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Pulmonary Morbidity 10–18 Years After Irradiation for Hodgkin's Disease

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Pulmonary function tests were performed in 78 patients who had been curatively treated for Hodgkin's disease with mantle field irradiation 10–18 years ago. Mean values of the total lung capacity (95.2%), vital capacity (VC) (95.9%), forced expiratory volume in 1 s (FEV_1) (90.6%), and carbon monoxide diffusing capacity per unit alveolar volume (82.7%) showed significant deviations from the predicted normal values, standardised for age, sex, race and height. In a multiple regression analysis the normalised total dose of irradiation, the field of irradiation, and the interval since irradiation had independent negative effects on the test results. Patients reported more coughing, wheezing and dyspnoea on exertion in comparison with hospital-visitors. Their smoking habits and reported pulmonary disease were not different. It is concluded that small, but significant impairment of pulmonary function exists after a follow-up of 14 (2) years [mean (S.D.)]. The clinical impact of these findings seems, however, minimal. Further avoidance of pulmonary toxicity requires a careful quantitative study of the effects of the radiation dose and irradiated volume.
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INTRODUCTION

SINCE RADIOTHERAPY and chemotherapy cure most patients with Hodgkin's disease, it is becoming increasingly important to avoid late side effects. Lung damage from mantle field irradiation can be observed as an acute radiation pneumonitis occurring 3–9 months after irradiation, and as pulmonary fibrosis developing more than 0.5 to 1 year after treatment. Most studies performed within 12–24 months after treatment have shown mixed restrictive and obstructive lung disease with impaired diffusion capacity [1–8]. After 12–24 months the functional lung volumes are usually restored unless fibrosis develops. In the latter situation changes of lung volumes may remain stable. So far, long-term follow-up studies performed up to 13 years after radiotherapy have shown that lung volumes may vary from 90% to 105% of predicted normal values [5, 7, 9–11]. To our knowledge no studies have yet been reported on pulmonary function more than 13 years after irradiation treatment.

We have performed an extensive study of late sequelae 10–18 years after radiotherapy for Hodgkin's disease. In this paper we describe the results of respiratory function tests in 78 patients. The effects of additional chemotherapy, normalised total dose of irradiation (NTD), field of irradiation and the interval since treatment on the function parameters were analysed.

PATIENTS AND METHODS

Study population

All patients who underwent radiotherapy for Hodgkin's disease between January 1972 and December 1979 in The Netherlands Cancer Institute (Antoni van Leeuwenhoek Huis), were identified by the hospital registry in November 1989. 98 patients without signs of relapse of Hodgkin's disease were invited to participate in this retrospective study. 1 patient was hospitalised at the time of study for unknown reasons, 9 patients were lost to follow-up, and 5 patients refused to participate. After informed consent was obtained, 83 patients entered the study.

2 patients who did not receive mantle field irradiation and 3 patients of whom pulmonary function tests were not available were excluded from the analysis. The resulting study group consisted of 78 patients, 41 males aged 25–69 years [mean (S.D.) 43 (10) years] and 37 females, aged 29 to 72 years [mean 43 (10) years]. The mean follow-up interval was 14 (2) years.

Patients were classified as life-time non-smokers, current smokers or ex-smokers. 2 patients with a typical history of bronchial asthma were excluded from the analysis.

Hospital visitors ($n=114$) who accompanied patients visiting the out-patient clinic or radiotherapy department served as a control group for pulmonary symptoms. The normal values for pulmonary function tests standardised by age, sex, height and race were derived from Quanjer *et al.* [12]. Approval of the study was obtained from the hospitals ethics committee.

Treatment details

Radiotherapy was given using an 8 MV linear accelerator. 71 patients received standard mantle field irradiation, including cervical, supra- and infraclavicular, axillary and mediastinal regions. In 1 patient both axillae were excluded, in 2 patients only one axilla and in 1 patient only the mediastinum was irradiated. We were unable to retrieve details of the radiotherapy given to 3 of the patients. Radiotherapy was delivered in mean daily doses of 1.9 Gy (5 days per week) to an average total central dose of 38.6 Gy (range 21–41.4 Gy). In 52 patients the para-aortic lymph node region was also irradiated, 19 patients receiving additional irradiation of the spleen. The mean daily dose to the spleen was 1.8 Gy given to a total central dose of 38.9 Gy (20.1–41 Gy). To take into account the effect of the dose per fraction, the linear quadratic model was applied [13]. With this model, the NTD [14] can be defined as the total dose, given in

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fractions of 2 Gy with the same biological effect as the actual treatment schedule, for the endpoint under consideration:

$$NTD = [D_1 (\alpha/\beta + d_1)]/(\alpha/\beta + 2) \quad (1)$$

where the value of the α/β ratio was chosen as 3.0 Gy for the endpoint of late lung damage [15] and D_1 and d_1 are the actual total dose and dose per fraction, respectively.

The mean delivered NTD to the supradiaphragmatic regions was 37.9 Gy. The spleen and para-aortic lymph node region received an average of 37.5 Gy (NTD). Patients were grouped according to the field of irradiation, as shown in Table 1. 21 patients received additional chemotherapy, consisting of either MOPP (nitrogen mustard, vincristine, procarbazine and prednisone) or vinblastine and/or procarbazine, given before and/or after treatment as an integral part of the primary treatment.

Evaluation of pulmonary function

Spirometry included vital capacity (VC), forced expiratory volume in 1 s (FEV_1), FEV_1/VC, and total lung capacity (TLC). Diffusion capacity for carbon monoxide (DL_{CO}) was measured and adjusted for alveolar volume, resulting in the K_{CO}. Pulmonary function tests (PFTs) were performed with a Jaeger Masterlab (Würzburg, Germany) by an experienced technician. Complete PFTs were obtained in 78 patients; from 1 patient only VC, FEV_1 and FEV_1/VC test results were available.

Individual test results were expressed as a percentage of predicted normal values according to Quanjer *et al.* [12].

Pulmonary symptoms

All patients (n = 83) and the hospital visitors control group (n = 114) (equally distributed for sex and age) received a questionnaire on smoking habits, dyspnoea, coughing, wheezing, phlegm, and history of asthma. 2 patients refused to fill out the questionnaire.

Statistical methods

Paired t-tests were carried out on log-transformed PFT results (observed vs. predicted). To control the effect of potential confounders and to analyse modifying factors, differences in log-transformed observed-minus-predicted lung functions were analysed by multiple regression analysis. The effects of current smoking habits (no, yes), chemotherapy (no, yes), NTD (Gy), irradiation field (mantle field, mantle field + para-aortic, mantle field + para-aortic + spleen), sporting habits (every day, more than once a week, less than once a week, never), follow-up (interval since irradiation) (years), age at diagnosis (years), and family history of bronchial disease (no, yes) were evaluated. The size of the study population was not large enough to investigate a possible dose–response relationship between the number of cigarettes smoked and pulmonary damage. Factors were removed from the multiple regression model if $P > 0.10$.

Table 1. Study groups according to field of irradiation

	Male	Female
Mantle field	14 (5)	12 (6)
Mantle field + para-aortic	17 (5)	16 (1)
Mantle field + para-aortic + spleen	10 (1)	9 (3)

( ) number of patients with additional chemotherapy.

Questionnaire scores of patients were compared with those of the hospital visitors by the χ^2 test. Results were considered significant when $P < 0.05$.

Statistical analyses were performed using SPSS (Superior Performing Software Systems) PC+, version 4.0.

RESULTS

In the univariate analysis patients showed DL_{CO} and FEV_1/VC values which were not significantly different from the predicted values, 10–18 years after mantle field irradiation. However, the mean values of TLC, VC, FEV_1, and K_{CO} deviated significantly as shown in Table 2.

As no significant differences in lung function were found between life-time non-smokers and ex-smokers, these two categories were combined. Patients who received chemotherapy in addition to radiotherapy received a lower NTD. A correlation was made by adding a modifying factor to the multiple regression model [NTD (Gy) * chemotherapy (no, yes)]. 2 patients received even less than 20 Gy (NTD) and were excluded from further analysis as 'outliers'. The resulting model is shown in the following equation:

$$\log(PFT_{observed}) - \log(PFT_{predicted}) = \text{constant} + C1*\text{irradiation field} + C2*NTD + C3*\text{chemotherapy} + C4*\text{follow-up} + C5*\text{smoking} + C6*\text{sporting} + C7*NTD*\text{chemotherapy} \quad (2)$$

where C1 to C7 are the regression coefficients belonging to the seven independent variables. Table 3 shows that NTD had a negative effect on VC and DL_{CO}. This effect was the greatest compared with the other factors. An inverse relationship was seen between the interval since irradiation and VC and TLC. The field of irradiation also appeared to have a negative influence on TLC.

Smoking had a negative impact on DL_{CO} and K_{CO}, while sports appeared to influence VC and FEV_1 favourably.

Significant differences between patients and hospital visitors in reported coughing (39.7% vs. 21.1%) and reported dyspnoea on exertion (44.7% vs. 32.7%) were noted. Patients complained twice as often of wheezing compared with controls (22.8% vs. 11.6%, respectively). Hospital visitors reported phlegm less frequently compared to the patients (16.3% vs. 23.1%; not significant). The smoking habits of patients were not significantly different from those of the hospital visitors.

Table 2. Pulmonary function tests (% of predicted) 10–18 years after mantle field irradiation: mean and 95% confidence interval (C.I.)

	Mean	95% C.I.	No. of patients
TLC	95.17	92.21–98.24	75
VC	95.90	92.50–99.42	76
DL_{CO}	99.59	95.62–103.71	75
K_{CO}	82.68	79.75–85.72	75
FEV_1	90.64	85.86–95.68	76
FEV_1/VC	97.70	95.09–100.38	76

Table 3. Multiple regression coefficients (C) ± S.E. of the log-transformed pulmonary function test results in relation to confounding and modifying factors

	VC		TLC		DL_{CO}		K_{CO}		FEV_1	
	C	S.E.	C	S.E.	C	S.E.	C	S.E.	C	S.E.
NTD	−0.014	0.005†			−0.008	0.004*				
Chemotherapy	−0.517	0.276								
Irradiation field	−0.022	0.011	−0.018	0.009*	−0.026	0.013				
Follow-up	−0.016	0.004‡	−0.010	0.003†	−0.008	0.004				
Smoking					−0.059	0.020†	−0.071	0.018‡		
Sports	0.021	0.012							0.059	0.020†
NTD*chemotherapy	0.013	0.007								
Constant	0.731	0.207‡	0.157	0.042‡	0.488	0.157†	−0.025	0.201	−0.204	0.055‡

NTD (Gy), chemotherapy (no = 0, yes = 1), irradiation field (mantle field = 1, mantle field + para-aortic = 2, mantle field + para-aortic + spleen = 3), interval since irradiation (years), smoking (no = 0, yes = 1) and sporting habits (every day = 0, more than once a week = 1, less than once a week = 2, never = 3). The significance of the regression coefficients are indicated by: *$0.01 < P \leq 0.05$, †$< P \leq 0.01$, ‡$P \leq 0.001$.

DISCUSSION

Our data indicate that 10 to 18 years after mantle field irradiation, relatively small but significant changes of pulmonary function can be observed. Although the pathophysiology of the development of acute radiation pneumonitis and pulmonary fibrosis is not understood completely, it is clear that the vasculature plays an important role in the development of early radiation injury [6, 7, 16, 17]. It has been reported that damage to the pulmonary endothelium leads to an increase of the permeability for plasma proteins, with subsequent oedema and fibrin deposition in the interstitial space and blood vessel walls. The newly deposited fibrin may be eventually replaced by collagen fibres resulting in lung parenchymal atrophy and fibrosis [16]. In addition to the mechanism of endothelial damage leading to fibrosis, the excessive accumulation of interstitial mast cells after irradiation has also been suggested to be a fundamental component of the fibrogenic response [18]. Recently, increasing evidence suggests that growth factors play an important role in the pathway leading to radiation-induced fibrosis [19, 20]. The development of fibrosis may start within 2 months after irradiation and continue for years. This could explain the statistically significant, slightly progressive reduction in VC and TLC with time, which we have observed in our patients, when corrected for the other significant factors. The possibility that the field of irradiation was chosen differently over the years was carefully checked and could be excluded.

Other follow-up studies of lung function performed from 1 week to 13 years after irradiation [1, 5, 7–11, 21], have shown rather variable results, which are summarised in Fig. 1. Most studies [1, 9, 21, 22], revealed a moderate restriction of lung function characterised by decreased static lung volumes (VC and TLC) accompanied by a normal FEV_1/VC- ratio, which is in agreement with our findings. In other studies no significant reduction of lung volumes was seen [7, 23]. Jensen *et al.* [11] observed that static lung volumes measured 8–13 years after treatment were larger than 4–8 years after therapy. Their explanation was that patients in the first years after treatment had more pulmonary infections. They also found a significant negative influence of young age at diagnosis, while we did not find any effect of this parameter.

Generally, values deviating < 20% from predicted are considered normal [5, 23, 24]. When this criterium is applied to our observations all pulmonary function test results are within the normal range. When compared with the pulmonary complaints reported by questionnaire (dyspnoea on exertion, coughing, wheezing and phlegm), our findings suggest that the PFTs used are not sensitive enough to explain subjective complaints. Measurement of the pulmonary compliance [2, 25] might have shown a better correlation with dyspnoea on exertion, compared with the PFT used in this study. Because we found no differences in smoking, sporting habits or pre-existing lung disease between patients and hospital visitors, the difference in respiratory complaints could not be ascribed to these factors.

Patients, and even former patients, may have a health perception which is different from that of the general population. When it is assumed that for this reason, our patients had a tendency to report pulmonary complaints more often the clinical significance of the observed changes becomes even less.

Previous studies have shown that hospital visitors, defined as individuals visiting hospitalised patients, are a reliable control group [26, 27]. The advantage of hospital visitors matched for age and sex as a control group is that they can be assumed to originate from a similar background as the patients and can be retrieved relatively easy.

Choi *et al.* [28] found that the FEV_1 could be predicted by the estimated volume of the irradiation field, in 68% of the lung cancer patients with a pre-treatment value of the FEV_1 greater than 50% of predicted normal values. Studies in breast cancer patients [29–32] also indicate an important effect of the irradiated volume on lung function. In our study, we were not able to determine the volume of the irradiated lung tissue with accuracy. However, since the irradiation field for the spleen also includes the basal part of the left lung, the observed difference in lung function between patients who received mantle field irradiation only, and patients with additional irradiation of the spleen, may be caused by a difference in irradiated lung volume. Fibrosis of the diaphragm from spleen irradiation could be another explanation of our findings.

We found that after combined modality therapy VC was independent of the given dose of irradiation and equal to the VC after 40 Gy (NTD) alone. So probably the effect of the chemotherapy given, although not significant in our analysis, is more or less equal to a radiation dose of 40 Gy (NTD). Some authors [9–11, 23] have also reported reduced PFT results after

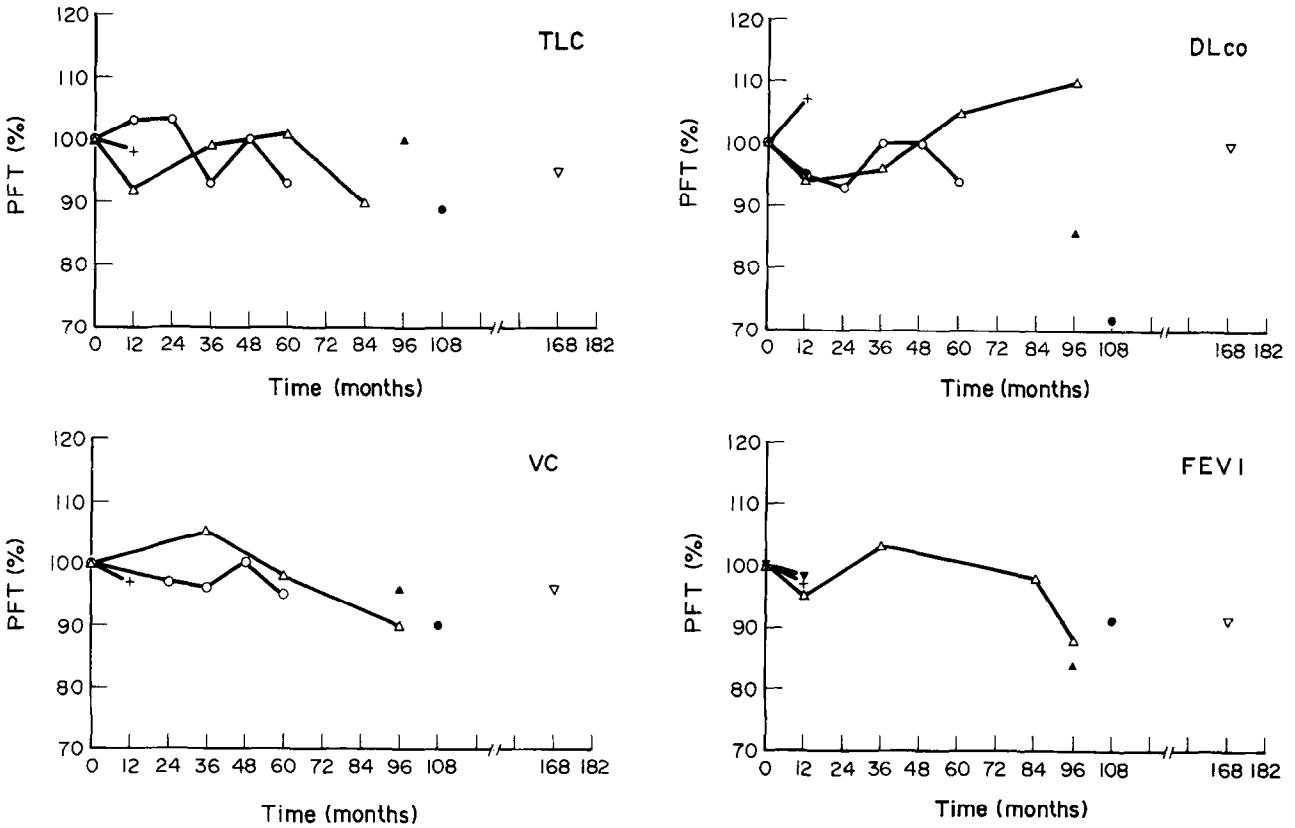

Fig. 1. Pulmonary function tests results as a function of interval since irradiation (months), derived from the present study and from other studies reported in the literature. PFT is expressed as a percentage of pre-treatment value by Cionini *et al.* [1] (+), Smith *et al.* [5] (△), Shapiro *et al.* [7] (○, do Pico *et al.* [8] (▼) and as a percentage of predicted in Morgan *et al.* [9] (●), Jensen *et al.* [10, 11] (▲), and this study (▽).

combined modality therapy. In an EORTC study [33] addition of the MOPP regimen did not significantly alter the PFT at 18–24 months after treatment.

In summary, overall lung function tests in former patients with Hodgkin's disease 10 to 18 years after mantle field irradiation, show small but significant impairments, accompanied by an increase of self-reported dyspnoea on exertion, coughing and wheezing compared with hospital-visitors. Generally, the clinical significance of these changes seems minimal. To reduce late pulmonary toxicity, more knowledge of the effects of irradiation dose and irradiated volume is needed. For this purpose, we have recently started a prospective study in patients treated with mantle field irradiation, quantifying local changes in perfusion and ventilation in relation to the locally delivered dose and the irradiated volume.

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A Phase II Study of Cisplatin Plus Methotrexate With Folinic Acid Rescue in Metastatic or Locally Recurrent Transitional Cell Carcinoma of the Urothelium

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34 patients with metastatic or recurrent transitional cell carcinoma (TCC) of the urothelium were treated with cisplatin 100 mg/m² plus methotrexate 250 mg/m² with folinic acid rescue every 3 weeks. A response rate of 55% was achieved with two complete and 15 partial responses in 31 evaluable patients. The overall median survival was 7 months, 9 months for responding and 4 months for non-responding patients. Toxicity was generally moderate. However, 1 patient with previous infectious problems died of neutropenic sepsis. Overall, 83% of the scheduled doses of cisplatin and 96% of the scheduled doses of methotrexate were given. In conclusion, this schedule of the combination of cisplatin and methotrexate did not improve response rate or survival compared with previous studies of this two-drug combination.
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INTRODUCTION

PATIENTS WITH metastatic transitional cell carcinoma (TCC) of the urothelium have a dismal prognosis with an expected survival of 3–5 months for patients who progress on chemotherapy [1]. Urothelial tract tumours are chemosensitive, but so far long-term benefit is limited to few patients. Cisplatin and methotrexate are considered the most effective single agents with response rates of about 30%, but complete response has been achieved in less than 5% [1, 2]. Combination chemotherapy has been reported to increase the number of patients achieving a complete response, but only the four drug combination M-VAC (methotrexate, vinblastine, doxorubicin and cisplatin) has demonstrated a significant survival benefit over single agent cisplatin in randomised trials [3]. Whether this apparent superiority of the M-VAC