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LATE PULMONARY SEQUELAE AFTER TREATMENT OF CHILDHOOD CANCER

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Objective – Increasingly successful treatment of childhood cancer during the last decades, resulting in a number of long term survivors, has made it possible to study late sequelae of this treatment in sizable cohorts of survivors. The aims were to determine the frequency and severity of pulmonary late sequelae among children treated for cancer to identify treatment risk factors and the methods for continued follow-up. **Materials and methods** – In 255 of the 1020 survivors, at least 18 years old, 5 years after treatment, who agreed with the examination protocol, testing was performed at the time of their follow up appointment. It was conducted 5 to 37 (mean 18) years after diagnosis. The examinations included physical examination, chest radiograms and pulmonary function testing. **Results** – Radiograms revealed 79 abnormalities in 53 patients and were most frequently found in patients with Hodgkin's disease (20/67) or non-Hodgkin's lymphoma treated with mediastinal radiotherapy (RT) (10/31), in patients with brain tumor treated with RT to the central nervous axis (CNA) (7/15), in Wilms' tumor patients, who had abdominal RT, scoliosis was found. (6/15). Lung function tests showed abnormal values, mostly restrictive changes, in 59 of 237 patients. **Conclusion** – Late pulmonary sequelae after treatment of childhood cancer are rare serious or life-threatening complications. Radiographic and pulmonary function abnormalities were most frequently found in patients who had mediastinal or CNA RT. Regular follow-up of these patients is therefore recommended. Spirometry has been a useful test for detection of pulmonary sequelae. Routinely follow-up radiography is always indicated in clinical suspicion of secondary tumors.

Key words: Late pulmonary sequelae ▪ Childhood cancer.

Introduction

Survival in all types of childhood cancer has improved during the past decades. By follow–up of the ever more numerous survivors the adverse consequences of treatment are becoming apparent. While recurrent disease remains a major contributor to late mortality in 5-year survivors of childhood cancer, significant excess in mortality risk associated with treatment-related complications, including respiratory disease, exist up to 25 years after the initial cancer diagnosis (1). Among survivors of childhood cancer treated between 1970 and 1986 the cumulative incidence of a chronic health condition reached

73% 30 years after diagnosis, with a cumulative incidence of 42% for severe, disabling, or life-threatening conditions or death due to a chronic condition (2).

Radiation is known to have damaging effect on lung tissue (3), particularly in form of late fibrosis that may cause chronic respiratory impairment (4, 5). Chemotherapeutic agents such as cyclophosphamide, doxorubicin, bleomycin, methotrexate, carmustine, busulphan, paclitaxel, cisplatin have been linked to late pulmonary sequelae (1, 4, 6-12) in form of restrictive lung disease and defects in diffusing capacity. Clinically**,** from 10% to 98% of these subjects are asymptomatic (6, 8, 13, 14, 15). Especially high incidence of restrictive (up to 47%) and diffusion lung function disorders (up to 62%) is common after bone marrow transplantation, being higher in patients treated with total body irradiation and/or experiencing graft-versus-host disease (13, 16–18). There are some reports that the detected abnormalities did not progress over the time of follow–up (17, 19). Children below 3 years of age at the time of treatment seem to be at higher risk to develop late pulmonary sequelae (18).

The aims of the study were to determine the frequency and severity of pulmonary late sequelae among children treated for cancer as well as to identify treatment risk factors and the methods for continued follow-up.

Methods

Study subjects were chosen from the Cancer Registry of Slovenia (CRS). Treatment of childhood cancer is centralized at the Hemato-oncological department of the Pediatric University clinic in Ljubljana and patients are followed there until they are 18 years old or at least five years after treatment. Later they are followed at the outpatient Clinic for Late Effects at the Institute of Oncology, Ljubljana, since 1986 (19, 20).

Of the 1884 children registered at CRS 1959-2002, there were 1020 survivors. Of these, 746 are regularly followed and 255 responded to our invitation for follow up in our study. The evaluation was performed from 1995 to 2008. There were 139 females and 116 males 5 to 37 (mean 18) after diagnosis. Their age was 0-16 (mean 9 years) and 39 were 3 years or less at diagnosis and 18-49 (mean 27) years old at the time of the investigation. Of the 255 patients, 185 were nonsmokers (73%), 65 were smokers and ex-smokers (25%) with no data in 5. Of the 255 patients, 242 patients had radiograms, 237 had pulmonary function tests and 224 had both tests performed.

Detailed history was taken and clinical examination performed. Chest radiograms were obtained. Pulmonary function tests included forced vital capacity, forced expiratory volume in 1 second, and carbon monoxide diffusing capacity. Interpretation of spirometric values was based on the measured value shown in percentage of reference values in healthy adults. Predicted values for lung volumes, spirometry and diffusion capacity data are based on European Respiratory society / American Thoracic society standards (21). All pulmonary function tests and radiograms performed during the follow-up of each patient were reviewed by one of the investigators, blinded to the clinical histories. Body mass Index (BMI) was calculated in 224 patients. Two hundred-six patients had radiotherapy (RT), 87 of them to the lung and/or mediastinum (73 patients > 20 Gy, 14 patients <20 Gy) and 229 patients received chemotherapy in different combinations.

Ethics statement

The study was performed in compliance with the Helsinki Declaration with the approval N° 38/11/96 of National Medical Ethics Committee of Slovenia. All patients gave their approval.

Statistical analysis

The following parameters for univariate analysis were used: age at diagnosis (0-3 and 4-16 years), sex, smoking, BMI, type of malignancy, type of treatment, site of RT, dose of irradiation and duration of follow-up. Values in the different groups were calculated using SPSS 17.0 and were expressed as mean and standard error of the mean. Differences between groups were evaluated using the t-test or the chi^2 test. A p-value of <0.05 was considered statistically significant.

Results

Of 255 childhood cancer survivors tested for respiratory damage with pulmonary function testing and radiogram, 224 patients had both tests. Abnormalities were most frequent among patients with Hodgkin's disease (HD) (52%), non-Hodgkin's lymphoma (NHL) (41%), Wilms' tumor (61%), neuroblastoma (80%) and bone tumors (42%). There was no statistical difference between smokers and non-smokers (Table 1).

We found more abnormalities among patients, treated with RT alone or in combination with surgery and/or chemotherapy (ChT) (40%) than in those who had no RT (33%). The difference in abnormal pulmonary function of the 33 out of 224 patients who had no ChT as compared to those who had ChT was not significant (p=0.12) (Table 2).

The highest incidence of abnormalities was found in patients who had irradiation to the lung. The results of testing in the 205 patients who had irradiation were normal in 106, one of the findings was abnormal in 51 patients, and out of the 178 patients who had both examinations it was abnormal in 21 (12%) (Table 3).

There was no statistical difference in the results between patients in the two different age groups (p=0.26). One patient less than 3 years old treated with a dose below 20 Gy had abnormal lung function. He has been treated for leukemia with RT to the head (12 Gy), and 4 years later had a bone marrow transplantation after high dose induction chemotherapy for recurrent disease.

Table 1 Spirometry and radiograms according to diagnosis

Disease	All patients (n)	Patients with both test performed (n)	Smokers and formers smokers (n)	Abnormal findings			
				All (n; %*)	Radiogram and spirometry (n)	Spirometry (n)	Radiogram (n)
Leukemia	60	50	15	8 (16)	–	4	4
Brain Tu	20	15	5	7 (47)	–	1	6
HD	67	62	17	32 (52)	9	11	12
NHL	31	29	13	12 (41)	3	6	3
WT	15	13	4	8 (61)	3	3	2
NBL	5	5	0	4 (80)	3	0	1
SMT	21	19	3	6 (32)	1	3	2
Bone Tu	14	12	3	5 (42)	2	1	2
Gonads	11	10	2	1 (10)	1	-	-
Other**	11	10	3	4 (40)	2	1	1
Total	255	224	65	87/(39)	24	30	33

HD=Hodgkin's disease; NHL=Non-Hodkin's Lymphoma; WT=Wilms' tumor; NBL=Neuroblastoma; SMT=Soft tissue tumor; *From patients with both tests performed; **Retinoblastoma (n=2); Carcinomas (n=6); Hepatoblastoma (n=1) one mediastinal and one bone not defined malignant tumors (n=2).

Table 2 Results of testing according to treatment

Therapy	All patients (n)	Patients with both test performed (n)	Abnormal findings			
			All (n; %*)	Radiogram and spirometry (n)	Spirometry (n)	Radiogram (n)
S+RT+ChT	66	57	26 (46)	12	9	5
S	2	2	2 (100)	0	0	2
RT	6	6	4 (67)	1	2	1
ChT	20	18	5 (28)	0	2	3
S+RT	18**	13	6 (46)	1	3	2
RT+ChT	116	103	36 (35)	7	14	15
S+ChT	27	25	8 (32)	3	3	2
Total	255	224	87 (39)	24	33	30

S=surgery; RT=radiotherapy; ChT=chemotherapy; *From patients with both tests performed; **1 patients with thyroid cancer had post operation ^{131}RaJ.

Table 3 Findings according to radiotherapy sites

Site of radiotherapy	All patients (n)	Patients with both test performed (n)	Abnormal findings			
			All (n; %*)	Radiogram and spirometry (n)	Spirometry (n)	Radiogram (n)
No radiotherapy	49	45	15 (33)	3	5	7
Radiotherapy to other organ	75	62	9 (15)	0	7	2
Upper and/or lower part of the chest	43	39	21 (54)	7	8	6
Radiotherapy to the lung or mediastinum	88	78	42 (54)	14	13	15
Total	255	224	87 (39)	24	33	30

*From patients with both tests performed.

Table 4 Pulmonary function according to site of radiotherapy

Site of radiotherapy	All patients (n)	All tested (n)	Abnormal spirometry		
			All, (n; %*)	Obstruction (n)	Restriction (n)
No radiotherapy	49	47	8 (17)	–	8
Radiotherapy to other organ	75	68	9 (13)	–	9
Upper and/or lower part of the chest	43	41	15 (37)	–	15
Radiotherapy to the lung or mediastinum	88	81	27 (33)	5	22
Total	255	237	59 (25)	5	54

*From all tested.

Radiograms of 242 patients were available and revealed no abnormality in 189 (78%), the 79 different abnormalities on radiograms in the remaining 53 (22%) patients were: lung scarring 10, loss of lung volume 5, pleural thickening 9, parenchymal calcification 17, lymphadenopathy 9, scoliosis 13, chest wall deformity 8, tracheal stenosis 1, phrenic nerve paralysis 1, nodule (1 cm diameter) or granuloma 3 and anomalous vessels 3.

Radiographic abnormalities were most frequently found in patients with HD

Table 5 Data on the 24 patients with abnormal findings on both tests

Patient	Sex	Age (y)		Year of Dg	Diagnosis	RT localization	Abnormal X-ray findings	RT dose (Gy)	ChT	Years to testing	Lung function
		Dg	Testing								
1	F	15	27	1991	HD	Mediastinum	Fibrosis	30	Yes	12	SLF
2	M	5	22	1986	HD	Paraortic LGL	Lymphadenopathy	24	Yes	17	LLF
3	M	11	24	1989	HD	Mediastinum	Fibrosis, D < volume		Yes	13	LLF
4	F	15	39	1981	HD	Mediastinum	Scarring, L < volume	>20	Yes	24	LLF
5	M	1	30	1975	Wilms' tumor	Whole abdomen	Scoliosis	33	Yes	28	LLF
6	M	1	31	1972	Wilms' tumor	Whole abdomen	Parenchymal calcification	29.7	Yes	31	LLF
7	M	1	19	1985	Wilms' tumor	Whole abdomen	Coin lesion	27.5	Yes	17	LLF
8	M	5	18	1992	Neuroblastoma	HBI + abdomen	Coin lesion	24+6	Yes	14	LLF
9	M	10	43	1974	Rhabdomiosa	L upper lung	First rib fracture, paresis n. phrenicus	60	Yes	32	LLF
10	F	5	22	1987	Bone tumor	L HTH + rib	Deformation after surgery	15+30	Yes	17	LLF
11	F	13	31	1989	Nasopharynx	Upper lung	Pleural thickening	52+32	Yes	18	LLF
12	F	3	20	1988	Bone tumor	R HTH	Pleural thickening	20+54*	Yes	18	LLF
13	F	1	38	1970	Neuroblastoma	Mediastinum	Chest wall deformity	30	No	37	LLF
14	F	16	21	1998	HD	Mediastinum	Scoliosis, pleural thickening, fibrosis, LGL calcifications	30+25	Yes	5	LLF
15	F	13	49	1966	HD	Mediastinum	Scoliosis, parenchymal calcification, L < volume	>20	Yes	36	MLF
16	F	9	40	1975	HD	Mediastinum	Scoliosis	30	Yes	31	MLF
17	F	1	25	1978	HD	Mediastinum	Chest wall deformity, kyphoscoliosis	30	No	24	MLF
18	M	11	41	1971	HD	Mediastinum	Lymphadenopathy	30	Yes	31	LLF
19	M	10	22	1989	HD	Mediastinum	Pleural thickening, fibrosis, LGL calcifications	25+16	Yes	12	LLF
20	F	16	33	1988	NHL	Mediastinum	Phrenic nerve paralysis	18	Yes	17	LLF
21	M	6	26	1983	NHL	Mediastinum	Chest wall deformity	24	Yes	20	LLF
22	M	14	26	1989	NHL	Mediastinum	Scoliosis, lung scarring, loss of volume (surgery)	–	Yes	12	LLF
23	F	14	23	1995	Bone tumor	Lung	Lung scarring (surgery)	–	Yes	9	LLF
24	M	16	29	1992	Testis	No RT	Lung scarring (surgery)	–	Yes	12	LLF

ChT=Chemotherapy; Dg=Diagnosis; HD=Hodgkin's disease; NHL=Non-Hodkin's Lymphoma; LLF=Light diminished lung function; MLF=Moderately diminished lung function; RT=Radiotherapy; SLF=Severely diminished lung function; HBI=Half body irradiation; LGL=Lymph gland; R=Right; L=Left; HTH=Hemithorax; *Head.

(20/67) or NHL (10/31) treated with mediastinal RT and those with brain tumor (7/15) treated with RT to the central nervous axis. Scoliosis was found in Wilms' tumor patients, who had abdominal RT (6/15).

Two patients with secondary malignant tumors died, one had mesothelioma and the second had lung cancer, both had been treated for HD with RT to the mediastinum. None of the other findings listed, were

deemed to be of such clinical significance as to warrant further measures, other than physiotherapy.

Lung function tests were performed in 237 patients with abnormal values in 59 (24.9%). Five patients (2.1%) had obstruction and 54 (22.8%) had restriction. Of the 237 patients who had pulmonary function tests performed, 59 (25%) had abnormalities: eight (with mild restriction) had been treated without RT. Radiotherapy to the chest and lung parenchyma and mediastinum were followed by restrictive ventilatory insufficiency more often than RT to other sites (Table 4).

Among 224 survivors, 7.7% patients were underweight and 9.5% overweight, but we found no significant correlation with diagnosis (p=0.5) or the method of therapy: ChT (p=0.3), RT (p=0.6).

Data on the 24 patients who had abnormal findings on both tests are shown in Table 5.

Discussion

We have found mild to moderate impairment of pulmonary function as well as radiographic changes of chronic, usually non-progressing kind, in a minority of survivors. Our findings are similar to that of most others, while some report higher percentage of radiographic abnormalities (3, 10).

The exception were 2 patients, who developed secondary malignancies, bronchial carcinoma and pleural mesothelioma, respectively. These two had been treated for mediastinal HD. For this reason we would recommend radiography to be included in follow-up protocols for this group of survivors. From the pulmologist's point of view these survivors are a high risk group, akin to smokers, those with chronic obstructive pulmonary disease (COPD), or exposure to asbestos and should be followed accordingly.

Most other radiographic findings in our study seem to be what is usually called "residua", are not expected to progress in time and did not do so in cases where we could observe them over a longer period of time. Pulmonary fibrotic changes, on the other hand, are more likely to progress and are better followed by clinical examination and pulmonary function testing. We could not find any severe fibrotic changes in our group of patients, but they have been evaluated only once. To continue follow up with pulmonary function testing is therefore recommended in patients with pulmonary fibrosis.

The average of the subjects' BMI is similar to that of the normal population in our country. Others found higher BMI in girls, treated for acute lymphocyte leukemia than in boys and other childhood cancer survivors (22, 23). There is a similar trend in our group of patients with leukemia as reported before (24), but the number of patients with leukemia in our group is too small for statistical evaluation.

The reasons for follow up with pulmonary function testing are mainly the uncertainty of progression of fibrosis and also the fact that 4 of our patients have developed asthma. Other studies have shown correlation of lung toxicity with RT and ChT (4–8, 11, 12). In our group we have 9 patients treated only with ChT, developing pulmonary restriction. Such patients should also be followed. Another reason for follow-up with lung testing is the possibility of the patient developing pulmonary obstruction, which ought to be detected and treated as soon as possible.

Among 225 patients with lung function testing 169 had normal findings on spirometry, 54 showed restriction and 5 reversible obstruction. Restrictive lung disease was mild in most patients and more common in those patients, who had RT to the lung, chest or mediastinum or central nervous system (CNS). Authors of other studies of lung function in survivors of childhood cancer reported different proportions of lung dam-

age depending on the type of treatment (3, 4, 7, 8, 9, 13). In long-term childhood cancer survivors, restrictive type of respiratory function defect is mostly found (in 10% to 87% of pts) (6, 9, 14, 15, 19, 24, 25). Impairment of diffusing capacity is reported in high proportion as well (6-8). In the population of childhood cancer survivors, obstructive type of pulmonary dysfunction is rarely reported. That is in concordance with our results. Namely, prevalence of obstruction in our group is almost the same as in the Slovenian population. In our study there were 9 patients out of 255, with restrictive changes treated with ChT (with or without surgery) without RT. There are numerous reports on pulmonary complications, caused by different chemotherapeutic agents, mostly as restrictive changes and impairment of diffusing capacity (3, 5, 6, 7, 8, 11, 12).

In our study, the highest proportion of pathological lung function tests was found among patients treated for brain tumors (especially those after CNS RT), neuroblastoma, HD and Wilms' tumor. Patients treated for leukemia had the lowest proportion of lung impairment (less than 10%). That is in concordance with other reports on long-term survivors of leukemia, where risk factors for lung damage were bone marrow transplantation, total body RT and spinal RT (8, 13, 14, 17, 18, 24).

In this study we did not find statistical difference in lung damage between patients under or above 3 years of age at diagnosis. Most other studies found that patients treated at lower age (under 8 years of age) were at higher risk to develop lung damage (8, 9, 19, 26, 27).

Our analysis did not show any difference in frequency of lung damage between smokers and non-smokers. Several other authors reported that smoking had no statistically significant impact on lung damage in long-term survivors of childhood cancer (5, 8, 18), but some found smoking having an important influence on lung function (28). Of course however, it is of importance for our survivors not to smoke, because it is well known that smoking increases the risk of emphysema, chronic bronchitis and lung cancer.

Conclusion

In a selected population of childhood cancer survivors, some may be at risk for late pulmonary sequelae, particularly those treated with radiation to the chest. Our findings are in agreement with most other studies also in one, essential, aspect: the apparent necessity of continuous follow-up in order to assess the progression of sequelae and looking out for secondary malignancies. Spirometry has proved to be the basic test for detection of pulmonary sequelae. Radiography is mainly indicated in clinical suspicion of secondary tumor.

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Conflict of interest: The authors declare that they have no conflict of interest.

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