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Pulmonary disease, its risk factors and necessity for long-term follow-up care in childhood cancer survivors

PhD Thesis submitted by

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Abstract

Treatment for childhood cancer puts the young patients at risk to develop adverse health outcomes. These adverse health outcomes can develop acute, already during treatment, or slowly over years to decades after completion of treatment. They can be of transient nature or long-lasting and chronic. Adverse health outcomes can potentially affect every organ system, including the lung. The term late effects is used to describe this heterogeneity of adverse health outcomes. Pulmonary late effects contribute to a higher morbidity and mortality in childhood cancer survivors compared to siblings or the general population.

Before starting this PhD project, knowledge on self-reported pulmonary symptoms, diseases and pulmonary function trajectories in Swiss childhood cancer survivors treated with hematopoietic stem cell transplantation (HSCT) was lacking. These survivors are often exposed to at least one known lung toxic treatment modality and additionally receive treatment of different intensity before HSCT. Therefore, this population is especially at risk to develop pulmonary late effects. Information on lung function trajectories was also lacking for Swiss childhood cancer survivors treated with known lung toxic chemotherapy or radiotherapy to the chest.

This PhD thesis primarily aimed to answer the open questions on frequency, severity, and risk factors for pulmonary late effects in childhood cancer survivors, especially in those treated with HSCT. To answer these questions data from the Swiss Childhood Cancer Registry (SCCR), the nested Swiss Childhood Cancer Survivor Study (SCCSS), and from medical records were used. The national, population-based SCCR registers all Swiss children and adolescents, who have been diagnosed with cancer since 1976 and below the age of 21 years. The SCCSS is a questionnaire-based survey including all ≥5-year survivors registered in the SCCR and incorporates a section on pulmonary health. For information on exact treatment exposure, HSCT, and pulmonary function test results, I searched the medical records of all eligible survivors in all Swiss Pediatric Oncology centers. To answer the question on pulmonary function trajectories, I could only rely on retrospectively collected data, which is subject to some unavoidable limitations. Therefore, the second aim of this PhD project was to set up the “Swiss Childhood Cancer Survivor Study - Follow-up”, a national, prospective, multicenter study to overcome the limitations of retrospective data collection in the future.

Four publications answer the main questions of my thesis. The following paragraphs summarize the methods used and the main findings of each publication.

Publication I: Transplant characteristics and self-reported pulmonary outcomes in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a cohort study (Chapter 4.1): I described changes in transplant characteristics in children and adolescents in Switzerland over the study period of 30 years. I compared self-reported pulmonary outcomes, including diseases and symptoms, in childhood cancer survivors exposed to HSCT to matched controls not exposed to HSCT by using data from the SCCSS. I additionally analyzed risk factors for pulmonary outcomes in the transplanted group. I collected the information on risk factors from the medical records. I could show that transplant characteristics changed over the study period with a reduced use of lung toxic treatment modalities, such as total body irradiation. Survivors exposed to HSCT reported pulmonary outcomes as frequent as not exposed survivors (20% versus 18%). Pneumonia was the most frequent pulmonary outcome in both groups. The risk factor analysis pointed to older age at diagnosis and thoracic surgery as possible risk factors for the reporting of pulmonary outcomes.

Publication II: Pulmonary function in long-term Swiss childhood cancer survivors after hematopoietic stem cell transplantation (Chapter 4.2) *(preliminary data as this manuscript was in progress)*: I described pulmonary function in childhood cancer survivors who survived ≥5 years from diagnosis and were treated with HSCT. I searched all available pulmonary function test results in the medical records of eligible survivors. I reported the longitudinal trajectory of six selected pulmonary function parameters (forced expiratory volume in first second [FEV1], functional vital capacity [FVC], total lung capacity [TLC], vital capacity [VC], diffusion capacity for carbon monoxide [DLCO], resistance). With the exception of resistance, I converted the parameters into age, height, weight, and sex standardized z-scores. I described the longitudinal trajectory of each of these six parameters and performed risk factor analysis with a multivariable linear regression model, taking time since cancer diagnosis and clustering per survivor into account. In this model each risk factor was described in relation to a male reference patient not exposed to any of the risk factors. I could show that the mean value of each of the six selected parameters was wavelike over the observed 15 years but did visually not show a prominent decrease or increase. In the regression model FEV1, FVC, and TLC decreased continuously with every additional year from cancer diagnosis in the male reference patient (FEV1 z-score -0.06 [95%CI -0.09 - -0.03], FVC -0.06 [95%CI -0.09- -0.02], TLC -0.092 [95%CI -0.22 – 0.04]). RV and DLCO showed a trend to increasing z-scores every year (RV z-score 0.11 [95%CI -0.02 - -0.23], DLCO 0.02 [95%CI -0.08 - 0.11]). Taking the risk factors into account, none had a significant

effect on the annual change of FEV1, FVC, and DLCO z-score. Allogeneic HSCT led to a significant annual increase in TLC z-score (0.216 [95%CI 0.059-0.373]) compared to autologous HSCT and relapse to a significant annual reduction in RV z-score (-0.231[95%CI -0.405 - -0.055]). The starting point of the regression line, corresponding to the time of diagnosis, was significantly lower for FEV1 z-score in case of female gender and radiotherapy (gender: p=0.013; radiotherapy: p=0.001) and for FVC z-score in case of radiotherapy (p<0.001). The starting point for TLC, RV, and DLCO z-scores were not significantly influenced by any risk factor.

Publication III: Lung function in Swiss childhood cancer survivors – a retrospective study (Chapter 4.3): I assessed changes in lung function trajectories in survivors exposed to known lung toxic chemotherapy or thoracic radiotherapy. I used the Global Lung Function Initiative 2012 reference values to calculate the z-score for FEV1, FVC, and DLCO and the reference equations by Stocks/Quanier to calculate TLC z-scores. Besides plotting the parameters for FEV1 and FVC over time, I used a linear mixed effects regression model with random intercept and random slope to take the effect of each individual risk factor on the changes of FEV1 and FVC and clustered by survivor into account. FEV1 and FVC z-scores did not prominently change over the observed time after first exposure to the lung toxic treatment. However, the median z-score was constantly below the expected. In the regression analysis I could show that treatment with thoracic surgery was associated with a lower FVC z-score at time zero (=first exposure; z-score -1.19 [95%CI -2.03 - -0.36]). None of the risk factor s had a significant effect on FEV1 z-score at time zero. The exposure to lung toxic chemotherapy led to a significant annual increase in FEV1 z-score (0.11 [95%CI 0.03 – 0.18]). None of the risk factiors was significantly associated with a change in the annual FVC z-score.

Publication IV: The Swiss Childhood Cancer Survivor Study – Follow-up (SCCSS-FollowUp) – Protocol of a prospective, national, multicenter cohort study (Chapter 4.4): Clinical data generated and collected prospectively and in a standardized way can facilitate current and future research in the field on late effects in childhood cancer survivors. Therefore, I have designed the SCCSS-FollowUp. The SCCSS-FollowUp has an umbrella-like design, under which various projects can be performed. The important key feature to fall under the umbrella of SCCSS-FollowUp is, that only data generated during regular follow-up care visits of childhood cancer survivors can be collected and reused for research. For this study proposal I have written the study protocol, the study information and informed consent in four versions (children, parents, adolescents, and adults) and in two languages (German and French). To start the project on pulmonary late effects as the first one, I have developed a lung-specific questionnaire in three versions (parents, adolescents, and adults) and a clinical report form for

clinicians. In addition, I have set up the RedCap database for the whole SCCSS-FollowUp project. All these steps are summarized in the manuscript of the study protocol and will be publicly available.

Within my PhD I could show that one fifths of ≥5-year childhood cancer survivors exposed to HSCT reported at least one pulmonary disease or symptom at a median of 10 years from diagnosis, with pneumonia being the most frequent. This proportion was the same as in survivors not exposed to HSCT. In this cohort of long-term survivors exposed to HSCT, FEV1, FVC, and TLC z-scores showed a slight decrease with every additional year from diagnosis. This constant decrease over time was modified by additional risk factors, which either aggravated or slowed down the annual deterioration. For survivors exposed to lung toxic chemotherapy or radiotherapy to the chest, the picture was very similar with a steady decrease for FEV1 and increase for FVC z-scores in the linear model. These changes were modified by additional factors, which finally led to an overall deterioiration or improvement over time. Both studies highlighted that deterioration in selected pulmonary function parameters was multifactorial, as some factors tended to contribute to an annual deterioration of z-scores, others to an improvement. For example FVC decreased by -0.058 z-scores per year, independent of the additional risk factors. Female gender mitigated this decrease. Female gender was associated with an annual improvement of 0.04 FVC z-scores compared to males. Relapsed disease on the other hand led do an annual decrease (-0.021). Finally, a female patient who suffered from relapsed disease would show an annual decrease of -0.039 in the FVC z-score. Taking into account that these survivors have many years of life ahead, even a small annual decrease becomes highly relevant. These annual changes in pulmonary function parameters in both cohorts highlight the importance of long-term follow-up care in survivors at risk. The important clinical questions on who is at risk and needs surveillance, with which surveillance modality, and at what frequency are not answered conclusively today. We have started answering these questions within the framework of the International Guideline Harmonization Group (IGHG) (see Chapter 5.4.2), where I am involved as a co-coordinator.

Content

Abbreviations

cGvHD	Chronic Graft versus Host Disease
CCS(s)	Childhood cancer survivor(s)
ChCR	Childhood Cancer Registry
CI	Confidence interval
CO	Carbon monoxide
DLCO	Diffusion Capacity of the lung for carbon monoxide
ECCS	European Community of Coal and Steel
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
Gy	Gray
HLA	Human Leukocyte Antigen
HSCT	Hematopoietic stem cell transplantation
ICCC-3	International Classification of Childhood Cancer, version 3
IGHG	International Guideline Harmonization Group
LTFU	Long-term Follow-up
OR	Odds ratio
RV	Residual volume
SCCR	Swiss Childhood Cancer Registry
SCCSS	Swiss Childhood Cancer Survivor Study
SCCSS-FollowUp	Swiss Childhood Cancer Survivor Study – Follow-up
SPOG	Swiss Pediatric Oncology Group
TBI	Total body irradiation
TLC	Total lung capacity
Tiffenau Index	Relative One-second-capacity (FEV1/FVC)
VC	Vital capacity

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Chapter 1 - Introduction

1.1 History of childhood cancer and situation in Switzerland

Cancer in childhood and adolescence is a rare diseases with differences in frequency and types of cancer depending on the geographical area (1). The annual incidence rate in children and adolescents aged 0-19 years is 186.6 per 1 million children per year in the US (2), 13.4 per 100'000 children aged 0-14 years per year in Europe (3), and 17.3 per 100'000 children aged 0-14 years in Switzerland. This leads to 250-300 children and adolescents under the age of 18 newly diagnosed with cancer in Switzerland per year (4).

The first step in the treatment of childhood cancer was surgery in the 1940s in children diagnosed with solid tumors. Local control improved through the addition of radiotherapy in the following years and decades. It was recognized that preoperative irradiation reduces the risk of tumor dissemination during surgery, but distant metastasis remained a major problem. A milestone in pediatric oncology was the discovery of the anti-leukemic effect of aminopterin, an antifolic agent, introduced by Dr. Sidney Farber in 1948 (5). Until that time the diagnosis of leukemia, first described in a child in 1860 by Michael Anton Biermer, was inevitable lethal (6). Farber's discovery led to high activity in the development of other antineoplastic drugs and their use in solid tumors and leukemias. The introduction of chemotherapeutic agents gave the possibility to treat the distant metastasis. In the following years and decades, oncologists also started using combinations of antineoplastic drugs and in the 1980s bone marrow transplantation became feasible in children.

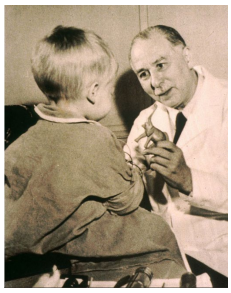


Figure 1: Dr. Sidney Farber (Photo from the National Institutes of Health)

Parallel to the progress in anti-cancer treatment, progress in supportive care contributed largely to increasing overall survival. Supportive care includes the management of anticipated toxicities, such as mesna for cyclophosphamide-toxicity to the urinary tract or folinic acid as rescue after high-dose methotrexate, management of emesis, management of pain during procedures, or antibacterial, antifungal, and antiviral prophylaxis in neutropenic patients.

From the very beginning it was evident, that treatment of pediatric cancer needs interdisciplinary care; in most cases neither the surgeon, the radiotherapist nor the oncologist alone can be successful. It was

also recognized that due to the rarity of pediatric cancer, relevant results and the required patient numbers can only be achieved through treatment within cooperative clinical trials internationally and at centers with experience.

Tumor-specific clinical trials/protocols guide oncologists through the whole cancer treatment. The protocols specify examinations and tests to confirm the diagnosis, to determine the extent of disease, to search for metastasis, and to assess organ function at baseline. This is followed by criteria to define the disease stage and to perform risk stratification. Then the protocol contains the detailed treatment plans for each risk group and time points and respective tests for the response assessment. Finally, the protocols also include a section on recommendations for follow-up care. These recommendations are normally outlined for 5-10 years following completen of treatment and mainly focus on relapsed disease or disease progression.

The improvements in diagnosing and treating childhood cancer and the management of toxicities has led to increased survival also in Swiss childhood cancer patients. One important reason might be, thet Switzerland, represented by the Swiss Pediatric Oncology Group (SPOG), also participates and treats children according to international treatment protocols. The 10-year survival rate over all diagnostic groups was 62% for patients diagnosed 1976 – 1988 and improved to 87% for those diagnosed 2009 – 2018 (**Figure 2**) (4). Even though the overall survival is high, it might be much lower for some diseases (e.g. DIPG or high-risk neuroblastoma) or even higher for others (e.g. standard-risk ALL, low grade glioma).

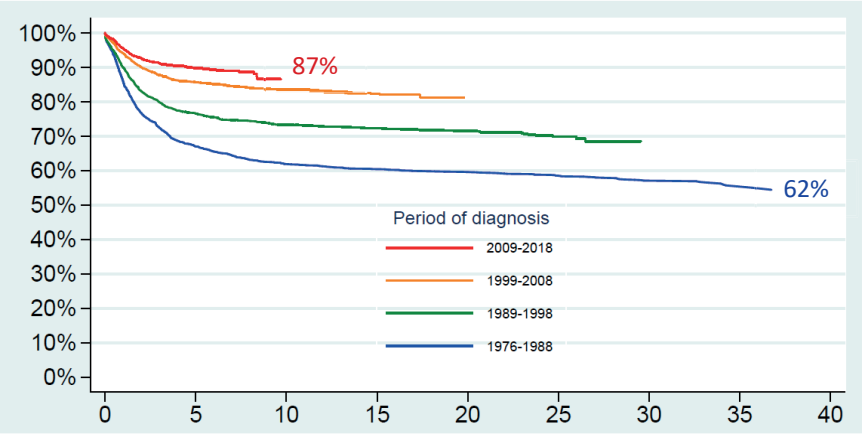


Figure 2: Survival of patients diagnosed at age 0-14 years and registered in the Childhood Cancer Registry, stratified by period of diagnosis (Figure adapted from SCCR Annual Report 2017/2018)

The treatment of children and adolescents diagnosed with cancer up to the age of 18 years takes place in one of nine pediatric oncology centers in Switzerland (Aarau, Basel, Bellinzona, Bern, Geneva, Lausanne, Lucerne, St. Gallen, Zurich).

1.2 Late effects in childhood cancer survivors

The term “childhood cancer survivor” (CCS) is used in most publications and research projects to describe former childhood cancer patients which are still alive five or more years after cancer diagnosis (7-9). This definition is also used in this thesis.

The term late effects refers to chronic medical conditions related to the cancer itself, its treatment, or treatment-related complications. Late effects can develop from acute toxicities or events during the treatment as chronification, or they develop newly years to decades after completion of treatment. Potentially every organ system can be affected by late effects and the severity range from asymptomatic and only detectable when specific tests are performed (e.g. pulmonary function testing, echocardiography, hormonal level in the blood) to mild, moderate, severe, life-threatening or even death (10, 11). The risk for each patient to develop late effects largely depends on the type of cancer, the age at diagnosis, and the treatment received, but also genetic factors or complications during the treatment are important factors.

The immense progress in pediatric oncology in the 1950s to 70s with rapidly rising survival rates, partly led to the motto "more treatment is better treatment". But Giulio d’Angio already raised concerns and worries about consequences and late effects of treatment given successfully to children and adolescents in 1974: ”It is clear that the child cured of cancer must be followed for life, no so much because late recurrence of disease is feared as to permit early detection of the delayed consequences of radio- and chemotherapy”. It is the non-targeted way of action of most chemotherapeutic agents and irradiation, which do not only destroy cancer cells but also cells of healthy tissue and thereby causes acute toxicities and late effects. In view of this, Giulio d’Angio stated that reduction of treatment intensity is necessary “to the minimum necessary to achieve cure” and that age, stage, site of origin, histologic type and grade have to be taken into account to stratify treatment intensity. Today, some of his considerations are reality:

- Where applicable, all treatment protocols include treatment stratification based on age, stage, biology and genetics, and treatment intensity varies by risk group.
- Randomized questions assess whether dose reduction of some chemotherapeutics is feasible without compromising the survival rate (e.g. randomization of 2 versus 4 doses of daunorubicine in AIEOP-BFM ALL 2009 trial).
- Most radiotherapeutic fields could be reduced and are more tailored to the initial tumor volume; in some cases irradiation can even be omitted completely (e.g. some low stages of Hodgkin’s lymphoma).

But even today we have room for improvement and Giulio d'Angios statement "**Cure is not enough**" is still valid. This is because many drugs inevitable to treat cancer in childhood are still the same as in the very beginning and the toxic effects of these substances to the healthy tissues remain. In addition, new therapeutic approaches, such as checkpoint inhibitors and other targeted therapies, can potentially lead to late effects of which we are not yet aware of. Chapter 1.4 focusses on the consequences of late effects and long-term follow-up care.

1.3 Pulmonary late effects in childhood cancer survivors

Pulmonary late effects in CCSs are multifactorial with involvement of different parts of the lung itself and adjacent structures. As the structures involved, also the manifestation of pulmonary late effects is heterogeneous ranging from asymptomatic pulmonary function impairment to clinical symptoms of various degrees, such as dyspnea at exertion or at rest or chronic cough. The following chapters summarize the factors and mechanisms leading to pulmonary late effects, its detection and clinical manifestation.

1.3.1 Anatomical structure of the lung

The smallest units of the air-filled parts of the lung are the alveoli. The alveoli are surrounded by capillaries of the pulmonary vascular system. The gas exchange, the vital function of the lung, takes place at the alveolar-capillary membrane: oxygen diffuses from the alveolar lumen into the blood and carbon monoxide diffuses back in the alveoli which can then be exhaled (**Figure 3**). The alveoli are connected to the trachea through ever-widening airways (bronichioli, bronchioles) (**Figure 4**). Damage to the alveolar-capillary membrane, the bronchioles, the pulmonary vascular system, and the connective tissue surrounding all these structures causes pulmonary function impairment.

In addition, decreased pulmonary function in CCSs may not only result from damage of the lung tissue itself, but also from osseous chest wall abnormalities or deformities of the thoracic spine. Osseous changes of the chest wall, for example after resection of multiple ribs, or thoracic spine deformity can lead to a stiffness and reduced volume of the thoracic cage or to scoliosis (12, 13).

1.3.2 Risk factors for pulmonary diseases

Several important treatment modalities known to be pulmonary toxic cannot be omitted in the treatment of childhood cancer. The treatment modalities best described and also include in long-term follow-up (LTFU) guidelines are the chemotherapeutic agents bleomycin, busulfan,

lomustine, and carmustine, radiation to the thorax, thoracic surgery and hematopoietic stem cell transplantation.

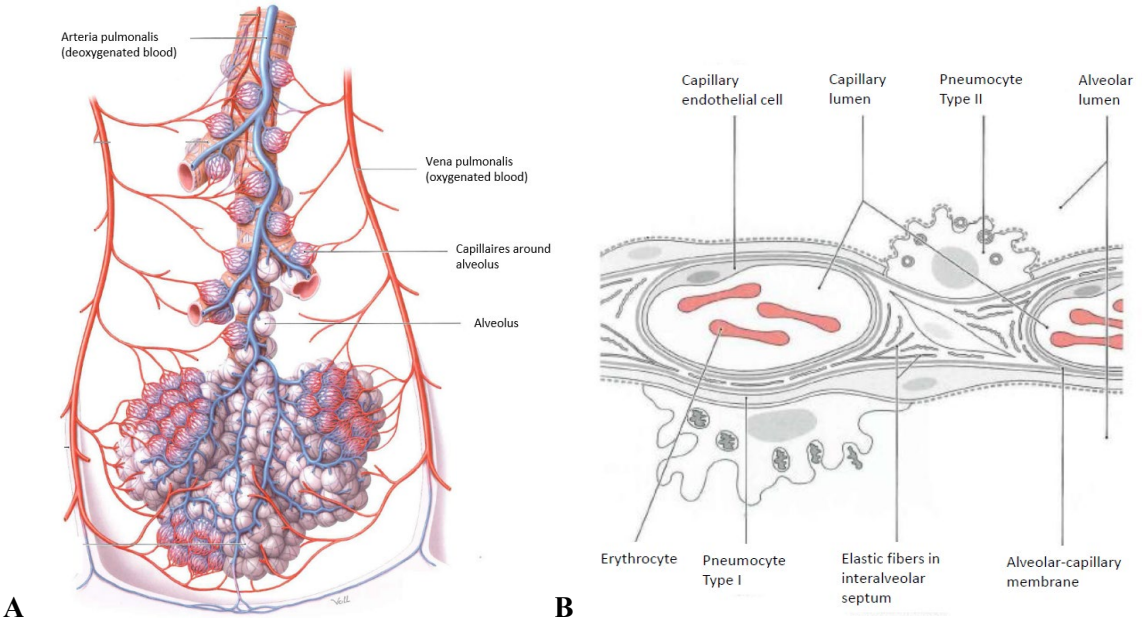


Figure 3: Structure of distal pulmonary vasculature and airways. A) Bronchiolus with vascular tree; oxygenated blood red, deoxygenated blood blue; B) Alveolar-capillary membrane and its structure with Pneumocyte I, Pneumocyte II, and capillary endothelial cells (Figure from Prometheus, LernAtlas der Anatomie, 2005).

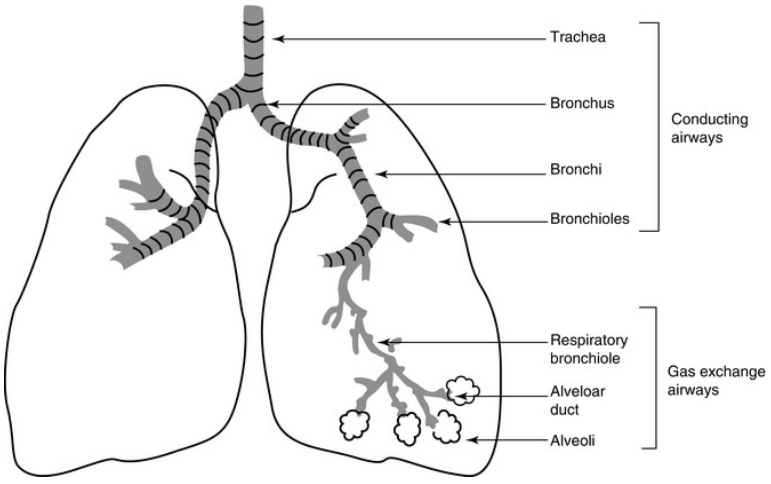


Figure 4: Structure of the bronchial tree (Figure from https://radiologykey.com).

1.3.2.1 Chemotherapeutic agents

Bleomycin

Bleomycin is a tumor-antibiotic and was an important component in the treatment of germ cell tumors and still is for relapsed or refractory Hodgkin's lymphoma. The lung toxicity of bleomycin results from a lack of the bleomycin-inactivating enzyme bleomycin hydrolase in the lung. This lack results in free radical formation and oxidative damage. Subsequent inflammatory processes lead to alveolar damage, hypersensitivity reaction, pneumonitis, and pulmonary fibrosis (14-16). The toxicity of bleomycin is dose dependent and more common with doses >400U/m2, which are rarely used in pediatrics (14, 17, 18). Simultaneous or subsequent radiotherapy to the lung, exposure to elevated oxygen concentrations, renal dysfunction, smoking, and higher age at treatment may exacerbate bleomycin toxicity (18). By knowing its pulmonary toxic effect, bleomycin could be reduced or even omitted for some indications during the last decades, such as in malignant germ cell tumors.

Busulfan

Busulfan is an alkylating agent mainly used in the conditioning of children and adolescents for autologous or allogeneic HSCT. The exact pathomechanism for pulmonary toxicity is unknown. It is unclear, whether a dose-response relationship exists in children. For adults it seems that cumulative doses lower than <500 mg do not cause pulmonary damage (14-16). In recent years, targeted dosing of busulfan has made it possible to individualize the absolute dose needed per patient. Dosing of busulfan is guided by a pharmacokinetic evaluation of the clearance and the resulting area under (AUC) the curve after the first dose. Patients with a fast clearance and a resulting lower AUC will receive a higher third dose than patients with a slow clearance. This allows to reduce toxicity while ensuring that patients receive the adequate busulfan dose to completely ablate the bone marrow.

Nitrosureas (Lomustine [CCNU], Carmustine [BCNU])

Nitrosureas are mainly used in the treatment brain tumors and to condition patients for autologous HSCT (BEAM conditioning). Nitrosureas predispose patients to the development of pneumonitis and pulmonary fibrosis (19, 20). Inflammatory reactions are the underlying mechanisms of nitrosurea-induced pulmonary fibrosis. The inflammation causes depletion of Type I pneumocytes and following hyperplasia of Type II pneumocytes, which results in increased collagen deposition in the lung. Higher cumulative doses are associated with increasing risk of lung injury and patients additionally exposed to thoracic irradiation may develop lung injury at lower doses of nitrosureas than non-exposed (14-16).

1.3.2.2 Radiotherapy to the chest

Pulmonary damage can result from direct irradiation of the lung or chest wall or from scattered radiation during radiotherapy applied to the abdomen or spine. The COG LTFU guidelines Version 4.0 defined the following fields as potential pulmonary toxic: subtotal lymphoid irradiation, axilla, chest (thorax), extended mantle, mantle, mini-mantle, mediastinal, whole lung, total body irradiation (TBI), and total lymphoid irradiation (**Figure 5**) (21).

The mechanism of pulmonary toxicity starts with DNA strand breaks due to ionizing radiation. These breaks initiate a cascade of inflammatory reactions, with subsequent capillary leaks and alveolar and interstitial exudate. These changes are reversible to a certain degree but later organize into collagen, leading to fibrosis. Clinically, radiation pneumonitis is the acute disease and progresses to fibrosis in most survivors (14, 15).

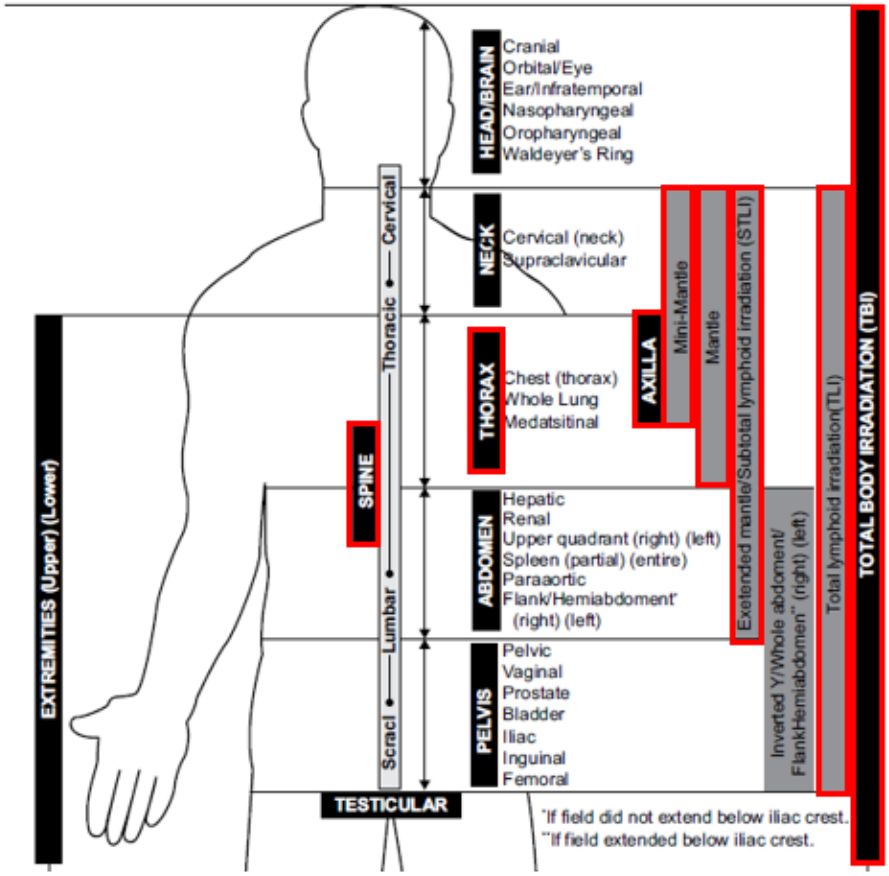


Figure 5: Radiation fields putting childhood cancer survivors at risk for pulmonary late effects (Figure from COG LTFU guidelines, v4.0)

Besides the radiation field, the irradiated volume, total dose, dose per fraction, source of radiation, and the additional application of radiosensiziter play important roles in the development and extent of pulmonary damage. The irradiation fields became smaller and more focused on the primary tumor site over the course of time. These changes are shown in **Figure 6** with the example of Hodgkin's lymphoma (22). Also radiation doses decreased over time. In earlier Hodgkin protocols, such as the HD82 protocol, the patients received 25-35 gray (Gy) involved field radiation. In the most recent protocol (EuroNet-PHL-C2), also used in Switzerland, the radiation dose depends on the treatment group and the response after the first two cycles of chemotherapy. In those with low-stage disease and good response, radiotherapy is replaced by an additional block of chemotherapy, whereas in the HD82 protocol even patients with low stage disease received irradiation with 35Gy. In the current protocol, patients with higher stage disease or inadequate first response to treatment either receive 20Gy or 30Gy depending on the second response assessment to chemotherapy. Even those with high risk disease and poor response to chemotherapy receive lower doses today than those treated in the 1980's. The aim of the EuroNET-PHL-C2 protocol is, that only 20% of patients will need radiotherapy.

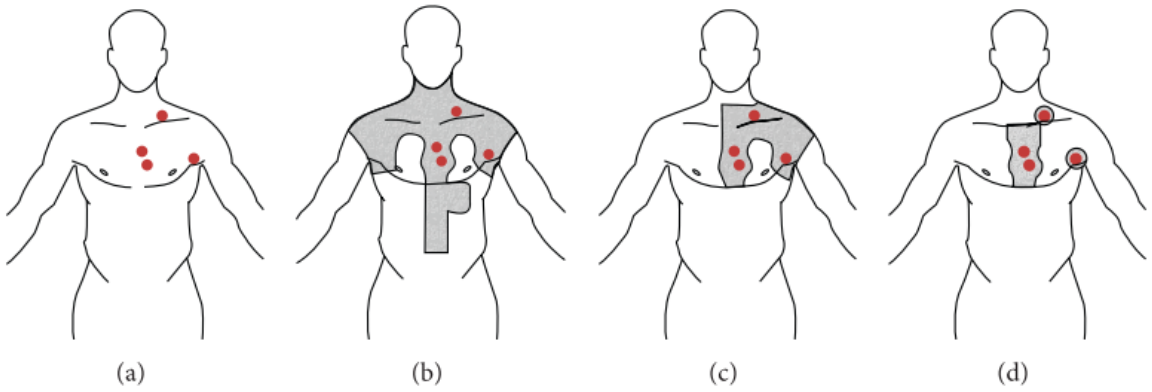


Figure 6: Changes in irradiation fields for a patient with Hodgkin lymphoma over time. Red dots represent involved lymph nodes, grey areas represent irradiated fields. (a) involved lymph nodes, (b) mantle field, (c) involved field radiation therapy, (d) involved nodal radiation therapy (Figure from Witkowska et al (22))

Using protons instead of photons may have an impact on pulmonary toxicity. Literature comparing both modalities in terms of pulmonary toxicity does not exist today. However, due to the physical properties of the protons, we can assume that they are less pulmonary toxic and cause less scattered radiation than photons. The most important general property of protons compared to photons is shown in **Figure 7**, where the radiation dose is shown on the y-axis and on the x-axis the depth in the water, representative for the body. The x-axis starts at zero, representing the surface of the water or the skin. In proton therapy, the peak of the proton beam is applied directly in the depth or at the tumor site respectively. The entry

dose is lower than in photon therapy and decelerates quicker behind the tumor, resulting in lower exit doses. In contrast, photon beam rises directly after entrance in the water or the body, and then declines exponentially as photons are absorbed. As tumor are not located at one single point, but have a given depth, the maximum dose range for proton irradiation must be expanded. This expansion is achieved through energy modulation, where the tumor is irradiated with different proton energies. The result of this energy modulation is a widening of the dose maximum at depth, which is called "spread out bragg peak" (SOBP).

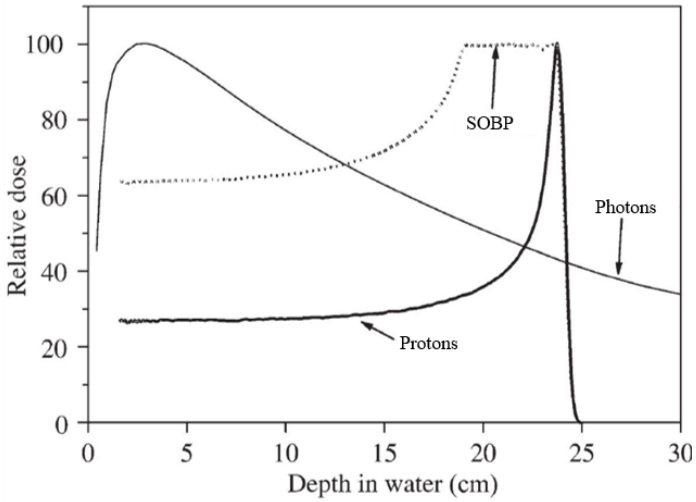


Figure 7: Depth-dose curve of photon and proton radiation. SOBP, spread-out Bragg peak (Adapted from Mohan et al. (23))

Protons can thus be better targeted on the tumor volume. **Figure 8** shows the example of craniospinal irradiation of a child with medulloblastoma. When using Intensity Modulated Radiation Therapy (IMRT) with photons, the lung is involved, which is not the case if protons are used (24). The target dose, 3600cGy in this example, corresponds to the yellow line and is reached through the whole target volume (=spinal axis). The scattered radiation, lower than 3600cGy, is also limited to the spinal axis for proton radiation but not for IMRT, where it involves part of the lung and heart.

1.3.2.3 Surgery of the lung and thorax

In the COG LTFU guidelines Version 4.0 the following procedures have been defined as risk factors: thoracotomy, pulmonary lobectomy, pulmonary metastasectomy, pulmonary wedge resection, chest wall surgery, and rib resection (21). Mechanisms leading to pulmonary dysfunction include reduction of lung volume, reduced volume of the thoracic cage or stiffness of the thoracic cage (14, 25).

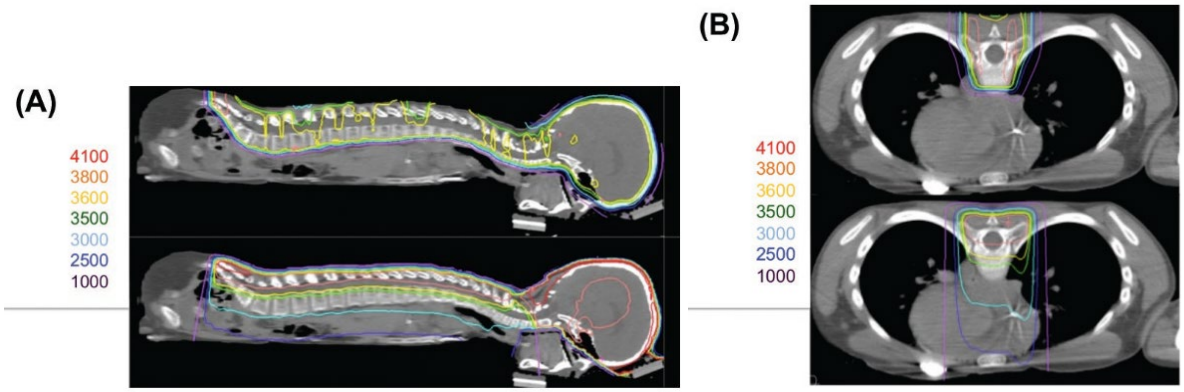


Figure 8: Comparison of proton radiation and Intensity Modulated Radiation Therapy (IMRT) with Photons. Sagittal (A) and axial (B) images with proton radiation in the upper image, IMRT in the bottom image. Doses in centiGray (cGy) listed to the left of each image (Figure Cotter at al. (24))

1.3.2.4 Hematopoietic stem cell transplantation (HSCT)

HSCT is divided into allogeneic and autologous. **Table 1** summarizes the most important features of both types and their differences. With some exception, allogeneic HSCT is not a first line treatment approach in pediatric oncology. Exceptions for allogeneic HSCT in the first line treatment are specific high riak and very-high risk acute lymphoblastic or acute myeloic leukemia and juvenile myelomonocytic leukemia (JMML). Allogeneic HSCT is most frequently indicated to treat refractory or relapsed leukemia. Autologous HSCT is included in the first line treatment of some high-risk diseases, such as high-risk neuroblastoma or high-risk sub-groups of medulloblastoma. Autologous HSCT is also a second line approach for refractory of relapsed solid tumors and lymphoma.

Table 1: Summary of differences between autologous and allogeneic hematopoietic stem cell transplantation

	Allogeneic HSCT	**Autologous HSCT**
Indications in oncology	Leukemia	Solid tumors (e.g. brain tumors, neuroblastoma), lymphoma
Aim	Replace patients bone marrow as the place of origin of the leukemic cells	Accelerate/ boost recovery of bone marrow which is depleted by high-dose chemotherapy needed to treat cancer outside of the bone marrow
Stem cell source	Stem cells of a (un-)related donor	Own stem cells
Risk of GvHD	Yes	Very rarely

Abbreviation: GvHD, graft versus host disease

Some pulmonary complications and late effects can occur more frequently in children and adolescents treated with HSCT, but are not unique to the HSCT population. Other late effects are transplant-specific. Infectious complications, such as pulmonary aspergillosis or CMV pneumonitis, are mainly caused by the prolonged period of aplasia and are not unique to HSCT patients. In contrast, non-infectious complications are generally transplant-specific, such as Bronchiolitis Obliterans Syndrome (BOS), diffuse alveolar hemorrhage (DAH), and idiopathic pneumonia syndrome (IPS) (26, 27). DAH and IPS typically present with an acute onset of respiratory failure within the first 1 to 4 months after HSCT and are associated with a high mortality. BOS is typically diagnosed >100 days after transplantation, has a variable clinical course, but most patients present with slowly progressive airflow obstruction. Stabilization or improvement of lung function in patients with BOS are rare. BOS is a form of pulmonary manifestation of graft versus host disease (GvHD). GvHD is an immunological condition in patients after allogeneic HSCT. The immune cells, transferred from the donor to the recipient during HSCT, recognize the recipients' cells as foreign and attack them. Acute GvHD (aGvHD) presents within the first 100 days after HSCT and chronic GvHD (cGvHD) after day 100 (28). Between 9 – 32% of children and adolescents develop cGvHD, which has a higher impact on the development of late effects than aGvHD (29-33).

1.3.3 Pathomechanism of pulmonary damage

Lung damage is caused by various pathomechanisms and different pulmonary structures can be affected (**Figure 9**). Diffuse damage to alveolar cells (pneumocyte I and II) causes inflammation and leads to thickening of the alveolar wall. Additional thickening is caused by the injured and desquamated cells and the deposition of lipoprotein material within the alveoli, which leads to the formation of hyaline membranes (26). These hyaline membranes are the underlying cause of alveolar proteinosis. Thickening of the alveolar wall goes in line with thickening of the alveolo-capillary membrane and causes impaired gas exchange. Triggers for diffuse alveolar damage are bleomycin and busulfan (15). Acute respiratory syndrome is the acute clinical picture of diffuse alveolar damage, characterized by diffusion capacity impairment.

Damage to the bronchial epithelium induces inflammatory processes, which lead to narrowing and obstruction of the small bronchioles and larger bronchi. Triggers for damage to the bronchial epithelium are bleomycin and radiation(15). The acute clinical manifestation is bronchiolitis obliterans–organizing pneumonia (BOOP) with shortness of breath and dyspnea (26, 27). Pulmonary function tests are characterized by diffusion capacity impairment and obstruction.

Damage of pulmonary vessels with resulting inflammation and intima-thickening leads to progressive obstruction of the small pulmonary arteries, capillaries, and venules. Trigger for damage to the vascular system are bleomycin, carmustine and lomustine (15). The acute clinical picture is pulmonary venoocclusive disease with diffusion capacity impairment, reduced oxygenation of the blood, and a

ventilation-perfusion mismatch.
Interstitial diseases are also caused by inflammatory processes. Proliferation of inflammatory cells cause a thickening and higher density of the interstitium. Interstitial pneumonitis is the acute manifestation, leading to diffusion impairment and ventilation inhomogeneity (15, 26). The triggers, underlying pathomechanisms and affected structures are listed here separately, but in most patients several structures are simultaneously affected to different degrees.

Independent of the exact structure affected and the trigger, inflammatory reactions represent the main underlying pathomechanism for acute lung damage. Most pulmonary late effects and chronic pulmonary damage, develop from remodeling of these acute processes. In a second stage of the inflammatory processes not only the inflammatory cells proliferate but also fibroblasts with subsequent production of collagen. Collagen deposition in the alveolo-capillary membrane aggravates diffusion impairment, its desposition in the bronchial and vascular wall leads to a fixation of the narrowing, and deposition in the interstitium causes a general stiffening of the lungs. In addition to collagen production and deposition, long-term pulmonary damage can be caused by remodeling of pulmonary cells. Damage to type I pneumocytes, which line the alveoli and build part of the alveolo-capillary membrane, leads to a hyperplasia of type II cells, which normally produce surfactant. This remodeling causes a reduction in the alveolar surface participating in the gas exchange.
Radiation to the lung harbors an additional pathomechanisms to the inflammatory processes: impaired chest wall growth. In addition, some experts suggest, that the cancer diagnosis and its treatment negatively affects lung development, similar to severe malnutrition. Prenatal malnutrition, resulting in low birth weight at term, leads to reduced lung function in infancy and childhood compared to children born with appropriate weight (34, 35). To be comaprabel with childhood cancer survivors, not prenatal malnutrition may be important but malnutrition at a later time in a child's life. This has been evaluated in two publications by Lelijveld et al, describing the "Chronic disease outcomes after severe acute malnutrition" (ChroSAM) cohort in Malawi. The authors could not show an association between severe acute malnutrition in children and subsequent reduced lung function compared to local controls.

This paragraph highlights that pulmonary function impairment in childhood cancer survivors is multifactorial, involves different structures, and even though a lot of research has been done, not all mechanisms and are well known today. The different risk factors with their resulting pulmonary diseases are summarized in **Table 2**. The list is not exhaustive, as some factors might be associated with different presentations.

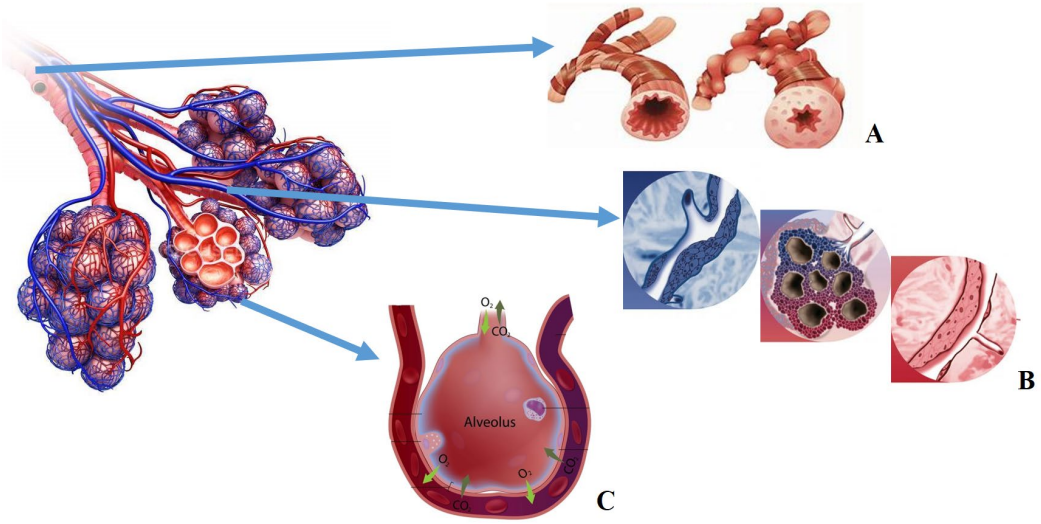


Figure 9: Illustration of the different pulmonary structures, whose damage can lead to pulmonary late effects: A) bronchioles and bronchi, B) vascular system, and C) alveoli

(Figure combined from different sources: https://www.pinterest.co.uk/pin/567523990533063737/, https://www.shutterstock.com/es/search/respiratory+membrane, https://erj.ersjournals.com/content/47/5/1518, https://www.normalbreathing.com/bronchoconstriction-natural-treat/)

Table 2: List of risk factors for pulmonary late effects and resulting diseases (Visscher et al (36))

Risk factors	Disease
Chemotherapy	
Bleomycin	• Acute respiratory distress syndrome • Interstitial or hypersensitivity pneumonitis • Bronchiolitis obliterans organizing pneumonia • Pulmonary veno-occlusive disease • Pulmonary fibrosis
Busulfan	• Acute respiratory distress syndrome • Alveolar proteinosis • Pulmonary fibrosis
Nitrosureas (Carmustine, Lomustine)	• Hypersensitivity pneumonitis • Alveolitis • Pulmonary veno-occlusive disease • Pulmonary fibrosis
Radiotherapy	• Bronchiolitis obliterans organizing pneumonia • Interstitial pneumonitis • Impaired chest wall growth • Pulmonary fibrosis
Surgery	• Restrictive lung function impairment • Scoliosis • Chest wall deformity

Continuation Table 2

Risk factors	Disease
Stem cell transplantation	
Lung toxic agents used for conditioning	See Busulfan and Nitrosureas
Transplant-specific non-infectious pulmonary complications	• Idiopathic pneumonia syndrome • Bronchiolitis obliterans syndrome • Bronchiolitis obliterans organizing pneumonia • Diffuse alveolar hemorrhage

1.3.4 Pulmonary dysfunction

Childhood cancer survivors can suffer from different types of pulmonary dysfunction. Pulmonary dysfunction can broadly be categorized in obstructive, restrictive, diffusion capacity impairment, and mixed forms, based on results from pulmonary function tests. The main pathophysiological characteristic of obstructive dysfunction is a narrowing of the airways, leading to a reduction of respiratory flow. The obstruction in CCSs can affect different areas of the bronchial system, such as more distal or more proximal parts. Thickening of the bronchial wall due to inflammatory processes or fibrotic narrowing are pathomechanisms underling airway obstruction. Restrictive dysfunction results from a reduced elasticity and expandability of the lung tissue itself or the adjacent structures, such as the chest wall. The mechanisms behind restrictive dysfunction in CCSs include fibrotic changes of the lung parenchyma or resection of larger parts of the chest wall. The underlying condition in diffusion capacity impairment is thickening of the alveolar-capillary membrane. Thickening can result from damage to the alveoli, to the capillaries or from deposition of fibrotic tissue in the space between alveoli and capillaries.

Besides describing pulmonary dysfunction in CCSs in terms of PFT results, it can also be described in terms of specific clinical diagnoses, such as bronchiolitis, bronchiolitis obliterans (BO), bronchiolitis obliterans organizing pneumonia (BOOP), idiopathic pulmonary syndrome (IPS), pulmonary fibrosis, or emphysema.

1.3.5 Methods to assess pulmonary function

Pulmonary late effects can lead to impairment in airflow, lung volume or gas exchange. Different test methods are available to objectify these impairments. This section focusses on spirometry, body plethysmography and measurement of diffusion capacity for carbon monoxide (DLCO), as these are the widely used test methods today, are recommended in long-term follow-up guidelines, and I used them for the publications included in this thesis.

Physiologic breathing and volumes assessed during respiratory cycle

Breathing leads to air flow by displacement of air in the lungs. Tidal volume (TV) is the normal volume of air moved between in-and expiration during quiet tidal breathing when no additional effort is applied (**Figure 10**). In the volume-time graph, the curve goes up with each inspiration and down with each expiration. The volume of air which remains in the lungs after each normal exhalation during quiet tidal breathing is the functional residual capacity (FRC). In forced breathing maneuvers additional volumes of air are moved between maximal in- and expiration. The volume which can maximally be exhaled after full inspiration is the forced vital capacity (FVC). Physiologically not all air can be exhaled and the remaining volume is the residual volume (RV). Finally, the total volume of the lungs, as the sum of the FVC and RV, is called the total lung capacity (TLC).

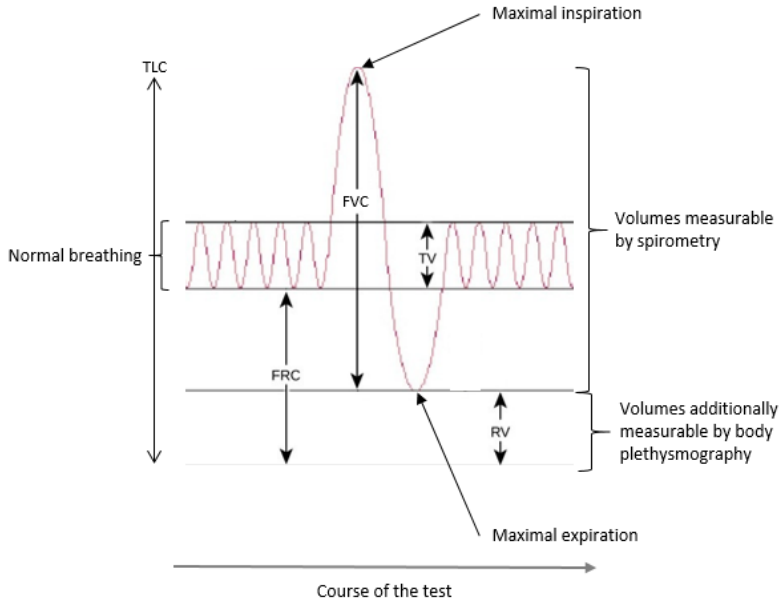


Figure 10: Volume-time graph with breathing patterns and respective volumes with five normal breaths followed by one maximum breathing maneuver and five normal breaths (Figure adapted from https://www.bromleyemergency.com/frcem-primary/core-physiology-can-measured-spirometry/)

Spirometry

Spirometry is widely used to record static and dynamic lung function parameters. Lung volumes that are not affected by air flow are termed static lung volumes, such as FVC or TV. Lung volumes that are affected by air flow are termed dynamic lung volumes and are measured during spirometry with a forced expiration, e.g. forced expiratory volume in one second [FEV1], which is measured exactly 1 second after starting forced exhalation. **Table 3** gives a brief summary on four important lung parameters that are assessed during spirometry. The spirometry results can be displayed in three different ways: 1) as

numerical output with absolute numbers, as percentage of predicted value (%pred), and as z-score (**Figure 11 a**), 2) graphically as volume-time-curve (**Figure 11 b**), or 3) graphically as flow-volume-curve (**Figure 11 c**) (37, 38).

Table 3: Explanation of important lung volumes assessed during spirometry

Parameter	Abbreviation	Explanation
Forced expiratory volume in one second	FEV1	Respiratory volume, which can be exhaled with force in the first second after maximum inspiration
Forced vital capacity	FVC	Respiratory volume, which can be maximally exhaled with force after complete inspiration
Relative one-second-capacity (Tiffenau-Index)	FEV1/FVC	FEV1 expressed in % of the FVC
Mid Forced Expiratory Flow Rates	$FEF_{25-75\%}$	Forced expiratory flow between 25% and 75% of the FVC

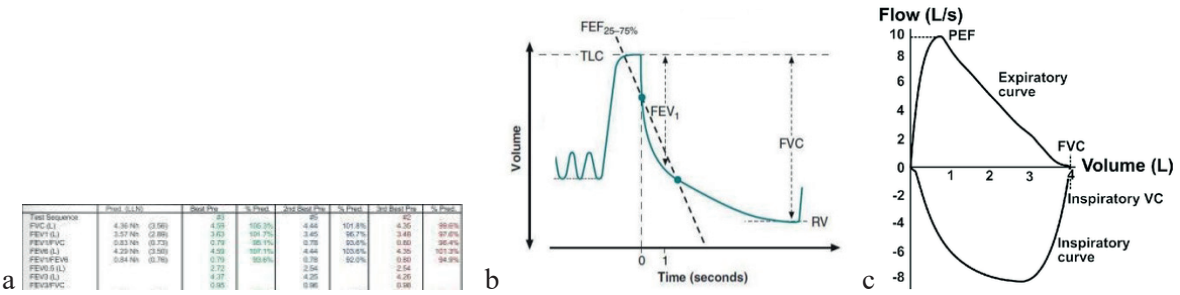


Figure 11: Display formats of spirometry; a) numerical output, b) volume-time-curve, c) flow-volume-curve (Figures adapted: https://www.researchgate.net/publication/233912835_Guideline_for_office_spirometry_in_adults_2012, https://www.slideshare.net/ashrafeladawy/spirometry-basics-2)

In the volume-time-curve, the x-axis represents the time in seconds and the y-axis represents the volume of air breathed in and out in liters. The curve in **Figure 11 b** starts with two normal breaths, followed by a maximal inspiration until TLC. This is followed by a maximal forced expiration until RV is reached. The curve runs out towards the end, as the respiratory flow and the exhaled volume per second decreases. The flow-volume-curve plots the in- and exhaled volume on the x-axis in relation to the flow of the volume shift on the y-axis. In this example, the person could breathe in 4 liters with a maximal flow of 10 liter per second. The shape of the flow-volume-curve is especially important to assess the quality of the test result (see Section 3.3.3).

To perform spirometry, patients have to breathe through a mouthpiece connected to a software, which measures the in- and exhaled flow and volumes (**Figure 12**). The tight mouth closure around the mouthpiece limits the use of spirometry in small children but also in persons with disabilities, hindering

them to seal the mouthpiece (neurological impairment, facial paralysis) (37-39). Spirometry can usually be performed in children aged 6 years and older.

Figure 12: Spirometer (Figure from https://www.paediatricpulmonologist.co.za/lung-function-test.php)

Body plethysmography

Body plethysmography allows a more detailed assessment of pulmonary function than spirometry alone. Body plethysmography provides additional information, especially concerning static lung volumes and capacities, such as RV and TLC. It additionally allows to determine airway resistance based on the relationship of the flow to volume displacement (**Figure 13**). Flow and oral pressure are plotted against displacement of volume. The shape of the curve allows statements on quality of the test and pulmonary dysfunction. The flow-volume curve provided by body plethysmography is identical to the one provided by spirometry (39, 40).

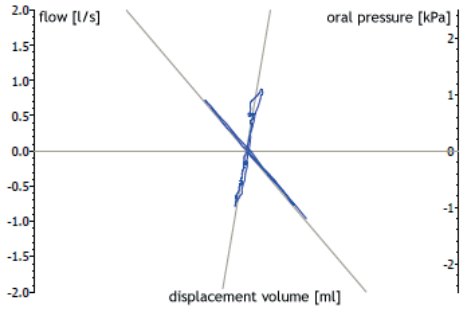


Figure 13: Flow-pressure-curve

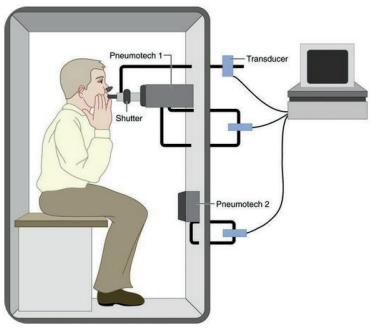


Figure 14: Body plethysmography

(Figures from http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/ and http://lungfunction.net/basics/body-plethysmography-flow-pressure-curve.htm)

For body plethysmography, the patients have to perform the breathing maneuvers in a sealed box with rigid walls (**Figure 14**). This setting allows to measure pressure changes in the box, which mirror the changes in the lung. The law of Boyle-Mariotte states that the product of pressure and volume stays constant for a gas. In other words, the pressure of a gas tends to increase as the volume of the box decreases. For body plethysmography, this means that during expiration the volume in the lung and the thoracic cage decreases and the volume in the box increases or is decompressed. This volume-shift in the box is measured during body plethysmography and allows to assess additional volumes which

cannot directly be measured. Compared to spirometry, body plethysmography is a more complex pulmonary function test which needs more time and might be more difficult in preschool children to perform.

Diffusion capacity for carbon monoxide (DLCO)

The diffusion capacity measures the ability of gas to diffuse from the air-filled alveoli into pulmonary capillaries. Carbon monoxide (CO) diffuses through the alveolar-capillary membrane in a very similar way as oxygen. As CO has a high affinity to hemoglobin and is simple to measure, it is used as a surrogate marker for the diffusion capacity of oxygen in the DLCO test.

DLCO measurement starts with normal breaths under room air, followed by a maximal expiration and a rapid and maximal inhalation. During rapid inhalation the test gas is switched on, consisting of carbon monoxide, a tracer gas (helium, methane or neon), and oxygen. After maximal inspiration the patient is asked to hold his breath for 10 seconds. Subsequently, the patient exhales completely and the exhaled gas is collected for analysis of the CO and tracer concentration. In case of diffusion capacity impairment less carbon monoxide can diffuse from the alveoli into the capillaries. This results in a higher concentration of test gas in the exhaled air than expected (39, 41).

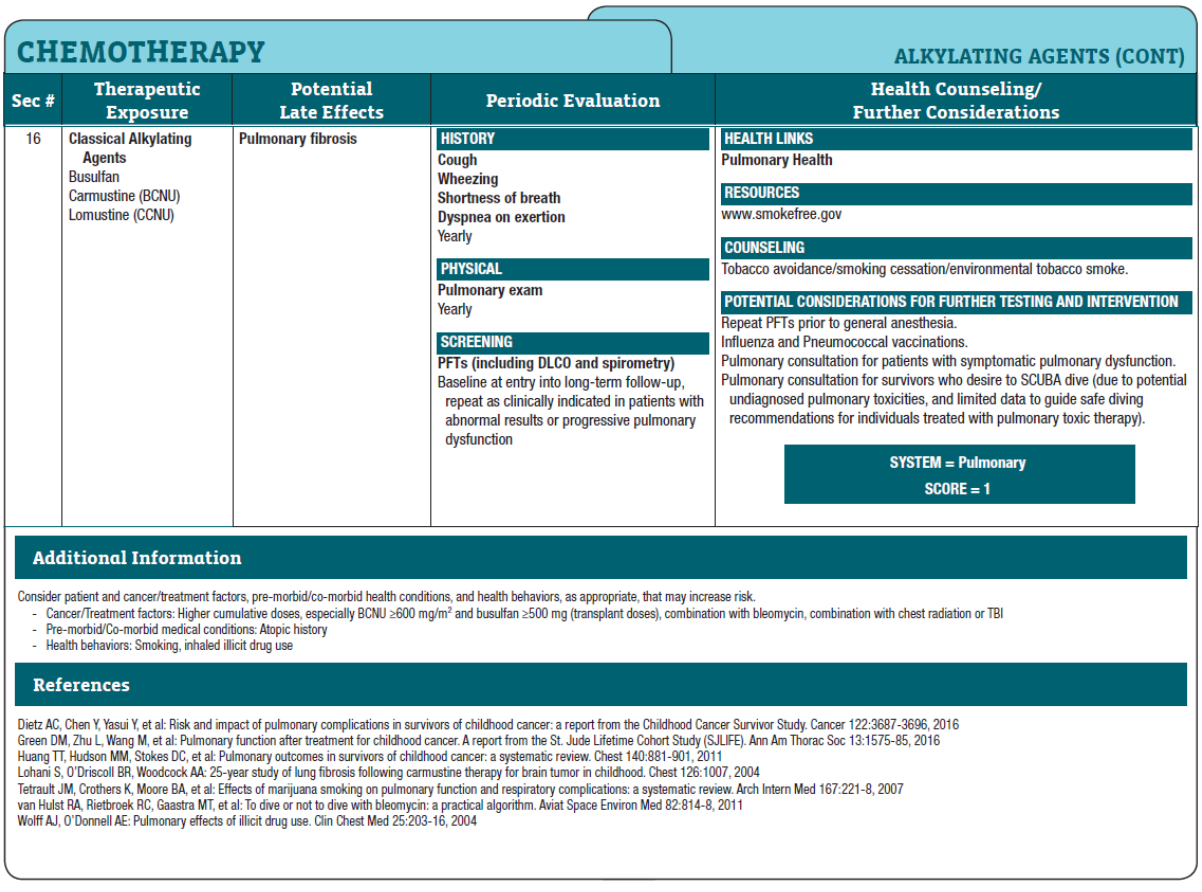
1.4 Aftercare in childhood cancer survivors

As recognized in 1975 by Giulio D'Angio, late effects play an important role in childhood cancer survivors (42). First recommendations for follow-up care were introduced in the treatment protocols and are still included today. However, these recommendations are rather general, do not differentiate between risk groups and treatment intensity within the same protocol, and are vague ten years and more after completion of treatment. In addition, these recommendations mainly focus on the detection and monitoring of acute toxicities and disease relapse rather than screening for late effects.

The increasing knowledge on late effects and the importance of long-term follow-up care led to the development and formulation of different national long-term follow-up (LTFU) care guidelines. The most comprehensive LTFU care guideline today is the one from the Children's Oncology Group (COG LTFU). It consists of a separate section for chemotherapeutic agents, radiotherapy, surgery, and HSCT. Each of these sections includes a separate summary for each potential late effect. **Figure 15** shows the example for pulmonary fibrosis in the context of exposure to chemotherapy. Each of these sections states the therapeutic exposure associated with the late effect, the recommended periodic evaluations and the test frequency. In September 2003, the first COG LTFU guidelines have been published; today the 5th version, updated in October 2018, is available (43). The COG LTFU guidelines are starting from

two years after completion of treatment onwards. Other national guidelines exist in the Netherlands or the United Kingdom (44, 45). Current international efforts aim to harmonize these different national guidelines within the International Guideline Harmonization Group (IGHG) (46). Switzerland does not have its own LTFU guideline, and the practice of using guidelines is heterogeneous (47, 48). Some clinics use the recommendations from the treatment protocols, others the recommendations by the German Pediatric Oncology-Hematology Group (GPOH), and about half of the clinics use the COG LTFU guidelines.

With today's knowledge, LTFU care is a continuous and life-long process for most childhood cancer survivors and continuation in adulthood is crucial. This transition into adult medicine needs to be well planned together with the survivors and it is not feasible without committed health care professionals in adult medicine (49). To keep survivors engaged in LTFU care, education of the survivors themselves but also of health care professionals is needed. A good balance must also be found between the frequency and intensity of screening and its benefits for the survivors. This is especially true for pulmonary dysfunction, as treatment options are still limited today (section 5.4.2).



CHEMOTHERAPY — ALKYLATING AGENTS (CONT)

Sec #	Therapeutic Exposure	Potential Late Effects	Periodic Evaluation	Health Counseling/ Further Considerations
16	**Classical Alkylating Agents** Busulfan Carmustine (BCNU) Lomustine (CCNU)	Pulmonary fibrosis	**HISTORY** Cough Wheezing Shortness of breath Dyspnea on exertion Yearly **PHYSICAL** Pulmonary exam Yearly **SCREENING** PFTs (including DLCO and spirometry) Baseline at entry into long-term follow-up, repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction	**HEALTH LINKS** Pulmonary Health **RESOURCES** www.smokefree.gov **COUNSELING** Tobacco avoidance/smoking cessation/environmental tobacco smoke. **POTENTIAL CONSIDERATIONS FOR FURTHER TESTING AND INTERVENTION** Repeat PFTs prior to general anesthesia. Influenza and Pneumococcal vaccinations. Pulmonary consultation for patients with symptomatic pulmonary dysfunction. Pulmonary consultation for survivors who desire to SCUBA dive (due to potential undiagnosed pulmonary toxicities, and limited data to guide safe diving recommendations for individuals treated with pulmonary toxic therapy). **SYSTEM = Pulmonary** **SCORE = 1**

Additional Information

Consider patient and cancer/treatment factors, pre-morbid/co-morbid health conditions, and health behaviors, as appropriate, that may increase risk.
- Cancer/Treatment factors: Higher cumulative doses, especially BCNU ≥600 mg/m^2 and busulfan ≥500 mg (transplant doses), combination with bleomycin, combination with chest radiation or TBI
- Pre-morbid/Co-morbid medical conditions: Atopic history
- Health behaviors: Smoking, inhaled illicit drug use

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Figure 15: Recommendations from the COG LTFU guidelines (version 5.0) to screen for pulmonary fibrosis after exposure to chemotherapy (43)

1.4.1 Pulmonary long-term follow-up (LTFU) care

Current LTFU care guidelines are in agreement, that children exposed to bleomycin, busulfan, nitrosureas (BCNU and CCNU), radiotherapy to the chest, and thoracic surgery need surveillance. The COG guidelines and the recommendations from the UK also include a separate section for survivors treated with hematopoietic stem cell transplantation. The recommendations however differ in depth and detail, as shown in **Table 4** for surveillance modality and frequency. Also recommendations on how to advice and counsel survivors differ (**Table 5**). This highlights that harmonization is needed.

Table 4: Recommended surveillance measurements and frequency by LTFU care guideline

Guideline	Measures	Frequency
COG	PFTs including DLCO and spirometry	Baseline at entry into long-term follow-up, repeat as clinically indicated in patients with abnormal results or progressive pulmonary dysfunction
DCOG	Flow-volume curve, diffusion capacity, lung volume (FVC and/or TLC by FV-curve and/or body pleth.)	5 and 10 years after diagnosis; if no abnormalities (>75% predicted), then stop
UK	Lung function test not specified	Perform baseline pulmonary function tests (PFTs) at end of treatment. If symptomatic or if abnormal PFTs (<2 SD below normal), repeat PFTs after 1 year and/or consider referral to Respiratory specialist.

Table 5: Recommended counseling for survivors at risk for pulmonary dysfunction by LTFU care guideline

Guideline	Counseling
COG	Counsel regarding tobacco avoidance/smoking cessation. Patients who desire to scuba dive should be advised to obtain medical clearance from a pulmonologist. In patients with abnormal PFTs, consider repeat evaluation prior to general anesthesia. Pulmonary consultation for symptomatic pulmonary dysfunction. Influenza and pneumococcal vaccines.
DCOG	Preventative measures (influenza vaccination, advice of career choice) if - FEV1%VC, TLC and/or TLCOc/VA < 75% predicted, or if these parameters have at least a 20% reduction from the baseline values. - Recurrent respiratory infections/ chronic cough occur If symptomatic consider referral to a pulmonologist. No exposure to FiO2>30% following bleomycine > 400 mg/m2 or demonstrated damage after bleomycine and/or radiotherapy to the thorax. This also applies to O2-inhalation in sports such as scuba-diving. Do not smoke.
UK	Advise patients and warn anaesthetists about previous bleomycin treatment. Consider pneumococcal immunisation and annual influenza immunisation in patients with established lung disease. Advise against smoking

Abbreviations: COG, children's oncology group; DCOG, Dutch children's oncology group; UK, United kingdom

Chapter 2 - Aims of this PhD Thesis

2.1 General aim

The general aim of this PhD thesis is to contribute to the growing knowledge on pulmonary late effects in childhood cancer survivors, especially in those treated with hematopoietic stem cell transplantation.

Aim I: Describe transplant characteristics and self-reported pulmonary diseases and symptoms in Swiss childhood cancer survivors after hematopoietic stem cell transplantation (HSCT)

- How did transplant characteristics change in the observed three decades, especially in relation to pulmonary toxic exposure? (Publication I, Chapter 4.1)
- Do childhood cancer survivors treated with HSCT report more often pulmonary diseases and symptoms than childhood cancer survivors not treated with HSCT? (Publication I, Chapter 4.1)
- What are the treatment related risk factors associated with the reporting of pulmonary diseases and symptoms in childhood cancer survivors treated with HSCT? (Publication I, Chapter 4.1)

Aim II: Describe the longitudinal course of pulmonary function in Swiss long-term childhood cancer survivors after hematopoietic stem cell transplantation (HSCT)

- How does the longitudinal course of selected pulmonary function parameters in Swiss long-term childhood cancer survivors treated with HSCT look like? (Publication II, Chapter 4.2)
- How do pulmonary function parameters obtained before transplantation differ from parameters obtained in the first two years after transplantation and in the years three to five after transplantation (analysis in sub-cohort) (Publication II, Chapter 4.2)
- How do pulmonary function parameters obtained in the first two years after transplantation differ from pulmonary function parameters obtained in the 3rd to 5th year and 6th to 10th year? (analysis in sub-cohort) (Publication II, Chapter 4.2)
- What are treatment related risk factors associated with changes in pulmonary function over time? (Publication II, Chapter 4.2)

Aim III: Describe pulmonary function in Swiss childhood cancer survivors after exposure to lung toxic treatment modalities

- How does the longitudinal course of pulmonary function in Swiss childhood cancer survivors exposed to pulmonary toxic chemotherapy or radiotherapy to the chest look like? (Publication III, Chapter 4.3)
- What are treatment related risk factors associated with changes in pulmonary function over time? (Publication III, Chapter 4.3)

Aim IV: Set up a national prospective cohort study to assess late effects in Swiss childhood cancer survivors, including pulmonary late effects

- Describe the setup and logistics behind a prospective national multicenter cohort study (Publication IV, Chapter 4.5)

2.2 Specific aims

2.2.1 Publication I: Transplant characteristics and self-reported pulmonary outcomes in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a cohort study

The burden of pulmonary symptoms and diseases, summarized as pulmonary outcomes, in Swiss childhood cancer survivors treated with HSCT was unknown. International literature on this topic has been sparse. Therefore, I aimed to describe self-reported pulmonary outcomes in Swiss childhood cancer survivors, who survived at least 5 years from diagnosis and were treated with HSCT. I compared their outcomes to CCSs not treated with HSCT and investigated the effect of treatment- and transplant-related risk factors on the reporting of pulmonary outcomes. I additionally aimed to describe changes in transplant characteristics and procedures over the observed period of three decades.

2.2.2 Publication II: Pulmonary function in long-term Swiss childhood cancer survivors after hematopoietic stem cell transplantation

Most studies describing the longitudinal course of pulmonary function in childhood cancer survivors treated with HSCT were single center studies and with a follow-up period less than 5 years. Therefore, I aimed to describe pulmonary function trajectories in a national sample of childhood cancer survivors who survived at least 5 years since diagnosis and have been treated with HSCT. I additionally aimed do analyze changes and differences in pulmonary function z-scores between given time spans and in two sub-cohorts. The first sub-cohort consisted of childhood cancer survivors with a baseline test performed before HSCT. In these survivors I aimed to analyze changes in z-scores between baseline and the first two years from transplantation and between baseline and more than two years from transplantation. The second sub-cohort consisted of childhood cancer survivors who had at least one test performed within the first two years after HSCT and at least one test in the following years. In this sub-cohort I aimed to analyze early versus late changes in pulmonary function z-scores. I additionally aimed to assess patient- and treatment-related factors which predict a change, either as improvement or deterioration, in pulmonary function with increasing time from cancer diagnosis.

2.2.3 Publication III: Lung function in Swiss childhood cancer survivors – a retrospective study

Pulmonary function trajectories in childhood cancer survivors are often described as percentage of predicted value (%pred), above or below a certain cutoff. Using %pred inevitably leads to the use different reference equations for children and adults. This can lead to abrupt changes in calculated %pred when survivors grew older and reference equations change from pediatric to adult. Therefore, I aimed to describe pulmonary function (FEV1, FVC, TLC, and DLCO) in childhood cancer survivors treated with pulmonary toxic chemotherapy or radiotherapy to the chest in terms of z-scores by using reference equations which cover all age categories. Additionally, I aimed to evaluate the effect of different risk factors on longitudinal changes in FEV1 and FVC in this population.

2.2.4 Publication IV: The Swiss Childhood Cancer Survivor Study – Follow-up (SCCSS-FollowUp) – Protocol of a prospective, national, multicenter cohort study

Many studies on late effects and organ function in childhood cancer survivors, including pulmonary function, obtained their outcome data retrospectively. This type of data collection is often associated with limitations and harbors the risk to introduce bias. Therefore, I have designed the set up of the Swiss Childhood Cancer Survivor Study – Follow-up (SCCSS-FollowUp) to overcome the limitations of retrospective data collection. The SCCSS-FollowUp is a prospective, national multicenter cohort study, tailored to all late effects in childhood cancer survivors of all age categoris with the aim to

1) collect medical data prospectively and repeatedly,
2) collect medical data produced during regular follow-up care visits in a standardized way,
3) acquire information on subjective symptoms (e.g. through questionnaire) in parallel with objectifiable test results, and
4) collect retrospectively all information of initial cancer diagnosis and its treatment.

Chapter 3 - Methods

3.1. Cohort description

For all publications and projects within this thesis, I used childhood cancer survivors from two cohorts: the Childhood Cancer Registry and the Swiss Childhood Cancer Survivor Study (SCCSS).

3.1.1 Childhood Cancer Registry

Before describing the characteristics of the Childhood Cancer Registry, I have to specify a legal aspect, as there was a relevant change during this PhD project, which also affected setting up the SCCSS-FollowUp study. Due to a change in law, the former Swiss Childhood Cancer Registry (SCCR) became a federal registry from January 1st 2020 onwards and is now called Childhood Cancer Registry (ChCR). Before January 1st 2020, the SCCR felt under the human research law (Humanforschungsgesetz, HFG) and was not under the supervision of a federal agency. From January 1st 2020 onwards the new ChCR falls under the cancer registration law (Krebsregistrierungsgesetzt, KRG) and newly belongs to the federal Office of Public Health. This change in legal affiliation and becoming a federal registry led to initial uncertainties, if informed consents and data collected under the HFG can still be used under the KRG. This was particularly relevant for SCCSS-FollowUp, as we need the contact information of patients who consented under the HFG to future use of their data and to be able to recruit them in the SCCSS-FollwoUp study. Mainly this aspect led to long delays in setting up the SCCSS-FollowUp and ethics approval is still pending. These changes in law did not affect the publications I-III, as they only relied on patients registered and data collected before January 1st 2020 and within the SCCR. Therefore, I will mainly use the term SCCR in this thesis.

The SCCR is a nationwide, population-based cancer registry including all Swiss children and adolescents who were diagnosed since 1976 and below the age of 21 years with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis (LCH). Diagnoses are classified according to the International Classification of Childhood Cancer, third edition (ICCC-3). The data collected in the SCCR include information on the cancer diagnosis, its treatment, long-term follow-up and patient`s personal data (50). By December 2019, the SCCR included 11’879 cancers in 11’722 children and adolescents.

3.1.2 Swiss Childhood Cancer Survivor Study (SCCSS)

The Swiss Childhood Cancer Survivor Study (SCCSS) is a long-term, questionnaire-based, national cohort study of childhood cancer survivors registered in the SCCR who have been diagnosed since 1976, have survived ≥ 5 years after initial diagnosis, and were alive at the time of study inclusion. The SCCSS questionnaire was sent to all eligible childhood cancer survivors in two waves: 2007 to 2013

and 2015 to 2017. For both waves the questionnaires were available in four versions (kids, parents, adolescents, and adults) and in three languages (German, French, Italian). For participants aged 5 to 15 years, the questionnaire was completed by their parents. Children aged between 8 and 15 years additionally completed a short questionnaire on their current well-being. Participants aged 16 to 19 years completed the version for adolescents and those aged ≥20 years received the adult version. The SCCSS aims to investigate physical and psychosocial health status and health behaviors in childhood cancer survivors. In addition, information on sociodemographic characteristics and cancer- and treatment related factors associated with health status or health behaviors is collected (9).

The Ethics Committee of the Canton of Bern approved the SCCR and SCCSS (KEK-BE: 166/2014). In addition, the SCCSS is registered at ClinicalTrials.gov (identifier: NCT03297034).

3.1.3 SCCSS-FollowUp

The Swiss Childhood Cancer Survivor Study Follow-up (SCCSS-FollowUp) is an extension of the SCCSS, which is questionnaire-based only. Every childhood cancer patient registered in the ChCR is eligible for SCCSS-FollowUp directly after completion of treatment. The recruitment however takes place in a project-specific approach. The SCCSS-FollowUp aims to collect medical data from regular follow-up care visits prospectively, repeatedly, and in a standardized way.

As the setup of this project is part of this thesis, it is described in more detail in chapter 4.4 and in the Appendix C.

3.2. Inclusion criteria for the publications in this thesis

Publication I: Transplant characteristics and self-reported pulmonary outcomes in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a cohort study

For this publication, all childhood cancer survivors who participated in the SCCSS, answered the questions on pulmonary diseases and symptoms, have been diagnosed with cancer between 1976 and 2010, and have been treated with autologous or allogeneic HSCT were eligible. For the matching process, I included participants of the SCCSS who fulfilled the same inclusion criteria but have not been treated with HSCT. I performed the matching by sex, diagnosis, age at diagnosis, and year of diagnosis. The age at diagnosis differed by ±2 years and the year of diagnosis by ±5 years between survivors treated with and without HSCT. With these ranges I targeted a 1:3 ratio.

Publication II: Pulmonary function in long-term Swiss childhood cancer survivors after hematopoietic stem cell transplantation

For this publication, the primary inclusion criteria were identical to the transplanted cohort from publication I. The additional inclusion criterion was, that at least two pulmonary function tests performed after the cancer diagnosis had to be available in the medical records.

Publication III: Lung function in Swiss childhood cancer survivors – a retrospective study

For this publication, I included all childhood cancer survivors registered in the SCCR, wo have been treated in one of the nine Swiss pediatric oncology centers up to the age of 16 years and were diagnosed between 1990 and 2013. In addition, they had to be exposed to at least one lung toxic chemotherapeutic agent or chest radiotherapy, had at least one pulmonary function test available in their medical records, and were aged ≥6 years when starting the study.

Publication IV: The Swiss Childhood Cancer Survivor Study – Follow-up (SCCSS-FollowUp) – Protocol of a prospective, national, multicenter cohort study

The manuscript for this publication is the study protocol for the SCCSS-FollowUp. Ethics approval was still pending. Therefore, I have not recruited any patients. In the future, this study will allow to include all childhood cancer patients as soon as they finished their cancer treatment. As the SCCSS-FollowUp has an umbrella-like design, the final inclusion criteria into SCCSS-FollowUp are given by the included projects.

3.3. Data collection

3.3.1 Questionnaire data (Publication I)

For the first publication on self-reported pulmonary health, I could use two questions from the SCCSS questionnaire. Both questions were asked in the questionnaires for parents, adolescents, and adults. One question asked about different pulmonary diseases and symptoms and one about smoking habits (Appendix A). All questionnaire data have been entered in a RedCap® database by previous PhD students and were available in four different data sets: one dataset with all questionnaire versions from wave 1 and three separate datasets for the parent, adolescent and adult versions from wave 2. To further analyze the data, I extracted the relevant questions from all four datasets, combined them, and harmonize the answers options. This harmonization into yes/no categories was necessary, as the answer options slightly differed between the parent and adolescent/ adult version of the questionnaire.

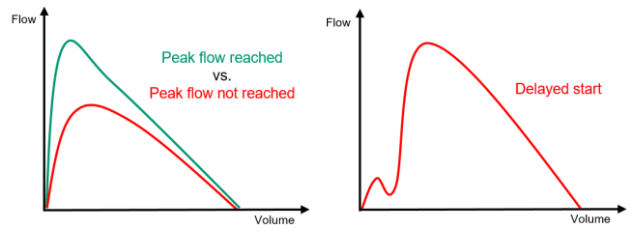
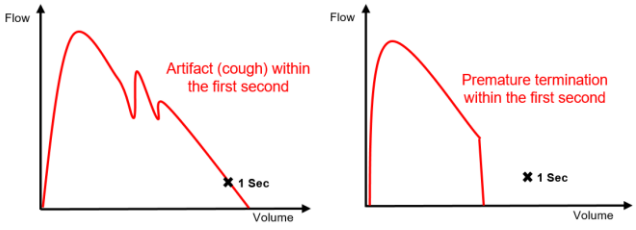
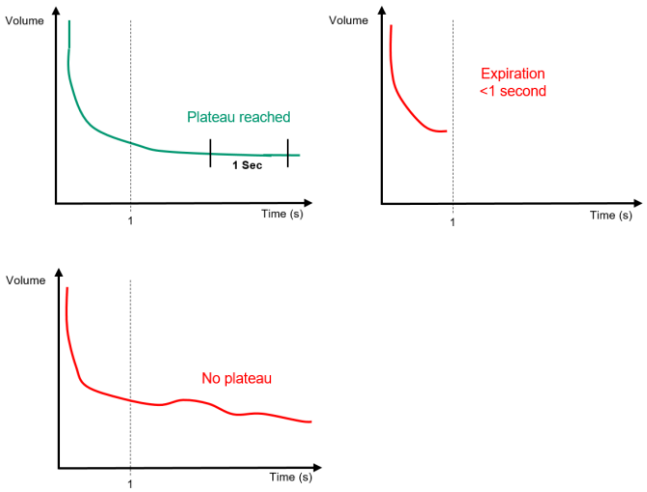
3.3.2 Medical data (Publication I, II, III)

Exact treatment exposure and information on hematopoietic stem cell transplantation is not registered in the SCCR. The protocol name is available from the SCCR for most patients, but often without the respective treatment arm. As treatment exposure is crucial in evaluating late effects in childhood cancer survivors, I organized a retrospective review of medical records for all eligible survivors in all nine pediatric oncology clinics. I searched the paper archives of the pediatric oncology departments and the separate transplant archives for children transplanted in Zurich and in the adult oncology department in Basel (in the past children were transplanted in the adult hospital). The records of pediatric oncology patients include all results of consults, including lung function tests and interpretation. For publications I and II, the data collection was done by myself. I have defined the information which needed to be extracted from the medical records in advance and compiled it in a data extraction sheet (Appendix B). I searched the whole medical record of each childhood cancer patient. For publication III, the search for medical data has been performed by a previous PhD student. The search startegies differed slightly, as the previous PhD student did not search the specific transplant archives in Zurich and Basel but searched the archives of the pediatric respiratory medicine departments.

3.3.3 Lung function data (Publication II, III)

I collected the pulmonary function test (PFT) results at the same time as I searched the medical data in the pediatric oncology clinics (Chapter 3.3.2). I collected all test results independent of their quality. In a following step I assessed pulmonary function quality of all collected PFTs. A master student supported me for this task. Prior to starting the assessment, I defined important quality criteria to be judged on during the quality assessment (**Table 6**). During the definition of quality criteria I was supported by a pediatric pulmonologist (Dr. Sophie Yammine from the division of pediatric pulmonology, university chilren's hospital Bern). The master student and I assessed the quality of each PFT independently. In case of different conclusions we discussed the PFT curves together. If we could not find a consensus we approached Dr. Sophie Yammine.

Table 6: Criteria included in the assessment of pulmonary function quality. Green curves correspond to good quality, red curves to bad quality

1. Start of breathing maneuver - Steep rise in the curve - Visually clear PEF reached - No delayed start	
2. Course of the curve - No glottis closure - No coughing - No premature termination - No obstruction of the mouthpiece - No leakage	
3. End of the forced expiration - Reaching of a plateau - No premature termination	

Medical records report pulmonary function test results as raw data and percentage of predicted (%predicted). The %predicted derives from the comparison of the expected value based on the age, gender, and height of patients and the effective test result. The reference equations used to calculate %predicted are often either for children (e.g. Zapletal) or adults only (e.g. the European Community of Coal and Steel equations), or do not cover younger children (51-53). The switch from pediatric to adult reference equation during adolescence can cause relevant changes in the %predicted. Also cutoff values used to define pulmonary dysfunction (e.g. DLCO <75 %predicted (54)) are not always applicable to children. As an example, children can physiologically breathe out a larger volume in the first second (FEV1) in relation to the FVC, compared to adults.

Using z-score instead of %predicted can overcome some of these limitations. As %predicted, z-scores are adjusted for age, gender, and height. Reference equations covering all age categories, from age 3 – 95 years, exist from the Global Lung Initiative (GLI) (55). The use of equations covering all age

categories, overcomes the "jump" in adolescents and young adults. Basically the z-score describes how many standard deviations a PFT result differs from the predicted. The predicted corresponds to the mean of the normally distributed pulmonary function parameter in the reference population. (**Figure 16**).

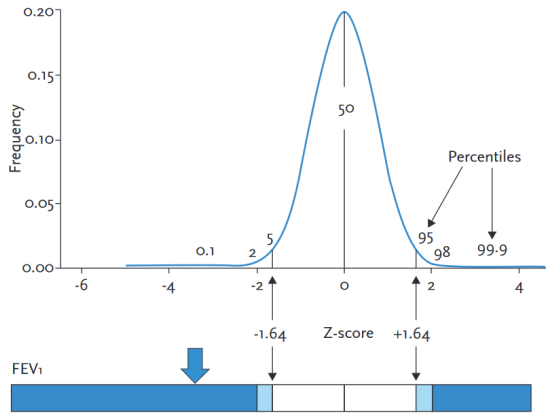


Figure 16: Illustration of the normal distribution of the FEV1 z-score and the respective percentile (https://breathe.ersjournals.com/content/breathe/9/6/462.full.pdf)

A z-score of zero corresponds to the mean value of the reference population. The z-scores of ±1,645 correspond to the 5th and 95th percentile. As a result, 90% of healthy subjects have a z-score within this range. Z-scores of ±1,645 are most frequently used to define pulmonary function parameters as abnormal. By expressing PFT results as z-scores, age-inapropriate cutoff values can be avoided.

Figure 17 summerizes the the cohorts and data sources used and the respective inclusion criteria for each of the four first-author publications and manuscripts of this thesis graphically.

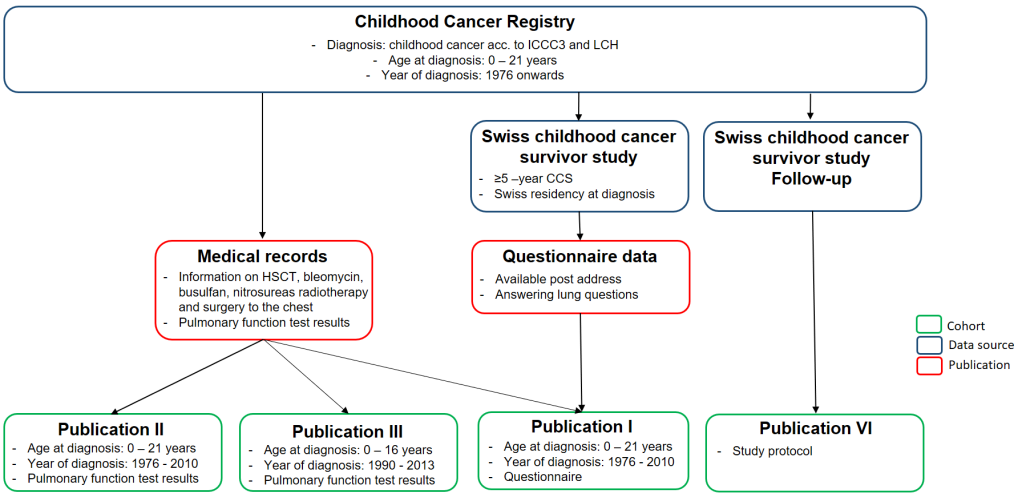


Figure 17: Cohorts and data sources used with their respective inclusion criteria for the first author publications of this thesis.

Chapter 4 – Results

4.1. Publication I

Transplant characteristics and self-reported pulmonary outcomes in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a cohort study

Original article

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Own contribution to the project: Concept and design of the study, organization and conduct of data collection, data analysis, interpretation of the results, writing manuscript with integration of co-authors comments, manuscript submission, point-by-point reply to peer reviewers

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ARTICLE

Transplant characteristics and self-reported pulmonary outcomes in Swiss childhood cancer survivors after hematopoietic stem cell transplantation—a cohort study

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Abstract

Childhood cancer survivors treated with hematopoietic stem cell transplantation are at high risk for pulmonary morbidity and mortality. In this retrospective study we described transplant characteristics of pediatric patients who underwent hematopoietic stem cell transplantation in Switzerland and how these characteristics changed over time, compared self-reported pulmonary outcomes between transplanted and non-transplanted survivors, and investigated risk factors for the reported pulmonary outcomes. As part of the population-based Swiss Childhood Cancer Survivor Study, we sent questionnaires to all ≥5-year childhood cancer survivors diagnosed 1976–2010 at age ≤20 years. We included 132 transplanted survivors and 368 matched non-transplanted survivors. During the study period transplant characteristics changed, with decreasing use of total body irradiation and increased use of peripheral blood stem cells and mismatched and unrelated donors as transplant source. One-fifth of transplanted survivors (20%, 95%CI 13–27%) and 18% of non-transplanted survivors (95%CI 13–21%) reported at least one pulmonary outcome. None of the analyzed factors was significantly associated with an increased risk of pulmonary outcomes in multivariable analysis. We found that pulmonary outcomes were frequently reported in transplanted and non-transplanted childhood cancer survivors, indicating a strong need for long-term pulmonary follow-up care.

Introduction

Hematopoietic stem cell transplantation (HSCT) is an effective but intensive treatment for childhood cancer. HSCT can be performed as allogeneic or autologous

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transplantation and is used either as first line or salvage treatment [1–4]. The history of allogeneic HSCT goes back to the 1980 s and indications, conditioning regimens, and donor sources have changed enormously since then [5, 6]. Pulmonary damage and late effects due to lung toxic treatments and complications prior to, during, or after transplantation can occur in childhood cancer survivors (CCS) [7–9]. Lung toxic treatments include the chemotherapeutics bleomycin, busulfan, carmustine (BCNU) or lomustine (CCNU), radiation involving the lung tissue, total body irradiation (TBI), and thoracic surgery [10–13]. Transplant-specific pulmonary complications include idiopathic pulmonary syndrome and complications from the spectrum of pulmonary graft versus host disease (GvHD), such as bronchiolitis obliterans or bronchiolitis obliterans organizing pneumonia [7, 14–16]. Severe pulmonary infections are additional complications due to long-lasting neutropenic episodes.

Pulmonary symptoms and diseases, summarized as pulmonary outcomes, are associated with high morbidity in survivors [17–19]. Cohort studies showed that survivors more often report pulmonary outcomes than siblings [20, 21]. To date, pulmonary outcomes in survivors after HSCT have only been reported by few single-center studies [22, 23]. Data based on national population-based assessments of pulmonary outcomes are lacking.

This nationwide retrospective study describes transplant characteristics, such as transplant indications and conditioning regimens, of pediatric patients who had HSCT in Switzerland and how these characteristics changed over time. Then, we compared self-reported pulmonary outcomes between transplanted and non-transplanted survivors and investigated risk factors for reporting pulmonary outcomes.

Methods

The Swiss Childhood Cancer Survivor Study

The Swiss Childhood Cancer Survivor Study (SCCSS) is a long-term national cohort study of all patients registered in the Swiss Childhood Cancer Registry (SCCR) who have been diagnosed since 1976, have survived ≥5 years after initial diagnosis, and were alive at the time of study inclusion [24]. The SCCR is a nationwide, population-based cancer registry including all patients diagnosed below age <21 years with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis [25]. From 2007 to 2017, we sent questionnaires to parents of children aged 5–15 years, adolescents aged 16–19 years, and adult CCS aged ≥20 years. The Ethics Committee of the Canton of Bern approved the SCCR and SCCSS (KEK-BE: 166/2014). The SCCSS is registered at ClinicalTrials.gov (identifier: NCT03297034).

Study population

We included all survivors who participated in the SCCSS and had been treated in a clinic affiliated to the Swiss Pediatric Oncology Group (SPOG) between 1976 and 2010. As the definition of 5-year survivors was based on the year of diagnosis and not the year of HSCT, some participants might have been transplanted <5 years before answering the questionnaire. As comparison group, we included survivors participating in the SCCSS who had not had a HSCT. Non-transplanted CCS were matched to transplanted CCS based on sex, diagnosis, age at diagnosis (range ± 2 years), and year of diagnosis (range ± 5 years) striving for a 1:3 ratio. Through this matching we wanted to achieve that CCS in both groups were as similar as possible in terms of sex, age at diagnosis and diagnosis, but did only differ by whether they had had HSCT or not. This matching did probably not eliminate all other differences between the groups since the reason for HSCT, such as high-risk status or relapse, already demands additional treatment for the HSCT patients.

Treatment and transplant characteristics

We collected treatment- and transplant-related characteristics of transplanted survivors from medical records. We calculated cumulative doses for eight known or suspected lung toxic agents: bleomycin, busulfan, carmustin (BCNU), cyclophosphamide, ifosfamide, lomustin (CCNU), melphalan, and thiotepa [11–13, 26]. We combined cumulative doses of alkylating agents (all chemotherapeutics except of bleomycin) by calculating the cyclophosphamide equivalent dose (CED) [27]. We categorized the cumulative CED as either lower/equal to or higher than 11,300 mg/m^2 with a median-split. We converted busulfan given orally to busulfan intravenously by multiplying it by factor 0.8 [28]. We categorized chest radiation as yes/no according to the Children's Oncology Group guidelines version 5.0 [13] and included irradiation of the upper abdomen. We recorded surgery to the thorax, lung, chest wall, mediastinum, and thoracic spine. Needle biopsies and implantation of venous devices were not coded as thoracic surgery. We collected date of transplantation, history of relapse, remission status, source of transplant, stem cell donor, cytomegalovirus (CMV) status, sex and blood group of donor and recipient, and information on graft versus host disease (GvHD). We categorized stem cell transplantation into autologous and allogeneic and further specified allogeneic transplantation into Human Leucocyte Antigen (HLA) matched (e.g., 12/12) and HLA-mismatched (e.g., 9/10) donors. As HLA

typing and documentation changed substantially in the last decades, it was not possible to assess exact HLA matching [29, 30]. We categorized GvHD into acute and chronic according to information from medical records.

Pulmonary outcomes

We collected information on pulmonary symptoms (chronic cough defined as ≥3 months) and diseases (pneumonia in last 2 years, lung fibrosis, emphysema, or chest wall abnormality) from the SCCSS questionnaires. We categorized the different pulmonary outcomes as yes/no (present/absent) variables. In addition to answering the questions, participants could describe other problems as free text. Responses we could not assign to one of the existing categories were coded as "other pulmonary problem". We had ≤5% missings on pulmonary outcomes except for pneumonia (6% missings). We allocated missing information to "not having the pulmonary outcome" assuming that survivors would mention pulmonary outcomes if they were clinically significant.

Clinical and lifestyle characteristics

We extracted the following clinical characteristics from the SCCR: sex, age at diagnosis, year of diagnosis, and cancer diagnoses according to the International Classification of Childhood Cancer, 3rd edition [31]. For analyses, we used the following four diagnostic categories: leukemia, where patients with relapsed and refractory disease often receive allogeneic HSCT, lymphoma, and neuroblastoma, where autologous HSCT is used for relapsed or high-risk disease, and other diagnoses, where HSCT is used less frequently. For lifestyle characteristics we extracted smoking status from the questionnaires (Supplementary Explanation E1).

Statistical analysis

We used descriptive statistics to describe sociodemographic, lifestyle, and clinical characteristics of transplanted and non-transplanted CCS. To assess trends in transplant characteristics across transplant eras we used the "nptrend" command in STATA software [32]. We compared the prevalence of pulmonary outcomes between transplanted and non-transplanted CCS using chi-square tests. We used logistic regression and likelihood ratio tests to quantify associations between sociodemographic, lifestyle, clinical, and transplant-related variables and pulmonary outcomes in transplanted CCS. We retained variables with a p value ≤ 0.1 in the univariable analysis for inclusion into the multivariable model and included radiotherapy as a priori confounder according to the literature. We compared sociodemographic and clinical characteristics of transplanted CCS who did or did not respond to the questionnaire by using chi-square tests and student's t-tests. We used STATA software (Version 16.0, Stata Corporation, Austin, TX) to analyze the data.

Results

Characteristics of study population

We included 132 transplanted and 368 matched non-transplanted CCS (Supplementary Figs. F1 and F2). Transplanted responders and non-responders did not differ in sociodemographic, lifestyle, and clinical characteristics (Supplementary Table S1). The median age of transplanted CCS was 6.5 years (interquartile range, IQR 2.9–11.6 years) at cancer diagnosis and 8.8 years (IQR 4.8–13.6) at transplantation. Median follow-up time was 9.8 years (IQR 7.2–15.9). Leukemia was the most frequent cancer diagnosis (55%), followed by lymphoma (15%), and neuroblastoma (14%) (Table 1).

Transplant characteristics and change over time

The absolute number of transplanted CCS who participated in the SCCSS increased over time. Leukemia remained the most common underlying cancer diagnosis in all three eras (Table 2). Conditioning regimens changed with a relative but non-significant reduction in TBI-containing regimens from 61% in the first to 39% in the other two eras (p for trend = 0.083). Among chemotherapeutics, the proportion of CCS who received ifosfamide increased ($p = 0.002$) but the median cumulative dose decreased non-significantly ($p = 0.477$). Also cyclophosphamide dosage decreased ($p < 0.001$) with no significant reduction in the proportion of CCS receiving it ($p = 0.186$). For bleomycin there was a trend towards lower cumulative doses in more recent eras ($p = 0.094$). Two-thirds (65%) of CCS had radiotherapy involving the thorax with no significant change over time, and 9% had thoracic surgery with a trend to an increasing proportion of CCS in more recent years. Nearly half of transplanted CCS received autologous HSCT (46%) and in 57% HSCT was performed in first remission or refractory disease. The proportion of transplanted CCS receiving peripheral blood stem cells increased from 27% to 71% with a corresponding reduction in the proportion of those receiving bone marrow stem cells (p for trend <0.001). Eight CCS developed chronic GvHD (cGvHD) but none had pulmonary GvHD (Supplementary Table S2). Supplementary Tables S2 and S3 provide summaries of clinical, treatment, and transplant characteristics for CCS transplanted in autologous or allogeneic settings, stratified by era of transplantation. Differences in CCS exposed to allogeneic or autologous HSCT are shown in Supplementary Table S4.

Table 1 Characteristics of transplanted ($N = 132$) and non-transplanted ($N = 368$) childhood cancer survivors, matched by sex, age at diagnosis, diagnosis, and year of diagnosis (1:3 ratio).

	Transplanted CCS ($n = 132$) *n* (%)	Non-transplanted CCS ($n = 368$) *n* (%)
Sociodemographic and lifestyle characteristics		
Sex, male	69 (52)	195 (53)
Age at questionnaire, median years (IQR)	18.4 (13.8–22.9)	18.5 (13.6–23.8)
Smoking status[a]		
Active smoking	7 (5)	27 (7)
Passive smoking	63 (48)	163 (44)
Former active smoking	9 (6)	20 (6)
Never smoking	54 (41)	158 (43)
Clinical characteristics		
Age at diagnosis, median years (IQR)	6.5 (2.9–11.6)	6.4 (2.7–11.4)
Age at transplantation, median years (IQR)	8.8 (4.8–13.6)	NA
Follow-up time[b], median years (IQR)	9.8 (7.2–15.9)	10.1 (7.9–15.1)
Era of diagnosis		
1976–1995	40 (30)	120 (33)
1996–2005	60 (45)	156 (42)
2006–2010	32 (25)	92 (25)
Childhood cancer diagnosis according to ICCC-3		
I: Leukemia	72 (55)	214 (58)
II: Lymphoma	20 (15)	60 (16)
IV: Neuroblastoma	19 (14)	44 (12)
Other[c]	21 (16)	50 (14)

CCS childhood cancer survivors, *ICCC-3* International Classification of Childhood Cancer, 3rd edition, *IQR* interquartile range.

[a]"Active" and "former active smoking" assessed in adolescents and adults; "passive smoking" in children corresponds to having parents who currently smoke or formerly smoked, "never smoking" in children corresponds to having both parents who never smoked.

[b]Time from first diagnosis until date of answering the questionnaire.

[c]Other tumors in transplanted survivors include: tumors of the central nervous system ($n = 6$), retinoblastoma ($n = 1$), malignant bone tumors ($n = 7$), soft tissue sarcomas ($n = 4$), malignant germ cell tumors ($n = 3$) Other tumors in non-transplanted survivors include: tumors of the central nervous system ($n = 12$), retinoblastoma ($n = 1$), malignant bone tumors ($n = 9$), soft tissue sarcomas ($n = 4$), malignant germ cell tumors ($n = 3$).

Prevalence of pulmonary outcomes

Any pulmonary outcome was reported as often in transplanted (20%) as in non-transplanted CCS (18%; $p = 0.507$). The occurrence of the listed pulmonary outcomes was not significantly different between transplanted and non-transplanted CCS. Pneumonia was the most frequently reported outcome (Fig. 1). The proportion of transplanted CCS reporting any pulmonary outcome did not change by era of transplantation (Table 2).

Risk factors for pulmonary outcomes

In univariable logistic regression analysis, we found associations between older age at cancer diagnosis (increase per year; odds ratio [OR] 1.2, 95% confidence interval [CI] 1.05–1.28), exposure to bleomycin (OR 4.63, 95%CI 1.08–19.97), and thoracic surgery (OR 7.44, 95%CI 2.13–25.92) with any pulmonary outcome (Table 3). We found no significant association with era of diagnosis, treatment with other chemotherapeutics, median CED, and thoracic radiotherapy, but numbers were small. Transplant-related factors were also not significantly associated with reporting of pulmonary outcomes (Table 3). In multivariable logistic regression analysis, the effect of thoracic surgery was reduced to an OR of 3.91 (95%CI 0.95–16.02), suggesting that it has been confounded by other factors related to disease and treatment (Table 4). Most of the 12 CCS treated with thoracic surgery have been diagnosed with Ewing sarcoma ($n = 7$) or lymphoma ($n = 4$). All except one CCS have been transplanted autologous, most suffered from relapsed disease ($n = 10$), received radiotherapy to the chest ($n = 10$), were treated with open thoracic surgeries ($n = 9$), received at least one lung toxic chemotherapeutic agent ($n = 7$), or have been exposed to a combination of radiotherapy and thoracic surgery or resection of lung tissue ($n = 9$) (Supplementary Table S5).

Discussion

This nationwide population-based cohort study found that transplant characteristics changed over time with fewer HSCT recipients receiving TBI or lung toxic chemotherapeutics. One-fifth of ≥5-year CCS reported at least one pulmonary outcome 10 years after cancer diagnosis irrespective of whether they had been transplanted or not. Our analyses point to older age at diagnosis and thoracic surgery as possible risk factors for self-reported pulmonary outcomes.

TBI is a crucial component of conditioning regimens for allogeneic HSCT, but known to be lung toxic. Even though TBI cannot completely be replaced by chemotherapy, such as in acute lymphoblastic leukemia [33], we found that the use of TBI has become less common in more recent eras. There was a non-significant trend towards lower cumulative doses of bleomycin and we found no evidence for a change in cumulative doses of carmustine, but numbers were small. The increasing use of peripheral blood stem cells in more recent eras is in line with literature [34–36] and the

Table 2 Characteristics of transplanted childhood cancer survivors ($N = 132$) stratified by era of transplantation.

	Total ($n = 132$)	1976–1995 ($n = 33$)	1996–2005 ($n = 51$)	2006–2015 ($n = 48$)	p value*
	n (%)	n (%)	n (%)	n (%)	
Clinical characteristics					
Cancer diagnosis according to ICCC-3					0.806
I: Leukemia	72 (55)	18 (55)	26 (51)	28 (58)	
II: Lymphoma	20 (15)	8 (24)	7 (14)	5 (10)	
IV: Neuroblastoma	19 (14)	5 (15)	8 (16)	6 (13)	
Other[a]	21 (16)	2 (6)	10 (19)	9 (19)	
Treatment characteristics					
Conditioning containing TBI	59 (45)	20 (61)	20 (39)	19 (39)	0.083
Conditioning regimens					0.003
TBI + cyclophosphamide ± others	34 (26)	16 (48)	12 (23)	6 (13)	
TBI + others	25 (19)	4 (12)	8 (16)	13 (27)	
Busulfan + cyclophosphamide ± other	28 (21)	7 (21)	11 (21)	10 (21)	
Busulfan ± others	8 (6)	1 (3)	4 (8)	3 (6)	
Carmustine ± others	9 (7)	3 (9)	3 (6)	3 (6)	
Cyclophosphamide ± others	9 (7)	1 (3)	6 (12)	2 (4)	
Melphalan ± carboplatin ± others	19 (14)	1 (3)	7 (14)	11 (23)	
Chemotherapeutic agents					
Alkylating agents combined[b]	131 (99)	33 (100)	50 (98)	48 (100)	
Busulfan	37 (28)	9 (27)	16 (31)	12 (25)	0.776
Carmustine	9 (7)	4 (12)	3 (6)	2 (4)	0.180
Cyclophosphamide	123 (93)	33 (100)	46 (90)	44 (92)	0.186
Ifosfamide	62 (47)	9 (27)	23 (45)	30 (63)	0.002
Lomustine	2 (2)	1 (3)	-	1 (2)	0.835
Melphalan	44 (33)	9 (27)	17 (33)	18 (38)	0.342
Thiotepa	14 (11)	3 (9)	8 (16)	3 (6)	0.563
Bleomycin	8 (6)	3 (9)	3 (6)	2 (4)	0.371
Chemotherapeutic agents, mg/m^2 (IQR)					
Alkylating agents combined[b]	11329 (5687–17164)	11658 (7924–17391)	11367 (5879–21425)	8546 (4447–16131)	0.199
Busulfan	443 (324–480)	480 (470–587)	344 (297–480)	440 (374–449)	0.021
Carmustine	300 (298–300)	300 (298–351)	300 (298–300)	300 (291–306)	0.737
Cyclophosphamide	4200 (3021–7535)	7299 (4200–8684)	4247 (3090–8230)	3439 (2634–5258)	<0.001
Ifosfamide	9941 (4032–22500)	11500 (5200–16032)	10227 (4032–22500)	8181 (4017–19767)	0.477
Lomustine	395 (190–600)	190	–	600	0.317
Melphalan	140 (139–169)	140 (140–142)	140 (140–140)	140 (139–180)	0.739
Thiotepa	680 (588–900)	750 (168–900)	749 (591–900)	610 (307–900)	0.921
Bleomycin	40 (40–46)	42 (40–80)	40 (40–50)	30 (20–40)	0.094

Table 2 (continued)

	Total ($n = 132$) n (%)	1976–1995 ($n = 33$) n (%)	1996–2005 ($n = 51$) n (%)	2006–2015 ($n = 48$) n (%)	p value*
Radiotherapy involving the thorax[c]	86 (65)	25 (76)	32 (63)	29 (60)	0.175
Thoracic surgery[d]	12 (9)	1 (3)	5 (10)	6 (13)	0.157
Transplant characteristics					
Remission status at transplantation					0.906
First remission	75 (57)	16 (48)	35 (69)	24 (50)	
Relapsed disease	57 (43)	17 (52)	16 (31)	24 (50)	
Stem cell donor					0.098
Autologous	61 (46)	17 (52)	25 (49)	19 (39)	
HLA identical sibling / HLA matched (un-) relative donor	56 (42)	16 (48)	19 (37)	21 (44)	
HLA mismatch (un-) related /haploidentical	15 (11)	0	7 (14)	8 (17)	
Source of transplant					<0.001
Cord blood	6 (5)	–	1 (2)	5 (10)	
Peripheral blood	75 (57)	9 (27)	32 (63)	34 (71)	
Bone marrow	46 (35)	22 (67)	17 (33)	7 (15)	
Unknown	5 (4)	2 (6)	1 (2)	2 (4)	
Pulmonary outcome	26 (20)	7 (21)	11 (22)	8 (17)	0.582

HLA human leukocyte antigen, *ICCC-3* International Classification of Childhood Cancer, 3rd edition, *IQR* interquartile range, *N* number, *TBI* total body irradiation.

*p value for trend.

[a]Other tumors include: tumors of the central nervous system ($n = 6$), retinoblastoma ($n = 1$), malignant bone tumors ($n = 7$), soft tissue sarcoma ($n = 4$), malignant germ cell tumors ($n = 3$).

[b]Combination according to Cyclophosphamide Equivalent Dose (CED) [27].

[c]Thoracic radiation fields according to COG guidelines, Version 4.0, Oct 2018, including radiation to the chest, whole lung, mediastinum, (mini-) mantle field, TBI and additionally upper abdomen and thoracic spine, including craniospinal irradiation.

[d]Thoracic surgery according to COG guidelines, Version 4.0, Oct 2018, including thoracotomy, chest wall surgery, rib resection, lobectomy, pulmonary metastasectomy and wedge resection.

increasing use of mismatched (un-) related donors reflects the overall progress in HSCT over time.

The proportion of transplanted CCS reporting any pulmonary outcome did not change during the three HSCT eras. Studies that compared self-reported pulmonary outcomes in transplanted CCS are few. Fanfulla et al. examined children during the first 18 months after allogeneic HSCT [22]. Cough was reported by 15–25% of children and pneumonia was diagnosed in the first 6 months in 19% of children. The occurrence of pneumonia in the first 6 months, is indicative of delayed immune reconstitution rather than late pulmonary outcomes. Since the follow-up (18 months) is shorter than in our population (10 years) direct comparison is difficult. Also in the entire cohort of Swiss CCS ($N = 1\ 894$) pneumonia was the most frequently reported pulmonary outcome (10%), and pulmonary fibrosis (0.8%) and emphysema (0.2%) were reported by few CCS [20]. CCS in the North American Childhood Cancer Survivor Study showed a different distribution of pulmonary outcomes with chronic cough being the most frequent outcome (7.8%), followed by pulmonary fibrosis (1.9%), and recurrent pneumonia (1.7%) [21]. We found no difference in the prevalence of pulmonary outcomes between transplanted and non-transplanted CCS in our study (20% vs. 18%). This could be explained by the high proportion of leukemia (58%) and lymphoma (16%) diagnoses in non-transplanted CCS due to the matching. A Danish cohort study included 94 leukemia survivors a median of 10 years from diagnosis, treated with chemotherapy only, and 11% suffered from pulmonary problems, mainly cough [37]. A

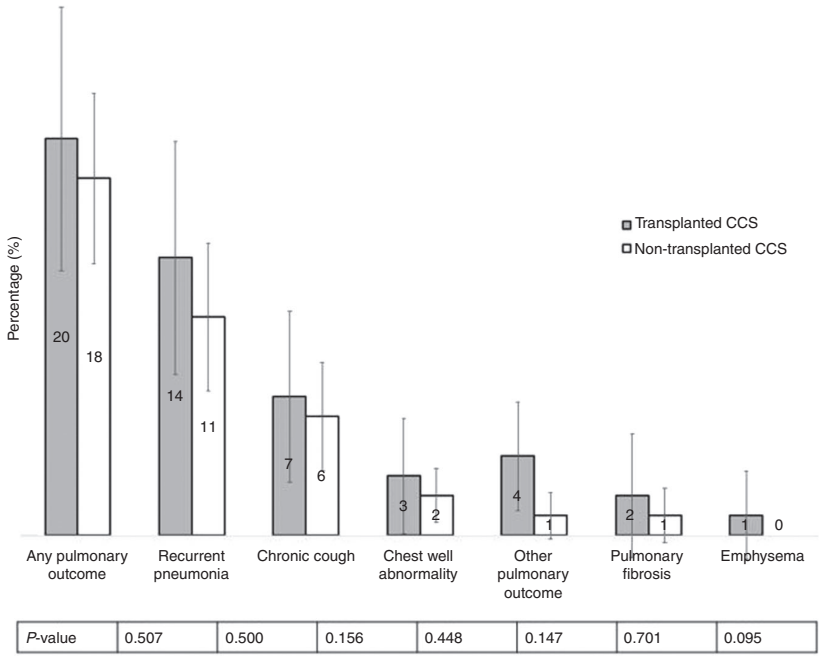

Fig. 1 Prevalence of self-reported pulmonary diseases and symptoms in transplanted ($N = 132$) and non-transplanted matched childhood cancer survivors ($N = 368$). Error bars represent 95% confidence intervals. *P* value comparing prevalence between transplanted and non-transplanted survivors. *Total N reduced for pulmonary fibrosis and emphysema because question only asked in adolescents and adults: $N = 85$ transplanted survivors, $N = 195$ non-transplanted survivors. ** "Other pulmonary outcome" includes reduced lung function ($n = 3$) and pulmonary GvHD ($n = 1$).

US study including Hodgkin's lymphoma survivors treated with chest radiation but without HSCT showed that 17% had at least one episode of pneumonia and 9% reported dyspnea [38].

CCS who had undergone thoracic surgery in addition to HSCT reported more pulmonary outcomes than those without thoracic surgery. This might be because this group of CCS had received more often thoracic radiotherapy or lung toxic chemotherapeutics, had more often been diagnosed with relapsed disease, and underwent open thoracic surgeries in most cases, which goes along with a more intensive treatment. Residual confounding by these additional lung toxic treatment modalities probably leads to an overestimation of the association between thoracic surgery and pulmonary outcomes. Older age at diagnosis, resulting in older age at HSCT, was another risk factor for pulmonary outcomes in univariable analysis. No study has assessed self-reported pulmonary outcomes in the context of age at HSCT, but four studies showed an association between older age at HSCT and deterioration in selected pulmonary function parameters [23, 39–41]. In multivariable analysis, bleomycin was not a risk factor for pulmonary outcomes anymore, which is in line with findings from the whole Swiss CCS cohort [20]. In our cohort, we found no significant effect of other selected chemotherapeutics and transplant-related factors on the reporting of pulmonary outcomes. All studies that evaluated the impact of cGvHD on the lung, used pulmonary function tests as outcome measure [41–44]. They reported a negative effect of cGvHD on pulmonary function. We explain the missing effect of cGvHD, lomustine, and carmustine by the low number of survivors exposed to each of these factors. Also some CCS with severe pulmonary cGvHD might have died before receiving the SCCSS questionnaire and missing or non-detailed documentation in the medical records might have led to an underestimation of the effect of cGvHD on pulmonary outcomes.

We found no difference in pulmonary outcomes between CCS treated with autologous and allogeneic HSCT. Thoracic surgery was overrepresented in the autologous group because of the underlying diagnoses, mainly bone tumors. In contrast, CCS treated with allogeneic HSCT were more often exposed to chest radiotherapy, which can lead to radiation pneumonitis and an increased risk of interstitial pneumonitis due to infections such as CMV. Both factors have not been assessed in detail.

The strengths of this study include the population-based national design of the SCCSS, the high response rate of transplanted CCS (71%), and the comparability between responding and nonresponding transplanted survivors. This makes us confident, that our results can be extrapolated to ≥5-year Swiss survivors who underwent HSCT. In addition, the completeness of exact treatment exposure, including cumulative doses of chemotherapeutics and detailed information on HSCT in transplanted CCS is another strength.

The reliance on self-reported outcome data is a limitation and our study did not include objective pulmonary function

Table 3 Association between sociodemographic, clinical, treatment, and transplant characteristics on self-reported pulmonary outcomes.

	Reporting of any pulmonary outcome					
	$n_{outcome}$	N_{total}	%	OR	95% CI	p value*
Sociodemographic and lifestyle characteristics						
Sex						0.795
Male	13	69	19	1		
Female	13	63	21	1.12	0.47–2.64	
Age at questionnaire, continuous (years)	26	132	20	1.05	0.99–1.11	0.088
Smoking status[a]						0.924
Never smoking	12	60	20	1		
Passive smoking	10	56	18	0.87	0.34–2.21	
Former active smoking	2	9	22	1.14	0.21–6.21	
Active smoking	2	7	29	1.60	0.27–9.28	
Clinical characteristics						
Age at diagnosis, continuous (years)	26	132	20	1.2	1.05–1.28	0.002
Follow-up time, continuous (years)	26	132	20	0.98	0.91–1.06	0.613
Era of diagnosis						0.800
1976–1990	5	20	25	1		
1991–2000	8	45	18	0.64	0.18–2.31	
2001–2010	13	67	19	0.72	0.22–2.35	
Cancer diagnosis according to ICCC-3						0.271
Leukemia	15	72	21	1		
Lymphoma	5	20	25	1.27	0.39–4.04	
Neuroblastoma	1	19	5	0.21	0.03–1.71	
Other[b]	5	21	24	1.18	0.37–3.76	
Treatment characteristics						
Bleomycin						0.040
No	22	124	18	1		
Yes	4	8	50	4.63	1.08–19.97	
Busulfan						0.190
No	16	95	17	1		
Yes	10	37	27	1.83	0.74–4.51	
Nitrosureas (BCNU and CCNU)						0.107
No	22	122	18	1		
Yes	4	10	40	3.03	0.79–11.65	
Cyclophosphamide						0.844
No	2	9	22	1		
Yes	24	123	20	0.84	0.16–4.34	
Ifosfamide						0.596
No	15	70	21	1		
Yes	11	62	18	0.79	0.33–1.88	
Melphalan						0.281
No	15	88	17	1		
Yes	11	44	25	1.62	0.67–3.91	
Treosulfan						0.400
No	24	126	19	1		
Yes	2	6	33	2.12	0.36–12.28	
Alkylating agents[c]						0.084
≤11,300 mg/m^2	9	66	14	1		
>11,300 mg/m^2	17	66	26	2.19	0.89–5.37	
Radiotherapy to chest (including TBI)						0.165
No	6	46	13	1		
Yes	20	86	23	2.02	0.75–5.45	
Thoracic surgery						<0.001
No	19	120	16	1		
Yes	7	12	58	7.44	2.13–25.92	

Table 3 (continued)

	Reporting of any pulmonary outcome					
	$n_{outcome}$	N_{total}	%	OR	95% CI	*p* value*
Transplant characteristics						
Remission status at transplantation						0.223
First remission/primary refractory	12	75	16	1		
Relapsed disease	14	57	24	1.71	0.72–4.05	
Type of transplantation						0.995
Allogeneic	14	71	20	1		
Autologous	12	61	20	0.99	0.42–2.35	
Stem cell donor						0.739
Autologous	12	61	20	1		
HLA ident. sibling, matched (un)related donor	11	56	20	0.99	0.40–2.48	
HLA mismatched (un)related, haploidentical	3	15	20	1.02	0.25–4.19	
Source of transplant ($n = 66$)[d]						0.933
Bone marrow	7	34	21	1		
Peripheral blood	6	26	23	1.15	0.34–3.98	
Cord blood	1	6	17	0.77	0.08–7.71	
Graft versus host disease ($n = 71$)[d]						0.449
No	4	15	27	1		
Yes	10	56	18	0.59	0.16–2.27	

Results from univariable logistic regression analysis. $N = 132$, median age at study 18.4 years.

BCNU Lomustine, *CCNU* Carmustine, *HLA* human leukocyte antigen, *ICCC-3* International Classification of Childhood Cancer, 3rd edition, *OR* Odds ratio, *TBI* total body irradiation, *CI* confidence interval.

*p value calculate by logistic regression (Wald test) for continuous and binary independent variables and by likelihood ratio test for independent variables with >2 categories.

[a]Active and former active smoking assessed in adolescents and adults. Passive and never smoking assessed in children, adolescent and adults.

[b]Other diagnostic groups include: malignant bone tumors ($n = 7$), tumors of the central nervous system ($n = 6$), soft tissue sarcomas ($n = 4$), germ cell tumors ($n = 3$), retinoblastoma ($n = 1$).

[c]Cumulative alkylating dose according to cyclophosphamide equivalent dose (CED); categorized in smaller or equal to the median or larger as the median cumulative dose.

[d]In survivors undergone allogeneic transplantation only.

tests. CCS treated with open thoracic surgery are reminded by the scar of their history and thus may be more sensitive in dealing with their lung health, and may remember and report pulmonary outcomes better. However, Louie et al. reported a high agreement between self-reported pulmonary outcomes, such as chronic cough, pulmonary fibrosis, and emphysema, and their validation by extractions from medical records (sensitivity 96.2%; specificity 90.8%) [45]. The SCCSS has not been designed for survivors after HSCT specifically, neither for the assessment of pulmonary outcomes only and did not include specific questions on exertion-induced dyspnea or effort intolerance. This might have led to underreporting of pulmonary outcomes in our study. Also "pneumonia" might have been misunderstood by lay persons, as it was not defined in the questionnaire. Survival bias due to inclusion of ≥5-year survivors could have led to underestimation of pulmonary outcomes as more severely affected patients might have died. The small number of transplanted CCS who have been exposed to specific chemotherapeutics and transplant-related exposures did not allow for a multivariable analysis of all exposures in a single model. Also the detailed information on treatment exposures, such as cumulative doses, was only available for transplanted CCS. Finally, the absolute numbers of CCS reporting pulmonary outcomes was small, because the study population was young with a relatively short follow-up time, and the incidence of pulmonary outcomes increases over lifetime [20, 21, 39, 46].

In summary, we found that one-fifth of CCS, including those who underwent HSCT and matched controls, developed long-term pulmonary outcomes. As we only assessed self-reported outcomes, using a limited number of questions, this proportion probably only represents the tip of the iceberg. This underlines that we should implement long-term pulmonary follow-up recommendations on a large scale [13, 47–49] using sensitive outcome measures, such as lung function tests, to assess the full spectrum of long-term pulmonary sequelae after childhood cancer at an early stage.

Table 4 Association between sociodemographic, clinical, treatment, and transplant characteristics on self-reported pulmonary outcomes.

	OR	95% CI	*p* value
Age at diagnosis	1.13	0.99–1.28	0.055
Age at questionnaire	1.00	0.91–1.08	0.892
Bleomycin exposure	1.57	0.28–8.81	0.608
Median CED dose >11,300 mg/m^2	1.74	0.57–5.33	0.330
Thoracic surgery	3.91	0.95–16.02	0.058
Thoracic radiotherapy	1.58	0.49–5.14	0.446

Results from multivariable logistic regression analysis, adjusted for all factors in the table. $N = 132$, median 18.4 years at study.

CED cyclophosphamide equivalent dose, *CI* confidence interval, *OR* Odds ratio.

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Compliance with ethical standards

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

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Online Supplement

Transplant characteristics and self-reported pulmonary outcomes in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a cohort study

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SUPPLEMENTAL EXPLANATON E1

This supplemental document describes how we categorized smoking status in childhood cancer survivors participating in the Swiss Childhood Cancer Survivor Study

Lifestyle variables

We combined the answers on active and passive smoking into one variable with four categories: “active smoking”, “passive smoking”, “former active smoking”, and “never active smoking”. The category “passive smoking” includes adolescent and adult CCS who state that they are exposed to passive smoking and minor CCS, whose parents currently smoke or are former smokers. The category “never smoking” includes adolescents and adults, who never smoked and were not exposed to passive smoking, and children, whose parents never smoked.

Smoking questions asked in the adult and adolescent version

Do you currently smoke cigarettes?

No, I never smoked

No, I stopped smoking since ___ month

Yes, I smoke irregularly: number ___ of cigarettes per week

Yes, I smoke regularly: number ___ of cigarettes per day

If you count up all the situations, how many hours per day are you normally exposed to tobacco smoke of other people?

___ hours

Smoking questions asked in parents’ version (separate for mother and father)

Have you ever smoked?

No, never

Yes, stopped since _____

Yes, still smoke today

SUPPLEMENTAL TABLE S1:
This supplemental table describes the characteristics of transplanted childhood cancer survivors eligible for the questionnaire stratified into responder and non-responder to the questionnaire, N=200. The patient tree is described in **Supplemental Figure F2**.

	Responder (n=132)	**Non-responder (n=68)**	**p value[1]**
	n (%)	n (%)	
Sociodemographic characteristics			
Sex, male	69 (52)	43 (63)	0.139
Age at survey, median years (IQR)	18.4 (13.8 – 22.9)	18.6 (14.3 – 22.6)[2]	0.933
Language region			0.975
German	89 (67)	46 (68)	
French or Italian	43 (33)	22 (32)	
Clinical characteristics			
Age at diagnosis, median years (IQR)	6.5 (2.9 - 11.7)	6.7 (2.8, 11.8)	0.876
Age at first HSCT, median years (IQR)	8.8 (4.8 - 13.6)	11.1 (4.7 – 14.1)	0.221
Follow-up time [2], median years (IQR)	9.8 (7.2 - 15.9)	10.8 (7.6 – 14.9)	0.978
Era of diagnosis			0.712
1976-1995	40 (30)	22 (32)	
1996-2005	60 (46)	33 (49)	
2006-2010	32 (24)	13 (19)	
Cancer diagnosis according to ICCC-3			0.561
I: Leukemia	72 (55)	32 (46)	
Ia: lymphoid leukemia	43 (33)	21 (31)	
Ib: acute myeloid leukemia	18 (14)	8 (11)	
Ic-e: CML, MDS, unspecified other leukemias	11 (8)	3 (4)	
II: Lymphoma	20 (15)	14 (21)	
IIa: Hodgkin lymphoma	7 (5)	1 (2)	
IIb: Non-Hodgkin lymphoma	8 (6)	7 (10)	
IIc: Burkitt lymphoma	4 (3)	6 (9)	
IId: miscellaneous	1 (1)	-	
IV: Neuroblastoma	19 (14)	8 (12)	
Other[5]	21 (16)	14 (21)	
History of any relapse			0.047
Yes	62 (47)	42 (62)	
No	70 (53)	26 (38)	

HSCT, hematopoietic stem cell transplantation; ICCC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range; N, number

[1] chi-squared for categorical variables; t-test for continuous variables

[2] Time from first diagnosis until answering the survey (responder) or sending the survey (nonresponder)

[3] Other diagnosis in nonresponder include: tumors of the central nervous system (n=6), retinoblastoma (n=1), renal tumors (n=1), hepatic tumors (n=1), malignant bone tumors (n=3), soft tissue sarcoma (n=1), malignant germ cell tumors (n=1)
Other diagnosis in responder include: tumors of the central nervous system (n=8), retinoblastoma (n=1), malignant bone tumors (n=7), soft tissue sarcomas (n=4), malignant germ cell tumors (n=1)

SUPPLEMENTAL TABLE S2:
This supplemental table describes clinical, treatment and transplant characteristics of childhood cancer survivors transplanted allogeneic (N=71) stratified by era of transplantation

	1976-1995 (n=16)	**1996-2005** (n=26)	**2006-2015** (n=29)	**Total** (n=71)
	n (%)	n (%)	n (%)	n (%)
Clinical characteristics				
Cancer diagnosis according to ICCC-3				
I: Leukemia	16 (100)	23 (88)	29 (100)	68 (96)
II: Lymphoma	0	3 (12)	0	3 (4)
IV: Neuroblastoma	0	0	0	0
Other[1]	0	0	0	0
Treatment characteristics				
Conditioning containing TBI	15 (94)	17 (65)	18 (62)	50 (70)
Conditioning regimens				
TBI + cyclophosphamide ± others	13 (81)	12 (46)	6 (21)	31 (44)
TBI + others	2 (13)	5 (19)	12 (42)	19 (27)
Busulfan + cyclophosphamide ± other	1 (6)	9 (35)	9 (31)	19 (27)
Busulfan ± others	-	-	1 (3)	1 (1)
Melphalan ± Carboplatin ± others	-	-	1 (3)	1 (1)
Chemotherapeutic agents				
Alkylating agents combined [2]	16 (100)	25 (96)	29 (100)	70 (99)
Busulfan	2 (13)	9 (35)	9 (31)	20 (28)
Carmustine	-	-	-	-
Cyclophosphamide	16 (100)	25 (96)	28 (97)	69 (97)
Ifosfamide	4 (25)	8 (31)	14 (48)	26 (37)
Lomustin	-	-	-	-
Melphalan	-	4 (15)	3 (10)	7 (10)
Thiotepa	1 (6)	1 (4)	1 (4)	3 (4)
Bleomycin	1 (6)	-	-	1 (1)
Chemotherapeutic agents, mg/m^2				
Alkylating agents combined [2]	7881 (4034 – 9588)	5892 (4000 – 10631)	5881 (3791 – 8006)	6100 (3871 – 9579)
Busulfan	520 (454 – 587)	320 (297 – 345)	431 (324 – 449)	360 (320 – 445)
Carmustine	-	-	-	-
Cyclophosphamide	5540 (3767 – 7881)	3738 (2983 – 5372)	3439 (2927 – 5570)	3990 (2983 – 6242)
Ifosfamide	7600 (4600 – 16948)	4003 (3052 – 6016)	4002 (2410 – 5923)	4011 (3879 – 6126)
Lomustine	-	-	-	-

Melphalan	-	140 (139 – 140)	140 (138 – 140)	140 (139 – 140)
Thiotepa	168	304	307	304 (168 – 307)
Bleomycin	80	-	-	80
Radiotherapy involving the thorax [3]	15 (94)	18 (69)	18 (62)	51 (72)
Thoracic surgery [4]	0 (0)	1 (4)	0 (0)	1 (1)
Transplant characteristics				
Remission status at transplantation				
First remission	8 (50)	17 (65)	13 (45)	38 (54)
Relapsed disease	8 (50)	9 (35)	16 (55)	33 (46)
Stem cell donor				
HLA identical sibling / HLA matched other relative	13 (81)	15 (58)	11 (38)	39 (55)
HLA matched unrelated	3 (19)	4 (15)	10 (34)	17 (24)
HLA mismatch related / haploidentical	-	5 (19)	2 (7)	7 (10)
HLA mismatch unrelated	-	2 (8)	6 (21)	8 (11)
Source of transplant				
Cord blood	-	1 (4)	5 (17)	6 (8)
Peripheral blood	1 (6)	10 (38)	15 (52)	26 (37)
Bone marrow	13 (81)	14 (54)	7 (24)	34 (48)
Unknown	2 (13)	1 (4)	2 (7)	5 (7)
CMV status				
Donor and recipient IgG negative	7 (44)	12 (46)	14 (48)	33 (46)
Donor and recipient IgG positive	2 (12)	7 (27)	5 (17)	14 (19)
Donor and recipient IgG mismatch	4 (25)	5 (19)	10 (35)	19 (26)
Donor or recipient missing	3 (19)	2 (8)	-	5 (9)
Sex match recipient/donor [6]				
Match	10 (62)	15 (58)	16 (55)	41 (58)
Mismatch	4 (25)	11 (42)	13 (45)	28 (39)
Missing	2 (13)	-	-	2 (3)
Blood group				
Match	9 (56)	13 (50)	10 (34)	32 (45)
Major mismatch	1 (6)	7 (27)	10 (34)	18 (25)
Minor mismatch	4 (25)	4 (15)	9 (31)	17 (24)
Bidirectional mismatch	-	1 (4)	-	1 (2)
Missing	2 (13)	1 (4)	-	3 (4)

Graft versus host disease				
Development of GvHD	12(75)	19 (73)	25 (86)	56 (79)
Type of GvHD (n=56)				
Acute	11 (92)	15 (79)	19 (76)	45 (80)
Grade I & II	7 (64)	13 (87)	15 (79)	35 (78)
Grade III & IV	3 (27)	2 (13)	4 (21)	9 (20)
Unknown	1 (9)	-	-	1 (2)
Chronic	1 (8)	4 (21)	3 (12)	8 (14)
Unknown	-	-	3 (12)	3 (5)
Location of acute GvHD (n=45)				
Skin only	7 (64)	10 (67)	15 (79)	32 (71)
Skin and other	2 (18)	2 (13)	4 (21)	8 (18)
Skin and intestine	1 (9)	3 (20)	-	4 (9)
Skin, intestine and other	1 (9)	-	-	1 (2)
Location of chronic GvHD (n=8)				
Skin only	-	4	1	5 (63)
Skin and other	1	-	2	3 (37)

GvHD, graft versus host disease; HLA, human leukocyte antigen; ICCC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range; TBI, total body irradiation

[1] Other tumors: tumor of the central nervous system (n=1)

[2] Combination according to Cyclophosphamide Equivalent Dose (CED) (Green et al; Pediatr Blood Cancer. 2014 January; 61(1): 53–67. doi:10.1002/pbc.24679)

[3] Thoracic radiation fields according to COG guidelines, Version 4.0, Oct 2018, including radiation to the chest, whole lung, mediastinum, (mini-)mantle field, TBI and additionally upper abdomen and thoracic spine, including craniospinal irradiation

[4] Thoracic surgery according to COG guidelines, Version 4.0, Oct 2018, including thoracotomy, chest wall surgery, rib resection, lobectomy, pulmonary metastasectomy and wedge resection

SUPPLEMENTAL TABLE S3:
This supplemental table describes clinical, treatment and transplant characteristics of childhood cancer survivors transplanted autologous (N=61) stratified by era of transplantation

	1976-1995 (n=17)	**1996-2005** (n=25)	**2006-2015** (n=19)	**Total** (n=61)
	n (%)	n (%)	n (%)	n (%)
Clinical characteristics				
Cancer diagnosis according to ICCC-3				
I: Leukemia	2 (12)	3 (12)	0	5 (8)
II: Lymphoma	8 (47)	4 (16)	5 (26)	17 (28)
IV: Neuroblastoma	5 (29)	8 (32)	6 (32)	19 (31)
Other[1]	2 (12)	10 (42)	8 (42)	20 (33)
Treatment characteristics				
Conditioning containing TBI	5 (29)	3 (12)	1 (5)	9 (15)
Conditioning regimens				
TBI + cyclophosphamide ± others	3 (18)	-	-	3 (5)
TBI + others	2 (12)	3 (12)	1 (5)	6 (9)
Busulfan + cyclophosphamide ± other	6 (35)	2 (8)	1 (5)	9 (15)
Busulfan ± others	1 (6)	4 (16)	2 (10)	7 (11)
Lomustine ± others	3 (18)	3 (12)	3 (16)	9 (15)
Cyclophosphamide ± others	1 (6)	6 (24)	2 (11)	9 (15)
Melphalan ± Carboplatin ± others	1 (6)	7 (28)	10 (53)	18 (30)
Chemotherapeutic agents				
Alkylating agents combined [2]	17 (100)	25 (100)	19 (100)	
Busulfan	7 (41)	7 (28)	3 (16)	17 (28)
Carmustine	4 (24)	3 (12)	2 (11)	9 (15)
Cyclophosphamide	17 (100)	21 (84)	16 (84)	54 (89)
Ifosfamide	5 (29)	15 (60)	16 (84)	36 (59)
Lomustine	1 (6)	-	1 (5)	2 (3)
Melphalan	9 (53)	13 (52)	15 (79)	37 (61)
Thiotepa	2 (12)	7 (28)	2 (11)	11 (18)
Bleomycin	2 (12)	3 (12)	2 (11)	7 (11)
Chemotherapeutic agents, mg/m^2				
Alkylating agents combined [2]	17164 (15921 – 18380)	17286 (12650 – 35807)	16522 (11894 – 31601)	17154 (12650 – 31601)
Busulfan	480 (470 – 600)	480 (480 – 480)	443 (374 – 470)	480 (456 – 481)
Carmustine	300 (298 – 351)	300 (298 – 300)	300 (291 – 306)	300 (298 – 300)
Cyclophosphamide	7454 (6970 – 9352)	7491 (4000 – 9600)	3385 (1704 – 4938)	5980 (3357 – 8845)

Ifosfamide	14000 (11500 – 16032)	22500 (10000 – 44782)	18903 (11628 – 55978)	18038 (10113 – 49792)
Lomustine	190	-	600	395 (190 – 600)
Melphalan	140 (140 – 142)	140 (140 – 179)	140 (139 – 180)	140 (140 – 179)
Thiotepa	825 (750 – 900)	894 (594 – 900)	755 (610 – 900)	894 (604 – 900)
Bleomycin	41 (40 - 42)	40 (40 - 50)	30 (20 – 40)	40 (40 – 42)
Radiotherapy involving the thorax [3]	10 (59)	14 (56)	11 (58)	35 (57)
Thoracic surgery [4]	1 (6)	4 (16)	6 (32)	11 (18)
Transplant characteristics				
Remission status at transplantation				
First remission	8 (47)	18 (72)	11 (58)	37 (61)
Relapsed disease	9 (53)	7 (28)	8 (42)	24 (39)
Stem cell donor				
Autologous marrow	8 (47)	3 (12)	0	11 (18)
Autologous apheresis	9 (53)	22 (88)	19 (100)	50 (82)
Source of transplant				
Peripheral blood	8 (47)	22 (88)	19 (100)	49 (80)
Bone marrow	9 (53)	3 (12)	-	12 (20)

ICCC-3, International Classification of Childhood Cancer, 3rd edition; IQR, interquartile range; TBI, total body irradiation

[1] Other tumors: tumor of the central nervous system (n=5), retinoblastoma (n=1), malignant bone tumor (n=7), soft tissue sarcoma (n=4), germ cell tumors (n=3)

[2] Combination according to Cyclophosphamide Equivalent Dose (CED) (Green et al; Pediatr Blood Cancer. 2014 January; 61(1): 53–67. doi:10.1002/pbc.24679)

[3] Thoracic radiation fields according to COG guidelines, Version 4.0, Oct 2018, including radiation to the chest, whole lung, mediastinum, (mini-)mantle field, TBI and additionally upper abdomen and thoracic spine, including craniospinal irradiation

[4] Thoracic surgery according to COG guidelines, Version 4.0, Oct 2018, including thoracotomy, chest wall surgery, rib resection, lobectomy, pulmonary metastasectomy and wedge resection

SUPPLEMENTAL TABLE S4:
This supplemental table compares clinical, treatment and transplant characteristics of childhood cancer survivors after allogeneic and autologous hematopoietic stem cell transplantation, N=132, 52%male

	Allogeneic HSCT N=71	**Autologous HSCT N=61**	**p value[1,2]**
	n (%)	n (%)	
Sociodemographic characteristics			
Sex, male	38 (54)	31 (51)	0.757
Age at survey, median years (IQR)	18.5 (13.8 – 23.5)	18.3 (13.8 – 22.6)	0.688
Smoking status			0.863
Active smoking	4 (6)	3 (5)	
Passive smoking	30 (42)	26 (43)	
Former active smoking	6 (8)	3 (5)	
Never active smoking	31 (44)	29 (47)	
Clinical characteristics			
Age at diagnosis, median years (IQR)	7.1 (3.2 - 11.1)	5.6 (2.6 – 12.9)	0.731
Age at diagnosis, years			0.083
0-4	26 (37)	27 (44)	
5-9	27 (38)	12 (20)	
10-14	15 (21)	15 (25)	
15-21	3 (4)	7 (11)	
Age at first HSCT, median years (IQR)	8.7 (5.7 - 13.0)	9.6 (3.1 – 14.3)	0.953
Follow-up time, median years (IQR)	10.2 (7.4 - 16.1)	9.5 (7.2 – 15.8)	0.420
Time to HSCT, median years (IQR)	0.9 (0.4 – 2.8)	0.7 (0.5 – 1.9)	0.511
Era of HSCT			0.501
1976 - 1995	16 (22)	17 (28)	
1996 - 2005	26 (37)	25 (41)	
2006 - 2015	29 (41)	19 (31)	
Cancer diagnosis according to ICCC-3			<0.005
I: Leukemia	67 (94)	5 (8)	
II: Lymphoma	3 (4)	17 (28)	
IV: Neuroblastoma	0	19 (31)	
Other[3]	1 (2)	20 (33)	
Treatment characteristics			
Conditioning regimens			<0.001
TBI + cyclophosphamide ± others	31 (44)	3 (5)	
TBI + others	19 (27)	6 (10)	
Busulfan + cyclophosphamide ± others	19 (27)	9 (15)	
Busulfan ± others	1 (1)	7 (11)	
BCNU ± others	-	9 (15)	
CYC ± others	-	9 (15)	
Melphalan ± Carboplatin ± others	1 (1)	18 (29)	
Chemotherapeutic agents			
Alkylating agents combined [7]	70	61	
Busulfan	21	16	
Carmustin	0	10	
Cyclophosphamide	69	54	
Ifosfamide	26	36	
Lomustin	0	2	
Melphalan	7	37	
Thiotepa	3	11	
Bleomycin	1 (1)	7 (12)	
Chemotherapeutic agents, mg/m^2 [3]			
Alkylating agents combined [7]	6,100 (3871 - 9579)	17,154 (12,650 – 31,601)	<0.001

Busulfan	360 (320 - 445)	480 (456 - 481)	0.0038
Carmustin	-	300 (298-300)	na
Cyclophosphamide	3990 (2983 - 6242)	5980 (3357 - 8845)	0.01
Ifosfamide	4011 (3879 - 6126)	18,038 (10,113-49,792)	0.0001
Lomustin	-	395 (190-600)	na
Melphalan	140 (139-140)	140 (140-179)	0.193
Thiotepa	304 (168 - 307)	894 (604 - 900)	<0.001
Bleomycin	80	40 (40-42)	na
Radiotherapy involving the thorax [8]			0.054
Yes	51 (72)	34 (54)	
No	20 (28)	27 (44)	
Thoracic surgery [9]			0.364
Yes	1 (1)	11 (18)	
No	70 (99)	50 (82)	
Transplant characteristics			
Remission status at transplantation			0.409
First remission	38 (54)	37 (61)	
Relapsed disease	33 (46)	24 (39)	

HSCT, hematopoietic stem cell transplantation; IQR, interquartile range

[1] p-value calculate by Pearson chi-square to compare categorical variables between allogeneic and autologous transplant cohort

[2] p-value calculate by t-test to compare categorical variables between allogeneic and autologous transplant cohort

[4] body mass index (BMI) defined as normal if z-score ≥-2 and ≤1 (responder ≤19) or kg/m^2 ≥18.5 and ≤24.9 (responder >19 years)

[6] Relation sex of donor to recipient: match= both male or female; mismatch= donor male and recipient female or vice versa

[7] Combination according to Cyclophosphamide Equivalent Dose (CED) (Green et al; Pediatr Blood Cancer. 2014 January; 61(1): 53–67. doi:10.1002/pbc.24679)

[8] Thoracic radiation fields defined according to COG guidelines, Version 4.0, Oct 2018

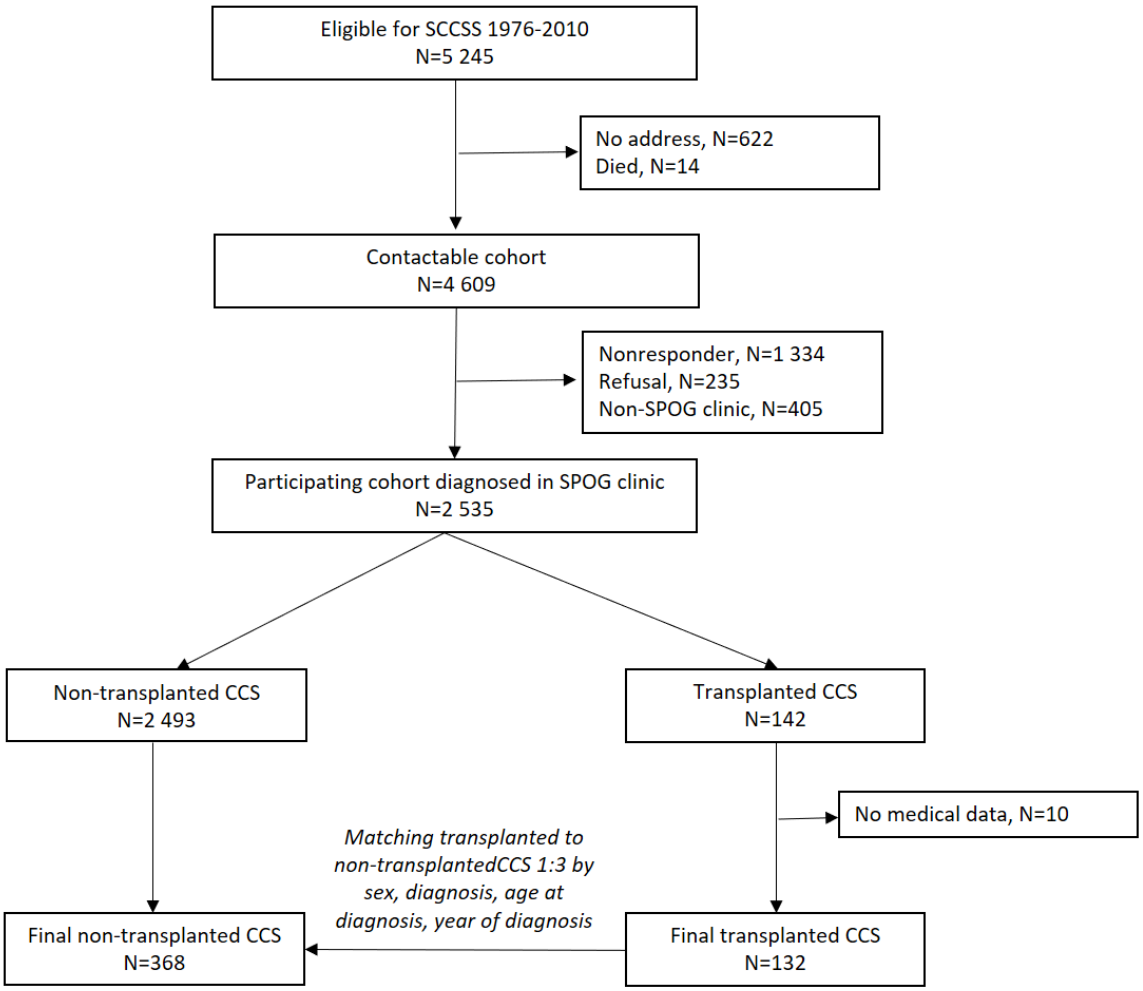
[9] Relevant thoracic surgery defined according to COG guidelines, Version 4.0, Oct 2018

SUPPLEMENTAL TABLE S5:
This supplemental table describes the characteristics of childhood cancer survivors who have been treated with hematopoietic stem cell transplantation and thoracic surgery, N=12

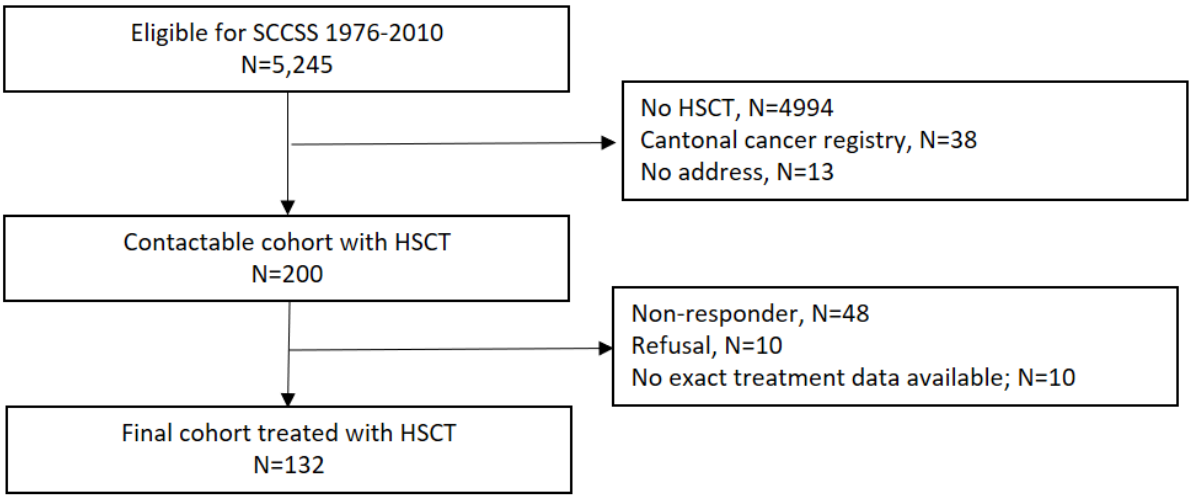
	Diagnosis	Year of diagnosis	Age at first thoracic surgery [years]	Relapse	Description of thoracic surgery/ surgeries	Lung toxic exposure
1	Hodgkin lymphomas	1986	10	Yes	Thoracotomy: tumor resection mediastinal	BCNU, Bleomycin, CCNU, CYC, Mel Radiotherapy: mediastinal, lung
2	Ewing sarcoma	1997	26	Yes	Thoracoscopy: metastasectomy	CYC, IFO, Mel
3	Non-Hodgkin lymphomas	1996	17	Yes	Thoracotomy: lobectomy upper lobe and lingual left side	Busulfan, CYC Radiotherapy: mediastinal
4	Acute myeloid leukemias	1999	5	Yes	Thoracoscopy: lobectomy left lower lobe due to infection	Radiotherapy: TBI, mediastinal
5	Ewing sarcoma	2002	14	No	1x Thoracoscopy: metastasectomy 3x Thoracotomy: 2x Metastasectomy and resection left lower lobe	Busulfan, CYC, IFO, Mel Radiotherapy: lung
6	Ewing sarcoma	2004	13	Yes	Thoracotomy: lobectomy left lower lobe and parietal pleura Thoracotomy: extended extrapleural residual pneumonectomy Thoracic wall: partial scapula resection	Busulfan, IFO, Mel Radiotherapy: lung
7	Ewing sarcoma	2004	5	Yes	Thoracotomy: subtotal tumor resection Thoracotomy: marginal tumor resection, resection of two ribs Thoracotomy: metastasectomy, partial resection right upper lobe	CYC, IFO, Mel Radiotherapy: lung, chest wall
8	Ewing sarcoma	2006	4	Yes	Thoracoscopy (VATS): two lung biopsies	Busulfan, CYC, IFO, Mel
9	Non-Hodgkin lymphomas	2006	13	No	Sternotomy and mediastinotomy: tumor biopsy Sternotomy: partial tumor resection	Busulfan, CYC, IFO Radiotherapy: mediastinal
10	Hodgkin lymphomas	2007	17	Yes	Thoracotomy: tumor resection	BCNU, Bleo, CYC, IFO, Mel Radiotherapy: mediastinal
11	Ewing sarcoma	2008	10	Yes	Thoracotomy and resection of two ribs	CYC, IFO, Mel Radiotherapy: thoracic spine

12	Ewing sarcoma	2008	19	Yes	Bilateral VATS: metastasectomy	CYC, IFO, Mel Radiotherapy: lung

BCNU, carmustin; CCNU, lomustin; CYC, cyclophosphamide; IFO, ifosfamide; Mel, melphalan;



SUPPLEMENTAL FIGURE F1: Population tree of transplanted and non-transplanted childhood cancer survivors eligible for this study – approach 1 with division into transplanted and non-transplanted survivors at the end.
CCS, childhood cancer survivor; SPOG, Swiss Pediatric Oncology Group



SUPPLEMENTAL FIGURE F2: Population tree of transplanted childhood cancer survivors eligible for this study – approach 2 with division into transplanted and non-transplanted survivors at the beginning.
CCS, childhood cancer survivor; HSCT, Hematopoietic Stem Cell Transplantation

4.2. Publication II

Pulmonary function in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a retrospective study

Original article

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Own contribution to the project when submitting the thesis: Concept and design of the study, organization and conduct of data collection, data analysis, preliminary interpretation of the results, start writing manuscript

Lung function in Swiss childhood cancer survivors after Hematopoietic Stem Cell Transplantation – a retrospective study

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Abstract

Background: Several treatment modalities used in the setting of hematopoietic stem cell transplantation (HSCT) in children and adolescents put the young patients at risk for pulmonary dysfunction. Information on longitudinal trajectories of pulmonary function and factors influencing changes over time was lacking.

Research Question: The purpose of this study was to evaluate longitudinal pulmonary function trajectories and treatment-related factors associated with changes over time in a cohort of 5-year childhood cancer survivors (CCSs) treated with allogeneic or autologous HSCT in Switzerland.

Study Design and Methods: This retrospective cohort study included 5-year CCSs registered in the Swiss Childhood Cancer Registry, diagnosed below 21 years of age, between 1980 and 2010, treated with allogeneic or autologous HSCT, and having at least two pulmonary function tests performed following the diagnosis. We described pulmonary function parameters as age-, sex-, and height-adjusted z-scores in terms of lung volumes (FVC, RV, TLC), air flow (FEV1), and diffusion capacity for carbon monoxide (DLCO). We assessed the influence of treatment factors and elapsed time since diagnosis on pulmonary function parameters using multivariable regression analysis with random intercept and slope.

Results: Seventy-four 5-year CCSs were included in this study. Median age at diagnosis was 7 years, with 9 years of follow-up. Most CCSs received allogeneic HSCT (68%) and radiotherapy involving the chest (70%). The median z-score of all analysed pulmonary function parameters were below the expected over the observed 15 years, but the individual trajectories differed largely between CCSs. The z-scores for FEV1 (-0.06, 95%CI -0.09 - -0.03) and FVC (-0.06, 95%CI -0.09 - -0.02) showed a significant annual decrease in multivariable regression analysis, which was not the case for TLC, RV, and DLCO. Relapsed disease had a significantly impact on the annual change of TLC and RV.

Interpretation: Our results show that pulmonary function in 5-year CCSs treated with HSCT was constantly below the expected but did not show a prominent deterioration over the observed first 15 years from diagnosis. In a sub-analysis of CCSs with a first test preformed before HSCT, FEV1 and

FVC z-scores have not significantly deteriorated in the first five years after HSCT, but subsequently. Our results illustrate that this population of 5-year CCSs needs long-term follow-up care. We also emphasize that longitudinal, prospective studies are needed to better understand the long-term course of pulmonary function in these CCSs.

Key words:

Childhood cancer, survivor, late effects, pulmonary function, hematopoietic stem cell transplantation

Abbreviations:

BCNU	Carmustine
CCNU	Lomustine
CCS	Childhood Cancer Survivors
CMV	Cytomegalovirus
DLCO	Diffusion capacity for carbon monoxide
FEV1	Forced expiratory volume in first second
FVC	Forced vital capacity
GLI	Global Lung Initiative
GvHD	Graft versus host disease
HLA	Human leucocyte antigen
HSCT	Hematopoietic stem cell transplantation
IQR	Interquartile range
PFT	Pulmonary function test
RV	Residual volume
SCCR	Swiss Childhood Cancer Registry
SCCSS	Swiss Childhood Cancer Survivor Study
SPOG	Swiss Pediatric oncology Group
TLC	Total lung capacity

Introduction

Childhood cancer survivors (CCSs) treated with allogeneic or autologous hematopoietic stem cell transplantation (HSCT) are at increased risk to develop pulmonary dysfunction (1-4). Pulmonary dysfunction reflects different underlying structural damages to the lung tissue. In CCSs treated with HSCT, these damages can result from oxidative stress induced by specific chemotherapeutic agents, from free radical formation due to radiotherapy, or from transplant-specific pulmonary complications. Lung-toxic chemotherapeutic agents include busulfan, bleomycin, carmustine and lomustine (5, 6). Transplant-specific complications include the idiopathic pulmonary syndrome and complications from the spectrum of pulmonary graft versus host disease (GvHD), such as bronchiolitis obliterans or bronchiolitis obliterans organizing pneumonia (7, 8). Because the lung has a large functional reserve, it can take years to decades until pulmonary dysfunction becomes clinically manifest. Pulmonary function testing (PFT) allows to detect pulmonary dysfunction in this asymptomatic period and different test modalities are available. Spirometry and body plethysmography, measuring lung volumes and flow, are widely available but seem to detect less survivors with pulmonary dysfunction than measuring the diffusion capacity for carbon monoxide (DLCO) (9, 10).

Most studies which assessed pulmonary function in CCSs treated with allogeneic or autologous HSCT longitudinally have rather short follow-up periods (3, 4, 11, 12). In addition, not all CCSs in these studies were long-term survivors and might have died within the first five years following the diagnosis. In this population-based, retrospective cohort study of Swiss CCSs treated with HSCT and surviving ≥5 years from diagnosis, we aimed to close this knowledge gap. We described pulmonary function trajectories over time, starting at diagnosis, and addressed risk factors associated with a decline in pulmonary function in the literature.

Methods

Study population

Eligible for this study was a subgroup of CCSs who participated in the Swiss Childhood Cancer Survivor Study (SCCSS), a long-term national cohort study of all children and adolescents who have

survived ≥5 years after initial cancer diagnosis and who have been registered in the Swiss Childhood Cancer Registry (SCCR) (13). The SCCR registers since 1976 all children and adolescents diagnosed with leukemia, lymphoma, central nervous system tumors, malignant solid tumors, or Langerhans cell histiocytosis below the age of 21 years (14). We finally included CCSs who had participated in the SCCSS, had answered the questions on pulmonary health, had been treated in a clinic affiliated to the Swiss Pediatric Oncology Group (SPOG) between 1976 and 2010, had undergone autologous or allogeneic HSCT, and had at least two pulmonary function tests (PFTs) performed at any time following the cancer diagnosis. We have decided to sample the cohort for this study from the SCCSS cohort because all CCSs eligible for the SCCSS have met the inclusion criterion of being a 5-year survivor. Furthermore, we know from a previous study, that the response rate of transplanted CCSs in the SCCSS is very good with 71% (15). The Ethics Committee of the Canton of Bern approved the SCCR and SCCSS (KEK-BE: 166/2014), and the SCCSS is registered at ClinicalTrials.gov (identifier: NCT03297034).

Pulmonary function test results and data cleaning

We searched pulmonary function test (PFT) results in the archives of the initially treating clinic and the transplant clinic. We collected all results performed by spirometry, body plethysmography, and measurement of diffusion capacity for carbon monoxide (DLCO). The following PFT parameters were considered for this study: forced expiratory volume in first second (FEV1 [liter]), forced vital capacity (FVC [liter]), residual volume (RV [liter]), total lung capacity (TLC [liter]), resistance ([kPa*s/liter]), and DLCO. If available we recorded DLCO corrected for hemoglobin ($DLCO_{corr}$ [mmol/min/kPa] or [cmH_2O/L/sec]) otherwise we recorded the uncorrected DLCO. We divided DLCO expressed as [cmH_2O/L/sec] by 2.98 to convert it into [mmol/min/kPa] (16). We used EpiData to enter the PFT results (17). To avoid data entry errors, the entry of every second PFT result in EpiData was double-checked for correctness.

Using the Global Lung function Initiative equations (GLI 2012), we converted FEV1, FVC, and DLCO into age-, height- and sex-standardized z-scores and percentage of predicted (18). To calculate the z-scores for TLC and RV we used the reference equations by Zapletal et al for children

aged 4-17 years and the European Community of Coal and Steel (ECCS) equations for adults aged ≥18 years (19, 20). We defined z-scores <-1.645 as abnormal (21). For resistance we used the cutoff value for sReff (sRtot) ≥1,2kPa*s for adults and ≥1,0kPa*s for children to define abnormal results (22). We performed quality checks by plotting the z-scores of each patient over time and checked for outliers. For all outliers we consulted the raw data and corrected data entry errors. We excluded PFT results if poor cooperation, cough or cold was noted on the test result. Two authors assessed the quality of the PFTs by evaluating the flow-volume curve and the respiratory loop independently and according to criteria from the American Thoracic Society and European Respiratory Society and the German Lung League (23, 24) (**Supplemental Explanation E1**). We excluded PTFs with bad quality. As this study focused on the longitudinal course of pulmonary function we excluded 12 CCSs who had one test of good quality performed only (**Supplemental S1**). We additionally excluded 23 tests of good quality (5% of all tests) of 8 CCSs which have been performed ≥15 years from cancer diagnosis (mean 23 years; range 15 – 34 years).

Treatment characteristics

We collected treatment information from medical records at the respective SPOG clinic where the patient was initially treated and received HSCT. If the initially treating clinic and the transplant clinic were not the same, we searched the records in both clinics. We recorded exposure to lung-toxic chemotherapeutic agents listed in the Children's Oncology Group (COG) long-term follow-up (LTFU) guidelines version 5.0, including bleomycin, busulfan, carmustin (BCNU), and lomustin (CCNU) as yes/no variable and additionally calculated the cumulative doses (25). We converted busulfan administered orally to intravenously by multiplying it by factor 0.8 (26). We categorized radiation to the chest and thoracic surgery as yes/no variables according to the COG-LTFU guidelines (25). For HSCT we collected information on remission status, source of transplant, stem cell donor, cytomegalovirus (CMV) status and sex of donor and recipient, and information on graft versus host disease (GvHD). For remission status, we assigned patients with initially refractory disease into the category "first remission". For patients transplanted allogeneic we recorded the Human Leucocyte

Antigen- (HLA-) match and differentiated between HLA-matched and HLA-mismatched donors (27). We categorized GvHD into acute and chronic according to information from medical records.

Statistical analyses

We used descriptive statistics, such as median and interquartile range (IQR), number and proportion to characterize the study population and to describe the PFT results. We used a cross-sectional approach to describe the pulmonary function parameters performed during the first and last available test of each CCS and compared them by using t-test for continuous variables. The parameters for resistance and DLCO were missing in >50% of first or last tests. Therefore we did not consider them in the cross-sectional description. To model the longitudinal course of pulmonary function parameters over time, we used multivariable logistic regression analysis with random intercept and random slope. The model with random intercept and random slope takes clustering by patient and the previous measurement at patient level into account. We used the command “mixed” in Stata. We modelled a random slope, by performing an interaction term between the respective risk factor and time since diagnosis, for each risk factor separately. To account for autocorrelation of the residuals of repeated measurements we introduced a respective exponential term in the analyses. We included time since diagnosis as continuous variable. We only kept the risk factors in the final model for the random slope with a significance level of $p<0.05$ at individual level. We visualized pulmonary function graphically by plotting the overlaid trajectories for all CCSs over time. We additionally analyzed two subgroup of CCSs. We compared changes from baseline (before HSCT) to <2 years from HSCT, to 3-5 years, and to ≥ 5 years from HSCT in CCSs with baseline measurement available. The second subgroup consisted of CCSs with at least one test performed in each of three defined categories: 1st and 2nd year from HSCT, 3rd to 5th year from HSCT, and 6th to 10th year from HSCT. If CCSs had more than one test performed within a category, we included the respective mean over all performed tests per CCS and per category. We used the statistical software Stata (StataCorp LLC) for analysis.

Results

Patient characteristics

Two hundred CCSs who received autologous or allogeneic HSCT could be contacted for the SCCSS. Of those, 142 responded to the survey (71%) and 74 CCSs (37%) could be included in our analysis as they received at least two pulmonary function tests of good quality after cancer diagnosis (**Supplemental Figure 1**). The median age at diagnosis was 7.4 years (interquartile range, IQR 3.5 – 12.2) and 9.4 years (IQR 5.6 – 14.5) at transplantation. The time between diagnosis and last available pulmonary function test (PFT) was 9.3 years (IQR 1.2 – 12.3). The most frequent diagnosis was leukemia (69%), followed by lymphoma (15%), and other tumors (15%). Half of the CCSs (55%) had suffered from relapsed disease and had been diagnosed between 2001 and 2010 (57%) (**Table 1**). Of the four assessed lung toxic chemotherapeutic agents, busulfan was the most frequently used (34%) with a median cumulative dose of 422mg/m^2 (IQR 324 – 470mg/m^2). Seventy percent (n=52) of CCSs received radiotherapy to the thorax, and 14% (n=10) thoracic surgery. For HSCT, two thirds were transplanted allogeneic (68%) and in half of the CCSs (55%) peripheral blood was the source of transplant (**Table 1**). Additional information on cancer diagnosis and transplant characteristics is available in **Supplemental Table S2**.

Pulmonary function

The 74 CCSs performed 411 PFTs of good quality with 5 tests per survivor on average (range 2-12). FEV1, as proxi for the performance of a spirometry, was carried out in 99% of PFTs (n=407 tests), in 95% of the tests (n=390) TLC was preformed, indicative for body plethysmography, and in 45% of the tests (n=185) DLCO measurement was performed. The median time from diagnosis to first PFT was 3.0 years (IQR 1.2 – 5.4) and 9.3 years (IQR 6.1 – 12.3) to the last test (**Supplemental Table S3**). The number of PFT results included in the comparison of first and last test differed slightly for each pulmonary function parameters. This difference is because the last available test did not always include all parameters or some CCSs only received spirometry for example. We excluded DLCO from this analysis, as it was missing in up to 80% of first or last tests. None of the five analysed pulmonary

function parameters (FEV1, FVC, FEV1/FVC, TLC, RV) showed a significant deterioration between first and last test (**Table 2**). FEV1 and FVC showed a tendency to worse median z-scores in the last compared to the first test. The TLC z-score showed a tendency to higher z-scores, but still below the predicted. The z-score for RV was even slightly higher than predicted at both time points. Stratification into CCSs with normal or reduced (z-score <-1.645) parameters only showed a significant decline in FEV1 z-score and FEV1/FVC ratio in the category of normal parameters.

We could graphically show that the median z-score of each pulmonary function parameter is constantly below the expected value for FEV1, FVC, and TLC, and most of the time for DLCO and RV (**Figure 1, Figure 2, Figure 3, Figure S2, and Figure S3**). Each longitudinal course is rather stagnant with no clear worsening in the observed 15 years. The variability in the longitudinal course between CCSs is large. Some CCSs show a deterioration with each PFT performed, others a steady improvement, and others an undulating course.

We included 25 CCSs in the subgroup analysis with available baseline testing before HSCT. In 24 CCSs FEV1 was available and FVC in 23 CCS. A total of 147 tests were performed in this subgroup. We excluded DLCO from these analyses because it was missing in a high proportion of baseline tests. The median FEV1 z-score was -0.96 at baseline (IQR -1.89 – 0.01) and did not significantly change in the following five years, but decreases to -1.66 (IQR -3.16 - -0.41; p=0.063) in the median of the test performed ≥ 5 years from HSCT (**Figure 4a**). The course for FVC z-score was very similar but on a lower z-score level (**Figure 4b**). The median FVC z-score was -1.1 (IQR -2.28 - -0.10) at baseline with no significant changes in the following five years but a significant decrease to -2.12 (IQR -3.28 - -1.14) in the median of tests performed ≥ 5 years from HSCT.

Risk factors for decrease in pulmonary function

In the risk factor analysis we examined the impact of the risk factors on the starting value of the longitudinal trajectory of each pulmonary function parameter (intercept) and on its annual change (slope). The reference in this analysis is a male patients treated with autologous HSCT, diagnosed

between 1980 and 1990 with no exposure to any of the risk factors. For FEV1 z-score, being female (Coefficient, Coeff. -0.664; 95% Confidence interval, 95%CI -1.187 - -0.140) and treated with radiotherapy to the lung (Coeff. -1.3; 95%CI -2.022 - -0.558) led to a significant reduction in the intercept. The annual decrease (slope) of FEV1 z-score was -0.06 (95%CI -0.094 - -0.027) in the reference person and was not significantly changed by any of the risk factors. For FVC z-score, radiotherapy (Coeff. -1.473; 95%CI -2.207- -0.739) led to a significant reduction in the intercept. The annual decrease of FVC z-score was -0.058 (95%CI -0.097 - -0.019) and was not significantly influenced by any of the risk factors. For TLC z-score, we adjusted the model by taking the interaction of time with type of transplantation into account. In the final model, no risk factor had a significant impact on the intercept of TLC z-score. TLC z-score decreased annually by -0.092 (95%CI -0.220 - 0.035). Treatment with allogeneic HSCT led to an annual improvement of 0.216 (95%CI 0.059 - 0.373) compared to autologous HSCT. For RV z-score, we adjusted the model and took the interaction of time with relapse into account. Afterwards, none of the risk factors was significantly associated with a change in the intercept. The annual increase in RV z-score was 0.108 (95%CI -0.019 - 0.234), but having suffered from relapse led to an annual decrease of -0.231 (95%CI -0.405 - 0.055). For DLCO, being diagnosed 1991-2000 (Coeff. -2.465; 95%CI -4.151- -0.780) and 2001-2010 (Coeff. -2.447; 95%CI -4.111- -0.784) led to a significant reduction in the intercept of DLCO z-score. None of the risk factors significantly influenced the annual increase of 0.015 (95%CI -0.079 - 0.111) z-scores. Finally, the results of this analysis allow to calculate the longitudinal course of each pulmonary function parameter for CCSs exposed to different combinations of risk factors. The term “intercept” in Table 3 corresponds to the starting value of the male reference patients. A female CCSs treated with radiotherapy to the lung would start at a FEV1 z-score of -1.471 (-0.664 for being female, -1.306 for radiotherapy). The annual decrease is -0.061 z-scores. As no factor was significantly associated at single levels, no time interaction was included in the final model **(Supplemental Table S4)**. The detailed risk factor analysis for each pulmonary function parameter is shown in **Supplemental Table S4 to S8)**.

Discussion

A median of 9 years from diagnosis on third of CCSs had a reduced z-score for FEV1 (34%), FVC (38%), or TLC (32%) and RV was reduced in 11%. None of the analyzed pulmonary function parameters showed a significant decrease between the first and last available test. However, the median z-score for FEV1, FVC, and TLC was constantly below the expected and most of the time also for DLCO and RV. In the sub-group analysis of CCSs with baseline testing, already the median z-score before HSCT was below the expected for FEV1 and FVC and did not significantly change in the following five years after HSCT. In the risk factor analysis only relapsed disease and type of HSCT were significantly associated with an annual deterioration of TLC and RV. Also only few factors were associated with a significant decrease in the intercept. All these findings highlight the complexity and multifactorial cause of pulmonary dysfunction in CCSs after HSCT and that most probably already the treatment preceding HSCT contributes to the long-term course.

Paragraph on contextualization with other literature and risk factors in progress

The findings from our sub-group analysis on CCSs with test results available before HSCT go partly in line with the publication from Cerveri et al (12). All 75 CCSs in this cohort treated with allogeneic (69%) and autologous HSCT had baseline testing available. As in our cohort, already the mean baseline FVC z-score was reduced (-0.3 ±1.1). Different from our cohort, the subsequent tests have been performed at defined time points (6 months, 12 months, and 24 months) and the mean FVC z-score was significantly lower compared to the baseline assessment (mean z-score -0.9, $p<0.001$). The results from both studies underline, that some CCSs already go into transplantation with reduced pulmonary function and that the lung may already be pre-damaged by the previous treatment or other underlying conditions. The question on the impact of cancer treatment preceding HSCT and underlying conditions can currently not be answered, as baseline testing before any cancer treatment is often lacking.

The strengths of this study are the large sample size of 74 CCSs with at least two pulmonary function tests performed and the high quality of patient, diagnosis, and treatment information. For pulmonary function data, the strengths are the check of pulmonary function quality and data entry into

EpiData by two persons, the control for outliers at z-score level and correction if needed, and most importantly, the exclusion of all PFT results with poor quality.

The results of this study have to be considered with some limitations. The retrospective design influenced the data availability and the data quality. Even though we searched different archives and tried to find all PFT results, we might have missed some results or the results got lost, which might especially have happened in CCSs diagnosed in the 80s and 90s. In addition, we did not know why the PFTs have been performed. We assume that some PFTs have been performed for surveillance purpose, but other tests may have been performed due to symptoms or other diseases, such as asthma. Retrospective data collection leads to specific limitations in the PFT quality. Tests have been performed in different laboratories over a long period with changes in equipment, staff, and testing procedures. We also had to assume that the tests have been performed according to standard practice and that the results we found in the medical records correspond to the best repetition out of three. Taking the SCCSS cohort to define 5-year survivors could have introduced selection bias. Our results might therefore not be representative for all 5-year CCSs treated with autologous or allogeneic HSCT. In addition, we cannot rule out, that the more symptomatic and sicker CCSs received PFT and are included in our cohort, which would lead to an overestimation of the burden of pulmonary dysfunction. Even though we included CCSs treated with HSCT only, the cohort is still very heterogeneous in terms of relapsed disease and exposure to different treatment modalities. This heterogeneity and the multimodal treatment approach in all included survivors has made it impossible for us to define risk factors associated with changes in pulmonary function parameters over time.

Interpretation

Pulmonary function z-scores in 5-year childhood cancer survivors treated with hematopoietic stem cell transplantation are constantly below the predicted, from shortly after diagnosis until 15 years later. These low parameters indicate that long-term follow-up care of these survivors is needed.

Take-Home Points

Study question: We aimed to evaluate pulmonary function longitudinally and treatment-related factors associated with changes in pulmonary function over time in a cohort of 5-year childhood cancer survivors (CCSs) treated with allogeneic or autologous hematopoietic stem cell transplantation (HSCT) in Switzerland.

Results: Most pulmonary function parameters were constantly below the predicted z-score over the observed period of 15 years in the 74 included CCSs with the risk factor analysis highlighting the multifactorial influence of each single risk factor, resulting in a complex interplay.

Interpretation: Our data underline the necessity that CCSs treated with HSCT are at risk for pulmonary dysfunction and that long-term pulmonary follow-up care may be indicated.

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Author contributions: M.O. performed funding acquisition, developed the study, performed data collection, analyzed and interpreted the data, and wrote the manuscript. S.Y., J.U., and P.L. provided important pediatric pulmonology input, helped in data interpretation, and revised the manuscript for important intellectual content. G.T. and K.S. provided important input on pediatric oncology and pediatric transplantation, helped in data interpretation, and revised the manuscript for important intellectual content. L.M. helped in data analysis and revised the manuscript for important intellectual content. B.S. helped in statistical design, data analysis, and revised the manuscript for important intellectual content. C.E.K. performed funding acquisition, developed the study, interpreted the data, and revised the manuscript for important intellectual content.

Names of collaborators: Swiss Paediatric Oncology Group (SPOG): Ansari M; Beck Popovic M; Bourquin JP; Brazzola P; Greiner J; Rössler J; Schilling F; Scheinemann K; von der Weid N

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TABLE 1: Characteristics of the study population (N=74)

Sociodemographic and lifestyle characteristics	
Sex, male	43 (58)
Ethnicity, white	72 (97)
Age at first lung function test, median years (IQR)	9.9 (7.9 – 14.0)
Age at last lung function test, median years (IQR)	16.2 (14.2 – 20.0)
Smoking status[1]	
Active smoking	4 (5)
Former active smoking	5 (7)
Passive smoking	32 (43)
Never active smoking	33 (45)
Clinical characteristics	
Age at diagnosis, median years (IQR)	7.4 (3.5 – 12.2)
Age at transplantation, median years (IQR)	9.4 (5.6 – 13.5)
Era of diagnosis	
1980-1990	8 (11)
1991-2000	24 (32)
2001-2010	42 (57)
Cancer diagnosis according to ICCC-3	
I: Leukemia	51 (69)
II: Lymphoma	12 (16)
Other[2]	11 (15)
Relapse	41 (55)
Treatment characteristics	
Lung toxic chemotherapeutic agents, type	
Busulfan	25 (34)
Carmustine	5 (7)
Lomustine	1 (1)
Bleomycin	4 (5)
Lung toxic chemotherapeutic agents, dose, mg/m^2 (IQR)	
Busulfan	422 (324 – 470)
Carmustine	300 (300 – 300)
Lomustine	190
Bleomycin	41 (30 - 46)
Radiotherapy involving the thorax [3]	52 (70)
Conditioning containing TBI	39 (53)
Thoracic surgery [4]	10 (14)
Transplant characteristics	
Stem cell donor	
Autologous	24 (32)
Allogeneic	50 (68)
HLA identical sibling / HLA matched (un-)related donor	29 (58)
HLA mismatch (un-)related / haploidentical	11 (22)
Source of transplant	
Cord blood	5 (7)
Peripheral blood	41 (55)
Bone marrow	26 (35)
Unknown	2 (3)

[1] For categorization of smoking status see supplemental material
[2] Other tumors include: tumor of the central nervous system (n=1), retinoblastoma (n=1), malignant bone tumor (n=5), soft tissue sarcoma (n=3), malignant germ cell tumor (n=1), neuroblastoma (n=1)
[3] Thoracic radiation fields according to COG guidelines, Version 4.0, Oct 2018, including radiation to the chest, whole lung, mediastinum, (mini-)mantle field, TBI and additionally
upper abdomen and thoracic spine, including craniospinal irradiation
[4] Thoracic surgery according to COG guidelines, Version 4.0, Oct 2018, including thoracotomy, chest wall surgery, rib resection, lobectomy, pulmonary metastasectomy and wedge resection

TABLE 2: Proportion of normal and reduced pulmonary function parameters for the first and last available test in childhood cancer survivors and its median z-score; N=74

	FIRST Test		**LAST Test**		
	Median (IQR)	n (%)	Median (IQR)	n (%)	p-value*
FEV1 z-score					
Whole cohort	-0.77 (-2.16 – 0.08)	73	-0.96 (-2.04 – -0.54)	73	0.215
normal	-0.08 (-0.76 – 0.23)	48 (65)	-0.63 (-0.91 – -0.13)	48 (65)	0.020
reduced	-2.52 (-3.16 – -2.16)	25 (34)	-2.62 (-3.54 – -2.04)	25 (34)	0.485
Missing		1 (1)		1 (1)	
FVC z-score					
Whole cohort	-0.91 (-2.25 – -0.23)	68	-1.20 (-2.24 – -0.61)	71	0.246
normal	-0.51 (-0.88 – -0.10)	45 (61)	-0.68 (-1.11 – -0.15)	43 (58)	0.217
reduced	-2.77 (-3.59 – -2.22)	23 (31)	-2.68 (-3.72 – -2.17)	28 (38)	0.762
Missing		6 (8)		3 (4)	
FEV1/FVC					
Whole cohort (ratio)	0.94 (0.89 – 0.97)	69	0.91 (0.87 – 0.94)	71	0.077
ratio ≥0.7	0.94 (0.89 – 0.97)	68 (92)	0.91 (0.87 – 0.94)	70 (95)	0.042
ratio <0.7	0.66	1 (1)	0.65	1 (1)	NA
Missing		5 (7)		3 (4)	
TLC z-score					
Whole cohort	-1.38 (-2.56 – -0.21)	64	-0.83 (-2.35 – 0.23)	66	0.887
normal	-0.25 (-1.16 – 1.13)	35 (47)	-0.17 (-0.80 – 0.38)	43 (58)	0.517
reduced	-2.59 (-3.26 – -2.46)	29 (39)	-3.68 (-4.39 – -2.26)	23 (32)	0.343
Missing		10 (14)		7 (10)	
RV z-score					
Whole cohort	0.36 (-1.34 – 2.05)	62	0.28 (-0.60 – 1.25)	66	0.345
normal	0.87 (-0.95 – 2.19)	53 (72)	0.52 (-0.32 – 1.51)	58 (78)	0.298
reduced	-2.24 (-2.96 – -1.96)	9 (12)	-3.49 (-4.09 – -2.27)	8 (11)	0.241
Missing		12 (16)		8 (11)	
Follow-up					
Time since diagnosis, years	3.0 (1.2 – 5.4)	74	9.3 (6.1 – 12.3)	74	

Normal: measured value ≥ -1.645 z-score
Reduced: measured value <-1.645
Resistance: normal if <1.2kPa*s in adults and <1.0kPa*s in children
*ttest for continuous variables comparing median z-score between first and last test

TABLE 3: Results of the final linear mixed-effect multilevel regression models. All coefficients are put in relation to a male reference patient treated with autologous HSCT between 1980-1990, with no radiotherapy to the chest, no lung toxic chemotherapy, and no relapse (N=74 CCSs)

	Coefficient	**P>|z|**	**95% Conf. Interval**	
FEV1 z-score (n=407 PFT)				
Final model: no time interaction				
Intercept (_cons)	0.499	0.69	-0.921	1.919
Gender (ref. male)	-0.664	0.013	-1.187	-0.140
Type of HSCT (ref. autologous)	0.481	0.113	-0.113	1.076
Radiotherapy to lung (ref. no)	-1.306	0.001	-2.055	-0.558
Lung toxic chemotherapy (ref. no)	-0.559	0.123	-1.270	0.152
Relapse (ref. = no)	0.395	0.154	-0.148	0.937
Decade of diagnosis (ref. 1980-1990)				
1991 – 2000	-0.667	0.183	-1.647	0.314
2001 - 2010	-0.197	0.678	-1.131	0.736
Time since diagnosis [decrease per year]	-0.061	0.000	-0.094	-0.027
FVC z-score (n=395 PTF)				
Final model: no time interaction				
Intercept (_cons)	0.147	0.837	-1.252	1.546
Gender (ref. male)	-0.387	0.152	-0.916	0.143
Type of HSCT (ref. autologous)	0.533	0.077	-0.058	1.123
Radiotherapy to lung (ref. no)	-1.473	<0.001	-2.207	-0.739
Lung toxic chemotherapy (ref. no)	-0.647	0.069	-1.347	0.051
Relapse (ref. = no)	0.237	0.395	-0.309	0.783
Decade of diagnosis (ref. 1980-1990)				
1991 – 2000	-0.312	0.531	-1.287	0.663
2001 - 2010	-0.083	0.861	-1.008	0.843
Time since diagnosis [decrease per year]	-0.058	0.003	-0.097	-0.019
TLC z-score (n=390 PFT)				
Final model: time interaction for type of HSCT and relapse				
Intercept (_cons)	-1.584	0.251	-4.293	1.124
Gender (ref. male)	0.729	0.134	-0.224	1.682
Type of HSCT (ref. autologous)	-0.510	0.479	-1.923	0.903
Radiotherapy to lung (ref. no)	-0.717	0.292	-2.051	0.616
Lung toxic chemotherapy (ref. no)	-0.587	0.364	-1.855	0.681
Relapse (ref. no)	1.704	0.015	0.333	3.075
Decade of diagnosis (ref. 1980-1990)				
1991 – 2000	-1.052	0.241	-2.814	0.711
2001 - 2010	-0.204	0.811	-1.874	1.465
Change in TLC z-score per year				
Time since diagnosis (continuous per year)	0.103	0.236	-0.067	0.272
Interaction Type of HSCT (ref. autologous)	0.123	0.136	-0.038	0.284
Interaction relapse (ref. no)	-0.258	0.001	-0.414	0.103
RV z-score (n=382 PFT)				
Final model: time interaction for relapse				
Intercept (_cons)	-0.309	0.764	-2.326	1.707
Gender (ref. male)	0.036	0.918	-0.650	0.722
Type of HSCT (ref. autologous)	-0.155	0.692	-0.923	0.612
Radiotherapy to lung (ref. no)	0.663	0.181	-0.307	1.634
Lung toxic chemotherapy (ref. no)	-0.298	0.518	-1.202	0.606
Relapse (ref. = no)	1.085	0.100	-0.208	2.378
Decade of diagnosis (ref. 1980-1990)	-0.785	0.226	-2.055	0.485
1991 – 2000	-0.127	0.838	-1.346	1.902
2001 - 2010				

Time since diagnosis (continuous per year)	0.108	0.095	-0.019	0.234
Time interaction with relapse (ref. no)	-0.231	0.010	-0.405	-0.055
DLCO z-score (n=185 PFT)				
Final model: no time interaction				
Intercept (_cons)	1.948	0.192	-0.977	4.872
Gender (ref. male)	-0.514	0.341	-1.575	0.546
Type of HSCT (ref. autologous)	0.498	0.381	-0.616	1.613
Radiotherapy to lung (ref. no)	-1.279	0.093	-2.773	0.213
Lung toxic chemotherapy (ref. no)	-0.707	0.296	-2.033	0.619
Relapse (ref. = no)	0.138	0.809	-0.986	1.263
Decade of diagnosis (ref. 1980-1990)				
1991 – 2000	-2.465	**0.004**	-4.151	-0.780
2001 - 2010	-2.447	**0.004**	-4.111	-0.784
Time since diagnosis [decrease per year]	0.015	0.748	-0.079	0.111

Abbreviations: HSCT, hematopoietic stem cell transplantation; lufutime, time variable from diagnosis to pulmonary function test; PFT, pulmonary function test result

Time interaction was only included in the model when risk factors were significant ($p < 0.05$) at separate levels. Additional information (results from separate analyses and random effects parameters) in the supplement

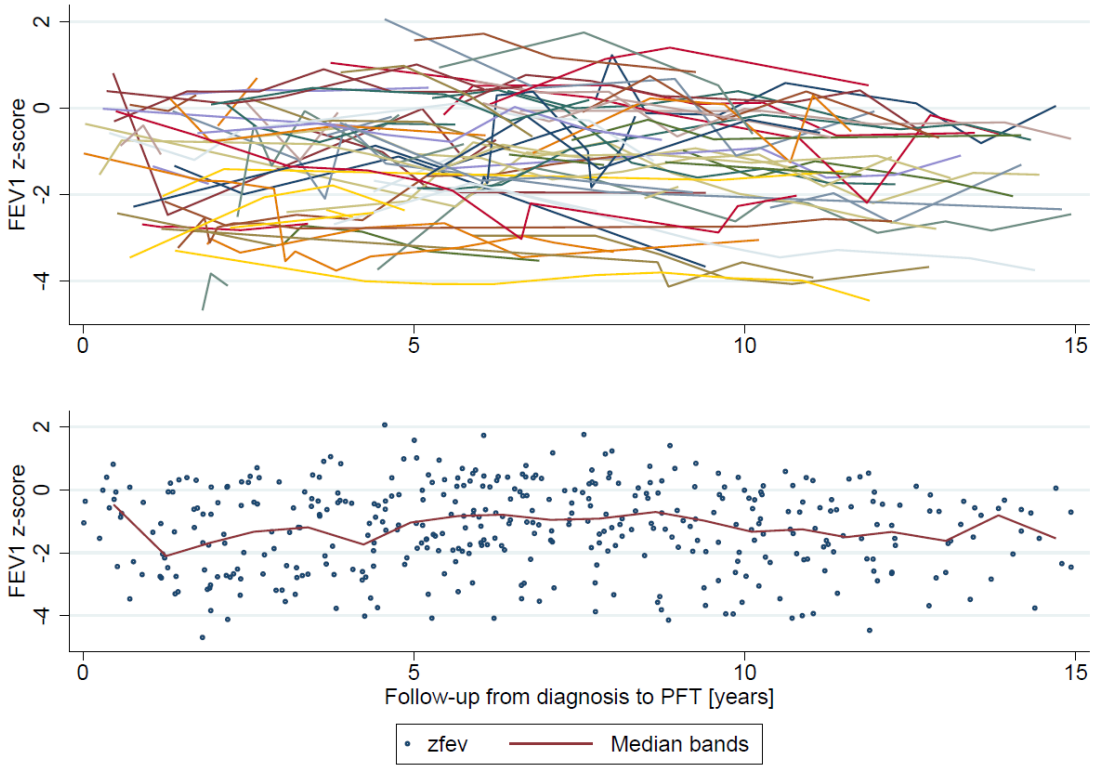


FIGURE 1: Longitudinal trajectory of FEV1 z-score over time, upper part with results of each patient connected, lower part showing the median of all observations over time (n=74; 411 tests)

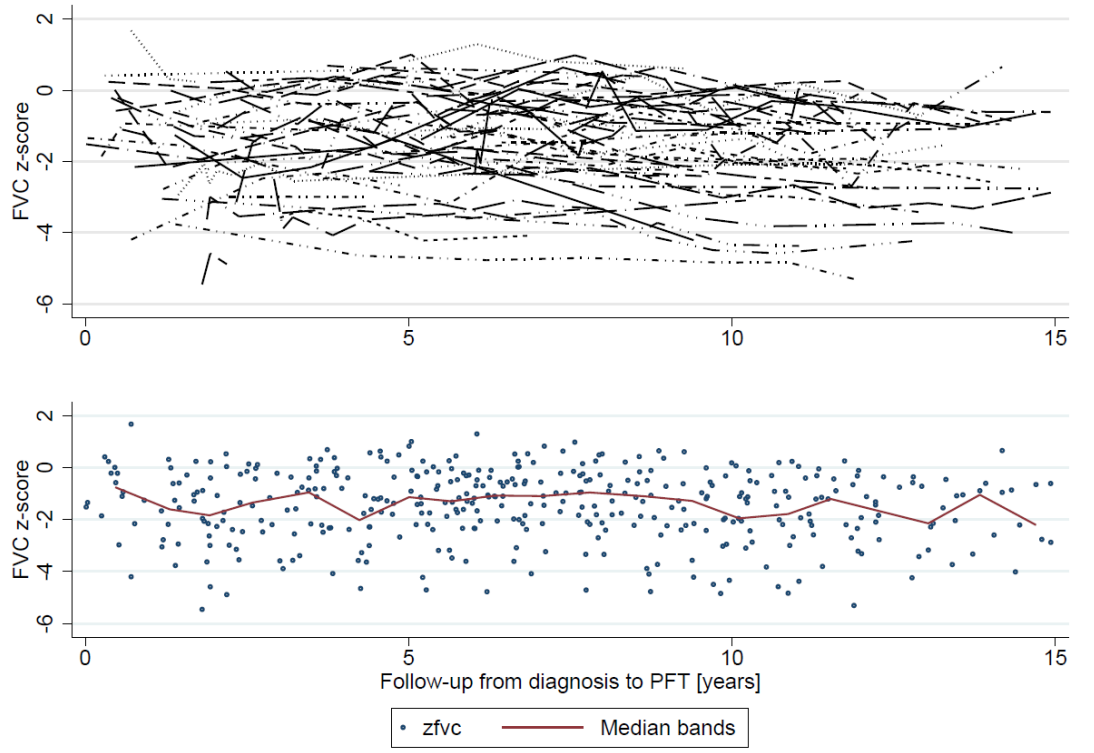


FIGURE 2: Longitudinal trajectory of FVC z-score over time (n=73; 395 tests)

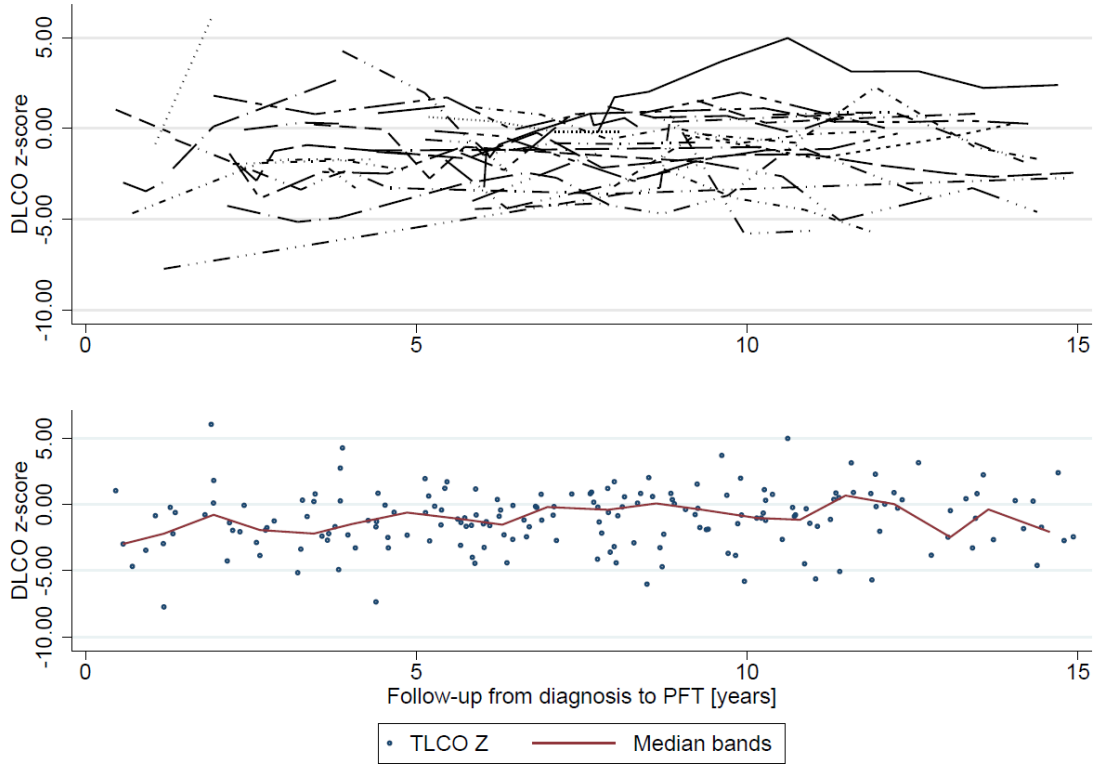
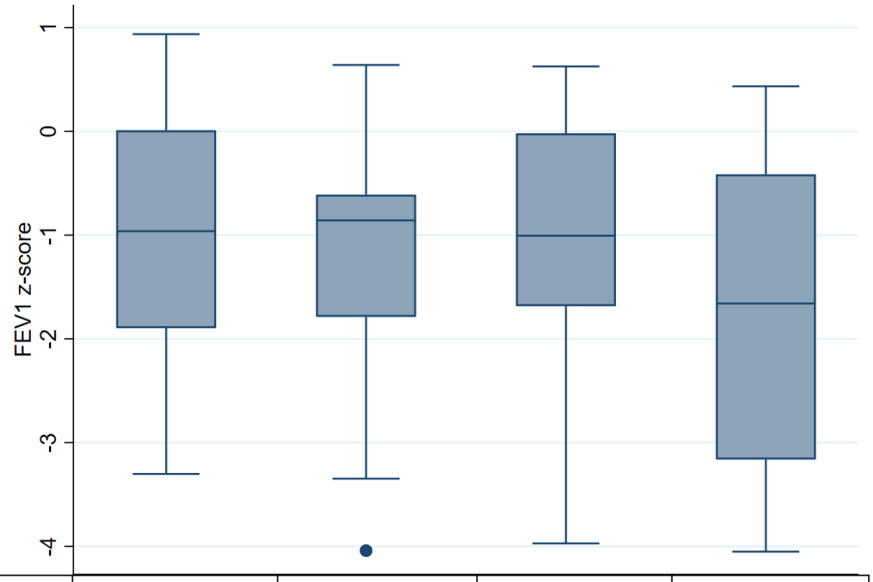
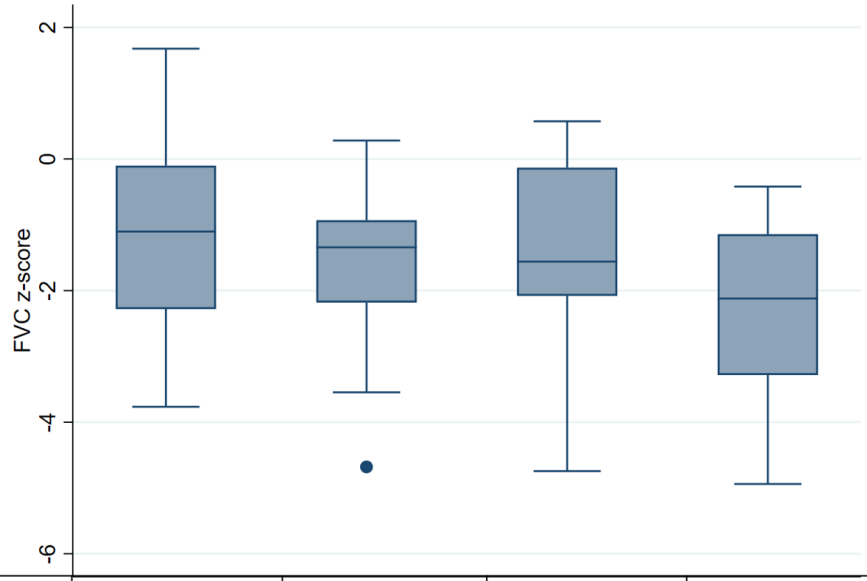


FIGURE 3: Longitudinal trajectory of DLCO z-score over time (n=46; 185 tests)



A

	Before HSCT	< 2 years	2 – 4.9 years	≥ 5 years
Number	24	20	18	15
Median (IQR) z-score	-0.96 (-1.89 – 0.01)	-0.86 (-1.79 - -0.61)	-1.00 (-1.68 - -0.02)	-1.66 (-3.16 - -0.41)
p-value (t-test)	reference	0.614	0.709	0.063



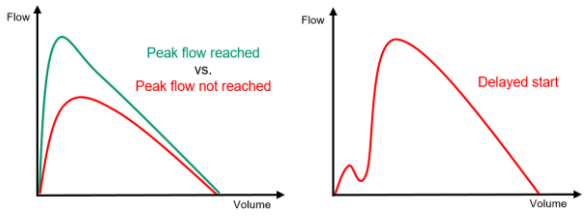
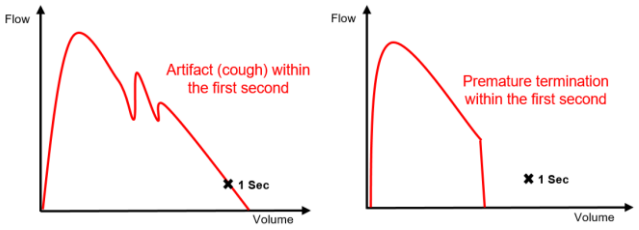
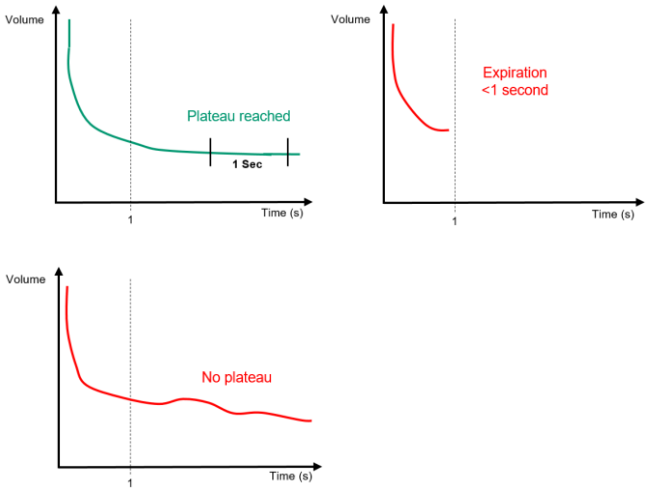
B

	Before HSCT	< 2 years	2 – 4.9 years	≥ 5 years
Number	23	18	16	14
Median (IQR) z-score	-1.10 (-2.28 - -0.10)	-1.34 (-2.18 - -0.93)	-1.56 (-2.08 - -0.13)	-2.12 (-3.28 - -1.14)
p-value (t-test)	reference	0.538	0.592	0.022

FIGURE 4: Median FEV1 and FVC z-score 24 childhood cancer survivors with testing before HSCT compared to their results <2 years from HSCT, 2-<5 years and ≥5 years from HSCT. A) Course of FEV1, B) Course of FVC

SUPPLEMENTAL EXPLANATION E1: Factors considered in the quality assessment of pulmonary function test results

Table and included figures adapted from Salem et al

1. Start of breathing maneuver	
- Steep rise in the curve - Visually clear PEF reached - No delayed start	
2. Course of the curve	
- No glottis closure - No coughing - No premature termination - No obstruction of the mouthpiece - No leakage	
3. End of the forced expiration	
- Reaching of a plateau - No premature termination	

SUPPLEMENTAL TABLE S1: Characteristics of childhood cancer survivors with one pulmonary function test (N=12)

	Total one test (n=12)	**Total ≥2 tests[2]** (n=74)
	n (%)	
Sociodemographic and lifestyle characteristics		
Sex, male	8 (67)	43 (58)
Ethnicity, white	12 (100)	72 (97)
Clinical characteristics		
Age at diagnosis, median years (IQR)	8.3 (3.5 – 15.1)	7.4 (3.5 – 12.2)
Age at transplantation, median years (IQR)	10.5 (3.9 – 15.6)	9.4 (5.6 – 13.5)
Era of diagnosis		
1980-1990	1 (8)	8 (11)
1991-2000	6 (50)	24 (32)
2001-2010	5 (42)	42 (57)
Cancer diagnosis according to ICCC-3		
I: Leukemia	4 (33)	51 (69)
II: Lymphoma	1 (9)	11 (15)
IV: Neuroblastoma	4 (33)	1 (1)
Other[2]	3 (25)	11 (15)
Relapse	2 (17)	41 (55)
Pulmonary function characteristics		
Follow-up[1] (years, IQR, range)	2.1 (0.6 – 10.6, 0.3 – 15.4)	9.3 (1.2 – 12.3, 1.2 – 14.9)
FEV1 z-score (median, IQR)	-0.8 (-1.8 - -0.4)	-0.8 (-2.2 – 0.08)
FVC z-score (median, IQR)	-1.2 (-2.4 - -0.4)	-0.9 (2.2 – -0.2)
TLC z-score (median, IQR)	-1.2 (-2.5 – 0.04)	-1.4 (-2.6 – 0.2)
RV z-score(median, IQR)	0.7 (-0.7 – 2.6)	0.4 (-1.3 – 2.1)
DLCO z-score (median, IQR)	-0.5 (-1.1 – 0.2)	-1.3 (-2.9 – -0.2)

[1] Follow-up: time from diagnosis to last PFT
[2] CCSs with at least two tests and follow-up time censored at 15 years

SUPPLEMENTAL TABLE S2: Additional characteristics of the included childhood cancer survivors (n=74)

	Total (n=74)
	n(%)
Diagnosis according to ICCC3	
Leukemia	51 (69%)
(Ia) Acute lymphoblastic leukemia	30 (59)
(Ib) Acute myeloid leukemia	12 (23)
(Ic) Chronic myeloproliferative syndrome	4 (8)
(Id) Myelodysplastic syndrome	5 (10)
Lymphoma	11 (14%)
(IIa) Hodgkin lymophoma	4 (36)
(IIb) Non-Hodgkin lymphoma	5 (45)
(IIc) Burkitt lymphoma	2 (18)
Neuroblastoma	1 (1%)
Other Tumors	11 (15%)
(IIIc) Embryonal brain tumor	1 (9)
(V) Retinoblastoma	1 (9)
(VIIIc) Ewing tumor	5 (45)
(IXd) Other specified soft tissue sarcoma	3 (27)
(Xc) Malignant gonadal germ cell tumor	1 (9)
Specific transplant characteristics in allogeneic population (n=50)	
CMV status	
Donor and recipient negative	25 (50)
Donor and recipient positive	12 (24)
Donor positive, recipient negative	6 (12)
Donor negative, recipient positive	5 (10)
Unknown	2 (4)
Blood group	
Match	23 (46)
Major mismatch	12 (24)
Minor mismatch	12 (24)
Bidirectional mismatch	1 (2)
Missing	2 (4)
GvHD	
No	8 (16)
Yes	42 (84)
Unknown	1 (2)
Acute	33 (79)
Chronic	6 (14)
Skin	5 (83)
Skin and other location	1 (17)

Abbreviations: CMV, cytomegalovirus; GvHD, graft versus host disease; HLA, human leukocyte antigen; ICCC-3, International Classification of Childhood Cancer, 3rd edition; TBI, total body irradiation

SUPPLEMENTAL TABLE S3: Characteristics of 411 pulmonary function test results in the study population (N=74)

	Total (n=411 PFTs)
	n (%)
Number of FEV1 measurements (indicative for spirometry)	407 (99)
Number of TLC measurements (indicative for body plethysmography)	390 (95)
Number of DLCO measurements	185 (45)
Pulmonary function test per survivor (n=74 survivors)	Mean 5 (range 2 – 12)
Median time between diagnosis and first PFT, years	Median 3.0 (IQR 1.2 –5.4)
Median time between diagnosis and last PFT, years	Median 9.3 (IQR 6.1 – 12.3)

SUPPLEMENTAL TABLE S4: Linear mixed-effect multilevel regression model for **FEV1** z-scores testing interaction with time since diagnosis for each risk factor separately

	Coefficient	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Model without time interaction (Final model)					
Intercept (_cons)	0.499	0.724	0.69	-0.921	1.919
Gender (ref. male)	-0.664	0.267	0.013	-1.187	-0.140
Type of HSCT (ref. autologous)	0.481	0.304	0.113	-0.113	1.076
Radiotherapy to lung (ref. no)	-1.306	0.382	0.001	-2.055	-0.558
Lung toxic chemotherapy (ref. no)	-0.559	0.363	0.123	-1.270	0.152
Relapse (ref. = no)	0.395	0.277	0.154	-0.148	0.937
Decade of diagnosis (ref. 1980-1990)					
1991 – 2000	-0.667	0.500	0.183	-1.647	0.314
2001 - 2010	-0.197	0.476	0.678	-1.131	0.736
Time since diagnosis [decrease per year]	-0.061	0.017	0.000	-0.094	-0.027
Random effects Parameters	**Estimate**	**Standard error**		**95% conf. Interval**	
Variance "random effect slope"[1] (lufutime)	0.009	0.003		0.005	0.019
Variance "random effect intercept"[2]	1.657	0.359		1.084	2.534
Covariance[3]	-0.076	0.029		-0.135	-0.018
Results from testing interaction with time	**Coefficient**	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Gender # lufutime	0.018	0.036	0.602	-0.051	0.089
Type of HSCT # lufutime	0.015	0.037	0.677	-0.057	0.088
Radiotherapy # lufutime	0.007	0.039	0.849	-0.070	0.085
Lung toxic chemotherapy # lufutime	-0.009	0.035	0.793	-0.077	0.059
Relapse # lufutime	0.008	0.034	0.820	-0.059	0.075
Decade of diagnosis # lufutime					
1991 – 2000	-0.015	0.060	0.808	-0.132	0.104
2001 - 2010	0.0004	0.772	0.994	-1.044	1.984

[1] Variance "random effect slope" = variance of average change in FEV1 per year of follow-up between patients (cluster)
[2] Variance "random effect intercept" = variance between patients in their average FEV1 z-scores at diagnosis
[3] Covariance = correlation between the variance of the slope and variance of the intercept; negative covariance ≈ the higher the intercept the lower the slope

Abbreviations: HSCT, hematopoietic stem cell transplantation; lufutime, time variable from diagnosis to pulmonary function test

SUPPLEMENTAL TABLE S5: Linear mixed-effect multilevel regression model for **FVC** z-scores testing interaction with time since diagnosis for each risk factor separately

	Coefficient	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Model without time-interaction (Final model)					
Intercept (_cons)	0.147	0.714	0.837	-1.252	1.546
Gender (ref. male)	-0.387	0.270	0.152	-0.916	0.143
Type of HSCT (ref. autologous)	0.533	0.302	0.077	-0.058	1.123
Radiotherapy to lung (ref. no)	-1.473	0.374	<0.001	-2.207	-0.739
Lung toxic chemotherapy (ref. no)	-0.647	0.357	0.069	-1.347	0.051
Relapse (ref. = no)	0.237	0.279	0.395	-0.309	0.783
Decade of diagnosis (ref. 1980-1990)					
1991 – 2000	-0.312	0.497	0.531	-1.287	0.663
2001 - 2010	-0.083	0.472	0.861	-1.008	0.843
Time since diagnosis [decrease per year]	-0.058	0.019	0.003	-0.097	-0.019
Random effects Parameters	**Estimate**	**Standard error**		**95% conf. Interval**	
Variance "random effect slope"[1] (lufutime)	0.015	0.004		0.008	0.027
Variance "random effect intercept"[2]	1.471	0.325		0.954	2.269
Covariance[3]	-0.077	0.035		-0.146	-0.008
Results from testing interaction with time	**Coefficient**	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Gender # lufutime	0.040	0.041	0.327	-0.040	0.121
Type of HSCT # lufutime	0.007	0.042	0.869	-0.076	0.089
Radiotherapy # lufutime	-0.006	0.044	0.888	-0.094	0.081
Lung toxic chemotherapy # lufutime	0.015	0.039	0.709	-0.063	0.093
Relapse # lufutime	-0.021	0.039	0.602	-0.098	0.057
Decade of diagnosis # lufutime					
1991 – 2000	-0.017	0.598	0.808	-0.155	0.121
2001 - 2010	0.019	0.559	0.770	-0.112	0.151

[1] Variance "random effect slope" = variance of average change in FVC per year of follow-up between patients (cluster)
[2] Variance "random effect intercept" = variance between patients in their average FVC z-scores at diagnosis
[3] Covariance = correlation between the variance of the slope and variance of the intercept; negative covariance ≈ the higher the intercept the lower the slope

Abbreviations: HSCT, hematopoietic stem cell transplantation; lufutime, time variable from diagnosis to pulmonary function test

SUPPLEMENTAL TABLE S6: Linear mixed-effect multilevel regression model for **TLC** z-scores testing interaction with time since diagnosis for each risk factor separately (n=390 tests)

	Coefficient	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Model without time-interaction					
Intercept (_cons)	-1.245	1.312	0.342	-3.816	1.326
Gender (ref. male)	0.628	0.484	0.194	-0.320	1.576
Type of HSCT (ref. autologous)	0.325	0.543	0.550	-0.738	1.388
Radiotherapy to lung (ref. no)	-0.788	0.679	0.246	-2.120	0.543
Lung toxic chemotherapy (ref. no)	-0.375	0.641	0.558	-1.632	0.881
Relapse (ref. = no)	0.135	0.500	0.787	-0.845	1.116
Decade of diagnosis (ref. 1980-1990)					
1991 – 2000	-1.104	0.900	0.220	-2.869	0.660
2001 - 2010	-0.280	0.854	0.743	-1.955	1.394
Time since diagnosis [decrease per year]	0.047	0.043	0.274	-0.037	0.130
Random effects Parameters	**Estimate**	**Standard error**		**95% conf. Interval**	
Variance "random effect slope"[1] (lufutime)	0.012	0.024		0.0002	0.626
Variance "random effect intercept"[2]	2.795	2.026		0.675	11.577
Covariance[3]	-0.053	0.194		-0.434	0.327
Results from testing interaction with time	**Coefficient**	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Gender # lufutime	0.016	0.089	0.857	-0.159	0.192
Type of HSCT # lufutime	0.216	0.079	**0.007**	0.059	0.372
Radiotherapy # lufutime	-0.034	0.098	0.733	-0.227	0.159
Lung toxic chemotherapy # lufutime	-0.060	0.084	0.472	-0.225	0.104
Relapse # lufutime*	-0.308	0.076	**<0.01**	-0.457	-0.157
Decade of diagnosis # lufutime					
1991 – 2000	0.003	0.123	0.979	-0.238	0.245
2001 - 2010	0.163	0.118	0.170	-0.069	0.395
Final Model	**Coefficient**	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Intercept (_cons)	-1.584	1.382	0.251	-4.293	1.124
Gender (ref. male)	0.729	0.486	0.134	-0.224	1.682
Type of HSCT (ref. autologous)	-0.510	0.721	0.479	-1.923	0.903
Radiotherapy to lung (ref. no)	-0.717	0.680	0.292	-2.051	0.616
Lung toxic chemotherapy (ref. no)	-0.587	0.646	0.364	-1.855	0.681
Relapse (ref. no)	1.704	0.699	0.015	0.333	3.075

Decade of diagnosis (ref. 1980-1990)					
1991 – 2000	-1.052	0.899	0.241	-2.814	0.711
2001 - 2010	-0.204	0.852	0.811	-1.874	1.465
Change in TLC z-score per year					
Time since diagnosis (continuous per year)	0.103	0.087	0.236	-0.067	0.272
Interaction Type of HSCT (ref. autologous)	0.123	0.082	0.136	-0.038	0.284
Interaction relapse (ref. no)	-0.258	0.079	0.001	-0.414	0.103

[1] Variance “random effect slope” = variance of average change in TLC per year of follow-up between patients (cluster)
[2] Variance “random effect intercept” = variance between patients in their average TLC z-scores at diagnosis
[3] Covariance = correlation between the variance of the slope and variance of the intercept; negative covariance ≈ the higher the intercept the lower the slope
* autocorrelation of residuals omitted because convergence not achievable

Abbreviations: HSCT, hematopoietic stem cell transplantation; lufutime, time variable from diagnosis to pulmonary function test

SUPPLEMENTAL TABLE S7: Linear mixed-effect multilevel regression model for **RV** z-scores testing interaction with time since diagnosis for each risk factor separately (n=382 tests)

	Coefficient	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Model without time-interaction					
Intercept (_cons)	0.481	0.999	0.48	-1.478	2.439
Gender (ref. male)	-0.072	0.347	0.836	-0.752	0.609
Type of HSCT (ref. autologous)	-0.084	0.391	0.831	-0.849	0.682
Radiotherapy to lung (ref. no)	0.562	0.497	0.259	-0.413	1.537
Lung toxic chemotherapy (ref. no)	-0.192	0.457	0.676	-1.088	0.705
Relapse (ref. = no)	-0.330	0.352	0.348	-1.019	0.359
Decade of diagnosis (ref. 1980-1990)					
1991 – 2000	-0.790	0.649	0.224	-2.063	0.483
2001 – 2010	-0.160	0.626	0.798	-1.387	1.067
Time since diagnosis [decrease per year]	-0.016	0.049	0.750	-0.112	0.081
Random effects Parameters	**Estimate**	**Standard error**		**95% conf. Interval**	
Variance "random effect slope"[1] (lufutime)	0.061	0.037		0.018	0.201
Variance "random effect intercept"[2]	3.084	1.708		1.042	9.131
Covariance[3]	-0.381	0.253		-0.878	0.115
Results from testing interaction with time	**Coefficient**	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Gender # lufutime	0.054	0.101	0.591	-0.144	0.252
Type of HSCT # lufutime	0.166	0.094	0.077	-0.018	0.349
Radiotherapy # lufutime	-0.071	0.111	0.522	-0.289	0.147
Lung toxic chemotherapy # lufutime	-0.036	0.099	0.718	-0.229	0.158
Relapse # lufutime	-0.231	0.089	**0.010**	-0.405	-0.056
Decade of diagnosis # lufutime					
1991 – 2000	0.217	1.110	0.845	-1.958	2.393
2001 - 2010	-0.469	1.032	0.649	-2.493	1.553
Final Model	**Coefficient**	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Intercept (_cons)	-0.309	1.029	0.764	-2.326	1.707
Gender (ref. male)	0.036	0.350	0.918	-0.650	0.722
Type of HSCT (ref. autologous)	-0.155	0.392	0.692	-0.923	0.612
Radiotherapy to lung (ref. no)	0.663	0.495	0.181	-0.307	1.634
Lung toxic chemotherapy (ref. no)	-0.298	0.461	0.518	-1.202	0.606
Relapse (ref. = no)	1.085	0.659	0.100	-0.208	2.378

Decade of diagnosis (ref. 1980-1990)	-0.785	0.648	0.226	-2.055	0.485
1991 – 2000	-0.127	0.622	0.838	-1.346	1.902
2001 - 2010					
Change in TLC z-score per year					
Time since diagnosis (continuous per year)	0.108	0.065	0.095	-0.019	0.234
Interaction with relapse (ref. no)	-0.231	0.089	0.010	-0.405	-0.055

[1] Variance “random effect slope” = variance of average change in RV per year of follow-up between patients (cluster)
[2] Variance “random effect intercept” = variance between patients in their average RV z-scores at diagnosis
[3] Covariance = correlation between the variance of the slope and variance of the intercept; negative covariance ≈ the higher the intercept the lower the slope

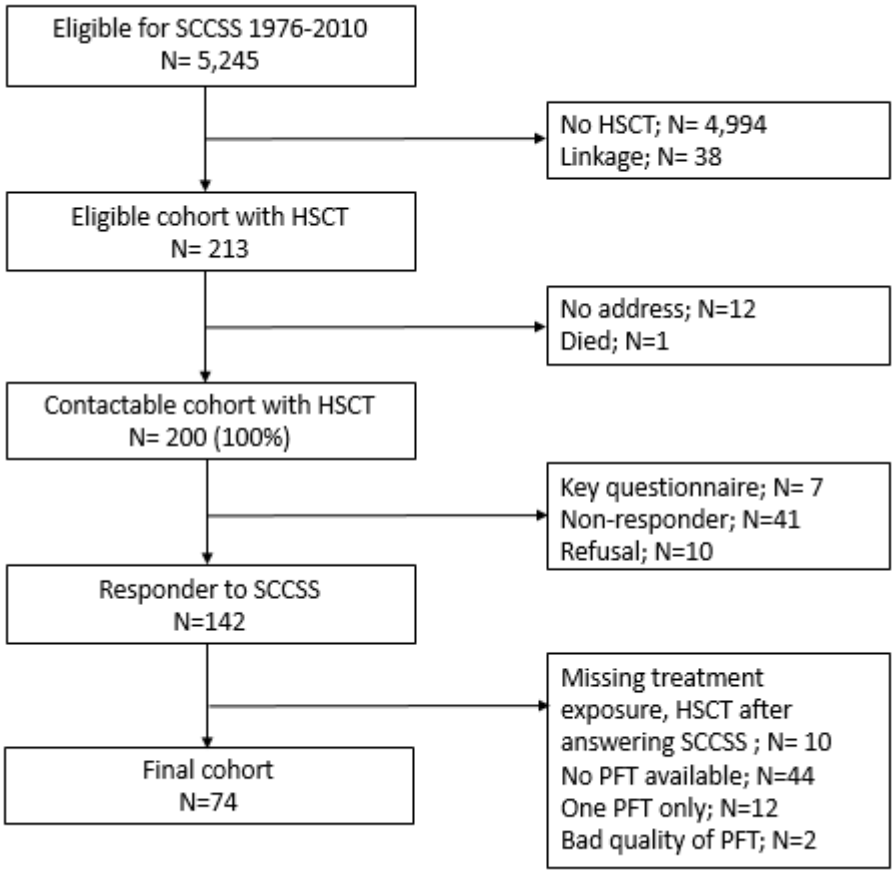
Abbreviations: HSCT, hematopoietic stem cell transplantation; lufutime, time variable from diagnosis to pulmonary function test

SUPPLEMENTAL TABLE S8: Linear mixed-effect multilevel regression model for **DLCO** z-scores testing interaction with time since diagnosis for each risk factor separately (n=185)

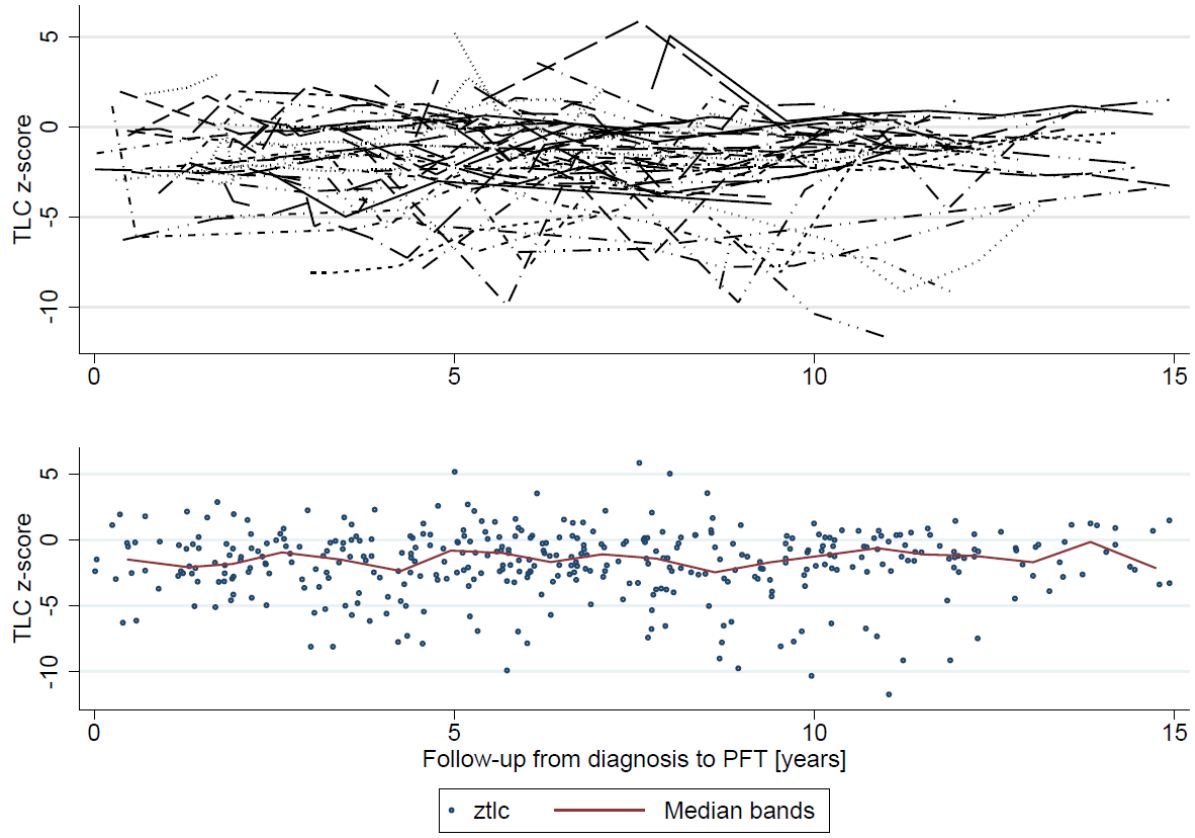
	Coefficient	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Model without time-interaction (Final model)					
Intercept (_cons)	1.948	1.492	0.192	-0.977	4.872
Gender (ref. male)	-0.514	0.541	0.341	-1.575	0.546
Type of HSCT (ref. autologous)	0.498	0.568	0.381	-0.616	1.613
Radiotherapy to lung (ref. no)	-1.279	0.762	0.093	-2.773	0.213
Lung toxic chemotherapy (ref. no)	-0.707	0.677	0.296	-2.033	0.619
Relapse (ref. = no)	0.138	0.574	0.809	-0.986	1.263
Decade of diagnosis (ref. 1980-1990)					
1991 – 2000	-2.465	0.859	**0.004**	-4.151	-0.780
2001 - 2010	-2.447	0.849	**0.004**	-4.111	-0.784
Time since diagnosis [decrease per year]	0.015	0.048	0.748	-0.079	0.111
Random effects Parameters	**Estimate**	**Standard error**		**95% conf. Interval**	
Variance "random effect slope"[1] (lufutime)	0.015	0.017		0.002	0.138
Variance "random effect intercept"[2]	3.311	1.872		1.094	10.026
Covariance[3]	-0.144	0.169		-0.475	0.188
Results from testing interaction with time	**Coefficient**	**Standard error**	**P>|z|**	**95% Conf. Interval**	
Gender # lufutime	0.183	0.098	0.063	-0.010	0.376
Type of HSCT # lufutime	0.059	0.100	0.558	-0.138	0.256
Radiotherapy # lufutime	-0.025	0.153	0.871	-0.325	0.275
Lung toxic chemotherapy # lufutime	-0.050	0.102	0.622	-0.251	0.149
Relapse # lufutime	0.051	0.106	0.627	-0.156	0.259
Decade of diagnosis # lufutime					
1991 – 2000	-0.128	0.124	0.302	-0.371	0.115
2001 - 2010	0.012	0.137	0.885	-0.249	0.289

[1] Variance "random effect slope" = variance of average change in DLCO per year of follow-up between patients (cluster)
[2] Variance "random effect intercept" = variance between patients in their average DLCO z-scores at diagnosis
[3] Covariance = correlation between the variance of the slope and variance of the intercept; negative covariance ≈ the higher the intercept the lower the slope

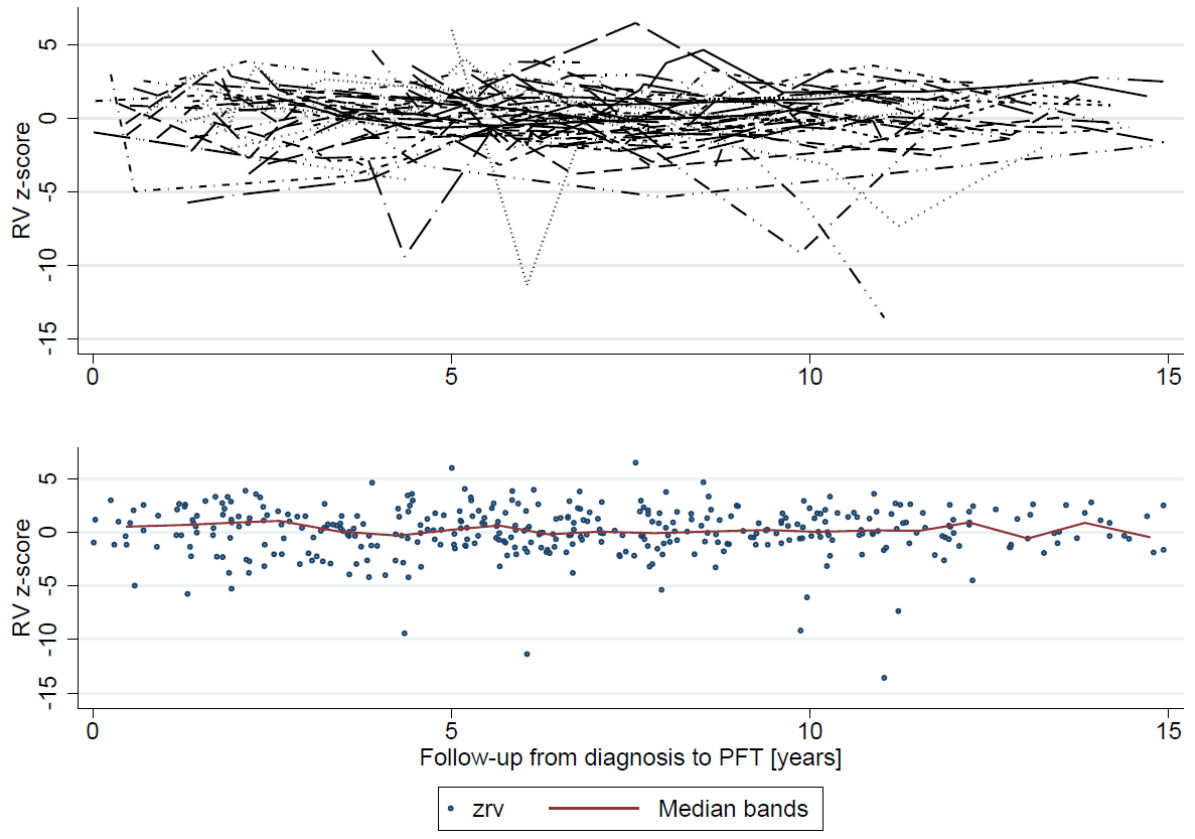
Abbreviations: HSCT, hematopoietic stem cell transplantation; lufutime, time variable from diagnosis to pulmonary function test



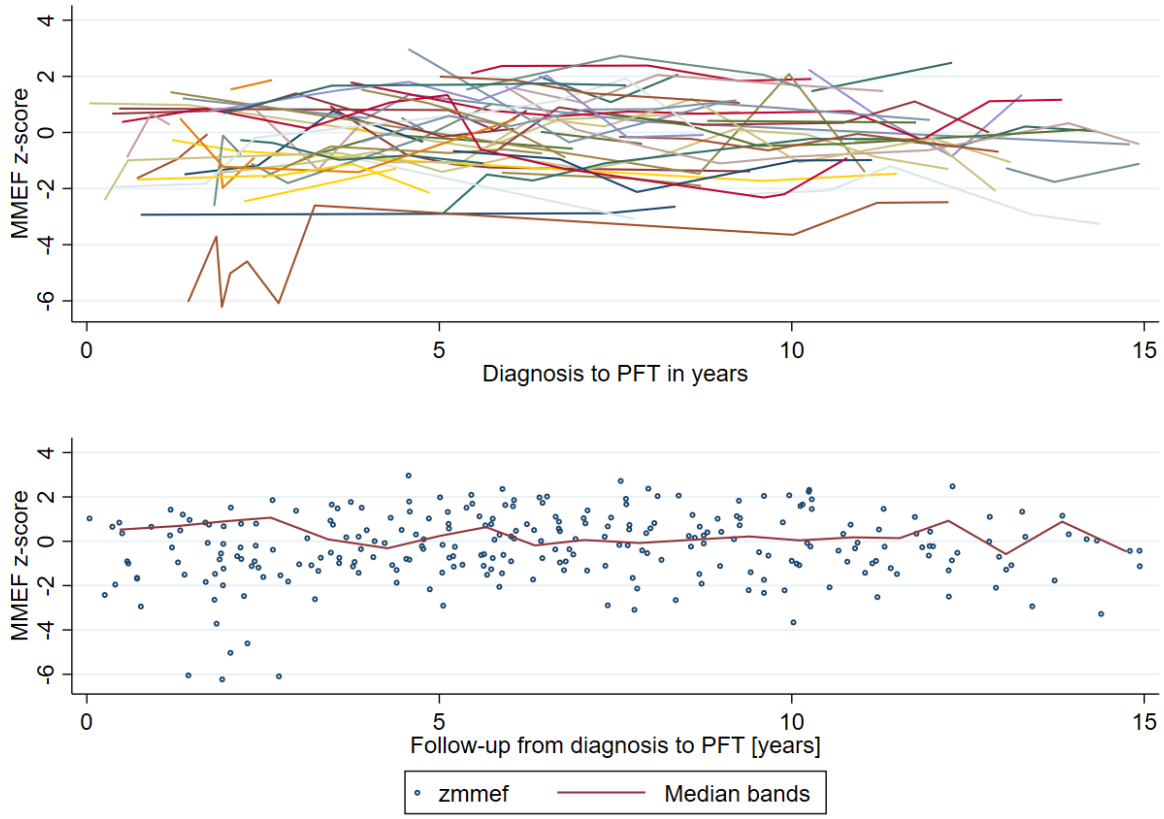
SUPPLEMENTAL FIGURE S1: Population tree of transplanted childhood cancer survivors eligible for this study.
CCS, childhood cancer survivor; HSCT, hematopoietic stem cell transplantation; SCCSS, Swiss Childhood Cancer Survivor Study; PFT, pulmonary function test



SUPPLEMENTAL FIGURE S2: Longitudinal trajectory of TLC z-score over time (390 tests)



SUPPLEMENTAL FIGURE S3: Longitudinal trajectory of RV z-score over time (390 tests)



SUPPLEMENTAL FIGURE S4: Longitudinal trajectory of MMEF z-score over time (270 tests)

ADDITIONAL SUPPLEMENTAL MATERIAL

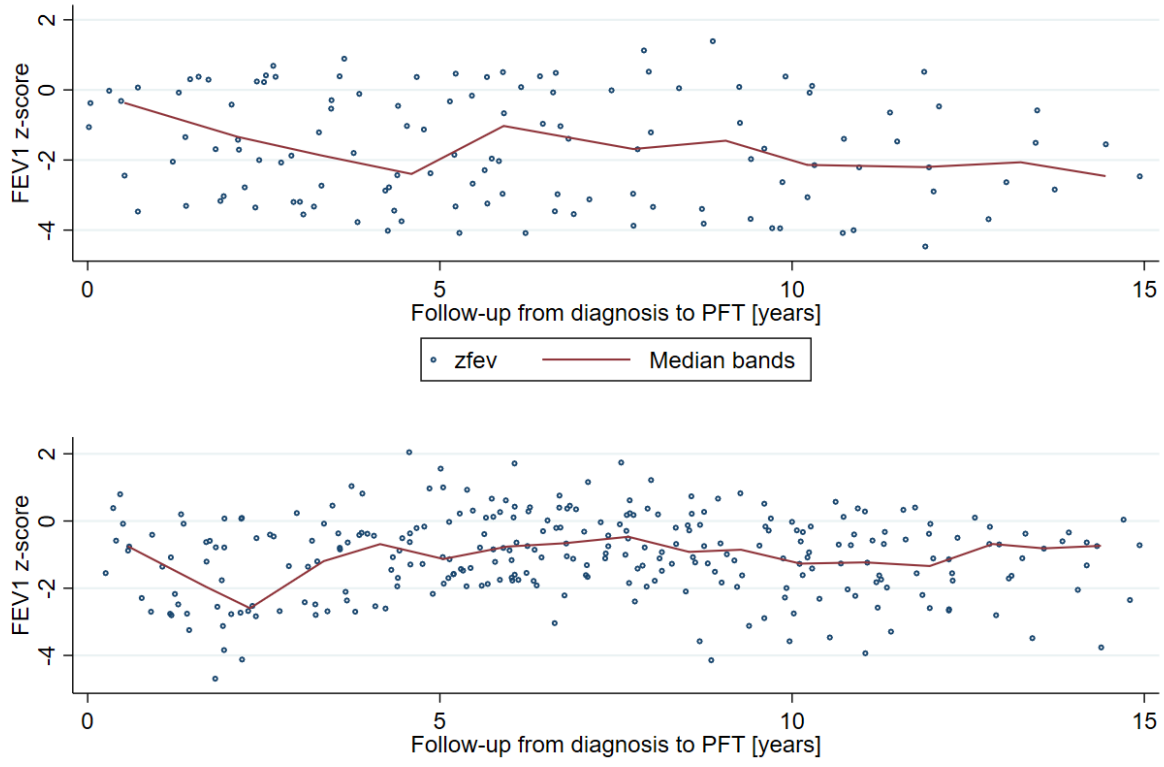


FIGURE xx: Longitudinal trajectory of FEV1 z-score in CCSs transplanted autologous (upper figure) and allogeneic (bottom figure)

4.3. Publication III

Lung function in Swiss childhood cancer survivors– a retrospective study

Original article

Rahel Kasteler*, **Maria Otth***, Florian Halbeisen, Florian Singer, Jochen Rössler, Nicolas X von der Weid, Marc Ansari, Claudia E Kuehni

*shared first authors

(Manuscript in preparation, to be submitted to European Respiratory Journal)

Own contribution to the project when submitting the thesis: Data analysis, interpretation of the results, writing manuscript, integration of co-authors comments

Lung function in Swiss childhood cancer survivors – a retrospective cohort study

Running title: Lung function in childhood cancer survivors

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CONFLICT OF INTEREST STATEMENT

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AUTHOR CONTRIBUTIONS

Maria Otth: Data analysis and interpretation, manuscript writing

Rahel Kasteler: Conceptualization, data collection, data analysis and interpretation, manuscript writing

Florian Halbeisen: Data analysis and interpretation

Florian Singer: Data interpretation

Marc Ansari: Manuscript review

Rössler J: Manuscript review

Nicolas X von der Weid: Manuscript review

Claudia E Kuehni: Conceptualization, funding acquisition, data analysis and interpretation, manuscript writing

All authors have revised earlier drafts and approved the final article.

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75 Julia Ruppel, and Ursina Roder).
76
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78 **Abbreviations:**

CCS	Childhood cancer survivors
CNS	Central nervous system
CSI	Craniospinal irradiation
CI	Confidence interval
DLCO	Diffusion capacity of the lung for carbon monoxide
FEV1	first second of forced expiration
FVC	forced vital capacity
HSCT	Hematopoietic stem cell transplantation
ICCC-3	International Classification of Childhood Cancer, Third edition
IQR	Interquartile range
PFT	Pulmonary function tests
SCCR	Swiss Childhood Cancer Registry
TLC	Total lung capacity

79

Abstract

Background

Many cancer treatments are lung toxic and contribute to increased pulmonary mortality and morbidity in childhood cancer survivors (CCSs). Pulmonary function tests allow to detect pulmonary dysfunction in early stages among asymptomatic patients. This study investigated pulmonary function in Swiss CCSs after exposure to lung toxic treatments, longitudinal pulmonary function trajectories, and associations with lung toxic treatments.

Methods

We retrospectively searched pulmonary function tests in hospital charts of CCSs who had been diagnosed with cancer between 1990 and 2013 and exposed to lung toxic chemotherapeutics or thoracic radiotherapy. We described pulmonary function (FEV1, FVC, FEV1/FVC, TLC and DLCO) as z-scores and percentage predicted, plotted lung function trajectories over time by fitting a loess curve, and determined risk factors for changes in FEV1 and FVC using multivariable linear regression models.

Results

We found 835 pulmonary function tests in 190 CCS, with a median of four spirometry and body plethysmography results per CCS and three DLCO measurements. 57% of 190 exposed CCSs showed at least one abnormal lung function parameter at median 6 years from diagnosis, with restrictive impairment being the most frequent (34%). The FVC and FEV1 trajectories started at z-scores around -1.5 at time of diagnosis and stayed lower than the general population mean (z-score of 0). CCSs

treated with thoracic surgery started at lower FEV1 compared to non-exposed CCSs (z-score: -1.19, 95%CI -2.03 – -0.36). None of the risk factors contributed significantly to an annual decrease in FVC or FEV1 z-scores, but exposure to lung toxic chemotherapeutics led to an annual increase in FEV1 (0.11, 95%CI 0.03 – 0.18).

Conclusion

A relevant proportion of CCSs showed reduced pulmonary function. The young age of the study population and rather short follow-up period indicate that long-term follow-up care is needed.

Keywords: childhood cancer survivors, lung toxic, lung function, longitudinal, Switzerland

Introduction

Childhood Cancer Survivors (CCSs) have an increased pulmonary mortality and morbidity compared to siblings or the general population (1-4). Lung toxic treatments, inevitable to treat cancer, can cause reversible and irreversible damage. Known for lung toxicity are chemotherapy with bleomycin, busulfan and nitrosureas (lomustine and carmustine), radiotherapy to the chest, and thoracic surgery. CCSs report more pulmonary symptoms, such as dyspnea at exertion or chronic cough, and suffer more often from recurrent pneumonia, fibrosis or emphysema than siblings (3-5). CCSs are more often hospitalized and die more frequently due to pulmonary diseases (6-8). All these outcomes are relatively late signs of pulmonary dysfunction, because the lung has a large functional reserve and pulmonary disease can be masked for a long time (9). Thus, data on self-reported diseases, hospitalization, and mortality are not representative of all CCSs with pulmonary dysfunction after lung toxic treatment. Pulmonary function tests (PFTs) may allow to detect pulmonary dysfunction at an earlier and often asymptomatic stage. Therefore, PFTs are recommended in several long-term follow-up guidelines for CCSs (10-12). Most studies described pulmonary function in CCSs based on percent predicted values calculated from different reference populations, with different reference values used for adults and children (13, 14). This makes it difficult to compare results across age groups and between studies. The Global Lung Initiative (GLI) published in 2012 spirometric prediction equations for patients aged 3-95 years and for all ethnic groups (15). In 2017 prediction equations for diffusion capacity of carbon monoxide (DLCO) have been published, which cover the age spectrum of 5-85 years (16).

In this study, we aim to describe pulmonary function in Swiss CCSs who had been exposed to lung toxic treatments, by comparing them to normal values from GLI and by describing the longitudinal trajectories. We also investigated associations with treatment exposure.

Methods

Study population

This study is nested in the Swiss Childhood Cancer Registry (SCCR). The SCCR is national, population-based registry of all children and adolescents diagnosed with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis prior to the age of 21 years who were living in Switzerland at diagnosis (17). The registered data include information on cancer diagnosis, classified according to the International Classification of Childhood Cancer, third edition (ICCC-3) (18), cancer treatments, and personal information such as date of birth or sex. Ethics approval was granted by the Ethics Committee of the Canton of Bern to the SCCR (KEK-BE: 166/2014). For the purpose of this study, we extracted information on date of birth, sex, diagnosis, date of diagnosis, and treatment protocol from the SCCR.

Inclusion criteria

We included all CCSs registered in the SCCR who have been diagnosed in one of the nine Swiss pediatric oncology centers before age of 16 years, between 1990 and 2013, have been exposed to at least one lung toxic chemotherapeutic agent or thoracic radiotherapy, and who have consented to further use of their medical data. We excluded CCSs with no medical records available in the clinics,

where we could not find a PFT, and those aged ≤6 years at time of the study due to feasibility of PFT.

We defined exposure to lung toxic chemotherapeutic agents as treatment with busulfan, bleomycin, and/or nitrosoureas (lomustine, carmustine) according to international long-term follow-up care guidelines (11, 12, 19). Radiotherapy was considered as lung toxic when administered as total body irradiation (TBI) or involving the mantle-field, chest, lungs, mediastinum or thoracic spine, which also includes craniospinal irradiation (11, 12, 19).

Medical records review and lung function measurements

We collected results of spirometry, body plethysmography, and diffusion capacity for carbon monoxide (DLCO), and information on treatment exposure during the year 2016. All medical records until 31th December 2015 were considered. We searched the electronic and paper-based medical records of all included CCSs in the Swiss pediatric oncology centers where the children had been diagnosed and treated, and the corresponding pediatric respiratory clinics. Swiss pediatric oncology centers refer CCSs to PFT laboratories on cite, which are all part of pediatric pulmonology departments in tertiary health centers. They generally perform PFTs according to ERS guidelines (20-22).

From the PFT results we extracted the test date, height and weight, and following outcome measures: forced vital capacity (FVC [l]) and forced expiratory volume in the first second (FEV_1 [l]) from spirometry, total lung capacity (TLC [l]) from body plethysmography, and diffusion capacity for carbon monoxide (DLCO [mmol/min/kPa]). As we assumed that the tests have been performed according to the ERS guidelines we did not check the test quality and did not assess the flow-

volume curve. We did check for consistency of the pulmonary function test results within patients. In case of outliers we consulted the original data again. We converted all outcomes into sex-, height-, and age-adjusted z-scores and percentage predicted using the Global Lung Initiative (GLI) 2012 reference values for FEV1, FVC, and DLCO (15, 23). For TLC z-score we used the reference equations by Stocks/Quanier (24). We plotted the raw data of each outcome and for each patient longitudinally over time since cancer diagnosis and evaluated them for outliers. If we detected outliers, we checked the entered raw data, corrected them if needed or kept them if the data had been entered correctly.

We calculated percentage predicted of FEV1, FVC, and DLCO to allow comparison of our results with existing literature. We categorized all outcome parameters calculated as z-scores as abnormal if they were <±1.645, which corresponds to the 5^{th} and 95^{th} percentile respectively of normally distributed lung function parameters (25). According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (26), we considered FEV1 <80% of predicted value and a FEV1/FVC ratio <0.70 as abnormal. Reduced FVC and diffusion capacity impairment were defined as <75% of predicted value, according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0) (27). We took CTCAE version 3.0 as the following versions no longer contain cutoff values for DLCO, and this version was also used by other authors assessing pulmonary function in CCSs (**Supplemental Table S4**). We grouped pulmonary dysfunction in three binary outcomes: restrictive impairment (TLC z-score <-1. 645), obstructive impairment (FEV1/FVC <0.70 and FEV1 <80% of predicted or FEV1/FVC <0.70 and FEV1<-1. 645), and diffusion capacity impairment (DLCO <75% predicted or z-score

<-1. 645). For this grouping we used the result of the last PFT in those with more than one test and the single available result in those with one test only.

For treatment exposure we collected detailed information on chemotherapeutics and radiation fields. We recorded information on thoracic surgery performed by thoracotomy or thoracoscopy for tumor/metastasis resection (wedge, lobe, whole lung), rib resection, laminectomy, bone biopsy, en bloc resection of rib, lung tissue, and/or diaphragm. We recorded autologous or allogeneic hematopoietic stem cell transplantation (HSCT) and we also collected information on relapse and survival. We classified CCS into three groups depending on the exposure to lung toxic treatment: chest radiotherapy, lung toxic chemotherapy, or both.

Statistical analysis

We used descriptive statistics, such as medians and interquartile ranges (IQR) to describe the study population and the presence of restrictive, obstructive and diffusion capacity impairment. In CCSs with at least two PFTs, we compared z-scores for FVC, FEV1, TLC, and DLCO between the first and last PFT by students t-test. We plotted trajectories of lung function z-scores for FEV1 and FVC by fitting a loess curve (locally weighted smoothing) and the respective 95% confidence interval.

We evaluated the association of potential risk factors with FEV1 and FVC trajectories, including time since first exposure to a lung toxic treatment, sex, cancer diagnosis, radiotherapy to the chest including CSI (yes/no), lung toxic chemotherapy (yes/no), HSCT (yes/no), and thoracic surgery (yes/no) by using multivariable linear mixed effects regression models with random intercept and random slope. This analysis allows to use repeated measurements per patient and takes clustering within each patient into account. We included time since first exposure to a lung toxic

treatment modality as a linear term. To evaluate whether changes over time in FEV1 or FVC were modified by the effect of a potential risk factor we included interaction terms between all a potential risk factor and time since first exposure to a lung toxic treatment. We performed likelihood ratio tests to assess whether each of the potential risk factors was associated with changes in FEV1 and FVC.

All analyses were performed using Stata (Version 16, Stata Corporation, Austin, Texas) or R 3.1.2 (www.r-project.org), linear mixed models were performed using the R-package lmer.

Results

Characteristics of study population

2989 CCSs had been diagnosed in a Swiss pediatric oncology center below the age of 16 years, between 1990 and 2013 and survived more than two years from cancer diagnosis. Of those, 14% (n=419) CCSs received lung toxic treatment according to the information on treatment protocols from the SCCR and were at least six years old at start of data collection. Medical records were not available for 47 CCSs (11%). In half (51%, n=190) of the remaining 372 CCSs we could find a PFT result **(Supplementary Figure S1)**. Half of the CCSs were male (57%, n=109), diagnosed with lymphoma (53%, n=100), and had a median follow-up time from diagnosis of 14 years (IQR 9 – 19). The most frequent lung toxic exposure was radiotherapy involving the chest (87%, n=165), followed by lung toxic chemotherapy (39%, n=49), HSCT (23%, n=44), and thoracic surgery (11%, n=21). One quarter of CCSs (26%, n=49) was exposed to a combination of radiotherapy involving the chest and lung toxic chemotherapy (**Table 1**).

Findings on pulmonary function test results

Most of the 190 eligible CCSs had at least one spirometry (n=188; 99%) or body plethysmography (n=179; 94%) performed during the follow-up period. DLCO had been performed in 137 CCS (72%). We collected 835 PFT results in total. The median number of spirometry tests per CCS was 4 (IQR 2-6, range 1-16), 4 (IQR 2-6, range 1-14) for body plethysmography, and 3 (IQR 2–5, range 1-13) for DLCO. In one fifth (n=36, 19%) of CCSs we found one PFT result only (data not displayed in table). As the last test of some CCSs did not include all measurements, only 187 CCS had data on FEV1, 186 on FVC, 178 on TLC, and 131 on DLCO. The median follow-up time from diagnosis to the last PFT was 6 years (IQR 3-9 years) **(Table 2)**.

In their last available test, one third (34%, n=64) of CCSs had a FEV1 z-score below -1.645 and slightly more (39%, n=72) had a FVC z-score below -1.645. Only two patients had a Tiffenau (FEV1/FVC ratio) below 0.7 plus FEV1 z-score below -1.645, meeting the GOLD-criteria for obstructive disease. TLC z-scores were lower than 1.645 in the last test of one third of CCSs (34%, n=64), indicating restrictive disease. Diffusion capacity impairment was present in 21% (n=28) **(Table 2, Supplementary table S1)**. Half of all CCSs (52%, n=99) had at least one outcome (z-score for FEV1, FVC, TLC or DLCO) below -1.645 in the last test. When looking at percentage predicted instead of z-scores to assess abnormal test results for FEV1, FVC, and DLCO, the proportion of CCSs with pathological values were similar for FEV1 (33% vs. 34%), FVC (30% vs. 39%), and DLCO (16% vs. 21%), eventhough z-score cutoffs detected more pathological tests **(Table 2, Supplementary Table S1)**.

Pulmonary function trajectories

The median time from diagnosis to first PFT was one year (IQR 0.3-2) and 6 years (IQR 4-9) to the last PFT with an average of 5 years evolved between first and last test. The median percent predicted or z-scores of the spirometric values (FEV1, FVC, FEV1/FVC) did not differ between the first and last test in CCSs with at least two tests performed **(Supplemental Table S2)**. The trajectories of FEV1 and FVC are displayed in **Figure 1** and **Figure 2**. For both outcomes, the curves started at z-scores around the value of -1.5 and did not show improvement or deterioration over the observed period. The course of the curves eight years and more from diagnosis has to be interpreted with caution as the number of tests diminishes rapidly and the 95% confidence is therefore becoming increasingly large but does not include the norm of the reference population (z-score of 0).

Risk factor analysis

Our multivariable linear mixed regression model showed that the intercept, corresponding to the starting point of the z-score at first exposure to a lung toxic treatment, starts at a z-score of -0.6 (95%CI -0.16 – 0.42) for FEV1 and -1.37 (95%CI -2.41 – -0.33) for FVC. For further explanation of the model see **Supplementary Explanation E1**. For FEV1, none of the analyzed risk factor led to an additional significant reduction in FEV1 z-score. For FVC, thoracic surgery led to an additional reduction in FVC z-score at time of first exposure (z-score estimate -1.19, 95%CI -2.03 – -0.36) (**Table 4**). Taking the intercept of the reference patient into account, CCSs treated with thoracic surgery started at a FVC z-score of -2.56 compared to CCSs not treated with thoracic surgery. Exposure to lung toxic chemotherapy was associated with an increase of FEV1 z-score over time of 0.11

(95%CI 0.03 – 0.18) per year, compared to CCSs without lung toxic chemotherapy. Taking the annual decrease of -0.07 for a reference patient without lung toxic chemotherapy into account, this results in an annual improvement of 0.04 (-0.07 + 0.11). None of the analyzed risk factors was significantly associated with a significant annual change in FVC z-score.

Discussion

PFT results of more than half of the CCSs in our cohort showed at least one abnormal parameter a median of 6 years after cancer diagnosis with no major changes in the longitudinal trajectories of FEV1 and FVC. CCSs treated with thoracic surgery started at a significantly lower FVC z-score compared to those not treated with thoracic surgery.

Prevalence of abnormal PFT measurements

The overall prevalence of any abnormal PFT measurement was 52% in our cohort. This proportion is slightly lower than in the SJLIFE cohort, where 65% showed at least one abnormal pulmonary function test (28). Applying the criteria of obstructive disease, restrictive disease and diffusion capacity impairment, 38% of CCSs from our cohort had at least one of these conditions. Again, this proportion was slightly lower than what had been found in two other publications, with 44% (29) and 45.5% (9) of CCSs who had obstructive disease, restrictive disease or diffusion capacity impairment. The proportion of CCSs having obstructive disease, defined as FEV1/FVC<0.7 and FEV1<80% of predicted value, was <5% in all three studies (our cohort: 1%, Mulder at al: 2%, Armenian et al: 4%) (9, 29). One third (34%) of CCSs in our cohort had restrictive disease, defined as TLC z-score <-1.645 and one fourth

(24%) to one fifth (18%) in the other two studies, which used the definition of TLC <75% of predicted value. For diffusion capacity impairment, a lower proportion of CCSs did suffer from diffusion capacity impairment, defined as <75% of predicted value, in our cohort (16%) compared to the other cohorts (40% and 35%). The difference in the prevalence of diffusion capacity impairment might be explained by the source of the PFT results. For this study we collected all available tests, independent of the reason why they were carried out. It might be that some tests had not been performed for surveillance purposes but for further evaluation of symptoms of lung disease, including asthma. For such questions DLCO is often not measured, but only spirometry and/or body plethysmography are done. The tests analyzed by Mulder and Armenian, in contrast, came from late effects outpatient clinics and had been performed for surveillance purpose only.

Comparing the proportion of CCSs with obstructive disease from our cohort with data from Record et al. underlines that different definitions of obstructive disease largely impact the primary outcome (**Supplemental Table S4**) (13). The broader definition used by Records et al resulted in a larger proportion of CCSs with obstructive disease (26%). This comparison highlights that results on pulmonary dysfunction can only be interpreted after taking the reference values used and cutoff values into account. The use of different cutoff values makes the interpretation and practical implementation of the results in clinics difficult. Also the use of z-scores instead of percentage predicted results in different proportions of pathological results (**Supplementary Table S1**). The research community should agree on standard cutoffs to make research on pulmonary disease in childhood cancer survivors more homogenous and comparable.

366

367 *Longitudinal trajectory*

368 The slightly undulating curve of FEV1 and FVC trajectories in our cohort is
369 similar to the results of other studies, which assessed pulmonary function in CCSs
370 after HSCT (30, 31) or CCSs exposed to whole lung irradiation (32).The initial
371 improvement might be explained by a recovery of partially reversible processes,
372 such as pneumonitis. This subsequent decrease could be due to progressive
373 irreversible changes, such as pulmonary fibrosis, or by physiological aging, which
374 has been shown to begin earlier in CCSs compared to the general population (33).
375 Despite this undulating shape, the best fitted line for the whole cohort is constantly
376 below -1 z-score for FEV1 and FVC. Considering that the population included in this
377 study is rather young and included mainly the first 10 years after diagnosis, it might
378 be that the deterioration would increase with longer observation. Research is needed
379 to determine how lung function develops in aging and adult survivors of childhood
380 cancer. Until then long term surveillance seems to be indicated in the CCSs.

381

382 *Risk factors*

383 We found that only thoracic surgery as a risk factor, was significantly
384 associated with lower PFT results, which was FVC z-score. This finding is most
385 probably due to the fact that the whole cohort was exposed to at least one lung toxic
386 treatment modality and therefore, the effects of single lung toxic treatment modalities
387 might be underestimated. The high exposure of the entire cohort is also supported
388 by the low z-scores of the evaluated PFT results (-1.5) compared to the general
389 population mean of z-scores of zero. As treatment with thoracic surgery alone was
390 not an inclusion criterion for this study, all CCSs exposed to thoracic surgery have

been exposed to at least one other lung toxic treatment modality, e.g. chemotherapy or radiotherapy. As a result, the negative effect of thoracic surgery on FEV1 and FVC in our population might result from an overrepresentation of heavily treated CCSs who received thoracic surgery as part of their multimodal treatment strategies. Of the 21 CCSs treated with thoracic surgery in our cohort, 19 have also been exposed to radiotherapy involving the chest, seven to autologous HSCT, and four to a known lung toxic chemotherapeutic agent (**Supplemental Table S3**). Nine (43%) have been exposed to at least two other lung toxic treatments in addition to surgery. When looking at thoracic surgeries in more detail, 85% of surgeries included thoracotomy, 42% a partial resection of the lung. Only two CCSs had a minor surgical intervention with thoracoscopic biopsies. This illustrates the intensive treatments these CCSs have been exposed to and point to multiple causes for the reduced FVC z-score, rather than surgery alone. None of the other risk factors was independently associated with a decrease in the intercept or slope of FEV1 and FVC z-scores.

Exposure to lung toxic chemotherapy was associated with an increase in the slope of FEV1 z-score. Only 39% of all CCSs have been exposed to lung toxic chemotherapy. As most of them additionally received radiotherapy to the chest, only a small proportion was exposed to lung toxic chemotherapy alone. The annual increase in FEV1 z-score might indicate a partly reversible effect, which might also explain the observed initial decrease in the longitudinal trajectories.

Strengths and limitations

This study describes a large national cohort of CCSs exposed to at least one lung toxic treatment. Treatments have been verified in the medical records. We used

internationally recognized reference equations to calculate percent predicted values and z-scores of pulmonary function values.

The results of this study have to be considered with some limitations. Although we tried to be as comprehensive as possible when collecting PFTs from hospital records, we could have missed some PFTs or the tests have been performed, but the results got lost. This might especially be the case for survivors diagnosed in earlier years. In addition, some tests might not have been performed for surveillance purpose due to the cancer treatment but due to other diseases. As the cohort is heterogeneous with regards to underlying diagnoses, treatments, and relapse status, it is difficult to draw conclusions for single cancer diagnoses. This heterogeneity resulted in small groups exposed to chemotherapy, HSCT or surgery. PFTs have been performed in different laboratories over a long period with changes in equipment, staff, and testing procedures and it was therefore not possible to uniformly assess quality of the test procedure. Our results might be limited by selection bias, as we could find medical records and at least one PFT result of only 45% of the original cohort. We cannot rule out, that the more symptomatic and sicker CCSs are included in our cohort and therefore rather overestimates the burden of pulmonary dysfunction. In contrast, the studies by Armenian, Mulder and Green recruited their cohorts from regular follow-up clinics with a response rate between 61-88%, where selection bias seems to be less likely.

Conclusion

Every second CCS exposed to lung toxic treatments in Switzerland showed at least one abnormal PFT parameter a median of 6 years after cancer diagnosis with reduced FVC being the most frequent. CCSs after multimodal treatment approaches

441 with more than one lung toxic treatment are particularly at risk. Our findings
442 underline the importance of surveillance screening for pulmonary dysfunction in long-
443 term CCSs beyond 10 years after cancer diagnosis to show and monitor changes
444 over time.

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Legends

Table 1 Characteristics of childhood cancer survivors, N=190

Table 2 Observed lung function parameters in last available lung function test. Results shown as median z-score for all test results and separate for those meeting the definition for abnormal (z-score <-1.645). Parameters compared to GLI 2012 reference. N=190

Table 3 FEV1 z-scores in childhood cancer survivors compared to GLI 2012 reference values; multivariable linear mixed regression analysis adjusted for all covariates in the model. N=190 survivors and 821 test results

Table 4 FVC z-scores in childhood cancer survivors compared to GLI 2012 reference values; multivariable linear mixed regression analysis adjusted for all covariates in the model. N=190 survivors and 821 test results

Figure 1 Longitudinal changes in FEV1 z-score of childhood cancer survivors compared to Global Lung Function Initiative 2012 reference. Time zero corresponds to time point of diagnosis. The loess curve (blue line) shows the best fitted line by taking each single data point into account at each time point on the x-line. The shaded band corresponds to the 95% confidence interval. Dots represent single test results, which are combined with a line and show the individual trajectories of each patient included in the study. The dashed red line represents the mean z-score of the normal population.

Figure 2 Longitudinal changes in FVC z-score, of childhood cancer survivors compared to Global Lung Function Initiative 2012 reference. Time zero corresponds to time point of diagnosis. The loess curve (blue line) shows the best fitted line by taking each data point into account at each time point on the x-line. The shaded band corresponds to the 95% confidence interval. Dots represent single test results,

574 which are combined with a line and show the individual trajectories of each patient
575 included in the study. The dashed red line represents the mean z-score of the
576 normal population.
577
578 **Supplementary Material**
579 **Supplementary Explanation E1** Explanation of multivariable linear mixed
580 regression analysis with random intercept and random slope
581 **Supplementary Table S1** Comparison of abnormal lung function parameters
582 assessed by percentage predicted and z-scores of last available lung function test,
583 N=190
584 **Supplementary Table S2** Observed spirometric lung function parameters assessed
585 as percentage predicted (% predicted) and z-scores in first and last available lung
586 function test in survivors with at least two tests, N=154
587 **Supplementary Table S3** Description of childhood cancer survivors treated with
588 thoracic surgery, N=21
589 **Supplementary Table S4** Characteristics of other studies assessing pulmonary
590 function in childhood cancer survivors
591 **Supplementary Figure S1** Flow chart of study population

TABLE 1 Characteristics of childhood cancer survivors, N=190

	Survivors N = 190	
	n	(%) [a]
Sex		
Male	109	(57)
Age at diagnosis, median (IQR) [years]	12.1 (6.5 – 14.1)	
0–4	30	(16)
5–9	49	(26)
10–15	111	(58)
Follow-up from diagnosis to data collection, median (IQR) [years]	14.2 (8.9 – 19.3)	
0–9	56	(29)
10-19	96	(51)
≥ 20	38	(20)
Period of cancer diagnosis		
1990–1997	65	(34)
1998–2005	82	(43)
2006–2013	43	(23)
Diagnosis (ICCC-3)		
I Leukemia	21	(11)
II Lymphoma	100	(53)
III CNS tumor	23	(12)
IV–XII all other tumors [b]	46	(24)
Relapse		
Yes, one relapse	32	(17)
Yes, two or more relapses	17	(9)
Death during follow-up [c]	20	(11)
Lung-toxic chemotherapy	74	(39)
Busulfan	14	(7)
Nitrosoureas (CCNU/BCNU)	15	(8)
Bleomycin	48	(25)
Chest radiotherapy incl. CSI	165	(87)
Lung-toxic chemotherapy and chest radiotherapy	49	(26)
Thoracic surgery	21	(11)
Hematopoietic stem cell transplantation	44	(23)
Autologous	24	(13)
Allogeneic	20	(10)
Pulmonary function tests (n=835)		
Spirometry (median, IQR, range) per CCS	4 (IQR 2 – 6, range 1 – 16)	
Body plethysmography (median, IQR, range) per CCS	4 (IQR 2 – 6, range 1 – 14)	
DLCO (median, IQR, range) per CCS	3 (IQR 2 – 5, range 1 – 13)	

Abbreviations: CNS, central nervous system; CSI, craniospinal irradiation; Gy, Gray; ICCC3, International Classification of Childhood Cancer, version 3; IQR, interquartile range

[a] Column percentages are given

[b] Other tumors: n=13 Ewing tumor and related sarcoma, n=11 malignant extracranial germ cell tumors, n=10 nephroblastoma, n=5 neuroblastoma, n=5 other specified soft tissue sarcoma, n=2 rhabdomyosarcoma

[c] Death during the whole time observed.

Table 2 Observed lung function parameters in last available lung function test [a]. Results shown as median z-score for all test results and separate for those meeting the definition for abnormal (z-score <-1.645). Parameters compared to GLI 2012 reference. N=190

	Survivors	
	n (%)	median (IQR)
Time from diagnosis to last test [years](median, IQR)	190 [b]	5.7 (3.2 – 9.4)
FEV1		
z-score	187	-1.1 (-1.9 - -0.3)
z-score <-1.645	64 (34%)	-2.4 (-3.1 - -1.9)
FVC		
z-score	186	-1.3 (-2.2 - -0.4)
z-score <-1.645	72 (39%)	-2.5 (-3.3 - -2.1)
FEV1/FVC		
z-score	184	0.3 (-0.5 – 1.1)
z-score FEV1/FVC <-1.645	4 (2%)	-2.1 (-2.4 - -1.8)
TLC		
z-score	178	-1.11 (-2.2 - -0.03)
z-score TLC <-1.645	61 (34%)	-2.2 (-3.2 - -2.2)
DLCO		
z-score	131	-0.5 (-1.5 - -0.5)
z-score DLCO <-1.645	28 (21%)	-2.7 (-3.9 - -1.8)
FEV1, FVC, TLC and/or DLCO z-score < -1.645	99 (52%)	n.a.
Obstructive[c], restrictive[d], or diffusion capacity impairment[e]	72 (38%)	

Abbreviations: IQR, interquartile range; n.a., not applicable
[a] Last lung function test: one results in those with one test only, last result in those with more than one test
[b] As not every last test included spirometry, body plethysmography and DLCO, the total number of CCSs per test parameter does not sum up to 190
[c] Obstructive = FEV17FVC<0.7 and FVC z-score <-1.645
[d] Restrictive = TLC z-score <-1.645
[e] Diffusion capacity impairment = DLCO z-score <-1.645

Table 3. FEV1 z-scores in childhood cancer survivors compared to GLI 2012 reference values; multivariable linear mixed regression analysis adjusted for all covariates in the model. N=190 survivors and 821 test results

	Estimate	95% CI		p-value
Intercept (FEV1 z-score at first exposure to lung toxic treatment for "reference patient"[2])	-0.60	-0.16	0.42	
Sex				0.527
Male	0.14	-0.30	0.58	
Cancer diagnosis (ref. Lymphoma)				0.172
CNS tumor	-0.13	-0.81	0.55	
Bone tumors	-1.27	-2.43	-0.12	
Germ cell tumors	0.86	-0.39	2.10	
Leukemia	0.19	-1.27	0.88	
Neuroblastoma	-0.52	-2.12	1.08	
Renal tumors	0.32	-0.72	1.37	
Soft tissue sarcoma	-0.95	-2.11	0.20	
Radiotherapy (ref. no)	-0.28	-1.19	0.63	0.542
Chemotherapy (ref. no)	-0.41	-0.93	0.09	0.113
HSCT (ref. no)	-0.08	-0.85	0.68	0.829
Thoracic surgery (ref. no)	-0.80	-1.69	0.09	0.077
Change of FEV1 z-score per year				
Time since first exposure to lung toxic treatment (continuous, per year)	-0.07	-0.21	0.08	
Interaction Sex				0.115
Male	-0.05	-0.11	0.01	
Interaction Cancer diagnosis (ref. Lymphoma)				0.357
CNS tumor	-0.09	-0.19	0.01	
Bone tumors	0.08	-0.07	0.24	
Germ cell tumor	-0.07	-0.24	0.08	
Leukemia	0.01	-0.13	0.16	
Neuroblastoma	0.04	-0.14	0.22	
Renal tumors	-0.08	-0.20	0.04	
Soft tissue sarcoma	0.01	-0.15	0.18	
Interaction Radiotherapy (ref. no)	0.09	-0.04	0.22	0.169
Interaction Chemotherapy (ref. no)	0.11	0.03	0.18	0.006
Interaction HSCT (ref. no)	-0.02	-0.12	0.08	0.670
Thoracic surgery (ref. no)	-0.06	-0.17	0.05	0.274

[1] Likelihood ratio test p-value indicating whether the characteristic explains differences in FEV_1 within the study population.
[2] Reference patient corresponds to a female person, at first exposure to lung toxic agent, diagnosed with lymphoma, and not exposed to radiotherapy, chemotherapy, HSCT, and thoracic surgery.

Table 4 FVC z-scores in childhood cancer survivors compared to GLI 2012 reference values; multivariable linear mixed regression analysis adjusted for all covariates in the model. N=190 survivors and 821 test results

	Estimate	95% CI		p-value[1¶]
a)				
Intercept (FVC z-score at first exposure to lung toxic treatment for "reference patient" [2])	-1.37	-2.41	-0.33	
Sex				0.599
Male	0.11	-0.31	0.53	
Cancer diangosis (ref. Lymphoma)				0.259
CNS tumor	-0.21	-0.83	0.42	
Bone tumors	-0.44	-1.53	0.62	
Germ cell tumors	1.18	-0.03	2.39	
Leukemia	0.11	-0.90	1.13	
Neuroblastoma	-0.59	-2.07	0.88	
Renal tumors	0.26	-0.71	1.24	
Soft tissue sarcoma	-0.79	-1.89	0.29	
Radiotherapy (ref. no)	0.24	-0.69	1.18	0.605
Chemotherapy (ref. no)	0.03	-0.46	0.51	0.909
HSCT (ref. no)	-0.42	-1.13	0.30	0.254
Thoracic surgery (ref. no)	-1.19	-2.03	-0.36	0.005
b)				
Change of FVC z-score per year Time since first exposure to lung toxic treatment (continuous, per year)	0.06	-0.07	0.21	
Interaction Sex				0.152
Male	-0.04	-0.09	0.02	
Interaction Cancer diagnosis (ref. Lymphoma)				0.168
CNS tumor	-0.11	-0.19	-0.02	
Bone tumors	-0.08	-0.22	0.05	
Germ cell tumor	-0.09	-0.24	0.05	
Leukemia	-0.06	-0.18	0.07	
Neuroblastoma	-0.002	-0.16	0.15	
Renal tumors	-0.10	-0.21	0.001	
Soft tissue sarcoma	0.001	-0.14	0.14	
Interaction Radiotherapy (ref. no)	-0.02	-0.15	0.09	0.704
Interaction Chemotherapy (ref. no)	0.02	-0.05	0.08	0.651
Interaction HSCT (ref. no)	0.02	-0.06	0.11	0.589
Thoracic surgery (ref. no)	0.02	-0.08	0.12	0.694

[1] Likelihood ratio test p-value indicating whether the characteristic explains differences in FVC within the study population.
[2] Reference patient corresponds to a female person, at first exposure to lung toxic agent, diagnosed with lymphoma, and not exposed to radiotherapy, chemotherapy, HSCT, and thoracic surgery.

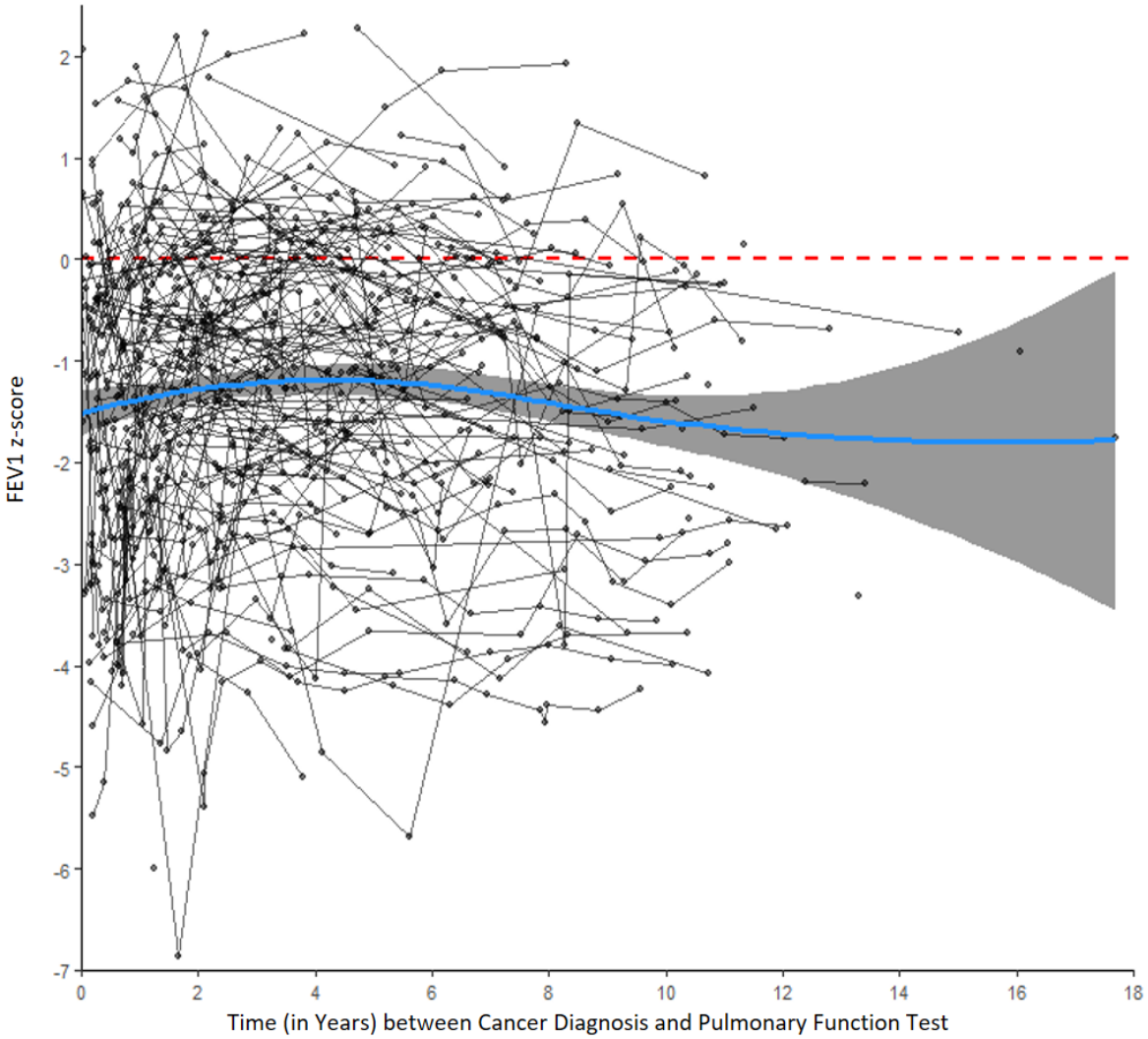

Figure 1: Longitudinal changes in FEV1 z-score of childhood cancer survivors compared to Global Lung Function Initiative 2012 reference. Time zero corresponds to time point of diagnosis. The loess curve (blue line) shows the best fitted line by taking each single data point into account at each time point on the x-line. The shaded band corresponds to the 95% confidence interval. Dots represent single test results, which are combined with a line and show the individual trajectories of each patient included in the study. The dashed red line represents the mean z-score of the normal population.

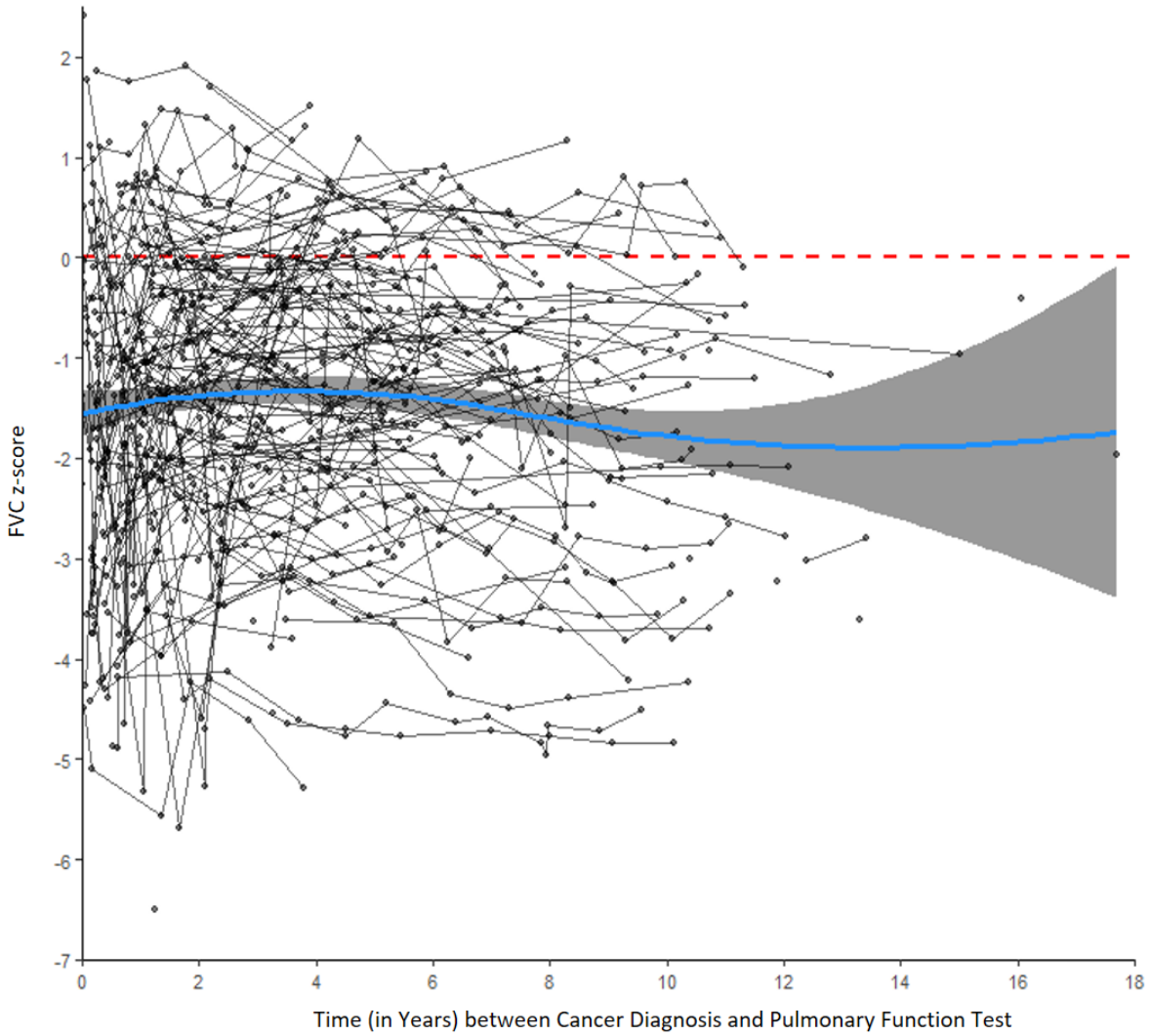

Figure 2: Longitudinal changes in FVC z-score, of childhood cancer survivors compared to Global Lung Function Initiative 2012 reference. Time zero corresponds to time point of diagnosis. The loess curve (blue line) shows the best fitted line by taking each data point into account at each time point on the x-line. The shaded band corresponds to the 95% confidence interval. Dots represent single test results, which are combined with a line and show the individual trajectories of each patient included in the study. The dashed red line represents the mean z-score of the normal population.

Lung function in Swiss childhood cancer survivors – a retrospective cohort study

Supporting information

Journal:

Lung function in Swiss childhood cancer survivors – a retrospective cohort study

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Lung function in Swiss childhood cancer survivors – a retrospective cohort study

Supplementary Explanation E1 Explanation of multivariable linear mixed regression analysis with random intercept and random slope

The multivariable linear mixed regression analysis with random intercept and random slope allows to take clustering and longitudinal trajectories of pulmonary outcomes by each patient into account.

Here we explain the data output with the example of FEV1:

The upper part of the table describes the FEV1 z-scores at time “zero”, which refers to the time of first exposure to a lung toxic treatment modality. It can be considered as the extrapolated baseline FEV1 z-score, where each patient starts at first exposure. Depending on the subsequent exposure to risk factors, this starting point might be higher or lower. The reference patient (female, with Lymphoma, no radiotherapy, no chemotherapy, no HSCT and no thoracic surgery) starts at a z-score of -0.60. If a person of interest is male (z-score estimate 0.14) and additionally received radiotherapy to the chest (z-score estimate -0.28), he starts at a modelled FEV1 z-score of -0.74 (-0.60 (baseline) + 0.14 (difference female to male) -0.28 (difference from no radiotherapy to radiotherapy)).

The lower part of the table describes the change of FEV1 z-score per year. The reference patient (female, with Lymphoma, no radiotherapy, no chemotherapy, no HSCT and no thoracic surgery) has an annual decrease in FEV1 z-score of -0.07. For the male person (z-score estimate -0.05) exposed to radiotherapy to the chest (z-score estimate 0.09) the annual change in FEV1 z-score would be +0.03.

Lung function in Swiss childhood cancer survivors – a retrospective cohort study

With this approach the starting point (intercept) and annual decrease (slope) can be calculated for patients with different diagnoses and exposure to different lung toxic treatment modalities.

Lung function in Swiss childhood cancer survivors – a retrospective cohort study

Supplementary Table S1 Comparison of abnormal lung function parameters assessed by percentage predicted and z-scores of last available lung function test[a], N=190

	Survivors		
	n	%	median (IQR)
FEV1			
FEV1% predicted	187		87.4 (77.0 – 96.5)
FEV1 <80%predicted[b]	61	33	70.6 (63.4 – 76.8)
FEV1 z-score	187		-1.1 (-1.9 - -0.3)
FEV1 z-score <-1.645	64	34	-2.4 (-3.1 - -1.9)
FVC			
FVC% predicted	186		84.6 (73.9 – 95.1)
FVC <75% predicted[c]	52	30	66.5 (58.2 – 71.6)
FVC z-score	186		-1.3 (-2.2 - -0.4)
FVC z-score <-1.645	72	39	-2.5 (-3.3 - -2.1)
FEV1/FVC			
FEV1/FVC% predicted	184		102 (96.7 – 107.3)
FEV1/FVC <0.7	2	1	0.67 and 0.68
FEV1/FVC <0.7 and FEV1<80%predicted	2		
z-score	184		0.3 (-0.5 – 1.1)
z-score FEV1/FVC <-1.645	4	2	-2.1 (-2.4 - -1.8)
DLCO			
DLCO% predicted	131		92.9 (79.8 – 107.4)
DLCO <75% predicted[c]	21	16	60.1 (48.5 – 67.9)
z-score	131		-0.5 (-1.5 - -0.5)
z-score DLCO <-1.645	28	21	-2.7 (-3.9 - -1.8)

Abbreviations: IQR, interquartile range
[a] Last lung function test: one results in those with one test only, last result in those with more than one test
[b] Cutoff value according to GOLD criteria (Global Initiative for Chronic Obstructive Lung Disease)
[c] Cutoff value according to CTCAE v3.0 (Common Terminology Criteria for Adverse Events version 3.0)

Supplementary Table S2 Observed spirometric lung function parameters assessed as percentage predicted (% predicted) and z-scores in first and last available lung function test in survivors with at least two tests, N=154

	Survivors				
	First Test		Last Test		p-value[a]
	n	median (IQR)	n	median (IQR)	
Time between lung toxic exposure and test [years] (median, IQR)	154	0.8 (0.3 – 1.7)	154	5.7 (3.6 – 8.7)	<0.005
Age, median (IQR) [years]		13.8 (9.7 – 15.8)		16.9 (13.7 – 19.5)	
6–9	50 (26%)		10 (5%)		
10–13	49 (26%)		40 (21%)		
14-17	84 (44%)		65 (34%)		
≥18	7 (4%)		75 (40%)		
FEV1					
FEV1% predicted	150	88.7 (74.3 – 97.7)	153	87.5 (77.1 – 97.5)	0.748
FEV1 z-score	150	-0.9 (-2.1 - -0.2)	153	-1.1 (-1.9 - -0.2)	0.866
FVC					
FVC% predicted	151	84.6 (74.6 – 98.3)	153	85.3 (74.1 – 96.8)	0.810
FVC z-score	151	-1.3 (-2.2 - -0.1)	153	-1.2 (-2.1 - -0.3)	0.853
FEV1/FVC					
FEV1/FVC% predicted	147	103.6 (96.2 – 108.8)	152	102.4 (96.7 – 106.7)	0.834
FEV1/FVC z-score	147	0.6 (-0.5 – 1.4)	152	0.3 (-0.4 – 1.0)	0.515

[a] t-test

Supplementary Table S3 Description of childhood cancer survivors treated with thoracic surgery, N=21

	Diagnosis	Year of diagnosis	Age at first thoracic surgery [years]	Relapse	Description of thoracic surgery/ surgeries	Additional lung toxic exposure[1]
1	(Xb) Malignant extracranial and extragonadal GCT	1990	4.8	No	Thoracotomy, tumor resection	No radiotherapy, bleomycin
2	(VIa) Nephroblastoma	1992	6.6	Yes	Thoracotomy, resection upper lobe left side, resection lower lobe right side	Mediastinal radiotherapy
3	(IIb) Non-Hodgkin lymphoma	1995	13.7	No	Laminectomy Th2-Th5	Craniospinal irradiation
4	(VIIIc) Ewing tumor	1995	5.6	Yes	Rib resection, resection of lingula	Whole lung irradiation
5	(IIb) Non-Hodgkin lymphoma	1996	16.4	Yes	Thoracotomy, en bloc resection upper lobe left side	Mediastinal radiotherapy, busulfan, autologous HSCT
6	(VIa) Nephroblastoma	1998	6.3	Yes	Thoracotomy, resection lower lobe right side	Whole lung irradiation, autologous HSCT
7	(VIIIc) Ewing tumor	1999	9.6	No	Rib resection en bloc (5-7)	Radiotherapy chest
8	(Xc) Malignant gonadal germ cell tumors	1999	15.3	No	Thoracotomy, resection upper lobe left side	Mediastinal radiotherapy, bleomycin
9	(VIa) Nephroblastoma	2000	2.3	Yes	Thoracotomy, wedge resection	Whole lung irradiation
10	(VIIIc) Ewing tumor	2001	10.0	Yes	Rib resection 7-9, Thoracotomy for resection of metastasis	Whole lung irradiation
11	(IIa) Hodgkin lymphoma	2001	15.1	No	Thoracoscopy, biopsy	Mantle irradiation, bleomycin
12	(VIIIc) Ewing tumor	2002	14.3	No	Thoracotomy, resection lower lobe left side, metastasectomy	Whole lung irradiation, autologous HSCT
13	(VIIIc) Ewing tumor	2003	13.5	No	Rib resection (6^{th} rib)	*Radiotherapy other*
14	(IXd) Other specified soft tissue sarcoma	2003	8.3	No	Thoracotomy, resection lower lobe left side, resection of pleura and part of the diaphragm	Whole lung irradiation
15	(VIIIc) Ewing tumor	2004	4.9	Yes	Rib resection (rib 9-10)	Chest irradiation, autologous HSCT
16	(VIIIc) Ewing tumor	2004	13.9	Yes	Rib resection (rib 3-9), partial resection of the diaphragm	Radiotherapy other, autologous HSCT
17	(IIa) Hodgkin lymphoma	2006	16.8	Yes	Thoracoscopy, biopsy	Mediastinal radiotherapy, autologous HSCT

18	(VIIIc) Ewing tumor	2007	12.9	Yes	Thoracotomy, tumor resection, rib resection (9th rib)	
19	(VIIIc) Ewing tumor	2009	14.6	Yes	Thoracotomy, wedge resection, rib resection (rib 8-9)	Whole lung irradiation, autologous HSCT
20	(IXd) Other specified soft tissue sarcoma	2009	8.1	No	Thoracotomy, metastasectomy	Whole lung irradiation
21	(IXa) Rhabdomyosarcoma	2012	14.6	Yes	Thoracotomy, tumor resection, partial rib resection (rib 3-5)	Radiotherapy other

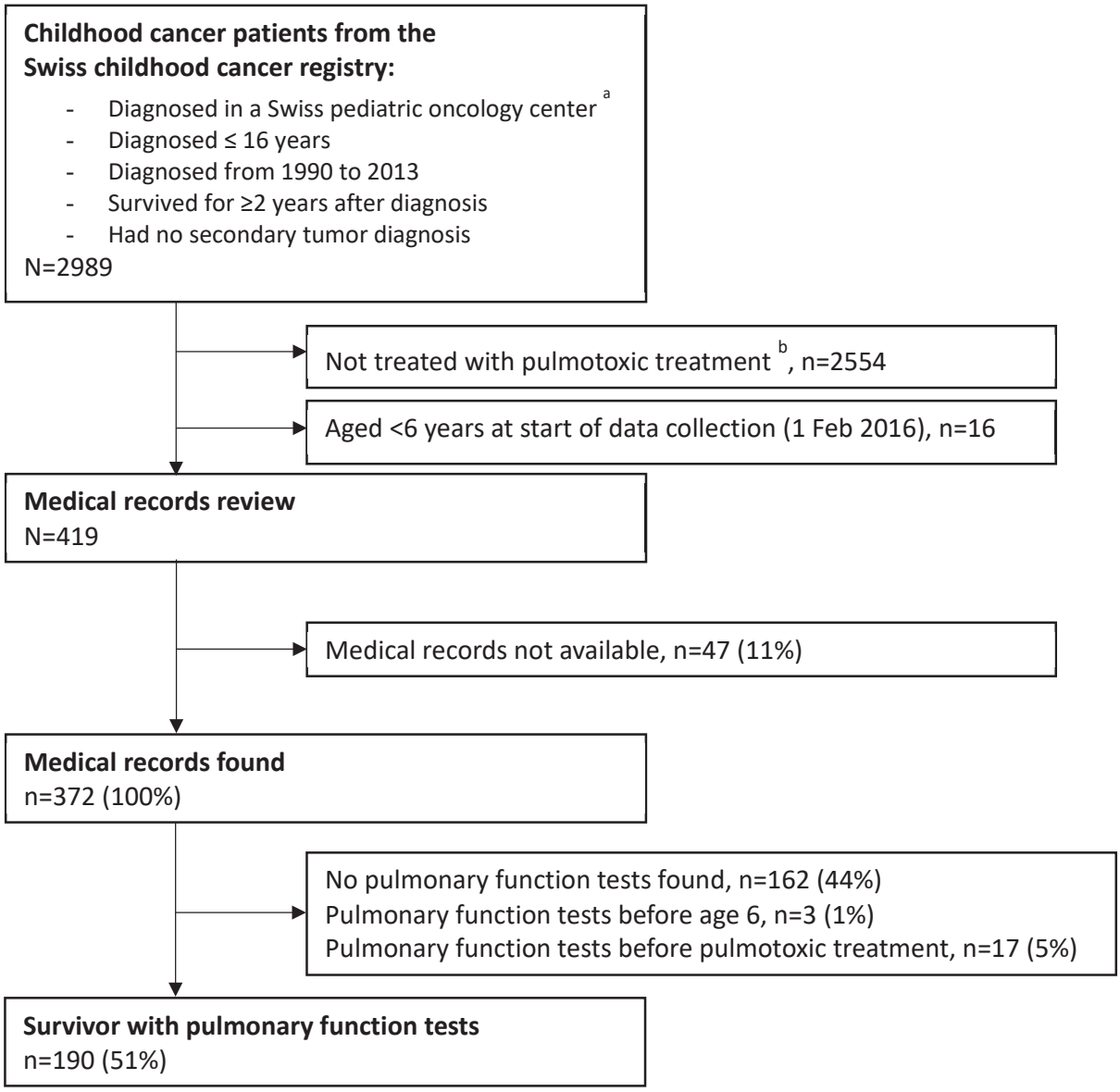
Supplementary Table S4 Characteristics of other studies assessing pulmonary function in childhood cancer survivors

Author, journal, year	Number (response rate)	Outcome variables	References and cutoff values	Results
Armeinan S et al, JCO, 2015	155 with baseline PFT at entry in COH Survivorship Clinic Final cohort: 121 with follow-up (78%)	FEV_1 FEV_1/FVC ratio DLCO adj A dn DLCI/VA TLC FVC	Reference values used to calculate percentage of predicted not stated. Obstructive: GOLD criteria; FEV_1/FVC <0.70 and FEV_1<80% predicted Restrictive: CTCAE v3.0; TLC <75% predicted and FEV_1 ≥80% predicted Diffusion capacity abnormality: CTCAE v3.0; $DLCO_{corr}$ <75% predicted	Obstructive: 4.1% Restrictive: 24.0% Diffusion capacity abnormality: 34.7% → obstructive, restrictive, and/or diffusion defect: 45.5%
Green DM et al, Ann Am Thorac Soc, 2016	989 eligible for SJLIFE and received pulmonary toxic therapy 606 completed PFT (61%)	FEV_1 FVC $DLCO_{corr}$ TLC	Equation for FEV_1 and FVC: Hankinson at al and GLI reference values (Quanjer PH et al) Equation for TLC: Goldman HI et al, Boren HG et al Equation for DLCO: Miller A et al CTCAE v4.03: FEV1, FVC <80% predicted CTCAE v3.0: $DLCO_{corr}$ <75% predicted TLC <75% predicted Obstructive: FEV_1/FVC <0.7 or FEV_1/FVC<LLN Restrictive: TLC<75% or FEV_1/FVC ≥LLN and FVC <LLN	FEV_1 <80%: 50.7% FVC <80%: 47.2% FEV_1/FVC ratio <0.7: 0.8% $DLCO_{corr}$<75%: 44.6% TLC <75%: 31.2% Obstructive: 0.8% Restrictive: 31.2% → At least one PFT abnormal: 65%

Mulder RL et al, Thorax, 2011	248 qualified for Late Effects Outpatient Clinic in EKZ/AMC and qualified for pulmo-toxic screening 220 participated 193 with PFT (88%)	FEV_1 FEV_1/VC_{max} ratio TLC FVC DLCO KCO	Reference values used to calculate percentage of predicted not stated. Obstructive: GOLD criteria; FEV_1/VC_{max}<0.70 and FEV_1<80% predicted Restrictive: CTCAE v3.0; TLC <75% predicted; if no TLC available: FVC<75% predicted with normal FEV_1/VC_{max} ratio Diffusion capacity impairment: CTCAE v3.0 DLCO or KCO <75% predicted	FEV_1<80%: 20.7% FEV_1/VC_{max}<0.70: 3.1% → obstructive: 2.1% TLC <75%: 18.7% FVC<75%: 11.4% → restrictive: 17.6% DLCO <75%: 39.9% KCO <75%: 4.3% → overall pulmonary function impairment: 44.0%
Record E, PBC, 2016	226 original cohort 143 PFT available (63%)	FEV_1 FEV_1/FVC ratio FEF25-75% TLC RV DLco adj	Reference equations used: Wang X et al, Hankinson JL et al Obstructive: FVC <80% predicted or FEV_1 <80% predicted or FEF25-75% <68% predicted or FEV_1/FVC <0.8 Restrictive: TLC <80% predicted Hyperinflation: RV >120% predicted and RV/TLC ratio >28% predicted Pulmonary vascular disease: DLco/VAadj <4 ml/mm Hg/min/l Any PFT abnormality: presence of one or more abnormalities	Obstructive: 25.9% Restrictive: 13.3% Hyperinflation: 41.3% Pulmonary vascular disease: 5.5% Any abnormal PFT: 65.0%

CTCAE v3.0, Common Terminology Criteria for Adverse Events version 3.0; GOLD, Global Initiative for Chronic Obstructive Lung Disease; DLco adj, DLco adjusted for hemoglobin; LLN, lower limit of normal

Lung function in Swiss childhood cancer survivors – a retrospective cohort study



Supplementary Figure 1 Flow chart of study population

[a] Including the following centers with pediatric oncology units: Kinderklinik Kantonsspital Aarau AG, Universitäts-Kinderspital Basel, Universitäts-Kinderklinik Inselspital Bern, Hospital des Enfants Geneve, CHUV Lausanne, Kinderklinik Kantonsspital Luzern, Ostschweizer Kinderspital St. Gallen, Universitäts-Kinderspital Zürich

[b] Pulmotoxic treatment defined as chemotherapy with busulfan, bleomycin, lomustine or carmustine and/or chest radiotherapy

4.4. Publication IV

The Swiss Childhood Cancer Survivor Study – Follow-up (SCCSS-FollowUp) – Protocol of a prospective, national, multicenter cohort study

Study protocol

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(Manuscript in preparation, to be submitted to BMC Cancer)

Own contribution to the project when submitting the thesis: Concept and design of the SCCSS-FollowUp study and the study protocol, writing manuscript, integration of co-authors comments

The Swiss Childhood Cancer Survivor Study – Follow-up: Study protocol of a prospective multicenter cohort study for standardized collection and analysis of medical conditions in Swiss childhood cancer survivors

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Abstract (275/350 words)

Background

The overall survival of childhood cancer reaches >80% in developed countries, but a majority of childhood cancer survivors (CCSs) develop late effects. Medical data of high quality are essential to perform research and to subsequently provide information relevant to clinicians and CCSs. Few national, prospective, and longitudinal CCS cohorts exist to date. Most of them include CCSs who survived more than 5 years from diagnosis. The main goal of the Swiss Childhood Cancer Survivor Study – Follow-up (SCCSS-FollowUp) is to describe the health status and development of late effects in CCSs prospectively and in a longitudinal way and starting directly after completion of treatment.

Methods

The SCCSS-FollowUp is a prospective longitudinal study, based on the recruitment of CCSs qualifying for follow-up care in Switzerland and is integrated in their regular follow-up care visits. With its umbrella-like design, the SCCSS-FollowUp study incorporates multiple projects evaluating late effects and its risk factors in different organ systems, starting directly after completion of treatment. All CCSs diagnosed and treated in Switzerland since 1976 qualifying for follow-up care are eligible for this study. Recruitment is done by a project-driven approach.

Discussion

The few national CCS cohorts existing to date, including CCSs who survived more than 5 years from diagnosis only, might miss conditions developing early in the post-treatment phase. These early conditions can contribute to the development of subsequent late effects or can even be fatal in the first five years. With the SCCSS-FollowUp study, we aim to close

this gap and to provide data and knowledge on the development and longitudinal course of late effects in CCSs.

Trial registration

ClinicalTrial.gov identifier SCCSS-FollowUp:

Keywords: childhood cancer, survivors, follow-up care, aftercare, longitudinal, clinical assessment, Switzerland

Background

Survival after childhood cancer has improved dramatically in recent decades and leads to increasing numbers of childhood cancer survivors (CCSs) (1). This increase is achieved through improvements in cancer treatment and supportive care. For chemotherapeutic agents, improvements include for example dose reduced of certain drugs (e.g. doxorubicin), the attempt to avoid others (e.g. bleomycin) or the more targeted administration according to disease stage. In addition, the introduction of new drugs increased survival, especially in relapsed diseases. Substantial improvement was also observed for radiotherapy. Radiation techniques changed to smaller radiation fields, lower doses and indications are made more stringent. Furthermore, improvement in supportive care such as antibiotic or antiviral treatments, antiemetics, immunosuppressive treatment in children after hematopoietic stem cell transplantation or specific antimetabolites, such as folinic acid for high-dose methotrexate, contributed to the improvement in overall survival. Despite all this progress, a large proportion of survivors suffer from chronic medical conditions, so called late effects (2-4). Late effects can be caused by the cancer itself, such as neurocognitive impairment after long-standing hydrocephalus or by the different treatment modalities. Regarding treatment modalities, chemotherapy, radiotherapy, surgery, and hematopoietic stem cell transplantation (HSCT) can cause late effects. Severe infections (e.g. shunt infection; colitis) can additionally contribute to late effects. Late effects can potentially affect every organ system and lead to increased morbidity and mortality in CCSs (2, 3, 5). Knowledge on late effects led to the development of different national and international long-term follow-up (LTFU) guidelines (6-8). These guidelines provide recommendations for follow-up care based on previous treatment exposure.

The increase in long-term survival and the growing knowledge on late effects led to the establishment of six prospective national cohort studies, including the French COHOPER,

FSSCC and LEA cohort, the Scandinavian ALiCCS, the St. Jude Lifetime Cohort (SJLIFE) in the US, and the Dutch DCOG LATER. The French COHOPER (9) and Scandinavian ALiCCS cohort (10) collect clinical data thorough linkage from the national health insurance database and health registries, respectively. The French LEA cohort includes children and adolescents diagnosed with leukemia and collects data from prospective follow-up examinations (11). The French FCCSS is the "solid" counterpart of the LEA cohort, includes all solid tumors, and collects prospective clinical data in a subset of CCSs only (12). The SJLIFE cohort in the US (13) and the Dutch DCOG LATER (14) collect follow-up information during the clinical visits. Both cohorts include CCSs with all types of childhood cancer. The SJLIFE cohort starts recruitment ten years after diagnosis and includes adult CCSs only. The DCOG LATER starts recruitment five years after cancer diagnosis.

In Switzerland, approximately 300 children and adolescents <21 years of age are diagnosed with cancer every year (15). Since 1976, these children and adolescents are registered in the Childhood Cancer Registry (ChCR; https://www.childhoodcancerregistry.ch). The ChCR is a nationwide, population-based cancer registry including all Swiss children and adolescents who were diagnosed below age <20 years with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis (LCH) (16). The registry receives data from persons with a reporting obligation, such as doctors, hospitals, institutes of pathology and medical laboratories that diagnose and/or treat cancer. For childhood cancer the nine specialized pediatric oncology centers, united in the Swiss Pediatric Oncology Group (SPOG), which diagnose and treat childhood cancer in Switzerland, are the main source. Besides data on newly diagnosed children or adolescents, the ChCR also receives annual updates on treatment and clinical course of the patients. Today there are around 7,000 CCSs living in Switzerland

and most of them need long-term follow-up care. According to a position paper, published in 2019, the situation for follow-up care for CCSs in Switzerland is very heterogeneous (17, 18). This heterogeneity is present in the use of follow-up care guidelines, treatment summaries, and transition into adulthood. Besides describing the current follow-up care practices, the authors identified possible approaches for harmonization between the centers.

The SCCSS-FollowUp aims to assess late effects early in survivors through standardized risk-adapted medical examinations starting directly after completion of treatment, and to study risk factors for late effects including information on treatment exposure, sociodemographic and socioeconomic characteristics, lifestyle factors, and comorbidities, such as arterial hypertension or obesity.

Methods/Design

Design of the SCCSS-FollowUp

The Swiss Childhood Cancer Survivor Study – Follow-up (SCCSS-FollowUp) is a national, observational, prospective, multicenter cohort study, which is is not limited to one specific late effect or cohort of CCSs. The study has an umbrella-like design and incorporates multiple projects evaluating late effects and its risk factors in different organ systems. Signing the informed consent corresponds to the “umbrella”. An example of a project incorporated in the SCCSS-FOllowUp study could be the assessment of bone mineral density in CCSs treated with high-dose steroids. If a CCS consents to participate in SCCSS-FollowUp, all already available data and all data newly generated during regular follow-up care visits can be collected and analyzed at a later stage. With the previously mentioned example this includes the collection of information on initial cancer diagnosis and its treatment, results of already performed and future bone mineral density tests. Importantly, the

159 data collection cannot be carried out freely but is always bound to a project and to a specific
160 research question. The incorporation of such projects within the SCCSS-FollowUp study is
161 illustrated in **Figure 1**.
162 Ethical approval of the SCCSS-FollowUp was granted by the Ethics Committee of the
163 Canton of Bern as lead ethics committee (KEK-BE: ___).
164
165 *Study population*
166 Eligible for the SCCSS-FollowUp study are all childhood cancer patients registered in
167 the ChCR since 1976, diagnosed with cancer before the age of 20 years, alive and residing in
168 Switzerland at recruitment for SCCSS-FollowUp, and ≥1 year since diagnosis or at the end of
169 active treatment, whichever comes first. Only CCSs who sign the SCCSS-FollowUp
170 informed consent are included. We exclude CCSs in palliative situations or with relapsed
171 disease in the 12 months prior to defining eligibility for project-specific research questions.
172 We continuously include all children and adolescents entering follow-up care.
173
174 *General considerations*
175 Data collection and eligibility criteria within SCCSS-FollowUp are always linked to a
176 specific project and research question. Therefore, depending on the exposure to certain
177 treatment modalities or risk to develop specific late effects, eligible survivors differ between
178 projects. In addition, SCCSS-FollowUp does not specify the time point and type of test
179 performed in participating CCSs. All data are generated during regular follow-up care visits
180 and are subsequently collected for the purpose of the SCCSS-FollowUp study. The approach
181 of integrating SCCSS-FollowUp in regular clinical visits leads to the involvement of different
182 teams and specialties which we describe here. The SCCSS-FollowUp team is located at the
183 Institute for Social and Preventive Medicine (ISPM) in Bern and leads the study and its

projects. The local team corresponds to members of the participating clinics involved in the SCCSS-FollowUp study, such as the heads of (pediatric) oncology departments, local physicians, office of oncology departments, or clinical research assistants. Lastly, close collaborations with specialists, such as cardiologist, pulmonologist, audiologists, endocrinologists, and their teams will be established depending on the project. The collaboration with clinics involved in follow-up care of CCSs is the key element of the SCCSS-FollowUp study. This collaboration will initially be established mainly with the SPOG clinics.

Eligibility, first recruitment and informed consent procedure

The SCCSS-FollowUp team identifies potentially eligible CCSs through information from the ChCR by applying general and project-specific inclusion criteria. Project-specific criteria correspond to exposure to specific treatment modalities or risk to develop specific late effects. The SCCSS-FollwoUp team generates a patient list for each center participating in the SCCSS-FollowUp study. (**Figure 2**). The local physician in charge of follow-up care at each center receives this list and verifies eligibility (e.g. remove CCSs who recently relapsed or are in a palliative situation). All finally eligible CCSs or his/her legal representatives receive the study documents shortly before the next planned regular follow-up visit via post mail. The study documents consist of an invitation letter, study information, informed consent form, and a reply form, where the CCS can decline participation (**Figure 2**). Sending the study documents is done either by the SCCSS-FollowUp team or the local team. In addition to the study documents, the letter may include a questionnaire, if the first recruitment is linked to a project including the collection of questionnaire data. The CCSs are asked to bring the study documents to the next follow-up care visit at the respective centre.

During the follow-up care visit, the CCSs or their legal representatives are orally informed about the study by the local physician and the informed consent must be signed by both parties to be included (**Figure 2**). The subsequent follow-up care visit does not change for the CCSs.

Following the CCSs' clinical visit, the SCCSS-FollowUp team starts with the extraction of medical data, including information on cancer diagnosis, treatment exposure, and clinical data generated during the follow-up visit. These clinical data are obtained by the local physicians (e.g. patient history, physical examination) and by the specialists (e.g. bone mineral density) (**Figure 2**). This information is entered in the study database by the SCCSS-FollowUp team.

Subsequent follow-up visits and recruitment for new project

Most CCS qualify for repeated standardized examinations of several organ systems at risk at repeated time points. If a CCS has consented to the SCCSS-FollowUp study and is included in a project, the data from all follow-up visits on this organ system can be collected. If a CCS has consented to the SCCSS-FollowUp study and is now eligible for a new project evaluating another organ system or risk factor, all data to answer the new research question can be collected. The CCS will not be informed with the exception if the new project is linked to a questionnaire (**Figure 3**). The approach to identify CCSs who already consented to the SCCSS-FollowUp study for new projects is identical to the first recruitment (**Figure 2**, "Eligibility"). Newly eligible CCSs will go through the consenting process as described for the first recruitment (**Figure 2**).

Data collection

The three main pillars of the SCCSS-FollowUp are retro- and prospectively collected medical data, results from regular follow-up visits, and information collected in project-specific questionnaires. Medical data collected retrospectively include information on cancer diagnosis, relapse, secondary malignancy, chemotherapy, including cumulative doses, radiotherapy, surgery and hematopoietic stem cell transplantation. Data collected prospectively result from regular follow-up care visits and include information from physical examinations and functional tests. Wherever possible, organ-specific case report forms (CRFs) are developed in cooperation with local physicians and specialists to enable standardization of the physical examination. If a questionnaire is considered helpful to assess subjective symptoms, risk factors, or quality of life, it can be added for individual projects and specific organ systems.

All data collected are entered in the study-specific database by the SCCSS-FollowUp team, built in RedCap® *(Reference)*. The database consists of five different modules: 1) Patient Data and Eligibility, 2) Medical Data Extraction, 3) Clinical Visit, 4) Physical Examination, 5) Functional Tests. The first three modules build a common part and can be used for all CCSs included in the SCCSS-FollowUp study. The fourth and fifth module are project- and organ-specific. The modules four and five have a longitudinal design and each visit can be added separately.

Data analysis

The exact approaches used for data analysis will differ between projects and specific research questions. This also applies to the selection and use of comparators to standardize test results, if appropriate. Whenever age-standardized reference values exist, they will be used.

For all projects, we will apply descriptive statistics (such as mean and standard deviation, median and range, summary tables and graphics) to describe organ function and the prevalence of late effects in CCSs. To examine differences in characteristics between groups we will use the appropriate tests depending on the type of variable in question (t test or Mann-Whitney test, chi-squared or Fisher's exact test). In addition, and if needed to answer the study question, the SCCSS-FollowUp dataset will allow longitudinal analysis of organ function. Time-to-event data can be analyzed non-parametrically using the Kaplan-Meier method for example. Associations with covariates can be modelled using Cox regression. For repeated data we will apply the respective statistical methods for longitudinal data (e.g., mixed-models). The collection of treatment data or socioeconomic data from the medical records and questionnaires, will additionally allow us to perform risk factor analysis. For this we will use uni- or multivariable regression models adjusted for possible confounders (e.g., age, gender, height, ethnicity, type of cancer).

Discussion

The national multicenter cohort study SCCSS-FollowUp enables the prospective collection and analysis of medical data generated during regular follow-up care visits of CCSs in Switzerland. Compared to the SJLIFE and DCOG LATER study, which also collect and analyze clinical data of CCSs prospectively, the SCCSS-FollowUp study starts recruitment earlier after completion of treatment. Information on medical conditions in the first years after completion of treatment are important to be able to evaluate pathological findings that occur later. This early recruitment into SCCSS-FollowUp is a key strength of the study. Additionally, survivors of all age categories, from infants to adults, can be included. The umbrella-like design enables the collection of longitudinal data and research on all organ systems potentially affected by late effects without the need of repeatedly asking the

CCSs for informed consent. By integrating the study into regular follow-up care, loss to follow-up can be reduced. The development of CRFs for the purpose of the SCCSS-FollowUp study might allow the harmonization of tests performed by participating centers and on a national level. The assessment of self-reported symptoms by questionnaires on the same day or close to the objective assessment of organ function enables to study the correlation between subjective symptoms and objective findings. In the longer term, the SCCSS-FollowUp study enables the generation of a rich database with prospectively collected data. Integrating SCCSS-FollowUp into regular follow-up care has one disadvantage. Examinations and tests performed during regular visits adhere to long-term follow-up guidelines and recommendations. Therefore only survivors exposed to known risk factors or symptomatic survivors receive certain tests. The assessment of potential risk factors for late effects, which are not required according long-term follow-up guidelines and without good evidence, is not possible or at least limited when it comes to time- and cost-consuming examinations. Looking in the future, the design and setup of the SCCSS-FollowUp study allows expansion of the study in different areas, including the recruiting centers, data entry in the study database, and initiators of projects. Regarding participating centers, the SCCSS-FollowUp study recruits CCSs in a stepwise approach, starting with those still in follow-up care in a SPOG center. At a later stage, also CCSs who left follow-up care in a SPOG center or are lost to follow-up will be recruited. The recruitment of these CCSs will be coupled with the possibility of continuing follow-up care. By providing different access rights to each participating center, only patients from the respective center can be seen. This can additionally divided in different specialties per center. This will allow data entry by members of the local teams in the future. And lastly, the design also allows the initiation of projects within the SCCSS-FollowUp study by clinicians from participating centers.

In conclusion, the SCCSS-FollowUp study enables the collection of medical data, including diagnosis and its course, treatment exposure, results from clinical examinations, organ-specific tests, and self-reported symptoms of Swiss childhood cancer survivors. Through this approach, all relevant information to analyze late effects in CCSs are located at one place, in the constantly growing SCCSS-FollowUp database. With results from the SCCSS-FollowUp study, we aim to contribute to the growing knowledge on clinical courses of late effects and to influence long-term follow-up care in CCSs within Switzerland and on an international level.

List of abbreviations

CCS(s)	Childhood cancer survivor(s)
ChCR	Childhood cancer registry
GLI	Global Lung Initiative
SCCSS-FollowUp	Swiss Childhood Cancer Survivor Study – Follow-up
SPOG	Swiss Pediatric Oncology Group

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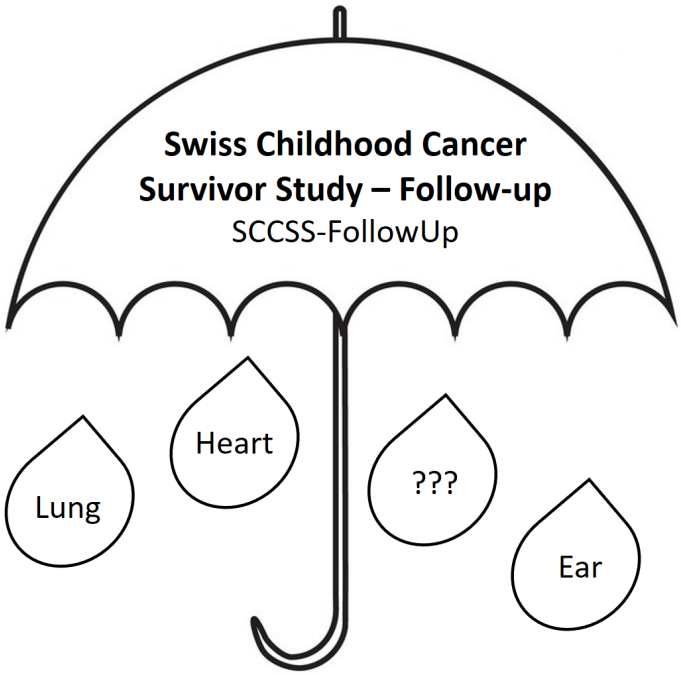

373

374 **Figure 1** Pictogram of SCCSS-FollowUp illustrating the umbrella-like design which allows to

375 perform research on several different late effects.

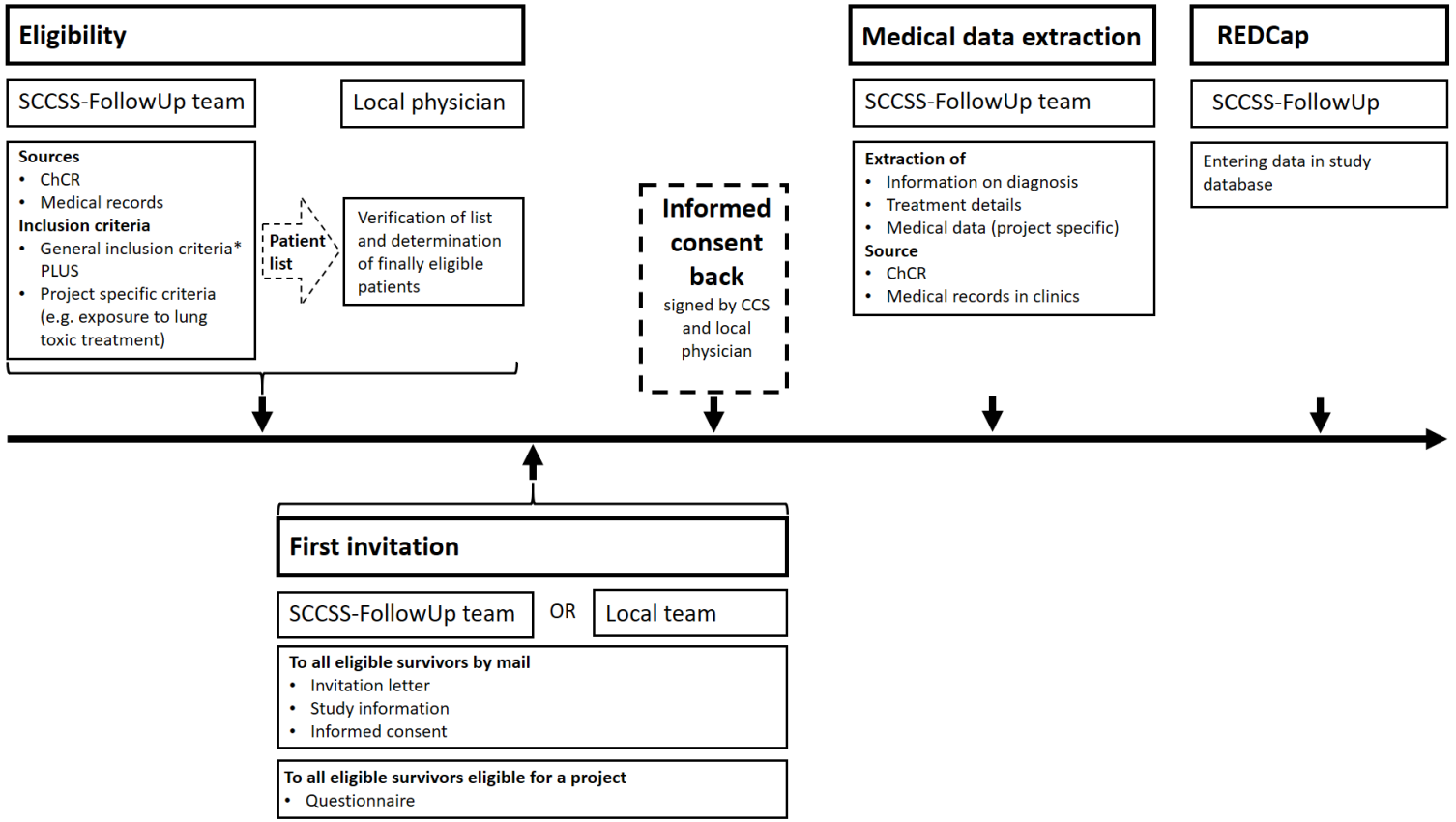

Figure 2 Timeline of tasks performed by different teams within SCCSS-FollowUp preceding and following the first invitation and follow-up visit of eligible survivors

*General inclusion criteria: registered in the ChCR since 1976, cancer diagnosis before age 21 years, alive and resident in Switzerland at recruitment, ≥1 year since diagnosis or at the end of active treatment, whichever comes first

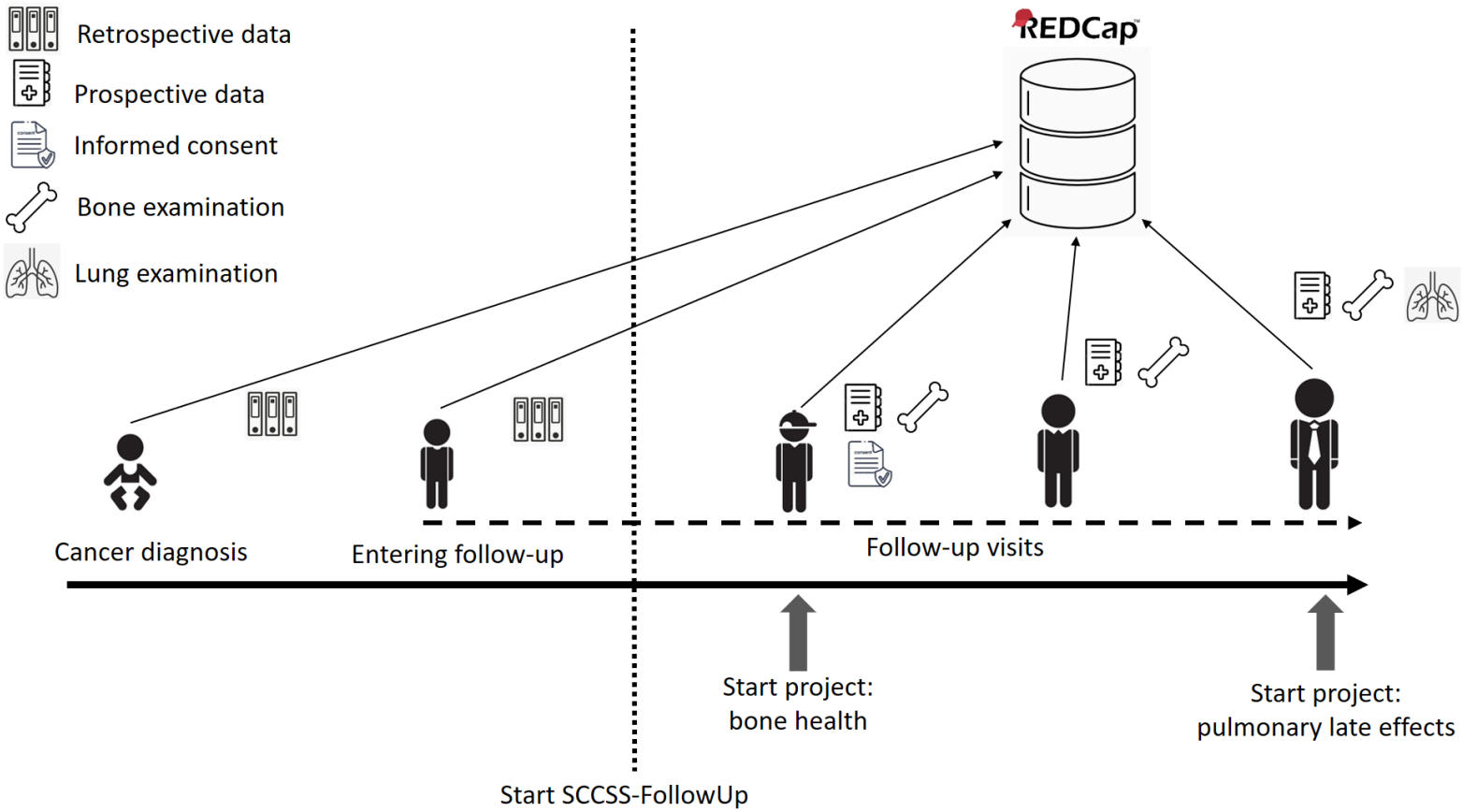

Figure 3 Umbrella-like design of the SCCSS-FollowUp study described with the example of a survivor who first qualifies for the project on bone health and later for project on pulmonary late effects

Chapter 5 - Discussion and outlook

5.1. Summary of findings

One out of five Swiss long-term childhood cancer survivors reported at least one pulmonary disease (lung fibrosis, emphysema or pneumonia) or symptom (chronic cough or other pulmonary problem) at a median of 10 years from diagnosis. This proportion was nearly identical between survivors treated with hematopoietic stem cell transplantation (HSCT) (20%, 95%CI 13-27%) compared to non-transplanted survivors (18%, 95%CI 13-21%). I could not identify factors significantly associated with more frequent reporting of pulmonary outcomes, but the results point to older age at diagnosis and thoracic surgery as possible risk factors in the multivariable analysis (**Publication I**). Self-reported outcome data on medical conditions have their limitations. This is especially true in diseases which can be asymptomatic for long period such as pulmonary fibrosis. These limitations are also true for diseases, which can be perceived differently by the general population than by doctors or researchers, such as pneumonia. Evaluating pulmonary function test results is therefore an objective approach to describe pulmonary function. In the last test of 75 CCSs treated with HSCT and a median of 9 years after cancer diagnosis, around one third had reduced z-score for FEV1 (34%, total n=73), FVC (39%, total n=71), and TLC (35%, total n=66), defined as z-score <-1.645. RV was reduced in 12% (total n=66) and DLCO in 43% (total n=35) (**Publication II**). With the exception of RV, the average z-score for each of the parameters was constantly below the expected z-score over time. In the preliminary results from the regression model FEV1, FVC, and TLC decreased continuously with every additional year from cancer diagnosis in the male reference patient and RV and DLCO showed a trend to increasing z-scores with every additional year. Taking the risk factors into account, allogeneic HSCT led to a significant annual increase in TLC z-score compared to autologous HSCT and relapsed disease led to a significant annual reduction in RV z-score. No risk factor had a significant effect on the annual change of FEV1, FVC, and DLCO z-score. The starting point of the regression line, corresponding to the time of diagnosis, was significantly lower for FEV1 z-score in case of female gender and radiotherapy and for FVC z-score in case of radiotherapy. The starting point for TLC, RV, and DLCO z-scores were not significantly influenced by any risk factor. One could assume that CCSs treated with HSCT represent a heavily treated population of survivors. However, the proportion of CCSs with z-scores for FEV1 (34%, total n=187), FVC (39%, total n=186), TLC (34%, total n=178) and DLCO (21%, total n=131) <-1.645 is very similar in CCSs treated either with lung toxic chemotherapy or radiotherapy (**Publication III**). The median follow-up in this cohort was 6 years and only 23% were treated with HSCT. The longitudinal course for FEV1 and FVC, plotted as median z-score over time, was constantly below the expected. Different to publication II, not radiotherapy to the chest had a significant association with lower intercept for FEV1 and FVC, but thoracic surgery. The risk factor analysis in both cohorts (publication II: HSCT only; publication III: pulmonary toxic chemotherapy or radiotherapy) highlighted the complexity and multifactorial etiology of pulmonary dysfunction. One factor might have a negative impact on the longitudinal course of a selected pulmonary function parameter, but might have a positive

impact on another parameter. Additional factors, such as host factors, possible genetic susceptibility or pulmonary infections were not included in all these analysis. Importantly, the findings from publication II and III highlight, that pulmonary function testing is more sensitive than questionnaire data to assess pulmonary dysfunction in childhood cancer survivors. On the other hand, abnormal pulmonary function test results do not necessarily reflect the survivors' health status in terms of symptoms, wellbeing or quality of life. With the SCCSS-FollowUp we aim to close this gap (**Publication IV**). In SCCSS-FollowUp information on subjective symptoms and wellbeing are collected at the same time as objective tests are performed, including pulmonary function tests.

5.2. Strength and limitations

The data sources used for this thesis go along with some overall strength and limitation, which I would like to discuss in this section. The strength and limitation specific for each publication can be found in Chapter 4.

Swiss Childhood Cancer Registry (SCCR)

Data from the SCCR served as a basis to identify childhood cancer patients and survivors for all my publications. The SCCR is described in chapter 3.1.1. Completeness of registration for children and adolescents <16 years of age is ≥ 95% (56). The diagnoses are coded according to the International Classification of Childhood Cancer, third edition (ICCC-3). Additional coding exists amongst other variables for tumor location according to the International Classification of Diseases for Oncology (ICD-O-3) and for the site of metastasis. For treatment exposure, the SCCR records the name of the treatment protocols. The treatment arm is often missing. This is especially the case for patients registered in the beginning of the SCCR and those with changes in treatment arms due to poor response to treatment. In addition, chemotherapeutic agents are recorded as free-text fields and not in a systematic way, such as tick boxes or drop-down lists. This results in very variable completeness of exact medical data in the SCCR, depending on the underlying disease and complexity of the patient history. As treatment exposure and its associated risk to develop pulmonary late effects was a key factor in all publications, I only used date and type of cancer diagnosis according to ICCC3 directly from the SCCR. I searched and collected all information on treatment exposure, relapse date, and transplant information in the medical records.

The big advantage of the SCCR is its high completeness in terms of registered patients. Also date and type of first cancer diagnosis are very accurate. With regards to treatment exposure, the SCCR has its limitations. This is also understandable, as a lot has changed in pediatric oncology since its establishment in 1976. The following four examples illustrate the complexity: 1) patient receive more

often second and third-line treatment, 2) patients change protocol arms or treatment protocols in case of refractory disease, 3) reading the treatment protocols with different arms, risk stratification, and individual modifications is not always straightforward for people not primary trained in pediatric oncology, and 4) the relevant information from medical letters is not always directly evident. This limitation regarding clinical data must be kept in mind and is especially important, when it comes to invite patients into clinics to perform specific screening tests based on treatment exposure. Here, review of the exposure in the medical records and verification of final eligibility by the treating pediatric oncologists is needed. This approach is also chosen to recruit patients and survivors for the SCCSS-FollowUp.

Swiss Childhood Cancer Survivor Study (SCCSS)

The SCCSS is a questionnaire-based study nested within the SCCR, including all ≥ 5-year childhood cancer survivors. It is described in more detail in Chapter 3.1.2. I used data from the SCCSS for publication I.

The strength of the SCCSS is its national and population-based nature. The high response rate (wave 1: 70 %; wave 2: 58 %) makes the study population representative for ≥ 5-year Swiss childhood cancer survivors. As shown in a publication by Rueegg et al., nonresponse bias seems to play only a minor role in the SCCSS (57). However, it is unclear if nonresponse bias is a relevant problem in sub-groups of survivors, for example in survivors treated with hematopoietic stem cell transplantation (HSCT). In addition, all outcomes are only representative for long-term survivors (≥ 5-year survivors) and may therefore lead to an underestimation of the true prevalence in all survivors, including those with a shorter follow-up. Survival bias caused by death within the first five years after completion of treatment might be especially relevant in children and adolescents treated with HSCT, as treatment with HSCT often implies an underlying diagnosis with a rather poor prognosis, such as refractory or relapsed acute lymphoblastic leukemia, relapsed Hodgkin's disease or Ewing sarcoma, or high-risk neuroblastoma. No study assessed pulmonary conditions as cause of death within the first five years after HSCT in children separately. Over all age categories, relapse, infections, and graft versus host disease are the most relevant contributors to cause of death in patients after HSCT. Styczynski et al evaluated causes of death in 114'491 pediatric and adult leukemia patients registered in the EBMT database. Slightly more than half of all death occurred within the first five years after HSCT with 58% in those transplanted allogeneic and 53% in those transplanted autologous, but only 15% of all death were linked to "other causes", including pulmonary conditions (58). This let us assume that only few patients, who die within the first five years, die due to a pulmonary disease, but probably a larger proportion might die with a pulmonary condition in the following years. In addition, the development of pulmonary conditions and becoming symptomatic can take up to several decades (e.g. pulmonary fibrosis). Therefore asking for

pulmonary diseases and symptoms at a too early stage may also lead to an underestimation of the true prevalence. This bias is similar to immortal time bias, which refers to a period of follow-up time during which the outcome cannot occur.

The questions on pulmonary health included in the SCCSS derive from other childhood cancer survivor studies from the US and UK (7, 8, 59). This allowed me to compare the results from Publication I in a global context. In addition, a previous PhD student evaluated the same questions in the whole cohort of Swiss CCSs and I could compare the prevalence in transplanted CCSs to the whole cohort of Swiss CCSs (60).

Despite the widespread use of the questions on pulmonary health, they bear some limitations. Key questions like absence or presence of shortness of breath and situations, where these symptoms occur, were missing. Additionally, some questions left room for interpretation by the participant. It was for example not defined, what the term "pneumonia" exactly means; for lay persons "pneumonia" may also include viral infections of the lower airways or a flue associated with cough and tightness in the chest. Retrospectively it would have been good to specify "pneumonia" by adding a short explanation. I assume that these limitations are related to the very comprehensive design of the SCCSS, where the addition of detailed questions would make the questionnaire even longer.

In summary, the SCCSS is a rich source for self-reported medical conditions, general health, and health behavior in long-term childhood cancer survivors in Switzerland. Due to the high response rate, the findings are representative for the whole cohort of Swiss long-term childhood cancer survivors. Still, the comprehensive approach goes to a certain extent at the expense of organ-specific questions, which would be important to make clinically meaningful conclusion.

Medical records

I used data collected from the medical records for publication I - III. The method of collecting information form medical records is described in Chapter 3.3.2.

I performed a retrospective medical records review for all patients, who participated in the SCCSS and have been treated with autologous or allogeneic HSCT. The collected data allowed me to describe the transplant characteristics in Switzerland over a period of 30 years (Publication I, Chapter 4.1), to perform risk factor analysis for self-reported pulmonary outcomes or changes in pulmonary function parameters over time (Publication I, Chapter 4.1 and Publication II, Chapter 4.2), and to describe pulmonary function trajectories in CCSs treated with HSCT (Publication II, Chapter 4.2).

During the data collection I found medical records of 132 (93%) of 142 transplanted CCSs, who participated in the SCCS. Until January 1st 2020, all medical records in Switzerland had to be archived

for a minimum of 10 years in any case and for a minimum of 20 years, if the patient received blood products. Since January 1st 2020 all medical records have to be archived for at least 20 years (61). Despite these requirements I found many files of CCSs diagnosed > 20 years prior to the data collection (30% diagnosed prior to 1995). This may be related to the fact, that these survivors are still in long-term follow-up care and that therefore all medical records are kept. I did not expect, that the 10 CCSs, I had to exclude due to missing medical records, would have changed the results of Publication I.

For publication III (Chapter 4.3), the medical records review has been performed by a previous PhD student and medical students supporting her. Of initially 419 eligible CCSs treated with lung toxic chemotherapy or radiotherapy to the chest, the medical records of 372 (89%) CCSs could be found.

I used information from the medical records to confirm or reject final eligibility of CCSs for a first phase of the SCCSS-FollowUp study (Chapter 5.4.1). CCSs from the SPOG centers in Aarau, Basel, Bern, and Geneva, were included. Preliminary eligibility to quality for screen for pulmonary dysfunction was based on information from the SCCR and included information on exposure to beomycin, busulfan, nitrosures, radiotherapy, and thoracic surgery. I additionally included all patients diagnosed with a cancer with a high possibility of having received one of the pulmonary toxic agents (e.g. germ cell tumors due to belomycin; Hodgkin lymphoma due to radiotherapy to the chest or BNCU in relapsed disease) in this preliminary group. I searched the medical records of all these preliminary eligible CCSs to verify or reject the expoures. The revised list of CCSs was subsequently checked by the division head.

Pulmonary function test results

To assess pulmonary function longitudinally in publication II (Chapter 4.2), I required at least two pulmonary function tests of good quality. The quality criteria are described in Chapter 3.3.3. This led to a reduction in the sample size from 132 to 74 (56%) CCSs.

For publication III, at least one pulmonary function test result could be found for 190 survivors (51%). For 44% of CCSs no pulmonary function test result could be found, 5% had pulmonary function tested before exposure to lung toxic treatment and 3 patients were <6 years of age at pulmonary function testing.

The retrospective collection of pulmonary function data goes in line with two main limitations:

1. We could not check the quality on how the tests have been performed. We had to assume that the archived tests have been performed according to established guidelines, such as the guidelines from the American Thoracic Society, and that the best result out of three has been archived.

2. The equipment used to perform pulmonary function tests differed between clinics and probably also differed within one clinic over the years. This can lead to minimal differences between the centers and within a center and over time.

To overcome these limitations I worked in close collaboration with pediatric pulmonologists. We defined some assumptions: we assumed that the test have been performed according to guidelines, that the tests have been performed three times, and that the best result was stored in the archive. To overcome the limitation of different machines, we only used the raw data and converted them into z-scores, using the same equations over the tested years.

In summary, searching medical records in different archives and with a national approach is very time consuming. This effort is worthwile, since the medical information is of the highes possible quality and it describes the cohort best. A reduction in the final cohort due to missing medical data is at a certain degree at the expense of generalizability. This can be neglected for Publication I, as I found the medical records of 93% of survivors. The results are therefore generalizable to all CCSs treated with HSCT who survived ≥ 5-years following the cancer diagnosis. For Publication II and III, we could find pulmonary function test results in half of eligible CCSs only. The results might therefore not be generalizable to all CCSs treated with HSCT and not to all CCSs exposed to at least lung toxic treatment modality respectively. A prospective study design including harmonization on how the tests should be performed and how the results should be reported would overcome these limitations. Until we have this prospective study and enough data collected, we have to clearly communicate this as limitations in each manuscript. Despite the limitations, these results are still very valuable for physicians and researchers.

5.3. Interpretation and implications for childhood cancer survivors and health care professionals

Despite the rather short follow-up period and young age of childhood cancer survivors assessed in publications I-III, a large proportion reported pulmonary symptoms or diseases or suffered from pulmonary dysfunction. Based on our results and by comparing the proportions of CCSs with abnormal pulmonary function test results, CCSs treated with HSCT (publication II) did not clearly perform worse than those treated with pulmonary toxic chemotherapy or radiotherapy (publication III). Even though we know from literature that certain treatment modalities put CCSs ar risk to develop pulmonary dysfunction, we could not clearly shown this in the publications included in this thesis. In the following paragraph I elaborate reasons and insurmountable limitations, which contributed to this “missing effect”. I am convinced, that most of the limitations can be solved through (inter-)national collaboration and prospective data collection.

The publication on self-reported pulmonary outcomes (publication I) and both studies on pulmonary dysfunction (publication II and publication III) included rather heterogeneous groups of Swiss childhood cancer survivors. Even though I restricted to survivors treated with hematopoietic stem cell transplantation for publications I and II, the cohorts still contain many different underlying diagnoses, combinations of treatment modalities, disease courses, and indications for transplantation. This heterogeneity makes it difficult to draw conclusions on sub-groups of survivors, such as leukemia or neuroblastoma patients, but this information would be important for health care professionals. Also the graphical illustration of the median z-score for separate pulmonary function parameters since cancer diagnosis was influenced by the heterogeneity. Even though the median value of the whole cohort was below the expected, the individual trajectories varied widely; some CCSs showed a steady decrease, others increase, and a third group showed an undulating course. Due to the heterogeneity, the number of CCSs exposed to separate risk factors, such as bleomycin or total body irradiation were too small to perform separate analysis. The same applies for separate diagnostic categories. Therefore we could not answer the clinically relevant question on which groups of survivors are at risk for a steady decrease in pulmonary function. Larger datasets and homogeneous cohort would be needed.

Other publications analyzing pulmonary function in relation to treatment exposure are often limited by low quality on how pulmonary function and its quality were assessed or reported (62, 63). We could show this within the International Guideline Harmonization Group (IGHG) on pulmonary dysfunction (see Chapter 5.4.2). National and international collaboration would help to overcome the limitations of heterogeneous study populations by increasing the number of CCSs per disease or treatment modality (e.g. busulfan in neuroblastoma survivors treated with autologous HSCT). Such collaboration could also be used as a starting point to generate and collect clinical data prospectively and on a larger scale. The prospective collection of medical data on a national level is the aim of the SCCSS-FollowUp study. On European level, PanCare (the Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer) launched the PanCareFollowUp project. Within PanCareFollowUp, the consortium aims to develop and evaluate care interventions (e.g. survivorship care plan), needs of survivors, and lifestyle intervention to improve long-term follow-up care. On an international level, the International Guideline Harmonization Group (IGHG) aims to achieve harmonized recommendations for long-term follow-up care (46). Different to SCCSS-FollwoUp and PanCareFollowUp, the harmonization within IGHG is not based on the generation and collection of medical data but on currently available evidence. To date, harmonized guidelines are available for surveillance for breast cancer, cardiomyopathy, premature ovarian insufficiency, male gonadotoxicity, thyroid cancer, ototoxicity, and cancer-related fatigue (64).

Performing research on late effects in childhood cancer survivors and providing information on prevalence, incidence, risk factors, and recommendations for screening is essential to improve care and

quality of life. In my opinion, the task of transferring these results in a meaningful way to health care professionals and survivors is as important as performing the research itself, but might be more demanding. Only when this transfer of knowledge from researcher to the health care professionals and survivors works, research is successful.

5.4. Outlook

In the following two chapters I summarize two projects I have worked on during my PhD and where I will continue working on until they are handed over to a next PhD student (Pilot Project SCCS-FollowUp, Chapter 5.4.1) or finalized (IGHG Pulmonary Dysfunction, Chapter 5.4.2).

5.4.1 Pilot Project SCCSS-FollowUp

In the initial assumption that the protocol and additional documents for SCCSS-FollowUp would go faster through all instances and the ethics committees, I have started working on a pilot project. Under the umbrella-structure of the SCCSS-FollowUp study, I have planned and initiated the first project on pulmonary health (**Figure 18**).

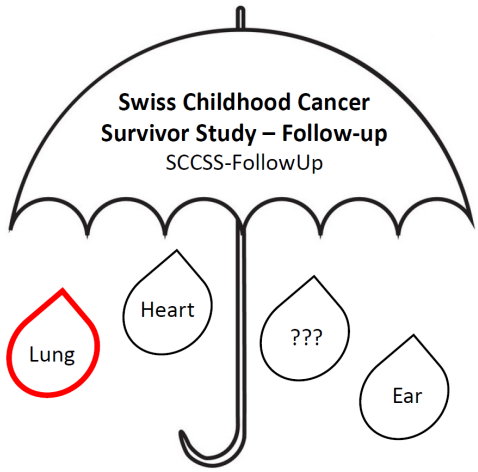

Figure 18: Pictogram of the umbrella-structure of SCCSS-FollowUp study under which several projects can be carried out

For the purpose of the project on pulmonary health, I developed a questionnaire focusing on pulmonary health. Compared to the SCCSS questionnaire, the new questions are more specific for pulmonary health, such as presence or absence of exercise induced dyspnea or dyspnea at rest, its trigger and intensity. Further questions cover the topics of wheezing, cough, pneumonia, otitis, sinusitis, hay fever, doctor visits for pulmonary problems, smoking habits, and sports. Appendix C contains the adult version of the questionnaire in German. Additional versions are available for parents, adolescents and legal representatives in German and in French. In addition, I developed a separate documentation sheet

for oncologists and pulmonologists to collect important medical data from the clinical visits and the pulmonary function test results in a standardized way (Appendix C). All this information can be entered in the study-specific RedCap® database, which I developed and coded for SCCSS-FollowUp. This database consists of two main parts: 1) a common part with information on diagnosis and treatment exposure, and 2) an organ-specific part, including individual variables for each project. The variables included in the common part and the part on pulmonary health of this database are summarized in Appendix C.

To summarize, I developed the following documents and database for the umbrella-structure of SCCSS-FollowUp and the project on pulmonary health:

1. Study protocol with a multicenter design
2. Data transfer and user agreement (DTUA) to be completed by the Institute od Social- and Preventive Medicine (ISPM) and each participating center, starting with the pediatric oncology centers
3. Information letter and informed consent document for three age categories (children, adolescents, adults) in two languages (German, French)
4. Questionnaire on pulmonary health for three age categories (children, adolescents, adults) in two languages (German, French)
5. Documentation sheet for oncologists and pulmonologists to be filled out during clinical visit
6. RedCap® database

To estimate the number of patient eligible for a first phase of SCCSS-FollowUp, I searched the medical records of patients from the SPOG clinics in Aarau, Basel, Bern, and Geneva, who fulfilled the following in inclusion criteria:

1. Initial treatment in one of the three clinics, registered in SCCR, signed SCCR consent
2. Age at first diagnosis 0 – 18 years
3. Current age ≥ 6 years (to perform pulmonary function tests)
4. Oncological treatment is finished (theoretically eligible from first day of follow-up care)
5. Treatment with at least one of the following modalities:
    a. Chemotherapy with busulfan, bleomycin or nitrosureas
    b. Radiotherapy to the chest wall, lung, mediastinum, craniospinal axis, thoracal or lumbal spine if performed with photons
    c. Surgery including muscular or sceletal chest wall, lung, mediastinum, open heart surgery. Not considered as thoracic surgery are insertion of central venous device, needle aspiration or biopsies.

   d. Allogeneic hematopoietic stem cell transplantation
   e. Autologous hematopoietic stem cell transplantation if conditioning included at least one lung toxic treatment modality
6. Still in follow-up care in the respective SPOG clinic

I used a rather inclusive approach to search for eligible patients and initially included all those treated for Hodgkin's disease, knowing that not all received radiotherapy, but that it might be missing in the treatment data from the SCCR. **Table 7** summarizes this approach for the four clinics. Initial eligibility was based on the information form the SCCR. CCSs eligible for PFT were assigned after checking medical records at the clinics.

Table 7: Eligible childhood cancer survivors for first phase of SCCSS-FollowUp

Clinic	Eligibility criteria	Initially eligible	Eligible for PFT	In regular follow-up care
Aarau	Diagnosed 1988 – 2018; age max. 30 years at follow-up	55	23	23
Basel	Diagnosed 1998 – 2018; age max. 20 years at follow-up	29	12	10
Bern	Diagnosed 1993 – 2018; age max. 25 years at follow-up	69	44	12
Geneva	Diagnosed 1993 – 2018; age max. 25 years at follow-up	36	20	20
Total		**189**	**99**	**65**

I searched the medical records of all 189 patients and proposed a summary Excel-sheet containing name, date of birth, diagnosis, date of diagnosis and exposure to all previously mentioned potential risk factors to the respective head of the pediatric oncology division. The head himself or a deputy checked the data and completed them in case a patent died or relapsed recently. Finally 65 patients would have been eligible to be recruited in the project on pulmonary dysfunction. Due to the delay in ethics approval, we could not start the recruitment yet. The population and the structure is now in place for the next PhD student.

5.4.2 International Guideline Harmonization Group - Pulmonary Dysfunction

This chapter summarized the current status of the project to harmonize long-term follow-up care for pulmonary surveillance worldwide, as part of the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) (46). The IGHG aims to provide comprehensive long-term

follow-up guidelines tailored to separate late effects. Besides screening available guidelines, the final recommendations will be based on available evidence, after a thorough systematic literature search, or based on expert opinion.

In autumn 2015 it was decided to start working on these recommendations and I have been involved in autumn 2018 after the PhD student previously working on the project (Rahel Kasteler) has successfully finished her PhD. Rahel Kasteler is still involved in the project. In the following paragraphs I mainly focus on the steps I have been involved and explain the initial steps only briefly.

The general approach of the IGHG, used for all recommendations, consists of three phases:

1. Preparation phase
2. Development phase
    a. Step 1: Evaluate concordances and discordances of current recommendations
    b. Step 2: Formulate clinical questions
    c. Step 3: Identify and select the evidence
    d. Step 4: Summarize and appraise quality of evidence
    e. Step 5: Formulate recommendations
3. Finalization phase

Independent of the late effect assessed, the IGHG recommendations aims to answer the following four questions in four working groups (WG):

WG 1: Who needs surveillance?
WG 2: What surveillance modality should be used? At what frequency should surveillance be performed?
WG 3: With what frequency should be screened? / When should follow up be initiated?
WG 4: What should be done when abnormalities are found?

Preparation phase

The guideline panel

The working group on pulmonary dysfunction consists of two chairs, two coordinators, five advisors, two members of the advisory board, and 21 additional working group members, being pediatric oncologists, pediatric or adult pulmonologists, radiotherapists and epidemiologists.

Scope of the guideline

The initial definition of pulmonary outcomes included 1) pulmonary function impairment assessed by pulmonary function tests and considered single parameters (e.g. FEV1, FVC, DLCO) and combined parameters (e.g. obstructive or restrictive disease), 2) self-reported pulmonary outcomes (e.g. chronic cough, pneumonia), and 3) doctors reported diseases (e.g. radiation induced pneumonia). In summer 2020 we decided in the whole guideline panel to restrict the outcome to pulmonary function test results only.

We included only studies if ≥ 50% of the study population were survivors of childhood, adolescent and young adult cancer diagnosed prior to age 30 years and if pulmonary function was assessed ≥ 2 years after completion of cancer treatment. We excluded reviews, case reports or studies with a sample size of < 20 survivors. We additionally excluded studies who reported only the prevalence of pulmonary outcomes but did not perform risk factor analysis.

Development phase

Step 1: Evaluate concordances and discordances of current recommendations

This step was performed by Rahel Kasteler. She compared the guidelines from the North American Children's Oncology Group, the Dutch Childhood Oncology Group, the UK Children's Cancer and Leukaemia Group, and from the Scottish Intercollegiate Guidelines Network for concordances and discordances (Appendix D).

Step 2: Formulate clinical questions

Based on the findings from step 1, twelve clinical PICO questions and sub-questions were formulated to answer the question of working group 1 (for simplicity I did not write down the sub-PICO on different doses and age at treatment for each PICO, but only for cyclophosphamide and abbreviated it with [plus a. and b.] for the following substances):

1. What is the risk of pulmonary dysfunction in childhood and young adult cancer survivors (CAYA) treated with **allogeneic hematopoietic stem cell transplantation** compared to CAYA not treated with allogeneic hematopoietic stem cell transplantation?
    a. What is the risk in younger compared to older age at treatment?
    b. What is the risk in patients with cGvHD compared to patients without cGvHD?
    c. What is the risk in patients who had a pulmonary infection during HSCT compared to patients without pulmonary infection during HSCT?

2. What is the risk of pulmonary dysfunction in CAYA treated with **cyclophosphamide** compared to CAYA not treated with cyclophosphamide?
    a. What is the risk associated with different doses?
    b. What is the risk in younger compared to older age at treatment?

3. What is the risk of pulmonary dysfunction in CAYA treated with **methotrexate** compared to CAYA not treated with methotrexate? [plus a. and b.]

4. What is the risk of pulmonary dysfunction in CAYA treated with **gemcitabine** compared to CAYA not treated with gemcitabine? [plus a. and b.]

5. What is the risk of pulmonary dysfunction in CAYA treated with **bleomycin** compared to CAYA not treated with bleomycin? [plus a. and b.]
    c. What is the risk in patients with renal dysfunction versus patients without renal dysfunction?

6. What is the risk of pulmonary dysfunction in CAYA treated with **busulfan** compared to CAYA not treated with busulfan? [plus a. and b.]

7. What is the risk of pulmonary dysfunction in CAYA treated with **lomustine** (CCNU) compared to CAYA not treated with lomustine (CCNU)? [plus a. and b.]

8. What is the risk of pulmonary dysfunction in CAYA treated with **carmustine** (BCNU) compared to CAYA not treated with carmustine (BCNU)? [plus a. and b.]

9. What is the risk of pulmonary dysfunction in CAYA treated with **radiotherapy exposing lung tissue** compared to CAYA not treated with radiotherapy exposing lung tissue?
    a. What is the risk associated with different doses and volumes?
    b. What is the risk in different radio therapeutic fields?
    c. What is the risk associated with patient age at the time of radiation?
    d. What is the risk of pulmonary dysfunction in CAYA treated with radiosensitizer combined with radiotherapy involving lung tissue compared to CAYA not treated with radiosesnitizer but with radiotherapy involving lung tissue?
    e. What is the risk for patients treated with total body irradiation in the setting of stem cell transplantation?

10. What is the risk of pulmonary dysfunction in CAYA treated with **surgery** (resection of lung tissue or resection of thoracic cage or respiratory muscles) compared to CAYA not treated with surgery?
    a. What is the risk associated with different resection volumes?
    b. What is the risk in younger compared to older age at treatment?

11. What is the risk of pulmonary dysfunction in CAYA treated with **combinations** of the therapies above?
    a. What is the risk of thoracic surgery combined with pulmotoxic chemotherapy?
    b. What is the risk of thoracic surgery combined with radiotherapy to the chest?
    c. What is the risk of pulmotoxic chemotherapy combined with radiotherapy to the chest?

12. What is the risk of pulmonary dysfunction in CAYA who have a history of **tobacco exposure** compared to CAYA with no history of tobacco exposure?
    a. What is the risk in smokers/ex-smokers compared to non-smokers?
    b. What is the risk associated with different doses (pack-years)?
    c. What is the risk in patients exposed to environmental tobacco smoke compared to not exposed?
    d. What is the risk in marijuana smokers compared to non-smokers?

For working group 2 to 4 it was decided at the very beginning by all members, that there will be no evidence in the available literature to answer these questions with a comprehensive literature search. We therefore searched existing guidelines of diseases with similar pathomechanisms or manifestations as expected in childhood cancer survivors. This task was coordinated by myself. For the extraction of information from the guidelines I was supported by four members of the group (Neel Bhatt, Christina Schindera, Nicolas Waespe, and Rahel Kasteler). The guidelines searched and the extracted information are summarized in Appendix D.

Step 3: Identify and select the evidence

A comprehensive PubMed and Embase literature search for studies published after January 1st 1990 has been performed by the Rahel Kasteler in January 2017. I updated the search in June 2019. For both searches we used the same strategy to answer the question from working group 1 (Who needs surveillance?) (Appendix D).

The screening of abstracts from the first search and the first extraction of evidence has already been performed when I entered the group. I entered as a second reviewer for the full text paper in the project.

For the search update I performed the literature search and the abstract and full text screening. Rahel Kasteler acted as second reviewer for the search update. After comparing the in- and excluded studies we discussed few studies with discrepancies and I subsequently performed the extraction of evidence.

After applying all in- and exclusion criteria to the initial literature search and the re-search, we came up with 22 eligible papers to answer the question on "Who needs surveillance" (**Figure 19**).

Step 4: Summarize and appraise quality of evidence

As we decided in the core group at a rather late stage to include only studies with pulmonary function test results and to exclude those with prevalence only, self-reported outcomes, and doctors' diagnoses, the evidence has initially been extracted for 94 studies. This task has been distributed by all members of working group 1 and was then checked by me and Rahel Kasteler (Appendix D). Later, the evidence of the 22 studies were combined in "summary of findings" tables. I generated separate tables for each PICO question and sub-PICO question, and additionally for each pulmonary outcome. For pulmonary outcomes, we decided to distinguish between obstructive and restrictive disease, hyperinflation, and diffusion capacity impairment. At this stage, I assessed the risk of bias for each study and assessed the overall quality of evidence for each PICO question. This was subsequently checked by Rahel Kasteler, and we received great support from Renée Mulder from the IGHG core group. **Figure 20** shows the criteria we used to assess the risk of bias for each study separately. **Table 9** summarizes how we assessed the overall quality per PICO based on adapted GRADE criteria, given by the IGHG group.

After grading all PICO questions we summarized the findings in an overall conclusion (**Table 9**). This summary shows, that there were several questions and outcomes where no study could be found (e.g. pulmonary infections in the setting of allogeneic HSCT or studies on gemcitabine). We could also show that the overall quality of evidence was low to very low for most PICO questions. This was mostly due to limitations in the way pulmonary function test results were reported in each study (e.g. reference equations not stated, ATS guidelines or similar not stated etc.), but also on how the risk factor analysis was performed. Most studies performed univariable analysis only, some showed p-values only or reported odds rations without confidence intervals. In addition, if only one study was available per PICO, the points in the GRADE assessment decreased.

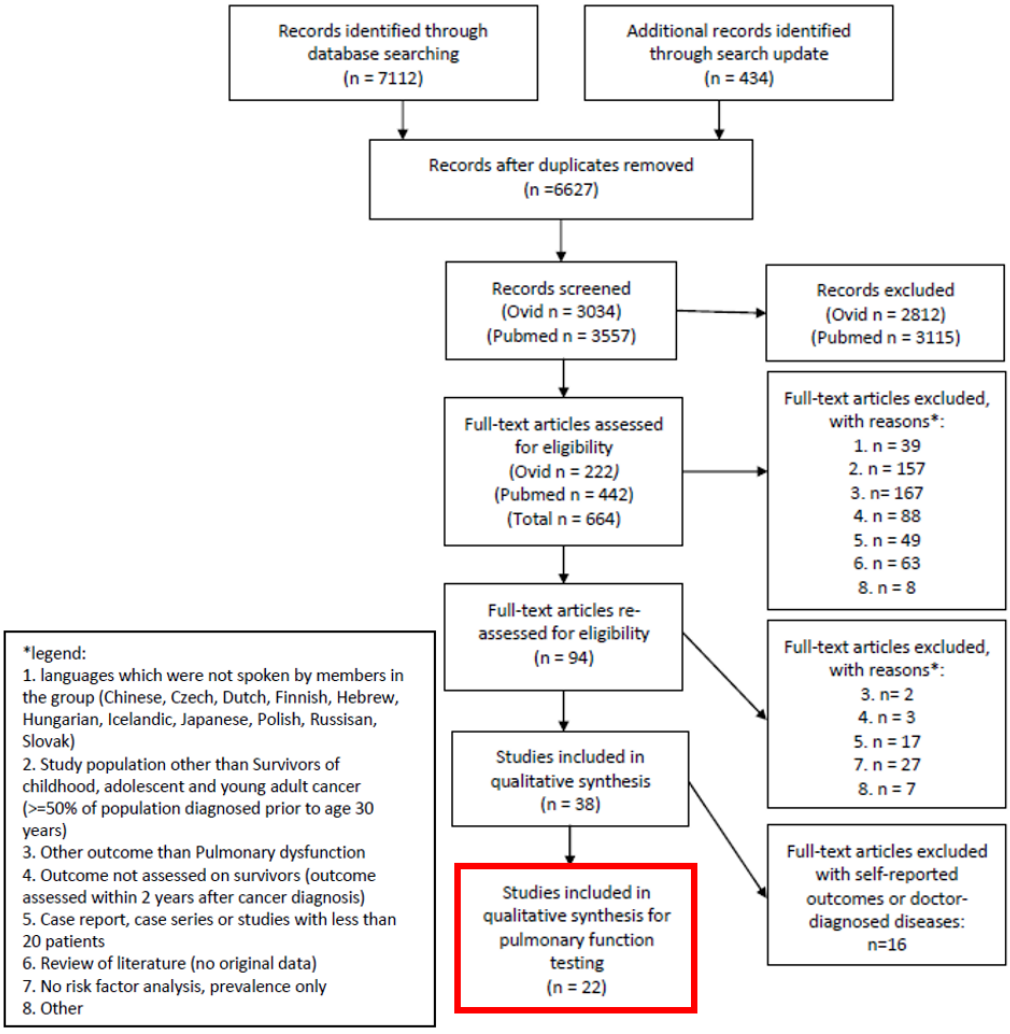

Figure 19: PRISMA flow diagram describing the selection of finally eligible publications for IGHG on pulmonary dysfunction

	Internal validity
Study group	Selection bias - Low risk/high risk/unclear Is the study group representative? Low risk if: • the study group consisted of more than 75% of the original cohort of childhood cancer survivors • *or* it was a random sample with respect to the cancer treatment
Follow-up	Attrition bias - Low risk/high risk/unclear Is the follow-up adequate? Low risk if: • the outcome was assessed for more than 75% of the study group
Outcome	Detection bias - Low risk/high risk/unclear Are the outcome assessors blinded for important determinants related to the outcome? Low risk if: • the outcome assessors were blinded for important determinants related to the outcome
Risk estimation	Confounding - Low risk/high risk/unclear Are the analyses adjusted for important confounding factors? Low risk if: • important prognostic factors (i.e. age, gender, co-treatment, follow-up) were taken adequately into account

Figure 20: Risk of bias assessment of observational studies, according to IGHG

Table 8: GRADE quality assessment according to IGHG

Initial score based on type of evidence

- +4: RCTs/ SR of RCTs
- +2: CCTs or observational evidence (e.g., cohort, case-control) for intervention questions
- +4: Observational evidence for etiologic, prognostic and diagnostic questions

Factors that might decrease the quality of the body of evidence

1. Study limitations: risk of bias based on selection bias, attrition bias, detection bias and confounding as defined in the risk of bias table.
   - 0: No problems
   - -1: Problem with 1 element
   - -2: Problem with 2 elements
   - -3: Problem with 3 or more elements
2. Consistency: degree of consistency of effect between or within studies
   - 0: All/most studies show similar results
   - -1: Lack of agreement between studies (statistical heterogeneity / conflicting result, e.g. effect sizes in different directions)
3. Directness: the generalizability of population and outcomes from each study to the population of interest
   - 0: Population and outcomes broadly generalizable
   - -1: Problem with 1 element (population different from the defined inclusion criteria OR outcomes different from the defined inclusion)
   - -2: Problem with 2 elements (population and outcomes)
4. Precision: the precision of the results
   - 0: No important imprecision when studies include many patients and many events and thus have narrow confidence intervals; Determine with the chairs and advisors what is seen as many patients, many events and narrow confidence intervals
   - -1: Important imprecision when studies include relatively few patients and few events and thus have wide confidence intervals (especially when the confidence interval cross the 0). Another criteria to consider is the clinical decision threshold. This is the threshold of the effect size that would change the decision whether or not to adopt a clinical action. Downgrade if the effect estimate and confidence intervals cross the clinical decision threshold. Determine with the chairs and advisors the clinical decision threshold.
   - OR if only one study has been identified
   - -2: If there is important imprecision (see -1) AND if only one study has been identified
5. Publication bias: if investigators fail to report studies and outcomes (typically those that show no effect)
   - 0: Publication bias unlikely
   - -1: Risk of publication bias when for example published evidence is limited to industry funded trials

Factors that might increase the quality of the body of evidence

1. Magnitude of effect:
   - +1: Large magnitude of effect; all studies show significant effect sizes (point estimate) >2 or <0.5
   - +2: Very large magnitude of effect; all studies show significant effect sizes (point estimate) >5 or <0.2
2. Dose response gradient:
   - +1: Evidence of clear relation with increases in the outcome with higher exposure levels across or within studies
3. Plausible confounding:
   - +1: If adjustment for confounders would have increased the effect size; for example the estimate of effect is not controlled for the following possible confounders: smoking, degree of education,

	but the distribution of these factors in the studies is likely to lead to an underestimate of the true effect
Total score	

⊕⊕⊕⊕ High quality evidence
⊕⊕⊕⊖ Moderate quality evidence
⊕⊕⊖⊖ Low quality evidence
⊕⊖⊖⊖ Very low quality evidence

Step 5: Formulate recommendations

When writing this thesis, we were in the middle to formulate recommendations and finding consensus. For working group 1, we will most probably only be able to formulate recommendations on exposure yes versus no (e.g. exposure to radiotherapy to the chest is a risk factor compared to no radiotherapy). The formulation of additional recommendations, taking age at exposure or cumulative dose into account, will most probably not be possible. For working group 2-4, the recommendations will most probably be based on expert opinion only. For surveillance modality, we will recommend tests, which are widely used internationally, such as spirometry and DLCO measurement and body plethysmography if available. For screening frequency, no consensus is found at this stage. The last question on "what should be done when abnormalities are found?" will be held most probably very general and recommend referral to pulmonologist or discussion in interdisciplinary teams. A separate section will focus on guidance for pulmonologists. This section will cover topics on how PFTs should be perforemed, which reference should be used and how results should be reported.

Finalization phase

We have not started this phase when writing this thesis, but we aim to have a first manuscript written in summer 2021.

↑	Increased risk
↓	Decreased risk
=	No significant effect
⇳	Conflicting evidence

Table 9: Overall conclusion of evidence on "Who needs surveillance" by PICO question and by pulmonary outcome

Who is at risk?				
Risk and risk factors for pulmonary dysfunction in survivors of childhood, adolescent and young adult cancer (≥50% of population diagnosed prior to age 30 years)				
	Obstructive dysfunction	**Restrictive dysfunction**	**Hyperinflation**	**Diffusion capacity impairment**
	Included studies used different cutoff-values to define pulmonary function as normal or pathological. Depending on PICO question, the outcome was dichtomous (normal/ abnormal) or continuous			
Treatment factors				
Allogeneic HSCT (y/n)	= ⊕⊖⊖⊖ VERY LOW (1)	= ⊕⊖⊖⊖ VERY LOW (1)	↑ ⊕⊖⊖⊖ VERY LOW (1)	No study
Older vs younger	↑ ⊕⊕⊖⊖ LOW (2)	↑ ⊕⊖⊖⊖ VERY LOW (2)	No study	↑ ⊕⊖⊖⊖ VERY LOW (3)
Chronic GvHD (y/n)	↑ ⊕⊖⊖⊖ VERY LOW (2)	↑ ⊕⊖⊖⊖ VERY LOW (1)	No study	↑ ⊕⊕⊖⊖ LOW (1)
Pulmonary infection (y/n)	No study	No study	No study	No study
TBI (y/n)	↑ ⊕⊖⊖⊖ VERY LOW (2)	↑ ⊕⊖⊖⊖ VERY LOW (2)	No study	↑ ⊕⊕⊕⊖ MODERATE (1)
Cyclophosphamide (y/n)	↑ ⊕⊖⊖⊖ VERY LOW (1)	↑ ⊕⊖⊖⊖ VERY LOW (2)	No study	= ⊕⊕⊖⊖ LOW (1)
Higher dose	= ⊕⊖⊖⊖ VERY LOW (1)	↑ ⊕⊖⊖⊖ VERY LOW (1)	No study	No study
Older vs younger	No study	No study	No study	No study
Methotrexate (y/n))	No study	No study	No study	No study
Higher dose	No study	= ⊕⊖⊖⊖ VERY LOW (1)	No study	No study
Younger vs older	No study	No study	No study	No study
Gemcitabine (y/n)	No study	No study	No study	No study
Different dose	No study	No study	No study	No study
Younger vs older	No study	No study	No study	No study
Bleomycin (y/n)	↓ ⊕⊖⊖⊖ VERY LOW (3)	= ⊕⊖⊖⊖ VERY LOW (5)	↓ ⊕⊖⊖⊖ VERY LOW (2)	↓ ⊕⊖⊖⊖ VERY LOW (4)
Higher dose	= ⊕⊖⊖⊖ VERY LOW (1)	= ⊕⊖⊖⊖ VERY LOW (1)	= ⊕⊖⊖⊖ VERY LOW (1)	= ⊕⊖⊖⊖ VERY LOW (2)
Older vs younger	No study	No study	No study	No study
Renal dysfunction (y/n)	No study	No study	No study	No study

Busulfan (y/n)	No study	= ⊕⊖⊖⊖ VERY LOW (1)	No study	= ⊕⊖⊖⊖ VERY LOW (1)
Higher dose	No study	No study	No study	No study
Younger vs older	No study	No study	No study	No study
Nitrosureas[a] (y/n)	No study	= ⊕⊖⊖⊖ VERY LOW (1)	No study	= ⊕⊖⊖⊖ VERY LOW (1)
Different dose	No study	No study	No study	No study
Younger vs older	No study	No study	No study	No study
Radiotherapy to lung tissue (y/n)	↑ ⊕⊖⊖⊖ VERY LOW (3)	↑ ⊕⊖⊖⊖ VERY LOW (4)	↑ ⊕⊖⊖⊖ VERY LOW (2)	↑ ⊕⊖⊖⊖ VERY LOW (4)
Higher doses & volumes	↑ ⊕⊖⊖⊖ VERY LOW (3)	↑ ⊕⊖⊖⊖ VERY LOW (5)	↑ ⊕⊖⊖⊖ VERY LOW (1)	↑ ⊕⊖⊖⊖ VERY LOW (5)
Different fields	No study	No study	No study	No study
Older vs younger	= ⊕⊖⊖⊖ VERY LOW (2)	= ⊕⊖⊖⊖ VERY LOW (2)	= ⊕⊖⊖⊖ VERY LOW (1)	= ⊕⊖⊖⊖ VERY LOW (2)
Radiosensitizer (y/n)	No study	No study	No study	No study
Surgery (y/n)	↑ ⊕⊖⊖⊖ VERY LOW (3)	↑ ⊕⊖⊖⊖ VERY LOW (4)	↑ ⊕⊖⊖⊖ VERY LOW (2)	= ⊕⊖⊖⊖ VERY LOW (3)
Different resection volumes	No study	No study	No study	No study
Younger vs. older	No study	No study	No study	No study
Combinations				
Surgery PLUS chemo	No study	= ⊕⊖⊖⊖ VERY LOW (1)	No study	= ⊕⊖⊖⊖ VERY LOW (1)
Surgery PLUS radio vs bleomycin	No study	↑ ⊕⊖⊖⊖ VERY LOW (1)	No study	↑ ⊕⊖⊖⊖ VERY LOW (1)
Chemo PLUS radio vs chemo	↓ ⊕⊖⊖⊖ VERY LOW (1)	↑ ⊕⊖⊖⊖ VERY LOW (2)	No study	↑ ⊕⊖⊖⊖ VERY LOW (2)
Health behaviors				
Tobacco exposure (y/n)	No study	No study	No study	No study
(ex)smoker vs non-smoker	↑ ⊕⊖⊖⊖ VERY LOW (1)	= ⊕⊖⊖⊖ VERY LOW (3)	No study	= ⊕⊖⊖⊖ VERY LOW (4)
Different doses (pack years)	No study	No study	No study	No study
Environmental tobacco	No study	No study	No study	No study
Marijuana vs. non-smoker	No study	No study	No study	No study

5.5. Conclusion

With the results from this PhD thesis I can answer the open questions on pulmonary health in Swiss childhood cancer survivors treated with hematopoietic stem cell transplantation (HSCT). I can additionally answer the question on how pulmonary function changes over time in childhood cancer survivors exposed to hematopoietic stem cell transplantation, lung toxic chemotherapy or radiotherapy to the chest– at least in a first general approach for those exposed to HSCT. I showed that one out of five survivors treated with HSCT reported at least one pulmonary outcome and that most pulmonary function parameters slightly declined over time. The same is true for survivors exposed to lung toxic chemotherapy or radiotherapy to the chest. These findings highlight that screening for pulmonary dysfunction, using pulmonary function tests, is needed in survivors at risk. But the questions on who is at risk exactly, cannot be answered straight forward with the current results from publications I-III. As shown in the systematic literature search performed within by the IGHG project, only a few studies really assessed different risk factors in relation to pulmonary function test results and many did not have a longitudinal design. In addition, the quality of evidence was low to very low in most studies. This highlights the need for prospective studies, which assess pulmonary function in childhood cancer survivors longitudinally. For that reason I have developed SCCSS-FollowUp. But even when SCCSS-FollowUp is running, the number of Swiss survivors is small. We need international collaboration to reach numbers of survivors high enough to assess the possible effect of different risk factors and in different sub-groups of survivors. But even if we, as researchers or clinicians involved in research, think we have a good study design and plan to invite survivors, we always have to consider the benefit and potential burden for the survivors. From this perspective, SCCSS-FollowUp is ideal, as it is integrated into regular follow-up care and it does not require any additional tests or examinations.

Chapter 6 - References

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Chapter 7 – Co-Author publications

7.1. Co-Author publication I

Cardiovascular and Pulmonary Challenges After Treatment of Childhood Cancer

Original article

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Own contribution to the project: Writing section on pulmonary challenges and integration of co-authors comments in this section

Cardiovascular and Pulmonary Challenges After Treatment of Childhood Cancer

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KEYWORDS

• Late effects • Childhood cancer survivor • Cardiovascular • Pulmonary

KEY POINTS

- Cardiovascular disease and pulmonary disease are the second leading nonrecurrence causes of death in childhood cancer survivors.
- Anthracyclines and radiotherapy to heart, head, and neck cause substantial cardiovascular disease, in particular, congestive heart failure, ischemic and valvular heart disease, and stroke.
- Bleomycin, busulfan, nitrosoureas, chest radiation, and lung surgery are the main contributors to pulmonary disease.
- Prevention and regular screening according to established are crucial because treatment options are limited once disease becomes clinically manifest.
- Childhood cancer survivors should be encouraged to adopt healthy lifestyles (exercise, healthy diet, and no smoking) and modifiable risk factors should be addressed.

INTRODUCTION

Both cardiovascular disease and pulmonary disease occur with increased frequency in childhood cancer survivors (CCSs), although both might not become apparent until many years after treatment.[1] These late effects of cancer therapy can vary from subclinical to life threatening and can substantially increase mortality and morbidity. After

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subsequent malignancies, cardiovascular disease and pulmonary disease are the leading nonrecurrence causes of death in CCSs.[2–4]

In particular, there is a 5-fold to 10-fold increase in mortality due to cardiovascular disease (CVD),[2–4] which is in large part due to the 5-fold to 15-fold increased risk of congestive heart failure (CHF)[5] and more than 10-fold increased risk of ischemic heart disease and stroke.[6] Similarly, the risk of death from a pulmonary event is 7-times to 14-times higher in CCSs compared with the general population,[2,7,8] and hospitalization due to respiratory conditions is 2-times to 5-times higher in survivors.[9–11]

The purpose of this review is to describe the current knowledge of cardiac and pulmonary late effects, including risk factors, early detection, possible treatments, and opportunities for prevention.

CARDIOVASCULAR DISEASE

CVD after childhood cancer usually manifests as left ventricular (LV) systolic dysfunction/heart failure, ischemic (coronary artery) heart disease, or stroke.[1,12–15] Patients, however, also can develop pericardial disease, arrhythmias, or valvular and peripheral vascular dysfunction.[13,16] Both chemotherapy and radiotherapy can contribute to these conditions either alone or in combination. For example, in a study of 5845 CCSs, those who received both cardiotoxic chemotherapy and radiotherapy involving the heart (7%) had a cumulative incidence of heart failure 40 years after diagnosis of 28%, whereas patients who received only cardiotoxic chemotherapy or only radiotherapy involving the heart had cumulative incidence of 11% and 3%, respectively.[17]

Risk Factors and Pathophysiology

The increased risk of CVD in CCSs is due mainly to exposure to anthracyclines and radiotherapy involving the heart.[4–6,13,18] Other conventional chemotherapeutic drugs, radiotherapy to head and neck, and a growing list of newer targeted agents that increasingly are used in children, however, all can affect this risk (**Table 1**).[4,6,13,15,16,18–21] In addition, standard risk factors for CVD, such as hypertension, dyslipidemia, diabetes mellitus, and obesity, many of which are more prevalent in CCSs, contribute to the increased CVD risk.[22–24]

Conventional chemotherapy

Anthracyclines (eg, doxorubicin, daunorubicin, idarubicin, and epirubicin), including the anthraquinone, mitoxantrone, commonly are used to treat a variety of childhood cancers and have been known for several decades to cause dose-dependent cardiotoxicity that can range from subclinical, with only mildly reduced shortening fraction,[25,26] to severe overt clinical heart failure.[13,17,27]

Anthracycline cardiotoxicity (ACT) historically has been described based on the time of onset, which can be acute, early (within the first year of treatment), or late (after the first year). Although early-onset ACT can resolve without intervention, some patients continue to have LV systolic dysfunction, which might be progressive, whereas others develop late-onset ACT after a latency period free of symptoms, suggesting this might be a continuum rather than clearly different entities and that additional myocardial injury or stress might contribute to developing later symptoms.[28–30]

The effects of anthracyclines are dose dependent and increase over time with CCSs who received a cumulative doxorubicin-equivalent dose greater than or equal to 250 mg/m^2, having a 30-year follow-up cumulative incidence of CHF of 8% to 13%.[17,27] Not all anthracyclines are equally cardiotoxic, with mitoxantrone carrying the highest risk for CHF and hence the conversion into doxorubicin equivalents.[31]

Table 1
List of treatments for childhood cancer associated with cardiovascular disease

Treatment Modality	Late Effect/Disease	References
Chemotherapy		
Anthracyclines (eg, doxorubicin, daunorubicin, idarubicin, and mitoxantrone)	LV systolic dysfunction/heart failure, pericardial disease, and arrhythmia	5,13,17,25–28
Alkylators (eg, cyclophosphamide, carmustine, lomustine, and ifosfamide)	Stroke, LV systolic dysfunction/heart failure, pericardial disease, and arrhythmias	6,15–17,19,27,35–37
Antimetabolites (eg, cytarabine and 5-Fluorouracil)	Pericardial disease, arrhythmias, ischemic heart disease, and heart failure	16,35
Platinums (eg, cisplatin)	Stroke, arrhythmias, vascular disease, and ischemic heart disease	6,16,35
Vinca alkaloids (eg, vincristine and vinblastine)	Ischemic heart disease	4,38
Radiotherapy		
Chest (heart)	Ischemic heart disease, valvular disease, pericardial disease, arrhythmia, and heart failure	5,6,13,17,27
Head/neck	Stroke	6,15,19,37
New targeted agents		
BCR-ABL TKIs (eg, imatinib, dasatinib, and ponatinib)	LV systolic dysfunction/heart failure, arrhythmias, ischemic heart disease, stroke, and vascular disease	39
Immune checkpoint inhibitors (eg, nivolumab, ipilimumab, and pembrolizumab)	Myocarditis and heart failure	21,40
Proteasome inhibitors (eg, bortezomib)	Heart failure, ischemic heart disease, and arrythmias	20
VEGF inhibitors or TKIs with anti-VEGF activity (eg, bevacizumab and sorafenib)	Vascular disease, ischemic heart disease, stroke, and cardiomyopathy/heart failure	20,41

Patients who were younger during the exposure and, although not consistently, female, also seem to be at higher risk.[5,17,27]

Despite being studied extensively, the exact mechanism of anthracycline toxicity has not been fully unraveled. Many preclinical studies have focused on redox cycling of anthracyclines and generation of reactive oxygen species (ROS), with cardiomyocytes particularly susceptible to ROS,[32] whereas others have found mitochondrial iron accumulation to be involved.[33] Another important mediator of ACT is topoisomerase IIb (Top2b): cardiomyocyte-specific deletion of this gene, which is one of the forms of topoisomerase 2, the presumed cellular target of doxorubicin, protects mice from doxorubicin cardiotoxicity.[34] Several of genetic risk factors for ACT that have been found (discussed later) are in genes related to ROS and iron metabolism or that interact with Top2b.

Alkylators are another large group of drugs commonly used in childhood cancer or hematopoietic stem cell transplantation (HSCT), some of which have been associated

with different types of CVD. Most of these toxicities initially were reported in adults but can occur in children.[16,35] In particular, cyclophosphamide at higher doses, such as in myeloablative HSCT conditioning, can cause acute myocarditis with subsequent LV systolic dysfunction and acute CHF, although most patients recover.[16,35] Similarly, ifosfamide can cause CHF as well as arrhythmias. More recently, cyclophosphamide, but not ifosfamide, was found to be associated with CHF in long-term CCSs.[17] Another study linked cyclophosphamide to pericardial disease, but not CHF.[27] Alkylators also were associated with a higher risk of stroke,[6,19,36] although this might be limited to certain subgroups, such as patients with brain tumors.[15,19,37]

Case reports in adults have noted pericarditis, arrhythmias, and CHF after high doses of the antimetabolite cytarabine.[35] While cytarabine frequently is used in children, it is unclear how often, if at all, cardiotoxicities occur and what the long-term outcomes are. Similarly, the antimetabolite 5-fluorouracil, although used only occasionally in children, has been linked to ischemic heart disease, arrhythmias, and heart failure, including in some pediatric case reports.[16]

Platinums, specifically cisplatin, have been found to cause arrhythmias, possibly through electrolyte disturbances.[35] In addition, vascular dysfunction, either through vasospasm or endothelial damage and platelet aggregation, can lead to myocardial infarction and stroke.[6,16,35]

Vinca alkaloids, such as vincristine and vinblastine, seem to increase risk for ischemic heart disease in adults.[38] Results in CCSs are more conflicting; one study found an increased risk of cardiovascular death after vinca alkaloid exposure,[4] whereas others failed to find such an association[13,17] or found even lower risk of myocardial infarction.[27] Possibly, the increased CVD death could be due to the often concomitant exposure to alkylators.[4]

Radiotherapy

Radiation involving the heart has been known for decades to cause ischemic heart disease and pericardial and valvular disease, and radiotherapy also can increase the risk of anthracycline-induced heart failure.[5,6,13,17,27] Arrhythmias also are common but might occur only after longer follow-up. These effects also are dose dependent, with patients treated with higher doses, in particular those greater than or equal to 35 Gy, at highest risk.[5,6,27]

Radiation to head and neck both has been consistently associated with stroke in CCSs, including transient ischemic attacks, cerebral infarction, and intracranial hemorrhage.[6,15,19,37] Again, this effect is dose-dependent, with patients receiving greater than or equal to 30 Gy to the brain at highest risk, in particular patients treated for brain tumors.[6,19] The risk of stroke increases over time and can be as high as 20% in high risk patients by age 50.[6,15,19] The toxic effect of radiotherapy is presumed to be through the cerebral vasculature, with radiation causing an inflammatory response in the vessel wall, leading to luminal narrowing and weakening of the wall that can over time result in occlusion or hemorrhage.[14]

New targeted agents

Better understanding of the biology and molecular pathways involved in cancers has led to the discovery and use of many new targeted agents, which have revolutionized the treatment of some cancers. Although these agents were developed against cancer-specific molecules or aberrant pathways, many have specific toxicities both on-target/off-tumor (target also expressed elsewhere) as well as off-target (drug not specific for the target), including the cardiovascular system.[20] Because some of these agents increasingly are used in children, the long-term impact of these toxicities in

CCSs needs to be considered, especially because these agents are given in addition to conventional treatments.[21]

BCR-ABL–directed tyrosine kinase inhibitors (TKIs), such as imatinib, but also the newer dasatinib and ponatinib, commonly are used in pediatric Philadelphia (Ph)-positive acute lymphoblastic leukemia (ALL) and chronic myelogenous leukemia (CML) and block the BCR-ABL fusion gene kinase. Newer TKIs, especially, have been associated with a variety of CVD toxicities, including LV dysfunction/cardiomyopathy, ischemic heart disease, stroke, and vascular disease.[39] Although they were developed primarily for targeting BCR-ABL, they are multikinase inhibitors that also affect kinases in the cardiovascular system, in particular vascular endothelial growth factor (VEGF) (discussed later), which might explain this toxicity.[39] Because some patients require long-term treatment with TKIs (eg, CML and Ph + ALL), these toxicities are becoming more important.

Immune checkpoint inhibitors restore antitumor immunity by blocking inhibitory signals or receptors on tumors or immune cells, such as PD-1, PD-L1 or CTLA-4.[40] Commonly used drugs in adults, such as nivolumab, ipilimumab, and pembrolizumab, are studied and used in children.[21] Blocking the inhibitory pathways, however, can shift the balance toward autoimmunity, including myocarditis with associated heart failure, which carries a high fatality rate.[40]

Proteasome inhibitors have been found to cause heart failure, ischemic heart disease, and arrythmias, although this risk might be lower for bortezomib, which is used for pediatric relapsed or refractory ALL.[20]

VEGF inhibitors or TKIs with anti-VEGF activity can have various cardiovascular toxic effects similar to BCR-ABL–directed TKIs. VEGF inhibitors, such as bevacizumab, used in certain central nervous system tumors (eg, gliomas), inhibit tumor angiogenesis by directly blocking VEGF, whereas the anti-VEGF effect of TKIs, including FLT3 inhibitors, such as sorafenib, used in certain high-risk acute myelogenous leukemia patients, is off-target.[41] Cardiovascular toxicity include thromboembolic events leading to ischemic heart disease, stroke, and cardiomyopathy with heart failure, which is mediated partly through an increased risk of hypertension.[20,41] These toxicities are important in CCSs, especially for acute myelogenous leukemia patients, who often receive anthracyclines and FLT3 inhibitors.

Genetic risk factors

In addition to exposure to specific therapies, certain germline genetic variations also have been found to modify CVD risk, in particular for ACT. Studies that focused specifically on ACT in CCSs have found variants in genes related to anthracycline transport and metabolism (*SLC28A3*,[42,43] *UGT1A6*,[42,43] *CBR3*,[44,45] *SLC22A7*,[46] *SLC22A17*,[46] and *ABCC5*[47]), iron metabolism (*HFE*[48]), oxidative stress (*CAT*,[49] *GSTP1*,[50] *NOS3*,[47] and *HAS3*[51]), hypertension (*PLCE1*[52] and *ATP2B1*[52]), cardiac physiology or structure (*HAS3*,[51] *CELF4*,[53] *GPR35*,[54] and *TTN*[55]), and DNA damage (*RARG*[56]). Some variants have been replicated in multiple cohorts, whereas others have not, and the functional consequences of these variants have been explored only partly.[57]

Diagnosis, Surveillance, Treatment, and Prevention

Echocardiography remains the mainstay for screening and diagnosis of cardiac disease in CCSs, in particular for LV dysfunction after anthracyclines and chest radiotherapy, measuring shortening or ejection fraction.[58] Echocardiography also can diagnose valvular abnormalities, diastolic dysfunction, and pericardial disease. When more sensitive parameters, such as global longitudinal strain, are used,

echocardiography can detect more subclinical systolic dysfunction than by measuring ejection fraction alone.[59] Cardiac magnetic resonance imaging is even more sensitive but also more costly and not readily available in every center.[58] Imaging to detect vascular or cerebrovascular disease are not used routinely to screen asymptomatic CCSs.

Currently, international harmonized guidelines provide recommendations for screening for cardiomyopathy in CCSs using echocardiography.[58] Further refinement of risk for CVD using clinical risk factors[5,6] or incorporating genetic variants[60] might aid to decide which CCSs to screen and how often, thereby likely improving screening cost effectiveness.[58,61,62]

Electrocardiography at baseline is recommended by most CCS long-term follow-up guidelines,[61,62] but its role to detect conduction abnormalities in asymptomatic CCSs is unclear.[63]

Cardiac biomarkers, such as troponins or the N-terminal prohormone of brain natriuretic peptide, have been studied extensively in CCSs, but although elevations of these markers during treatment might predict long-term LV dysfunction, their role for screening asymptomatic survivors is limited due to their low sensitivity.[58,64] These markers may be used to monitor or screen symptomatic patients similar to the general population.[58]

Prevention

To prevent cardiovascular toxicities from occurring, treatment protocols have evolved over time, reducing, omitting, or replacing certain chemotherapeutic agents and radiotherapy without affecting cancer treatment outcome. For example, maximum cumulative doses for anthracyclines are recommended in many protocols, and radiotherapy has been successfully reduced in the treatment of Hodgkin disease.[16] Risk prediction models might identify patients who will benefit most from these preventative measures.[5,6,57,60] Newer radiation techniques, including intensity-modulated radiation therapy or proton therapy, might further reduce the harmful effects to cardiovascular structures.[16] Cardioprotective agents, specifically dexrazoxane, have been studied extensively, and dexrazoxane seems to reduce ACT without affecting antitumor efficacy or increasing secondary malignancies.[65]

Secondary prevention, aimed at preventing CVD after treatment exposures, relies in part on screening and early detection of subclinical disease to initiate pharmacologic treatment, as discussed previously for heart failure. In adult cancer survivors, the combination of angiotensin-converting enzyme (ACE) inhibitors and β-blockers was shown to help recover cardiac function after early detection of LV dysfunction, even in asymptomatic survivors.[30] Although the role of pre-emptive heart failure treatment in asymptomatic CCSs is less clear, it still is employed often.[16,66] Other strategies focus on targeting modifiable risk factors, such as hypertension, dyslipidemia, diabetes mellitus, obesity, and adopting a healthy lifestyle (ie, regular exercise, healthy diet, and no smoking),[16,24] which have been incorporated in survivor guidelines.[61,62]

Treatment

Treatment of CVD in CCSs depends on the type of disease and usually is managed similar to the general population.[16] Childhood Cancer Survivors patients with heart failure commonly are treated with ACE inhibition often in combination with β-blockers, although the evidence in children is scarce.[16,67,68] Once symptoms occur, heart function can rapidly decline and become refractory to treatment necessitating mechanical support or heart transplant.[16]

PULMONARY DISEASE

Pulmonary disease is another important long-term complication in CCSs with high morbidity and mortality. It is due to a range of pulmonary conditions, such as fibrosis, emphysema, recurrent pneumonia, or chronic cough, that affects survivors throughout their life and increases in frequency with longer time elapsed from cancer treatment.[1,69,70]

Risk Factors and Pathophysiology

Several important treatment modalities, such as bleomycin, busulfan, lomustine (CCNU) or carmustine (BCNU), radiation of the thorax, and surgery to the lung or chest wall, impart a risk of pulmonary damage. Patients after HSCT are at particular risk because their treatment often incorporates more than one treatment-related risk factor. Unlike in CVD, no studies have systematically investigated genetic risk factors for pulmonary toxicity.

Chemotherapy

For most categories of chemotherapeutic agents and their combinations, reports of chemotherapy-induced lung injuries have been published, although often only as case reports or case series. Consistent and robust evidence for pulmonary toxicity is available for bleomycin, busulfan, and nitrosoureas (BCNU and CCNU).[71–73]

Bleomycin is used to treat Hodgkin lymphoma and germ cell tumors. The lung is vulnerable to this agent because it lacks the bleomycin-inactivating enzyme bleomycin hydrolase. This leads to free radical formation and oxidative damage to lung tissues. Subsequent inflammatory processes eventually cause alveolar damage, hypersensitivity reaction, pneumonitis, and pulmonary fibrosis (**Table 2**). Reported prevalence of bleomycin-induced pneumonitis (BIP) ranges from 0% to 46%. BIP usually develops during treatment, resulting in cough, dyspnea, and fever.[74] Data on long-term prognosis after BIP are inconsistent. One review concluded that radiographic changes and lung function abnormalities usually resolve completely.[74] However, 2 studies that assessed lung function by spirometry, body plethysmography, and measurement of diffusion capacity for carbon monoxide (DLCO) in children, 2 years and 4 years after exposure to bleomycin, found that 41% and 52% of children, respectively, had pathologic test results at these time points.[75,76] The toxicity is dose dependent and more common with doses greater than 400 U/m^2, which seldom are used in pediatrics. Simultaneous or subsequent radiotherapy to the lung, exposure to elevated oxygen concentrations, renal dysfunction, smoking, and higher age at treatment may exacerbate bleomycin toxicity.[72,74,77]

Busulfan is an alkylating agent used mainly to condition children before autologous or allogeneic HSCT. The exact mechanism of lung injury is unknown, and the dose-response relationship is unclear. It seems, however, that cumulative doses less than 500 mg do not cause pulmonary injury in adults.[72,73,78] As with bleomycin, concomitant irradiation may magnify the toxic effect of busulfan.[72]

Nitrosoureas, including CCNU and BCNU, mainly are used to treat brain tumors and to condition patients for autologous HSCT. Nitrosoureas are risk factors for pneumonitis and pulmonary fibrosis (see **Table 2**). Pulmonary fibrosis usually develops slowly over years or decades with asymptomatic periods of various length.[79] In nitrosourea-induced pulmonary fibrosis, inflammatory reactions followed by depletion of type I pneumocytes and hyperplasia of type II pneumocytes lead to increased collagen deposition.[80] Higher cumulative doses are associated with increasing risk of lung injury. Patients exposed to thoracic irradiation may develop lung injury at lower doses of nitrosoureas than those not exposed.[72,73,81] A case series followed 17 long-term

Table 2
List of treatments for childhood cancer associated with pulmonary disease

Treatment Modality	Late Effect/Disease	References
Chemotherapy		
Bleomycin	Acute respiratory distress syndrome Interstitial or hypersensitivity pneumonitis Bronchiolitis obliterans organizing pneumonia Pulmonary veno-occlusive disease Pulmonary fibrosis	72–76
Busulfan	Acute respiratory distress syndrome Alveolar proteinosis Pulmonary fibrosis	72,73,78
Nitrosoureas (carmustine, and lomustine)	Hypersensitivity pneumonitis Alveolitis Pulmonary veno-occlusive disease Pulmonary fibrosis	72,73,79,81,82
Radiotherapy to the chest	Bronchiolitis obliterans organizing pneumonia Interstitial pneumonitis Impaired chest wall growth Pulmonary fibrosis	71–73,83,84
Surgery		
(eg, pulmonary lobectomy, pulmonary wedge resection, pulmonary metastasectomy, and chest wall resection)	Restrictive lung function impairment Scoliosis Chest wall deformity	72,85
Stem cell transplantation		
Lung toxic agents used for conditioning	See Busulfan and Nitrosoureas	
Transplant-specific noninfectious pulmonary complications	IPS BOS Bronchiolitis obliterans organizing pneumonia DAH	72,86,87

brain tumor survivors treated with high-dose BCNU and spinal irradiation (n = 12) for up to 25 years. Half (53%) of the survivors died of pulmonary fibrosis, whereas all 7 patients who were still alive after 25 years of follow-up showed radiologic and physiologic (ie, lung function) evidence of pulmonary fibrosis.[79,82]

Radiotherapy

Direct irradiation of the lung, but also scattered radiation after radiotherapy to the chest wall, abdomen, or spine, increases the risk for pulmonary damage. Radiation can lead to DNA strand breaks and trigger lung injury by starting a cascade of inflammatory reactions, with capillary leaks and alveolar and interstitial exudate, which later organizes into collagen. Acute radiation pneumonitis usually develops within 6 weeks to 3 months after radiotherapy (see **Table 2**). The most frequent symptoms are dyspnea and cough. Although early stages of radiation pneumonitis can be self-limited and resolve completely, most patients develop progressive fibrosis.[80] Toxicity due to radiation depends on the irradiated lung volume; total dose; method of irradiation, such as dose fraction; and application of radiosensitizer. At least 10% of the lung volume has to be irradiated to produce significant toxicity. Radiation pneumonitis rarely

develops in cases of fractionated radiotherapy with a total dose less than 20 Gy, but is common if the cumulative dose exceeds 40 Gy to 60 Gy.[71,73,83,84]

Surgery

Extensive pulmonary and chest wall surgery can alter pulmonary function.[85] Lobectomy or resection of multiple metastases leads to reduced lung volumes. Removal of ribs or part of the chest wall can cause restrictive ventilation impairment due to a reduction in expansibility of the chest wall.

Hematopoietic stem cell transplantation

Children treated with HSCT face transplant-specific pulmonary complications and late effects, in addition to those discussed previously. Approximately 37% of patients after HSCT develop pulmonary complications.[86] Pulmonary complications are divided in infectious and noninfectious, depending on the underlying cause. The noninfectious complications generally are transplant-specific, such as bronchiolitis obliterans syndrome (BOS), diffuse alveolar hemorrhage (DAH), and idiopathic pneumonia syndrome (IPS) (see **Table 2**). DAH and IPS typically present with an acute onset of respiratory failure within the first 30 days and 120 days after HSCT, respectively.[86] Both diseases have a high mortality, but no data on long-term outcomes exist.[86] BOS typically is diagnosed greater than 100 days after transplantation.[86,87] The main symptoms of BOS are dry cough and dyspnea. BOS has a variable clinical course, but most patients have slowly progressive airflow obstruction. Stabilization or improvement of lung function is rare.[87]

Diagnosis, Surveillance, Treatment and Prevention

Lung function tests

Lung function impairment in CCSs is assessed by pulmonary function tests. Pulmonary symptoms, such as chronic cough or dyspnea at exertion, are late signs of pulmonary dysfunction. One study found that only 24% of those with restrictive disease diagnosed by lung function tests reported symptoms using the Medical Research Council dyspnea questionnaire.[88]

Lung function usually is assessed by spirometry, body plethysmography, and measurement of the diffusing capacity for carbon monoxide (DLCO), with restrictive, obstructive, mixed restrictive-obstructive patterns, and decreased diffusion capacity having been reported. Decreased diffusion capacity is the most frequent abnormality (35%–45%), followed by restrictive (13%–32%) and obstructive disease (1%–4%).[75,76,88–91] Few studies have assessed lung function longitudinally, so that knowledge on long-term prognosis is scarce. Repeated lung function tests in survivors after HSCT found 3 phases in lung function trajectories: (1) an initial decrease in lung function after completion of treatment, lasting for 3 months to 6 months; (2) a subsequent recovery until 1 year to 2 years after completion, usually not reaching baseline values; and (3) stable values or slow deterioration in the long-term follow-up.[92–94]

Multiple breath washout tests (MBWs) might be more sensitive to identify early changes. They measure ventilation inhomogeneity in the lung, which is increased in case of central and peripheral airway obstruction. One study assessed pulmonary function in adults (n = 225) with BOS after HSCT with MBW and found the test highly sensitive for detecting abnormal lung function in their cohort (95% abnormal MBW test compared with 56% abnormal forced expiratory volume in the first second of expiration/forced vital capacity [FEV1/FVC]).[95] Whether this test will be valuable in the early detection of lung function impairment in CCSs still must be evaluated. Additional examinations, such as imaging or lung biopsy, are used in case of suspected pulmonary disease but not in regular follow-up care.

Surveillance

National and international follow-up guidelines concerning pulmonary late effects specify that the use of the chemotherapeutic agents (discussed previously), radiotherapy to the chest, and thoracic surgery are indications for pulmonary follow-up using lung function tests.[61,62,96] The available evidence is scarce, however, and the effect of other chemotherapies unclear, so more dedicated research is needed.

Treatment and prevention

Treatment options for pulmonary diseases and functional impairment in CCSs depend on the underlying disease. In general, treatment options are limited but the field is evolving quickly. This article focuses on treatment options for noninfectious pulmonary diseases beyond the acute-phase. BOS can be treated with systemic steroids, but these can increase the risk of pulmonary infection.[97,98] Inhaled bronchodilators do not improve pulmonary function in these patients.[98] One case series reported that patients with BOS who received inhaled fluticasone, azithromycin, and montelukast (FAM) could reduce their doses of systemic steroids compared with those not treated with FAM, thereby sparing them from the serious toxicities associated with long-term steroid use.[98] The subsequent phase II study confirmed that the FAM-regimen with reduced doses of systemic steroids was well tolerated and resulted in a reduction in pulmonary function decline in most patients.[99] Systemic steroid therapy improves radiation pneumonitis, but most experts agree that corticosteroid therapy is ineffective for the treatment of pulmonary fibrosis.[71,73] A few newer drugs, such as the TKI nintedanib, are available for adults with idiopathic pulmonary fibrosis. Data for the use in children are lacking. Nintedanib slows lung function decline and acute exacerbations in patients with idiopathic pulmonary fibrosis.[100,101]

Because treatment options are limited, prevention of pulmonary damage has high priority. Bleomycin no longer is a first-line therapy for lymphoma, although it remains a core component of germ cell tumor therapy, and radiotherapy has been reduced in many protocols, but avoidance of pulmonary toxic chemotherapy or radiation not always is possible. Therefore, any additional damage to the lung should be avoided throughout a survivor's life. Survivors must be counseled to not smoke and to avoid secondhand smoke exposure. Pneumococcal and influenza vaccinations should be considered in survivors with established pulmonary disease. Survivors should be advised to inform anesthetists about previous bleomycin treatment in cases of general anesthesia, because high fraction of inspired oxygen (>30%) concentration may further affect preexisting pulmonary damage.[102] Also survivors who desire to scuba dive should have a pulmonary consultation prior to undertaking the activity.[61,62,96]

SUMMARY

Cardiovascular disease and pulmonary disease after childhood cancer treatment impose great challenges for survivors. The cardiovascular system and lungs can be severely affected by cancer treatment in many ways, resulting in increased morbidity and mortality. Treatment options once disease becomes clinically manifest are focused on decreasing symptoms but do not cure cardiovascular or pulmonary disease. Therefore, prevention and regular screening according to established follow-up guidelines are crucial, even in the absence of symptoms, which generally occur rather late. Survivors should be encouraged to adopt a healthy lifestyle, and modifiable risk factors should be addressed. Close collaboration and early referral to experienced specialists (eg, cardiologist and pulmonologist) are essential for optimal diagnosis and management.

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7.2. Co-Author publication II

Physical activity and screen time in children who survived cancer – A report from the Swiss Childhood Cancer Survivor Study

Original article

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RESEARCH ARTICLE

Physical activity and screen time in children who survived cancer: A report from the Swiss Childhood Cancer Survivor Study

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This study has been previously reported as a meeting abstract. Name of presentation: "Physical activity and screen time in children after childhood cancer: A report from the Swiss childhood cancer survivors study," 2019 National Symposium on Late Complications after Childhood Cancer (NASLCCC), Atlanta, GA, USA, June 21, 2019, abstract number P48.

Abstract

Background: Physical activity (PA) can reduce the risk of chronic adverse health conditions in childhood cancer survivors. We examined PA and sedentary screen time behavior in a nationwide study in Switzerland.

Procedures: The Swiss Childhood Cancer Survivor Study sent questionnaires to parents of all Swiss resident ≥5-year survivors diagnosed between 1995 and 2010. We assessed PA including compulsory school sport, recreational sport, commuting to school, and time spent with screen media in those aged 5-15 years, and compared results with international recommendations.

Results: We included 766 survivors with a median age at diagnosis of 2.8 (interquartile range 1.4-5.0) years and a median age at study of 12.5 (10.0-14.3) years. Median PA time was 7.3 (4.8-10.0) h/week and median screen time was 82 (45–120) min/day. Compulsory school sport hours and walking or cycling to school contributed significantly to total PA. Note that 55% of survivors met PA and 68% screen time recommendations. PA was lower for children living in regions of Switzerland speaking French or Italian compared to German, and for those who had a relapse or musculoskeletal/neurological conditions. Screen time was higher in males, children with lower parental education, and a migration background.

Conclusions: PA and sedentary screen watching were associated with social factors, and PA also with clinical risk factors. Structural preventions that afford active commuting to school and sufficient school sport are essential, as is counseling vulnerable survivor groups such as those with musculoskeletal and neurological problems, and those who have had a relapse.

KEYWORDS
childhood cancer survivors, chronic health conditions, exercise, late effects, Swiss Childhood Cancer Registry

Abbreviations: AAP, American Academy of Pediatrics; BMI, body mass index; CCS, childhood cancer survivor; ICCC-3, International Classification of Childhood Cancer, third edition; MICE, multivariate imputation by chained equations; PA, physical activity; TBI, total body irradiation; WHO, World Health Organization.

1 | INTRODUCTION

Adult childhood cancer survivors (CCS) have an elevated risk of poor health[1,2] and early death[3]: almost 75% suffer from a chronic adverse health condition[2] and their cumulative mortality reaches nearly 10% 30 years after cancer diagnosis.[3] Physical activity (PA) can reduce the risk of cancer and inhibit chronic health conditions such as diabetes and hypertension in the general population,[4] while among adult CCS, PA has been associated with reduced risk factors for cardiovascular disease[5] and cardiovascular disease itself,[6] and with lower overall mortality.[7] Yet while PA can mitigate many health hazards,[6,7] only half of adult CCS meet PA recommendations.[8–10]

An active lifestyle might be even more important for young children and teenage survivors, but only a few studies, usually at single centers or with low participant numbers, have been performed in this age group.[11–14] Their results vary, with 31–74% meeting recommendations for PA[11–15] and 28–46% meeting those for screen time behavior.[11,14] Research also has neither distinguished between different types of physical activities nor described how school sports or an active daily commute to school might contribute to overall PA. Better knowledge of screen time behavior and PA and the factors influencing both could inform recommendations for structured prevention and identify risk groups that could profit from counseling or focused interventions.

We aimed to investigate PA and screen time behavior in Swiss CCS aged 5-15 years to assess how PA and screen time are compared with international recommendations, and to examine demographic, socioeconomic, lifestyle, and clinical factors associated with PA and screen time.

2 | METHODS

2.1 | The Swiss Childhood Cancer Survivor Study

The Swiss Childhood Cancer Survivor Study is a population-based, long-term cohort study of all children registered in the Swiss Childhood Cancer Registry who have been diagnosed since 1976, survived ≥5 years after initial diagnosis, and were alive at the time of the study.[16] The registry includes all patients in Switzerland who were diagnosed at age <21 years with leukemia, lymphoma, central nervous system tumors, malignant solid tumors, or Langerhans cell histiocytosis.[17] Recent estimates indicate that the registry includes 95% of those diagnosed below age 16 since 1995 in Switzerland.[18] We included survivors aged 5-15 years at survey who had been diagnosed between 1995 and 2010. From 2010 to 2016, we traced addresses and sent a questionnaire to parents. We mailed the questionnaire a second time to those who did not respond, and further lack of response included an attempt to reach parents by phone. Among 1068 survivors whose parents were contacted, we received responses from parents of 766 (72%) (Table S1, Figure S1).

Ethics approval was granted by the Ethics Committee of the Canton of Bern, Switzerland, to the Swiss Childhood Cancer Registry and the Swiss Childhood Cancer Survivor Study (KeK-BE: 166/2014), and the Swiss Childhood Cancer Survivor Study is registered at ClinicalTrials.gov (identifier: NCT03297034).

2.2 | Outcomes: PA and screen time

We examined PA as compulsory school sport, recreational sport, and commuting to school. We derived the time for compulsory school sport, 2.3 h/week (3 × 45 min), from the Swiss school curriculum, which is regulated by "The federal Council of Switzerland" both for regular and special needs schools.[19] Children going to special needs schools might do different exercises in their sports lessons than children attending regular schools, but have the same weekly time. Information on recreational sport activities and the commute to school were obtained via questionnaire. Parents were asked about types of recreational sports and how many hours per week CCS devoted to each (Figure S2, question 1), and we categorized answers into 16 different types of sports. We also asked how the child usually went to school (on foot or by bike/kickboard, by bus/streetcar, or by car) and the time required (<10 min, 10-20 min, or >20 min; Figure S2, questions 2-3); the durations observed in the analysis were 5, 15, and 30 min. We considered only transit by foot or bike/kickboard as active. To obtain weekly estimates, we multiplied the times reported for one way to school by 15 to account for 5 school days per week, and an average of three trips to school per day because there are two to four afternoon school sessions per week at Swiss schools, with most children going home for lunch. Questions on PA (Figure S2, questions 1-3) were taken from established studies of unselected Swiss school children from the general population, which were derived from validated questionnaires.[20–23]

We used the World Health Organization (WHO) recommendations to characterize whether a child had sufficient PA (≥7 h/week or ≥60 min/day of any PA for children aged 5-17 years).[24] We created the binary outcome of those who had "sufficient" PA and those who did not.

Screen time was assessed by asking parents how much time their child spent on average each day interacting with screen media including television, computer games, game boys, PlayStation, or Nintendo (Figure S2, question 4). We used the 2013 American Academy of Pediatrics (AAP) recommendations for screen-based media exposure to determine acceptable screen time, less than 120 min/day,[25] as the current 2016 AAP recommendations only give qualitative, but no quantitative screen time recommendations.[26] We created the binary outcome of those who had media exposure that was "acceptable" screen time and those who did not.

2.3 | Clinical characteristics

We extracted the following clinical characteristics from the cancer registry: age at cancer diagnosis, cancer diagnosis, year of cancer diagnosis, treatment protocol, chemotherapy, radiotherapy, surgery, and hematopoietic stem cell transplantation. We classified cancer diagnoses in terms of 12 main groups and Langerhans cell histiocytosis

TABLE 1 Demographic, socioeconomic, lifestyle, and clinical characteristics of childhood cancer survivors included in the study, N = 766

	N = 766	
	N	%[a]
Demographic and socioeconomic characteristics		
Male sex	428	56
Age at study, years		
5-7	65	8
8-10	196	26
11-13	282	37
14-15	223	29
Language region		
German	535	70
French	197	26
Italian	34	4
Migration background[b]	212	28
Parental education[c]		
Primary education	61	8
Secondary education	462	60
Tertiary education	219	29
Lifestyle characteristics		
Child's BMI (kg/m^2) z-scores		
Underweight	124	16
Normal	456	59
Overweight	89	12
Obese	23	3
Clinical characteristics		
Age at diagnosis, years		
<1	149	20
1-4	423	55
5-10	194	25
Time since diagnosis, years		
5-10	607	79
11-15	159	21
Cancer diagnoses[d]		
Leukemia	286	37
Lymphoma	52	7
Central nervous system tumor	125	16
Other tumors	303	40
History of relapse	100	13
Any chemotherapy	624	82
Anthracyclines	388	51
Any radiation	122	16
Stem cell transplantation	55	7
Chronic health conditions		
Cardiopulmonary	72	9
Endocrine	82	11
Hearing and vision	210	27
Musculoskeletal/neurological	275	36
Number of chronic health conditions		
None	354	46
1	239	31
≥2	173	23

Abbreviations: BMI, body mass index; N, number.

[a]Column percentages are given.

[b]Migration background: survivors who were not Swiss citizens at birth, not born in Switzerland, or had at least one parent who was not a Swiss citizen were defined as having a migration background.

[c]Parental education categorized by three categories: Primary education (compulsory schooling only [≤9 years]), secondary education (vocational training [10–13 years]), and tertiary education (higher vocational training, college, or university degree). If parents achieved different levels of education, we selected the parent with the highest education.

[d]More detailed cancer diagnoses according to ICCC-3, International Classification of Childhood Cancer, third edition, in Table S4.

according to the International Classification of Childhood Cancer, third edition (ICCC-3).[27] We assessed whether children had been treated with anthracyclines. Thoracic radiation included the mantle field, mediastinum, thoracic spine, and total body irradiation (TBI); abdominal radiation included the abdomen, the pelvis, testis, and TBI; and radiation to the head/neck included the head, the neck, and TBI. We went back to medical records when registry treatment information was incomplete. The questionnaire collected information on chronic health conditions involving the cardiopulmonary and endocrine systems, problems affecting ears and eyes, and musculoskeletal/neurological conditions (Table S2). Chronic health conditions were asked using questions from the North American[28] and British[29] Childhood Cancer Survivor Studies with some adaptions because of the younger age in our Swiss Childhood Cancer Survivor Study.[16] The questions on chronic health conditions included multiple choice questions and additional free text options where parents of survivors could specify and add chronic health conditions not asked in the questions. Free text answers were classified by a pediatric oncologist (CS) and discussed with other experienced pediatricians (CEK, MO) when in doubt.

2.4 | Demographic, socioeconomic, and lifestyle characteristics

The questionnaire included demographic (sex, age at study, Swiss language region), socioeconomic (migration background, parental education), and lifestyle characteristics (child's body mass index [BMI], mother's BMI). We used self-reported weight and height and calculated children's BMI and corresponding *z*-scores.[30] BMI z-scores lower than −2 were classified as underweight, −2 to 1 as normal weight, >1 to 2 as overweight, and >2 as obese.[31] Self-reported mother's BMI was calculated and categorized according to the National Institutes of Health.[32]

2.5 | Statistical analyses

We compared characteristics of participating survivors and those in families from whom we received no response using chi-square tests. We used multivariate imputation by chained equations (MICE) to complete missing values in the outcome variables and demographic, socioeconomic, lifestyle, and clinical variables. Missing values for hours of recreational sport were predicted by corresponding description of recreational sport. All other variables with missing values were imputed by using all other variables with the exception of the outcome variables (Supporting Information Text). In an alternative approach, we determined PA and screen times using the original data before MICE (Table S3). Using multivariable logistic regression, we explored the association between the two binary outcomes, sufficient PA (meeting the WHO recommendations) and acceptable screen time (according to AAP recommendations), and demographic, socioeconomic, lifestyle, and clinical characteristics using an a priori selection of clinically important variables. We also investigated the correlation between PA and screen time using the pooled Spearman correlation coefficient. We used STATA software (Version 15.1, Stata Corporation, Austin, TX) and R (Version 3.5.2; R Foundation for Statistical Computing, Vienna, Austria).[33]

3 | RESULTS

3.1 | Study population

The median age at diagnosis of the study population of 766 children (428 were male) was 2.8 years (interquartile range, 1.4-5.1), median age at survey was 12.5 years (10.1-14.3), and median time since diagnosis was 9.0 years (7.5-10.8) (Table 1). The two most frequent diagnoses were leukemia (37%) and central nervous system tumor (16%), and 51% received anthracyclines and 16% any radiation. Overall, 54% of children reported one or more adverse chronic health condition. At survey, the median BMI *z*-score in children was 0.08 (−0.7 to 0.9), and 59% of survivors were of normal weight. Full demographic, socioeconomic, lifestyle, and clinical characteristics of CCS are given in Table 1 and Table S4. Participants were compared with surviving nonparticipants for the following characteristics obtained from the Swiss Childhood Cancer Registry: sex, age at study, language regions, migration backgound, age at diagnosis, time since diagnosis, cancer diagnosis, history of relapse, time era of treatment, and chemotherapy being part of cancer treatment (Table S1). Characteristics on lifestyle and chronic conditions were unavailable for nonparticipants as this information was collected from the questionnaire.

3.2 | Physical activity

Over one-half of CCS (55%) had sufficient PA according to the WHO recommendations and the median time devoted to PA was 7.3 h/week, with recreational sport contributing 3.0 h/week (Table 2, Figures S3 and S4). The most common recreational sports were soccer (13%), gymnastics (12%), swimming (11%), cycling/driving a scooter (10%), and free outdoor/indoor play (10%). For male survivors, soccer (21%), scooter (11%), and free indoor/outdoor play (10%) were most relevant, and for female survivors, gymnastics (17%), swimming (13%), and dancing (12%) were most relevant (Figure 1). We found no important difference using the alternative analysis approach that assessed PA time and meeting the WHO recommendations using the original data before MICE (Table S3).

3.3 | Screen time

Median screen time was 82 min/day, and 68% of children had acceptable screen time in accordance with AAP recommendations (Table 2, Figure S3). We found no important difference in the alternative analysis approach that assessed screen time and meeting AAP recommendations using the original data before MICE (Table S3).

3.4 | Predictors for PA and screen time

PA was lower for children who lived in the French and Italian language regions than it was in the German-speaking region of Switzerland. It was also lower for those who had a relapse or suffered from musculoskeletal/neurological conditions (Table 3, Figure 2). We observed no association between PA and sex, age at study, BMI of survivors and mothers, cancer diagnoses, cardiopulmonary conditions, and treatment exposures. Screen time was higher in male survivors, children with lower parental education, or migration background (Table 4, Figure 2), but not associated with sex, age at study, endocrine and musculoskeletal/neurological problems, and all other clinical characteristics.

3.5 | Correlation between low PA and high screen times

We found no correlation between PA and screen time in survivors (pooled Spearman correlation coefficient −0.05), and no correlation between time spent for recreational sports and an active way to school (pooled Spearman correlation coefficient 0.16) (Figure S5).

4 | DISCUSSION

This comprehensive survey of PA and screen time in children and adolescents who have survived cancer found that half of young survivors met the recommendation for PA and two-thirds did not exceed the maximum recommended for screen time. Having an active way to get to school and compulsory school sport greatly contributed to overall hours of PA.

Our results for PA are superior compared to those of a cohort study that included 1300 Swiss children and adolescents between 6 and 16 years of age, among whom only 39% of children aged 12-13 years met or exceeded PA recommendations assessed by accelerometer.[34] Young survivors in our study preferred recreational sports including soccer

TABLE 2 Compulsory school sport, recreational sport, active way to school, total physical activity, screen time, and adherence to WHO/AAP recommendations in childhood cancer survivors, N = 766, 56% males, median age 12.5 years

	N = 766				
	Median[a], IQR	Mean[b], SD	10th–90th percentile	Range	Adherence[c] to WHO/AAP
Compulsory school sport (h/week)[d]	2.3, NA	2.3, NA	NA	NA	
Recreational sport (h/week)[e]	3.0, 1.0-5.0	3.7, 3.9	0-8.0	0-32	
Active way to school (h/week)[f]	1.3, 0-3.8	2.0, 1.9	0-3.8	0-7.5	
Total physical activity (h/week)[g]	7.3, 4.8-10.0	8.0, 4.5	3.3-13.5	2.3-35.5	55%
Screen time (min/day)[h]	82, 45-120	91, 66	15-180	0-480	68%

Abbreviations: AAP, American Academy of Pediatrics, (recommending <120 min screen time per day); IQR, interquartile range; N, number; NA, not applicable; SD, standard deviation; WHO, World Health Organization (recommending ≥7 h of physical activity per week).
[a]Pooled median over the complete imputed dataset.
[b]Pooled mean over the complete imputed dataset.
[c]Percent of adherence refers to the pooled medians.
[d]Compulsory school sport defined as 3 × 0.75 h/week = 2.3 h/week.
[e]Recreational sport as asked in the questionnaire (question 1, Figure S2): Which types of sport does your child perform?
[f]Active way to school by foot or bike/kickboard as asked in the questionnaire (questions 2 and 3, Figure S2): How does your child usually go to the kindergarten or to school? How long is your child's way to the kindergarten or school?
[g]Total physical activity consisting of compulsory school sport, recreational sport, and an active way to school. Please indicate, how often your child performs different types of sports (h/week).
[h]Screen time as asked in the questionnaire (question 4, Figure S2): How much time does your child spend on average with the following activities per day? Watching television, computer games, game boy, PlayStation, Nintendo.

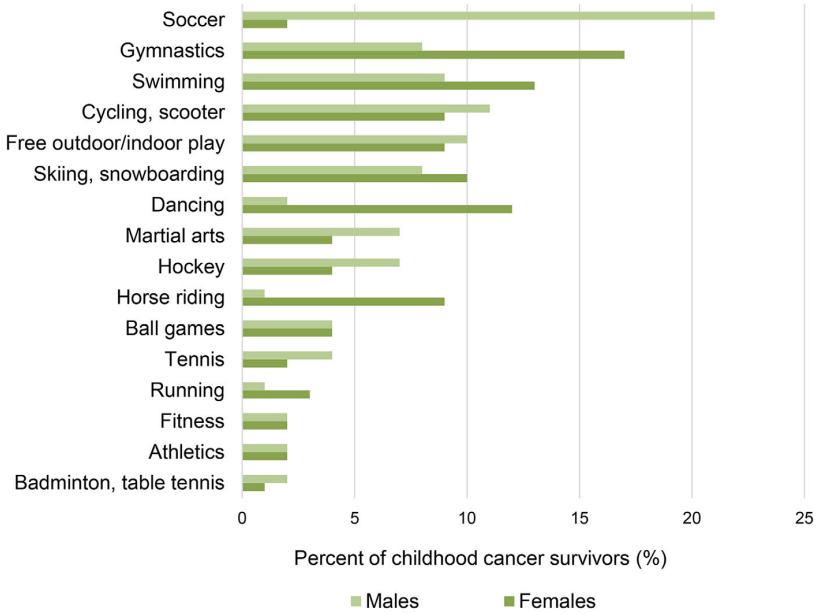

FIGURE 1 Frequencies of the 16 different recreational sports in childhood cancer survivors (N = 766, 56% males, median age 12.5 years), stratified by sex; there can be multiple (1-5) different recreational sports per child

for males, and gymnastics, swimming, and dancing for females, and these preferences are similar to those of other school children.[35] A study of screen time in healthy adolescent school children in Switzerland found higher median screen times of 122 min/day (compared to 82 min/day in our population), although screen time was assessed differently and focused on internet use.[36]

Studies of PA and screen time in children after cancer are few and report variable results. A 2012 Australian study assessed 40 children in two centers after hematopoietic stem cell transplantation at a mean age of 12.5 years by questionnaire; 48% of the children met the PA recommendation and 28% that for screen time.[11] Another single-center Australian study that used a 3-day diary assessed 74 young survivors with a mean age of 15.0 years between 2012 and 2014 and reported that 74% adhered to PA and 46% to screen time recommendations.[14] Gilliam and colleagues performed phone interviews between 2010 and 2011 in 105 North American survivors aged 11.1 years who reported

TABLE 3 Factors associated with sufficient physical activity (WHO recommendation) in childhood cancer survivors, N = 766, 56% males, median age at study 12.5 years

	Sufficient physical activity			
	%[a]	Odds ratio[b]	95% CI	*P*-value[c]
Demographic characteristics				
Sex				
Female	50	1.0		
Male	60	1.3	0.9-1.8	.113
Age at study, years				
5-7	48	1.4	0.4-4.4	
8-10	55	1.5	0.7-3.3	
11-13	60	1.6	1.0-2.6	.306
14-15	51	1.0		
Language region				
German	59	1.0		
French/Italian	48	0.6	0.4-0.9	.005
Socioeconomic characteristics				
Migration background				
No	57	1.0		
Yes	51	0.9	0.6-1.3	.473
Parental education				
Tertiary education	60	1.0		
Secondary education	54	0.8	0.6-1.1	
Primary education	48	0.6	0.3-1.1	.218
Lifestyle characteristics				
Child's BMI (kg/m^2) z-scores				
Normal weight	43	1.0		
Underweight	50	0.8	0.5-1.2	
Overweight/obesity	45	1.0	0.7-1.7	.409
Mother's BMI (kg/m^2) (continuous)	NA	1.0	0.9-1.0	.381
Clinical characteristics				
Cancer diagnoses				
Leukemia	59	1.0		
Lymphoma	60	1.1	0.6-2.1	
CNS tumor	46	0.7	0.4-1.3	
Other tumor	55	0.9	0.6-1.4	.588
Relapse				
No	58	1.0		
Yes	40	0.5	0.4-1.0	.030
Cardiopulmonary conditions				
No	55	1.0		
Yes	56	1.1	0.7-1.9	.642
Endocrine conditions				
No	57	1.0		
Yes	42	0.6	0.4-1.1	.112
Hearing/vision conditions				
No	56	1.0		
Yes	54	1.3	0.9-1.9	.195
Musculoskeletal/neurological conditions				
No	59	1.0		
Yes	49	0.7	0.5-0.9	.017
Anthracyclines				
No	53	1.0		
Yes	57	0.9	0.6-1.3	.506
Radiotherapy				
No	55	1.0		
Yes	59	1.2	0.8-1.9	.410
Stem cell transplantation				
No	55	1.0		
Yes	55	1.2	0.5-1.5	.543

Abbreviations: BMI, body mass index; CI, confidence interval; CNS, central nervous system; N, number; NA, not applicable; WHO, World Health Organization.

[a]Column percentages are given.

[b]Pooled odds ratios from multivariable logistic regression comparing those with high physical activity to those with low physical activity, adjusted for demographic, socioeconomic, lifestyle, and clinical characteristics.

[c]*P*-value from likelihood ratio tests.

a mean PA time of 6.7 h/week, which is lower than the mean 8.0 h we observed,[12] but times since diagnosis differed between the two cohorts (9.0 years in our study versus 4.6 years in the North American study). Another study from two North American centers reported a mean PA time of 47 min/day for 319 survivors aged 14.6 years, which corresponds to 5.5 h/week and again is lower than in our cohort.[15] But that study used questionnaires that focused on past-year leisure-time PA, whereas our questionnaire also included the way to school and school sport. This could explain the difference.

Important predictors for higher PA in our study were living in the German-speaking region compared to the French and Italian linguistic regions of Switzerland. This was also shown in studies in healthy Swiss school children.[34] Also, Swiss school children from the French- compared to the German-speaking regions were less likely to play outside and to actively commute to school[37,38] and PA behavior was not associated with sociodemographic and neighborhood factors.[39] This indicates that the language spoken is a marker of underlying cultural factors that influence PA behavior. In adults, prevalence of physical inactivity, smoking, alcohol consumption, and unhealthy diet was higher in the French- compared to the German-speaking part of Switzerland, highlighting possible cultural differences within Switzerland.[40] Other important predictors for PA in young survivors in other studies are social support from family and peers.[12] Additional predictors reported for adolescent and adult survivors include female sex,[8,9] low parental[8] or survivor education,[9,13,41]

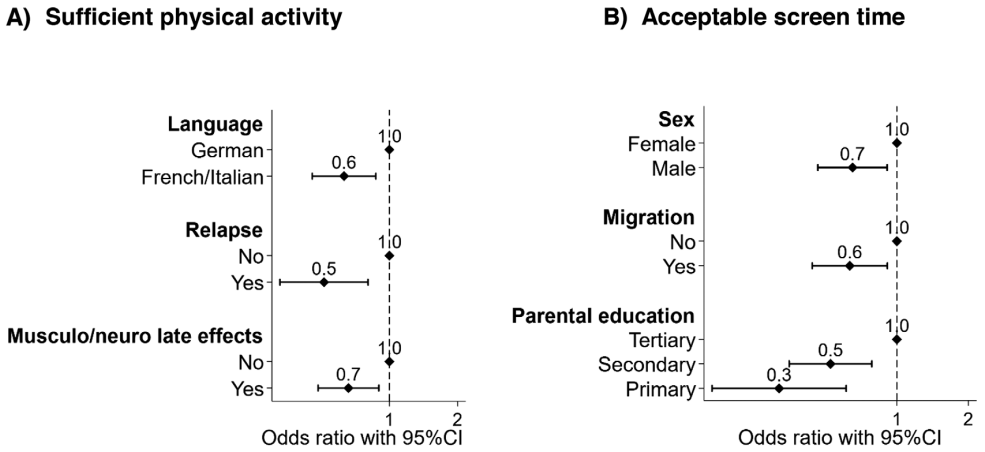

FIGURE 2 Factors associated with (A) sufficient physical activity, and (B) acceptable screen time in childhood cancer survivors (N = 766, 56% males, median age 12.5 years). Pooled odds ratios from multivariable logistic regression adjusted for demographic, socioeconomic, lifestyle, and clinical characteristics. CI, confidence interval; Musculo/neuro, musculoskeletal/neurological

cranial radiation,[8,9,41] overweight and obesity,[9,41] physical limitations,[8,41] and a diagnosis of central nervous system tumors and sarcomas.[41,42] We also found that musculoskeletal/neurological problems are a predictor for PA and we also saw a trend for parental education, central nervous system tumors, and endocrine conditions.

Among our study's limitations is the reliance of the outcome variables PA and screen time on parental reporting. Parents might have overestimated PA and underestimated screen time because of both social desirability and recall biases. A second problem involves the questionnaire's having inquired about structured physical activities even though young children in particular are active mainly in an unstructured way with free inside and outside play.[34] This differential misclassification bias could have led to underestimation of activity in younger survivors. However, parents did mention free outdoor and indoor play in 10% of boys and 9% of girls (Figure 1). Accelerometers and pedometers may overcome this problem[34,43]; although worn only for study purposes and short periods, their data might not be representative of daily life. A third limitation is that we assumed that all children participated in compulsory school sport according to the Swiss curriculum,[19] which might have overestimated PA in this special population. However, we also asked parents whether and—if yes—why their child is unable to perform sports. None of the survivor's parents affirmed this question. Some parents stated that their child goes to a special needs school. Also special needs schools in Switzerland are obliged to involve students to 3 × 45 min of compulsory school sport per week according to federal law.[19] The exercises they do in these lessons may, however, differ somewhat from those done in regular schools. Forth, PA in Swiss school children differs between winter and summer,[34] but we did not account for the season when parents filled out the questionnaire. The questionnaire design did not allow to differentiate the different activity intensities light, moderate, and vigorous PA. Questions asked in the Swiss Childhood Cancer Survivor Study were based on the North American and British Childhood Cancer Survivors Studies[28,29] to enable comparison, but the questionnaire has not formally been validated. Our screen time questions assessed traditional screen activities such as watching television and computer games, and did not account for the use of social media, mobile phones, iPads, and the use of multiple devices at the same time, such as mobile phone and television; the average screen time we observed might be an underestimate. Further, we did not differentiate between screen time for educational purposes and leisure screen time. Finally, our study had no control group because too few siblings met our inclusion criteria.

This study is the first nationwide, population-based study of PA and screen time in children who survived cancer. Among its strengths is its relatively high response rate, 72%, which makes us confident that the results are representative for Swiss CCS. Also, being nested in the Swiss Childhood Cancer Registry provided us with important and comprehensive data on demographic, socioeconomic, lifestyle, and clinical characteristics.

Our results indicate that structural support via compulsory school sport and an active daily commute to school are important contributors to PA. Public health policy should at least preserve if not increase support for both compulsory and voluntary school sport. Further research should inquire into why PA is lower in the parts of Switzerland speaking French and Italian than in the German-speaking part, and how PA levels might be increased in all three. Also, it goes without saying that family and community support for actively commuting to school should be maintained or increased.

For individual prevention, clinicians should counsel young survivors and their families to pursue active lives. In a German study, only 25% of 83 young survivors with a median age of 14 years and 3.8 years after cancer diagnosis participated in school sport, and medical advisories against sports participation were frequent.[44] Parents also might overprotect their children during and after completion of cancer therapy. PA not only is safe both during and after cancer therapy, it may positively influence evolving chronic health conditions. Pediatric oncologists therefore can and should assure families that PA is of particular importance to CCS and encourage participation in compulsory and

TABLE 4 Factors associated with acceptable screen time (AAP recommendation) in childhood cancer survivors, N = 766, 56% males, median age at study 12.5 years

	Acceptable screen time			
	%[a]	Odds ratio[b]	95% CI	*P*-value[c]
Demographic characteristics				
Sex				
Female	72	1.0		
Male	64	0.7	0.4-0.9	.007
Age at study, years				
5-7	88	4.5	1.1-18.0	
8-10	78	2.9	1.2-6.9	
11-13	68	2.0	1.1-3.4	.074
14-15	52	1.0		
Language region				
German	68	1.0		
French/Italian	65	0.8	0.6-1.2	.354
Socioeconomic characteristics				
Migration background				
No	71	1.0		
Yes	59	0.6	0.4-0.9	.018
Parental education				
Tertiary education	77	1.0		
Secondary education	65	0.5	0.3-0.8	
Primary education	50	0.3	0.2-0.6	.004
Lifestyle characteristics				
Child's BMI (kg/m^2) z-scores				
Normal weight	66	1.0		
Underweight	74	1.2	0.7-2.1	
Overweight/obesity	64	0.8	0.6-1.6	.803
Mother's BMI (kg/m^2) (continuous)	NA	1.0	0.9-1.0	.247
Clinical characteristics				
Cancer diagnoses				
Leukemia	61	1.0		
Lymphoma	73	1.8	0.8-3.8	
CNS tumor	71	2.2	1.1-4.7	
Other tumor	71	1.3	0.8-2.1	.111
Relapse				
No	67	1.0		
Yes	67	1.0	0.6-1.8	.975
Cardiopulmonary conditions				
No	67	1.0		
Yes	68	1.1	0.6-1.9	.805
Endocrine conditions				
No	68	1.0		
Yes	59	0.8	0.4-1.4	.360
Hearing/vision conditions				
No	66	1.0		
Yes	70	1.0	0.7-1.6	.887
Musculoskeletal/neurological conditions				
No	67	1.0		
Yes	69	1.0	0.7-1.5	.936
Anthracyclines				
No	68	1.0		
Yes	67	1.2	0.7-1.9	.492
Radiotherapy				
No	68	1.0		
Yes	66	1.1	0.7-1.9	.654
Stem cell transplantation				
No	68	1.0		
Yes	59	0.7	0.3-1.4	.300

Abbreviations: AAP, American Academy of Pediatrics; BMI, body mass index; CI, confidence interval; CNS, central nervous system; N, number; NA, not applicable.

[a]Column percentages are given.

[b]Pooled odds ratios from multivariable logistic regression comparing those with low screen time to those with high screen time, adjusted for demographic, socioeconomic, lifestyle, and clinical characteristics.

[c]*P*-value from likelihood ratio tests.

voluntary school sports, and keep medical restrictions on activity to a minimum. Further research should include interventions that include social support as an important contributor to children's PA.[12]

In summary, we found that half of young cancer survivors are not active enough and one-third devote too much time to sedentary screen viewing. Compulsory school sport and an active commute to school are important components of an active lifestyle. Therefore, we need both individual-based prevention, such as better counseling of survivors and families, and structural prevention addressing all children in Switzerland, such as promotion of active commuting to school and extended school sport lessons.

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CONFLICT OF INTEREST

The commercial funders of the Swiss Childhood Cancer Registry support the daily running of the registry and have not had and will not have any role in the design, conduct, interpretation, or publication of the Swiss Childhood Cancer Registry itself as well as the related research projects.

DATA AVAILABILITY STATEMENT

The Swiss Childhood Cancer Registry and Swiss Childhood Cancer Survivor Study are a collaborative project of the Swiss Pediatric Oncology Group (SPOG) and the Institute of Social and Preventive Medicine, University of Bern, Switzerland. Our homepage displays detailed information in methods, results, and publications (www.childhoodcancerregistry.ch). Researchers interested in collaborative work can contact the corresponding author (Claudia E. Kuehni; claudia.kuehni@ispm.unibe.ch) to discuss planned projects or analyses of existing data. The final decision will be made upon presentation of the project to the Scientific Council of the Swiss Pediatric Oncology Group.[16]

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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7.3. Co-Author publication III

Nutritional Assessment of Childhood Cancer Survivors (the Swiss Childhood Cancer Survivor Study-Nutrition): Protocol for a Multicenter Observational Study

Original article

Fabiën N Belle, Maja Beck Popovic, Marc Ansari, **Maria Otth**, Claudia E: Kuehni, Murielle Bochud

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Own contribution to the project: Involved in several reviews of the manuscript

JMIR RESEARCH PROTOCOLS Belle et al

Original Paper

Nutritional Assessment of Childhood Cancer Survivors (the Swiss Childhood Cancer Survivor Study-Nutrition): Protocol for a Multicenter Observational Study

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Background: Childhood cancer survivors are at high risk of developing adverse late health effects. Poor nutritional intake may contribute to this risk, but information about dietary intake is limited.

Objective: This study will assess childhood cancer survivors' dietary intake and compare two dietary assessment tools: a self-reported food frequency questionnaire, and dietary measurements from urine spot samples.

Methods: In a substudy of the Swiss Childhood Cancer Survivor Study (SCCSS), SCCSS-Nutrition, we assessed childhood cancer survivors' dietary intake via a validated food frequency questionnaire. We sent a urine spot collection kit to a subset of 212 childhood cancer survivors from the French-speaking region of Switzerland to analyze urinary sodium, potassium, urea, urate, creatinine, and phosphate content. We will compare the food frequency questionnaire results with the urine spot analyses to quantify childhood cancer survivors' intake of various nutrients. We collected data between March 2016 and March 2018.

Results: We contacted 1599 childhood cancer survivors, of whom 919 (57.47%) returned a food frequency questionnaire. We excluded 11 childhood cancer survivors who were pregnant or were breastfeeding, 35 with missing dietary data, and 71 who had unreliable food frequency questionnaire data, resulting in 802 childhood cancer survivors available for food frequency questionnaire analyses. To a subset of 212 childhood cancer survivors in French-speaking Switzerland we sent a urine spot collection kit, and 111 (52.4%) returned a urine sample. We expect to have the results from analyses of these samples in mid-2019.

Conclusions: The SCCSS-Nutrition study has collected in-depth dietary data that will allow us to assess dietary intake and quality and compare two dietary assessment tools. This study will contribute to the knowledge of nutrition among childhood cancer survivors and is a step toward surveillance guidelines and targeted nutritional recommendations for childhood cancer survivors in Switzerland.

Trial Registration: ClinicalTrials.gov NCT03297034; https://clinicaltrials.gov/ct2/show/NCT03297034

International Registered Report Identifier (IRRID): DERR1-10.2196/14427

(JMIR Res Protoc 2019;8(11):e14427) doi: 10.2196/14427

KEYWORDS

child; cancer survivors; urine specimen collection; diet surveys; food frequency questionnaire; Swiss Childhood Cancer Registry; Switzerland

Background

Survival rates among childhood cancer patients have increased markedly and, due to new and improved treatments, now exceed 80% [1]. As patients live longer, strategies to promote long-term overall health of childhood cancer survivors (CCSs) become increasingly important. Complications and disabilities from treatment, such as chemotherapy and radiotherapy, cancer recurrence, or both, can affect morbidity and mortality many years after a cancer diagnosis [1,2]. The St. Jude Lifetime Cohort Study showed that a large proportion of CCSs experience late effects 25 years after diagnosis; 95% have had at least one chronic health condition and 80% have had a severe, life-threatening, or disabling condition [3]. Frequently reported late effects include cardiovascular diseases (CVDs), endocrine disorders, musculoskeletal problems, and secondary malignancies [2]. Such late effects may be increased by lifestyle habits and choices. Accumulating research in CCSs shows that late effects such as type 2 diabetes, metabolic syndrome, and CVD can be reduced through diet adaptations, weight management, and physical activity [4-7]. Nutrition is an important determinant of the health of CCSs.

However, little is known about the dietary habits of CCSs [8,9], and studies have shown that CCSs adhere poorly to dietary recommendations [10-13]. No evidence-based nutritional guidelines exist specifically for CCSs. Nutritional information can be obtained from, for example, self-reported food frequency questionnaires (FFQs) or 24-hour dietary recalls, whereas assays of biochemical indicators—nutrients or their metabolic products—in tissues or fluids, such as nails, feces, blood, and urine, can more directly quantify intake of nutrients [14]. Since self-reported dietary assessment tools are limited by misreporting and recall bias, which can lead to over- or underreporting, results need to be handled with caution [14]. This holds especially true for dietary assessment using FFQs; underestimation of dietary intake in 16 CCSs was greater when measured by the Block FFQ than by repeated 24-hour dietary recalls, validated by the doubly labelled water method [15]. A Canadian study among 80 CCSs showed that an FFQ could correctly rank CCSs according to their dietary intake when comparing it with 3-day food records [16].

The use of 24-hour urine samples to assess alkaline minerals, halide ions, and protein intake can complement self-reported dietary questionnaires, as well as producing nutritional indicators that potentially are more valid than data from questionnaires [14]. But collection of 24-hour urine samples can be a considerable burden for survivors, and it risks bias due to undetected incomplete sample collection and low response rates. Recent research has focused on the utility of estimating 24-hour urinary output from single spot urine samples [17]. These samples are less burdensome for participants and are more easily obtained by researchers, and potential under- or overcollection is irrelevant [14,17]. By adjusting for parameters such as age, sex, height, and weight, and by taking urinary creatinine into account, samples can yield interpretable results [18]. This makes spot urine samples a practical and cost-saving alternative to collection of 24-hour urine samples. To the best of our knowledge, neither spot urine nor 24-hour urine samples have been studied in CCSs to assess dietary intake.

This study will, to our knowledge, for the first time obtain insight into the dietary intake of CCSs from self-reported FFQs and urinary measurements. It will compare the 2 dietary assessment tools and determine whether spot urine collection from CCSs is feasible.

Objectives

This study will generate detailed data on the diets of Swiss long-term CCSs. The study's main objective is to compare the self-reported FFQ dietary assessment tool with assays of urine spot samples. This will give us more information about the reliability of the FFQ, the actual dietary intake of CCSs, and potential associations between dietary intake and the occurrence of somatic late effects. A secondary objective is to evaluate this study itself—that is, to determine the response rate, cost, and CCS reactions of the self-reported FFQ and the dietary markers in spot urine of CCSs.

Study Design

This is a multicenter, observational study incorporated into the Swiss Childhood Cancer Survivor Study (SCCSS). The SCCSS is a population-based, long-term follow-up study of all childhood cancer patients registered in the Swiss Childhood Cancer Registry (SCCR [19]) with leukemia, lymphoma, central nervous system tumors, malignant solid tumors, or Langerhans cell histiocytosis diagnosed in Switzerland; who were under the age of 21 years at the time of diagnosis; who survived 5 years or more after the initial diagnosis of cancer; and who were alive at the time of the study [20-22]. This study is registered at clinicaltrials.gov (NCT03297034).

Eligibility

CCSs were eligible to participate in the SCCSS-Nutrition study if they had childhood cancer diagnosed between 1976 and 2005, completed a baseline SCCSS questionnaire between 2007 and 2013 [20], and were 18 years of age or older at the time of the follow-up survey in 2017. All CCSs who were enrolled in SCCSS-Nutrition received a follow-up questionnaire including an FFQ. CCSs living in the French-speaking part of Switzerland who returned the questionnaire were invited to provide a urine spot sample. Exclusion criteria were being pregnant or lactating at the time of the study, or having missing or implausible dietary intake information reported in the FFQ [23].

Recruitment

We traced the addresses of all adult CCSs who had completed the baseline questionnaire (n=2527 CCSs) between 2007 and 2013 [20]. Among these, 1749 were 18 years old or older at the time of the survey and thus were eligible for the follow-up questionnaire. In February 2017, we traced 1599 CCSs and sent them a follow-up questionnaire (Figure 1). Nonresponders received a reminder after 8 weeks (Figure 2). If they again did not respond, we sent a second reminder. Finally, 919 (57.47%) CCSs completed the FFQ. We excluded 11 survivors who were pregnant or lactating, 35 who did not report their dietary intake, 71 who had implausible dietary intake data (<850 kcal or >4500 kcal per day) [24], and 581 who lived outside the French-speaking region in Switzerland. We thus sent an information letter signed by the project leader to 221 CCSs who lived in the French-speaking part of Switzerland and asked them for informed consent to provide a urine spot sample. Among these CCSs, 8 were no longer traceable, 1 was abroad, and 15 declined to participate. We sent urine collection kits to the CCSs who agreed to participate and asked them to collect a first morning sample within 2 weeks and post the sample by mail within 24 hours to the pediatric hematology-oncology unit of the University Hospital of Canton Vaud (Centre Hospitalier Universitaire Vaudois [CHUV]; Lausanne, Switzerland). Among these 212 CCS participants, 111 (52.4%) returned a sample. All 111 urine samples met the study protocol and will be available for dietary intake assessment comparison. Those enrolled received no compensation.

Figure 1. Response rates in the Swiss Childhood Cancer Survivor Study (SCCSS)-Nutrition study. The SCCSS-Nutrition study is subdivided into a food frequency questionnaire assessment (FFQ; gray) and a urine spot collection (black).

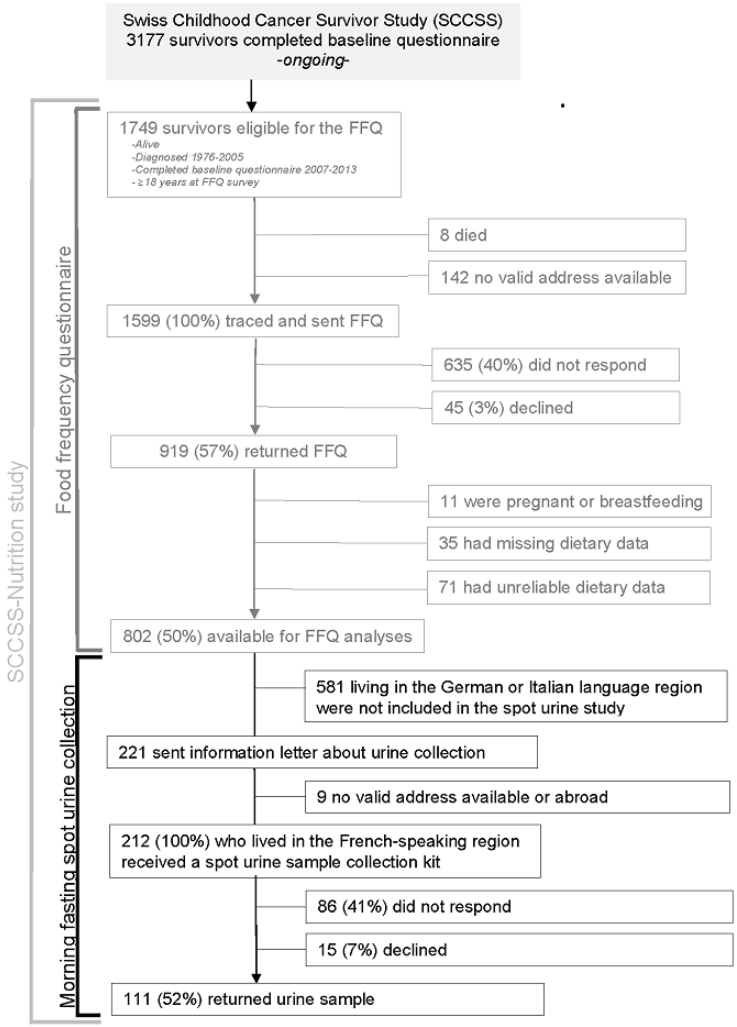
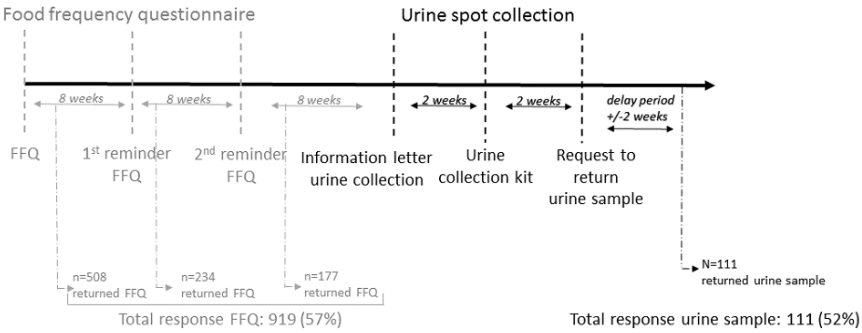


Figure 2. Timelines and response rates of food frequency questionnaire (FFQ) assessment and urine spot collection.



Data Collection

Baseline and Follow-Up Questionnaire

From baseline or follow-up questionnaires, we collected CCSs' data on sex, age at survey, language region in Switzerland in which they lived, country of birth, educational level, living situation, physical activity, smoking status, and height and weight to calculate body mass index. The baseline questionnaire included core questions from the US and UK CCS studies [25,26], with further questions from the Swiss Health Survey and the Swiss census of health-related behaviors and sociodemographic measures [27,28]. The main domains covered by the questionnaire were quality of life, somatic health, fertility, current medication and health services use, psychological distress, health behaviors, and socioeconomic status. The follow-up questionnaire repeated baseline questions on quality of life, somatic health, health behaviors, and socioeconomic status, with the addition of an FFQ to assess dietary intake in detail [29,30].

Food Frequency Questionnaire

We assessed CCSs' dietary intake, including information on portion sizes, with a self-administered, semiquantitative FFQ [31,32] (Multimedia Appendix 1). The FFQ was originally developed and validated against 24-hour dietary recalls for the adult Swiss population who are French speaking [29,31,33,34]. It solicits information on consumption frequency and portion sizes during the 4 previous weeks for 97 fresh and prepared food items organized into 12 food groups (dietary supplements not included). Consumption frequencies range from "never during the last 4 weeks" to "2 or more times per day," and portion sizes are recorded as equal to, or smaller or larger than, a reference size. The reference portions were defined as common household measures representing the median portion size of a previous validation study performed with 24-hour dietary recalls [29]. The "smaller" and "larger" portions represented the first and fourth quartiles of this distribution. We used the French Information Center on Food Quality (Maisons-Alfort Cedex, France) food-composition table to convert the food portions into macro- and micronutrients [35].

Urine Collection

CCSs received a home specimen collection kit including an information sheet on how to perform first morning urine spot collection, a 50 mL plastic specimen tube with a screw-on lid, a sealed plastic bag, and a bubble-lined return envelope with postage-paid labels addressed to the pediatric hematology-oncology unit of CHUV. We asked CCSs to collect a first morning urine sample, filling the tube up to 40 mL, and to seal the tube and write the sample date and time on the lid. We asked CCSs not to mark personal information on the tube to preserve confidentiality, and to send their sample by post. The medical staff of the pediatric hematology-oncology unit cooled the urine spot samples as soon as they received them. They divided the samples into one 8-mL aliquot for direct urine chemistry and nine 3-mL aliquots for biobank storage; the 8-mL sample was sent within 1 hour to the CHUV laboratory for analyses. Levels of potassium, sodium, phosphate, urate, urea, and creatinine were measured using routine laboratory procedures (Table 1). The 3-mL urine samples were frozen at –80°C and stored in a biobank at CHUV for later analyses.

Table 1. Primary and secondary end points and outcomes of interest.

End points and outcomes	Method	Quality promotion	(Expected) time point or window
Primary			
Detailed dietary intake, macro- and micronutrients	Dietary intake assessed by a validated FFQ[a] providing information on consumption frequency and portion sizes during the 4 previous weeks for 97 fresh and prepared food items organized in 12 food groups.	Validated FFQ	CCSs[b] were expected to fill in and return the FFQ within 8 weeks. In case of nonresponse, a first and second reminder were sent.
Urinary measurements	Laboratory methods: • Sodium: indirect potentiometry • Potassium: indirect potentiometry • Urea: urease • Urate: uricase • Creatinine: Jaffe reaction • Phosphate: phosphomolybdate	Standard laboratory procedures	Analyses were performed together with routine analyses in the hospital laboratory of Centre Hospitalier Universitaire Vaudois with Cobas 8000 (Roche Diagnostics). Analyses were performed during the whole study period.
Secondary			
General response rate	The SCCSS[c] tracking system tracked the number of CCSs who did not respond or declined participation.	N/A[d]	Evaluation after finalizing the study.
Costs	Recording of costs, eg, laboratory, mailing, printing, urine collection sample kits.	N/A	Midterm evaluation and after finalizing the study.
Participants' reactions	Recording CCSs' reactions by telephone, emails, or letter.	N/A	Evaluation after finalizing the study.

[a]FFQ: food frequency questionnaire.

[b]CCS: childhood cancer survivor.

[c]SCCSS: Swiss Childhood Cancer Survivor Study.

[d]N/A: not applicable.

Data Management

Coding

We gave each participant an 8-digit identification (ID) code number to maintain anonymity. We used these ID codes in lieu of patient names for all data and urine spot samples. Data labelled with participant ID codes are stored on encrypted devices or secured servers. All participant data and biological samples are strictly confidential, and disclosure to third parties is prohibited. The coding key is stored at the Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland, and is only available to authorized personnel.

Storage

All biomedical material is archived for 10 years at CHUV. In case there is no intention for use or a participant withdraws consent, the respective biological material will be destroyed. FFQ answers and urine spot laboratory results will be archived on servers of the ISPM, Lausanne, Lausanne, Switzerland, and ISPM, Bern for at least 10 years. Timelines that record and archive outcomes are in line with Swiss regulation. All results will be archived at and analyzed by ISPM, Bern as a nested study of the SCCSS.

Statistical Analyses

We will include all CCSs who provided reliable dietary intake information and were neither pregnant nor lactating during the survey for FFQ analyses. Table 1 indicates the primary and secondary end points and outcomes of interest of the SCCSS-Nutrition study. We will evaluate whether CCSs meet dietary recommendations for Germany, Austria, and Switzerland [36]. We will compare mean intake with the recommended intake or, when not available, the adequate intake. We will calculate mean intake based on age and sex recommendations weighted by the age and sex distribution of the study population. Nutritional goals will be set at 100, where the mean intake meets the recommended or adequate intake. Total energy intake will be calculated including calories from alcohol consumption. We will calculate correlation coefficients to examine the strength and direction of the associations between the FFQ and urinary spot measurements. To validate the agreement between the 2 dietary assessment tools, we will perform cross-classification analyses to investigate whether the 2 dietary assessment tools rank CCSs' dietary intake similarly. We will calculate the proportion of CCSs correctly classified in the same or contiguous category or in the opposite category (misclassified). We will use Bland-Altman plots to assess the level of agreement between the FFQ and the urine spot samples at the CCS group level. We will plot the difference between the 2 measurements against the mean of the 2 measurements for each CCS. We will use Stata (version 14; StataCorp LLC) for all analyses.

Ethics

The cantonal ethics committee Commission cantonal d'éthique de la Recherche sur l'être humain, Lausanne approved the SCCSS-Nutrition study in March 2016. In July 2017, the cantonal ethics committee Geneva Commission Cantonal

d'éthique de la Recherche approved the study with an amendment (protocol of both approvals: 2016-00031). Ethical approval of the SCCR and the SCCSS questionnaires was granted by the Ethics Committee of the Canton of Bern (KEK-BE: 166/2014).

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Characteristics of Participants and Nonparticipants

Table 2 presents the sociodemographic and lifestyle characteristics of both CCSs who completed the FFQ and those who did not, and those who participated in the collection of urine spot samples. The most common cancer diagnoses among CCSs completing the FFQ were leukemia, lymphoma, and central nervous system tumors (Table 3). Median age at diagnosis was 10 years (interquartile range 4-14 years) and median time from diagnosis to survey was 26 years (interquartile range 20-32 years). Of the 902 FFQ participants, 99 (12.34%) experienced a relapse.

Costs

The costs of this study have remained within budget (Table 4). Costs include material, shipment of FFQs and urine spot sample collection kits, reminders, data entry, data management, and laboratory urine analyses.

Table 2. Sociodemographic and lifestyle characteristics of participants and nonparticipants in the food frequency questionnaire (FFQ) and the urine spot sample collection.

Characteristics	FFQ		Urine spot sample	
	Participants (n=802)	Nonparticipants[a] (n=797)	Participants (n=111)	Nonparticipants[b] (n=110)
Male sex, n (%)	401 (50.0)	443 (55.6)	49 (44.1)	53 (48.2)
Age at survey (years), n (%)				
≤30	248 (30.9)	328 (41.2)[c]	26 (23.4)	44 (40.0)
31-39	320 (39.9)	305 (38.3)	37 (33.3)	37 (33.6)
≥40	234 (29.2)	164 (20.6)	48 (43.2)	29 (26.4)
Country of birth, n (%)				
Switzerland	763 (95.1)	736 (92.3)	101 (91.0)	98 (89.1)
Other	39 (4.9)	60 (7.5)	10 (9.0)	12 (10.9)
Missing data	N/A[d]	1 (0.1)	N/A	N/A
Education (highest degree), n (%)				
Lower than university	527 (65.7)	681 (85.4)[e]	69 (62.2)	71 (64.6)
University	270 (33.7)	98 (12.3)	42 (37.8)	39 (35.5)
Missing data	5 (0.6)	18 (2.3)	N/A	N/A
Living situation, n (%)				
Alone	164 (20.4)	129 (16.2)[e]	19 (17.1)	24 (21.8)
Other	634 (79.1)	655 (82.1)	91 (82.0)	86 (78.2)
Missing data	4 (0.5)	13 (1.6)	1 (0.9)	N/A
Physical activity[f], n (%)				
Inactive	165 (20.6)	204 (25.6)[e]	32 (28.8)	32 (29.1)
Active	628 (78.3)	572 (71.8)	76 (68.5)	77 (70.0)
Missing data	9 (1.1)	21 (2.6)	3 (2.7)	1 (0.9)
Smoking status, n (%)				
Never	532 (66.3)	511 (64.1)[e]	69 (62.2)	65 (59.1)
Former	132 (16.5)	79 (9.9)	15 (13.5)	24 (21.8)
Current	128 (16.0)	207 (26.0)	25 (22.5)	21 (19.1)
Missing data	10 (1.3)	N/A	2 (1.8)	N/A
Body mass index at survey (kg/m^2), n (%)				
Underweight (<18.5)	39 (4.9)	57 (7.2)[e]	7 (6.3)	3 (2.7)
Normal (18.5-24.9)	490 (61.1)	500 (62.7)	76 (68.5)	67 (60.9)
Overweight (25-29.9)	177 (22.1)	141 (17.7)	15 (13.5)	25 (22.7)
Obese (≥30)	75 (9.4)	59 (7.4)	10 (9.0)	14 (12.7)
Missing data	21 (2.6)	40 (5.0)	3 (2.7)	1 (0.9)

[a]Includes 635 childhood cancer survivors (CCSs) who did not respond, 45 who declined, 11 who were pregnant or breastfeeding, 35 with missing dietary data, and 71 with unreliable dietary data.

[b]Includes 9 CCSs with no valid address available anymore or who were abroad, 15 who declined, and 86 who did not respond.

[c]Age at survey is calculated for FFQ nonparticipants by taking the average participants' date of filling in the questionnaire.

[d]N/A: not applicable.

[e]Based on information from the Swiss Childhood Cancer Survivor Study baseline questionnaire filled in between 2007 and 2013 by FFQ nonparticipants.

[f]Active: ≥150 minutes of moderately intense or 75 minutes of vigorously intense or a combination of moderately and vigorously intense physical activity per week.

Table 3. Clinical characteristics of participants and nonparticipants in the food frequency questionnaire (FFQ) and the urine spot sample collection.

Characteristics	FFQ		Urine spot sample	
	Participants (n=802)	Nonparticipants[a] (n=797)	Participants (n=111)	Nonparticipants[b] (n=110)
ICCC-3[c] diagnosis, n (%)				
I: Leukemia	246 (30.7)	264 (33.1)	30 (27.0)	27 (24.6)
II: Lymphoma	173 (21.6)	139 (17.4)	30 (27.0)	30 (27.3)
III: CNS[d] tumor	81 (10.1)	140 (17.6)	9 (8.1)	17 (15.5)
IV: Neuroblastoma	28 (3.5)	31 (3.9)	4 (3.6)	3 (2.7)
V: Retinoblastoma	12 (1.5)	22 (2.8)	2 (1.8)	3 (2.7)
VI: Renal tumor	52 (6.5)	41 (5.1)	4 (3.6)	3 (2.7)
VII: Hepatic tumor	6 (0.8)	3 (0.4)	1 (0.9)	1 (0.9)
VIII: Bone tumor	50 (6.2)	29 (3.6)	11 (9.9)	5 (4.6)
IX: Soft tissue sarcoma	66 (8.2)	32 (4.0)	7 (6.3)	10 (9.1)
X: Germ cell tumor	43 (5.4)	42 (5.3)	8 (7.2)	4 (3.6)
XI and XII: Other tumor	26 (3.2)	17 (2.1)	4 (3.6)	3 (2.7)
Langerhans cell histiocytosis	19 (2.4)	37 (4.6)	1 (0.9)	4 (3.6)
Age at diagnosis (years), n (%)				
<5	251 (31.3)	262 (32.9)	28 (25.2)	29 (26.4)
5-9	164 (20.4)	211 (26.5)	19 (17.1)	23 (20.9)
10-14	239 (29.8)	222 (27.9)	34 (30.6)	27 (24.6)
15-20	148 (18.5)	102 (12.8)	30 (27.0)	31 (28.2)
Time since diagnosis (years), median (interquartile range)	26.1 (20.2-31.7)	N/A[e]	28.3 (21.0-32.7)	22.8 (18.5-30.1)
History of relapse, n (%)	99 (12.3)	107 (13.4)	18 (16.2)	15 (13.6)

[a]Includes 635 childhood cancer survivors (CCSs) who did not respond, 45 who declined, 11 who were pregnant or breastfeeding, 35 with missing dietary data, and 71 with unreliable dietary data.

[b]Includes 9 CCSs with no valid address available anymore or who were abroad, 15 who declined, and 86 who did not respond.

[c]ICCC3: International Childhood Cancer Classification, Third Edition.

[d]CNS: central nervous system.

[e]N/A: not applicable.

Table 4. Costs to perform the Swiss Childhood Cancer Survivor Study-Nutrition study.

Expenses	Costs (US $)
Material, eg, (return) envelopes, questionnaires, urine tubes	6514
Address update for childhood cancer survivors	20,232
Mailings	7125
Data entry for food frequency questionnaires	13,360
Laboratory analyses of urine spot samples	2908
Ethics committee approval	602
Total costs	50,741

Childhood Cancer Survivor Reactions

CCSs had varied reactions to the FFQ. The majority of CCSs wanted to participate and welcomed a follow-up questionnaire. Only a small number of the 1599 CCSs to whom FFQs were sent (n=45, 2.81%) declined to complete the FFQ. Of the 221 CCSs to whom information letters for urine collection were sent, 15 declined to collect a urine spot sample (Figure 1). All CCSs who declined participation expressed a willingness to participate in future studies. A total of 26 CCSs contacted us by telephone (n=13), email (n=5), or letter (n=8) with questions about the purpose of the study, its setup, eligibility, or another question, or to notify the study team about a delay in FFQ response or urine collection. Overall, the CCSs were supportive and open to participation in the study. We received no angry or aggressive reactions.

We anticipate that the results of the SCCSS-Nutrition study will be available mid-2019.

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Principal Findings

SCCSS-Nutrition is, to our knowledge, the first study in Switzerland that has collected in-depth dietary data. It will allow researchers to assess dietary intake and quality in CCSs and to compare 2 dietary assessment tools: urine measurements and FFQs. Urine spot sample measurements can quantify nutrient intake objectively and can therefore complement self-reported dietary information from the FFQ.

Unhealthy dietary intake is an important element in the development of chronic morbidities such as type 2 diabetes, metabolic syndrome, and CVD in the general population. Populations with these morbidities are therefore widely recommended to consume a healthy and balanced diet. The extensively investigated Mediterranean diet, with high intakes of fish, fruit, vegetables, legumes, nuts, whole grains, and monounsaturated fats from olive oil, has been shown to reduce, or even prevent, CVD, diabetes, obesity, metabolic syndrome, and cancer in the general population [37-41] and in CCSs [5]. This makes nutrition one of the main determinants of health in the general population, and is particularly relevant for people with additional risk factors, including CCSs. Nevertheless, knowledge about CCSs' dietary intake and their nutritional status is lacking within Switzerland and is limited worldwide.

Strengths and Limitations

This study, nested within the SCCSS, assesses dietary intake information of CCSs and compares 2 dietary assessment tools: the FFQ and dietary measurements from urine spot samples. We found the SCCSS-Nutrition study to be well received and feasible. This is, to our knowledge, the first study to provide detailed dietary information on Swiss CCSs and to demonstrate the feasibility of such a study. With the addition of dietary indicators from urine spot samples, SCCSS-Nutrition makes further comparison possible. Additionally, we had high response rates for completing the FFQ and collecting urine spot samples. Finally, we have access to detailed sociodemographic data from the SCCSS baseline and follow-up questionnaire, and high-quality clinical information extracted from medical records in the SCCR. This a very rich dataset available for analysis.

Limitations of this study were that some CCSs said the FFQ was too long. This might have influenced CCSs to either under- or overreport dietary intake. Also, we asked CCSs for a single spot urine sample rather than multiple spot samples or a 24-hour urine collection to minimize participation burden. Comparison of the self-reported FFQ data, representing habitual dietary intake over 4 weeks, with urine spot analysis data, indicative of the dietary intake during the day before, should therefore be regarded with caution. Seasonal influences could play a role in the FFQ assessment, as we assessed dietary intake for the past 4 weeks rather than the past year. Finally, the interval between the FFQ assessment and urine spot collection could produce differences in dietary intake due to seasonal influences.

Lessons Learned

Setting up this study provided valuable insight into several methodological and logistic issues. We asked CCSs to return urine samples within 2 weeks and to post their urine samples between Monday and Thursday. This prevented the samples from arriving during the weekend. The time frame of 2 weeks was too short; several CCSs contacted us to ask for an extension. The urine collection tubes had a diameter of 3 cm and did not fit the opening slit of an official Swiss mailbox when the CCSs placed a sample in a sealed plastic bag and a bubble-lined postal return envelope. Given this, the response rate was higher than we expected, and we reached the recruitment target because of the up-to-date address list and personal information of SCCR, and the high motivation of CCSs to participate. Furthermore, including a study center took longer than expected, due to arranging appropriate urine storage within the hospital, and an extra briefing about the potential hazards of CCSs' urine contaminated with chemotherapeutic agents in case of cancer recurrence to safeguard the safety of laboratory staff.

Conclusions

The SCCSS-Nutrition study collected in-depth dietary data that will enable an assessment of dietary intake and dietary quality in CCSs and a comparison of dietary assessment tools. The study will help fill nutrition knowledge gaps and is a first step toward surveillance guidelines and targeted nutritional recommendations in Switzerland.

Acknowledgments

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Authors' Contributions

FB wrote the manuscript, which was modified and adapted by all other authors. MBP and MA were the principal investigators. CEK and MB supported study setup.

Conflicts of Interest

None declared.

Multimedia Appendix 1

Food frequency questionnaire in French.
[PDF File (Adobe PDF File), 1882 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Peer-review report ethical committee.
[PDF File (Adobe PDF File), 301 KB-Multimedia Appendix 2]

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Abbreviations

CCS: childhood cancer survivor
CHUV: Centre Hospitalier Universitaire Vaudois
CVD: cardiovascular disease
FFQ: food frequency questionnaire
ID: identification
ISPM: Institute of Social and Preventive Medicine
SCCR: Swiss Childhood Cancer Registry
SCCSS: Swiss Childhood Cancer Survivor Study
SCCSS-Nutrition: Swiss Childhood Cancer Survivor Study-Nutrition study

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7.4. Co-Author publication IV

Paediatric cohort studies on lower respiratory diseases and their reporting quality: systematic review of the year 2018

Review

Cristina Ardura-Garcia, Rebeca Mozun, Eva S.L. Pedersen, **Maria Otth**, Chritsina M. Mallet, Myrofora Goutaki, Claudia E. Kuehni

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Own contribution to the project: Involved in title and abstract screening, full text screening, data extraction, interpretation of results, and review of the manuscript

EUROPEAN RESPIRATORY *journal*

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Early View

Original article

Paediatric cohort studies on lower respiratory diseases and their reporting quality: systematic review of the year 2018

Cristina Ardura-Garcia, Rebeca Mozun, Eva S.L. Pedersen, Maria Otth, Maria Christina Mallet, Myrofora Goutaki, Claudia E. Kuehni

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Paediatric cohort studies on lower respiratory diseases and their reporting quality: systematic review of the year 2018

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Take home message: We need a joined effort of editors, reviewers and authors to improve the reporting quality of paediatric cohort studies for respiratory problems.

Conflict of interest: None

Authors contributions: Claudia E Kuehni, Myrofora Goutaki, Cristina Ardura-Garcia, Eva Pedersen, and Rebeca Mozun conceptualised and designed the study. Cristina Ardura-Garcia, Rebeca Mozun, Eva SL Pedersen, Maria Otth, and Maria Christina Mallet performed the screening and data extraction. Cristina Ardura-Garcia analysed the data and drafted the manuscript. All authors critically revised the manuscript and approved the final manuscript as submitted.

Key words: systematic review, paediatric, cohort studies, respiratory symptoms

Abstract

The paediatric respiratory research community uses cohort studies extensively. However, the landscape of these studies and their quality of reporting has not been assessed.

We performed a systematic review of publications on cohort studies reporting on paediatric lower respiratory problems published in 2018. We searched Medline and EMBASE and extracted data on the studies' and journals' characteristics. We assessed the number of items of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) checklist that a random sample (100 papers) reported. We analysed factors associated with the STROBE score and with the most poorly reported items, using Poisson and logistic regression

Of the 21 319 records identified, 369 full-text articles met our inclusion criteria. Most papers studied asthma aetiology through birth cohorts and were based in Europe or North America. The reporting quality was insufficient: 15% reported the 22 STROBE items; median score: 18 (IQR: 16-21). The most poorly reported items were: sources of bias, sample size, statistical methods, descriptive results and generalisability. None of the studies' or journals' factors were associated with the STROBE score.

We need a joined effort of editors, reviewers and authors to improve the reporting quality of paediatric cohort studies on respiratory problems.

Introduction

Cohort studies are extensively used in paediatric respiratory research to investigate risk factors, incidence and natural history of disease. The strengths of the longitudinal design include establishing temporality and reducing information bias. However, the study design has limitations, like high costs, selection bias, attrition bias, and residual confounding. There are solutions to overcome or mitigate these disadvantages like retrospective cohort design, nested case-control studies or linkage to nationwide available datasets. The use of these strategies, the type of questions investigated and the quality of reporting of cohort studies has not been assessed in paediatric respiratory research.

Adequate reporting is key for reproducibility of research and translation of results into clinical practice. STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) is an international, multidisciplinary and collaborative initiative started in 2004 to enhance the reporting quality and dissemination of observational studies [1]. The STROBE statement is being increasingly endorsed by journals, but mandatory submission of its checklist is not yet common practice for observational studies as it is for randomized controlled trials. Studies assessing the fulfilment of the STROBE criteria suggest that reporting quality is generally poor and that some items are frequently underreported [2-4]. Certain factors have been associated with reporting quality, such as journal's impact factor and STROBE endorsement policy, the authors' affiliation, and publication type (peer reviewed or not) [3,5-7]. Identifying which STROBE items are commonly misreported in paediatric respiratory cohort papers and which modifiable factors are associated with poor reporting may raise awareness and help improve the quality of publications in this area. We therefore conducted a systematic review of papers published in 2018 to present the landscape of cohort studies addressing paediatric lower respiratory problems, to describe the reporting quality of these papers according to STROBE guidelines and to examine characteristics associated with reporting quality.

Methods

The predefined review protocol that we followed for this systematic review has been registered in the Open Science Framework (OSF) repository (Registration DOI 10.17605/OSF.IO/F8X3B). We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, research checklist online) [8] to report our findings.

Eligibility criteria

We searched for papers reporting on lower respiratory problems from paediatric cohort studies worldwide, published in 2018 in peer-reviewed journals. For this we used all the following specific inclusion criteria: (1) cohort study design (exposure measured before outcome, with at least two time points with prospective data collection), including nested case-control studies; (2) children under 18 years of age at study baseline, or with separate results reported for children, or for rare diseases, if more than 50% of the study population were children; (3) lower respiratory problems and evaluations of lower respiratory health as outcomes (including respiratory symptoms, test results such as lung function, diagnosis and prognosis) or lower respiratory problems and evaluations of lower respiratory health as exposures (including respiratory symptoms, test results such as lung function, diagnosis, management and prognosis).

We excluded studies with any of the following criteria: (1) reports not in English, (2) published before 1st January 2018 or after 31st December 2018, (3) non-original papers (conference abstracts, editorials and reviews), (4) follow-up time <3 months (to exclude papers on short-term outcomes of hospitalised patients), and (5) studies with <50 participants to exclude small case series (for rare diseases where smaller sample sizes are expected we excluded if there were <20 participants). If exact sample size was not stated but we could assure that it was greater than our selected limits for paper exclusion, the manuscript was included in the study.

Information sources and search strategy

We searched Medline and EMBASE from 1st January 2018 to 31st December 2018, on April 17th 2019. We used a reference management software (EndNote X8, Thomson Reuters) to import the records and remove duplicates. We provide the full search strategy in the online supplementary information.

Study selection

One reviewer screened titles and abstracts to assess eligibility according to the described criteria. In a second step, a single reviewer screened full-text papers of selected studies and recorded the reasons for exclusion in an Excel form.

Data extraction

We extracted data from the selected papers using a standardised pre-piloted data collection Excel form. We extracted information on the characteristics of the manuscript (author, journal, location and year of publication) and the study (cohort name and size, study design, type of research question, main diseases of interest, source of exposure and outcome data, use of longitudinal analysis, follow-up time and age at baseline). We did not include a risk of bias assessment, as the results were not extracted and evaluated.

Definitions

Journals were classified into thematic categories according to the InCites Journal Citation Report classification. If a journal appeared in two different categories, it was classified as the first in which it appeared in this order: respiratory, allergy, infectious diseases, public health/ epidemiology/ environment, paediatrics, general medicine and any other category (Supplementary Table 1). The diagnoses studied were grouped into: asthma or wheeze, respiratory infectious diseases, rare diseases (defined as occurring in fewer than 1 in 2000

people, and including bronchopulmonary dysplasia, diaphragmatic hernia, cystic fibrosis and primary ciliary dyskinesia), lung function in healthy children and other problems (including cough, respiratory distress syndrome, pneumothorax and unspecific respiratory symptoms).

Assessment of reporting quality

We selected a random sample of 100 (27%) of the included papers and assessed how close the manuscript followed the STROBE recommendations for the reporting of cohort studies. We used a standardised data collection Excel form and recorded the adherence to each of the 22 items present in the STROBE checklist for the reporting of cohort studies. The STROBE statement recommends the reporting of all the elements in their checklist. For this reason, we considered insufficient reporting if not all the elements (22) were reported. We did not evaluate the items that are only 'suggested', such as the inclusion of a flow diagram. We defined an item as not reported if it was not present or insufficiently reported. For example, for item 7, if they defined the outcome and main exposure, but not other variables (e.g. confounders and important effect modifiers). To examine characteristics associated with reporting quality, we also extracted information of variables that have been previously associated with reporting: journal's impact factor, percentage ranking, category, reporting recommendations and if it belonged to a scientific society; and the study's location, research question and main diagnosis of interest. We used data from the InCites Journal Citation Report to record the impact factor and ranking of the journal where the manuscript was published, and from the journals' webpages to collect information on whether the journal belonged to a scientific society and on the reporting recommendations (classified into no recommendation (none), recommending to follow any reporting guideline, recommending to follow STROBE reporting guidelines and mandatory attachment of the STROBE checklist at the time of manuscript submission).

Synthesis of results and analysis

We summarised the results (absolute numbers and proportions) of the study characteristics, the journals where they were published and the reporting quality according to the STROBE statement using tables and graphs. We used Poisson regression to study univariable associations between the study's characteristics and the number of items from the STROBE checklist that were reported in the manuscript. We reported the rate ratio with 95% confidence interval, and the p value of the likelihood ratio test. We then applied logistic regression to study univariable associations between the study's characteristics and the reporting of the 4 items from the STROBE checklist that were most poorly reported: item 9 (bias), item 12 (statistics), item 14 (descriptive results) and item 21 (generalisability). We reported the odds ratio with 95% confidence interval for each item separately. For both regression analyses, we included the following factors based on previous findings and plausibility of association with reporting quality: journal's impact factor, ranking, category, reporting recommendations and if it belonged to a scientific society; and the study's location, research question and main diagnosis of interest.

Results

Of the 15 846 records identified through database searching, 890 were selected based on title and abstract and 369 full-text articles were finally included in the systematic review (Figure 1). Of the 521 full-text articles excluded, 77 were not a cohort study and 24 did not include a longitudinal analysis (e.g. used cross-sectional data from a cohort study).

Most studies were located in Europe (161, 44%) or North America (108, 29%), with few from other locations, especially Africa (17, 5%) and South America (12, 3%) (Figure 2). The median sample size was of 746 children (IQR 187-4535). Forty one percent of the studies had a birth or pregnancy cohort design, followed by prospective clinical cohorts (109, 30%) and non-birth

population-based cohorts (56, 15%). Median follow-up time was 5 years (IQR: 1-10 years). A quarter (85, 23%) used linkage with routine datasets and there were very few nested case-control studies (7, 2%). The most frequent sources of exposure data were questionnaires/ interviews (128, 35%) or direct examination/ diagnostic tests (134, 36%), while outcomes were normally obtained from questionnaires/ interviews (157, 43%).

The main diagnosis of interest in the included studies was asthma or wheeze (214, 58%) and the main research questions related to aetiology (194, 53%) followed by natural history or prognosis (116, 31%). The research questions varied by diagnosis of interest (Figure 3a). Studies on asthma and lung function answered questions mostly on aetiology or risk factors, while natural history and prognosis was more common in studies of rare diseases and other diagnoses. Disease phenotyping was mostly studied in papers on respiratory infectious diseases or rare diseases. Similarly, sample size of the study population also varied by diagnosis of interest (Figure 3b). More than half of the studies on asthma had more than 1000 participants, while 40% of those on rare diseases had less than 100 participants.

The included cohort studies were mostly published in respiratory (103, 28%) or allergy/immunology journals (88, 24%) (Figure 2). Of the individual journals, those with 10 or more papers were either highly specific (Paediatric pulmonology, Paediatric Allergy& Immunology and Journal of Asthma) or high impact respiratory journals (Journal of Allergy and Clinical Immunology, Thorax and European Respiratory Journal). There was only one general journal (PlosONE) with 10 or more included papers (data not shown). There were some differences in the study design, sample size and research question between journals, though the largest differences were observed in the diagnosis of interest (Supplementary Table 2). Papers on asthma were published mainly in allergy/immunology or respiratory journals and those on respiratory infectious diseases in their respective journals. Papers on other diagnoses were more evenly distributed, with the exception of the allergy/immunology journals that published almost exclusively on asthma.

Table 1: Number of manuscripts that accurately followed each of the STROBE checklist items for the reporting of cohort studies from a random subsample (N=100)

	Item No	Recommendation	N
Title and abstract	1	All criteria for item 1	81
		(*a*) Indicate the study's design with a commonly used term in the title or the abstract	83
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	97
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	100
Objectives	3	State specific objectives, including any prespecified hypotheses	97
Methods			
Study design	4	Present key elements of study design early in the paper	93
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	90
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	94
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	84
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	96
Bias	9	Describe any efforts to address potential sources of bias	58
Study size	10	Explain how the study size was arrived at	64
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	92
Statistical methods	12	All criteria for item 12	38
		(*a*) Describe all statistical methods, including those used to control for confounding	92
		(*b*) Describe any methods used to examine subgroups and interactions	83
		(*c*) Explain how missing data were addressed	43
		(*d*) If applicable, explain how loss to follow-up was addressed	59
		(*e*) Describe any sensitivity analyses	66
Results			
Participants	13*	All criteria for item 13 (except c)	72
		(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	78
		(b) Give reasons for non-participation at each stage	76
		(c) Consider use of a flow diagram	-
Descriptive data	14*	All criteria for item 14	56
		(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	90
		(b) Indicate number of participants with missing data for each variable of interest	59
		(c) Summarise follow-up time (eg, average and total amount)	82
Outcome data	15*	Report numbers of outcome events or summary measures over time	98
Main results	16	All criteria item 16 (except c)	82
		(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	84
		(*b*) Report category boundaries when continuous variables were categorized	98

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	85
Discussion			
Key results	18	Summarise key results with reference to study objectives	100
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	94
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	96
Generalisability	21	Discuss the generalisability (external validity) of the study results	51
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	84

Colour code for proportion of manuscripts that reported each item:
<50%; 50-70%; 70-90%; >90%
Items in white were not evaluated as they are not compulsory but should be only 'considered'. We did not evaluate item 6b as none of the studies included were matched.

The reporting quality of the papers was insufficient (Table 1). Only three (0.8%) of the 369 included papers mentioned the STROBE statement in the text, and none of them stated using any other reporting guideline. Of the 100 subsampled publications, only 15% included all the 22 items mentioned in the STROBE checklist. The median number of elements missing from the checklist was 4 (IQR 1-6). The most frequently missed items were a correct description of the efforts to address potential sources of bias (item 9, missing in 42%), the study size explanation (item 10, missing in 36%), description of the statistical methods (item 12, missing in 62%), of the study participants' characteristics (item 14, missing in 44%), and the discussion of the generalisability of the study findings (item 21, missing in 49%). For the reporting of statistical methods and the descriptive data of the study participants (items 12 and 14), one frequent flaw was the lack of description of the number of participants with missing data for each variable (item 14b, missing in 41%) and the explanation of how the missing data were addressed (item 12c, missing in 57%).

Table 2: Association between studies' and journal's characteristics, and the total score on STROBE reporting recommendations for cohort studies' checklist from a Poisson regression (N=100)

	STROBE score		Poisson regression	
	Median	IQR	Crude IRR (95% CI)	Global P value[##]
Society journal: Yes	18	16-21	1.0 (0.9-1.1)	0.562
No	18	15-20		
Journal reporting recommendation				
None	17	16-18	(ref)	0.698
Follow any	19	16-21	1.1 (0.9-1.2)	
Follow STROBE	18	15-21	1.0 (0.9-1.2)	
Attach STROBE checklist	19	14-20	1.0 (0.8-1.2)	
Impact factor			1.0 (1.0-1.1)	0.387
Percentage ranking			1.0 (1.0-1.0)	0.279
Journal category[#]				
Respiratory	18	15-20	(ref)	0.762
Allergy	18	16-20	1.0 (0.9-1.2)	
Paediatrics	18	16-20	1.0 (0.9-1.2)	
General medicine	18	14-20	1.0 (0.8-1.2)	
Infectious diseases	15	15-15	0.9 (0.5-1.4)	
Pub health/epidemiology/environment	19	18-21	1.1 (0.9-1.2)	
Other	22	15-22	1.1 (0.9-1.3)	
Continent of study				
Europe	20	17-21	(ref)	0.493
North America	19	16-21	1.0 (0.9-1.1)	
South America	15	14-16	0.8 (0.6-1.1)	
Africa	16	16-18	0.9 (0.7-1.1)	
Asia	18	13-18	0.9 (0.7-1.03)	
Pacific	16	15-18	0.9 (0.8-1.1)	
Several	21	15-21	1.0 (0.8-1.3)	
Research question				
Aetiology	19	17-21	(ref)	0.078
Natural history / prognosis	18	16-20	1.0 (0.9-1.1)	
Diagnosis	14	14-14	0.7 (0.4-1.3)	
Treatment effects	16	15-17	**0.8 (0.7-0.97)**	
Main diagnosis of interest				
Asthma or wheeze	19	16-21	(ref)	0.825
Respiratory infectious diseases	18	16-18	0.9 (0.8-1.1)	
Rare diseases*	18	15-21	1.0 (0.9-1.1)	
Lung function (healthy children)	20	20-21	1.1 (0.9-1.4)	
Other**	17	16-21	1.0 (0.8-1.2)	

*Rare diseases include: bronchopulmonary dysplasia, diaphragmatic hernia, cystic fibrosis and primary ciliary dyskinesia. **Other diagnoses include: cough, respiratory distress syndrome, pneumothorax and unspecific respiratory symptoms. [#]Categories according to the InCites Journal Citation Report, if a journal appeared in 2 categories, it was classified as the first in which it appears in this order: respiratory, allergy, infectious diseases, public health/epidemiology/environment, paediatrics, general medicine and any other category. [##]**:** Estimated with the likelihood ratio test**.** IQR: inter-quartile range, RCT: randomized controlled trial.

Table 2 shows the results of the univariable Poisson regression analysis of the factors associated with the number of reported items from the STROBE checklist for cohort studies. None of the studied factors was clearly associated with the STROBE score. The journal's characteristics (belonging to a society, impact factor, percentage ranking and journal category), continent of study and main diagnosis of interest were not associated with the STROBE score. Only studies on treatment effects had a lower score (poorer reporting) when compared to those with an aetiological research question (IRR 0.8, 95% CI 0.7-0.97). Table 3 shows the association between these same characteristics and the reporting of 4 specific items (those that had been reported in less than 60% of the manuscripts). As previously, most tested factors were not associated with the reporting of any of the 4 specific items, except for the location of the study, showing a smaller odds to report these items if the study was undertaken in Africa, Asia or the Pacific, compared to Europe. The study of treatment effects or of natural history of disease/prognosis vs. aetiology, had also a lower odds of reporting 3 of the items. As for the journal reporting recommendations, manuscripts published in journals that recommended following any reporting guideline were more likely to discuss the generalisability of the study findings compared to those published in journals with no recommendations.

Table 3: Association between studies' and journal's characteristics, and reporting of the 4 most poorly reported items (<60% of the manuscripts) from a logistic regression (N=100).

	Crude OR (95%CI) for reporting items			
	Item 9 (Bias)	**Item 12 (Statistics)**	**Item 14 (Descriptive)**	**Item 21 (Generalisability)**
Society journal	1.7 (0.7-3.8)	1.7 (0.7-3.9)	1.0 (0.5-2.3)	1.1 (0.5-2.4)
Journal reporting recommendation				
None	(ref)	(ref)	(ref)	(ref)
Follow any guideline	3.0 (0.9-9.5)	1.1 (0.4-3.6)	1.2 (0.4-3.8)	**3.7 (1.1-12.1)**
Follow STROBE	2.0 (0.6-6.1)	1.1 (0.3-3.4)	0.7 (0.2-2.3)	1.2 (0.4-3.8)
Attach STROBE checklist	1.4 (0.3-5.9)	0.9 (0.2-3.9)	0.7 (0.2-3.1)	1.7 (0.4-7.4)
Impact factor	1.1 (0.96-1.2)	1.1 (0.99-1.2)	1.0 (0.9-1.1)	1.1 (0.99-1.2)
Percentage ranking	1.0 (0.9-1.03)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)
Journal category*				
Respiratory	(ref)	(ref)	(ref)	(ref)
Allergy	2.3 (0.8-6.7)	1.6 (0.5-5.0)	1.8 (0.6-5.1)	0.6 (0.2-1.8)
Paediatrics	0.9 (0.3-3.4)	1.3 (0.3-5.1)	1.5 (0.4-5.3)	0.4 (0.1-1.6)
General medicine	0.5 (0.08-3.5)	2.6 (0.4-15.9)	1.3 (0.2-7.6)	0.3 (0.05-2.2)
Infectious diseases	-	-	-	-
Pub health/epidemiology/ environment	4.9 (0.9-27.3)	1.5 (0.3-6.6)	2.2 (0.5-9.6)	0.8 (0.2-3.3)
Other	1.3 (0.3-5.4)	4.5 (1.0-20.3)	3.4 (0.7-15.9)	1.2 (0.3-5.1)
Continent of study				
Europe	(ref)	(ref)	(ref)	(ref)
North America	0.4 (0.1-1.03)	0.5 (0.2-1.3)	0.7 (0.3-1.9)	1.4 (0.6-3.7)
South America	0.4 (0.2-6.8)	-	-	-
Africa	**0.1 (0.01-0.97)**	0.6 (0.9-4.0)	0.8 (0.1-5.7)	0.6 (0.1-4.0)
Asia	**0.2 (0.05-0.9)**	**0.1 (0.01-0.8)**	0.5 (0.1-1.8)	**0.1 (0.01-0.8)**
Pacific	1.3 (0.2-7.6)	0.5 (0.1-2.1)	**0.2 (0.02-0.9)**	3.1 (0.6-17.2)
Several	0.8 (0.06-9.5)	0.5 (0.04-5.4)	1.1(0.1-13.7)	0.5 (0.04-5.4)
Research question				
Aetiology	(ref)	(ref)	(ref)	(ref)
Natural history / prognosis	1.0 (0.4-2.4)	**0.4 (0.2-0.97)**	0.7 (0.3-1.6)	1.0 (0.4-2.4)
Diagnosis	-	-	-	-
Treatment effects	**0.2 (0.04-0.7)**	-	**0.2 (0.07-0.9)**	0.4 (0.1-1.3)
Main diagnosis of interest				
Asthma or wheeze	(ref)	(ref)	(ref)	(ref)
Respiratory infectious dis.	1.0 (0.3-3.4)	0.6 (0.2-2.0)	1.1 (0.3-3.6)	**0.2 (0.06-0.98)**
Rare diseases*	1.2 (0.4-3.7)	0.5 (0.2-1.6)	0.6 (0.2-1.7)	1.2 (0.4-3.5)
Lung function (healthy)	-	2.5 (0.2-28.7)	1.3 (0.1-15.3)	1.6 (0.1-18.9)
Other**	3.0 (0.6-15.9)	0.2 (0.2-1.3)	0.3 (0.07-1.4)	0.7 (0.2-2.7)

*Rare diseases include: bronchopulmonary dysplasia, diaphragmatic hernia, cystic fibrosis and primary ciliary dyskinesia. **Other diagnoses include: cough, respiratory distress syndrome, pneumothorax and unspecific respiratory symptoms. #Categories according to the InCites Journal Citation Report, if a journal appeared in 2 categories, it was classified as the first in which it appears in this order: respiratory, allergy, infectious diseases, public health/epidemiology/environment, paediatrics, general medicine and any other category. IQR: inter-quartile range, RCT: randomized controlled trial.

Discussion

Summary of main findings

This systematic review found that reporting quality of cohort studies on paediatric lower respiratory problems was insufficient; only 15% of the manuscripts included all the recommended items from the STROBE checklist and 42-63% missed specific items such as a correct description of statistical methods**.** Most published paediatric cohort studies were based in Europe and North America, answering research questions on aetiology and risk factors, and centred on asthma or wheeze. The most frequently used design were birth cohorts with only limited use of alternative strategies that may reduce the costs of cohort studies, such as record linkage or nested case-control studies. Finally, most studies were published in specialised respiratory or allergy journals.

Interpretation of results

During the screening process, we found that one fifth (101) of the 521 excluded full-text papers were actually not cohort studies (77) or did not use a longitudinal analysis (24), despite appearing in a search using specific search terms such as “cohort” or “follow-up”, and although we had already excluded papers based on the information in the title or abstract. This was sometimes due to the incorrect use of the word “cohort” and the absence of a clear description of the study design in the abstract or title. This information was still missing in 17% of the included manuscripts. The cohort studies on paediatric lower respiratory problems in 2018 that we analysed, focused mostly on aetiology of asthma and were based in Europe or North America. Lower respiratory infectious diseases, such as pneumonia or tuberculosis, which are a major cause of death in children under 5 years of age worldwide [9], were the focus of only 15% of the studies. This may be because most of the studies are based in high income countries, whereas the burden of respiratory infectious diseases is much higher in low and middle-income countries [9]. The most commonly used design was the birth or pregnancy cohort study. This is

an excellent design to study early life factors and their influence on disease, but also quite expensive as it needs a large sample size to achieve an adequate number of children with a specific outcome and a long follow-up. Adaptations of cohort studies that are cheaper such as case-control studies nested in cohort studies were rarely used (3%). Linking available routine data is often an elegant way to obtain a cohort dataset with little or no selection bias or attrition bias, and achieve large sample sizes at a low cost (even whole population studies)[10]. As a disadvantage, studies based on linked routine data often lack clinically relevant details on exposure and outcome, resulting in measurement bias. This design was used in one quarter (85) of the included studies, and limited to countries with adequate electronic record keeping and unique personal identifiers (such as the social security number) that enables linkage between different datasets.

Even though reporting quality of observational studies improved after the publication of the STROBE statement [6], current studies in different medical fields have shown that adherence to STROBE reporting criteria remains poor or at most moderate [2-7,11-15]. Poor reporting quality does not necessarily imply that the conduct and analysis of the study has been poor. On the other hand, a high STROBE score does not allow to conclude that the study planning and conduct have been excellent. But good reporting is essential, as it enables readers and reviewers to assess the quality and risk of bias of a study. For example, we cannot assess attrition bias if authors do not report how many participants were lost to follow-up in a cohort study. There are multiple tools available to assess the methodological quality or the risk of bias of observational studies [16], such as the Newcastle-Ottawa Scale, an easy tool that assesses the quality of non-randomised studies included in a systematic review based on the selection of the study groups, the comparability of the groups, and the ascertainment of the exposure or outcome of interest [17]. The items we identified as being frequently missed, such as the description of statistical methods, the sample size estimation or the potential sources of bias have been also reported in previous studies [3,6,7,11,12,14,15]. These items are essential to

enable other researchers to reproduce the study and to evaluate its internal and external validity. The handling of missing information was insufficiently reported in the papers included in this review, both in the methods (43% of papers) and results (59%) section, resulting in a possible source of bias. Missing data and loss to follow up are common limitations of cohort studies, but the implementation of specific statistical strategies, like multiple imputation or inverse probability weighting [18], may attenuate its impact. Reporting bias and confounding is even more important in cohort studies analysing causal associations. Experts recommend specific strategies for adequate variable selection and interpretation of results in causal inference studies, such as the use of Direct Acyclic Graphs to identify possible confounders and mediators [19], and the presentation of effect estimates with their measures of variability (confidence intervals) instead of P values in isolation [20]. These strategies were discussed in a recent editorial by editors of respiratory, sleep, and critical care journals, where they also highlighted the importance of adhering to STROBE guidelines when reporting sources of bias and confounding [21].

A plausible reason for not reporting all the STROBE items may be the limitation of manuscript's length, reducing the amount of information that may be included in the paper. Although most journals offer the possibility of including supplementary online text and tables, they should adjust their policies and guidelines to ensure authors are able to comply with reporting guidelines. For example, to allow longer titles to include the study design, and longer methods sections to encourage a more detailed description of the statistical methods (e.g. handling of missing data and identification of confounders). On the other hand, authors may not be aware of the existence of the STROBE statement [22] or they may deliberately omit certain information such as missing data to increase the publication chances. In this case, it is the journals' responsibility to inform the authors about the different reporting guidelines for each study design. Cohort studies may need to also adhere to other reporting guidelines depending on the aim of the manuscript, such as the TRIPOD (Transparent reporting of a multivariable

prediction model for individual prognosis or diagnosis)[23], or to specific STROBE extensions, such as RECORD (REporting of studies Conducted using Observational Routinely-collected health Data)[24]. There are several other STROBE extensions for specific clinical areas, but these all include additional criteria to the basic STROBE checklist, so the standard criteria remain valid. We did not assess the adherence to any other reporting guideline, but none of the 100 subsampled manuscripts stated using them. These reporting guidelines are all listed in the EQUATOR (Enhancing the QUAlity and Transparency Of health Research) Network homepage [25]. Journals should promote adherence to reporting guidelines through a compulsory attachment of the reporting checklist at submission and as an online supplement for readers. In addition, journals should implement further measures such as involving reviewers in checking reporting quality or even employing a journal methodologist to check manuscripts substantially before final acceptance. Only by applying this measure in a strict way, as it is done with randomized controlled trials, will the reporting quality of observational studies improve and become standardised.

Quality of reporting was not associated with the characteristics of the journal in our study. It did not depend on the journal's impact factor, percentage ranking, society ownership, category (by subject), or reporting recommendations. Similarly, it was not associated with the study's location, research question or main diagnosis of interest, except for a decreased STROBE score of papers reporting on treatment effects compared to aetiology. Previous studies have found quality of reporting of observational studies to be associated with some of these factors, such as the journal's impact factor [7] and authors guidelines [6], the publication type (peer-reviewed vs report) [3,5] or the author's affiliation (public health agency vs academic) [5]. However, these findings are not consistent [15] and are sometimes based on small samples (<80 manuscripts) in specific fields. This shows that reporting quality of cohort studies in paediatric respiratory research needs to be improved globally.

Strengths and limitations

This systematic review is the first to describe the characteristics of cohort studies reporting on paediatric lower respiratory problems published recently and to assess their reporting quality according to the STROBE statement. We collected detailed information on a large number of studies published worldwide. However, the review has some limitations. First, we did not extend our search to specific databases from South America, Africa or Asia and limited the included studies to those published in English. This may have been one of the reasons for the under-representation of these regions of the world. However, the most important and relevant studies are normally published in English and indexed in Medline or Embase to increase accessibility. Second, the large number of studies included precluded a duplicate screening and data extraction. This may be more relevant for the evaluation of the STROBE checklist items, some of which may be rather subjective. However, all assessors were from the same research team; we used well-defined criteria for manuscript inclusion and exclusion, and for the assessment of adherence to each of the STROBE checklist's elements; and papers where the assessor was uncertain, were discussed in the team until agreement was reached.. Third, the criteria we used to evaluate the adherence to each of the STROBE checklist's items were not very strict. For example, when evaluating the information on confounders or reporting of limitations, we only evaluated if confounders were considered or if limitations were mentioned. We did not study in detail each manuscript to assess if the confounders included or the limitations described were correct and complete. Therefore, our evaluation of the reporting quality is quite optimistic and reporting quality may be even poorer.

Conclusion

The findings of this review may inform both authors and editors on how to increase reporting quality of papers of cohort studies reporting on paediatric lower respiratory problems and what areas of research are neglected. Researchers should follow reporting guidelines (either STROBE

or as appropriate) closely when submitting a manuscript and should check these when reviewing other researchers' manuscripts. The use of nested case-control studies, well designed retrospective chart reviews and linkage of routine data with study data should be borne in mind when designing a cohort study to reduce costs. On the other side, editors from international journals should encourage the publication of studies focused on lower respiratory infections and rare diseases, and those based in low and middle-income countries. Journals should not only endorse the STROBE statement for the reporting of cohort studies, but should demand authors to attach the STROBE checklist during the submission process and ask reviewers to report any missing item in the manuscript. Only through a joined effort of editors, reviewers and authors may we improve the reporting quality of paediatric cohort studies on respiratory problems.

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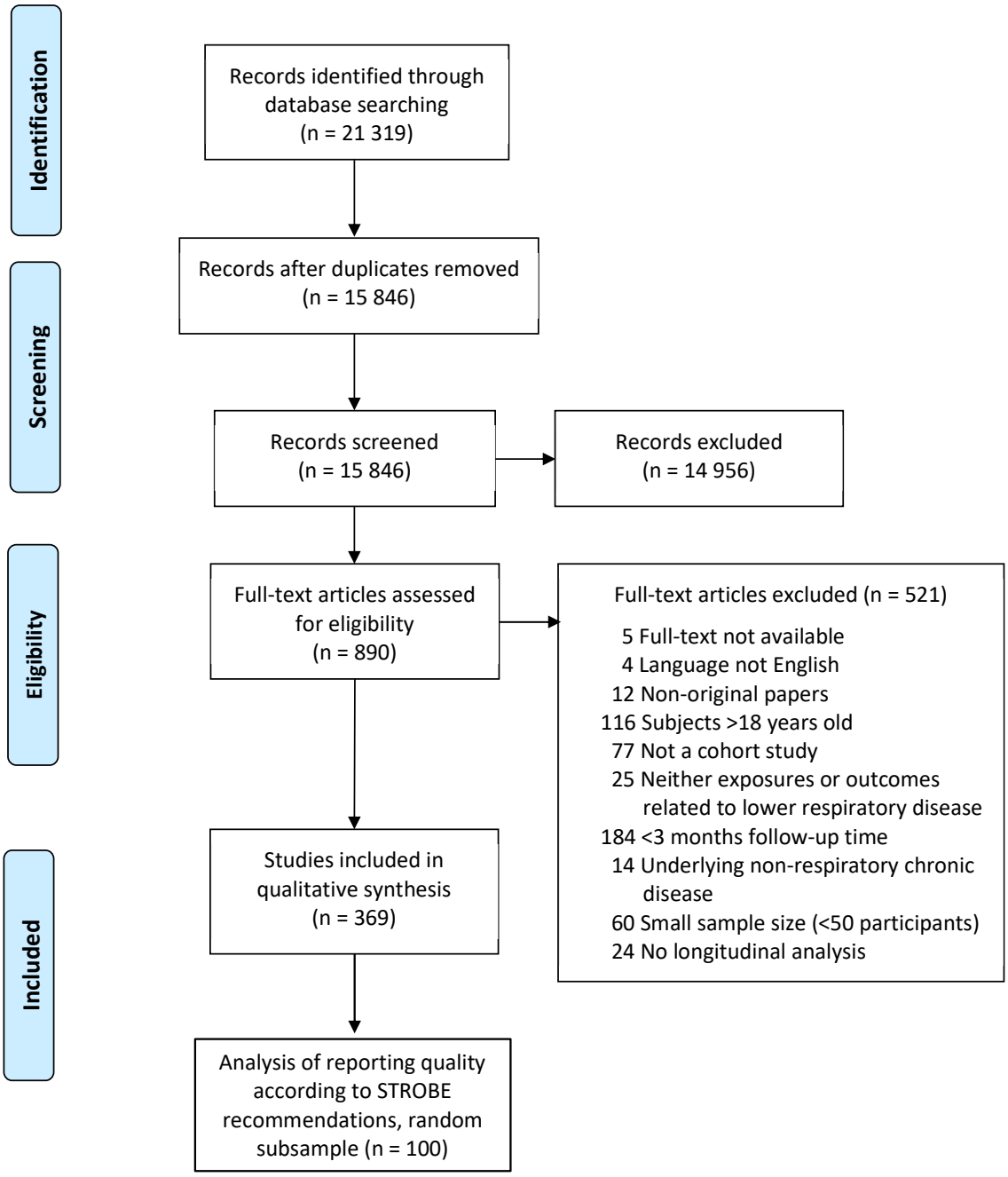
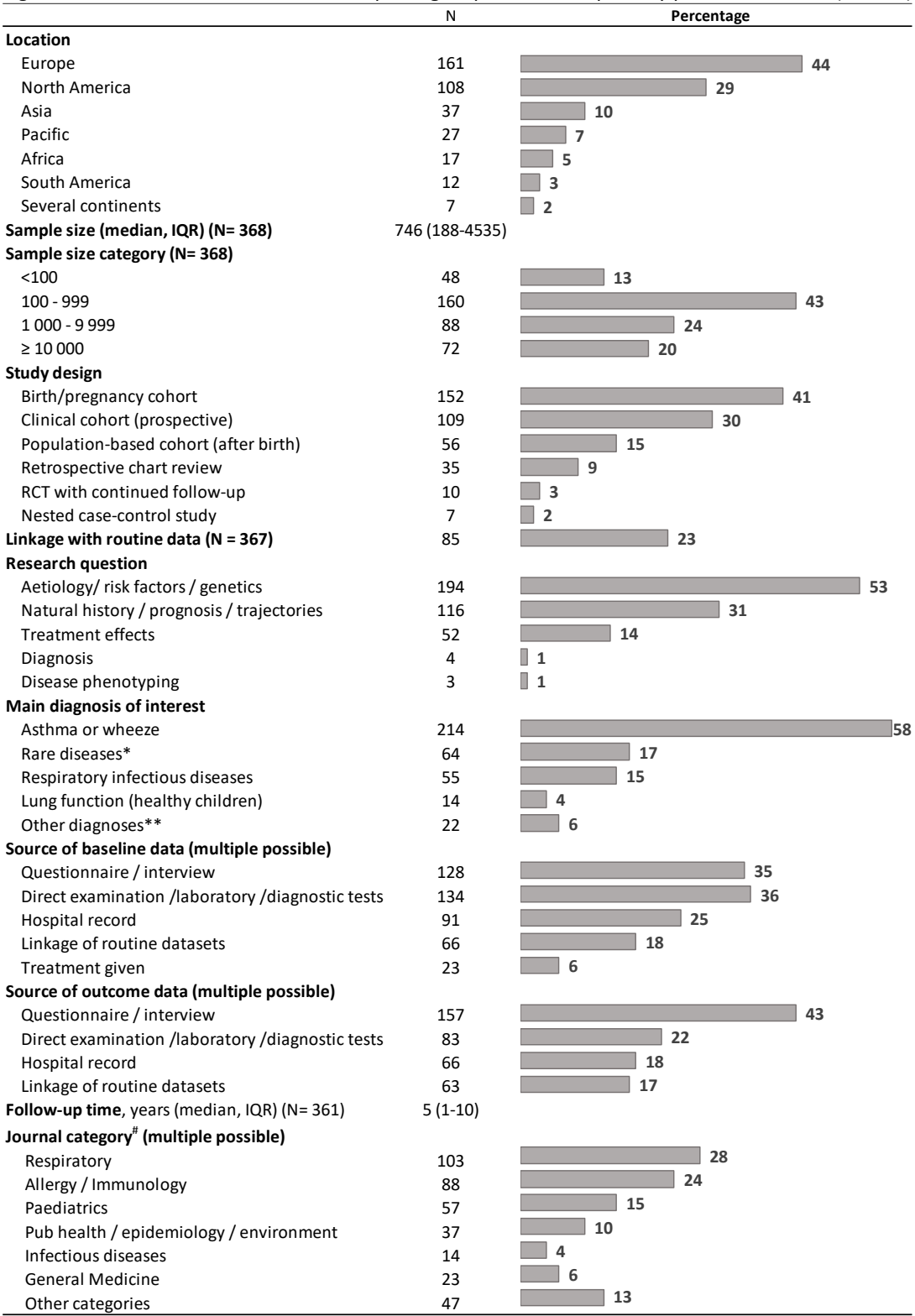


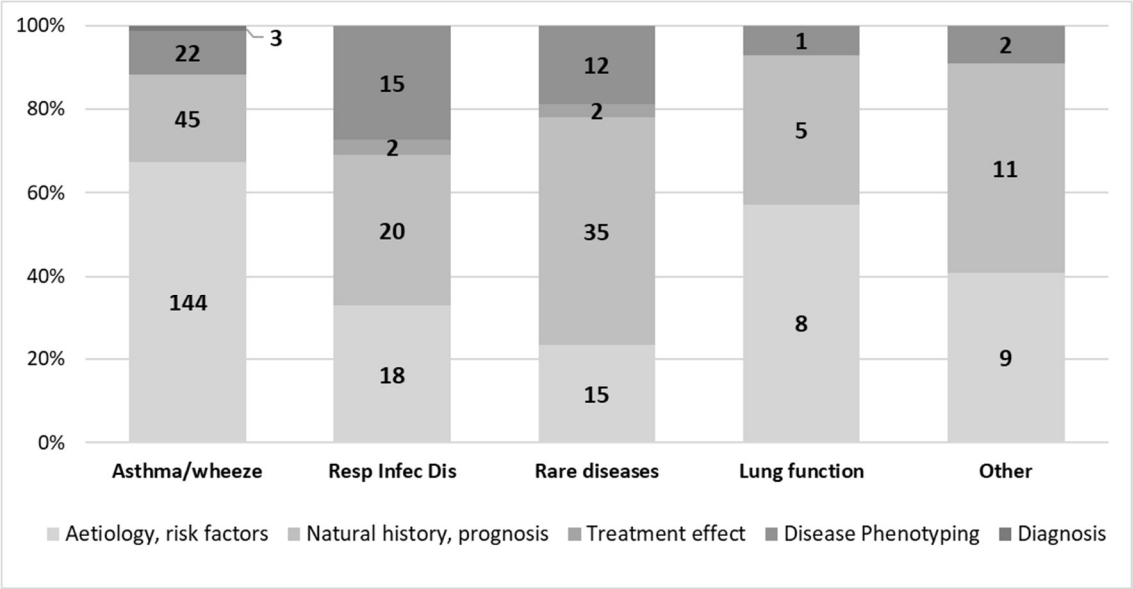
Figure 1: Flow diagram of included and excluded studies.

Fig. 2: Characteristics of cohort studies reporting on paediatric respiratory problems in 2018 (N= 369)



*Rare diseases include: bronchopulmonary dysplasia, diaphragmatic hernia, cystic fibrosis and primary ciliary dyskinesia.
**Other diagnoses include: cough, respiratory distress syndrome, pneumothorax and unspecific respiratory symptoms.
#Categories according to the InCites Journal Citation Report, if a journal appeared in 2 categories, it was classified as the first in which it appears in this order: respiratory, allergy, infectious diseases, public health/epidemiology/environment, paediatrics, general medicine and any other category. IQR: inter-quartile range, RCT: randomized controlled trial.

A. Research question by diagnosis of interest



B. Sample size by diagnosis of interest

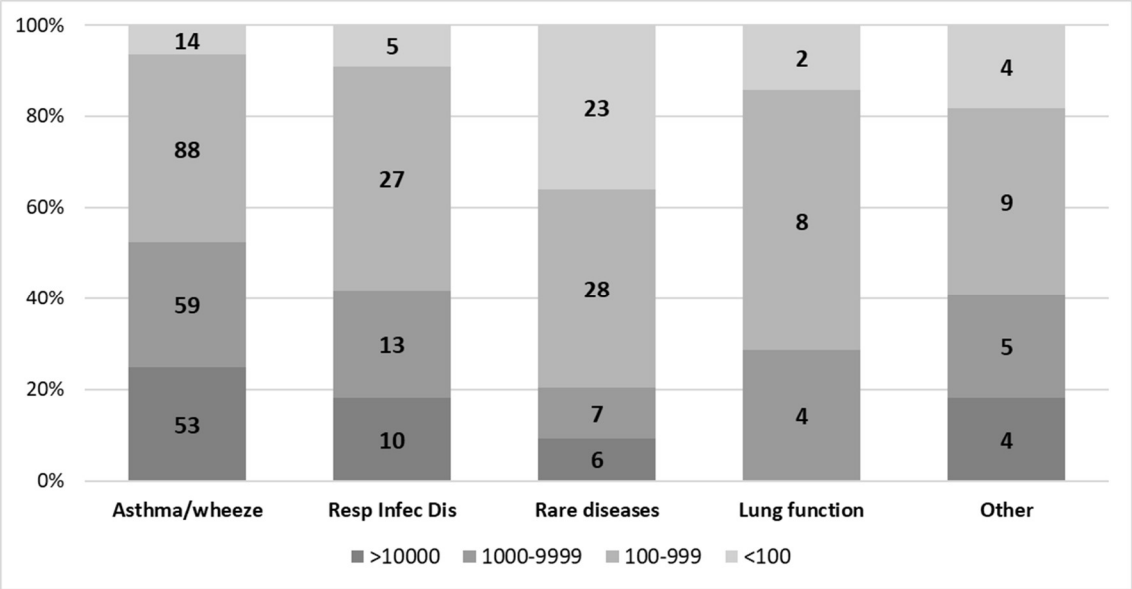


Figure 3: Type of research question (A) and sample size (B) by diagnosis of interest, of cohort studies reporting on paediatric respiratory outcomes or exposures in 2018 (N= 369).

The number inside each bar is the total number of manuscripts for each section.

Supplementary Text

Search terms used for Medline (Ovid)

1. exp cohort studies /

2. (cohort* or prospectiv* or longitudinal* or nested or retrospectiv* or follow*).ti,ab,kw.

3. exp pediatrics/ or exp adolescent/ or exp child/ or exp infant/

4. (toddler* or infan* or child* or schoolchild* or adolescen* or teen* or pediatr* or paediatr*).ti,ab,kw

5. exp "Respiratory Tract Diseases"/ or exp "signs and symptoms, respiratory"/

6. (asthma* or wheez* or bronch* or trache* or laryng* or "vocal cord*" or "primary ciliary dyskinesia" or "cystic fibrosis" or "lung disease*" or "lung infection" or respirat* or cough* or dyspn* or pneumo* or pleura* or pulmonar* or chest or thora* or empyema or "lung abscess" or legionell* or tuberculos* or aspergill* or blastomycos* or "syncytial virus").ti,ab,kw.

7. exp Respiratory Function Tests/

8. ("Airway Resistance" or "Blood Gas Analysis" or Oximetry or Capnography or "Exercise Test*" or "Lung Compliance" or "Lung Volume" or "Lung Capacity" or Plethysmography or "Ventilation-Perfusion" or "forced expiration" or "expiratory flow" or "expiratory volume" or "Maximal Voluntary Ventilation" or "maximal expiratory" or spirometry or "Valsalva Maneuver" or "lung function" or "lung examination" or sputum or "lung biopsy" or "multiple breath washout" or "transthoracic" or "lung angiography" or "lung lavage").ti,ab,kw.

9. exp respiration/

10. (breathing or "breath holding" or exhalation or inhalation or "mucociliary clearance" or "lung clearance" or "lung diffusion" or "lung gas exchange" or "lung mechanics" or "lung ventilation").ti,ab,kw.

11. 1 or 2

12. 3 or 4

13. 5 or 6 or 7 or 8 or 9 or 10

14. 11 and 12 and 13

15. limit 14 to english language

16. limit 15 to year=’2018’

TOTAL: 7610 references

Supplementary Table 1: Classification of journals according to the categories used by the In Cites Journal Citation Report.

Respiratory	- American Journal of Respiratory & Critical Care Medicine - Annals of the American Thoracic Society - BMC Pulmonary Medicine - ERJ Open Research - European Respiratory Journal - International Journal of Tuberculosis & Lung Disease - Journal of Asthma - Journal of asthma and allergy - Journal of Cystic Fibrosis - Journal of Thoracic Disease - NPJ Primary Care Respiratory Medicine - Pediatric Pulmonology - Respiratory Care - Respiratory Medicine - Respiratory Physiology & Neurobiology - Respiratory Research - The Lancet Respiratory Medicine - Thorax
Allergy/immunology	- Allergologia et Immunopathologia - Allergology International - Allergy - Allergy & Asthma Proceedings - Allergy: European Journal of Allergy and Clinical Immunology - Annals of Allergy, Asthma, & Immunology - Asian Pacific Journal of Allergy & Immunology - Asim, Allerji, Immunoloji - Clinical & Experimental Allergy - Journal of Allergy & Clinical Immunology - Journal of Allergy & Clinical Immunology: In practice - Journal of Immunology - Journal of Investigational Allergology & Clinical Immunology - Pediatric Allergy & Immunology - World Allergy Organization Journal
Epidemiology, public health and environmental	- American Journal of Epidemiology - BMC Public Health - Clinical Epidemiology - Epidemiology - Epidemiology & Infection - European Journal of Epidemiology - International Journal of Epidemiology - Iranian Journal of Allergy Asthma & Immunology - Journal of Epidemiology & Community Health - Public Health - Archives of Environmental & Occupational Health - Atmospheric Environment - Environment International - Environmental Epidemiology - Environmental Health Perspectives - Environmental Health: A Global Access Science Source - Environmental Research - Environmental Science & Pollution Research - International Journal of Environmental Research & Public Health - Science of the Total Environment

Paediatrics	- Acta Paediatrica - American Journal of Perinatology - Archives of Disease in Childhood - BMC Pediatrics - BMJ Paediatrics Open - Clinical Pediatrics - Early Human Development - Egyptian Pediatric Association Gazette - European Journal of Pediatrics - International Journal of Pediatrics - Jornal de Pediatria - Journal of Adolescent Health - Journal of Pediatrics - Journal of Perinatology - Maternal & Child Health Journal - Minerva Pediatrica - Neonatology - Paediatrics & Child Health - Pediatric Research - Pediatrics - Pediatrics & Neonatology - Prenatal Diagnosis - Revista Paulista de Pediatria - The Lancet Child & Adolescent Health
Infectious diseases	- AIDS Research & Human Retroviruses - Antibiotics - Clinical Infectious Diseases - Emerging Infectious Diseases - European Journal of Clinical Microbiology & Infectious Diseases - Journal of Infectious Diseases - Journal of Medical Virology - Journal of Microbiology, Immunology & Infection - Open Forum Infectious Diseases - Pediatric Infectious Disease Journal - Vaccine
General Medicine	- African Health Sciences - BioMed Research International - Bjgp Open - BMJ Open - Bosnian Journal of Basic Medical Sciences - Colombia Medica - Cureus - Eastern Mediterranean Health Journal - eLife - Eurosurveillance - International journal of general medicine - JAMA Pediatrics - Jci Insight - Nature Communications - PeerJ - PLoS ONE - Revista Da Associacao Medica Brasileira - Sao Paulo Medical Journal = Revista Paulista de Medicina - Saudi Medical Journal - Scientific Reports - Southern Medical Journal

Other	- Acta Obstetricia et Gynecologica Scandinavica - American Journal of Clinical Nutrition - American Journal of Managed Care - American Journal of Obstetrics & Gynecology - American Journal of Respiratory Cell & Molecular Biology - American Journal of Tropical Medicine & Hygiene - Annals of Behavioral Medicine - Annals of Surgery - Arthritis care & research - British Journal of Dermatology - British Journal of Nutrition - CJEM Canadian Journal of Emergency Medical Care - Clinical Nutrition - Clinical Otolaryngology - ClinicoEconomics and Outcomes Research - CMAJ - European Journal of Clinical Nutrition - European Journal of Obstetrics, Gynecology, & Reproductive Biology - European Journal of Psychotraumatology - European Radiology - Frontiers in Pharmacology - Frontiers in Physiology - Health Promotion Practice - Health Services Insights - Hypertension - International Journal of Eating Disorders - Journal of Laparoendoscopic & Advanced Surgical Techniques. - Journal of Pediatric Gastroenterology & Nutrition - Journal of Pediatric Nursing - Journal of Pediatric Surgery - Journal of Racial & Ethnic Health Disparities - Journal of Voice - Maternal & Child Nutrition - Metabolomics - Nature Plants - Nutrients - Oncotarget - Orphanet Journal Of Rare Diseases - Pediatric Critical Care Medicine - Pharmacoepidemiology & Drug Safety - Postepy Dermatologii I Alergologii - Psychology & Health - Ultrasound in obstetrics & gynecology

Supplementary Table 2: Characteristics of cohort studies reporting on paediatric respiratory outcomes or exposures in 2018, by journal categories (N=369)[#]

	Respira-tory (N=103)	Allergy/ Immun (N=88)	Resp. infect dis. (N=14)	PH /epi /envir. (N=37)	Paedia-trics (N=57)	General med. (N=23)	Other (N= 47)
Location							
Europe	45 (44)	40 (45)	3 (21)	17 (46)	23 (40)	6 (26)	27 (57)
North America	31 (30)	21 (24)	6 (43)	9 (24)	23 (40)	6 (26)	12 (26)
South America	2 (2)	3 (3)	0	0	3 (5)	4 (17)	0
Africa	4 (4)	5 (6)	0	3 (8)	1 (2)	3 (13)	1 (2)
Asia	6 (6)	14 (16)	2 (14)	4 (11)	3 (5)	4 (17)	4 (9)
Pacific	10 (10)	4 (5)	3 (21)	3 (8)	4 (7)	0	3 (6)
Several continents	5 (5)	1 (1)	0	1 (3)	0	0	0
Sample size (median, IQR) (N= 368)	564 (144-3277)	769 (250-2892)	1403 (158-15504)	3537 (641-23100)	701 (145-4475)	432 (77-10476)	664 (161-9038)
Sample size category (N= 368)							
<100	20 (19)	5(6)	1 (7)	1 (3)	8 (14)	6 (26)	7(15)
100 - 999	42 (41)	46 (52)	5 (36)	11 (30)	26 (46)	8 (35)	22(47)
1 000 – 9 999	28 (27)	25 (28)	4 (29)	11 (30)	10 (18)	3 (13)	7(15)
≥ 10 000	13 (13)	12 (14)	4 (29)	14 (38)	13 (23)	6 (26)	11(23)
Study design							
Birth/pregnancy cohort	44 (43)	42 (48)	2 (14)	20 (54)	22 (39)	5 (22)	17(36)
Population-based (after birth)	12 (12)	10 (11)	2 (14)	10 (27)	8 (14)	6 (26)	8(17)
Clinical cohort (prospective)	31 (30)	28 (32)	9 (64)	6 (16)	14 (25)	7 (30)	14(30)
Retrospective chart review	13 (13)	0	0	0	12 (21)	4 (17)	6(13)
Nested case-control	1 (1)	3(3)	1(7)	0	0	1 (4)	1(2)
RCT with continued follow-up	2 (2)	5 (6)	0	1(3)	1 (2)	0	1(2)
Linkage with routine data (N= 367)	18(18)	19 (22)	5 (36)	10 (27)	13 (23)	5 (22)	15(32)
Research question							
Aetiology	42(41)	50 (57)	4 (29)	27 (73)	27 (47)	15 (65)	29(62)
Natural history / prognosis	40(39)	28 (32)	7 (50)	4 (11)	20 (35)	4 (17)	13(28)
Diagnosis	4 (4)	0	0	0	0	0	0
Treatment effects	17(17)	8 (9)	3 (21)	5 (14)	10 (18)	4 (17)	5 (11)
Aetiology	0	2 (2)	0	1 (3)	0	0	0
Main diagnosis of interest							
Asthma or wheeze	56 (54)	72 (82)	1(7)	25 (68)	22 (39)	13 (57)	25(53)
Respiratory infectious dis.	7 (7)	11 (13)	9 (64)	5 (14)	14 (25)	4 (17)	5 (11)
Rare diseases*	27(26)	0	4 (29)	0	16 (28)	4 (17)	13(28)
Lung function (healthy)	7 (7)	1 (1)	0	4 (11)	0	0	2 (4)
Other**	6 (6)	4 (5)	0	3 (8)	5 (9)	2 (9)	2 (4)

Figures represent 'n (%)' unless otherwise stated *Rare diseases include: bronchopulmonary dysplasia, diaphragmatic hernia, cystic fibrosis and primary ciliary dyskinesia. **Other diagnoses include: cough, respiratory distress syndrome, pneumothorax and unspecific respiratory symptoms. IQR: inter-quartile range, RCT: randomized controlled trial, CF: cystic fibrosis, PCD: Primary ciliary dyskinesia.

Chapter 8 - Other activities

8.1 Grant applications

Pulmonary function in long-term childhood cancer survivors after hematopoietic stem cell transplantation; Otth M (PI), Kuehni C (Co-PI), Latzin P (Co-PI); Lungenliga Bern 2020; CHF 33'570 (salary funding for primary applicant for 7 month)

8.2 Teaching activities

During my PhD I have participated in the following teaching activities at the Institute of Social and Preventive Medicine at the University of Bern.

Internal teaching	EndNote course at the IPSM, open for all interested employees
Medical students of the University of Bern	2019-2020: Writing of multiple choice questions for the exam of medical students
	2019: Tutor in Problem Based Learning (PBL) of medical students (1st year) at the University of Bern
Co-supervision of Master thesis of medical students (main supervisor: Claudia Kuehni)	Master student: Morena Elber. Thesis title: Prävalenz abnormer Spirometrie bei ehemaligen Kinderkrebspatienten nach hämatopoetischer Stammzelltransplantation
	Master student: Sophie Käser. Thesis title: Prevalence and Severity of Hearing Loss in Childhood Cancer Survivors exposed to Platinum Chemotherapy and/or Cranial Radiation

8.3 Peer review activity

During my PhD I have contributed to several peer reviews in the cancer and respiratory group of Claudia Kuehni in Thorax, Electronic Journal of General Medicine, and Pediatrics. As invited reviewer, I have performed reviews for PLOS ONE.

8.4 International Guideline Harmonization Group - Metabolic Syndrome

Since May 2018 I am involved in the International Guideline Harmonization Group on metabolic syndrome. I have been mainly involved in evidence extraction and being a second reviewer to assess the extracted evidence by other members.

8.5 Life After Childhood Cancer (LACC) research group

Since January 2019 I am working parttime (20%) as staff physician with focus in research for the newly established Life After Childhood Cancer (LACC) research group at the Kantonsspital Aarau (KSA), under the leadership of Dr. med. Katrin Scheinemann. Research within this group focusses on survivorship care and late effects. We organized an information event for survivors, parents, and health care professionals focusing on survivorship care. We have established the multicenter prospective longitudinal After Childhood Cancer Study (ACCS) to evaluate the transition process from pediatric to adult long-term follow-up care at three different pediatric oncology centers in Switzerland. The project is funded by Cancer Research Switzerland with myself as sub-investigator. We have established the "Young Survivor at KSA" registry, focusing on standardized collection of medical conditions (late effects) in survivors. This registry is supported by a grant from the KSA. Most recently I received a grant from the KSA to perform a study on needs of schools and teachers in reintegrating childhood and adolescent cancer patients into school life during and after completion of treatment.

8.6 Young SIOPE – Essential Medicines project

I am actively involved in Young SIOPE, a newly launched group within SIOP Europe in May 2019. Young SIOPE is a group for young members of the European pediatric oncology community and intends to foster a closer community and facilitate involvement of SIOPE's youngest members in research, development and education. I am one of the six board members of Young SIOPE. I have coordinated several pan-European projects, mainly the Essential Medicines project, which aims to:

1. provide an evidence based reference list of essential medicines for all pediatric cancer diseases to stakeholders in Europe,
2. contribute to the next revisions of the WHO Essential Medicines list for children (EMLc), start proposing new diseases and drugs to be added to the new version in 2021, and
3. assess how different European health technology agencies (HTAs) evaluate newly approved expensive anti-cancer medicines for children.

This project was also presented as a poster during the SIOP congress in 2020 and aims to result in several publications.

Appendix A - Questions on pulmonary health and smoking from the SCCSS used in publication I

Have you ever been told by a doctor that you have, or have had…	**Ever in life?**		**Since when?**	**Currently?**	
	Yes	**No**		**Yes**	**No**
Chronic Cough (for more than 3 months)	☐	☐	(Year)	☐	☐
Pneumonia If yes, how many in the last two years? _____Pneumonia	☐	☐	(Year)	☐	☐
Lung fibrosis (scarring of the lung)	☐	☐	(Year)	☐	☐
Changes on your thorax and/or ribs	☐	☐	(Year)	☐	☐
Emphysema (Overinflation oft he lungs)	☐	☐	(Year)	☐	☐
Any other breathing or lung problem? If yes, please describe this problem _____ _____	☐	☐	(Year)	☐	☐

Smoking (version adolescents and adults)

Have you ever smoked cigarettes?

No, I never smoked ☐
No, I stopped smoking since ___ month ☐
Yes, I smoke irregularly: number ___ of cigarettes per week ☐
Yes, I smoke regularly: number ___ of cigarettes per week ☐

How many hours a day are you exposed to tobacco smoke from other people?

_____ hours and _____ minutes per day (max. 24 hours)
Don't know ☐
No answer ☐

Smoking (version parents)

Have you ever smoked cigarettes?

Mother

No, never ☐
Yes, but stopped since ___ years ☐
Yes, still smoke today ☐

Father

No, never ☐
Yes, but stopped since ___ years ☐
Yes, still smoke today ☐

Appendix B - Data extraction sheet used for publication I and publication II

Identification

PidN: _____ **OR** Name: _____

Given name: _____

Date of birth: _____

Diagnosis / protocol

First diagnosis

Date: _____

Treatment protocol: _____

Treatment arm (if applicable): _____

Protocol complete ☐ yes ☐ no

First relapse

Date: _____

Treatment protocol: _____

Treatment arm (if applicable): _____

Protocol complete ☐ yes ☐ no

Second relapse

Date: _____

Treatment protocol: _____

Treatment arm (if applicable): _____

Protocol complete ☐ yes ☐ no

Secondary tumor

Date: _____

Treatment protocol: _____

Treatment arm (if applicable): _____

Protocol complete ☐ yes ☐ no

Chemotherapy

Known pulmonary toxicity

Drug	**Cumulative dose and unit** (e.g. mg/m², mg/kg) **state if Busulfan is AUC**	**Way of administration (IV/PO/IM)**	**Dose quality** (1=acc. to protocol 2= intended to treat, 3=incomplete dose 4= no dose available)	**Data quality** (1=duration acc. to protocol 2=duration application unknown)
Bleomycin				
Busulfan				
BCNU (Carmustine)				
CCNU (Lomustine)				
Cyclophosphamide				

HSCT conditioning regimen or other suspected lung toxic agents

Drug	**Cumulative dose and unit** (e.g. mg/m², mg/kg) **state if Busulfan is AUC**	**Way of administration (IV/PO/IM)**	**Dose quality** (1=acc. to protocol 2= intended to treat, 3=incomplete dose 4= no dose available)	**Data quality** (1=duration acc. to protocol; 2=duration not acc. to protocol; 3=application unknown)
Fludarabine				
Ifosfamide				

Melphalan				
Other conditioning				
Other conditioning				
Other conditioning				
Other conditioning				

State all chemotherapeutic agents given (also when already mentioned in cumulative doses)

Name		**Name**		**Name**	
Alemtuzumab (Campath)	☐	Etoposide (VP-16)	☐	Mitoxantrone	☐
Asparaginase	☐	Fludarabine	☐	Procarbacine	☐
Anti-Thymocyte Globulin (ATG, ATGAM)	☐	Idarubicin	☐	Temozolomide	☐
Bleomycin	☐	Ifosfamide	☐	6-Thioguanine	☐
Busulfan	☐	Lomustine (CCNU)	☐	Thiotepa	☐
Carboplatin	☐	Mechloretha-mine	☐	Vinblastine	☐
Carmustin (BCNU)	☐	Melphalan	☐		☐
Chlorambucil	☐	Methotrexate	☐	Vincristine	☐
Cisplatin	☐	Methotrexate i.v. (HD = >1g/m^2/Dosis)	☐	Vindesine	☐
Cyclophosphamide	☐	Methotrexate i.v. (NOT HD)	☐	Prednison:	☐
Cytarabine (Ara-C)	☐	Methotrexate p.o.	☐	Dexamethason	☐
Dacarbacine (DTIC)	☐	Methotrexate i.th/i.ventr.	☐	Other: _____	☐
Dactinomycin/Actinomycin D	☐	6-Mercapto-purine	☐	Other: _____	☐
Daunorubicin	☐			Other _____	☐
Doxorubicin	☐	**Epirubicin**	☐		

MTX IV/PO/IT/Ommaya

Drugs in blue color = calculation of cumulative doses in CCSS

Radiotherapy

Date of start radiotherapy	
Location of radiotherapy	**Dose [Gy]**
☐ thorax, whole	
☐ thorax, partially ☐ mantle ☐ extended mantle ☐ mini mantle ☐ mediastinal ☐ involved site RT (ISRT) ☐ involved field RT (IFRT) ☐ extended field RT (EFRT) ☐ subtotal lymphoid irradiation (STLI) (mantle + paraaortic field) ☐ other	
☐ chest wall (e.g. muscle oft he chest wall, rib)	
☐ thoracic spine	
☐ craniospinal axis	
☐ left kidney	
☐ right kidney	
☐ whole abdomen	
☐ total body irradiation (TBI)	
☐ total lymphoid irradiation (TLI)	

In case more than one radiotherapy has been performed to the same field: take additional CRF and number the radiotherapy episodes

Modality		**Source**	
2D conformal	☐	Protontherapy	☐
3D conformal	☐	Photontherapy	☐
IMRT	☐		

Surgery

☐ Biopsy

☐ All other than biopsy

Thoracic wall (Rib, scapula, thoracic muscle)	**Lung** (Thoracotomy, metastasectomy, lobectomy, wedge resection)	**Mediastinal**	**Thoracic spine** (laminectomy)

Exact description of surgery according to surgery protocol: _____

Hematopoietic Stem Cell Transplantation (HSCT)

Date of HSCT	
Time point of HSCT	☐ first remission ☐ first relapse ☐ second relapse ☐ third relapse ☐ for secondary tumor
HSCT	☐ autologous marrow (marrow harvest) ☐ autologous stem cells (apheresis) ☐ allogeneic ☐ HLA identical sibling ☐ HLA matched other relative ☐ HLA matched unrelated ☐ HLA mismatch related ☐ haploidentical ☐ HLA mismatch unrelated
Source of transplant	☐ cord blood ☐ peripheral blood / PBSC ☐ bone marrow
Procedures before transplantation	☐ T cell sorting ☐ T cell depletion ☐ other _____ ☐ unknown/ no data
Protocol name	
Conditioning regimen (Chemotherapeutic doses mentioned in …)	☐ Busulfan ☐ Melphalan ☐ VP16 ☐ CYC ☐ Thiotepa ☐ TBI ☐ _____ ☐ _____ ☐ _____ ☐ _____
HLA- match (e.g. 10/10)	☐ _____ ☐ unknown/ no data
CMV status recipient	☐ positive ☐ negative ☐ unknown/ no data
CMV status donor	☐ positive ☐ negative ☐ unknown
Gender donor	☐ male ☐ female ☐ unknown/ no data
Gender recipient	☐ male ☐ female
Blood group donor	
Blood group recipient	
GvHD	☐ no ☐ yes ☐ chronic ☐ acute ☐ unknown/no data ☐ unknown/ no data ☐ location ☐ skin ☐ gut ☐ oral ☐ other: _____ ☐ unknown/ no data

	☐ time point of occurrence (days after HSCT) _____ ☐ unknown/ no data ☐ Grade of GvHD _____ _____ _____ ☐ unknown/ no data ☐ Treatment for GvHD _____ _____ _____ ☐ unknown/ no data
Infectious pulmonary complication during HSCT or during follow-up (up to time point of data extraction)	☐ Pneumonia ☐ Pulmonary aspergillosis ☐ CMV pneumonitis ☐ other: _____ ☐ unknown/ no data/ not mentioned
If at least one infectious pulmonary episode occurred fill in this section	☐ Date of episode1 _____ ☐ Hospitalization for episode1 ☐ Yes ☐ No ☐ ICU stay for episode1 ☐ Yes ☐ No ☐ Treatment for episode1 (e.g. antibiotics, oxygen) _____ _____
If at least one infectious pulmonary episode occurred fill in this section	☐ Date of episode2 _____ ☐ Hospitalization for episode2 ☐ Yes ☐ No ☐ ICU stay for episode2 ☐ Yes ☐ No ☐ Treatment for episode2 (e.g. antibiotics, oxygen) _____ _____ If additional episodes happened, add them on the back of this page
Non-infectious pulmonary complication during or after HSCT when correlation with HSCT	☐ acute and chronic graft versus host disease (GvHD) ☐ idiopathic pneumonia syndrome (IPS) ☐ bronchiolitis obliterans (BO) ☐ bronchiolitis obliterans organizing pneumonia (BOOP) ☐ unknown/ no data

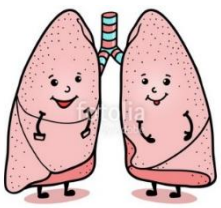
In case more than one HSCT has been performed: take additional CRF and number the HSCT episodes

Pulmonary function test results

☐ found in archive

☐ found in digital medical record

☐ not found



Appendix C - Documents for SCCSS-FollowUp

Fragebogen zur Lungengesundheit

Patient sticker

Heutiges Datum: Tag _____ Monat _____ Jahr _____

Das Beantworten des Fragebogens dauert ungefähr 5-15 Minuten.

Bitte nehmen Sie den ausgefüllten Fragebogen mit zum nächsten Arzttermin.

Bei Fragen oder Unklarheiten dürfen Sie sich jederzeit bei folgender Stelle melden:

Anschrift SPOG-Leiter bzw. Sekretariat Poliklinik
(Wird vorgängig mit jedem SPOG-Leiter separat abgeklärt)

Anleitung zum Ausfüllen des Fragebogens

Es ist wichtig, dass Sie die Fragen gut durchlesen und wenn immer möglich beantworten. Wenn Sie die Antwort nicht genau wissen, so geben Sie die bestmögliche Antwort an.

Bitte kreuzen Sie das zutreffende Kästchen an.
Beispiel: Machen Sie Sport? ☒ Ja ☐ Nein

Wenn Sie eine Antwort korrigieren möchten, streichen Sie diese zweimal durch und machen Sie ein neues Kreuz am richtigen Ort.
Beispiel: ☒ Ja: Fehler zweimal durchstreichen ☒ **Nein**: Neu markieren

Bedeutet, dass Sie etwas reinschreiben können
Beispiel: Wie gross sind Sie? *185* (cm) (ohne Schuhe)

Bedeutet, dass Sie diese Frage überspringen können
Beispiel: Haben Sie Geschwister? ☐ Ja ☒ Nein **Falls Nein**, weiter zu **2.1**

- Falls Ihnen bei einer Frage etwas unklar ist, können Sie von Hand einen Kommentar bei dieser Frage anfügen. Falls Sie mehr Platz benötigen, dürfen Sie gerne ein separates Blatt beifügen.
- Im Fragebogen wurde auf eine Aufzählung beider Geschlechter (Arzt/Ärztin) zugunsten der Lesbarkeit verzichtet. Es sind aber immer beide Geschlechter gemeint.

1. Fragen zu Atembeschwerden und Erkrankungen von Lunge, Nase und Ohren

1.1 Haben Sie manchmal **Atembeschwerden bei Anstrengung**?

☐ Ja ☐ Nein **Falls nein**, weiter zu Frage 1.2

Falls ja, welche Beschwerden haben Sie?

	Ja	Nein
Pfeifende oder keuchende Atmung	☐	☐
Husten	☐	☐
Atemnot oder Engegefühl	☐	☐
Raschere Ermüdbarkeit/ Erschöpfung im Vergleich zu Gleichaltrigen	☐	☐
Andere Beschwerden	☐	☐

Falls **andere Beschwerden**, welche? (zum Beispiel Schmerzen in der Brust, Seitenstechen)

✍ _____

✍ _____

In welchen der **folgenden Situationen** treten die Atembeschwerden auf?

Beim Rennen von…	Nie	Manchmal	Oft
Kurzen Strecken (50-100m)	☐	☐	☐
Mittellangen Strecken (bis 1km)	☐	☐	☐
Langen Strecken (über 1km)	☐	☐	☐
Beim Fahrradfahren (schnell)	☐	☐	☐
Beim Bergauf gehen/wandern	☐	☐	☐
Beim anstrengenden Sportspiel wie Fussball	☐	☐	☐
Beim Schwimmen	☐	☐	☐
Bei anderen Aktivitäten: welche?			
✍ _____	☐	☐	☐
✍ _____	☐	☐	☐

1.2 Haben Sie manchmal **Atembeschwerden in Ruhe bzw. ohne Anstrengung**? (z.B. Buch lesen, Computer)

☐ Ja ☐ Nein Falls nein, weiter zu Frage 1.3

Falls ja, welche Beschwerden haben Sie ohne körperliche Anstrengung?

	Ja	Nein
Pfeifende oder keuchende Atmung	☐	☐
Husten	☐	☐
Atemnot oder Engegefühl	☐	☐
Andere Beschwerden	☐	☐

Falls **andere Beschwerden**, welche? (zum Beispiel Schmerzen in der Brust, Atempausen)

✍ _____

✍ _____

In **welchen Situationen** treten die Atembeschwerden auf (z.B. Stress, rauchige Umgebung)?

✍ _____

1.3 Hatten Sie jemals in Ihrem Leben eine **pfeifende oder keuchende Atmung**? Darunter verstehen wir leise Geräusche (pfeifend, quietschend), die beim Atmen im Brustkorb entstehen, nicht in der Nase oder im Hals.

☐ Ja ☐ Nein ☐ Weiss nicht

Falls ja: Während welchen Lebensphasen? (Mehrere Antworten sind möglich)

☐ Erste 3 Lebensmonate ☐ Mit 4-11 Monaten ☐ Mit 1-3 Jahren (Kleinkind) ☐ Mit 4-6 Jahren (Kindergarten)
☐ Mit 7-10 Jahren (1.-4. Klasse) ☐ Mit 11-12 Jahren (5.-6. Klasse) ☐ Mit 13 Jahren oder später

Falls ja: Welche der folgenden Situationen hat bei Ihnen in den letzten 12 Monaten Husten oder pfeifende oder keuchende Atmung ausgelöst? (Kreuzen Sie bitte alle zutreffenden Situationen an)

	Husten			**Pfeifende/keuchende Atmung**		
	Nie	Manchmal	Oft	Nie	Manchmal	Oft
Erkältung, Grippe	☐	☐	☐	☐	☐	☐
Hausstaub	☐	☐	☐	☐	☐	☐
Blütenstaub (Gräser, Bäume)	☐	☐	☐	☐	☐	☐
Kalte Luft oder Nebel	☐	☐	☐	☐	☐	☐
Wetter- oder Temperaturwechsel	☐	☐	☐	☐	☐	☐
Lautes Lachen	☐	☐	☐	☐	☐	☐
Bestimmte Speisen oder Getränke	☐	☐	☐	☐	☐	☐
Falls Speisen oder Getränke: welche? ✍_____						
Tiere (Katze, Hund, Pferd, Vogel, etc.)	☐	☐	☐	☐	☐	☐
Falls Tiere: welche? ✍_____						
Andere Situationen	☐	☐	☐	☐	☐	☐
Falls andere Situationen: welche? ✍_____						

1.4 Wie viele **Erkältungen** hatten Sie in den letzten 12 Monaten?

☐ Keine ☐ 1-3 ☐ 4-6 ☐ 7-9 ☐ 10 oder mehr

1.5 Denken Sie, dass Sie häufiger **husten** als andere Personen im gleichen Alter?

☐ Ja ☐ Nein

1.6 Hatten Sie in den letzten 12 Monaten jemals einen **Husten,**

der länger als **3 Wochen** am Stück gedauert hat? ☐ Ja ☐ Nein
der länger als **2 Monate** am Stück gedauert hat? ☐ Ja ☐ Nein

1.7 **Husten** Sie auch wenn Sie nicht erkältet sind?

☐ Ja, häufig ☐ Ja, manchmal ☐ Nein, nie

1.8 Ist Ihr **Husten** meist **trocken** (Reizhusten) oder **feucht**/ mit Sekret?

☐ Meist trocken ☐ Meist feucht ☐ Beides, manchmal trocken und manchmal feucht

1.9 Hatten Sie in den letzten 12 Monaten eine **Lungenentzündung**, welche mit einem **Antibiotikum** behandelt wurde?

☐ Nein → weiter zu Frage 1.10

☐ Ja

Falls ja: Angaben zur letzten Lungenentzündung:

Wie war der Name des Antibiotikums? ✍_____

Mussten Sie wegen dieser Lungenentzündung eine oder mehrere Nächte im Spital bleiben? ☐ Ja ☐ Nein

Falls ja: Hatten Sie mehr als eine Lungenentzündung in den letzten 12 Monaten?

☐ Ja, mehr als eine; wie viele? ✍_____

☐ Nein, nicht mehr als eine

1.10 Hatten Sie in den letzten 12 Monaten eine **Mittelohrenentzündung (Otitis media)**, welche mit einem **Antibiotikum** behandelt wurde?

☐ Nein → weiter zu Frage 1.11

☐ Ja

Falls ja: Angabe zur letzten Mittelohrenentzündung:

Wie war der Name des Antibiotikums? ✍_____

Falls ja: Hatten Sie mehr als eine Mittelohrenentzündung in den letzten 12 Monaten?

☐ Ja, mehr als eine; wie viele? ✍_____

☐ Nein, nicht mehr als eine

1.11 Hatten Sie in den letzten 12 Monaten eine **Stirn- oder Nasennebenhöhlenentzündung (Sinusitis)**, welche mit einem **Antibiotikum** behandelt wurde?

☐ Nein → weiter zu Frage 2.1

☐ Ja

Falls ja: Angabe zur letzten Stirn- oder Nasennebenhöhlenentzündung:

Wie war der Name des Antibiotikums? ✍_____

Falls ja: Hatten Sie mehr als eine Stirn- oder Nasennebenhöhlenentzündung in den letzten 12 Monaten?

☐ Ja, mehr als eine; wie viele? ✍_____

☐ Nein, nicht mehr als eine

2. Fragen zu Heuschnupfen und Haut

2.1. Hatten Sie irgendeinmal in Ihrem Leben **Heuschnupfen**?

☐ Ja ☐ Nein ☐ Weiss nicht

Falls ja: Haben Sie heute noch Heuschnupfen? ☐ Ja ☐ Nein

2.2. Hatten Sie irgendeinmal in Ihrem Leben einen **juckenden Hautausschlag**, der während mindestens 6 Monaten stärker oder schwächer auftrat?

☐ Ja ☐ Nein ☐ Weiss nicht

Falls ja: Trat dieser juckende Hautausschlag in den letzten 12 Monaten auf? ☐ Ja ☐ Nein

Falls ja: Hat Ihnen der Arzt gesagt, dass es sich dabei um **Neurodermitis oder Ekzem** handelt? ☐ Ja ☐ Nein

3. Diagnosen zu Erkrankungen der Lunge

3.1. Wurde Ihnen durch einen Arzt gesagt, dass Sie an einer der folgenden Erkrankungen der Lunge leiden?

Asthma	☐ Ja	☐ Nein
Bronchitis	☐ Ja	☐ Nein
Lungenfibrose (=Vernarbung der Lunge)	☐ Ja	☐ Nein
Lungenemphysem (=Überblähung der Lunge)	☐ Ja	☐ Nein
Graft versus Host Disease der Lunge («Spender-gegen-Empfänger-Reaktion»; nur bei transplantierten Patienten möglich)	☐ Ja	☐ Nein
Andere Erkrankung der Lunge	☐ Ja	☐ Nein

→ **Falls ja,** welche? ✍ _____

✍ _____

3.2. Waren Sie schon einmal bei einem Pneumologen (Lungenspezialisten) in Kontrolle/ Behandlung?

☐ Ja ☐ Nein

→ **Falls ja**, geben Sie bitte an, wann das war und bei wem

Datum der letzten Untersuchung (Monat/Jahr)	**Ort der Untersuchung** (Name des Arztes und Ort der Klinik oder der Praxis)

3.3 Haben Sie in den letzten 12 Monaten ein Medikament für die Lunge oder die Atemwege benötigt (z.B. Spray oder Pulver zum inhalieren oder kortisonhaltige Tabletten)?

☐ Ja ☐ Nein

→ **Falls ja,** welches Medikament?

Name	**Spray**	**Pulver**	**Tablette**	**Sirup**
	☐	☐	☐	☐
	☐	☐	☐	☐
	☐	☐	☐	☐

→ **Falls ja,** wie lange wurde das Medikament genommen? ☐ nur kurzfristig

☐ total mindestens 3 Monate oder länger

4. Fragen zu Lifestyle

4.1. Haben Sie je geraucht?

☐ Nein, ich habe nie regelmässig geraucht und rauche auch zurzeit nicht → weiter zu Frage 4.4

☐ Ja, ich rauche zurzeit, aber nicht regelmässig → weiter zu Frage 4.2

☐ Ja, ich rauche zurzeit regelmässig → weiter zu Frage 4.2

☐ Ja, ich habe früher geraucht und rauche jetzt nicht mehr → weiter zu Frage 4.3

→ Falls Sie bei einer der vier Antwortmöglichkeiten **«ja»** gekreuzt haben: Was rauchen Sie bzw. was haben Sie geraucht?

☐ «Normale Zigarette» ☐ E-Zigarette ☐ Shisha

☐ iQOS oder Ploom *(Bei iQOS und Ploom wird der Tabak erhitzt und nicht wie bei einer normalen Zigarette verbrannt)*

☐ Anderes: ✍ _____

4.2. Wie viel rauchen Sie im Moment pro Tag?

☐ Weniger als 1 Zigarette pro Tag
☐ 2 – 9 Zigaretten pro Tag
☐ 10 – 19 Zigaretten pro Tag
☐ 1 Päckli pro Tag
☐ Mehr als 1 Päckli pro Tag

Wie alt waren Sie, als Sie mit Rauchen begonnen haben? _____ (Jahre)

4.3. In der Zeit, während Sie am meisten geraucht haben, wie viel haben Sie geraucht?

☐ Weniger als 1 Zigarette pro Tag
☐ 2 – 9 Zigaretten pro Tag
☐ 10 – 19 Zigaretten pro Tag
☐ 1 Päckli pro Tag
☐ Mehr als 1 Päckli pro Tag

Wie alt waren Sie, als Sie mit regelmässigem Rauchen begonnen haben? _____ (Jahre)

Vor wie vielen Jahren haben Sie aufgehört? _____ (Jahre) → weiter zur Frage 4.4

4.4. Wie viele Stunden sind Sie täglich dem Tabakrauch von anderen Leuten ausgesetzt (Passivrauchen)?

✍ _____Stunden pro Tag
☐ Weiss nicht
☐ Bin nicht Passivrauchen ausgesetzt

4.5. Treiben Sie Gymnastik, Fitness oder Sport?

☐ Ja

Welche Sportart?	Anzahl Stunden pro Woche
✍ _____	_____
✍ _____	_____
✍ _____	_____

☐ Nein

Haben Sie eine Behinderung oder Erkrankung, die das Ausüben von Sport erschwert? ☐ Ja ☐ Nein

Was hindert Sie daran Sport zu treiben?

✍ _____

SCCSS-FollowUp – Documentation sheet

Data extraction – Pulmonary follow-up

Identification

Name: _____

Date of birth: _____

Institution: _____

Date of examination: _____

Vital signs

☐ Puls (/min)_____
☐ Blood pressure (mmHg) _____
☐ Weight (kg) _____
☐ Height (cm) _____

Current respiratory history

☐ Current respiratory tract infection?

- ☐ No
- ☐ Yes
  - ☐ Symptoms: _____

☐ Respiratory tract infection in the last 4 weeks?

- ☐ No
- ☐ Yes
  - ☐ Symptoms, date and duration: _____

☐ Intake of bronchodilatators in the last 24 hours?

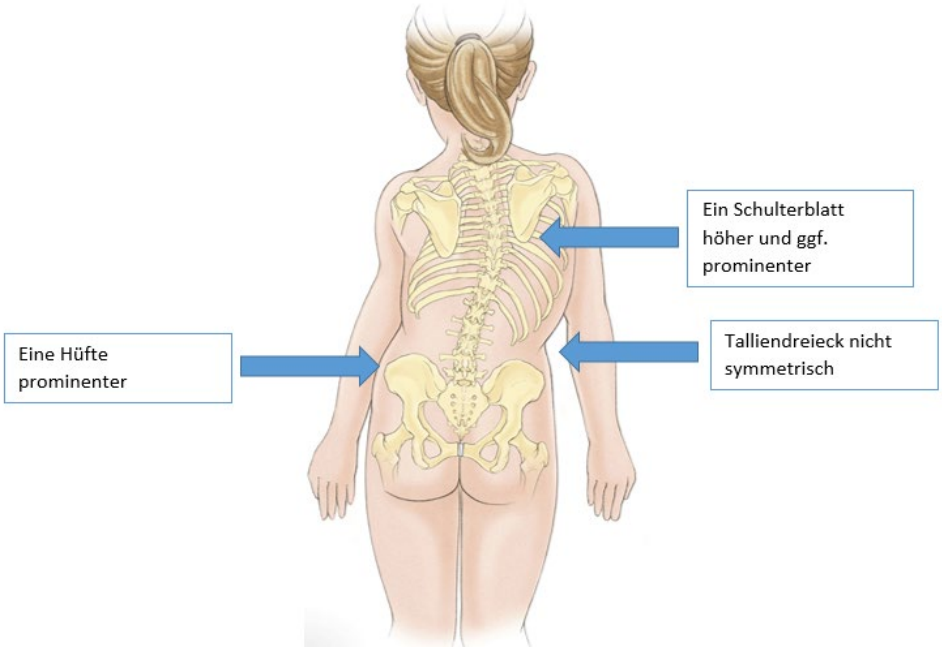
- ☐ No
- ☐ Yes, short-acting (4h)
- ☐ Yes, long-acting (24h)

If yes, when was the last intake? _____

Which medication has been taken? _____

Clinical examination

Chest wall	
Scars	☐ No (Do not count scars due to Port-à-Cath) ☐ Yes ☐ after thoracotomy ☐ after thoracoscopy ☐ after surgery of the spine ☐ after rib resection ☐ after surgery to soft tissue (e.g. muscles) ☐ other: _____
Deformity	☐ No ☐ Scoliosis (see picture) ☐ Light scoliosis, no referral to orthopedist ☐ pronounced scoliosis, referral to orthopedist needed ☐ Other: _____
Inspection	☐ No signs of shortness of breath present ☐ Signs of shortness of breath present ☐ tachypnea ☐ retractions ☐ stridor ☐ cyanosis ☐ No muscular atrophy/asymmetry thoracic present ☐ Muscular atrophy/asymmetry thoracic present Localization: _____ ☐ Other: _____
Auscultation	☐ Lung auscultation ☐ normal ☐ pathological ☐ If pathological, what do you hear? ☐ Attenuated breathing sound Localization (right/left/bilateral/basal/apical): _____ ☐ Fine crackling, fine rattling noise Localization: _____ ☐ Rough rattling noise Localization: _____ ☐ Whistling/ wheezing Localization: _____



Clinical signs of scoliosis

SCCSS-FollowUp Study - Study visit (Pulmonary function test)

Identification

Name: _____
Date of birth: _____
Institution: _____
Date study visit: _____
Weight (kg): _____
Length (cm): _____
Ethnicity: _____
Nationality: _____

Current respiratory history

☐ Current respiratory tract infection?
  ☐ No
  ☐ Yes
    ☐ Symptoms: _____

☐ Respiratory tract infection in the last 4 weeks?
  ☐ No
  ☐ Yes
    ☐ Symptoms, date and duration: _____

☐ Intake of bronchodilatators in the last 24 hours?
  ☐ No
  ☐ Yes, short-acting (4h)
  ☐ Yes, long-acting (24h)

If yes, when was the last intake? _____
Which medication has been taken? _____

Lung function testing

Lung function test performed? *(multiple answers possible)*
  ☐ None
  ☐ Yes, Spirometry
  ☐ Yes, Body plethysmography
  ☐ Yes, DLCO
  ☐ Yes, Single breath washout test
  ☐ Yes, Multiple breath washout test

Quality of Spirometry
  ☐ Bad
  ☐ Acceptable
  ☐ Good

Quality of Body plethysmography
  ☐ Bad
  ☐ Acceptable
  ☐ Good

SCCSS-FollowUp Study - Study visit (Pulmonary function test)

Has the child taken any bronchodilatation on the day lung function test was performed before the test? (not as part of the test)

☐ No
☐ Yes

TLC _____
(Liter, example 3.00)

FRC _____
(Liter, example 3.00)

RV _____
(Liter, example 3.00)

FVC _____
(Liter, example 3.00)

FEV1 _____
(Liter, example 3.00)

Rtot _____
(kPa/(L/s), example 0.40)

R EX _____
(kPa/(L/s), example 0.40)

sR eff _____
(kPa*s, example 1.00)

sR tot _____
(kPa*s, example 1.00)

R mid _____
(kPa/(L/s), example 0.50)

MEF 75 _____
(Liter, example 3.00)

MEF 50 _____
(Liter, example 3.00)

MEF 25 _____
(Liter, example 3.00)

Conclusive results of lung function test

☐ Normal lung function
☐ Obstructive ventilation
  ☐ mild
  ☐ severe
☐ Restrictive ventilation
  ☐ mild
  ☐ severe
☐ Other result
  _____

Comments to the lung function test:

_____

SCCSS-FollowUp Study - Study visit (Pulmonary function test)

Multiple Breath Washout

Quality of multiple washout test
- ☐ Bad
- ☐ Acceptable
- ☐ Good

Was LCI 2.5 or LCI 5 done?
- ☐ LCI 2.5
- ☐ LCI 5

Lung clearance index (LCI) _____
(Liter, example 2.00)

Functional residual capacity (FRC) _____
(Liter, example 2.00)

Moment Ratio (MR) _____

Sacin _____

Scond _____

Comments to the washout test:

_____

Variables in RedCap® for SCCSS-FollowUp

The RedCap® database consist of five instruments: three general instrumenst and two project-specific instruments. The two project-specific instruments are specific for the project on pulmonary dysfunction. In the following section I give an overview over the instruments and a short extract of their content.

Overview over Data Collection Instruments

Data Collection Instruments

Create a new instrument from scratch
Import a new instrument from the official REDCap Shared Library
Upload instrument ZIP file from another project/user or external libraries

Instrument name	Fields	View PDF	Instrument actions
Patient Data And Eligibility	12		Choose action
Medical Data Extraction	250		Choose action
Clinical Visit	9		Choose action
Physical Examination	45		Choose action
Clinical Measures (=Pulmonary Function Tests)	23		Choose action

Instrument for "Patient Data And Eligibility"

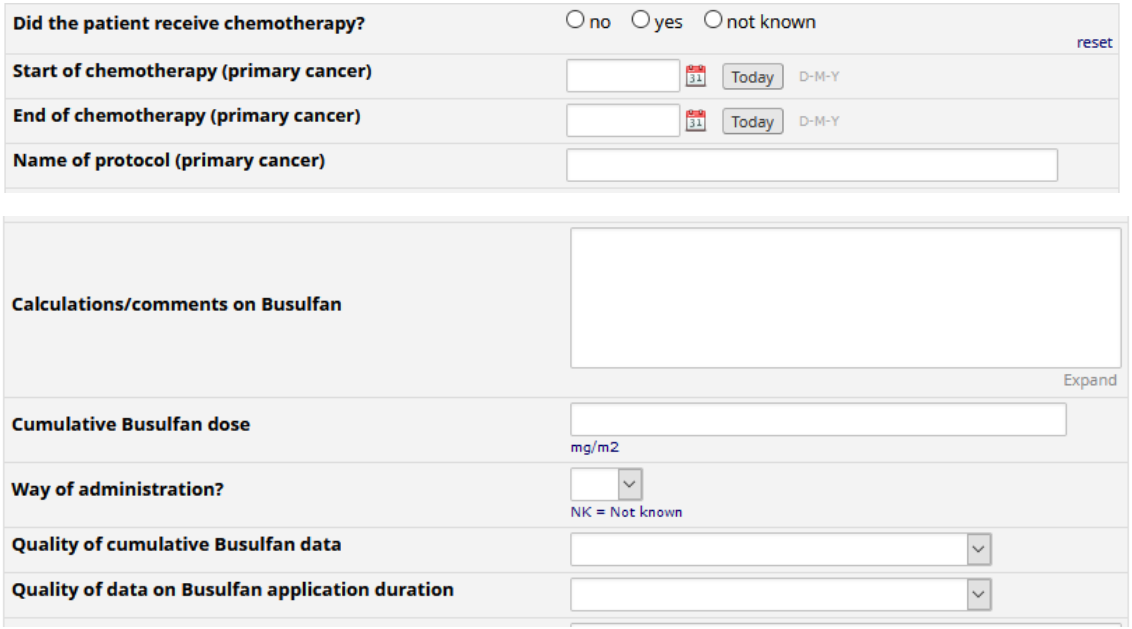
REDCap ID	
VARIA	
SCCR ID * must provide value	xxxx xxxx
Patient ID data entered by * must provide value	○ Maria Otth ○ other person reset
Name of other person * must provide value	
PATIENT DATA AND ELIGEBILITY	
Day of birth	
Month of birth * must provide value	
Year of birth * must provide value	yyyy
Gender * must provide value	
Inclusion criteria fullfilled? * must provide value	☐ age at diagnosis 0-21 years ☐ diagnosis according to ICCC3 I-XII or LCH must all be fullfilled
SPOG Patient? * must provide value	○ No ○ Yes reset
Send date of information letter * must provide value	Today D-M-Y DD-MM-YYYY
Send date of reminder letter	Today D-M-Y DD-MM-YYYY

Instrument for "Medical Data Extraction" – First questions

REDCap ID * must provide value	
Date of data extraction * must provide value	Today D-M-Y DD-MM-YYYY
Data extracted by * must provide value	○ Maria Otth ○ other person reset
Name of other person * must provide value	
1.1 CANCER DIAGNOSIS	
Primary cancer diagnosis (acc. to ICCC-3)	○ leukemias ○ lymphomas ○ central nervous system neoplasms ○ neuroblastomas ○ retinoblastomas ○ renal tumours ○ hepatic tumours ○ malignant bone tumours ○ soft tissue sarcomas ○ germ cell tumours ○ other malignant epithelial neoplasms ○ LCH ○ other specified and unspecified malignant neoplasm reset
Detailed primary cancer diagnosis * must provide value	detailed cancer diagnosis according to medical letter (e.g. acute lymphoblastic leukemia or alveolar rhabdomyosarcoma)
Date of primary cancer diagnosis	Today D-M-Y e.g. first day of therapy, date of biopsy
Location of primary cancer (categories)	☐ lungs ☐ bones ☐ bone marrow ☐ lymph nodes ☐ central nervous system ☐ liver ☐ spleen ☐ soft tissue ☐ other

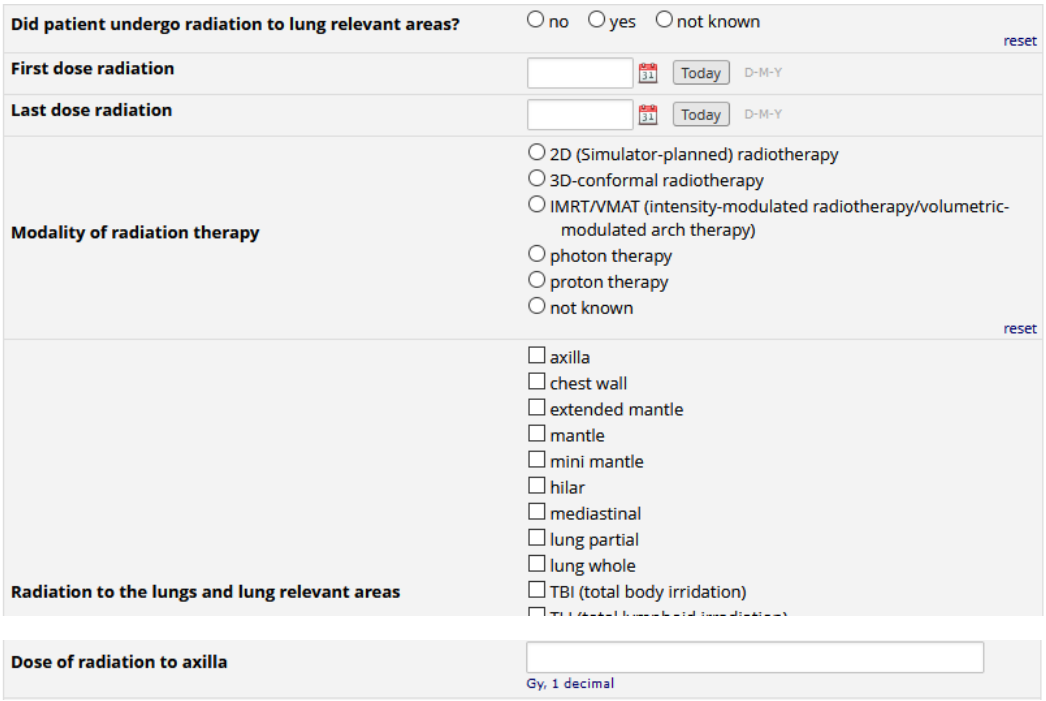
Information is collected on primary cancer diagnosis, further relapses and secondary malignancy

Instrument for "Medical Data Extraction" – Chemotherapy



Chemotherapeutic agents included: Asparaginase, Anti-Thymocyte Globulin (ATG), Bleomycin, Busulfan, Carboplatin, Carmustin (BCNU), Chlorambucil, Cisplatin, Cyclophosphamide, Cytarabine (Ara-C), Dacarbacine (DTIC), Dactinomycin/ Actinomycin D, Daunorubicin, Doxorubicin, Epirubicin, Etoposide (VP-16), Fludarabine, Idarubicin, Ifosfamide, Lomustine (CCNU), Mechlorethamine, Melphalan, Methotrexate (i.v. low dose, i.v. high dose, p.o, i.th./i.ventr.), 6-Mercaptopurine, Mitoxantrone, Procarbacine, Temozolomide, 6-Thioguanine, Thiotepa, Vinblastine, Vincristine, Vindesine, Other

Instrument for "Medical Data Extraction" – Radiotherapy



Instrument for "Medical Data Extraction" – HSCT

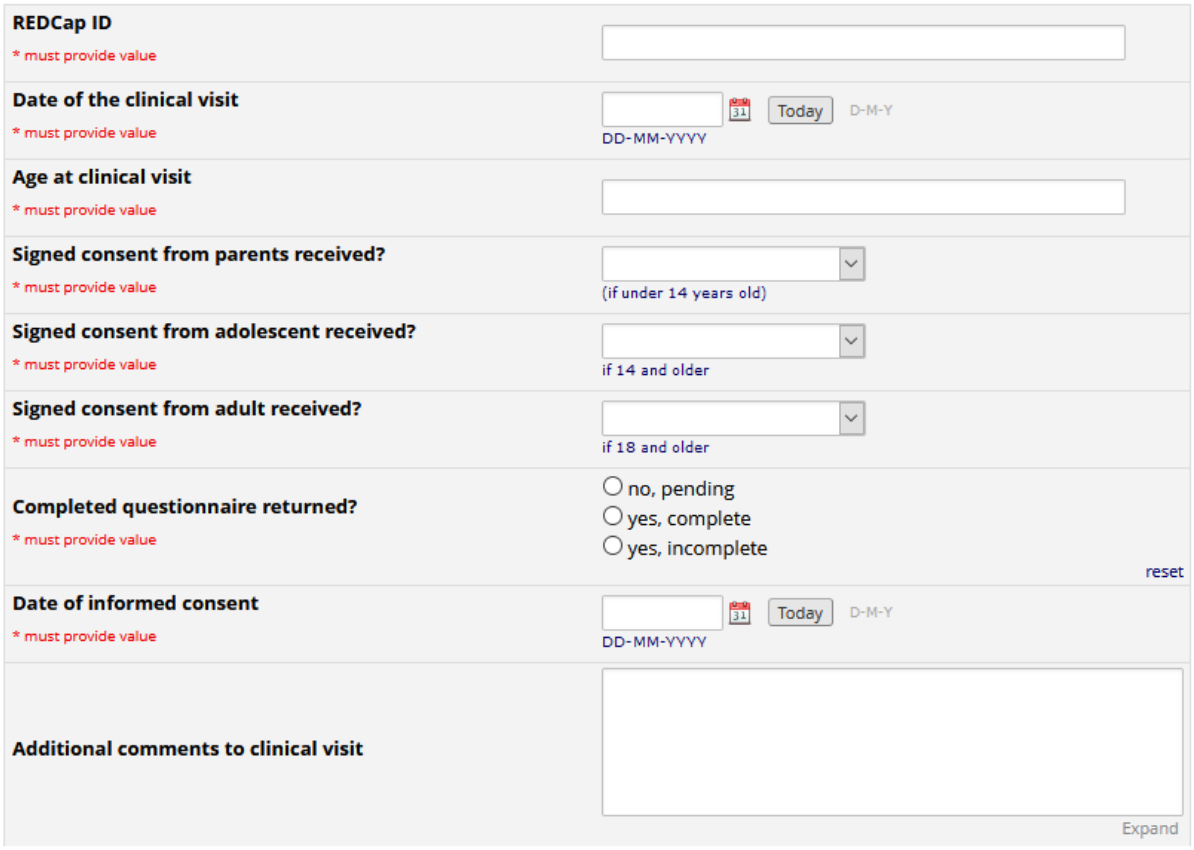
Did patient undergo HSCT?	○ yes ○ no reset
Date of HSCT	Today D-M-Y
Type of HSCT	○ autologous ○ allogeneic reset
Donor type of autologous HSCT	☐ related ☐ unrelated ☐ HLA-match ☐ HLA-mismatched ☐ haploidentical
Source of Transplant	○ peripheral stem cells ○ bone marrow ○ cord blood reset
HLA match	e.g. 10/10 or 6/6

Additional information on CMV status of donor and recipient, gender of donor and recipient, blood group of donor and recipient, drugs ued for conditioning, development of graft verus host disease and its degree and affected organ systems

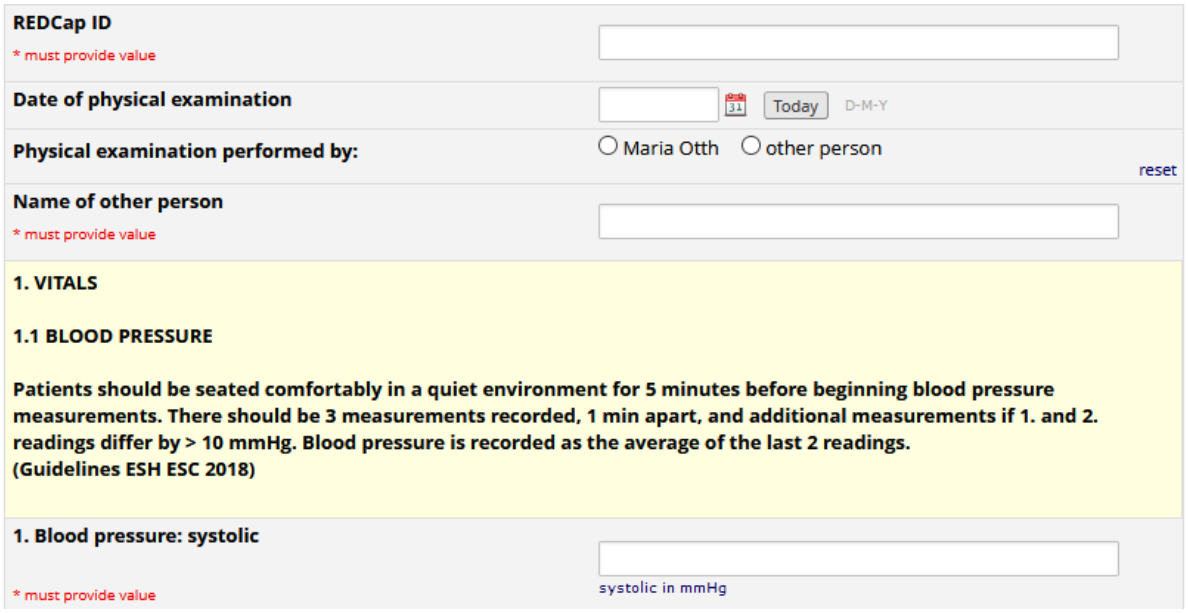
Instrument for "Medical Data Extraction" – Thoracic surgery

Did patient undergo 1st thoracic surgery?	○ yes ○ no ○ not known reset
Date 1st thoracic surgery	Today D-M-Y
Location 1st thoracic surgery	
Description of 1st thoracic surgery	Expand

Instrument for "Clinical Visit"



Instrument for "Physical examination"



Additional informarion on heart rate, weight, height, current pulmonary history, clinical examination of the lung including signs of dyspnea and signs of heart failure

Instrument for "Clinical Measures (=Pulmonary Function Test)"

REDCap ID * must provide value	
Patient's ethnicity	○ White/ European descent ○ Arab (e.g. Egypt, Iraq, Jordan, Lebanon) ○ West Asian (e.g. Turkey, Iran, Afghanistan) ○ Indian subcontinent ○ Pakistani/Bangladeshi ○ Southeast Asian (e.g. Malaysia, Indonesia, Vietnam) ○ East Asian (e.g. China, Japan, Korea, Taiwan) ○ African/ African American ○ Latin American/Hispanic ○ American Indian/ Alaska Native ○ Australian aboriginal ○ Native Hawaiian or other Pacific Islander ○ Caribbean ○ Jewish ○ Roma/ Irish traveler ○ Other ethnic group ○ Don't know ○ Prefer not to answer reset
Other ethnicity	
Nationality	
1. Lung Function Test	
Lung function test performed	○ None ○ Yes, Spirometry ○ Yes, Bodyplethysmography ○ Yes, DLCO ○ Yes, Single breath washout test ○ Yes, Multiple breath washout test reset
Reason if no test was performed	
1.1 SPIROMETRY AND BODYPLETHYSMOGRAPHY	
Quality of Spirometry	○ bad ○ acceptable ○ good ○ not mentioned reset
Quality of Bodyplethysmography	○ bad ○ acceptable ○ good ○ not mentioned reset
Has the patient taken any bronchodilatation on the day of the lung function test before the test?	○ no ○ yes, short-acting ○ yes, long-acting reset
Value of TLC (total lung capacity)	Liter, 2 decimals
Value of FRC (functional residual capacity)	Liter, 2 decimals

Additional information on RV, FVC, FEV1, resistance, MEF75%, MEF50%, MEF25%

Appendix D - International Guideline Harmonization Group Pulmonary Dysfunction

Step 1: Evaluate concordances and discordances of current recommendations

Workgroup 1:

	Who needs surveillance?				
	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordant/ Discordant
At risk					
Allogeneic HSCT	**Yes**	**No**	**Yes**	Not included in guideline	**Discordant**
Bleomycin	**Yes**	**Yes**	**?Yes** (little evidence of late toxicity in children)	Not included in guideline	**Concordant**
Busulfan	**Yes**	**Yes**	**Yes**	Not included in guideline	**Concordant**
Nitrosureas	**Yes**	**Yes**	**Yes**	Not included in guideline	**Concordant**
Radiotherapy	**Yes** (≥10 Gy)	**Yes**	**Yes**	Not included in guideline	**Concordant**
Surgery	**Yes**	**Yes**	**Yes**	Not included in guideline	**Concordant**
High risk					
Allogeneic HSCT	**Yes** (especially if cGvHD)	**No** (Not listed separately)	**Yes** (especially if TBI, busulfan, cGvHD)	Not included in guideline	**Discordant**
Higher bleomycin dose	**Yes** (≥400 U/m^2)	**No** (No dose specified)	**No** (No dose specified)	Not included in guideline	**Discordant**
Higher busulfan dose	**Yes** (≥500 mg)	**No** (No dose specified)	**No** (No dose specified)	Not included in guideline	**Discordant**
Higher cumulative dose BCNU	**Yes** (≥600 mg/m^2)	**No** (No dose specified)	**Yes** (No dose specified)	Not included in guideline	**Discordant**
Higher radiotherapy dose	**Yes** (RT ≥15 Gy; TBI ≥6 Gy single fraction, TBI ≥12 Gy fractionated)	**No** (No dose specified)	**Yes** (but: no dose specified)	Not included in guideline	**Discordant**
Larger radiotherapy	**No**	**No**	**Yes**	Not included in guideline	**Discordant**

treatment volume	(Not mentioned)	(No volume specified)	(but: no volume specified)		
Combinations, others					
Combinations of above	**Yes** Busulfan, BCNU combined with chest RT or TBI Belomycin combined with chest RT or TBI Surgery combined with alkylating agents or bleomycin or chest RT or TBI	**No** (No combinations specified)	**No** (No combinations specified)	Not included in guideline	**Discordant**
Combination of radiotherapy and radiomimetic chemotherapy	**Yes** (doxorubicin, dactinomycin)	**No** (No combinations specified)	**No** (No combinations specified)	Not included in guideline	**Discordant**
Younger age	**Yes** (bleomycin, radiotherapy no age specified)	**No** (Not mentioned)	**Yes** (BCNU <5yrs, radiotherapy)	Not included in guideline	**Discordant**
Renal dysfunction (bleomycin)	**Yes** (not further specified)	**No** (Not mentioned)	**No** (Not mentioned)	Not included in guideline	**Discordant**
cGvHD / Immunosuppress.	**Yes**	**No** (Not mentioned)	**Yes**	Not included in guideline	**Discordant**
Pulmonary infection (HSCT)	**No** (Not mentioned)	**No** (Not mentioned)	**Yes**	Not included in guideline	**Discordant**
Tobacco: smoking/ETS/ marijuana	**Yes**	**No** (Not mentioned)	**No** (Not mentioned)	Not included in guideline	**Discordant**

Legend: cGvHD = chronic graft versus host disease; ETS= environmental Tobacco smoking; HSCT= Hematopoietic stem cell transplantation; TBI = total body Irradiation

Risk factors added by experts and not in current guidelines

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordant/ Discordant
Cyclophosphamide	Not included in guideline	Not included in guideline	Not included in guideline	Not included in guideline	-
Methotrexate	Not included in guideline	Not included in guideline	Not included in guideline	Not included in guideline	-
Gemcitabine	Not included in guideline	Not included in guideline	Not included in guideline	Not included in guideline	-

Workgroup 2-4:

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordant/ Discordant
What surveillance modality should be used?					
Clinical history	**Yes** (cough, SOB, DOE, Wheezing)	**No** (Not mentioned)	**Yes** (exercise tolerance, smoking)		**Discordant**
Physical examination	**Yes** (pulmonary exam)	**No** (Not mentioned)	**Yes** (respiratory system)	Not included in guideline	**Discordant**
Pulmonary function tests	**Yes** (further specified)	**Yes** (further specified)	**Yes** (PFT, not further specified)	Not included in guideline	**Concordant**
Spirometry	**Yes**	**Yes** (flow volume curve)	Not specified	Not included in guideline	**Discordant**
Bodyplethismography	**No** (Not mentioned)	**Yes** (TLC)	Not specified	Not included in guideline	**Discordant**
DLCO	**Yes**	**Yes** (DLCocorr/VA)	Not specified	Not included in guideline	**Discordant**
Radiology examination	**Yes**	**No** (Not mentioned)	**Yes**	Not included in guideline	**Discordant**
Chest x-ray	**No** (deleted in version 4.0)	**No** (Not mentioned)	**Yes** (if symptomatic or PFT abnormal)	Not included in guideline	**Discordant**
CT	**Yes** Discuss for patient for high risk for Lung cancer (chest RT and smoking)	**No** (Not mentioned)	**Yes** (HR CT if symptomatic or abnormal)	Not included in guideline	**Discordant**

At what frequency should surveillance be performed?					
Physical examination	**Yes** (Yearly)	**No** (Not mentioned)	**Yes** (at LTFU clinic, all patients)	Not included in guideline	**Discordant**
Clinical history	**Yes** (Yearly)	**No** (Not mentioned)	**Yes** (at LTFU clinic, all patients)	Not included in guideline	**Discordant**
Pulmonary function tests	At entry into LTFU, at least 2 years after end of cancer treatment, thereafter as clinically indicated in pat with abnormal results or progressive dysfunction	5 and 10 years after diagnosis, then every 5 years if abnormal PFT (<75% predicted)	End of treatment, then after 1 year if symptomatic or abnormal PFT (<2SD below normal)	Not included in guideline	**Discordant**
Pulmonary function tests post-HSCT	At entry into LTFU, thereafter as clinically indicated	**No** (Not mentioned)	Pre-HSCT, 1 year post-HSCT, then every 1-3/5 years depending on symptoms and PFTs results	Not included in guideline	**Discordant**
Radiology examination	**Yes** Discuss for patient for high risk for Lung cancer (chest RT and smoking)	**No** (Not mentioned)	**Yes** (if symptomatic)		**Discordant**
What should be done when abnormalities are identified?					
Consider specialist referral	**Yes** (if symptomatic or progressive)	**Yes** (if symptomatic)	**Yes** (if symptomatic or abnormal PFT)	Not included in guideline	**Concordant**
Warn anaesthesist about previous bleomycin treatment	**Yes** (consider repeated PFT before anesthesia if bleomycin busulfan, BCNU, CCNU)	**Yes** (no exposure to FiO2>30% after bleomycin >400mg/m2 and/or RT to thorax)	**Yes** (but nothing specified)	Not included in guideline	**Concordant**

Preventive measures	**Yes**	**Yes** if (FEV1/FVC or DLCOcorr/VA <75%predicted or have >20% reduction from baseline) or (recur. infection/ chronic cough)	**Yes**	Not included in guideline	**Partly concordant**
Consider pneumococcal and influenza immunization	**Yes** influenza and pneumococcal	**Yes** influenza (if abnormalities in PFT as described above)	**Yes** influenza and pneumococcal (if established lung disease)	Not included in guideline	**Partly concordant**
Tobacco smoking	**Yes** (abstain)	**Yes** (abstain)	**Yes** (abstain))	Not included in guideline	**Concordant**
Inhaled drug use (marijuana)	**Yes** (abstain)	**No** (Not mentioned)	**No** (Not mentioned)	Not included in guideline	**Discordant**
Physical exercise	**Yes** (get regular physical exercise)	**No** (Not mentioned)	**No** (Not mentioned)	Not included in guideline	**Discordant**
ETS (parents)	**Yes** (avoid)	**No** (Not mentioned)	**No** (Not mentioned)	Not included in guideline	**Discordant**
Advice on career choice	**Yes** Follow safety rules, don't' inhale toxic substances (chemicals, solvents, paints) use protective ventilators and report unsafe work conditions	**Yes** (avoid toxic substances)	**No** (Not mentioned)	Not included in guideline	**Discordant**
Scuba diving	**Yes**	**Yes**	**No**	Not included in guideline	**Discordant**

	(if busulfan, BCNU, CCNU, HSCT, RT to chest, bleomycin get advice from pulmonologist)	(Not mentioned)	(Not mentioned)		
Therapeutic approaches	**No** (Not mentioned)	**No** (Not mentioned)	**Yes** (consider immunosuppression in chronic pulmonary disese wit cGvHD)	Not included in guideline	**Discordant**

Surveillance modalities added by experts not included in current guidelines for WG2-4

	North American Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Scottish Intercollegiate Guidelines Network	Concordant/ Discordant
What surveillance modality should be used?					
Single Breath/Multiple Breath Washout measurements	No (Not mentioned)	No (Not mentioned)	No (Not mentioned)	Not included in guideline	-
BGA	No (Not mentioned)	No (Not mentioned)	No (Not mentioned)	Not included in guideline	-
MRI	No (Not mentioned)	No (Not mentioned)	No (Not mentioned)	Not included in guideline	-
What should be done if abnormalities are identified?					
Overweight	No (Not mentioned)	No (Not mentioned)	No (Not mentioned)	Not included in guideline	-
High altitudes	Not included in guideline	Not included in guideline	Not included in guideline	Not included in guideline	-

Step 2 (WG 2-4): Results of search for clinical practice guidelines

Year	Bibliography	Author
Interstitial lung disease		
2015	European protocols for the diagnosis and initial treatment of interstitial lung disease in children (Review)	Bush et al
2013	An Official American Thoracic Society Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy	Kurland et al Interstitial lung disease in **infants**
2008	Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society	Wells et al
2004	ERS - Task force on chronic interstitial lung disease in immunocompetent children	Clement et al
Chronic Obstructive Pulmonary Disease (COPD)		
2020	AWMF - S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD)	Vogelmeier et al
2020	The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2020	TSANZ
2018	NICE - Chronic obstructive pulmonary disease in over 16s: diagnosis and management	NICE
(Idiopathic) Pulmonary Fibrosis		
2019	AWMF – Leitlinie zur Diagnostik der Idiopathischen Lungenfibrose	Behr et al
2018	Diagnosis of Idiopathic Pulmonary Fibrosis An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline	Raghu et al Not include – in primary diagnosis only, no information on surveillance and treatment
2017	Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia	Jo et al
2017	French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis – 2017 update	Cottin et al
2015	An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis An Update of the 2011 Clinical Practice Guideline	Raghu et al
2013	NICE – Idiopathic pulmonary fibrosis in adults: diagnosis and management	NICE
2011	An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management	Raghu et al

Guidelines to answer the question on "What surveillance modality should be used?"

Year	Bibliography	Author
Interstitial lung disease		
2015	European protocols for the diagnosis and initial treatment of interstitial lung disease in children (Review)	Bush et al
2013	An Official American Thoracic Society Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy	Kurland et al
2008	Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society	Wells et al
2004	ERS - Task force on chronic interstitial lung disease in immunocompetent children	Clement et al
Chronic Obstructive Pulmonary Disease (COPD)		
2020	AWMF - S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD)	Vogelmeier et al
2020	The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2020	TSANZ
2018	NICE - Chronic obstructive pulmonary disease in over 16s: diagnosis and management	NICE
(Idiopathic) Pulmonary Fibrosis		
2019	AWMF – Leitlinie zur Diagnostik der Idiopathischen Lungenfibrose	Behr et al
2017	Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia	Jo et al
2017	French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis – 2017 update	Cottin et al
2015	An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis An Update of the 2011 Clinical Practice Guideline	Raghu et al
2013	NICE – Idiopathic pulmonary fibrosis in adults: diagnosis and management	NICE
2011	An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management	Raghu et al

No evidence in the guidelines: All guidelines start with symptomatic patients or patients with radiological changes. They do not have an asymptomatic interval where the guidelines already recommend surveillance for.

Guidelines to answer the question on "At what frequency should surveillance be performed? / When should surveillance be initiated?"

Year	Bibliography	Author
Interstitial lung disease		
2015	European protocols for the diagnosis and initial treatment of interstitial lung disease in children (Review)	Bush et al
2013	An Official American Thoracic Society Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy	Kurland et al
2008	Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society	Wells et al
2004	ERS - Task force on chronic interstitial lung disease in immunocompetent children	Clement et al
Chronic Obstructive Pulmonary Disease (COPD)		
2020	AWMF - S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD)	Vogelmeier et al
2020	The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2020	TSANZ
2018	NICE - Chronic obstructive pulmonary disease in over 16s: diagnosis and management	NICE
(Idiopathic) Pulmonary Fibrosis		
2019	AWMF – Leitlinie zur Diagnostik der Idiopathischen Lungenfibrose	Behr et al
2017	Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia	Jo et al
2017	French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis – 2017 update	Cottin et al
2015	An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis An Update of the 2011 Clinical Practice Guideline	Raghu et al
2013	NICE – Idiopathic pulmonary fibrosis in adults: diagnosis and management	NICE
2011	An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management	Raghu et al

No evidence in the guidelines: All guidelines start with symptomatic patients or patients with radiological changes. They do not have an asymptomatic interval where the guidelines already recommend surveillance for.

Guidelines to answer the question on "What should be done when abnormalities are found?"

We excluded recommendations on:

Recommendations excluded	**Reason**
BAL and lung/tissue biopsy	These invasive procedures go beyond tests which would be performed for surveillance
Tests to exclude other systemic disorders (e.g. immunodeficiency, collagen vascular disease), pulmonary infections or allergies.	This is one step further than surveillance and the responsibility of (pediatric) pneumologists.
Pharmacological treatment and oxygen therapy	This is one step further than surveillance
Indications for lung transplantation	This is one step further than surveillance
Diagnosis and management of acute exacerbations	This is one step further than surveillance
Diagnosis and management of comorbidities	This is one step further than surveillance

Abbreviations:

chILD childhood interstitial lung disease

FVC functional vital capacity

HRCT high-resolution computed tomography

ILD interstitial lung disease

IPF idiopathic pulmonary fibrosis

TLCO transfer capacity of the lung for carbon monoxide

For simplicity, the summaries provided in this thesis to not include the grading of level of evidence as this differs between the studies

Recommendations on initial diagnosis and follow-up examinations to extrapolate recommendations for **surveillance modality**

Interstitial Lung Disease

What should be done when abnormalities are found?	
Clement A et al, ERS Task force on chronic interstitial lung disease in immunocompetent children. Eur Respir J, 2004	
Recommendation	**Level of evidence**
Initial diagnosis - Taking family history - Chest radiographs: provide limited information - HRCT as key chest imaging tool, thin sections; the ERS Task Force recommends the use of 120 kVp and 50 mAs for performing chest HRCT in paediatric patients - Pulmonary function testing represents a useful tool for the diagnosis of ILD	strength of the evidence was not assessed (n.a.), more like an expert opinion
Pulmonary function testing represents a useful tool for the management of ILD - age group 0-2 years: pulse oximetry, BGA with SaO2, SaCO2. Eventually FRC via body plethysmography or by gas dilution techniques - age group 2–6 years: pulse oximetry, BGA. In addition, SaO2 and/or blood gases may also be determined during exercise. If child cooperative perform spirometry - children aged >6 years: spirometry, lung volumes by body plethysmography or by gas dilution techniques. Pulse oximetry and BGA at room air at rest and during exercise. DLCO whenever possible	strength of the evidence n.a.
HRCT may also contribute to monitor disease activity and/or severity	strength of the evidence n.a.
Kurland et al, An Official American Thoracic Society Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy. Am J Respir Crit Care Med, 2013	
Important comments	
Focusing on neonates and infants <2 years of age ILD in infants are distinct from those that cause ILD in older children and adults	
Recommendation[1]	**Level of evidence**
Weak: For infants with ILD, infant pulmonary function testing to better characterize physiologic alterations is suggested	Level of evidence not reported

Bush et al, European protocols for the diagnosis and initial treatment of interstitial lung disease in children (Review), Thorax, 2015	
Important comments	
Delphi process to achieve a consensus on treatment protocols to harmonize treatment approaches	
Recommendation[2]	**Level of evidence[3]**
Initial diagnosis: - Chest radiograph: non specific - Lung function testing: the role in infants is unclear - Chest CT scanning in centers experienced in pediatric radiology	Strength of the evidence n.a.
Monitoring with: - Clinical (respiratory rate, heart rate, weight, oxygen saturation in air awake, oxygen saturation including overnight while asleep and on exercise, evidence of pulmonary hypertension) and radiologic (chest X-ray, a limited cut thin-section HRCT of areas of interest if justifiable) testing - In older children, spirometry at each observational monitoring visit, with DLCO and body plethysmography recommended as indicated	Strength of evidence assessed but not clearly provided

Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Well et al, Thorax, 2008	
Recommendation[4]	**Level of evidence[5]**
Initial diagnosis: - Taking detailed history to identify respiratory risk factors both past and present **[D]**. - Spirometric and gas transfer (see next section) - Maximal exercise data (see next section) - HRCT in patients for whom the diagnosis is uncertain after chest radiography and clinical assessment. **[C]** - HRCT is valuable in detecting ILD in patients with a normal chest radiograph. **[B]**	
Lung function testing: - All patients with ILD should have resting spirometric and gas transfer measurement at presentation, which provides a reasonable measure of disease severity **[C]** - Desaturation during the 6-minute walk test at presentation is a stronger prognostic determinant in IPF than resting lung function **[C]**. However, additional studies are required to define the role of exercise testing in routine staging and follow-up both in IPF and other ILDs. **[C]** - Maximal exercise data probably add little to resting lung function in assessing the severity of ILD but are sometimes useful, when normal, in excluding clinically significant diffuse lung disease. **[C]**	Level of evidence not explicitly reported for each recommendation

What should be done when abnormalities are found?	
Vogelmeier C, et al. AWMF - S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD), 2020	
Recommendation[1]	**Level of evidence**
Strong: COPD should be diagnosed by 1) taking a personal history (including smoking exposure), 2) asking for characteristic symptoms (dyspnea, cough, and expectoration), and 3) performing lung function test before and after bronchodilatation. **Strong**: Lung function testing should include whole body plethysmography, blood gas analysis, DLCO, imaging (CT thorax), and exercise tests.	Strength of the evidence n.a.
Regular follow-up examinations are recommended - ask for symptoms (CAT) and exacerbations - pulmonary function testing, including diffusion capacity in those with severe disease at rest and with exertion - pulse oximetry is suitable for monitoring oxygenation as a progression parameter.	
NICE - Chronic obstructive pulmonary disease in over 16s: diagnosis and management, 2018	
Recommendation	**Level of evidence**
Use spirometry to monitor disease progression.	Strength of the evidence n.a.
TSANZ - The COPD-X Plan: Australian and New Zealand Guidelines for the management of COPD, 2020	
Recommendation[2]	**Level of evidence**[3]
Strong: Diagnosis of COPD through history and examination and confirmed by presence of persistent airflow limitation post-bronchodilator (FEV1/FVC < 0.7).	III-2

What should be done when abnormalities are found?	
Behr J et al., AWMF - S2K Leitlinie zur Diagnostik der Idiopathischen Lungenfibrose, 2019	
Important comments	
Consensus guidelines; the AWMF guidance group has decided to adapt the ATS-ERS-JRS-ALAT Guidance 2018 in this consensus statement.	
Recommendation[1]	**Level of evidence**
Initial diagnosis: - Perform a volumetric CT in high-resolution technique without X-ray contrast medium in inspiration and supine position in all patients with suspected IPF **(strong consensus)**. - The multidisciplinary discussion represents the diagnostic gold standard in the view of the guideline group **(strong consensus)**.	Strength of the evidence n.a.
Important parameters for the assessment of the clinical course of the disease: - pulmonary function (FVC and TLC) including diffusion capacity (TLCO), - blood gas analysis at rest and under stress, - 6 minutes walking test, - quality of life (including SGRQ questionnaire or the K-BILD), and - imaging techniques (HRCT), - cumulative scores (e.g. GAP Index and TORVAN) to assess the severity and the associated prognosis.	Strength of the evidence n.a.
Follow-up exams are usually carried out at 3-4 monthly intervals.	Strength of the evidence n.a.
NICE: Idiopathic pulmonary fibrosis in adults: diagnosis and management (CG163)	
Recommendation[2]	**Level of evidence[3]**
Assess everyone with suspected idiopathic pulmonary fibrosis by: - taking a detailed history, carrying out a clinical examination (see recommendation 1 for clinical features) - performing lung function testing (spirometry and gas transfer) and - reviewing results of chest X-ray and - performing CT of the thorax (including high-resolution images).	Recommendation bases on GDG consensus, as **evidence was of low to very low quality** due to limitations in study design and inconsistency across populations and diagnostic procedures.
Assess lung function during follow-up appointments of people with idiopathic pulmonary fibrosis	Recommendation bases on GDG consensus, as no evidence was retrieved to inform this question.

Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. 2018	
Recommendation	**Level of evidence**
Recommendations only about exclusion of differential diagnoses and confirming the diagnosis by performing BAL or biopsy	

Ganesh Raghu et al, An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis An Update of the 2011 Clinical Practice Guideline, 2015	
Recommendation	**Level of evidence**
Recommendations only about treatment of IPF	

Ganesh Raghu et al, An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management, 2011	
Recommendation	**Level of evidence**
Monitoring clinical course - Objective assessment of dyspnea (e.g. with dyspnea scores/ validated tools; University of California San Diego shortness of breath questionnaire) - Pulmonary function testing recommended. Combination of FVC and diffusion capacity may be useful in assessing progression of disease - Monitor for worsening oxygenation (at rest and with exertion) regardless of symptoms recommended	strength of the evidence n.a.

Cottin V et al. French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis - 2017 update, 2017	
Recommendation[4]	**Level of evidence**
Workup if pulmonary fibrosis is <u>suspected</u>: - It is **recommended** to consider that a HRCT scan pattern of definite UIP, including honeycombing, is sufficient to make the diagnosis of IPF, after ruling out the other causes of UIP (secondary forms).	Strength of the evidence n.a.
Baseline workup if IPF is <u>diagnosed</u>: - It is **recommended** to assess forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLCO). - It is **proposed** to also assess total lung capacity, arterial blood gas at rest, and a 6-minute walk test	Strength of the evidence n.a.
Tests used during monitoring after diagnosis: • It is **recommended** to perform a clinical examination and a pulmonary function test with FVC measurement • It is **proposed** to perform DLco measurement • It is **recommended** to perform a chest CT scan in special situations (e.g. suspicion of exacerbation, unexplained change in clinical status, assessment for lung transplantation)	strength of the evidence n.a.

• It is **proposed** to perform annually a CT scan	

Jo HE, et al. Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia, 2017	
Recommendation	**Level of evidence**
No recommendations on diagnostic measures or tests how to follow-up these patients	

Recommendations on initial diagnosis to extrapolate for **frequency of surveillance**

Interstitial Lung Disease

What should be done when abnormalities are found?	
Clement A et al, ERS Task force on chronic interstitial lung disease in immunocompetent children. Eur Respir J, 2004	
Recommendation	**Level of evidence**
Response to treatment should be assessed at regular intervals of 3-6 months or more frequently for severely ill patients.	strength of the evidence n.a.
Kurland et al, An Official American Thoracic Society Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy. Am J Respir Crit Care Med, 2013	
Recommendation	**Level of evidence**
No information on frequency of follow-up	
Bush et al, European protocols for the diagnosis and initial treatment of interstitial lung disease in children (Review), Thorax, 2015	
Recommendation	**Level of evidence[1]**
Monitoring with: - clinical and radiologic (chest X-ray at diagnosis, 6 and 12 months, a limited cut thin-section HRCT of areas of interest if justifiable) testing is recommended at months 1, 2, 3, 6, and 12 and annually thereafter. - In older children, spirometry at each observational monitoring visit should be recorded, with DLCO and body plethysmography recommended as indicated but at least once per year.	Strength of evidence assessed but not clearly provided
Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Well et al, Thorax, 2008	
Recommendation[4]	**Level of evidence[5]**
No information on frequency of follow-up	

Chronic obstructive disease (COPD)

What should be done when abnormalities are found?	
Vogelmeier C, et al. AWMF - S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD), 2020	
Recommendation	**Level of evidence**
No information on frequency of follow-up care	
NICE - Chronic obstructive pulmonary disease in over 16s: diagnosis and management, 2018	
Recommendation	**Level of evidence**
Primary care F/U: - mild/moderate/severe: annual - very severe: twice a year	Strength of the evidence n.a.
TSANZ - The COPD-X Plan: Australian and New Zealand Guidelines for the management of COPD, 2020	
Recommendation[1]	**Level of evidence[2]**
Strong: Severity of COPD should be assessed regularly (no time periods given).	III-2

(Idiopathic) Pulmonary Fibrosis

What should be done when abnormalities are found?	
Behr J et al., AWMF - S2K Leitlinie zur Diagnostik der Idiopathischen Lungenfibrose, 2019	
Recommendation[1]	**Level of evidence**
Follow-up exams are usually carried out at 3-4 monthly intervals.	Strength of the evidence n.a.
NICE: Idiopathic pulmonary fibrosis in adults: diagnosis and management (CG163)	
Recommendation[2]	**Level of evidence[3]**
Consider follow-up of people with idiopathic pulmonary fibrosis: - every 3 months or sooner if they are showing rapid disease progression or rapid deterioration of symptoms or - every 6 months or sooner if they have steadily progressing disease or - initially every 6 months if they have stable disease and then annually if they have stable disease after 1 year.	This recommendation was based on GDG consensus, as no evidence was retrieved to inform this question.

Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. 2018	
Recommendation	**Level of evidence**
Recommendations only about exclusion of differential diagnoses and confirming the diagnosis by performing BAL or biopsy	

Ganesh Raghu et al, An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis An Update of the 2011 Clinical Practice Guideline, 2015	
Recommendation	**Level of evidence**
Recommendations only about treatment IPF	

Ganesh Raghu et al, An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management, 2011	
Recommendation[4]	**Level of evidence**[5]
Monitoring clinical course - A **flexible approach to monitoring for disease progression;** lower threshold for earlier repetition of FVC and DLCO in the presence of progressive dyspnea or other features of a more rapidly progressive course. - Monitor every **4-6 months** or sooner as clinically indicated	strength of the evidence n.a.

Cottin V et al. French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis - 2017 update, 2017	
Recommendation[6]	**Level of evidence**
Monitoring after diagnosis: - It is **recommended** to at least perform a clinical examination and a pulmonary function test with FVC measurement every 3—6 months in patients with a confirmed diagnosis of IPF. - It is **proposed** to perform DLco measurement every 3—6 months in patients with a confirmed diagnosis of IPF. - It is **recommended** to perform a chest CT scan in case of suspicion of acute IPF exacerbation, unexplained change in clinical status, suspicion of lung cancer, and in case of assessment for lung transplantation. - It is **proposed** to perform annually a CT scan. When a CT scan is performed, it also allows detecting lung cancer, in particular in patients in whom respiratory functional data would allow surgical resection in case of localized lung cancer.	strength of the evidence n.a.

Jo HE, et al. Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia, 2017	
Recommendation	**Level of evidence**
No recommendations on diagnostic measures or tests how to follow-up these patients. Therefore no information on frequency of follow-up	

Recommendations on initial diagnosis and follow-up to extrapolate for **general management / follow-up care**

Interstitial Lung Disease

What should be done when abnormalities are found?	
Clement A et al, ERS Task force on chronic interstitial lung disease in immunocompetent children. Eur Respir J, 2004	
Recommendation	**Level of evidence**
Immunization with influenza vaccine on an annual basis is recommended along with other routine immunizations against major respiratory pathogens	strength of the evidence n.a.
Avoid general anesthesia for high-resolution CT scan and use conscious sedation only if necessary	strength of the evidence n.a.
Kurland et al, An Official American Thoracic Society Clinical Practice Guideline: Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy. Am J Respir Crit Care Med, 2013	
Recommendation[1]	**Level of evidence**
All patients with ILD should receive supportive and preventive care such as treatment of hypoxemia, nutritional failure, and comorbidities, as well as interventions to prevent infection.	Strength of the evidence n.a.
Weak: For patients with ILD, thin section CT scanning of the chest using the lowest radiation dose to optimally characterize the nature and distribution of the lung disease is suggested, and if possible, it should be performed at centers with expertise in performing pediatric chest CT	Level of evidence not reported
Strong: For patients with ILD, performing thin-section CT using the lowest radiation dose that provides adequate diagnostic information is recommended	Level of evidence not reported
Bush et al, European protocols for the diagnosis and initial treatment of interstitial lung disease in children (Review), Thorax, 2015	
Recommendation	**Level of evidence**
- CT scan in patients with suspected ILD should only be performed at centers experienced in pediatric radiology, with a goal to minimize radiation dosage, while maximizing information obtained - The optimal CT scan should be a volumetric scan during inspiration, performed in tandem with high-resolution CT (HRCT) fine-cut spaced expiratory scan. Ventilation should be controlled to ensure satisfactory, interpretable, scan output - Careful consideration should be given as to the risk/ benefits of using contrast medium based on anticipated diagnosis, since the administration of contrast medium will make the assessment of ground glass shadowing almost impossible, but the need to assess the pulmonary vasculature will require the use of contrast - Faster CT scans without the need for anesthesia are not recommended unless anesthesia is thought to be unsafe	strength of the evidence n.a.

Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Well et al, Thorax, 2008	
Recommendation[2]	**Level of evidence[3]**
- Patients with ILD should have access to a multidisciplinary team based in a regional center with expertise in ILD **[C]**. - Referral to a regional ILD clinic should be made if there are perceived difficulties in diagnosis and/or management, but a tailored shared care model is advocated. **[D]** - Patients with ILD who are current smokers should receive opportunistic smoking cessation advice from healthcare professionals and this advice should be recorded in the clinical notes. **[B]** - Patients with ILD should have access to a local pulmonary rehabilitation program. **[D]**	Level of evidence not explicitly reported for each recommendation
- Best supportive care should be considered a specific and important treatment strategy in all patients with idiopathic pulmonary fibrosis (IPF). It is a proactive approach to symptomatic treatment and may include oxygen therapy, pulmonary rehabilitation, opiates, anti-reflux therapy, withdrawal of steroids and other immunosuppressants, early recognition of terminal decline and liaison with palliative care specialists. **[D]**	Level of evidence not explicitly reported for each recommendation
- Radiologists with an interest in thoracic imaging and respiratory physicians should meet regularly to evaluate imaging in patients with ILD. **[D]** - Radiologists involved with determining the protocol and interpretation of HRCT scans should have expertise in the technique be responsible for quality assurance and ensure that an appropriate radiation dose protocol is used. At least one radiologist in any department should have a declared interest and be trained in chest radiology and HRCT. **[D]** - Consider to establishing a reference panel of radiologists with particular expertise in HRCT. **[D]**	Level of evidence not explicitly reported for each recommendation

Chronic obstructive disease (COPD)

What should be done when abnormalities are found?	
Vogelmeier C, et al. AWMF - S2k-Leitlinie zur Diagnostik und Therapie von Patienten mit chronisch obstruktiver Bronchitis und Lungenemphysem (COPD), 2020	
Recommendation[1]	**Level of evidence**
Additional recommendations on: - smoking cessation - **Weak:** influenza vaccination: once per year - **Strong:** pneumococcal vaccination according to STIKO (PSV23 once, then after 6 years again (no more details)	Strength of the evidence n.a.

- pneumological rehabilitation programs - oxygen support if necessary.	

NICE - Chronic obstructive pulmonary disease in over 16s: diagnosis and management, 2018	
Recommendation	**Level of evidence**
Information on vaccination	Strength of the evidence n.a.

TSANZ - The COPD-X Plan: Australian and New Zealand Guidelines for the management of COPD, 2020	
Recommendation[2]	**Level of evidence[3]**
Strong: Referral specialist respiratory services may be required. **Strong**: Pulmonary rehabilitation should be offered to all patients with COPD. **Strong**: Smoking cessation is most important intervention preventing worsening of COPD. **Strong**: Vaccination reduces risks associated with influenza and pneumococcal infection.	III-2 I II I

(Idiopathic) Pulmonary Fibrosis

What should be done when abnormalities are found?	
Behr J et al., AWMF - S2K Leitlinie zur Diagnostik der Idiopathischen Lungenfibrose, 2019	
Important comments	
The AWMF guidance group has decided to adapt the ATS-ERS-JRS-ALAT Guidance 2018 in this consensus statement.	
Recommendation[1]	**Level of evidence**
- Perform a volumetric CT in high-resolution technique without X-ray contrast medium in inspiration and supine position in all patients with suspected IPF. **(strong consensus)** - The multidisciplinary discussion represents the diagnostic gold standard in the view of the guideline group. **(strong consensus)**	Strength of the evidence n.a.
- The care of patients in specialized ILD centers enables the extensive workup to be carried out at initial diagnosis and the cases to be discussed in institutional multidisciplinary ILD boards. - Also in the follow-up, a periodic presentation of the patients is useful to ensure an optimal therapy offer. In practice, the alternating presentation at the resident pneumologist and at the ILD center is often practiced.	Strength of the evidence n.a.

NICE: Idiopathic pulmonary fibrosis in adults: diagnosis and management (CG163)	
Recommendation[2]	**Level of evidence[3]**

At each stage of the diagnostic care pathway the multidisciplinary team **should** consist of a minimum of the healthcare professionals, all of whom should have expertise in interstitial lung disease: consultant respiratory physician, consultant radiologist, interstitial lung disease specialist nurse, multidisciplinary team coordinator	Low to moderate quality
Offer best supportive care to people with idiopathic pulmonary fibrosis from the point of diagnosis. Best supportive care should be tailored to disease severity, rate of progression, and the person's preference, and should include if appropriate information and support, symptom relief, management of comorbidities, withdrawal of therapies suspected to be ineffective or causing harm, and end of life care.	This recommendation was partially based on GDG consensus. Very low to moderate quality in studies assessing "best supportive care"
- Assess people with idiopathic pulmonary fibrosis for pulmonary rehabilitation at the time of diagnosis, including 6-minute walk test and a quality-of-life assessment. - Repeat the assessment for pulmonary rehabilitation for people with idiopathic pulmonary fibrosis at 6-month or 12-month intervals. - If appropriate after each assessment, **offer** pulmonary rehabilitation including exercise and educational components tailored to the needs of people with idiopathic pulmonary fibrosis in general. - Pulmonary rehabilitation **should** be tailored to the individual needs of each person with idiopathic pulmonary fibrosis. Sessions should be held somewhere that is easy for people with idiopathic pulmonary fibrosis to get to and has good access for people with disabilities.	The GDG considered patient access to pulmonary rehabilitation programmes to be important. Studies in QoL with moderate to very low quality. Conflicting findings.

Raghu G, Remy-Jardin M, Myers JL, et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. 2018

Recommendation	Level of evidence
Recommendations only about exclusion of differential diagnoses and confirming the diagnosis by performing BAL or biopsy	

Ganesh Raghu et al, An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis An Update of the 2011 Clinical Practice Guideline, 2015

Recommendation	Level of evidence
Recommendations only about treatment IPF	

Ganesh Raghu et al, An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management, 2011

Recommendation[4]	Level of evidence[5]
We recommend that a multi-disciplinary discussion should be used in the evaluation of IPF (**strong recommendation**)	⊕⊕⊖⊖

The recommendation **for** pulmonary rehabilitation in patients with IPF is **weak**; that is, pulmonary rehabilitation should be used in the majority of patients with IPF, but not using pulmonary rehabilitation may be a reasonable choice in a minority	⊕⊕⊖⊖

Cottin V et al. French practical guidelines for the diagnosis and management of idiopathic pulmonary fibrosis - 2017 update, 2017	
Recommendation[6]	**Level of evidence**
- It is **recommended** to integrate all the data available for the definitive diagnosis of IPF during a multidisciplinary discussion involving pulmonologists, radiologists and pathologists experienced in the field of ILD. - It is **recommended** to refer difficult cases, depending on their proximity, to the Reference Center or a regional Expertise Center.	Strength of the evidence n.a.
- It is **recommended** to carry out annual influenza vaccination and pneumococcal vaccination in patients with a confirmed diagnosis of IPF. - It is **proposed** to prescribe a respiratory rehabilitation program to patients with a confirmed diagnosis of IPF and with a limited exercise capacity with a significant disability.	Strength of the evidence n.a.
It is **recommended** to advise patients to quit smoking if they are smokers and to inform them about the smoking cessation support services.	Strength of the evidence n.a.

Jo HE, et al. Treatment of idiopathic pulmonary fibrosis in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Lung Foundation Australia, 2017	
Recommendation	**Level of evidence**
Patients with IPF can be successfully managed in existing pulmonary rehabilitation programs and early referral to pulmonary rehabilitation is encouraged.	Strength of the evidence n.a.

Step 3: Literature search

Strategy for re-search for IGHG on pulmonary dysfunction in PubMed, including studies between January 1st 2018 and February 28th 2019

Search	Add to builder	Query	Items found	Time
#43	Add	Search **(#41 AND #42)**	154	04:08:11
#42	Add	Search **("2018/01/01"[Date - Publication] : "2019/02/28"[Date - Publication])**	1522089	04:07:46
#41	Add	Search **(#39 NOT #40)**	4229	04:05:34
#40	Add	Search **(animals[mh] NOT humans[mh])**	4553519	04:04:22
#39	Add	Search **(#37 OR #38)**	4256	04:03:28
#38	Add	Search **(#21 AND #27 AND #32 AND #35)**	157	04:02:53
#37	Add	Search **(#21 AND #26 AND #32 AND #35)**	4110	04:00:17
#36	Add	Search **(#21 AND #26 AND # 32 AND #35)**	2467	03:59:50
#35	Add	Search **(#33 OR #34)**	1508069	03:56:05
#34	Add	Search **("late effect" OR "late effects" OR "late effect*" OR "late side effect" OR "late side effects" OR "late side effect*" OR "late adverse effect" OR "late adverse effects" OR "late adverse effect*" OR long term effect[tiab] OR long term effect* OR long term adverse effects[mh] OR follow up studie* OR follow up study OR aftercare [mh] OR aftercare* OR after treatment [tiab])**	1373864	03:55:30
#33	Add	Search **(Survivor OR survivors OR survivor* OR long term survivor OR long term survivors OR long term survivor* OR survivo* OR surviving OR long term survival[tiab] OR survival[mh])**	180625	03:55:03
#32	Add	Search **(#28 OR #29 OR #30 OR #31)**	2254984	03:52:59
#31	Add	Search **(respiratory function tests[mh] OR (function test AND (lung OR pulmonary OR respiratory)) OR spirometry OR bronchospasmolysis OR plethysmography OR DLCO OR diffusion capacity OR breath washout OR pulsoxymetry OR therapeutic irrigation[mh] OR broncho alveolar lavage[tiab] OR bronchoscopy OR blood gas analysis OR FEV1 OR forced expiratory volume OR LCI OR lung clearance index OR TLC OR total lung capacity OR FVC OR forced vital capacity OR PEF OR peak expiratory flow OR forced expiratory flow OR FEF OR maximum expiratory flow OR MEF OR KCO OR diffusion capacity OR maximal inspiratory pressure OR maximal expiratory pressure OR respiratory muscle pressure OR ((HR-CT OR MRI OR X-ray OR Biopsy OR lavage) AND (lung OR pulmonary OR chest OR thorax)) OR (transfer factor AND lung))**	858054	03:51:23
#30	Add	Search **(dyspnea OR cough OR mucus OR sputum OR hypoxia OR oygen requirement[tiab] OR exercise intolerance[tiab] OR respiratory sounds[mh] OR wheeze OR wheeze* OR breathlessness[tiab] OR shortness of breath OR chest pain OR chest discomfort[tiab] OR snore OR snoring OR hemoptysis OR oxygen requirement)**	407445	03:50:42
#29	Add	Search **(((Pulmonary OR respiratory) AND dysfunction) OR lung diseases, obstructive[mh] OR obstructive lung disease[tiab] OR restrictive lung disease[tiab] OR gas exchange impairment[tiab] OR ((ventilation OR respiration) AND (inhomogeneity OR inhomogeneous OR mismatch)) OR impaired diffusion capacity OR diffusion capacity impairment)**	381598	03:50:15

#28	Add	Search **(Pulmonary Fibrosis OR lung fibrosis OR (scarring AND (lung OR lungs*)) OR interstitial lung disease OR acute respiratory distress syndrome[tiab] OR ARDS OR respiratory distress syndrome OR shock lung[tiab] OR pneumonia OR COP[tiab] OR pneumonitis[tiab] OR pulmonitis[tiab] OR (lung AND (cancer OR carcinoma OR tumor)) OR lung neoplasms[mh] OR (lung AND (infection OR disease)) OR lung diseases[mh] OR (chest wall AND (abnormalit* OR disease)) OR kyphoscoliosis OR fibrothorax OR bronchitis OR bronchiectasis OR emphysema OR fibroelastosis OR Bronchiolitis OR BOS[tiab] OR BOOP OR cryptogenic organizing pneumonia[mh] OR cryptogenic organizing pneumonia[tiab] OR pulmonary disease OR pulmonary disease, chronic obstructive[mh] OR COPD OR pulmonary complications OR OSA OR respiratory tract diseases[mh] OR respiratory disease* OR low infectious respiratory disease OR respiratory defect OR apnea OR asthma)**	1700498	03:49:20
#27	Add	Search **(tobacco OR nicotine OR cigarette OR e-cigarette OR cigar OR pipe OR environmental tobacco smoke OR second hand smoke OR ETS OR waterpipe OR narghile OR arghile OR shisha OR hookah OR marijuana OR joint OR MJ[tiab] OR spice OR thc OR cannabis) AND (smoking OR smoke OR smoke*)**	119390	03:48:30
#26	Add	Search **(#22 OR #23 OR #24 OR #25)**	2020213	03:46:31
#25	Add	Search **(pulmonary metastasectomy OR pulmonary lobectomy OR thoracotomy OR sternotomy OR thoracoscopy OR rib resection[tiab] OR spinal surgery OR spinal fusion OR (resection AND (pulmonary wedge OR lung OR claviculae OR scapulae OR muscle tissue on thorax)))**	210174	03:45:35
#24	Add	Search **(Stem cell transplant[mh] OR stem-cell transplant OR stem cell transplant* OR stem cell transplantation OR bone marrow transplantation[mh] OR transplantation, conditioning[mh] OR hematopoetic stem cell transplantation[mh] OR reduced-intensity conditioning regimen OR myeloablative agonists[mh])**	155106	03:45:00
#23	Add	Search **((Radiotherapy OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation injuries OR injuries, radiation OR injury, radiation OR radiation injury OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation OR radiation* OR irradiation OR radiations) AND (TBI OR total body OR whole body OR total body* OR body whole* OR chest OR lung OR axilla OR mediastinal OR mantle OR supraclavicular OR susclavicular OR cranial axis OR total axis OR supra diaphragm[tiab] OR abdominal OR Inverted Y[tiab] OR Left Flank OR Hemiabdomen OR Left upper quadrant OR Paraaortic OR Spleen OR craniospinal))**	129702	03:44:30
#22	Add	Search **(Antineoplastic Protocols OR Antineoplastic Combined Chemotherapy Protocols OR Chemoradiotherapy OR Chemoradiotherapy, Adjuvant OR Chemotherapy, Adjuvant OR Consolidation Chemotherapy OR Induction chemotherapy OR Maintenance chemotherapy OR Chemotherapy, Cancer, Regional Perfusion OR Antineoplastic agents OR chemotherap* OR busulphan OR busulfan* OR Carmustine OR BCNU OR Chlorambucil OR cyclophosphamide OR cyclophosphane OR cytophosphan OR endox* OR cyclophospha* OR Lomustine OR CCNU OR lomustine* OR Mechlorethamine OR mechlorethamine* OR Chlormethine OR Mustine OR Chlorethazine OR doxorubicin OR doxorubic* OR bleomycin OR dactinomycin OR gemcitabine OR irinotecan OR methotrexate OR topotecan OR tacrolimus OR immunotherapy)**	1642658	03:43:10
#21	Add	Search **(#19 AND #20)**	577270	03:42:22

#20	Add	Search **(Infan* OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR young adult[mh] OR young adult)**	5112271	03:41:56
#19	Add	Search **((leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR sarcoma, Ewing's OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom*) OR (pediatric oncology OR paediatric oncology) OR (childhood cancer OR childhood tumor OR childhood tumors) OR (brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm*) OR (leukemia, lymphocytic, acute) OR (leukemia, lymphocytic, acute*))**	1793356	03:41:13

Step 4: IGHG Pulmonary Dysfunction - Example of an extraction table

PICO question: 5, 9a, 12
Main findings:
5. In univariate analysis no significant association between bleomycin exposure and restrictive disease (OR 0.7, 95%CI 0.3-1.6) and DLco abnormalities (OR 0.8, 95%CI 0.4-1.7)
6. In univariate analysis no significant association between busulfan exposure and restrictive disease (OR 0.8, 95%CI 0.2-2.9) and DLco abnormalities (OR 0.4, 95%CI 0.1-1.6)
7/8. In univariate analysis no significant association between CCNU or BCNU exposure and restrictive disease (OR 1.1, 95%CI 0.3-4.2) and DLco abnormalities (OR 1.4, 95%CI 0.6-4.7)
9a. In multivariable analysis significant association between increasing doses of chest radiation and restrictive disease (20 Gy: OR 5.6 (95%CI 1.5-21.0), p<0.05). Significant association between increasing doses of chest radiation and DLCO abnormality (≤20 Gy: OR 6.4 (95%CI 1.7-24.4), p<0.01; 20 Gy: OR 11.3 (95%CI 2.6-49.5). p<0.01). Increasing chest radiation doses are significant predictors of decline in DLco longitudinally (20 Gy: OR 24.4 (95%CI 5.7-38.3), p<0.01).
12. In univariate analysis no significant association between history of smoking and restrictive disease (OR 0.9, 95%CI 0.7-1.9) and DLco abnormalities (OR 0.9, 95%CI 0.2-5.3)

4027. S. H. Armenian, et al. Long-term pulmonary function in survivors of childhood cancer. 2015;33:1592-600. 10.1200/jco.2014.59.8318

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment** (= treatment analyzed in the paper)	**Main outcomes**	**Additional remarks**
☒ **Cohort** ☐ **Cross-sectional** ☐ **Case-control** ☐ **Other:** _____ ☐ **Retrospective** ☒ **Prospective**	Study population (N) ➢ Original cohort: ? ➢ Eligible cohort: 155 Analysed cohort: 121	☐ 1 **HSCT a, b** ☐ **2 Cyclophosphamid** ☐ **3 Methotrexate** ☐ **4 Gemcitabine** ☒ **5 Bleomycin** ☒ **6 Busulfan** ☒ **7 Lomustin (CCNU)** ☒ **8 Carmustin (BCNU)** ☒ **9 Radiotherapy lung, 9a** ☐ **10 Surgery** ☐ **11 Combinations** ☒ **12 Tobacco exposure**	☐ **Pulmonary diseases** ☐ **Pulmonary symptoms** ☒ **Pulmonary function test** ☐ **Absolute values** ☐ **Z-scores** ☒ **Percentage predicted** ☐ **Percentage pathological tests** (e.g. 24% with reduced FEV1)	☒ **Longitudinal data available** ☒ **Control group mentioned** ☐ **Reference values stated** **Not stated**_____ ☐ **Quality check performed** ☒ **Lung function procedure stated** ☐ **Cleaning of lung function data described** ☒ **Person who analyzed PFT was blinded to the exposure**
Centres: Single center, City of Hope Survivorship Clinic Country: USA Treatment era: 1972-2007 Years of Follow-up: Time dx to t2: 17.1 yrs (range 6.3-40.1 yrs)	Study population: Eligible at t1 (N): 155 Analysis at t2 (N): 121 Response rate=78.1% Controls: General population, age- and sex-matched Inclusion criteria: Survivors diagnosed <age 22, with ≥2 yrs post diagnosis, treated with pulmonary-toxic chemotherapy and/or	Chemotherapy (median doses) and %any Bleomycin (60 IU/m2), 35% Busulfan (436 mg/m2), 12% BCNU/CCNU (450 mg/m2), 10% Radiotherapy(median doses, range) chest (13.2 Gy, 2-76): 26% no radiotherapy 50% ≤20 Gy 24% >20 Gy Surgery	Pulmonary function assessment: - PFT at baseline (t1) and at follow-up (t2) - Compared with healthy controls (at t2) - PFTs performed according to ATS protocols - PFT parameters measured: TLC, FVC, FEV1, FEV1/FVC, DLco, DLco/Va - %-predicted calculated by using established reference values (reference not stated) - cut-offs: obstructive FEV1/FVC<0.7, FEV1<80% predicted; restrictive TLC<75%, FEV1≥80% predicted diffusion DLco<75% predicted	**Analysis:** - Cross-sectional and longitudinal analysis - Univariable logistic regression - Multivariable logistic regression, adjusted for , adjusted for race, health insurance status, smoking, heart failure Limitations: - Single center - Data collection not clearly prospective/retrospective - Selection bias – only survivors at follow-up at a tertiary center

Time t1 to t2: median of 5 yrs (1-10.3 yrs)	radiation and/or allogeneic HCT with cGVHD or pulmonary and/or surgery <u>Cancer diagnoses:</u> HL 34% NHL 6% Leukemia 36% Sarcoma 11% Other 14% (not specified) <u>Age at diagnosis (yrs):</u> Median (range): 16.5 (0.2-21.9) <u>Age at follow-up (t2) (yrs):</u> Median (range): 32.2 (14.6-58.9)	6% lobectomy, wedge resection or metastasectomy <u>HSCT (53%)</u> Autologous 17% Allogeneic 36%	**Comparison survivors – survivors with risk factor analysis** (univariable analysis, if sig -> multivariable regression analysis) **<u>Bleomycin</u>**: - no significant association between bleomycin exposure and restrictive disease: univariable OR 0.7, 95%CI 0.3-1.6 - no significant association between bleomycin exposure and DLCO abnormality: univariable OR 0.8, 95%CI 0.4-1.7 (no multivariable anaylsis performed because not significant!) **<u>Busulfan</u>**: - no significant association between busulfan exposure and restrictive disease: univariable OR 0.8, 95%CI 0.2-2.9 - no significant association between busulfan exposure and DLCO abnormality: univariable OR 0.4, 95%CI 0.1-1.6 (no multivariable anaylsis performed because not significant!) **<u>BCNU or CCNU</u>**: - no significant association between BCNU or CCNU exposure and restrictive disease: univariable OR 1.1, 95%CI 0.3-4.2 - no significant association between BCNU or CCNU exposure and DLCO abnormality: univariable OR 1.4, 95%CI 0.6-4.7 (no multivariable anaylsis performed because not significant!) **<u>Smoking</u>** - no significant association between smoking history and restrictive disease: univariable OR 0.9, 95%CI 0.7-1.9 - no significant association between smoking history and DLCO abnormality: univariable OR 0.9, 95%CI 0.2-5.3 (no multivariable anaylsis performed because not significant!)	- No lung function quality checks reported, no missing values reported - Healthy control group not well characterized - No baseline PFT before cancer treatment/pulmotoxic treatment - Time between t1 and t2 highly variable <u>Strength:</u> - Longitudinal PFT assessment - PFT assessment blinded to exposure

			<u>Chest radiation</u>: - significant association (multivariable) between increasing doses of chest radiation and restrictive disease: - ≤20 Gy: OR 1.6 (95%CI 0.5-5.7), not sign. - >20 Gy: OR 5.6 (95%CI 1.5-21.0), p<0.05 - significant association (multivariable) between increasing doses of chest radiation and DLCO abnormality: - ≤20 Gy: OR 6.4 (95%CI 1.7-24.4), p<0.01 - >20 Gy: OR 11.3 (95%CI 2.6-49.5). p<0.01 **Longitudinal comparison t1 – t2 for DLco:** - t1: 89 normal DLco patients - t2: 23/89 (25.8%) abnormal DLco test -> predictors for decline in DLco: - ≤20 Gy: OR 6.4 (95%CI not stated), not sign. - >20 Gy: OR 24.4 (95%CI 5.7-38.3), p<0.01	

IGHG Pulmonary Dysfunction - Example of "summary of findings table" for radiotherapy to the lung and obstructive disease as pulmonary outcome

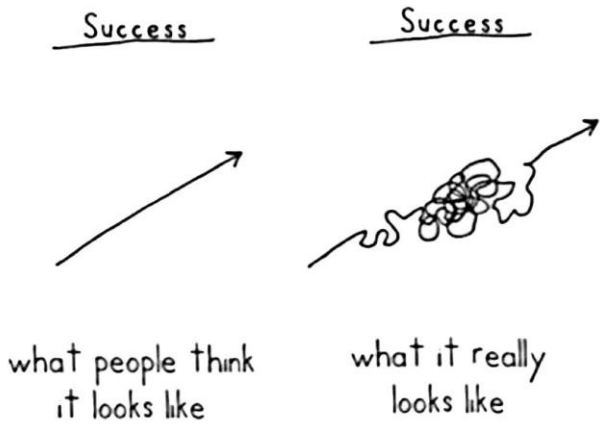
PICO	Study	No. of participants	Follow-up (median/mean, range) yr	Radiotherapy exposing lung tissue	Pulmonary function Outcomes	Effect size	PFT quality	Risk of bias
8 What is the risk of <u>obstructive</u> abnormalities in CAYA treated with radiotherapy exposing lung tissue compared to CAYA not treated with radiotherapy exposing lung tissue?	Oguz 2007	75 Lymphoma survivors	Median 5 (2-13)	Group 1: Chemo and Radio (n=23) Group 2: Chemo only (n=52)	Mean (±SD) of selected % predicted values **FEV1** Group 1: 95.43 (± 16.47) Group 2: 105.09 (± 19.01) **FEV1/FVC** Group 1: 96.43 (± 9.15) Group 2: 99.88 (± 11.93)	Comparison Group I vs Group II (student t-test) p=0.038 p=0.221	1. No 2. Yes: References recommended by European Coal and Steel Community; Severity acc. to ATS pulmonary function laboratory guidelines 3. No 4. No 5. No 6. No	Retrospective cross-sectional SB unclear AB: low risk DB: unclear CF: unclear
	Jenney 1995	70 Leukemia survivors	Median 4.2 (0.6-18.5)	14% (CSI, n=10) 20% (TBI, n=14)	Number of CCS with respective parameter below predicted values 36/69 FEV1 <85% predicted 23/69 FEV1 <80% predicted	Multivariable analysis, CSI (yes/no) leads to reduction in FEV1: p<0.001	1. Yes 2. No 3. No 4. No 5. No 6. No	Prospective cross-sectional SB: high risk AB: low risk DB: unclear CF: unclear
	Record 2016	143 CCS	Mean 14.1 ±4.8	67.8% (n=97)	Obstructive (FVC, FEV1, FEV1/FVC <80% predicted or FEF25–75% <68%) 25% (24/97)radiotherapy 28% (13/46) no radiotherapy	Univariable comparison Chi2 radiation yes/no p=0.66	1. No 2. Yes: Wang X, Pediatr Pulmonol 2005; Hankinson JL, Am J Respir Crit Care Med 1999 3. No 4. Yes 5. No 6. Yes	Retrospective cohort SB: high risk AB: low risk DB: low risk CF: high risk

GRADE assessment:		
Study design:	+4	1 retrospective cohort study, 1 retrospective cross-sectional study, 1 prospective cross-sectional study
Study limitations:	-2	Some limitations: Selection bias high in 2/3, unclear in 1/3; Attrition bias low in 3/3; Detection bias low in 1/3, unclear in 2/3; Confounding high in 1/2,unclear in 2/3
Consistency:	-1	No important inconsistency. Two studies show significant effect of radiotherapy exposing lung tissue on FEV1, no significant association for FEV1/FVC and a non-significant inverse effect on "obstructive", where non-exposed CAYA cancer survivors show more often obstructive abnormalities than exposed
Directness:	-1	Population and outcomes broadly generalizable, PFT quality unsure (reference mentioned in 2/3, lung function procedure mentioned in 0/3)
Precision:	-1	Important imprecision, precision cannot be judged as 3/3 report p-values only, 1/3 performed multivariable analysis
Publication bias:	0	Unlikely
Effect size:	0	No large magnitude of effect
Dose-response:	0	Not applicable
Plausible confounding:	0	No plausible confounding
Quality of evidence:	⊕⊖⊖⊖ Very low	
Conclusion:	Increased risk for obstructive abnormalities (FEV1) after radiotherapy exposing the lung tissue vs. no radiotherapy in CAYA cancer survivors. (3 studies; 2 studies significant effect [FEV1], 1 study non-significant effect ["obstructive]; 288 participants; 144 exposed to radiotherapy exposing lung tissue)	
Comment:	All studies report their results as p-values only. Outcome assessed differently (FEV1, "obstructive") and cutoff values differ between studies.	

Appendix E - Acknowledgements

This PhD has opened my eyes in many ways. In this section I would like to thank a few important people for that.

But first I have to share what a PhD journey can feel like, which also explains why some people become especially important in this phase. Even though I did not expect that doing a PhD would be a straight way, as shown on the left side of the cartoon, it was nevertheless sometime even more turbulent than on the right side. I was told that these turbulent periods can be part of research and most importantly, I have also grown in these challenging situations.



I would like to thank Claudia Kuehni, my supervisor, for giving me the opportunity to do this PhD and the guidance through these three years. I am especially thankful for her critical and valuable feedbacks for research ideas, approaches for analyses, manuscripts, and most importantly for the way of "epidemiological thinking".

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When I extend my thanks geographically and leave Bern, I thank all the data manager at the nine SPOG centers who supported me with the data collection. A special thank goes to the pediatric oncologists and transplant specialists who read through the manuscripts critically and provided valuable feedback: Tayfun Güngör, Marc Ansari, Katrin Scheinemann, and Nicolas von der Weid. In addition, I thank all SPOG heads for their critical feedback to the SCCSS-FollwoUp study protocol and DTUA. Similarly, I also thank the pediatric pneumologist Sophie Yammine and the pediatric pulmonology fellow Jakob Usemann.

Some projects and persons I met outside of the official "PhD topic" were very important and supported me in the last three years. First, this is the whole Life After Childhood Cancer (LACC) study group at the Kantonsspital Aarau. I always liked the taste of "hospital air" once per week and working clinically in follow-up care. Second, these are all board members of Young SIOPE, the members of the SIOPE office, and Gilles Vassal, who initiated the Essential Medicines Project, and all participating members.

And last, but most importantly, I thank my wife, my mother and sisters who supported me through this turbulent time and were very supportive.

Appendix F - Curriculum vitae and list of publications

Curriculum vitae

Maria Otth

Working address	University of Bern Institute of Social and Preventive Medicine (ISPM) Mittelstrasse 43 CH – 3012 Bern phone: 0041 31 631 39 75 email: maria.otth@ispm.unibe.ch
Date of birth	15.06.1985
Nationality	Switzerland

Education

Degrees

2017	Board certification in General Pediatrics (FMH), Switzerland
2011	Doctoral thesis "Organ donation in Switzerland: a survey on marginal or extended criteria donors (ECD) from 1998 to 2009", University of Berne, Switzerland
2004-2010	Medical school, Berne, Switzerland

Professional Career

Clinical education

Since 01/2019	Research associate and staff physician Pediatric Oncology-Hematology, Kantonsspital Aarau
Since 01/2018	PhD candidate at ISPM, University of Bern
01/2017 – 12/2017	Fellow Pediatric Hematology/ Oncology, Children's Hospital Zurich, Switzerland
04/2014 – 12/2016	Resident General Pediatrics, Children's Hospital Lucerne, Switzerland
04/2013 – 03/2014	Resident General Pediatrics, Children's Hospital Wildermeth, Biel/Bienne, Switzerland
11/2012 - 03/2013	Resident Internal Medicine, Hospital STS AG, Zweisimmen, Switzerland
11/2011 - 10/2012	Resident Surgery, Hospital STS AG, Zweisimmen, Switzerland
11/2010 - 10/2011	Resident Internal Medicine, Hospital STS AG, Zweisimmen, Switzerland

Courses relevant for pediatric oncology

11/2020	SIOPE Neuro-oncology course (virtual)
01/2017	German School of Pediatric Oncology and Hematology III (GsoPOH), Oberstdorf, Germany
03/2016	Course in developmental pediatrics, Childrens Hospital, Zurich, Switzerland
01/2016	German School of Pediatric Oncology and Hematology II (GsoPOH), Oberstdorf, Germany
12/2015	Good Clinical Practice (Modul 1 and 2), Clinical Trial Center, University Hospital Zurich, Switzerland
11/2015	20th Course for clinical hemostaseology, Giessen, Germany

10/2015	5th Symposium for integrative oncology and research, focus on integrative pediatric oncology, Hospital St. Gallen, Switzerland
10/2015	Pediatric Update Refresher, Zurich, Switzerland
10/2014	Pediatric Update Refresher, Interlaken, Switzerland
02/2014	Basic in pediatric sonography, Blaubeuren, Germany
11/2013	SGDV Course in pediatric dermatology, University Hospital Basel, Switzerland
02/2013	PALS, University Hospital Basel, Switzerland

Courses relevant to perform science

08/2017	Introduction to Probability and Data (an online non-credit course authorized By Duke University and offered through Coursera)
02/2017	Understanding Clinical Research: Behind the Statistics, Coursera (an online non-credit course authorized by University of Cape Town and offered through Coursera)
01-03/2018	Course Biostatistics II, Prof. M. Zwahlen, ISPM, University of Bern
06/2018	Project Management for Researchers, Dr. Dimitrije Krstic, University of Bern
09/2018	Using DAGs for Causal Inference, Dr. J. Textor, University of Lucern
11/2018	Fundamental Concepts in Epidemiology, Prof. A. Hofman, University of Bern
11-12/2018	An introduction to systematic reviewing: From literature search to meta-analysis, University of Basel
01/2019	Statistical analysis with missing data using multiple imputation and inverse probability weighting, Prof. J. Carpenter, Swiss Epidemiology Winter School, University of Bern
01/2019	Causal Inference in Observational Epidemiology, Prof. M. Hernan, Swiss Epidemiology Winter School, University of Bern
03/2019	Applied logistic regression, Prof. S. Lemeshow, University of Bern
03/2019	Writing a journal article and getting it published, Prof. Dr. C, Kühni, University of Bern
11/2019	Qualität und Sicherheit im Gesundheitswesen, Prof. Dr. D. Schwappach, University of Bern
01/2020	Tools to Assess RIsk of Bias in Randomized and Non-Randomized Studies: Cochrane ROB2 and ROBINS-I, Prof. Jonathan Sterne, Prof. Julian Higgins; Swiss Epidemiology Winter School, University of Bern
02/2020	Soziokulturelle Kontexte, Migration und gesundheitliche Chancengleichheit, Prof. T. Abel, Universit of Bern
08/2020	Policy Options on Mental Health; Prof. E. Albanese, Prof. B. Saraceno, Dr. M. Fada, Dr. D. Krupchanka; SSPH+ Lugano Summer School
08/2020	Multisectorial Approaches for Health: Implications for Policy and Practice; Prof. C. Williams, N. Valentine; SSPH+ Lugano Summer School

Publications (ORCID: 0000-0002-2839-502X)

Peer reviewed

1. **Otth M**, Greiner-Lang J, Scheinemann K; Médecine intégrative en oncologie pédiatrique (Integrative medicine in pediatric oncology); Rev Med Suisse. 2020 Nov 25;16(716):2293-2296
2. **Otth M**, Schindera C, Güngör T, Ansari M, Scheinemann K, Belle FN, Latzin P, von der Weid N, Kuehni CE; Transplant characteristics and self-reported pulmonary outcomes in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a cohort study; Bone Marrow Transplant 2020 Nov 25. doi: 10.1038/s41409-020-01137-1

3. Visscher H, **Otth M**, Feijen EAM, Nathan PC, Kuehni CE; Cardiovascular and pulmonary challenges after treatment for Childhood Cancer; Pediatr Clin North Am. 2020 Dec;67(6):1155-1170. doi: 10.1016/j.pcl.2020.07.007
4. **Otth M***, Denzler S*, Koenig C, Koehler H, Scheinemann K; Transition from pediatric to adult follow-up care in childhood cancer survivors – a systematic review; J Cancer Surviv 2020 Jul 16. doi: 10.1007/s11764-020-00920-9
5. Denzler S*, **Otth M***, Scheinemann K; Aftercare of Childhood Cancer Survivors in Switzerland – the ACCS Switzerland Project: Protocol for a Prospective Multicenter Observational Study; JMIR Res Protoc 2020 Aug 26;9(8):e18898. doi: 10.2196/18898
6. **Otth M**, Denzler S, Schmid S, Setz B, Scheinemann K; Perception of inpatient oncologic rehabilitation in children, adolescents and young adults diagnosed with cancer in Switzerland; Klin Padiatr 2020; 232: 1–6. DOI https://doi.org/10.1055/a-1210-2599
7. Ardura-Garcia C, Mouzon R, Pedersen E, **Otth M**, Mallet M, Goutaki M, Kuehni CE; Paediatric cohort studies on lower respiratory diseases and their reporting quality: systematic review of the year 2018; Eur Respir J; 2020 May 26; 2000168. doi: 10.1183/13993003.00168-2020.
8. Belle F, Beck Popovic M, Ansari M, **Otth M**, Kuehni CE, Bochud M; Nutritional Assessment of Childhood Cancer Survivors (the Swiss Childhood Cancer Survivor Study-Nutrition): Protocol for a Multicenter Observational Study; JMIR Res Protoc. 2019 Nov 18;8(11):e14427. doi: 10.2196/14427.
9. Schindera C, Weiss A, Hagenbuch N, **Otth M**, Diesch T, von der Weid N, Kuehni CE; Physical activity and screen time in children who survived cancer – A report from the Swiss Childhood Cancer Survivor Study; Pediatr Blood cancer. 2020 Feb; 67(2):e28046. doi: 10.1002/pbc.28046. Epub 2019 Nov 20.
10. **Otth M**, Scheinemann K; Surveillance imaging for high-grade childhood brain tumors: what to do ten years after completion of treatment?; Pediatr Blood Cancer. 2018 Nov;65(11):e27311. doi: 10.1002/pbc.27311. Epub 2018 Jul 15
11. **Otth M**, Rödder S, Immer FF, Marti HP; Organ donation in Switzerland: a survey on marginal or extended criteria donors (ECD) from 1998 to 2009; Swiss Med Wkly. 2011;141:w13230

Not peer reviewed

1. **Otth M**, Pfeiffer V, Kuehni CE, Scheinemann K; Kinderkrebs in der Schweiz; Paediatrica; Vol 31-1/2020
2. Denzler S, **Otth M**, Scheinemann K; Spätfolgen und Langzeit-Nachsorge nach einer Krebserkrankung im Kindes- und Jugendalter; Paediatrica; Vol 31-1/2020
3. **Otth M**, Denzler S, Merki R, Janthur WD, Janz I, Klein-Franke A, Wechsler P, Scheinemann K; Childhood Cancer Suvivors: Transition into Adulthood; Swiss Cancer Bulletin; Issue 01/2019

Submitted

1. **Otth M**, Wechsler P, Denzler S, Koehler H, Scheinemann K; Determining transition readiness in Swiss childhood cancer survivors – a feasibility study; BMC Cancer

Ongoing research projects Bern

1. International Guideline Harmonization Group (IGHG) – Recommendations for pulmonary guidelines; function as co-coordinator
2. Pulmonary function in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a retrospective study
3. Lung function in Swiss childhood cancer survivors– a retrospective study

Ongoing research projects Aarau (LACC study group)

1. Aftercare of Childhood Cancer Survivors in Switzerland –a Prospective Multicenter Observational Study
2. Educational attainment in Swiss childhood cancer survivors treated for central nervous system tumors
3. "Young Survivors at KSA" Registry – A Standardized Assessment of Long-Term and Late-Onset Health Events in Survivors of Childhood and Adolescent Cancer

Fundraising

1. Back to school after childhood cancer; **Otth M** (PI), Scheinemann K (Co-PI); Forschungsprojekt 1410.000.135 KSA 2020; CHF 7'000
2. Pulmonary function in long-term childhood cancer survivors after hematopoietic stem cell transplantation; **Otth M** (PI), Kuehni C (Co-PI), Latzin P (Co-PI); Lungenliga Bern 2020; CHF 33'570
3. Young Survivors at KSA – a cohort study to assess chronic late effects following childhood cancer; Scheinemann K (PI), **Otth M** (Co-PI), Denzler S (Co-PI); Forschungsprojekt 1410.000.113 KSA 2020 – 2021; CHF 57'717.00
4. Aftercare of childhood cancer survivors in Switzerland – the ACCS Switzerland project; Scheinemann K (PI), Diesch T (Co-PI), Eisenreich B (Co-PI), **Otth M** (Co-PI); Grant HSR-4359-11-2017, Krebsforschung Schweiz 01.07.2018 – 30.06.2021; CHF 183'100

Presentations

Poster

1. **Otth M**, Schoot R, Brack E, Ocokoljic M, Kozhaeva O, Vassal G, and the Essential Medicines Group. «The SIOPE Essential Anticancer Medicines Project - Creating an evidence based list of essential anticancer medicines to treat childhood cancer in Europe». SIOP Congress. October 2020.
2. **Otth M**, Schindera C, Güngör T, Ansari M, Belle FN, Scheinemann K, Latzin P, Kuehni CE. «Pulmonary late effects in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a report from the Swiss Childhood Cancer Survivor Study». Swiss Public Health Conference, Winterthur. August 2019
3. **Otth M**, Schindera C, Güngör T, Ansari M, Belle F, Scheinemann K, Latzin P, Kuehni C. «Pulmonary late effects in Swiss childhood cancer survivors after hematopoietic stem cell transplantation – a report from the Swiss Childhood Cancer Survivor Study». North American Symposium on Late Complications After Childhood Cancer (NSALCCC), Atlanta, USA. June 2019
4. Scheinemann K, **Otth M** , Duckworth J, Stein NR, Whitton A, Greenspoon J, Singh S. "Radiation necrosis in children – an underreported problem?!" ?" International Society of Pediatric Oncology: 47th Congress, Cape Town, South Africa. October 2015.
5. Scheinemann K, **Otth M**, Duckworth J, Stein NR, Singh S. "Early post-operative MRI following a resection of a pediatric brain tumor – what is the right timepoint?" International Society of Pediatric Oncology: 47th Congress, Cape Town, South Africa. October 2015
6. **Otth M**, Hartmann K, Rischewski J, Dirnhofer S, Klapper W, Scheinemann K. Generalized lymphadenopathy and B- symptoms – it's not always cancer" Swiss Pediatric Society, Interlaken, Switzerland, June 2015
7. Gut – Eberle D, **Otth M**, Rischewski J, Hartmann K, Schmitt – Mechelke T, Berger T, Hürlimann S, Gähler A, Scheinemann K. „Status asthmaticus – not always what it looks like" Swiss Pediatric Society congress, Interlaken, Switzerland, June 2015

Oral presentations

Local

1. Case presentation Children's Hospital Zurich, Switzerland, 03/2017
2. Cardiotoxicity in pediatric oncology, Children's Hospital Lucerne, Switzerland, 04/2016
3. Aftercare in Pediatric Oncology, Children's Hospital Lucerne, Switzerland, 06/2016
4. Bone density in long-term survivors of Cancer in Childhood, Children's Hospital Lucerne, Switzerland, 01/2016
5. Tumor predisposition syndrome, Children's Hospital Lucerne, Switzerland, 03/2016
6. Emergencies in Pediatric Oncology, Children's Hospital Lucerne, Switzerland, 01/2015
7. Brain tumors in childhood, Children's Hospital Lucerne, Switzerland, 01/2015

National

1. Educational achievement in childhood cancer survivors treated for a tumor of the central nervous system, SPOG meeting, Lugano, Switzerland, 01/2020
2. Pulmonary disease in childhood cancer survivors after hematopoietic stem cell transplantation, SPOG meeting, Lugano, Switzerland, 01/2019
3. Pulmonary late effects in childhood cancer survivors after HSCT, Annual meeting Swiss Society of Pneumology, Montreux, Switzerland, 05/2019
4. Pulmonary dysfunction after childhood cancer: diagnosing early stage disease, SPOG meeting, Lugano, Switzerland, 01/2018

International

1. Pulmonary disease in childhood cancer survivors after hematopoietic stem cell transplantation, PanCare meeting, Basel, 11/2019
2. Perception of inpatient oncologic rehabilitation in children, adolescents and young adults diagnosed with cancer in Switzerland, PanCare meeting, Basel, 11/2019
3. Pediatric Palliative Care in Switzerland GSoPOH, Oberstdorf, Germany, 01/2017
4. Offspring in female CCS in Switzerland, PanCare meeting, Lübeck, 10/2017
5. Follow up after brain tumors, GSoPOH, Oberstdorf, Germany, 01/2016

Invited speech

1. "Good or bad – How to read an epidemiological paper", Hematology-Oncology-Weekend, Children's Hospital Zurich, Switzerland, 03/2019
2. Pulmonary late effects in childhood cancer survivors, Cancer Survivorship, University Cancer Center Inselspital, 05/2019
3. "Follow-up after childhood cancer", Hematology-Oncology-Weekend, Children's Hospital Zurich, Switzerland, 03/2018

Professional organizations

- Member of SIOP Europe, since 2020
- Board member of Young SIOPE, since May 2019
- Member of Young SIOPE (European Society for Paediatric Oncology), since July 2018
- Member of PanCare (Pan-European Network for Care of Survivors after Childhood and Adolescent Cancer), since 2018
- Member of the International Guideline Harmonisation Group (IGHG) - Pulmonary Dysfunction, since February 2018
- Member of the International Guideline Harmonisation Group (IGHG) – Metabolic Syndrome, since May 2018

Appendix G - Declaration of originality

Declaration of Originality

Last name, first name: Otth, Maria

Matriculation number: 04-132-486

I hereby declare that this thesis represents my original work and that I have used no other sources except as noted by citations.

All data, tables, figures and text citations which have been reproduced from any other source, including the internet, have been explicitly acknowledged as such.

I am aware that in case of non-compliance, the Senate is entitled to withdraw the doctorate degree awarded to me on the basis of the present thesis, in accordance with the "Statut der Universität Bern (Universitätsstatut; UniSt)", Art. 69, of 7 June 2011.

Place, date

Biberstein, 13.12.2020

Signature