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Original Article

Evaluation of Long Term Respiratory Complications in Childhood and Adolescent Cancer Survivors

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ABSTRACT

Aim: In addition to increased survival rates, systemic complications which can impair the quality of life have been seen in 25-30% of childhood and adolescent cancer cases. The respiratory system is one of the severely affected systems. We aimed to evaluate late respiratory complications and risk factors in pediatric and adolescent cancers.

Materials and Methods: We examined the pulmonary complications of 50 cancer patients and 40 control cases. We asked about environmental exposures, physical examinations performed, and pulmonary function tests (PFT) spirometry, diffusing capacity of the lungs for carbon). X-ray was performed on all patients in the patient group and on patients with indications in the control group.

Results: In the patient group, there was impairment of pulmonary function in 52%, [24% small airway disease (SAD)], 14% diffusion disorders (DD) and 14% combined disorders (CD) compared to 22.5% in the control group (p=0.007). There was a higher risk of restrictive disorder and/or SAD in those cancer patients who were diagnosed prior to 2 years of age. Additionally, there was a higher rate of SAD in those patients with soft tissue sarcomas and a higher rate of restrictive disease in those patients who had received high-dose alkylating agents. No significant PFT impairment was observed in the other patient groups.

Conclusion: There is a high incidence of respiratory impairment in childhood and adolescent cancer survivors. They need to be followed up by a multidisciplinary team and be informed about the additional risk factors which may cause lung function loss.

Keywords: Survivors of childhood cancer, pulmonary injury, pulmonary function tests

Introduction

Childhood and adolescent cancers are an increasing health problem and constitute 1-2% of all lifelong cancers. According to US data, the incidence of cancer in children and adolescents was 14.2/100,000/year in 1975, and this increased to 17.4/100,000/year in 2009.

Correspondingly, there was a notable reduction in mortality in these patients (from 5.2/100,000 to 2.4/100,000) (1). More than 1% of the young adult population are survivors of childhood cancer (2). Two-thirds of long-term survivors had at least one health problem in the late period. According to the results of the Childhood Cancer Survivors Study, for at least 5 years after cancer diagnosis,

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the cumulative death rate from cancer was 18% and deaths from lung causes were 8.8 times higher than in the normal population. The most common causes of death are tumor recurrence, secondary cancer development, cardiac toxicity, pulmonary disorders, and infections (3). Serious late respiratory complications are observed in patients treated for childhood cancer. Age at diagnosis, type of cancer, presence of respiratory system involvement, chemotherapy (CT), pulmonary radiotherapy (RT) and thoracic surgery are important factors in the development of pulmonary problems in the late period. In addition, previously known respiratory diseases, serious lung problems in the treatment process and environmental factors adversely affect the respiratory system. CT is one of the most important factors which can cause respiratory disorders (4,5). In this study, we aimed to determine respiratory problems and their risk factors in childhood cancer survivors by evaluating their pulmonary functions.

Materials and Methods

The study was approved by the Ethics Committee of Ege University Faculty of Medicine (approval date: 10.08.2011, approval no:11-6.1/11).

Fifty patients aged 7 years and older who had been in remission for at least 3 years after treatment were included in this study and evaluated for any pulmonary complications. In the control group, 40 siblings or healthy individuals in the same age range, without any history of cancer, were evaluated.

The age distribution of the patients was 10-34 years, and the control group was 11-30 years. In terms of the distribution by gender, 42% were female in the study group, and 37.5% were female in the control group. In the patient group, the median age at diagnosis was 11.5 (1-17 years), and the median age at the study time was 19.5 (10-34 years). The median age in the control group was 21 (11-30 years). The study group included 16 cases with acute leukemia, 15 with lymphoma, 10 with bone and soft tissue sarcoma, 4 with central nervous system tumors and 5 with other solid tumors. We aimed to evaluate respiratory disorders in the patients via spirometry, diffusing capacity of the lungs for carbon monoxide (DLCO) and radiological imaging (if necessary). All results were evaluated by a multidisciplinary team including a pediatric oncologist, a pulmonologist and a radiologist. The PFT parameters of the case and control groups were compared (Table I), and then the pulmonary function test (PFT) parameters were evaluated according to the diagnoses and diagnostic groups of the cases (Tables II and III) and the risk factors of the patients for restrictive disorder (RD), diffusion disorder (DD) and small airway disease (SAD) were calculated (Table IV).

Diagnostic Evaluation

The type of cancer, age at diagnosis, the presence of pulmonary involvement, the type and dose of the chemotherapeutic agents [alkylating agents ifosfamide (IFO), cyclophosphamide (CYC), bleomycin], thoracic RT, and severe pulmonary problems following surgical treatment (infections, infarction, etc.) were recorded from the follow-up files. Lung problems before and after cancer, and smoking (passive-active) were investigated. The cancer survivors were grouped into Leukemia+lymphoma patients (Group A), bone and soft tissue tumor patients (Group B), and other solid tumor patients (Group C).

PFT

PFTs were performed by the same technician with V-max spectra 22 in the pulmonary function laboratory of Ege University Faculty of Medicine, Department of Chest Diseases.

The patients rested for at least 5 minutes before the test and the test was performed in an upright position. During the test, the patient's nostrils were closed with a soft latch, all participants were required to perform the maneuvers three times and their best result was accepted for analysis.

For participants over the age of 18, spirometric tests were evaluated according to the Common Terminology Criteria for Adverse Events v3.0 criteria (6) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) (7).

For those participants under 18 years of age, spirometric tests were evaluated by a pediatric pulmonologist according to their age, weight and height serıes ATS/ERS task force: standardization of lung function testing (8-12).

The classification of PFT disorders were defined as follows;

Restrictive disorder (RD): FEV1<80%, FVC<80%, FEV1/FVC>70,

Small airway disorder (SAD): FEF_{25-75}<80%,

Diffusion disorder (DD): DLCO<75%,

Obstructive disorder (OD): FEV1<80%, FVC; N/low, FEV1/FVC<70

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 24.0 for Windows. In comparison of two independent groups, the t-test was used for parametric test assumptions and the Mann-Whitney U test was used for

Table I. Comparison of case group and control group respiratory function tests

PFT	Groups	Mean ± SD (minimum-maximum)	p-value
FVC	Patients	96.46±14.3 (53-128)	0.015
	Control	103.40±11.7 (81-125)	
FEV1	Patients	99.10±14.1 (55-135)	0.103
	Control	103.55±10.7 (79-131)	
FEV1/FVC	Patients	87.54±5.8 (71-99)	0.107
	Control	85.52±5.8 (70-98)	
FEF_{25-75}	Patients	87.12±21.5 (43-141)	0.245
	Control	92.20±19 (48-141)	
DLCO	Patients	93.91±18.7 (52-132)	0.322
	Control	97.82±17.8	

SD: Standard deviation, DLCO: Diffusing capacity of the lungs for carbon, PFT: Pulmonary function test

Table II. Evaluation of respiratory function tests according to the diagnoses of the cases

	FVC		FEV1		FEV1/FVC		FEF_{25-75}		DLCO	
Group	Mean-SD	p-value	Mean-SD	p-value	Mean-SD	p-value	Mean-SD	p-value	Mean-SD	p-value
B (n=10)	96.7 (10.1)	0.760	94.9 (10.2)	0.357	84.9 (6.4)	0.092	78.7 (20.7)	0.399	85.8 (11.9)	0.522
C (n=9)	95 (13.7)		101.2 (18.1)		89.8 (5.7)		87.3 (22.7)		81.1 (17.2)	
B (n=10)	96.7 (10.1)	0.984	94.9 (10.2)	0.314	84.9 (6.4)	0.184	78.7 (20.7)	0.160	85.8 (11.9)	0.05
A (n=31)	96.8 (15.8)		99.8 (14.0)		87.7 (5.4)		89.7 (21.6)		99.7 (18.3)	
C (n=9)	95 (13.7)	0.759	101.2 (18.1)	0.809	89.8 (5.7)	0.306	87.3 (22.7)	0.768	81.1 (17.2)	0.01
A (n=31)	96.8 (15.8)		99.8 (14.0)		87.7 (5.4)		89.7 (21.6)		99.7 (18.3)	

Table III. Evaluation of pulmonary function tests by diagnostic groups

	Group A	Group B	Group C	p-value
FVC	96.8	96.7	95	0.967
FEV1	99.8	94.9	101.2	0.584
FEV1/FVC	87.7	84.9	89.8	0.229
$FEF_{(25-75)}$	89.7	78.7	87.3	0.345
DLCO	99.7	85.8	81.1	0.014

*Group A (Leukemia and lymphoma group). Group B (Bone and Soft Tissue group). Group C: (The other group)

Table IV. Evaluation of risk factors of patients in terms of RD, DD, and SAD (odds ratio and 95% confidence interval)

Variables	RD	DD	SAD
Age (<2 years)	2.5 (0.22-28.81)	-	2.71 (0.41-18.00)
Gender (female)	2.25 (0.34-14.83)	2 (0.46-8.65)	1.00 (0.31-3.20)
Diagnosis (Group B)	2.3 (0.34-15.95)	0.41 (0.04-3.79)	3.11 (0.74-12.98)
Time after treatment*	0.77 (0.07-7.66)	0.62 (0.14-2.72)	0.76 (0.19-3.00)
Pulmonary disorders	0.58 (0.07-4.55)	1.25 (0.27-5.76)	0.75 (0.23-2.43)
Alkylating	4.77 (0.37-61.06)	5.28 (0.63-44.03)	5.62 (0.54-58.57)

* >5 years compared to <5 years
RD: Restrictive disorder, DD: Diffusion disorder, SAD: Small airway disease

those which were not provided. In the comparison of more than two groups in terms of numerical variables; The One-Way ANOVA test was used for normal distribution and the Kruskal-Wallis test was used for non-normal distributions. The difference between groups in terms of categorical variables was examined by Pearson or Fisher's exact test. The significance level was taken to be $p<0.05$.

Results

We observed respiratory impairment in 52% of the cancer survivors group (24% SAD, 14% DD and 14% combined disorders) and 22.5% in the control group (17.5% SAD, 2.5% DD and 2.5% combined disorders) (p=0.007). Compared to the control group, FVC was found to be significantly lower in the cancer survivors (p=0.015) (Table I).

FEV1/FVC values were impaired in those patients with pulmonary involvement at the time of diagnosis or during their follow-up (p=0.037). No deterioration was detected in the other PFT parameters. Seven Hodgkin lymphoma (HL) patients with impaired PFTs received an average of 30 Gy RT and pulmonary/mediastinal involvement was observed in these patients. In 7 patients with leukemia who had severe lung infections during their treatment, there was no statistically significant difference in any of the PFT parameters.

The cancer survivors were grouped into Leukemia+lymphoma patients (Group A), bone and soft tissue tumor patients (Group B), and other solid tumor patients (Group C). PFT disorders in these groups were compared. SAD was observed more in Group B (60%) but it was not significant. DLCO was lower in Groups B and C compared to Group A (p=0.014). No other differences were observed among the three groups (Tables II and III).

The mean of FEF25-75 under 2 years old was 67.2% and for over 2 years old, it was 89.3% (p=0.027).

PFT values were found to be lower in patients more than 5 years after the end of their treatment compared to patients less than 5 years, but this was not statistically significant. No significant difference was observed when the PFTs of the patients in the follow-up period of less than 5 years, 5-10 years and more than 10 years were compared. Although the change in DLCO was observed to be more pronounced, this change was not found to be significant (p=0.468) (Figure 1).

Alkylating agents were given to 44 patients. CYC (1-16 gr/m^2) was given to 22 patients, IFO (4-54 gr/m^2) to 10 patients, and their combination (IFO+CYC) to 14 patients. We observed that alkylating agents increased the risk of RD by 4.7 times [odds ratio (OR): 0.37-61.06] and SAD by 5.6 times (OR: 0.54-58.57), but these were not found to be statistically significant. RD was determined to be similar in all three drug groups (9%, 10%, 7%, respectively).

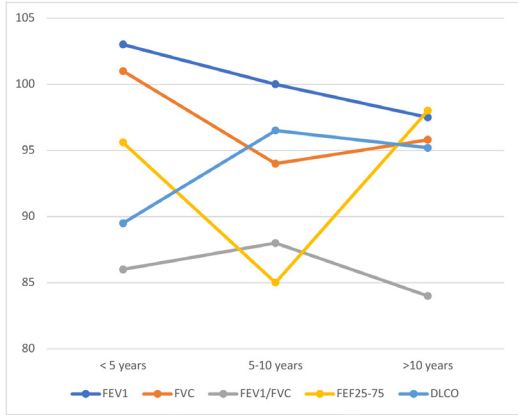

Figure 1. PFT disorder according to the post-treatment follow-up processes

There was a non-significant trend for a higher risk of developing RD and/or DD in females (Table IV).

Discussion

Survival rates in childhood and adolescence cancers have increased significantly in the last 20 years. It is known that 75% of surviving patients face at least one health problem, and 25% have serious complications which impair their quality of life (3,5). An important part of these complications is related to the respiratory system. Age, thoracic involvement, time elapsed after treatment, treatment modalities used (CT, thoracic RT and/or surgery), pre-existing respiratory disorders, active-passive smoking and gender have been reported to be some of the risk factors associated with respiratory complications (3).

An increase in respiratory disorders is expected in cancer survivors in the late period. In a series of 27 cases with HL, 48% had respiratory problems during a follow-up period of 76 months (13). Miller et al. (14) found low TLC levels in 48% of the patients in the spirometric evaluation of 29 patients. Respiratory impairment was observed in 43% of patients with malignant brain disease (15). Similarly, in a study of 5,760 ALL patients, there was a 4.2-fold increased risk of lung fibrosis compared to the normal population (16). In addition, other similar studies have reported that respiratory complications in children with cancer vary between 7.8% and 65% (14,17,18). In our study, we observed a higher rate of respiratory impairment in cancer survivors than in the control group.

Generally, pulmonary function disorders are classified into groups (RD, SAD, DD, OD). In other studies, it was observed that RD was between 7.5-87% and DD was between 10-40%

(13,15,19-21). In our cases, SAD was 24%, DD was 14%, and 14% were combined disorder.

It is known that diagnosis at a young age increases the susceptibility to pulmonary dysfunction in cancer survivors. O'Driscoll et al. (22) showed that the risk of severe fibrosis leading to death in patients diagnosed before 6 years of age increased significantly. In another study of 22 NHL and 19 HL case groups, the mean age at diagnosis was shown to be a significant risk factor for low total pulmonary capacity (23). In a pulmonary toxicity study, TLC was found to be decreased in those patients diagnosed before 3 years of age (14). In another study, lung toxicity was found to be higher in children diagnosed with ALL at an early age (23). In our study, for those under 2 years of age, the risk of RD increased by 2.5 times (OR: 0.22-28.81), and SAD by 2.71 times (OR: 0.41-18.00). Although the FVC and FEV1 values were lower, this did not reach statistical significance.

It has been shown that respiratory functions are affected in the follow-up process of child and adolescent cancer survivors (4). O'Driscoll et al. (22) reported that FVC decreased in the first 3 years after treatment in patients with CNS, and there was no significant change in FVC in the 10-year follow-up. Bossi et al. (13) reported that there was no change in PFT during the post-treatment follow-up. In our case group, a decrease in FEV1, FVC, FEF_{25-75} values were observed in the 5-10 year follow-up subgroup, followed by a partial improvement beyond ten years. This improvement after 10 years may be due to the fact that children reach adulthood, increase in their physical activity and move away from the effects of their treatment.

Studies suggest that CT, especially alkylating, bleomycin, and methotrexate, may cause respiratory complications. Mertens et al. (4) reported that the risk of recurrent lung infection and chronic cough is higher in cancer survivors, especially in alkylating users. In a similar study, it was reported that the risk of RD development increased 1.5 times and that the risk of DD increased 1.25 times in HD-CYC users (24). Another study showed that the use of another alkylating agent HD-IFO increased toxicity (25). In our study, RD and DD were observed in 9 and 22% in CYC and 7 and 14% in CYC+IFO users, while no RD developed in patients who received IFO monotherapy. IFO treatment was not associated with RD and DD.

It has been shown in many studies that RT applied to the thorax can cause late respiratory complications (5,26). It has been reported that respiratory complications occur at a rate of 5-15% in child and adolescent cancer survivors exposed to total RT>30 Gy (27). Many studies on children and adolescents undergoing thoracic RT have shown that these patients develop pulmonary fibrosis and PFT impairment (22-75%) (4,28-31). All three patients with HL-related thoracic involvement who received RT in our study developed respiratory impairment.

In a cohort study of childhood cancer survivors (606 RMS cases and 3,701 sibling controls), 3% of RMS cases (due to lung RT) were shown to have pulmonary fibrosis (32). In addition, in another study, PFT disorders were found in 19% of patients with thoracic involvement neuroblastoma (which developed as RD in half and OD in the other half) (33).

In the results of our patient groups, FEF 25-75 values were found to be lower in Group B patients. These results showed that lung tumor involvement, thoracic surgery and the use of RT and HD alkylating agents were effective in this group. On the other hand, DD was more frequent in Group C. The mean PFT values in those patients with leukemia-lymphoma were within normal limits and no significant change was observed.

Late term respiratory complications have been reported to develop more frequently in girls (19,24). There was also 2 times and 2.5 times higher risks of developing DD and RD, respectively, in this study, although this trend did not reach statistical significance, possibly due to relatively low number of patients.

Late effects on the respiratory system are manifested by various clinical symptoms and PFT disorders, and they may have serious consequences which lead to secondary lung cancer and/or death in the following years (4,34). In our group, secondary lung malignancy and fatal respiratory complications were not observed during a follow-up period of 3-21.6 years.

Study Limitations

The heterogeneity of the diagnoses of the case group in our study led to differences in terms of treatment modalities. However, the cases were grouped according to cancer types and/or the similar treatment modalities applied, the results were examined and the results obtained were generally parallel to other studies reported to date.

Conclusion

In our study, the rate of impairment of PFTs was found to be 52% and age at diagnosis, gender, cancer type, the presence of lung involvement, and the treatment modalities contributed to the development of PFT disorders. It was observed that especially being diagnosed under 2 years of age increased the risk of RD and SAD. Also, bone and soft tissue tumors increased the risk of SAD, and additionally, the use of HD alkylating agents increased the risk of RD, DD and SAD.

As a result, childhood and adolescent survivors have to be followed up with a multidisciplinary approach.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Ege University Faculty of Medicine (approval date: 10.08.2011, approval no:11-6.1/11).

Informed Consent: Informed consent was obtained from the parents/legal guardians of the patients.

Authorship Contributions

Medical Practices: F.E., N.Ç., E.D., A.S., H.A., F.G., Concept: F.E., N.Ç., F.G., Design: F.E., N.Ç., Data Collection or Processing: F.E., N.Ç., Analysis or Interpretation: F.E., N.Ç., E.D., A.S., H.A., F.G., Literature Search: F.E., N.Ç., E.D., Writing: F.E., N.Ç., E.D., A.S., H.A., F.G.

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