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Pulmonary Function in Long-Term Survivors of Testicular Cancer

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ABSTRACT

Purpose
Long-term toxicity after cancer treatment has gained increasing clinical attention. We evaluated pulmonary function in long-term survivors of testicular cancer (TC).

Patients and Methods
The pulmonary function of 1,049 TC survivors treated during 1980 to 1994 at three university hospitals in Norway was assessed by spirometry and a questionnaire (1998 to 2002). The patients were categorized into five treatment groups, as follows: surgery only (n = 202); radiotherapy only (n = 449); chemotherapy (cisplatin ≤ 850 mg; n = 306); chemotherapy (cisplatin > 850 mg [higher-dose group]; n = 62); and chemotherapy and pulmonary surgery (cis/pulmsurg; n = 30). Spirometry variables included forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1). Actual values and percentages of predicted normal values (FVC%pred and FEV1%pred, respectively) are reported. Restrictive lung disease was defined as FEV1/FVC ≥ 70% and FVC%pred less than 80%.

Results
Median observation time was 11.2 years (range, 5 to 21 years). Compared with the surgery group, the higher-dose or cis/pulmsurg groups had considerably lower age-adjusted FVC (higher-dose: $\beta = -.37$; $P = .001$; cis/pulmsurg: $\beta = -.58$; $P < .001$), FEV1 (higher-dose: $\beta = -.24$; $P = .014$; cis/pulmsurg: $\beta = -.55$; $P < .001$), FVC%pred (higher-dose: $\beta = -8.3$; cis/pulmsurg: $\beta = -10.5$; both $P < .001$), and FEV1%pred (higher-dose: $\beta = -6.8$; $P = .003$; cis/pulmsurg: $\beta = -12.4$; $P < .001$). Adjustment for total testosterone, body mass index, smoking, and physical activity did not change these associations. Eight percent of all patients had restrictive lung disease, and the highest prevalence was in the higher-dose group (17.7%) and the cis/pulmsurg (16.7%) group. Compared with patients who underwent surgery only, these groups had odds ratio for restrictive disease of 3.1 (95% CI, 1.3 to 7.3) and 2.5 (95% CI, 0.8 to 7.6), respectively.

Conclusion
Large doses of cisplatin-based chemotherapy and combined chemotherapy/pulmonary surgery are significantly associated with decreased pulmonary function several years after TC treatment.

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INTRODUCTION

Today, germ cell testicular cancer (TC) has a favorable prognosis because of the introduction of cisplatin-based chemotherapy in the late 1970s, a multimodal treatment approach, disease monitoring by tumor markers, and more reliable radiologic staging.[1] The overall cure rate exceeds 95%, and approximately 80% of patients with advanced disease achieve a durable remission.[2] TC is the most common malignancy in men aged 15 to 44 years,[2] and these young men have a near-normal life expectancy after being successfully treated. Thus, evaluation of long-term complications is increasingly important.

Previous studies concerning pulmonary toxicity in TC patients have focused on the toxic effects of bleomycin during or after treatment. Bleomycin was introduced in the treatment of disseminated TC in the early 1970s, and pulmonary toxicity was the major dose-limiting adverse effect.[3] Bleomycin may cause pneumonitis, which may occasionally progress to pulmonary fibrosis during or shortly after treatment.[4-7] The majority of prior studies on pulmonary function during or after treatment for TC focused on chemotherapy-treated patients only, included a small number of individuals, and/or had a short follow-up period.[8-16] In these studies, spirometric changes observed during treatment were all normalized at follow-up.

Recently, a large international study reported a significantly increased mortality as a result of respiratory diseases among chemotherapy-treated TC survivors compared with the general population.[17] Population-based epidemiologic studies have demonstrated an association between pulmonary function and all-cause mortality, and these data suggest that pulmonary function could be used as a predictor for overall survival.[18,19] Moreover, decreased pulmonary function is associated with a reduced quality of life.[20] Thus, the pulmonary function of long-term TC survivors is an important issue.

Table 1. Patient Characteristics and Spirometry Results According to Treatment Group

	Treatment Group									
	Surgery (n = 202)		Radiotherapy (n = 449)		Cis ≤ 850 mg (n = 306)		Cis > 850 mg (n = 62)		Cis/Pulmsurg (n = 30)	
Characteristic or Result	No.	%	No.	%	No.	%	No.	%	No.	%
Age, years										
At diagnosis										
Median	29		36		30		26		26	
Range	16-64		18-64		15-61		15-58		17-64	
At follow-up										
Median	41		48		43		36		41	
Range	24-73		28-75		23-74		25-68		27-72	
Follow-up time, years										
Median	11.8		11.1		11.9		8.8		13.2	
Range	5-21		5-21		5-21*		5-19		6-20	
Initial RMH stage										
I	196	97	423	94	109	35	8	13	2	7
IM to II	6	3	26	6	147	48	25	40	3	10
III					14	5	7	11	1	3
IV					36	12	22	36	24	80
Histology										
Nonseminoma	194	96	3	1	241	79	53	86	27	90
Seminoma	8	4	446	99	65	21	9	14	3	10
Physical activity										
None	25	13	58	14	36	12	9	16	6	21
Moderate	83	43	192	45	135	47	21	36	13	47
High	86	44	176	41	117	41	28	48	9	32
Pack years†										
0‡	80	42	163	40	116	41	36	60	10	34
0.1-9.9	47	24	80	19	56	20	13	22	9	31
10-19.9	27	14	84	20	41	14	9	15	6	21
≥ 20	38	20	87	21	73	25	2	3	4	14
BMI, kg/m^2										
Mean	26.4		26.5		26.1		27.9		25.0	
SD	3.5		3.5		3.8		4.7		2.5	
Total serum testosterone, nmol/L										
Mean	16.6		15.6		16.1		14.9		15.0	
SD	5.0		5.5		5.7		5.8		3.6	
FVC, L										
Mean	4.95		4.69		4.84		4.77		4.39	
SD	0.84		0.91		0.85		0.99		0.85	
FEV1, L/sec										
Mean	3.93		3.69		3.84		3.87		3.40	
SD	0.70		0.83		0.76		0.77		0.67	
FVC % predicted										
Mean	99.7		97.5		97.1		92.2		89.3	
SD	13.5		14.1		13.3		14.5		13.9	
FEV1 % predicted										
Mean	97.1		95.3		94.4		91.2		84.8	
SD	13.9		17.2		14.9		13.9		14.6	

NOTE. Nos. of missing data are as follows: physical activity, n = 55; pack years, n = 68; BMI, n = 7; total testosterone, n = 7.
Abbreviations: Cis, cisplatin; Cis/Pulmsurg, cisplatin-based chemotherapy and pulmonary surgery; RMH, Royal Marsden Hospital; BMI, body mass index; SD, standard deviation; FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second.
*One patient had follow-up time < 5 years (ie, 4.3 years).
†No. of cigarette packs per day multiplied by number of smoking years.
‡Pack year of 0 indicates never smoker.

The aim of this study was to evaluate pulmonary function according to treatment (surgery, radiotherapy, and chemotherapy) in a large, unselected group of long-term TC survivors.

PATIENTS AND METHODS

Study Patients

All Norwegian long-term survivors (≥ 5 years) of unilateral germ cell TC who were aged 18 to 75 years and who were treated during 1980 to 1994 were invited to participate in a national, multicenter, follow-up survey at five university hospitals. The follow-up was carried out during 1998 to 2002 and consisted of a 219-item, mailed questionnaire and an outpatient clinical examination that included spirometry.[21,22]

Of 1,814 eligible patients, 1,463 (81%) signed the informed consent form and participated in the study.[22] This report is based on data from 1,049 participants investigated with spirometries as part of their outpatient visit at three of the five participating hospitals (Norwegian Radium Hospital [NRH], n = 711; Haukeland University Hospital [Haukeland], n = 232; and University Hospital of North Norway [UNN], n = 106). The study was approved by the Committee for Medical Research Ethics, Region South.

Treatment

On the basis of previously described treatment principles,[21,23] the TC survivors were categorized into five treatment groups according to initial and eventual relapse treatment: surgery only, including orchiectomy and possibly retroperitoneal lymph node dissection (RPLND); radiotherapy (RT) only; chemotherapy with a cumulative dose of cisplatin ≤ 850 mg (lower-dose group); chemotherapy with a cumulative dose of cisplatin greater than 850 mg (higher-dose group); or cisplatin-based chemotherapy (any dose) and pulmonary surgery (cis/pulmsurg).

The cutoff point for the two chemotherapy groups was set at cisplatin 850 mg to roughly differentiate between patients who received standard four courses or fewer and those who received more than four courses or higher-dose chemotherapy regimens as a result of poor prognosis, inadequate response, progression, or relapse.[23] Most chemotherapy-treated patients (n = 375 [94%] of 398) received cisplatin-based chemotherapy, primarily in combination with etoposide and bleomycin (BEP) or vinblastine and bleomycin (CVB). Twenty-three patients (6%) who received carboplatin instead of

Table 2. Treatment Details in Chemotherapy-Treated Patients

Characteristic	Treatment Group: Cis ≤ 850 mg (n = 306) No.	%	Cis > 850 mg (n = 62) No.	%	Cis/Pulmsurg (n = 30) No.	%
First chemotherapy regimen						
CVB	125	41	7	11	13	43
BEP	139	45	49	79	10	33
EP	5	2	0	0	0	0
CEB	18	6	1	2	0	0
BOP	2	1	0	0	0	0
BOP/VIP	0	0	4	6	7	24
HOP	7	2	1	2	0	0
Other	10	3	0	0	0	0
Patients who received second-line chemotherapy	26	8	29	47	13	43
Patients who received third-line chemotherapy	0	0	6	10	3	10
Chemotherapy doses*						
Cisplatin, mg						
Mean	683		1,187		1,079	
Median	725		1,165		1,060	
Range	185-850		855-2,405		685-3,095	
Bleomycin, mg						
Mean	254		279		250	
Median	300		300		300	
Range	30-360		120-390		90-360	
Etoposide, mg						
Mean	2,957		3,980		2,973	
Median	2,965		3,800		2,200	
Range	300-8,550		67-8,460		820-9,720	
Vinblastine, mg						
Mean	66		68		72	
Median	69		70		80	
Range	18-108		24-90		19-104	
Additional treatment						
RPLND	190	62	52	84	18	60
Radiotherapy	39	13	5	8	6	20

Abbreviations: Cis, cisplatin; Cis/Pulmsurg, cisplatin-based chemotherapy and pulmonary surgery; CVB, cisplatin, vinblastine, bleomycin; BEP, bleomycin, etoposide, cisplatin; EP, etoposide, cisplatin; CEB, carboplatin, etoposide, bleomycin; BOP, bleomycin, vincristine, cisplatin; VIP, etoposide, ifosfamide, cisplatin; HOP, ifosfamide, vincristine, cisplatin; RPLND, retroperitoneal lymph node dissection.

*Chemotherapy doses are listed for those who received the actual chemotherapy agent.

cisplatin according to research protocols[24,25] were included in the lower-dose group.

Assessments

The spirometries were carried out with Welch Allyn Pneumocheck 61000 (Welch Allyn Inc, Skaneateles, NY) at NRH, Vitalograph (Vitalograph Inc, Lenexa, KS) at Haukeland, and Sensormedics VMAX227 (Cardinal Health Inc, Dublin, OH) at UNN. Spirometry variables included forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1). The largest FVC and FEV1 from at least three maneuvers were reported for patients at Haukeland and UNN, in accordance with recommendations for spirometry maneuvers.[26] For patients at NRH, one successful maneuver was performed and was reported accordingly. The spirometry variables were expressed in absolute values and in percentages of predicted normal values (FVC%pred and FEV1%pred respectively, of FVC and FEV1). Predicted normal values were calculated on the basis of internationally approved equations.[27] Restrictive lung disease was defined as FEV1/FVC $\geq$ 70% and FVC%pred less than 80%.[18,28]

Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Nonfasting blood samples were drawn at each hospital laboratory primarily between 8:00 AM and 12:00 PM. Levels of serum total testosterone were determined by using a commercial immunoassay, and similar reference ranges were used at each hospital.

Information regarding self-reported dyspnea, pulmonary disease, use of asthma medication, smoking habits, and physical activity were obtained from the questionnaire. Respondents with missing data on pulmonary disease or use of asthma medication were classified without such disease or medication, respectively. Participants who reported having asthma and/or regular use of asthma medication were classified as having asthma. Dyspnea was assessed by the following question: "To what degree have you suffered from dyspnea during the last 12 months?" The response alternatives were much, some, or not at all. All patients who reported some or much were classified as having dyspnea.

Physical activity was assessed by two questionnaire items, which assessed activity at a low physical activity level (eg, walking) and a high level (ie, exercises leading to sweating and breathlessness). On the basis of the responses, physical activity was divided into three categories: none, moderate, or high.[29] Cigarette smoking was assessed by pack years, as described in a previous publication.[22]

Statistical Analysis

Mean doses of cytotoxic drugs in the two chemotherapy groups were compared by using the *t* test. FVC, FEV1, FVC%pred, and FEV1%pred were considered normally distributed. Continuous variables were analyzed by using multiple linear regression, whereas dichotomous variables were analyzed by using multiple logistic regression. The surgery group was used as reference to compare the different treatment groups.

All regression analyses were adjusted for age. Analyses of FVC, FVC%pred, FEV1, and FEV1%pred were additionally adjusted for total testosterone, BMI, pack years, and physical activity. To evaluate the impact of smoking on pulmonary function, spirometry variables were additionally analyzed to compare ever- versus never-smokers.

For chemotherapy-treated patients, age at diagnosis ($>$ 40 years *v* $\leq$ 40 years [reference]) and major abdominal surgery (ie, RPLND; yes *v* no [reference]) were evaluated as possible predictors for restrictive lung disease.

Because one of the three involved centers deviated from the standardized maneuver of spirometry,[26] we evaluated if there was any interaction between institution and treatment group (categoric variables). The multiple regression analyses revealed no significant interactions for the different dependent variables (FVC: $P = .14$; FVC%pred: $P = .12$; FEV1: $P = .48$; FEV1%pred: $P = .46$; restrictive lung disease: $P = .88$). The treatment institution also was evaluated as a possible confounding factor. None of the estimates changed significantly when the treatment institution was included in the analyses.

The regression coefficient β indicated the mean difference (in liters [FVC] or liters per second [FEV1]) compared with the reference group. All *P* values were two-tailed, and statistical significance was set at $P < .05$. The data were analyzed with SPSS 15.0 (SPSS Inc, Chicago, IL).

RESULTS

Patient Characteristics

Patient characteristics are listed in Table 1. Median age at follow-up was 44 years (range, 23 to 75 years) for all study patients. Median observation time was 11.2 years (range, 5 to 21 years). The age of the RT group was significantly older than that of the surgery group at diagnosis ($P < .001$) and at follow-up ($P < .001$), whereas the age of the higher-dose group was significantly younger than that of the surgery group at follow-up ($P = .002$). The higher-dose group also had a shorter observation time than the surgery group ($P = .001$). The cis/pulmsurg group had a longer observation time compared with the surgery group ($P = .04$). Compared with the surgery group, the higher-dose group had lower levels of total serum testosterone ($\beta = -2.1$; $P = .009$), higher BMI ($\beta = 1.5$; $P = .006$), and fewer pack years of smoking ($\beta = -3.4$; $P = .047$), whereas the cis/pulmsurg group had significantly lower BMI ($\beta = -1.5$; $P = .04$).

Details regarding chemotherapy treatment are listed in Table 2. Only two patients received more than 360 mg of bleomycin. Although the median bleomycin dose did not differ between the chemotherapy groups (median, 300 mg), the mean bleomycin dose was higher for patients in the higher-dose group than in the lower-dose group ($P = .02$). The mean etoposide dose was higher ($P < .001$), and RPLND was performed more frequently ($P = .001$), in the higher-dose group compared with the lower-dose group. Only two patients in the RT group and three chemotherapy-treated patients received mediastinal irradiation, including one patient in the higher-dose group and one patient in the cis/pulmsurg group.

The majority of patients treated with pulmonary surgery had minor resections (n = 17; 57%). Six patients (20%) had wedge/segmental resections, three (10%) had lobectomies, three (10%) had

Table 3. Age-Adjusted Regression Analyses With FVC and FEV1 As Dependent Variables

Characteristic by Dependent Variable	Analyses	
	β*	*P*
FVC		
Surgery group	Reference	
Radiotherapy	−.01	.95
Cis ≤ 850 mg	−.10	.17
Cis > 850 mg	−.37	.001
Cis/pulmonary surgery	−.58	< .001
FEV1		
Surgery group	Reference	
Radiotherapy	.01	.94
Cis ≤ 850 mg	−.08	.19
Cis > 850 mg	−.24	.014
Cis/pulmonary surgery	−.55	< .001

Abbreviations: FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; Cis, cisplatin.
*β indicates the difference (in liters for FVC or in liters per second for FEV1) compared with the surgery group.

thoracotomy with resections of only mediastinal tumors, and one patient (3%) had combined surgery with lobectomy and several resections. No pneumonectomies were performed.

Spirometry Data

Mean unadjusted FVC, FEV1, FVC%pred, and FEV1%pred results according to treatment group are listed in Table 1. Compared with the surgery group, both the higher-dose group and the cis/pulmsurg group had significantly lower age-adjusted FVC (higher-dose: $\beta = -.37$; $P = .001$; cis/pulmsurg: $\beta = -.58$; $P < .001$; Table 3) and FEV1 (higher-dose: $\beta = -.24$; $P = .014$; cis/pulmsurg: $\beta = -.55$; $P < .001$; Table 3).

Table 4 lists the results of age-adjusted and multiple linear regression analyses, with predicted spirometry values as dependent variables. Compared with the surgery group, all the chemotherapy groups had significantly lower FVC%pred, whereas the higher-dose group and the cis/pulmsurg group had significantly lower FEV1%pred in the age-adjusted analyses. FVC%pred and FEV1%pred were negatively associated with BMI and smoking (pack years) and were positively associated with total testosterone and physical activity in the age-adjusted analyses. In the multiple model, only treatment group (higher-dose and cis/pulmsurg), BMI, and pack years were significantly associated with FVC%pred, whereas treatment group (higher-dose and cis/pulmsurg), total testosterone, and pack years were significantly associated with FEV1%pred.

Compared with never-smokers, ever-smokers had lower FVC%pred ($\beta = -2.1$; $P = .02$) and FEV1%pred ($\beta = -3.2$; $P = .002$) results in age-adjusted analyses.

Table 4. Results of Age-Adjusted and Multiple-Adjusted Analyses of Multiple Linear Regression, With FVC%Predicted and FEV1%Predicted As Dependent Variables

Factor by Dependent Variable	Analyses by Adjustment Type			
	Adjusted for Age		Multiple Model†	
	β*	*P*	β*	*P*
FVC%predicted				
Treatment group				
Surgery	Reference		Reference	
Radiotherapy	−1.05	.37	−.11	.93
Cis ≤ 850 mg	−2.57	.038	−1.66	.20
Cis > 850 mg	−8.30	< .001	−6.57	.001
Cis/pulmonary surgery	−10.5	< .001	−9.70	.001
Total testosterone	.20	.013	.14	.09
BMI	−.49	< .001	−.47	< .001
No. of pack years				
0 (never smoker)	Reference		Reference	
0.1-9.9	.04	.97	−.72	.55
10-19.9	−3.52	.006	−4.31	.001
≥ 20	−3.62	.003	−3.65	.004
Physical activity				
None	Reference		Reference	
Moderate	1.22	.37	−.02	.99
Hard	3.30	.016	1.38	.33
FEV1%predicted				
Treatment group				
Surgery	Reference		Reference	
Radiotherapy	−.68	.62	−.09	.95
Cis ≤ 850 mg	−2.63	.063	−1.53	.30
Cis > 850 mg	−6.79	.003	−6.00	.011
Cis/pulmonary surgery	−12.4	< .001	−11.2	.001
Total testosterone	.16	.074	.20	.044
BMI	−.28	.038	−.20	.16
No. of pack years				
0 (never smoker)	Reference		Reference	
0.1-9.9	.09	.95	−.48	.73
10-19.9	−3.59	.013	−4.19	.004
≥ 20	−7.36	< .001	−7.08	< .001
Physical activity				
None	Reference		Reference	
Moderate	2.68	.085	1.18	.46
Hard	5.21	.001	2.75	.089

Abbreviations: Cis, cisplatin; FVC, forced vital capacity; BMI, body mass index; FEV1, forced expiratory volume in 1 second.
*β indicates the difference (in liters for FVC or in liters per second for FEV1) compared with the surgery group.
†Adjusted for age and for all listed factors.

Dyspnea, Asthma, and Restrictive Lung Disease

Overall, 101 patients (10%) reported having dyspnea, and 27 (2.6%) were classified as having asthma. The higher-dose group had the highest percentage of both dyspnea and prevalent asthma (Fig 1), but the odds for that group did not differ significantly from those of the surgery group (data not shown).

In total, 84 patients (8.0%) were classified with a restrictive lung disease, and the highest percentages were in the higher-dose group (17.7%) and the cis/pulmsurg group (16.7%; Fig 1). These two groups also had the highest age-adjusted odds for restrictive lung disease compared with the surgery group (Fig 2), but a significant difference was noted only for the higher-dose group (odds ratio [OR], 3.1; 95% CI, 1.3 to 7.3). Only eight (9.5%) of the patients classified with restrictive lung disease had self-reported dyspnea, and six (7.5%) had prevalent asthma.

For chemotherapy-treated patients, age older than 40 years at diagnosis was associated with an increased risk for restrictive lung disease (OR, 4.0; 95% CI, 1.2 to 13.4). Major abdominal surgery was not related to risk for restrictive lung disease (OR, 0.83; 95% CI, 0.42 to 1.61).

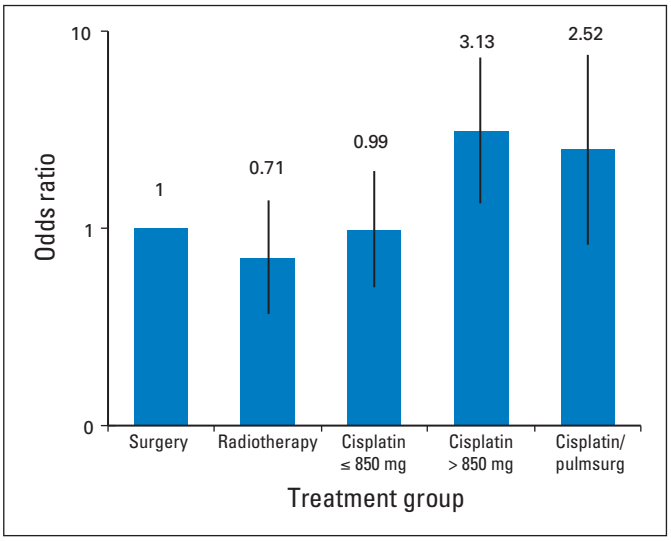

Fig 2. Odds ratios (OR) for having a restrictive lung disease in different treatment groups when the surgery group is used as reference. Bars indicate 95% CIs for ORs.

Impact of Chemotherapy

FVC%pred was negatively associated with cumulative cisplatin ($P < .001$), etoposide ($P < .001$), and bleomycin ($P = .006$) doses but not with vinblastine dose ($P = .69$). In a multiple model that included age and all chemotherapy variables listed in Table 2, cumulative bleomycin dose ($P = .034$), cisplatin dose ($P < .001$), and age ($P < .001$) were significantly associated with FVC%pred.

FEV1%pred was negatively associated with cumulative cisplatin ($P < .001$), etoposide ($P = .001$), and bleomycin ($P = .010$) doses but not with vinblastine dose ($P = .37$). In a multiple model, only cisplatin and age ($P < .001$ for each) were significantly associated with FEV1%pred.

Cumulative cisplatin dose ($P = .007$) and etoposide dose ($P = .005$) were positively associated with the risk for restrictive lung disease, but bleomycin dose ($P = .19$) and vinblastine dose ($P = .90$) were not. In a multiple model, only cisplatin ($P = .007$) and age ($P = .008$) were associated with the risk for restrictive lung disease.

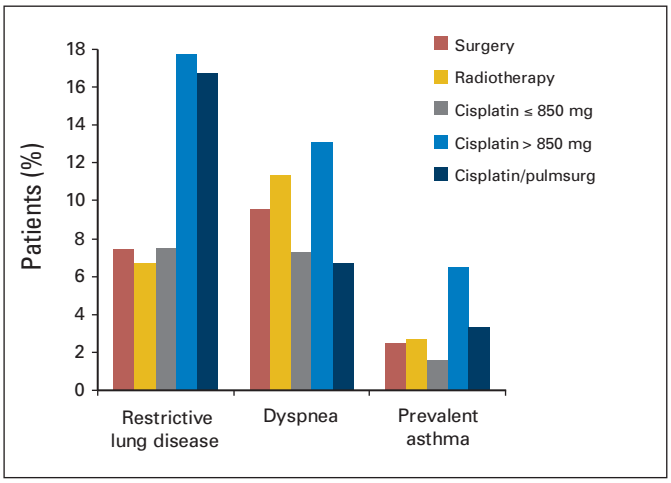

Fig 1. Percentage of patients with restrictive lung disease, dyspnea, and prevalent asthma at follow-up according to treatment group.

Impact of Disease Burden in the Higher-Dose Group

Overall, 22 patients (36%) in the higher-dose group had stage IV (metastatic) disease at initial presentation (Table 1). Compared with men who were diagnosed with stages I to III disease, these men had received slightly more bleomycin (mean, 299 mg *v* 263 mg; $P = .08$) and significantly more cisplatin (mean, 1,302 mg *v* 1,124 mg; $P = .03$).

FVC%pred tended to be lower for men who initially had stage IV disease compared with men who had stages I to III disease (88.6% *v* 94.2%; $P = .07$). FEV1%pred did not differ between these two groups (89.9% *v* 91.9%; $P = .44$), and the risk for restrictive lung disease was similar (18.2% *v* 17.5%; OR, 1.01; 95% CI, 0.94 to 1.07).

DISCUSSION

To our knowledge, this is the first study to report long-term follow-up spirometry data in a large group of unselected TC survivors. Patients treated with large, cumulative cisplatin doses or with chemotherapy combined with pulmonary surgery had a significantly reduced pulmonary function compared with TC patients treated with surgery only.

The major strength of this study is the large patient population. We have detailed treatment data, which make it possible to study the impact of different treatment modalities and specific chemotherapy agents. Limitations include the cross-sectional study design. Respiratory symptoms, disease status, and medication were self-reported and have not been validated. Another possible limitation is the lack of comparisons to controls from the general population. Limitations with regard to interpretation of our results include the small sample sizes of the higher-dose and the cis/pulmsurg groups.

Prior studies on pulmonary function have focused on lung toxicity as a result of bleomycin. A decrease in the lung transfer capacity

for carbon monoxide during chemotherapy treatment is indicative of subclinical bleomycin pulmonary toxicity,[4,11] but these reductions in capacity are mostly completely reversible during follow-up.[9,11,14] In the majority of previous studies, a decreased vital capacity (VC) and/or FVC was observed during chemotherapy, and normalization was noted at follow-up.[8,12-14] There were no spirometry changes during or after chemotherapy treatment in two small, previous clinical studies.[10,11] Thus, this is the first study to indicate that large cumulative chemotherapy doses are associated with reduced pulmonary function several years after treatment.

Previous studies failed to detect a relationship between cumulative bleomycin doses and spirometry values,[10,11,13] except for one study, in which an association was shown between bleomycin dose and VC.[14] Although we found that bleomycin was significantly associated with FVC%pred, our results indicate a more profound association between the cumulative cisplatin dose and FVC%pred or FEV1%pred. These results are supported by Stuart et al,[16] as they found that VC correlated to number of chemotherapy courses but not to the cumulative bleomycin dose.[16] In fact, the bleomycin dose was not associated with restrictive lung disease in this study. Because the maximum cumulative bleomycin dose was set at 360 mg, the cumulative cisplatin dose, instead, appeared to be the pivotal factor that influences long-term pulmonary function.

Low serum testosterone levels have been associated with a reduction in spirometric variables[30] and an increased risk for respiratory disease mortality in recently published epidemiologic studies.[31,32] Because cisplatin-based chemotherapy may lead to Leydig cell dysfunction,[33,34] part of our findings could be related to low serum testosterone. Yet, after the analyses were controlled for testosterone, the cumulative cisplatin dose still had a highly significant impact with respect to the pulmonary function. Cisplatin-based chemotherapy has several long-term organ toxicities,[35-37] and it is not unlikely that this anticancer agent also affects the lungs. Possible mechanisms include vascular damage and induction of endothelial dysfunction.[38,39]

We found that patients older than 40 years of age at diagnosis had an increased risk for restrictive lung disease. This is in line with a previous large clinical study.[6] As the renal function decreases with age, this increased risk may be due to a reduced renal clearance of chemotherapy agents, such as cisplatin and bleomycin. The small fraction of study participants with a restrictive lung disease pattern who reported having dyspnea may be explained, in part, by coping. We did not ask specifically whether they had exertional dyspnea, which probably would be a better indicator of restrictive lung disease.[40]

Because it is well known that thoracic surgery with lung tissue resections influences pulmonary function,[41] we have allocated chemotherapy-treated patients who underwent pulmonary surgery into a separate group. As expected, this group had the largest reductions in the spirometry values. However, because this subgroup included only 30 patients, the number with restrictive disease was merely five patients. Whether abdominal surgery through anesthesia may affect pulmonary function has been more debated, however. Some reports indicate that high oxygen concentrations inspired during surgery in patients who were previously treated with bleomycin may trigger bleomycin-induced pulmonary toxicity, but data are conflicting.[42-46] Restrictive lung disease did not correlate to major abdominal surgery in our patients, which is in concordance with results presented by O'Sullivan et al.[6]

Our findings are of clinical significance for several reasons. First, the effect on the pulmonary function by large cumulative cisplatin doses or by combined chemotherapy and pulmonary surgery equals two- to four-fold the effect of smoking. Second, as much as 17% to 18% of patients in the higher-dose and cis/pulmsurg groups were classified with restrictive lung disease, which is consistent with cisplatin toxicity data presented by Strumberg et al.[7] Third, chemotherapy-treated TC survivors have been reported to have an increased respiratory disease mortality with a standardized mortality rate of 2.53.[17] Hence, the chemotherapy treatment appears to result in reduced pulmonary function and is a potential health problem for these survivors.

The reduced pulmonary function among men in the higher-dose group may be caused by factors other than cytotoxic treatment alone. High tumor burden in the lungs and/or recurrent disease may affect the pulmonary status. Our results indicate that men in this subgroup who had stage IV disease tended to have a lower FVC%pred. However, FEV1%pred and the risk for restrictive lung disease did not differ from men who had stages I to III disease.

Nevertheless, intensive treatment with both chemotherapy and surgery is required to maintain and to additionally improve the cure rates for TC patients who have advanced disease. There are, however, several modifiable factors that can be altered to improve the pulmonary status after intensive treatment for TC. These lifestyle factors include smoking cessation, weight control, and regular exercise.

In conclusion, we have identified reduced pulmonary function as a long-term adverse effect after cisplatin-based chemotherapy. Our results are only hypothesis generating, and they need to be confirmed by large prospective studies. This study also underlines the need for long-term follow-up guidelines with regard to pulmonary function. Physicians involved in the treatment and follow-up of these relatively young men should offer essential information about the potential benefits of lifestyle factors and should be aware of early signs of reduced pulmonary function.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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