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Multidisciplinary Late Effects Clinics for Childhood Cancer Survivors in Germany – a Two-Center Study

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Keywords

Childhood cancer survivor · Late effects clinic · Long-term follow-up · Subsequent neoplasms · Endocrine disorders

Summary

Background: Childhood cancer survivors are at risk for therapy-related sequelae and, therefore, require long-term follow-up. At 2 university hospitals in Germany collaborative multidisciplinary late effects clinics were installed to provide specialized care and to evaluate the current health status of these patients in a clinical setting. **Patients and Methods**: Every patient who visited the late effects clinics at the university hospital in Lübeck and Erlangen over a period of 3 years and met the inclusion criteria was included in the study. Patients' characteristics as well as cancer diagnosis, treatment related factors and the prevalence of chronic health conditions were assessed. **Results**: 220 patients attended the late effects clinics during the observation period. The median follow-up period was 16 years (range 5–45 years). In total over 64% of the patients were affected by at least 1 chronic health condition, including endocrine disruptions in 19.1% of the patients. Moreover, secondary neoplasms occurred in 9.1% of the study participants. **Conclusion**: German childhood cancer survivors are affected by multiple therapy-related sequelae. A comprehensive network of late effects clinics should be established to ensure specialized and risk-adapted care for every childhood cancer survivor in Germany.

Introduction

As survival rates of pediatric cancer patients improved significantly over the last decades, the number of childhood cancer survivors is growing worldwide [1]. However, several studies demonstrated that these patients face a reduced life expectancy compared to sex- and age-adjusted peers [2]. Moreover, they can be affected by multiple therapy-related sequelae, determined by different factors such as initial cancer diagnosis, treatment, sex and age. These late effects mainly consist of endocrine, cardiac, renal and pulmonary conditions as well as secondary malignancies. Radiotherapy constitutes an important risk factor for the development of endocrine disruptions as well as secondary neoplasms necessitating early diagnosis and treatment to prevent late deaths [3, 4]. Thirty years after cancer diagnosis, although still in early adulthood, about 70% of cancer survivors struggle with at least 1 chronic condition [5].

With the knowledge of late effects, the need for late effects clinics for adult childhood cancer survivors was expressed. Their aim

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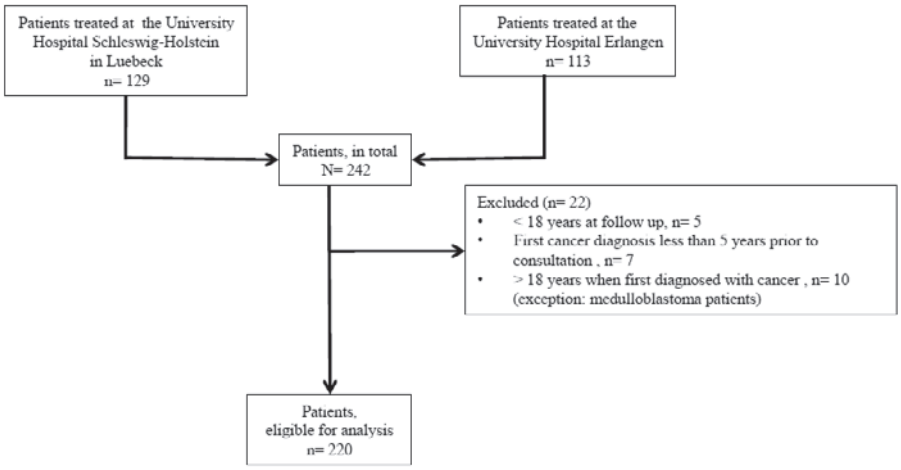

Fig. 1. Study flow chart.

should be to offer specialized care as well as routine follow-up investigations to ensure early diagnosis and treatment of possible cancer-therapy-related problems [6–8]. Based on treatment- and patient-related factors, standard surveillance is supposed to be modified and adapted individually attempting to create a personal risk-adapted surveillance program for each survivor. National and international guidelines recommending risk-adapted surveillance have been developed in the last decade to optimize and standardize long-term follow-up (LTFU) [9, 10].

Current estimations assume there are more than 25,000 adult former childhood cancer survivors more than 5 years after end of therapy in Germany (P. Kaatsch, personal communication, June 28th, 2017). Several mainly questionnaire-based surveys revealed an elevated risk for late effects in this cohort, although clinical data is still lacking [11, 12]. However, there are only a few late effects clinics in Germany and these have not yet created a comprehensive network to offer localized and structured care.

Therefore, late effect clinics at 2 German university hospitals (Lübeck and Erlangen) covering the upper North as well as the Southeast of Germany were established to illuminate the current health status of German childhood cancer survivors as well as their need for specialized routine care. To the best of our knowledge the present study is the first to characterize this currently insufficiently attended population based on clinical data. Moreover, it illustrates a possible structure of multidisciplinary late effects clinics at different locations as a basis for a collaborative network.

Patients and Methods

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its amendments. The study protocol was specifically approved by the ethical review boards of the Universities of Lübeck and Erlangen. Informed consent was obtained from all individual participants included in the study.

Potential study participants were seen in 2 separate late effects clinics at 2 university hospital centers in Germany – at the university hospital Schleswig-Holstein in Lübeck and the university hospital Erlangen in Bavaria. In 2014 both institutions established outpatient clinics for a yearly long-term follow-up of childhood cancer survivors. Potential patients and study participants were informed about these clinics via 3 different approaches. First, every patient that turned 18 during the study period was routinely transferred from the local departments of Pediatric Hematology and Oncology to the late effects clinics in a structured transition process. Second, all former patients from Lübeck and Erlangen, who were treated at the local departments of Pediatric Hematology and Oncology and were already adults, were contacted via mail to inform them about the initiation of these clinics. Furthermore, the late effects clinics were presented on the clinic homepages to enable additional patients, who had not already been approached, to attend the clinics.

For this report, we restricted our analysis to patients visiting the late effects clinics between March 2014 and February 2017 (Lübeck) and January 2014 and December 2016 (Erlangen), respectively, and met the inclusion criteria (fig. 1).

Former medulloblastoma patients that were >18 years, when first diagnosed with cancer, were included in the analysis, as these patients were treated in Departments of Pediatric Hematology and Oncology according to German Pediatric Oncologic Clinical Trials.

The patients were examined by a pediatric oncologist in both centers as well as by an endocrinologist (Lübeck) and a medical oncologist (Erlangen), respectively. This included a physical examination and a basic laboratory workup with a complete blood count, serum electrolytes and an assessment of liver and kidney function. Based on their risk of developing late effects, the patients underwent additional examinations, such as lung function tests, echocardiographies or magnetic resonance imaging and had consultations with specialists e.g. dermatologists, orthopedists or human geneticists. The underlying risk stratifications were performed according to existing guidelines and recommendations [9, 10, 13–16]. Chronic health conditions were diagnosed by specialists of the corresponding discipline based on standard diagnostic approaches for the general population (e.g. diagnosis of hearing loss in case of a pathologic audiogram; diagnosis of cardiomyopathy in case of a pathologic echocardiography). Patients at the late effects clinic in Lübeck were also seen by a social worker for a socioeconomic consultation. Most patients attended the late effects clinics several times but for this report we only collected data from the latest physician's documentation of the medical history and the physical examination.

Statistical Analysis

Data on quantitative characteristics are expressed as median and range. Data on qualitative characteristics are expressed as percent values or absolute numbers as indicated. Comparisons between 2 groups were calculated using Fisher's exact test, for comparisons between more than 2 groups we employed the chi-square test. A value of $p < 0.05$ was considered statistically significant. Comparative curve analysis was performed employing the Mantel-Cox test. All statistical analyses were performed using IBM SPSS Statistics 22.0 and GraphPad Prism 6.0.

Table 1. Patients' characteristics (n = 220)

Characteristic	Years
Age at cancer diagnosis	
Median	8.5
Range	0–27
Age at last follow-up	
Median	24
Range	18–57
Time since diagnosis	
Median	16
Range	5–45
	n (%)
Sex	
Female	112 (50.9)
Male	108 (49.1)
Primary cancer diagnosis	
Leukemia	79 (35.9)
Lymphoma	46 (20.9)
Intracranial malignancy	29 (13.2)
Sarcoma	27 (12.3)
Renal tumor	13 (5.9)
Germ cell tumor	8 (3.6)
Neuroblastoma	5 (2.3)
Other[a]	13 (5.9)
Cancer treatment	
No chemotherapy, no radiotherapy	15 (6.8)
Chemotherapy	205 (93.2)
Radiotherapy	
Any irradiation	99 (45.0)
Cranial irradiation	67 (30.5)
Neck or chest irradiation	38 (17.3)
Abdominal or pelvic irradiation	24 (10.9)
Total body irradiation	10 (4.5)
Combined radiochemotherapy	96 (43.6)

[a]Myelodysplastic syndrome, retinoblastoma, thyroid carcinoma, hepatocellular carcinoma, histiocytosis, inflammatory myofriboblastic tumour, papillary cystadenofibroma, lipoblastoma and a ganglioneuroma.

Results

Patient Characteristics

Of the 220 patients eligible for this analysis, 112 (50.9%) were treated in Lübeck and 108 (49.1%) in Erlangen. A total of 108 patients were transferred to the clinics through a structured transition process from the local departments of Pediatric Hematology and Oncology during the study period. As 8 of these patients did not meet the inclusion criteria for the present study, 100 patients (92.6%) of this cohort were included constituting almost half (45.5%) of the study participants. Furthermore, 80 (36.4%) patients that were contacted via mail followed the invitation for a long-term follow-up. As a total of 472 former patients were approached via mail, this corresponds to a response rate of 17%. An additional 40 (18.2%) patients found information about the new institutions online and thus decided to attend the clinics.

Table 2. Non-malignant chronic health conditions

Health condition	Patients, n (%)
Overall	141 (64.1)
Endocrine disruptions	42 (19.1)
Fertility issues	38 (17.3)
Neurologic impairment	37 (16.8)
Metabolic changes	35 (15.9)
Psychiatric disorders	33 (15.0)
Benign tumors (extracranial)	26 (11.8)
Orthopaedic complaints	24 (10.9)
Cardiac diseases	19 (8.6)
ENT dysfunctions	19 (8.6)
Gastrointestinal diseases	18 (8.2)
Pulmonary diseases	16 (7.3)
Hematological disorders	13 (5.9)
Ophthalmologic diseases	13 (5.9)
Nephropathy	12 (5.5)
Bone health impairment[a]	10 (4.5)
Dermatological diseases	8 (3.6)
Hypogammaglobulinemia	5 (2.3)
Chronic graft-vs-host-disease	4 (1.8)

[a]Excluding patients with a singular vitamin D deficiency.

Of the patients seen in Lübeck, 84 patients (75% of all patients in Lübeck) were originally treated at the local Department of Pediatric Hematology and Oncology, 96 (88.9% of all patients in Erlangen) in Erlangen. The patients attended the late effects clinic a mean of 1.72 times during the study period (range 1–8 times). About half of the patients (103, 47.8%) visited the clinics twice or more often. For a more detailed overview of patients' characteristics see table 1.

Chronic Health Conditions

In this study, 141 patients (64.1%) suffered from at least 1 chronic health condition (range 1–15 chronic health conditions). Out of these, 54 patients (24.5%) were affected by 1 chronic health condition, 22 patients (10%) by 2 and 65 patients (29.6%) were diagnosed with 3 or more health impairments. Types and distribution of chronic health conditions are summarized in table 2.

Endocrine Disruptions and Fertility Issues

Among all documented health conditions, most patients suffered from endocrine disruptions (19.1%). Hypothyroidism was the most frequent endocrine dysfunction affecting 36 patients (16.4%). It was diagnosed more often in women (22, 19.6% of all female participants) than in men (14, 6.8% of all male participants). Out of all irradiated patients, 28 patients (28.3%) developed hypothyroidism after any type of radiotherapy, 15 patients (41.7%) after neck or chest irradiation. In comparison, only 21 of 182 patients (11.5%) without any neck or chest irradiation suffered from the same condition ($p < 0.001$). Furthermore, a trend towards a correlation between radiation dose and hypothyroidism ($p = 0.222$) could be demonstrated (fig. 2). We have not seen any significant correlation between primary cancer diagnosis, sex or patients' origin and the development of hypothyroidism in later life.

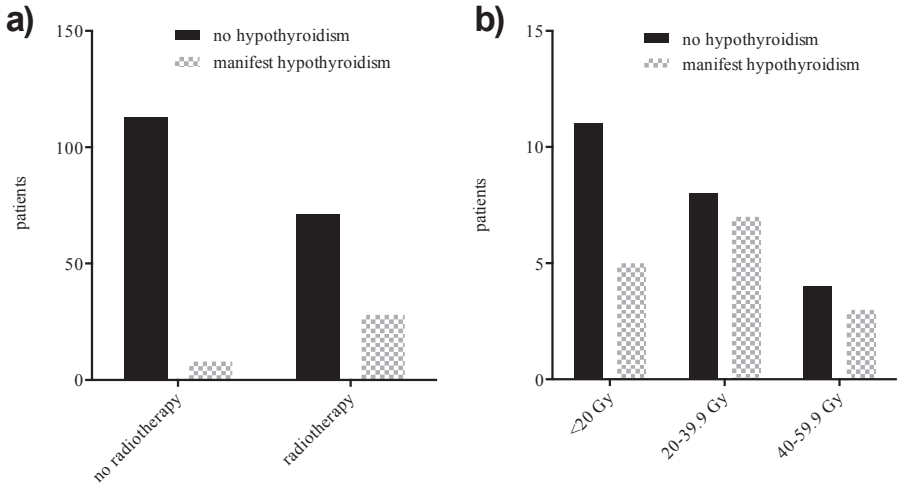

Fig. 2. Correlation between radiotherapy and hypothyroidism. a) Hypothyroidism in patients treated with or without radiotherapy; b) Hypothyroidism in patients after cervicothoracic irradiation, subdivided according to the applied radiation doses.

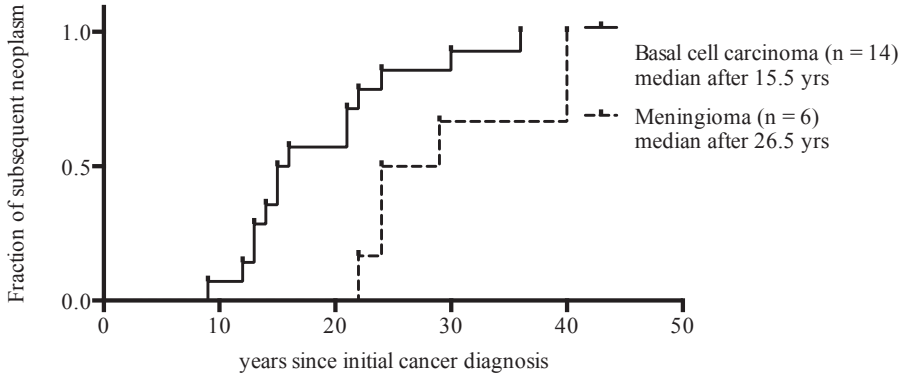

Fig. 3. Occurrence of basal cell carcinomas and meningiomas after initial cancer diagnosis.

Eight patients (3.6%) were diagnosed with growth hormone deficiencies. 4 patients (1.8%) were affected by hyperparathyroidism. 3 out of these 4 patients (75%) received cranial or mediastinal irradiation.

Fertility problems occurred in 38 patients (17.3%) mostly associated with hypogonadism in 15 patients (6.8%). Low serum anti-Mullerian hormone (AMH) affected 10 patients (8.9% of all female patients). It was only routinely assessed at 1 study site (Lübeck). Therefore 9 out of these 10 affected female patients were diagnosed at this center (15.5% of females treated in Lübeck). Erectile dysfunction occurred in 2 patients (1.9% of all male patients). Furthermore, 14 patients (6.4%) were affected by additional fertility problems including hysterectomy and oophorectomy. Supplemental table 1 summarizes the detailed analysis of all endocrine deficits (*www.karger.com/?DOI=488203)*.

Subsequent Neoplasms

Overall, 39 subsequent neoplasms occurred in 20 patients (9.1%). 9 Patients developed 1 additional neoplasm, 6 were affected by 2 subsequent neoplasms, 3 by 3 and 1 patient each by 4 or 5, respectively. This analysis excluded late relapses as well as extracranial benign tumors. All patients with 3 or more subsequent neoplasms were female.

The median interval between the first oncologic diagnosis and the diagnosis of the first subsequent neoplasm was 15 years (range: 8–42 years). Median intervals for further subsequent neoplasms were longer with 21 years (range: 13–40 years) for the second, 22 years (range: 15–28 years) for the third, 29.5 years for the fourth (range: 29–30) and 31 years for the fifth subsequent neoplasm. Figure 3 illustrates the increasing cumulative incidence for the most frequent subsequent neoplasms, basal cell carcinoma (BCC) and meningioma, emerging with increasing time after primary cancer diagnosis. BCCs occurred significantly earlier than meningiomas ($p = 0.016$).

All subsequent neoplasms but 1 occurred in previously irradiated areas ($p < 0.001$). Intracranial tumors only occurred after cranial irradiation. Some of the entities occurred more than once in 1 patient and were diagnosed as independent neoplasm events rather than relapses by histopathologic examination. For a more detailed overview of patients' characteristics see table 3.

Additional Chronic Health Conditions

Neurologic impairment including epileptic seizures, strokes, mental and/or motoric retardation, was documented in 37 patients (16.8%). Psychiatric disorders were diagnosed in 33 patients (15%).

Metabolic changes were detected in 35 patients (15.9%) including hypercholesterolemia in 14 patients (6.4%), obesity in 14 patients (6.4%), dyslipidemia in 3 patients (1.4%), diabetes mellitus type 1 in 3 patients (1.4%) and diabetes mellitus type 2 in 2 patients (0.9%).

Table 3. Subsequent neoplasms

Entity	Patients, n (%)	Diagnoses, n
Basal cell carcinomas	9 (4.1)	14
Meningiomas	3 (1.4)	6
Cavernomas	3 (1.4)	4
Thyroid cancer	3 (1.4)	3
Breast cancer	2 (0.9)	3[a]
Melanoma	1 (0.5)	1
Lentigo maligna	1 (0.5)	1
Renal cell carcinoma	1 (0.5)	1
Gastric cancer	1 (0.5)	1
Leukemia	1 (0.5)	1
Osteosarcoma	1 (0.5)	1
Prolactinoma	1 (0.5)	1
Acoustic neurinoma	1 (0.5)	1
Trigeminal neurinoma	1 (0.5)	1

[a]One patient was affected by bilateral breast cancer.

Benign extracranial tumors occurred in 26 patients (11.8%), including uterine myoma, fibroadenomas of the breast, neurinomas, focal nodular hyperplasias of the liver and lipomas. Thyroid adenomas affected 11 patients (5%). Of these 9 patients (81.8%) received cervical and/or thoracic irradiation.

Orthopedic complaints affected 24 patients (10.9%). Ten patients (4.5%) were affected by bone health impairment, including 6 patients (2.7%) with osteonecrosis and 2 patients (0.9%) with osteoporosis. Additionally, vitamin D deficiency was diagnosed in 34 patients (15.5%).

Cardiovascular diseases affected 19 patients (8.6%). More than half of these patients (10 patients, 4.5%) suffered from arterial hypertension. Cardiomyopathies occurred in 6 patients (2.7%) including 1 patient (0.5%) after heart transplantation due to congestive heart failure.

Lung diseases were documented in 16 patients (7.3%). Obstructive lung disease constituted the most frequent finding (10 patients, 4.5%).

Additionally, ear, nose and throat dysfunctions occurred in 19 patients (8.6%), including high frequency hearing loss in 13 patients (5.9%).

One patient (0.5%) died due to multiple subsequent chronic health conditions and second neoplasms during the time the study was conducted. Table 2 summarizes all non-malignant chronic health conditions.

Discussion

Optimal care and structured risk-adapted surveillance for long-term childhood cancer survivors is still subject of research and ongoing development. Several models of care for LTFU of these patients have been proposed including shared care LTFU programs as a collaboration between general practitioners (GPs) and cancer centers, GP-led models as well as clinic-based models of LTFU by a multidisciplinary team [6, 17–19]. Patients' satisfaction with LTFU was mostly dependent on coordination and communication between the involved specialists as well as their expertise concerning late effects and LTFU [18, 20]. As the management of therapy-related chronic health conditions often requires multidisciplinary cooperation, we favored a clinic-based model of LTFU [19]. A team of clinic physicians cooperates closely in order to facilitate risk-adapted surveillance at a single institution including all required specialist's consultations in 1 day [21, 22]. GPs were included in the LTFU process as they conduct follow-up examinations that do not require specialists' consultation.

After 3 years a first evaluation of 220 patient characteristics and health status was performed to verify the prevalence of late effects in clinical examinations by a multidisciplinary team in German cancer survivors that has to date only been assessed in questionnaire-based surveys.

Over 64% of the study participants were diagnosed with chronic health impairment a median of 16 years after childhood cancer diagnosis, revealing a high number of German childhood cancer survivors struggling with possible therapy-related sequelae. However, the prevalence of chronic diseases in the present study was lower than in the North American St. Jude Lifetime Cohort Study, which might be due to the fact that median age and time passed since cancer treatment were significantly lower in our cohort [16].

Endocrine disruptions affected a fifth of the study participants and were the most common chronic health condition in the study population. This is in keeping with previously published data, demonstrating that endocrine late effects constitute one of the most frequent sequelae [23, 24]. Almost every fifth female childhood cancer survivor was affected by hypothyroidism, which renders the disorder significantly more common in our study group than in age-adjusted controls from general population [25]. Furthermore, cervical and thoracic irradiation could be demonstrated as major risk factors for the development of hypothyroidism. Although the absolute number of irradiated patients with subsequent hypothyroidism was low, a dose-dependent correlation, as postulated in previous papers, could be observed [26].

Further endocrine deficits were documented illustrating the complexity of possible late effects that must be considered in a clinical setting. Interestingly, primary hyperparathyroidism, a rather rare disease in the general population, was diagnosed in almost 2% of the study participants [27]. The majority of the affected patients was exposed to therapeutic irradiation emphasizing a previously discussed link [28].

Moreover, approximately 17% of our patients reported fertility issues. About half of these patients were affected by primary or secondary hypogonadism constituting a frequent sequela after cranial or pelvic irradiation and/or chemotherapy. The relevance of low serum AMH in the early detection of premature ovarian insufficiency has been controversially discussed [15, 29]. However, its role as a screening tool is more widely accepted and may be helpful in a multidisciplinary setting to decide which patient should be transferred to the associated fertility clinic. The lower overall prevalence of premature ovarian insufficiency in our cohort compared

to previously published data, revealing a prevalence over 10% at a median age of 31.7 years, may be due to the younger median age of 24 years in our study group [30].

The development of a subsequent neoplasm is one of the most life-threatening late effects after childhood cancer and constitutes an especially troubling worry for cancer survivors [31]. Radiotherapy has been demonstrated to be a major risk factor [3]. In our cohort 9% of patients developed subsequent neoplasms occurring almost exclusively in irradiated patients. BCCs as well as thyroid and breast cancer constituted the most frequent secondary malignancies in concordance with previously published data [32, 33]. Furthermore, BCCs occurred significantly earlier after initial cancer diagnosis than meningiomas, which should be considered with regard to risk-adapted surveillance programs [33].

The fact that subsequent neoplasms occurred up to 42 years after initial cancer diagnosis emphasizes the need for life-long follow-up including regular examinations and cancer prevention measures [34]. Cancer prediction models for certain entities and risk groups as well as recommendations for early detection programs in formerly irradiated patient already exist [12, 35]. However, most patients in our study group were not aware of their elevated risk for subsequent neoplasms and the need for regular examinations revealing a relevant lack of information concerning late effects in German childhood cancer survivors.

In our cohort, some patients developed up to 5 additional neoplasms after childhood cancer, possibly indicating a genetic cancer predisposition. However, although genetic counseling and testing constitutes an important part of our multidisciplinary team, no patient was identified to be affected by a genetic cancer predisposition. Genetic testing might nonetheless help to identify very high-risk patients among all irradiated patients for intensive early detection programs [36].

Above all, study participants were affected by a wide range of additional health conditions including cardiac, pulmonary, orthopedic and dermatologic diseases as well as metabolic changes.

There are several limitations to the present study. First, due to the study design and the small study size no direct comparison with the prevalence of the different chronic health conditions in an age- and sex-adjusted general population or in a sibling control cohort was performed. Although this complicates the interpretation of the study findings, the documented diseases clearly exceed the expected prevalence for young adults with a median age of 24 years.

Besides, as the application of instrument-based examinations to the patients resulted from a risk stratification based on LTFU guidelines, some patients with a low risk of developing late effects did not receive additional examinations. Thus, the true prevalence of chronic health conditions in the study group might be underestimated. Furthermore, almost half of the study participants were routinely transferred from the local departments of Pediatric Hematology and Oncology in a transition process and are supposed to represent the standard distribution of childhood cancer survivors including patients with various primary cancer diagnoses and different risk profiles regarding potential late effects. However, as only 17% of all former patients that were contacted via mail and invited for long-term follow-up attended the clinics and an additional share of patients independently decided to visit the clinics without medical referral as they found information online, a selection bias comprising patients with a higher risk profile into the study cannot be excluded. The low response rate in the cohort contacted via mail may be due to the fact that no prior address verification was performed. Thus, a relevant share of patients that were treated in the local departments of Pediatric Hematology and Oncology several years ago may not have been contacted successfully.

Previous studies already demonstrated an elevated risk for German childhood cancer survivors, comparably high to that in American and British Childhood Cancer survivors. However, most studies assessed therapy sequelae via questionnaire without ascertaining results in a clinical setting or offering specialized care.

This study thus represents to the best of our knowledge the first study on German childhood cancer survivors based on clinical examination. It demonstrates the quantity and complexity of possible late effects that have to be considered in a multidisciplinary setting. However, the quantitative results require additional confirmatory studies in a prospective setting.

Beyond that, the study demonstrates possible structures of comprehensive care for this at-risk population. Consequently, a collaborating network consisting of several late effects clinics at university hospitals in Germany, to establish standardized and risk-adapted care for long-term childhood cancer survivors, is currently under development.

Online Supplemental Table

Supplemental Table 1. Non-malignant chronic health conditions (with subcategories).

To access the supplemental table, please refer to *www.karger.com/?DOI=488203.*

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Disclosure Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationship that could be constructed as a potential conflict of interest.

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