ORIGINAL ARTICLE

Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer

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ABSTRACT

Background Childhood cancer survivors (CCSs) have an increased risk of morbidity and mortality. The prevalence and risk factors of pulmonary function impairment were investigated in a large cohort of CCSs treated with potentially pulmotoxic therapy with a minimal follow-up of 5 years after diagnosis.

Methods The study cohort consisted of all adult 5-year CCSs who were treated with bleomycin, pulmonary radiotherapy and/or pulmonary surgery in the Emma Children’s Hospital/Academic Medical Center between 1966 and 1996. Pulmonary function tests were performed to diagnose obstructive and restrictive pulmonary function impairment, and diffusion capacity impairment.

Results The study population consisted of 220 out of 248 eligible CCSs, of whom 193 (87.7%) had performed a pulmonary function test at a median follow-up of 18 years after diagnosis. 85 (44.0%) out of 193 CCSs developed a pulmonary function impairment. Pulmonary function impairments occurred in all treatment groups. Most prevalent were restrictive pulmonary function impairment (17.6%) and a decreased carbon monoxide diffusion capacity (39.9%). Multivariate logistic regression models showed that, compared with bleomycin treatment only, treatment with radiotherapy, radiotherapy combined with bleomycin and radiotherapy combined with surgery were associated with the highest risk of pulmonary function impairment.

Conclusions The prevalence of pulmonary function impairment in long-term adult CCSs who received potentially pulmotoxic therapy is high. Bleomycin, pulmonary radiotherapy and pulmonary surgery are all associated with pulmonary function impairment. Pulmonary radiotherapy, especially in combination with bleomycin or surgery, is the most important risk factor. This emphasises the need for adequate counselling and follow-up for this patient population.

INTRODUCTION

Due to improvement of cancer treatment over the last 40 years there has been a dramatic increase in survival of childhood malignancies. At present, the 5-year survival reaches 80% in developed countries.1 2 Unfortunately, the improved prognosis has allowed the occurrence of late, treatment-related complications.3 4

Childhood cancer survivors (CCSs) treated with bleomycin, pulmonary radiotherapy and/or pulmonary surgery are at risk for pulmonary function impairment. The lungs are liable to suffer from the adverse effects of radiotherapy. Abnormalities in pulmonary function have been observed in patients after low doses of pulmonary irradiation. Apart from bleomycin, which is commonly recognised as a cause of chemotherapy-related pulmonary toxicity, busulphan, carmustine, lomustine, melphalan and cyclophosphamide are also reported to cause pulmonary function impairment.5–7

Treatment-related pulmonary function impairment may cause symptoms of chronic cough, recurrent respiratory tract infections, shortness of breath and/or exercise intolerance, and may involve early and late effects. Late pulmonary function impairment includes obstructive and restrictive pulmonary disease, and diffusion capacity impairments.5–7 This may affect quality of life and can lead to increased risks of premature morbidity and mortality.8

Several studies have evaluated the prevalence of pulmonary function impairment in CCSs.9–17 The reported prevalence varied widely. Most studies, however, had limited sample size, short follow-up duration and/or studied specific patient populations. The Childhood Cancer Survivor Study showed that the risk of pulmonary complications
detected by self-reports is more than three times higher in childhood cancer survivors (CCSs) than in their siblings. However, in that study, no pulmonary function tests were performed. Until now, no studies have investigated the risk of pulmonary function impairment measured by pulmonary function tests in a large cohort of long-term adult CCSs.

In order to establish adequate follow-up protocols for CCSs, it is important to estimate the risk of pulmonary function impairment. Therefore, the aim of this study was to evaluate the prevalence and risk factors of pulmonary function impairment measured by pulmonary function tests in a large cohort of adult CCSs treated with potentially pulmotoxic therapy with a minimal follow-up of 5 years after diagnosis.

METHODS

Study population

In 1996, the Late Effects Outpatient Clinic for CCSs was established in the Emma Children’s Hospital/Academic Medical Center (EKZ/AMC). All 5-year CCSs were identified using the Childhood Cancer Registry, which was established in 1966 and contains data on all patients treated for childhood cancer in the EKZ/AMC regarding diagnosis, treatment and follow-up. All CCSs surviving for at least 5 years were invited to participate and enrolled into prospective follow-up study protocols tailored to previous diagnosis and treatment. CCSs treated with bleomycin, pulmonary radiotherapy or pulmonary surgery were enrolled in the pulmotoxic screening protocol. To be eligible for this study, patients had to meet the following criteria: (1) diagnosed between January 1966 and January 1996 and treated for a primary malignancy; (2) aged <18 years at diagnosis; (3) treated mainly in the EKZ/AMC; (4) survived for at least 5 years after diagnosis at 1 January 2007; (5) qualified for the pulmotoxic screening protocol; and (6) aged 18 years or older at pulmonary function testing.

Follow-up and data collection

All CCSs who visited the Late Effects Outpatient Clinic between January 1996 and January 2009 received a full medical assessment according to the previously mentioned protocols. This medical assessment consisted of a medical history, physical examination and additional risk-based diagnostic tests and counselling. The pulmotoxic screening protocol included pulmonary function testing. For each CCS information was recorded concerning patient and treatment characteristics and pulmonary function testing.

Definition of pulmonary function impairment

For the evaluation of pulmonary function impairment we assessed the first complete pulmonary function test performed at least 5 years after diagnosis. We evaluated the total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), FEV1/maximal vital capacity (VCmax) ratio, carbon monoxide diffusion capacity corrected for haemoglobin concentration (DLCO) and carbon monoxide diffusion capacity corrected for alveolar volume, also called the carbon monoxide transfer coefficient (KCO).

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, obstructive pulmonary function impairment was defined as an FEV1/VCmax ratio <0.70 and FEV1 <80% of the predicted value. The disease severity was graded as follows: (0) no impairment, FEV1/VCmax ratio >0.70 and FEV1 >80% of predicted value; (1) mild impairment, FEV1/VCmax ratio <0.70 and FEV1 ≥80% of predicted value; (2) moderate impairment, FEV1/VCmax ratio <0.70 and FEV1 <80% of predicted value; (3) severe impairment, FEV1/VCmax ratio <0.70 and FEV1 <50–30% predicted value; and (4) very severe impairment, FEV1/VCmax ratio <0.70 and FEV1 <30% of predicted value or FEV1/VCmax ratio <0.70 and FEV1 <50% of predicted value with chronic respiratory failure.

Restrictive pulmonary function impairment and diffusion capacity impairment were defined according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). Restrictive pulmonary function impairment was defined as TLC <75% of the predicted value. If no TLC measurements were available, it was defined as FVC <75% of the predicted value with a normal FEV1/VCmax ratio. Diffusion capacity impairment was measured using the DLCO and KCO and was defined as <75% of the predicted value. The disease severity of restrictive pulmonary function impairment was graded from 0 to 5: (0) no impairment, >90% of predicted value; (1) mild impairment, 90–75% of predicted value; (2) moderate impairment, <75–50% of predicted value; (3) severe and undesirable impairment, <50–25% of predicted value; (4) life-threatening or disabling impairment, <25% of predicted value; and (5) death.

By definition, pulmonary function impairment of grade 2 or higher can be considered abnormal, reflecting physiological impairment.

Statistical analysis

We performed multivariate logistic regression analyses to evaluate possible risk factors for restrictive pulmonary function impairment and diffusion capacity impairment measured by DLCO. Because of small event numbers, it was not possible to evaluate risk factors for obstructive pulmonary function impairment and diffusion capacity impairment measured by KCO.

We constructed two models in which the following risk factors were evaluated: sex, age at diagnosis, follow-up duration and treatment with bleomycin, pulmonary radiotherapy, pulmonary surgery and high-dose cyclophosphamide (high-dose was defined as ≥1 g/m² per course or a total cumulative dose of ≥10 g/m²). In model 1, potentially pulmotoxic treatments were modelled as independent risk factors consisting of yes/no variables, whereas in model 2 these treatments were modelled as a categorical risk factor consisting of mutually exclusive groups.

Analyses were performed using statistical software SPSS for Windows 15.0.1 (release 2007).

Figure 1 Flowchart of childhood cancer survivors included in this study. *None of the 15 childhood cancer survivors who died before they could visit the outpatient clinic died because of pulmonary disease.
Table 1: Clinical characteristics of childhood cancer survivors treated with potentially pulmotoxic therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Original cohort n (%)</th>
<th>Study group n (%)</th>
<th>Follow-up group* n (%)</th>
</tr>
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<tbody>
<tr>
<td>No. of childhood cancer survivors</td>
<td>248</td>
<td>220</td>
<td>193</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>136 (54.8)</td>
<td>117 (53.2)</td>
<td>103 (53.4)</td>
</tr>
<tr>
<td>Female</td>
<td>112 (45.2)</td>
<td>103 (46.8)</td>
<td>90 (46.6)</td>
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<td>Primary childhood cancer diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukaemia</td>
<td>34 (13.7)</td>
<td>28 (12.7)</td>
<td>23 (11.9)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>131 (52.8)</td>
<td>121 (55.0)</td>
<td>110 (57.0)</td>
</tr>
<tr>
<td>Hodgkin</td>
<td>62 (25.0)</td>
<td>57 (25.9)</td>
<td>52 (26.9)</td>
</tr>
<tr>
<td>Non-Hodgkin</td>
<td>69 (27.8)</td>
<td>64 (29.1)</td>
<td>58 (30.1)</td>
</tr>
<tr>
<td>Renal tumour</td>
<td>19 (7.7)</td>
<td>16 (7.3)</td>
<td>13 (6.7)</td>
</tr>
<tr>
<td>Brain/CNS tumour</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Bone tumour</td>
<td>30 (12.1)</td>
<td>23 (10.4)</td>
<td>20 (10.4)</td>
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<tr>
<td>Soft tissue sarcoma</td>
<td>6 (2.4)</td>
<td>5 (2.3)</td>
<td>4 (2.1)</td>
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<td>Neuroblastoma</td>
<td>9 (3.6)</td>
<td>9 (4.1)</td>
<td>7 (3.6)</td>
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<tr>
<td>Other</td>
<td>19 (7.7)</td>
<td>18 (8.2)</td>
<td>16 (8.3)</td>
</tr>
<tr>
<td>Age at diagnosis, median (range) years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis, median (range) years†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0—4 years</td>
<td>51 (20.6)</td>
<td>47 (21.4)</td>
<td>34 (17.6)</td>
</tr>
<tr>
<td>5—9 years</td>
<td>71 (28.6)</td>
<td>65 (29.5)</td>
<td>59 (30.6)</td>
</tr>
<tr>
<td>10—14 years</td>
<td>100 (40.3)</td>
<td>84 (38.2)</td>
<td>78 (40.4)</td>
</tr>
<tr>
<td>15—18 years</td>
<td>26 (10.5)</td>
<td>24 (10.9)</td>
<td>22 (11.4)</td>
</tr>
<tr>
<td>Follow-up duration after diagnosis, median (range) years†</td>
<td>NA</td>
<td>NA</td>
<td>17.9 (5.6—36.8)</td>
</tr>
<tr>
<td>5—9 years</td>
<td></td>
<td></td>
<td>20 (10.4)</td>
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<td>30—34 years</td>
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<td>20 (10.7)</td>
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<tr>
<td>35—39 years</td>
<td></td>
<td></td>
<td>35 (18.1)</td>
</tr>
<tr>
<td>Bleomycin, median cumulative dose (range) mg/m²</td>
<td>60.0 (6.0—594.0)</td>
<td>60.0 (10.0—594.0)</td>
<td>60.0 (10.0—594.0)</td>
</tr>
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<td>Radiotherapy, median cumulative dose (range) Gy</td>
<td>21.0 (3.0—60.0)</td>
<td>24.3 (3.0—60.0)</td>
<td>23.0 (3.0—60.0)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>134 (54.0)</td>
<td>124 (56.4)</td>
<td>110 (57.0)</td>
</tr>
<tr>
<td>No</td>
<td>114 (46.0)</td>
<td>96 (43.6)</td>
<td>83 (43.0)</td>
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<tr>
<td>Thoracic wall resection</td>
<td>5 (2.0)</td>
<td>5 (2.3)</td>
<td>5 (2.8)</td>
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<tr>
<td>Other</td>
<td>8 (3.2)</td>
<td>8 (3.6)</td>
<td>6 (3.1)</td>
</tr>
<tr>
<td>No</td>
<td>201 (81.0)</td>
<td>180 (81.8)</td>
<td>161 (83.4)</td>
</tr>
<tr>
<td>Overall treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleomycin only</td>
<td>120 (48.4)</td>
<td>111 (50.5)</td>
<td>98 (50.8)</td>
</tr>
<tr>
<td>Radiotherapy only</td>
<td>70 (28.2)</td>
<td>59 (26.8)</td>
<td>54 (28.0)</td>
</tr>
<tr>
<td>Surgery only</td>
<td>22 (8.9)</td>
<td>20 (8.1)</td>
<td>13 (6.7)</td>
</tr>
<tr>
<td>Bleomycin with radiotherapy</td>
<td>11 (4.4)</td>
<td>10 (4.5)</td>
<td>9 (4.7)</td>
</tr>
<tr>
<td>Bleomycin with surgery</td>
<td>3 (1.2)</td>
<td>3 (1.4)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Radiotherapy with surgery</td>
<td>22 (8.9)</td>
<td>17 (7.7)</td>
<td>16 (8.3)</td>
</tr>
<tr>
<td>Bleomycin with radiotherapy and surgery</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

Continued
RESULTS

Study population

The study population consisted of 220 out of 248 eligible CCSs. Thirteen CCSs of the total potential CCSs who lived at least 5 years from diagnosis were lost to follow-up and 15 CCSs died before the first outpatient clinic visit (none of pulmonary disease) (figure 1). Clinical characteristics of the study population are presented in table 1. Out of 220 CCSs, 195 (87.7%) performed a pulmonary function test at the age of 18 years or older. The median follow-up time since diagnosis was 17.9 years, ranging from 5.6 to 36.8 years. There were no differences in clinical characteristics between the CCSs in the original cohort, the CCSs in the entire study group and the CCSs in whom pulmonary function tests were performed.

Prevalence of pulmonary function impairment

Table 2 shows the prevalence of pulmonary function impairment (grade 2 or higher) by therapy subgroup in 193 CCSs with pulmonary function tests. In figure 2, the severity of pulmonary function impairment is presented. Four CCSs (2.1%) had an obstructive pulmonary function impairment. The disease severity in these patients was moderate (grade 2). None had a severe obstructive pulmonary function impairment (grade 3–5). Two CCSs (1.0%) had a mild obstructive pulmonary function impairment (grade 1).

Thirty-four CCSs (17.6%) had a restrictive pulmonary function impairment. The highest prevalence was seen in CCSs treated with the combination of radiotherapy and surgery; that is, 10 (62.5%) out of 16. The severity was moderate (grade 2) in 31 patients (16.1%) and severe (grade 3) in 5 patients (1.6%). None had restrictive pulmonary function impairment of grade 4 or 5. Moreover, 78 CCSs (40.4%) had grade 1 restrictive pulmonary function impairment.

For 188 (97.4%) out of 195 CCSs, carbon monoxide diffusion capacity measurements were available. The prevalence of a decreased $D_{L}CO$ was 39.9% (75 CCSs). The highest prevalence was seen in CCSs treated with the combination of radiotherapy and surgery; that is, 11 (73.5%) out of 15. In 73 CCSs (38.8%) the $D_{L}CO$ was moderately decreased (grade 2) and in 2 CCSs (1.1%) severely decreased (grade 3). None had a diffusion capacity impairment of grade 4 or 5. Furthermore, in 78 patients (41.5%), the $D_{L}CO$ was mildly decreased (grade 1).

Eight CCSs (4.3%) had a decreased carbon monoxide diffusion capacity corrected for alveolar volume ($KCO$), of whom four were treated with bleomycin only and four with radiotherapy only. The disease severity in these patients was moderate (grade 2). None had severe reductions in $KCO$ (grade 3–5). In addition, 57 CCSs (30.3%) had a mild diffusion capacity impairment (grade 1).

In total, 88 (44.0%) out of 193 CCSs had pulmonary function impairments (grade 2 or higher) defined as either obstructive or restrictive pulmonary function impairment, decreased $D_{L}CO$ or decreased $KCO$. Pulmonary function impairments occurred in all treatment groups, with a prevalence ranging from 28.6% in CCSs treated with bleomycin only up to 81.5% in CCSs treated with the combination of radiotherapy and surgery. Twenty-eight CCSs (14.5%) had both restrictive pulmonary function impairment and a decreased $D_{L}CO$ of whom 1 (0.5%) had a decreased $KCO$ as well. Moreover, 1 CCS (0.5%) had obstructive pulmonary function impairment and a decreased $D_{L}CO$. In addition, 6 CCSs (3.1%) had both a decreased $D_{L}CO$ and $KCO$ without obstructive or restrictive pulmonary function impairment. One-hundred and forty-one CCSs (75.1%) had one or more mild pulmonary function impairments (grade 1).

Risk factors for pulmonary function impairment

The results of the multivariate logistic regression analyses of the risk factors for pulmonary function impairment are presented in table 3. Please note that all CCSs were treated with potentially pulmotoxic therapy.

According to model 1, pulmonary radiotherapy (OR 12.87; 95% CI 3.57 to 49.08) and pulmonary surgery (OR 3.79; 95% CI 1.25 to 11.50) were significantly associated with restrictive pulmonary function impairment. As shown in model 2, radiotherapy only (OR 6.99; 95% CI 2.27 to 21.54), bleomycin combined with radiotherapy (OR 9.41; 95% CI 1.71 to 51.86) and radiotherapy combined with surgery (OR 33.44; 95% CI 7.81 to 143.09) were significantly associated with restrictive pulmonary function impairment, compared with bleomycin only.

Regarding diffusion capacity impairment, pulmonary radiotherapy (OR 5.84; 95% CI 1.88 to 18.14) was significantly associated with a decreased $D_{L}CO$ (model 1). In addition, model 2 showed that radiotherapy only (OR 2.85; 95% CI 1.32 to 6.19), bleomycin combined with radiotherapy (OR 6.17; 95% CI 1.37 to 27.84) and radiotherapy combined with surgery (OR 5.98; 95% CI 1.64 to 21.81) were significantly associated with a reduced $D_{L}CO$, compared with bleomycin only.
Table 2  Prevalence of pulmonary function impairment (grade 2 or higher) in 193 childhood cancer survivors with pulmonary function tests*

<table>
<thead>
<tr>
<th>Therapy subgroup</th>
<th>Obstructive parameters</th>
<th></th>
<th>Restrictive parameters</th>
<th>Ventilation parameters</th>
<th>Overall pulmonary function impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV&lt;sub&gt;1&lt;/sub&gt;/&lt;FVC&lt;sub&gt;max&lt;/sub&gt; ratio &lt; 0.70</td>
<td>(n (%))</td>
<td>TLC &lt; 75%</td>
<td>FVC &lt; 75%</td>
<td>Restrictive pulmonary function impairment (n (%))</td>
</tr>
<tr>
<td>Bleomycin only</td>
<td>7/98 (7.1)</td>
<td>1/98 (1.0)</td>
<td>4/79 (5.1)</td>
<td>1/98 (1.0)</td>
<td>5/98 (5.1)</td>
</tr>
<tr>
<td>Radiotherapy only</td>
<td>13/54 (24.1)</td>
<td>1/54 (1.9)</td>
<td>12/41 (29.3)</td>
<td>8/54 (14.8)</td>
<td>15/54 (27.8)</td>
</tr>
<tr>
<td>Surgery only</td>
<td>3/13 (23.1)</td>
<td>1/13 (7.7)</td>
<td>0/0 (0.0)</td>
<td>0/13 (7.7)</td>
<td>0/13 (0.0)</td>
</tr>
<tr>
<td>Bleomycin with radiotherapy</td>
<td>4/9 (44.4)</td>
<td>1/9 (11.1)</td>
<td>3/6 (50.0)</td>
<td>3/9 (33.3)</td>
<td>3/9 (33.3)</td>
</tr>
<tr>
<td>Bleomycin with surgery</td>
<td>1/3 (33.3)</td>
<td>0/3 (0.0)</td>
<td>0/0 (0.0)</td>
<td>0/3 (0.0)</td>
<td>0/3 (0.0)</td>
</tr>
<tr>
<td>Radiotherapy with surgery</td>
<td>12/16 (75.0)</td>
<td>1/16 (6.3)</td>
<td>9/13 (69.2)</td>
<td>8/16 (50.0)</td>
<td>10/16 (62.5)</td>
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<tr>
<td>Total</td>
<td>40/193 (20.7)</td>
<td>6/193 (3.1)</td>
<td>28/193 (14.7)</td>
<td>22/193 (11.4)</td>
<td>34/193 (17.6)</td>
</tr>
</tbody>
</table>

*According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for obstructive pulmonary function impairment (FEV<sub>1</sub> < 80% of predicted) and Common Terminology Criteria for Adverse Events v3.0 for restrictive pulmonary function impairment (TLC < 75% of predicted). Overall pulmonary function impairment is defined as either decreased DLCO and/or decreased K<sub>CO</sub>, or decreased FVC < 75%, or decreased FEV<sub>1</sub> < 75%. To retrieve data, we included patients who had undergone pulmonary function tests. Only patients with complete data were included. The data was analyzed using SPSS (version 15.1). Multivariate logistic regression analyses were performed to identify risk factors for pulmonary function impairment. All variables with a p-value < 0.1 in univariate analysis were included in the multivariate analysis. The cut-off for significance was set at p < 0.05. No patients were lost to follow-up. The study was approved by the institutional review board.

DISCUSSION

We have shown that pulmonar function impairment in the long-term follow-up of childhood cancer survivors is associated with radiation therapy, chemotherapy, and surgery. In particular, the combination of bleomycin with chemotherapy or radiation therapy is associated with an even higher risk of pulmonary function impairment. This is the first large cohort study investigating long-term pulmonary function impairments in childhood cancer survivors treated with pulmonary toxic therapy. Our results indicate that bleomycin is the most important risk factor for pulmonary function impairment, followed by chemotherapy and radiation therapy.

Since our study population consisted of CCSs treated in different eras, we conducted a subgroup analysis on CCSs treated before and after 1985 to evaluate whether the results may have been biased by a cohort effect. The logistic regression analyses on both groups, however, showed similar results to the analyses on the whole group of CCSs (see online appendix 1).
lung volumes observed in these patients. It may be hypothesised
in seven patients, surgery does not appear to explain the lower
were treated with pulmonary radiotherapy, eight of whom also
such as underdevelopment of the thorax. Of these patients, 23
indicative of a loss of lung volume or extra-pulmonary factors,
K
a normal

Figure 2 Severity of pulmonary function impairment in 193 childhood
cancer survivors with pulmonary function tests.

lomustine, it was impossible to investigate whether these
chemotherapeutics were associated with an additional increased
risk of pulmonary function impairment. However, since we only
included patients treated with bleomycin, pulmonary radio-
therapy and/or pulmonary surgery, we were not able to inves-
tigate the possible separate pulmotoxic effects of these
chemotherapeutics.

Twenty-seven out of 34 CCSs (79.4%) with restrictive
pulmonary function impairment had a decreased D\textsubscript{1}\textsubscript{CO} but
a normal K\textsubscript{CO}. This type of diffusion capacity abnormality is
indicative of a loss of lung volume or extra-pulmonary factors,
such as underdevelopment of the thorax. Of these patients, 23
were treated with pulmonary radiotherapy, eight of whom also
underwent surgery. Since surgery only involved metastasectomy
in seven patients, surgery does not appear to explain the lower
lung volumes observed in these patients. It may be hypothesised
that pulmonary radiotherapy limits the development of new
alveoli by limiting the ability of cells to proliferate or by inter-
fering with vascular supply, and affects the development of the
bony parts of the chest, which may explain these pulmonary
function impairments. Moreover, only one CCS with restrictive
pulmonary function impairment, treated with radiotherapy
only, had both a decreased D\textsubscript{1}\textsubscript{CO} and K\textsubscript{CO} suggesting increased
vascular impairment that could be explained merely by loss of
lung volume. Therefore, a vascular impairment disproportionate
to the loss of lung volume, as reflected by a reduction in K\textsubscript{CO}
due to therapy-induced damage to the alveocapillary membrane,
appeared not to be a major problem in our cohort.

Bleomycin is the most commonly recognised cause of
pulmonary function impairment in CCSs. However, the exact
threshold dose for developing pulmonary function impairment
after treatment with bleomycin is unclear. Cumulative doses
>450 mg/m\textsuperscript{2} were reported to be associated with a higher risk of
pulmotoxicity, although doses as low as 20 mg/m\textsuperscript{2} may also
induce pulmonary function impairment.\textsuperscript{24} We observed limited
pulmonary function impairment in CCSs treated with bleo-
mycin only. This may be explained by the fact that the median
bleomycin dose was relatively low (60 mg/m\textsuperscript{2}). Only four CCSs
were treated with a bleomycin dose >500 mg/m\textsuperscript{2}, of whom two
devolved pulmonary function impairments.

Since exercise intolerance in CCSs is most often multicausal in
nature, with pulmonary function impairment being one possible
factor, we did not study symptoms experienced and limitations.
CCSs are prone to a high rate of concurrent illness\textsuperscript{3 4} and may,
apart from pulmonary function impairment, suffer from addi-
tional problems that may contribute to exercise intolerance (eg,
chemotherapy-induced congestive heart failure). To discriminate
between exercise intolerance due merely to pulmonary function
impairment and/or other organ dysfunctions would have
involved additional diagnostic procedures, including exercise
testing. These procedures were not part of our routine follow-
up. By definition, however, an FEV\textsubscript{1} <80%, and a TLC, FVC,
D\textsubscript{1}CO and KCO <75% (grade 2) can be considered abnormal, reflecting physiological impairment. In addition, a predicted value <60% in either FEV\textsubscript{1}, TLC, FVC, D\textsubscript{1}CO or KCO can be considered proportionate to a 10–25% functional impairment. Clinically, these CCSSs will have a 10–25% reduction in general functioning as represented by a decrease in the ability to perform daily life activities. A TLC or FVC <50% and a FEV\textsubscript{1}, D\textsubscript{1}CO or KCO <40% are proportionate to a 51–100% functional impairment.

Our study has some limitations. As our study population consisted of CCSSs treated in different eras, cohort effects might have been of influence on our study estimates. However, when performing a subgroup analysis on CCSSs treated before and after 1985 there was no indication that our results were biased, since the effects of pulmototoxic therapy on pulmonary function impairment did not differ between CCSSs treated in earlier and more recent eras. Moreover, we do not have baseline pulmonary function tests before the onset of childhood cancer. Consequently, it is impossible to evaluate which part of the pulmonary function impairment was caused by the cancer treatment. In addition, we did not investigate the longitudinal development of pulmonary function impairment. The natural history of pulmonary function impairment has not been well recognised. Recently, Inaba et al\textsuperscript{19} investigated the pattern of pulmonary dysfunction over time in 89 CCSSs. They showed that pulmonary function progressively declined. However, this study only included patients treated with allogeneic haematopoetic stem cell transplantation for childhood haematological malignancies. Moreover, we were not able to take detailed radiation dosimetry into account, including the volume of the lungs irradiated and the dose to different parts of the lungs. Finally, we did not take smoking status into consideration, since we do not have precise and accurate data on smoking frequency and duration.

In conclusion, this cohort study shows that the prevalence of pulmonary function impairment in long-term adult CCSSs is high. This may have long-term clinical consequences as these patients have a long life expectancy. During their lifetime, CCSSs might be exposed to additional health risks, such as smoking, pollution and infections. Bleomycin, pulmonary radiotherapy and pulmonary surgery are all associated with pulmonary function impairment. Pulmonary radiotherapy, especially in combination with bleomycin or surgery, is the most important risk factor. The Dutch guidelines advise performing a pulmonary function test in CCSSs treated with bleomycin, pulmonary radiotherapy and/or pulmonary surgery 5 and 10 years after diagnosis.\textsuperscript{35} Since we do not know if pulmonary function will worsen over time, individualised education and prevention appear to be justified. For example, for CCSSs with asymptomatic pulmonary function impairment, influenza vaccination may be recommended. Future studies should focus on the evaluation of pulmonary function over time in CCSSs treated with pulmototoxic therapy, and on the influence of radiotherapy dose and the extent of pulmonary surgery. Based upon these studies, decisions can be made about the optimal interval and duration of follow-up of pulmonary function in high-risk CCSSs.

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Contributors RLM collected data, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper. NMT designed the study protocol, collected data, and drafted and revised the paper. HvDP designed the study protocol, collected data, wrote the statistical analysis plan, contributed to the interpretation of the results and revised the paper. PB and LDMK designed the study protocol, wrote the statistical analysis plan, contributed to the interpretation of the results and revised the paper. WH designed the study protocol, collected data and revised the paper. ODG, FO, WAH and HNC contributed to the interpretation of the results and revised the paper.

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