients with Hodgkin's disease are known to suffer from a selective impairment of cell-mediated immunity which persists after cure [21]. This deficit is expressed as an increased susceptibility to certain bacterial, fungal and viral infections, including a high frequency of herpes zoster compared to the general population. In this study group seven (7 of 23) nonsmoking patients had herpes zoster eruptions during the follow-up period. They had significantly higher RV/TLC values than the sixteen (16 of 23) nonsmokers without herpes zoster eruptions (mean 106.2 *versus* 84.3, $p<0.001$). Patients with a history of herpes zoster eruptions presumaby had a high frequency of pulmonary infections than patients without such evidence of immunosuppression. A high frequency of pulmonary infections in patients with Hodgkin's disease compared to the general population may, thus, account for the increase in static lung volumes observed after a prolonged follow-up period.

In conclusion this study demonstrates that aggressive therapy with mantle-field irradiation followed by MOPP chemotherapy is associated with a significantly more pronounced restrictive lung function impairment in younger than older patients. Moreover, the young patients were found to be more susceptible to the pulmonary adverse effects of tobacco smoke than older patients. As it would seem probable that this type of therapy would cause even more damage to the growing lungs in children than in young adults, these findings should stimulate investigations of the pulmonary toxicity of intensive therapy in children where the late-effects are not fully appreciated [1]. This study also suggests that late pulmonary complications may result from infections as well as directly from chemotherapy and radiotherapy.

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Atteinte pulmonaire tardive après radiothérapie et chimiothérapie pour une maladie de Hodgkin. B.V. Jensen, N.L.T. Carlsen, N.I. Nissen.

RÉSUMÉ: Nous avons étudié la fonction pulmonaire chez 48 patients, entre 4 et 13 ans après traitement pour maladie de Hodgkin, au moyen d'une irradiation par champ en manteau suivie d'une chimiothérapie standard MOPP. Les patients ont une maladie pulmonaire restrictive suggestive de fibrose pulmonaire. Un âge bas au début du traitement (≤30 ans, médiane 24 ans) est associé à une atteinte pulmonaire fonctionelle restrictive plus marquée que les âges avancés (>30 ans, médiane 40 ans), ce qui suggère chez les jeunes une susceptibilité accrue aux effets collatéraux pulmonaires du traitment. En outre, les fumeurs jeunes ont une réduction significativement plus grande de leur capacité de diffusion et de leur VEMS que les vieux fumeurs, ce qui suggère une susceptibilité accrue à l'effet défavorable complémentaire du tabagisme. Dans les follow-up prolongés, les non-fumeurs ont une augmentation des volumes pulmonaires statiques. L'on suggère que ceci pourrait être la conséquence d'infections pulmonaires plus fréquentes chez ces patients par comparaison avec la population générale. Toutefois, la durée du follow-up fut sans relation avec d'autres modifications fonctionnelles pulmonaires.

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