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ORIGINAL ARTICLE

Pulmonary fibrosis in youth treated with radioiodine for juvenile thyroid cancer and lung metastases after Chernobyl

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Abstract
Purpose The objective of this project was to systematically determine the prevalence and consequences of pulmonary fibrosis in youth with thyroid carcinoma and lung metastases from Belarus who were treated with radioiodine (^{131}I).
Methods A total of 69 patients treated for juvenile thyroid carcinoma and lung metastasis with ^{131}I were assessed. A group of 29 patients without lung metastases and prior ^{131}I treatment served as controls. The assessments included a CT scan of the lungs, extensive pulmonary function testing and an incremental cycle test to volitional fatigue with measurements of oxygen uptake ($\dot{V}O_2$), oxygen saturation and alveolar-arterial difference in oxygen partial pressure (ΔaaO_2).
Results Five patients with lung metastases showed advanced pulmonary fibrosis on CT scans and also had poorer lung functions compared with the 62 patients with none or minor signs of fibrosis and the 29 controls. Furthermore, these five patients showed lower peak $\dot{V}O_2$, lower oxygen saturation at peak exercise and higher exercise ΔaaO_2. They were younger at the time of cancer diagnosis and had received chemotherapy more frequently than youth with pulmonary metastases who did not develop fibrosis. One of the five patients subsequently died from pulmonary fibrosis.
Conclusion Following the Chernobyl catastrophe, about 7% of children treated with radioiodine for thyroid carcinoma and lung metastases displayed pulmonary fibrosis which was associated with functional impairments. Based on the characteristics of affected individuals, the number of radioiodine courses may have to be limited, especially in young children, and chemotherapy should be avoided.

Keywords Radioactive fallout · Exercise test · Oncology · Respiratory · Radionuclide therapy

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Introduction

Differentiated thyroid carcinoma is extremely rare in children and adolescents. The yearly incidence in Western European countries is estimated to be 0.2–0.5 per 100,000 [1]. Therefore, relatively little is known about the development of long-term sequelae of thyroid cancer itself and the consequences of cancer therapy.

Following the Chernobyl catastrophe on 26 April 1986, the incidence of thyroid carcinoma increased to about 4 per 100,000 individuals in the age group younger than 19 years in Belarus, amounting to approximately 5,000 cases [2]. A clear dose-response relationship between radiation to the thyroid from radioactive fallout following the Chernobyl accident and thyroid cancer risk has been established [3]. Compared with patients suffering from thyroid carcinoma not exposed to radioactive fallout, the patients in Belarus were younger at the time of diagnosis, the female to male ratio is lower and the tumours seem to be more aggressive as indicated by more patients with growth into extra-thyroid tissue and involvement of regional lymph nodes [4].

Lung metastasis are estimated to occur in about 2–20% of patients with differentiated thyroid carcinoma who were not exposed to radioactive fallout [5–7]. Patients from the area surrounding Chernobyl have a comparable incidence of lung metastases [8].

Radioactive iodine (^{131}I) is highly effective to treat remaining tumour tissue after thyroidectomy as well as metastases in the regional lymph nodes and distant metastases and is therefore part of standard care [1]. With treatment, mortality in children and adolescents with thyroid cancer is low, usually about 1–2% [2, 9] .

It has been hypothesized that the therapeutic use of radioiodine in patients with pulmonary metastasis might lead to a (local) radiation fibrosis. Furthermore, chemotherapeutic agents like bleomycin, which has been used occasionally in patients with thyroid cancer from Belarus, might also have contributed to the development of pulmonary fibrosis. Indeed, there are some reports on patients with thyroid carcinoma who developed pulmonary fibrosis [10, 11]. Reiners et al. reported pulmonary fibrosis in about 5% of youth with diffuse pulmonary metastases and intense ^{131}I treatment [2]. However, nothing is known about the functional impairments resulting from pulmonary fibrosis. Given the excellent prognosis of thyroid cancer, pulmonary fibrosis may become a major problem for those patients affected and may impact survival. We hypothesized that the prevalence of pulmonary fibrosis among patients with thyroid carcinoma and lung metastases was higher than previously reported—at least in patients from Belarus—and that it was associated with pulmonary impairment.

Thus, this study had two major objectives: (1) to systematically determine the prevalence of pulmonary fibrosis in a large group of patients with thyroid carcinoma and pulmonary metastasis from Belarus and (2) to assess functional consequences of pulmonary fibrosis. Furthermore, we intended to identify risk factors for the development of pulmonary fibrosis in this population and to search for a method to identify patients with pulmonary fibrosis based on the assessment of lung volumes and pulmonary function including exercise testing.

Materials and methods

Subjects

All 119 patients from Belarus who developed thyroid cancer before the age of 18 years and who were seen at the Hospital for Nuclear Medicine in Würzburg, Germany for treatment with radioiodine (^{131}I) or follow-up between 1999 and 2004 were considered for inclusion in this study. Patients without pulmonary metastases who had previously received ^{131}I were excluded. In total, 98 patients participated in the cross-sectional part of the study which included extensive pulmonary function testing, exercise testing and CT imaging of the thorax (see below for details). A total of 69 patients showed lung metastases in a postoperative ^{131}I scan and 60 had received ^{131}I for therapeutic purposes at least once. A group of 29 patients with thyroid cancer from Belarus but without lung metastases who had never received ^{131}I prior to the assessment in Würzburg served as controls. If patients were seen more than once during the above time period, the first visit was chosen for assessment for this project. All participants had undergone thyroidectomy including extirpation of local lymph nodes in Belarus. Histological examination of the primary tumour in the 69 patients with lung metastases showed a papillary type in 61 patients, follicular type in 1 patient and a mixed type in 7 patients. Tumour histology in all 29 control patients revealed a papillary type. The primary tumour was restricted to the capsule in 17 of the 69 patients with lung metastases (tumour stage $\leq$3), while it extended beyond the capsule in the remaining 52 patients (tumour stage 4). All but two of these patients showed involvement of the regional lymph nodes. In the 29 control patients without lung or other distant metastases, only 2 had a tumour extending beyond the thyroid capsule, while all showed involvement of the regional lymph nodes.

In the patients with lung metastases, the first ^{131}I scan of the lungs showed focal uptake in 6 patients, a diffuse uptake in 41 patients and a mixed pattern in 22 patients. Nine of the patients with lung metastases were assessed before any ^{131}I therapy was given, and the remaining patients of this group had received between one and ten courses of ^{131}I therapy (cumulative activity 0–61.7 GBq) with an average time period of 4.6 months between doses [2].

A detailed description of the ^{131}I therapy in the patients with thyroid cancer and lung metastases is beyond the scope of this paper and has been published elsewhere [2]. Briefly, after surgery, patients withheld thyroid hormone replacement therapy for 4 weeks prior to ^{131}I treatment and then received 50 MBq of ^{131}I per kg body weight to eliminate thyroid remnants. In subsequent treatment courses, 100 MBq of ^{131}I per kg body weight was applied, again after stopping thyroid hormone replacement for 4 weeks. Ten patients with lung metastasis but none of the control group had received

radiation therapy to the neck (16–40 Gy). Chemotherapy had been given to four patients with lung metastasis (two to eight cycles of vincristine, bleomycin and cisplatin).

After participating in the cross-sectional part of this study, patients were seen at least annually for medical assessment at the Thyroid Cancer Centre in Belarus. There was no loss to follow-up except for two deceased participants. The median follow-up period was 10.1 years (range 6.7–11.2 years).

Patients and their guardians, if applicable, signed an informed consent form in Belarus for all diagnostic and therapeutic procedures, including a statement that the data may be used for scientific purposes. All measurements taken for this study were routinely done because of the risk for pulmonary fibrosis associated with thyroid cancer, as outlined above. The Ethics Committee of the local medical faculty approved the study. Four weeks prior to ^{131}I therapy, patients stopped their thyroid hormone replacement therapy. In consequence, all patients were assessed in a state of severe acute hypothyroidism as indicated by a thyroid-stimulating hormone (TSH) level >80 IU/ml.

Measurements of pulmonary function and lung volumes

Vital capacity (VC), forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC) and single-breath transfer factor of the lung for carbon monoxide (TLCO) were measured (Master Screen Body, Erich Jaeger-Toennies GmbH, Würzburg, Germany). TLCO was corrected for haemoglobin levels [12]. For each variable, the best value was chosen and expressed in % predicted (VC and FEV_1: [13]; TLC: [14]; TLCO: [15]).

Exercise test

Patients performed an incremental exercise test to volitional fatigue on a calibrated cycle ergometer in semi-supine position (Ergometrics 900 L, Ergoline GmbH & Co KG, Bitz, Germany). Initial work rate was set to 0.6 W/kg in female and 0.7 W/kg in male subjects. Work rate was increased every 3 min by 0.6 or 0.7 W/kg, respectively. The 12-lead ECG (Custo Card M, Custo med, Munich, Germany) and oxygen saturation (Nellcor NPB-290 with Nellcor SCP-10 forehead sensor, Nellcor Inc., Pleasanton, CA, USA) were monitored continuously. Ventilation, oxygen uptake ($\dot{V}O_2$) and carbon dioxide output ($\dot{V}CO_2$) were measured breath by breath using a metabolic cart (CPX/D, St. Paul, MN, USA) calibrated before each test with two gases of known concentrations. VO_2peak was taken as the highest $\dot{V}O_2$ during 30 s. For the same time period, $\dot{V}CO_2$peak was determined and peak respiratory exchange ratio (RER) was calculated as $\dot{V}CO_2$peak/$\dot{V}O_2$peak.

Two capillary blood samples for blood gas analysis were collected from the hyperaemized right ear lobe simultaneously with measurements of PO_2 and PCO_2 in expired gases, one at rest before the exercise test and one starting 60 s into the third exercise stage. Alveolar-arterial pressure differences for O_2 (ΔaaO_2) and CO_2 ($\Delta aaCO_2$) were computed at rest and during submaximal exercise.

Computed tomography

A CT scan of the lungs without contrast medium was performed (Somatom Volume Zoom, Siemens, Erlangen, Germany; 5 mm slices, pitch 1.5, 80–140 kV, 50–77 mAs). Each scan was analysed independently by two experienced radiologists who were blinded to the other findings. Pulmonary fibrosis was rated according to a classification which was especially developed for this study based on our extensive previous experience with CT changes in youth with thyroid cancer. The scale was based on the principles of the SOMA/LENT scoring system [16]. Interestingly, although developed completely independently, a score similar to that used in the present investigation was used to assess pulmonary damage using CT imaging after radiation in breast cancer patients [17].

Figure 1 shows examples of CT images from patients involved in the present study demonstrating the different stages of fibrosis:

Stage 0 fibrosis:	Normal CT images, no signs of fibrosis
Stage 1 fibrosis:	Discrete signs of fibrosis in the periphery of the lungs (subpleurally, <2 cm) or thickening of septa or irregularities of the pleura
Stage 2 fibrosis:	Discrete streaks of fibrosis in the centre of the lungs
Stage 3 fibrosis:	Net-like fibrosis in the centre of the lung without destruction of architecture
Stage 4 fibrosis:	Honeycomb changes in the centre of the lung with destruction of lung architecture

Although there are no published data from presumably healthy individuals on the incidence of pulmonary changes described as fibrosis grade I in our study, clinical experience shows that such changes may be observed in some people not at risk for—and not suffering from—pulmonary fibrosis

In the patients with stage 2, 3 and 4 fibrosis, the CT images obtained prior to the start of radioiodine therapy were reassessed and in none of the patients were signs of fibrosis present prior to therapy. Figure 2 shows an example from one patient with thyroid cancer and lung metastases demonstrating a progressive pulmonary fibrosis to stage 3 over 3 years while receiving ^{131}I therapy.

Data analysis

The patients with lung metastases were compared to the control patients without lung metastases employing non-

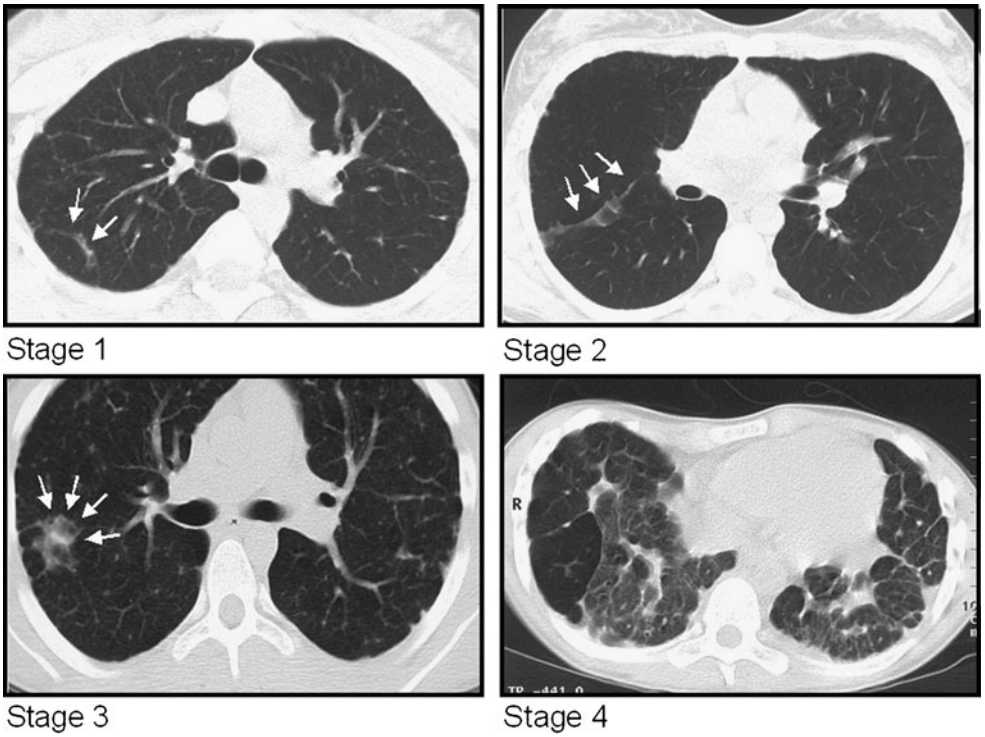

Fig. 1 Example of CT images of stages 1 through 4 of pulmonary fibrosis. The images are from patients with thyroid cancer and pulmonary metastases

parametric statistics (Fisher's exact test for dichotomous data, Wilcoxon rank test for all other comparisons). Likewise, within the group of patients with lung metastases, patients with advanced signs of fibrosis on CT images (stages 3 and 4) were compared to patients without such changes (stages 0 through 2).

Results

Of the 29 patients without lung metastases and prior ^{131}I treatment, 22 showed a completely normal CT scan (stage 0 fibrosis) and 7 had some discrete signs of fibrosis (stage 1) (Fig. 3). Likewise, the majority of the 69 patients with lung metastases demonstrated no fibrosis on CT or had only minor signs of fibrosis in the lung periphery. However, seven patients with lung metastases showed fibrosis affecting the centre of the lung, and five of these had advanced pulmonary fibrosis.

Compared with the control group of patients without lung metastases, the group of patients with lung metastases as a whole was younger at the time of diagnosis but older at the time of assessment and had received much more therapy (Table 1). Nevertheless, pulmonary volumes and function at rest as well as gas exchange at rest and during exercise

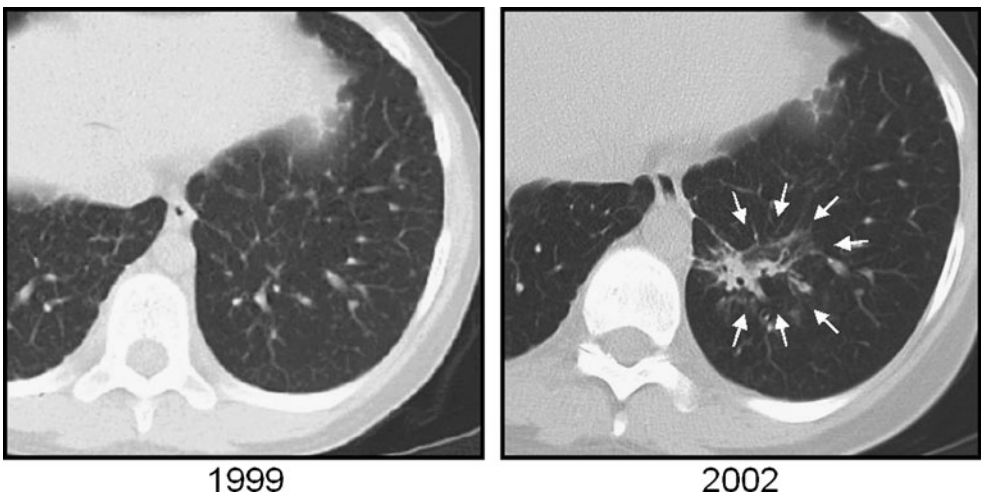

Fig. 2 CT images of the lung in a patient with thyroid cancer and lung metastases who developed pulmonary fibrosis. The image from 1999 was taken prior to any ^{131}I therapy. Three years later, after six cycles of ^{131}I with a cumulative dose of 21.63 GBq, stage 3 fibrosis has developed

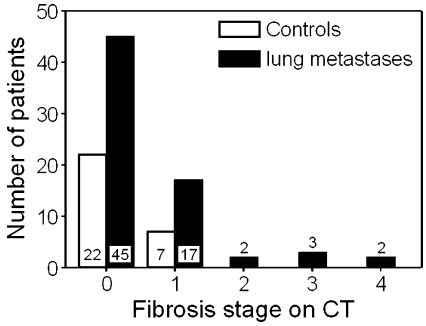

Fig. 3 Number of patients with pulmonary fibrosis in stages 0–4 in the control group and the group of patients with lung metastases

were similar between the groups except for FEV_1 and oxygen saturation at peak exercise (Table 2).

Within the group of patients with lung metastases, patients with stage 3 and 4 fibrosis had smaller lung volumes, a lower FEV_1 and an impaired gas exchange of oxygen especially during exercise (Table 2, Fig. 4 and Fig. 5). These five patients were younger at the time of thyroid cancer diagnosis and a longer time period had elapsed between diagnosis and assessment for this study (Table 1). Furthermore, chemotherapy had been employed significantly more frequently in the group of patients with advanced signs of fibrosis on CT.

One patient with stage 4 fibrosis and severe impairment of pulmonary function died 8 years after assessment for this study from pulmonary fibrosis. He had not received any additional ^{131}I therapy. One further patient with pulmonary metastases committed suicide several years after therapy, for unknown reasons but not related to his cancer.

Discussion

The prevalence of advanced pulmonary fibrosis observed in the group of patients treated for pulmonary metastases of thyroid carcinoma was 7.2% and thus somewhat higher than previously reported [2]. The five patients identified in this study showed impaired pulmonary volumes and function at rest as well as a reduced exercise capacity and impaired exercise gas exchange. While mortality directly associated with thyroid carcinoma was zero in the high-risk group of 69 patients with pulmonary metastases studied between 1999 and 2004 until now, 1 patient died from respiratory failure as a consequence of pulmonary fibrosis. Thus, the development of pulmonary fibrosis during the treatment of pulmonary metastases of juvenile thyroid cancer poses a significant problem for the management of the patients.

Table 1 Patient characteristics

	Controls	Patients with pulmonary metastases		
		Total group	Without advanced pulmonary fibrosis	With advanced pulmonary fibrosis
Gender (female/male)	17/12	35/34	33/31	2/3
Age at diagnosis of thyroid cancer (years)	16.0 (14.6, 16.8)	13.3*** (10.5, 15.2)	13.4*** (10.7, 15.3)	8.6**, & (8.0, 12.4)
Distribution of lung metastases		Diffuse: 41	Diffuse: 37	Diffuse: 4
		Diffuse-focal: 22	Diffuse-focal: 21	Diffuse-focal: 1
		Focal: 6	Focal: 6	
Patients who received chemotherapy (*n*)	0	4	2	2*, &
Patients with local radiotherapy of the neck (*n*)	0	10*	9*	1
Age at assessment (years)	16.0 (14.6, 16.9)	17.1* (15.8, 18.4)	17.0* (15.6, 18.2)	17.7 (16.6, 20.2)
Time since diagnosis (years)	0.3 (0.1, 0.3)	4.2*** (0.9, 6.9)	3.6*** (0.6, 6.7)	8.4***, && (5.0, 11.6)
Number of previous ^{131}I courses	0	3*** (2, 6)	3*** (1, 6)	5*** (4, 6)
Cumulative activity prior to assessment (GBq)	0	14.3*** (4.6, 22.1)	13.4*** (3.1,22.7)	20.6*** (14.1,21.7)
Height (cm)	165 (162, 169)	168 (162, 174)	168 (161, 174)	171 (165, 175)
Weight (kg)	56.0 (50.0, 66.0)	58.0 (53.0, 69.0)	58.5 (53.0, 69.8)	56.0 (45.5, 65.0)
Hb (g/dl)	13.9 (13.6, 15.0)	14.5 (13.4, 15.7)	14.5 (13.3, 15.4)	16.4 (13.6, 16.8)

Data are mean (interquartile range). Please note that the measurements of height, weight and haemoglobin (Hb) were taken at the time of systematic assessment for this study (extensive lung function testing, exercise testing, CT imaging of the lungs)

*, **, *** indicate a significant difference to the control patients from Belarus with thyroid cancer but without pulmonary metastases and without previous ^{131}I treatment at the $p<0.05$, $p<0.01$ and $p<0.001$ levels, respectively

&, && indicate significant differences between the patients with advanced pulmonary fibrosis on CT (stages 3 and 4) and the patients without such changes within the group of patients with lung metastases at the $p<0.05$ and $p<0.01$ levels, respectively

Table 2 Lung volumes, pulmonary function and gas exchange at rest and during exercise in patients with thyroid cancer—effect of pulmonary metastases and signs of advanced fibrosis on CT

Parameter	Controls	Patients with pulmonary metastases		
		Total group	Without advanced pulmonary fibrosis	With advanced pulmonary fibrosis
VC (% predicted)	109.4 (95.5, 116.6)	102.9 (90.5, 112.2)	103.7 (92.1, 112.4)	79.0***, &&& (33.9, 81.6)
FEV_1 (% predicted)	115.1 (107.8, 125.5)	108.5** (91.7, 118.1)	109.5* (93.2, 119.4)	58.3***, && (31.2, 89.3)
TLC (% predicted)	92.2 (85.5, 95.5)	90.0 (85.0, 94.6)	90.5 (86.4, 94.7)	77.0***, &&& (55.1, 79.2)
TLCOc (% predicted)	88.1 (72.0, 105.3)	91.0 (80.1, 101.6)	92.0 (83.4, 101.7)	79.5& (55.8-80.4)
KCOc (%)	79.5 (71.9, 91.4)	81.7 (73.3, 90.2)	80.8 (73.3, 90.2)	86.4 (74.2, 92.8)
SpO_2 at rest (%)	99 (99, 100)	99 (98, 100)	99 (99, 100)	99 (98, 99)
Resting aDO_2 (mmHg)	7.9 (2.0, 12.7)	7.1 (2.2, 13.3)	7.0 (2.2, 13.3)	11.3 (1.8, 19.5)
Resting $aDCO_2$ (mmHg)	3.5 (1.9, 5.1)	3.7 (2.2, 6.3)	3.70 (2.1, 6.0)	7.6 (1.3, 10.2)
$\dot{V}O_2$peak (% predicted)	74.2 (64.1, 85.9)	70.0 (62.0, 76.3)	70.8 (62.9, 77.0)	53.0**, && (36.9, 63.0)
RER at peak exercise	1.12 (1.07, 1.17)	1.12 (1.04, 1.17)	1.11 (1.04, 1.16)	1.18 (0.99, 1.47)
HR at peak exercise (min^{-1})	168 (159, 176)	163 (155, 173)	164 (155, 173)	157 (153, 168)
Exercise ΔaaO_2 (mmHg)	15.5 (11.5, 20.5)	14.3 (10.3, 19.6)	14.0 (10.1, 18.4)	29.3**, && (22.4, 41.2)
Exercise $\Delta aaCO_2$ (mmHg)	8.7 (5.4, 10.8)	7.4 (5.5, 10.3)	7.4 (5.5, 9.9)	14.8 (−0.3, 21.9)
Peak exercise SpO_2 (%)	98 (98, 99)	97** (95, 98)	97** (96, 99)	94**, & (80, 96)
Change in SpO_2 rest-exercise (%)	−1 (−2, 0)	−2*** (−4, −1)	−2** (−3, −1)	−5**, & (−18, −3)

Values are median (interquartile range)

*, **, *** indicate a significant difference to the control patients with thyroid cancer but without pulmonary metastases and without previous ^{131}I treatment at the $p<0.05$, $p<0.01$ and $p<0.001$ levels, respectively

&, &&, &&& indicate significant differences between the patients with advanced pulmonary fibrosis on CT (stages 3 and 4) and the patients without such changes within the group of patients with lung metastases at the $p<0.05$, $p<0.01$ and $p<0.001$ levels, respectively

The pathogenesis of pulmonary fibrosis in patients treated for thyroid cancer is not fully understood. Currently it is hypothesized that exposure of lung tissue to radiation in patients with pulmonary metastasis receiving ^{131}I therapy induces fibrosis [2]. Following radiation therapy, a cascade of alveolar damage with inflammatory response and subsequent fibrotic changes has been demonstrated [18].

The five patients with advanced pulmonary fibrosis differed from the remaining patients with pulmonary metastases who did not develop pulmonary fibrosis in that they were younger at the time the thyroid carcinoma was diagnosed and in that more time had elapsed after the start of therapy. It has been stated that young children are especially prone to develop pulmonary fibrosis after irradiation of the lung [19]. It has been shown that the cumulative incidence of pulmonary fibrosis in paediatric cancer survivors who received radiation to the chest increases up to 25 years after diagnosis [20]. Thus, it might be possible that the time elapsed after initiation of ^{131}I therapy allowed the development of fibrosis in these patients, while some of the other patients with pulmonary metastases could still be affected in the future.

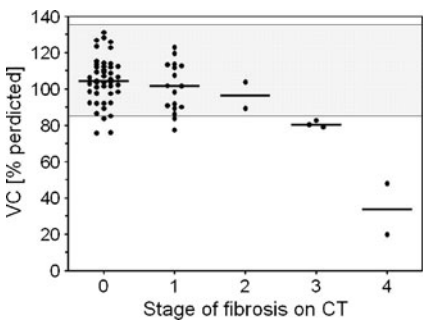

Fig. 4 Vital capacity (*VC*) in patients with thyroid cancer and lung metastases grouped by the stage of fibrosis determined from CT images. The *shaded area* indicates the range of VC measured in the control group. The *horizontal bars* represent the median in each group

Two of the five patients with pulmonary fibrosis had received chemotherapy with vincristine, bleomycin and cisplatin. These drugs have been associated with the development of pulmonary fibrosis [20–22], and paediatric patients treated with a combination of chemotherapeutic agents and irradiation of the lungs are at an increased risk for pulmonary fibrosis [19].

In view of the hypothesized importance of lung tissue irradiation for the development of pulmonary fibrosis, it seems surprising that individuals with advanced pulmonary fibrosis did not differ in the cumulative dose of ^{131}I or the number of ^{131}I treatments from patients without pulmonary fibrosis. However, as pointed out above, the concomitant

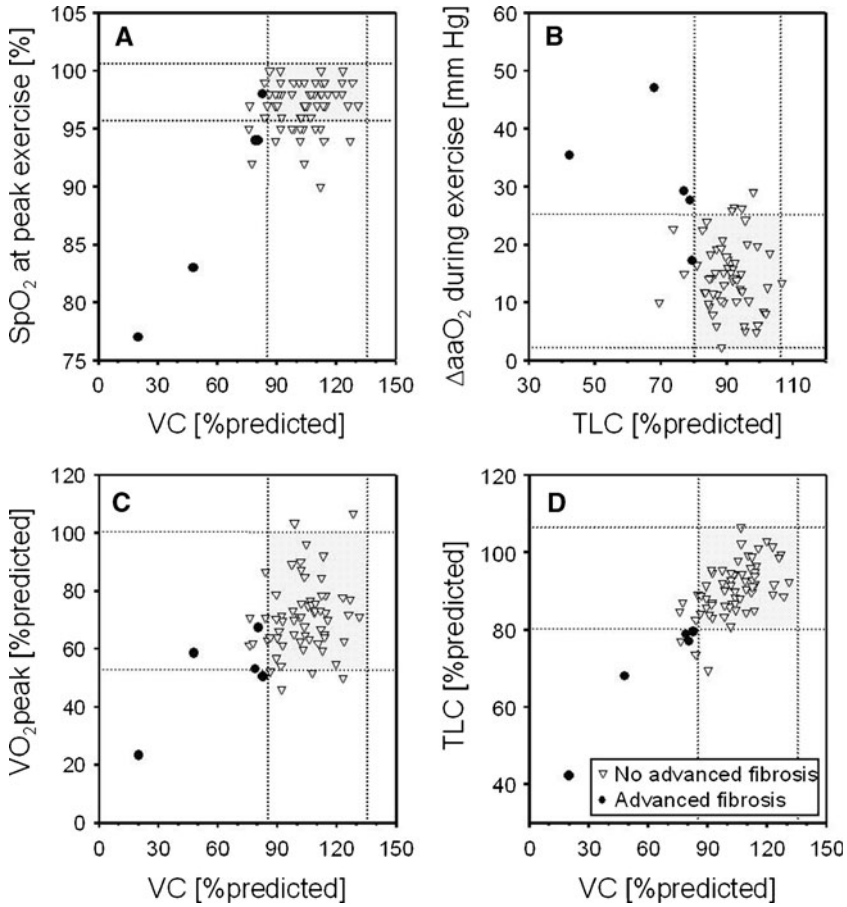

Fig. 5 Identifying patients with advanced pulmonary fibrosis based on pulmonary volumes and exercise gas exchange variables using a combination of two variables: **a** vital capacity (*VC*) and oxygen saturation (SpO_2) at peak exercise, **b** total lung capacity (*TLC*) and alveolar-arterial difference in oxygen partial pressure (ΔaaO_2), **c** vital capacity (*VC*) and peak oxygen uptake (VO_2peak), **d** vital capacity (*VC*) and total lung capacity (*TLC*). The *dotted lines* indicate the lowest and highest value measured for each respective variable in the control group of 29 patients without lung metastases. The *shaded area* depicts the range of data from the 29 control patients who are not individually represented by symbols in this figure

use of chemotherapeutic drugs in some individuals and the differences between groups in time elapsed since the initiation of treatment might have influenced our results and could thus have masked a radiation dose-pulmonary fibrosis relationship.

We considered only 5 of the 69 patients with pulmonary metastases as suffering from pulmonary fibrosis. This decision was based on both CT findings and pulmonary function testing. Taking only the CT findings into account, two additional patients might be included in the group of patients with fibrosis. Looking only at pulmonary function data, even more additional patients could be considered to suffer from some form of restrictive lung disease. Furthermore, if fibrosis could also develop in youth many years after radiation [19], it cannot be excluded that fibrosis might still manifest in some additional individuals from our population. Thus, a long-term pulmonary follow-up is recommended in addition to the recommended monitoring for secondary malignancies observed after ^{131}I therapy [2]. Furthermore, in light of the excellent long-term survival of youth with thyroid cancer, limiting the number of ^{131}I therapies may be considered even in the case of persisting pulmonary ^{131}I uptake indicating active metastasis [23, 24].

Limitations

The relatively small number of patients with advanced pulmonary fibrosis did not allow us to identify which of the potential risk factors are independent indicators of future pulmonary fibrosis in youth with lung metastases of a thyroid cancer. However, considering the incidence of thyroid cancer with pulmonary metastases in European children and adolescents not exposed to radioactivity (1 in 1,000,000–15,000,000), the study sample represents a population equivalent to about 70,000,000–1,000,000,000 youth from Western countries.

Lung dosimetry could have helped to establish a clear dose-response relationship. However, this technique was not established at the time of treatment of our patients with ^{131}I and the data cannot be generated retrospectively.

Conclusion

Advanced pulmonary fibrosis occurs in about 7% of youth with thyroid carcinoma and lung metastases undergoing treatment. In view of the good long-term survival of these patients with respect to the thyroid cancer, the impairments in lung functions and oxygen uptake during exercise

observed in youth with advanced pulmonary fibrosis as well as the possible impact on long-term survival will pose a severe burden on these patients' lives. Based on the characteristics of affected individuals, the number of radioiodine courses may have to be limited, especially in young children, and chemotherapy should be avoided.

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Contributors HH, JB and CR conceived and designed the study, HH, JB, AB, AT, and MB undertook the trial and collected data. HH and AB were responsible for data analysis. HH, JB, VD, YD, MB and CR interpreted the data. HH drafted the manuscript with input and editing from all authors.

Conflicts of interest None.

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