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Retina

Altered Neuroretinal Tissue in Childhood Cancer Survivors: Data From the German CVSS Study

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Purpose: This study reports on alterations of the peripapillary retinal nerve fiber layer (pRNFL) in long-term childhood cancer survivors (CCS) for the first time.

Methods: In the Cardiac and Vascular Late Sequelae in Long-Term Survivors of Childhood Cancer-Study (CVSS), a cross-sectional study, 1002 CCS (aged 23–48 years) diagnosed with neoplasia before the age of 15 years were prospectively enrolled in an ophthalmological examination including pRNFL-measurements with spectral-domain optical coherence tomography. An age- and sex-matched sample of the population-based Gutenberg Health Study (GHS) served as the comparison group. Differences in pRNFL in CCS with cancer types and treatments were explored.

Results: Four hundred forty-nine CCS had pRNFL imaging and were included with a mean follow-up of 28.9 years. The pRNFL was 3.38 µm thinner in CCS compared with the GHS controls ($P < 0.0001$). The pRNFL was thinner in CCS with central nervous system tumors ($P < 0.001$), leukemia ($P < 0.001$), renal tumors ($P = 0.004$), neuroblastoma ($P < 0.001$), soft-tissue sarcoma ($P = 0.003$), and malignant bone tumor ($P = 0.004$), but not different after lymphoma and germ cell tumor. Treatment with platin derivates ($P = 0.02$) and cranial radiation ($P = 0.02$) were negatively associated with pRNFL. Subgroup analysis revealed a thinner pRNFL in leukemia CCS and treatment with anthracyclines ($P < 0.001$) and methotrexate ($P = 0.01$). No association was found for ifosfamide, vinca alkaloids, asparaginase chemotherapy, and cardiac radiation.

Conclusions: The pRNFL is thinner in CCS with most common tumor entities, except lymphoma and germ cell tumors. Cranial radiation and platin derivates had negative effects on the pRNFL thickness.

Translational Relevance: Follow-ups are needed to evaluate if this might result in increased risk for neurodegenerative ophthalmic diseases, like glaucoma.

translational vision science & technology

Introduction

In the last decades, new and optimized treatment regimens have significantly increased survival of childhood cancer resulting in an average overall survival of above 80% in most high-income countries.[1,2] Due to the improvement in therapy and lack of prevention of childhood cancer the number of childhood cancer survivors (CCS) is steadily increasing.[3]

Therefore, adverse late effects of treatment in long-term CCS have gained interest in survivorship research. Increased risk for various disease has been reported. CCS face a five-fold increase for secondary cancer as reported by a Teepen et al. in a Dutch study.[4] CCS are especially vulnerable for primary bone cancer, sarcoma, and leukemia, but various other associated secondary malignant neoplasms have been reported.[4–7] Furthermore, increased risk for cardiovascular disease,[8–12] endocrine disorders with hormonal imbalance of growth hormone, thyroid hormone, adrenocorticotropin and gonadotropin hormones,[13] impaired fertility[14] or mental health,[15] damage to the central and peripheral nervous system,[16–18] and overall increased mortality compared to the general population have been shown.[19]

A dependence of the cancer entity and performed treatment (radiation and/or chemotherapy) to secondary health issues is known. Age at treatment, intensity, and regarding radiation, the localization plays a crucial role for the risk of secondary morbidity.[20] Both radiation of the brain and chemotherapy are described to lead to neurocognitive impairment in cancer survivors.[21] Examination of the neuroretina gives the unique opportunity to noninvasively examine and quantify nerve tissue being part of the central nervous system. In recent years, several neurological diseases, such as dementia,[22,23] Alzheimer's,[24] Parkinson's,[25] and multiple sclerosis,[26,27] were shown to be linked with a thinner retinal nerve fiber layer (RNFL). Additionally, Whelan et al.[28] reported an increased risk of self-reported glaucoma 5+ years after cancer treatment in CCS. However, no correlation to chemotherapy or radiation or increased risk of any self-reported retinal disease was found.

The Cardiac and Vascular late Sequelae in long-term Survivors of childhood cancer (CVSS) study was designed to incorporate an ophthalmological examination including spectral-domain optical coherence tomography (OCT) of the retina. This allows to investigate alterations of peripapillary RNFL (pRNFL) in CCS compared with data from a population-based sample. Alterations of RNFL could explain the previous reported association to glaucoma and enrich the knowledge on the damage of the central nervous system. Furthermore, this study will differentiate the impact of different tumor entities and treatment for the first time in a large cohort.

Materials and Methods

Participants

In the CVSS study, a cross-sectional study, German CCS were eligible for participation when diagnosed between 1980 and 1990 with a neoplasia prior to 15 years of age according to the International Classification of Childhood Cancer (ICCC3)[29] and registered at the German Childhood Cancer Registry. Included CCS needed to be treated at 1 of 34 pediatric cancer centers taking part in the CVSS study and have survived more than 5 years after the initial cancer diagnosis. Further details are described elsewhere.[8]

Among 2894 invited CCS, 1002 subjects took part in the general examination at the study center at the University Medical Center Mainz between October 2013 and February 2016. These study participants underwent a standardized clinical examination at the population-based Gutenberg Health Study (GHS) examination platform.[30] The study was carried out in accordance with the Declaration of Helsinki and was approved by the ethics committee of Rhineland-Palatinate Chamber of Physicians. All participants gave written informed consent prior to study participation.

Medical Data

A computer-assisted personal interview (CAPI) was conducted to collect medical history data and, if available, medical records were retrieved. Cancer- and treatment-related data were obtained from primary health records of former treating medical centers and/or individual therapy data at the respective study centers.

Assessment of Ophthalmological Parameters

For each study participant, a comprehensive ophthalmological investigation was performed including imaging with spectral-domain OCT. In addition, objective refraction (Humphrey Automated Refractor/Keratometer [HARK] 599, Carl Zeiss Meditec AG, Jena, Germany) was performed and visual acuity was determined. Non-contact tonometry (Nidek NT-2000; Nidek Co., Japan) was repeated three times to determine intraocular pressure. Visual field testing was performed with the frequency doubling technology (FDT) Humphrey Matrix Perimeter (program N-30-5).

Evaluation of Peripapillary and Macular Retinal Nerve Fiber Layer Thickness

OCT is a non-contact and noninvasive imaging technique to determine the reflectivity in various levels of the retina and to separate them. We used a Spectralis-OCT from Heidelberg Engineering (Heidelberg, Germany) and the associated Heidelberg Eye Explorer (HEYEX) software. The device measures multiple wavelengths of reflected light across a spectrum simultaneously, hence the name spectral-domain OCT. During recording, a circle scan was manually placed around the optic disc with the eye tracking system activated. Twenty-five scans were averaged to receive high resolution images. The RNFL was automatically segmented in each of the averaged peripapillary scans based on the detection of the RNFL boundaries (border to the internal limiting membrane and to the retinal ganglion cell layer) by the HEYEX software algorithm. The mean pRNFL was automatically calculated by the software for both the global measure and the sectors (temporal, temporal superior, nasal superior, nasal, nasal inferior, and temporal inferior sectors). Furthermore, a macular volume scan of 15 × 15 degrees with 37 horizontal scans was performed.

All OCT scans were manually reviewed for quality control. Decentered scans or scans with failed automated segmentation were excluded. The refraction of the examined eye was set before data acquisition and no pupil dilation was performed. For each eye of every subject, one peripapillary and one macular scan was acquired, an example for the peripapillary scan is given in Supplementary Figure S1.

Comparative Data From the Gutenberg Health Study

The pRNFL measures of the CVSS study were compared to a sample of the GHS population as general and ophthalmological examinations were obtained in an identical study setup. The GHS is a population-based, prospective, single-center, observational cohort study including 15,010 study participants from the general population of Mainz and Mainz-Bingen.[30] As part of the 5-year follow-up examination, OCT imaging took place. Previously, normative data on pRNFL and its associations were published in this cohort.[31] Additional to the 15,010 participants from the baseline examination (the so-called core cohort), 4000 participants within the age range of 25 to 44 years (the so-called young cohort) were recruited, who underwent OCT imaging as well. Based on these two cohorts we draw controls for the CVSS sample matched on age and sex. The matching was conducted in a 1:4 ratio with nearest neighbor matching by age and gender, thus the controls are slightly older which was incorporated in the multivariable analysis. The CVSS and GHS/GHS young participants are Caucasian which is why ethnicity was not considered as a potential confounder. We generated a formula based on the GHS and GHS young data to calculate the expected pRNFL thickness in the general population between the ages of 25 and 80 years:

$$\begin{aligned}\text{Expected pRNFL thickness} &= 106.16\,\mu\text{m} - 0.18 \times \text{age (years)} \\ &+ 1.16 \times \text{sex } (1 = \text{female};\ 0 = \text{male}) \\ &+ 1.72 \times \text{spherical equivalent (dpt)}\end{aligned}$$

Statistical Analysis

Descriptive statistics were calculated for demographic, clinical, and treatment parameters. Measures of global pRNFL were computed stratified to ICCC3 diagnoses.

Linear regression analysis with generalized estimating equations was conducted to analyze the impact of childhood cancer on global pRNFL with adjustment on age, sex, and spherical equivalent. Of 1002 CCS subjects 51 had a secondary neoplasm. For a sensitivity analysis, they were excluded. The impact of different ICCC3 diagnosis compared with control subjects were analyzed in model #2 adjusted for the same confounders. Within the CVSS study, the impact of types of chemotherapy and of radiotherapy (head/neck, and other body parts) was further examined. Furthermore, we analyzed the effect of different treatment modalities on the six different sectors of the pRNFL (temporal, temporal superior, nasal superior, nasal, nasal inferior, and temporal inferior sector) using linear regression analysis with generalized estimating equations.

Statistical analyses were performed using Software R (version 3.4.0; The R Foundation for Statistical Computing, Vienna, Austria).

Results

Among 1002 examined participants in the CVSS study, 449 individuals (44.8% of all participants) were analyzed with complete data of pRNFL. This subset of the CVSS study comprised more male participants (44.8% female participants) with a mean age of 34.24 ± 5.6 years at study examination. These subjects had a mean age of 5.55 ± 4.17 years (range = 0–14 years) at initial childhood cancer diagnosis. The leading cancer

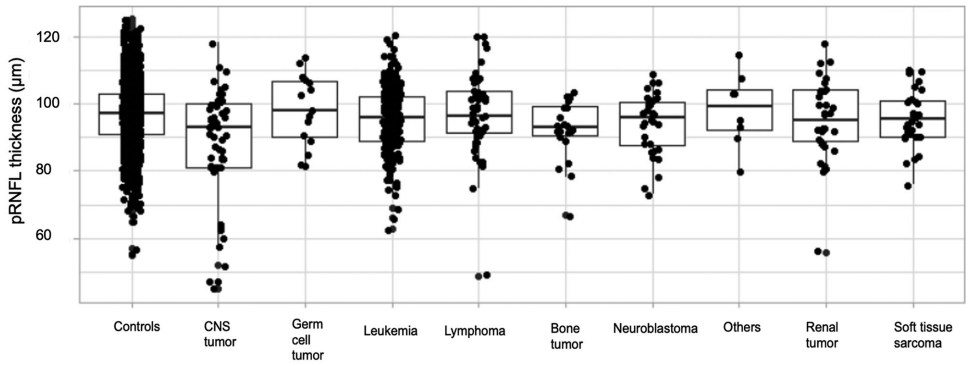

Figure 1. Retinal nerve fiber layer thickness stratified on childhood cancer diagnosis. The peripapillary retinal nerve fiber layer thickness was examined with spectral-domain OCT in the CVSS Study ($n = 449$) and stratified on diagnosis according to the International Classification of Childhood Cancer (ICCC3). The control group is an age- and sex-matched sample from the population-based Gutenberg-Health Study ($n = 1796$) and is displayed in *light grey*. CVSS, cardiac and vascular late sequelae in long-term survivor of childhood cancer. Right eyes are illustrated. pRNFL, peripapillary retinal nerve fiber layer; CNS tumor, central nervous system tumor.

entities were leukemia and lymphoma: more than half of the study participants had been diagnosed with these diseases (leukemia = 44.1%, $n = 198$ and lymphoma = 10.2%, $n = 46$). The majority of participants with leukemia had acute lymphoblastic leukemia ($n = 185$), whereas the other leukemia subtypes were rare (11 with acute myeloblastic leukemia, 1 with biphenotypic leukemia, and 1 with chronic myeloblastic leukemia). Other malignant entities were central nervous system tumor (12.9%, $n = 58$), neuroblastoma (7.6%, $n = 34$), renal tumor (7.6%, $n = 34$), soft-tissue sarcoma (6.9%, $n = 31$), malignant bone tumor (5.3%, $n = 24$), germ cell tumor (3.6%, $n = 16$), and others including hepatoblastoma and carcinoma (1.8%, $n = 8$; Fig. 1).

Antineoplastic treatment data were obtained for 94.4% ($n = 424$) of this subgroup of the CVSS study: the majority either received chemo- (84.4%, $n = 379$) or radiotherapy (50.8%, $n = 228$). Further demographic, diagnostic, and treatment characteristics are presented in Table 1. The analyzed study participants with pRNFL measure did not differ significantly from the rest of the CVSS study except cranial or head and neck radiation. The age- and sex-matched sample of the GHS and GHS young cohort included 1796 participants (mean age = 41.83 years and 48.8% female participants). Details of the control sample of the GHS and GHS young cohort are displayed in Supplementary Table S1.

In CCS subjects, pRNFL was thinner (96.1 ± 10.5 µm) than in GHS subjects (98.7 ± 10.1 µm). Linear regression analysis revealed that pRNFL was 3.38 µm (95% confidence interval [CI] = –4.44 to −2.31, $P < 0.0001$) thinner in CCS than GHS subjects after adjustment for sex, age, and spherical equivalent (Fig. 2). Older age was associated with thinner pRNFL (B estimate = –0.15, 95% CI = −0.22 to 0.08, $P < 0.001$), whereas female sex (B estimate = 2.5, 95% CI = 1.93–3.07, $P < 0.001$) was associated with a thicker pRNFL. The sensitivity analysis after the exclusion of the 51 CCS with secondary neoplasm confirmed a significantly thinner pRNFL in CCS than in GHS subjects. The excessive loss of pRNFL thickness of CCS compared to the control group was only seen more than 14 years after the diagnosis: an excessive loss at 15 years was observed with a relative stable excessive RNFL loss for longer times after diagnosis (Fig. 3).

CCS previously having central nervous system tumor (B estimate = −9.76 µm, 95% CI = −12.79 to −6.73, P value < 0.001), renal tumor (B estimate = −4.27 µm, 95% CI = −7.16 to −1.38, P value = 0.004), malignant bone tumor (B estimate = −3.56 µm, 95% CI = −5.97 to −2.24, P value = 0.004), neuroblastoma (B estimate = −4.34 µm, 95% CI = −6.78 to −2.0, P value < 0.001), soft-tissue sarcoma (B estimate = −3.05 µm, 95% CI = −5.06 to −1.04, P value = 0.003), and leukemia (B estimate = –2.08 µm, 95% CI = −3.29 to −0.88, P value < 0.001) had a thinner pRNFL after adjusting for age, sex, and spherical equivalent, whereas those with previous lymphoma, germ cell tumors, and other tumor entities did not differ significantly from the controls (Table 2). Because no association of lymphoma and pRNFL thickness was detectable and the group of participants with lymphoma was the second largest group, we additionally set the lymphoma group as a reference and compared the influence of other tumor entities on the pRNFL. Multivariable regression revealed a reduction in pRNFL thickness in CCS with central nervous system tumors (B estimate = −10.4 µm, 95% CI = −14.21 to −6.59, P value <

Table 1. Demographic, Diagnostic, and Treatment Characteristics of CVSS-Study Participants With Retinal Nerve Fiber Layer Measurement ($n = 449$) and Item-Non-Responders ($n = 553$)

Variables	CVSS (449) With pRNFL Measurement	CVSS (553) Without pRNFL Measurement	*P* Value
Sex (female in %)	44.8% (201)	46.1% (255)	0.72
Age, y	34.24 ± 5.6	34.19 ± 5.6	0.89
Arterial hypertonia (in %)	25.7% (115)	22.8% (126)	0.32
Diabetes (in %)	2.0% (9)	2.4% (13)	0.88
Best corrected visual acuity (right eye) (logMAR)	0.0 [0.0 to 0.1]	0.0 [0.0 to 0.1]	0.81
Best corrected visual acuity (left eye) (logMAR)	0.0 [0.0 to 0.1]	0.0 [0.0 to 0.1]	0.35
Intraocular pressure (right eye) (in mm Hg)	14.31 ± 2.78	14.52 ± 2.78	0.27
Intraocular pressure (left eye) (in mm Hg)	14.21 ± 2.85	14.53 ± 2.95	0.09
Spherical equivalent (right eye) (in Diopter)	−0.88 [−2.00 to −0.25]	−0.75 [−2.00 to −0.25	0.14
Spherical equivalent (left eye) (in Diopter)	−0.75 [−1.88 to −0.25]	−0.81 [−2.12 to −0.12]	0.9
Mean FDT sensitivity (right eye) (0–10 scale)[a]	6.11 [6.0 to 6.32]	6.11 [6.0 to 6.58]	**0.01**
Mean FDT sensitivity (left eye) (0–10 scale)[a]	6.11 [6.0 to 6.42]	6.21 [6.0 to 6.59]	**0.01**
Diagnosis			
Central nervous system tumor	12.9% (58)	13.4% (74)	0.9
Leukemia	44.1% (198)	42.5% (235)	0.26
Germ cell tumor	3.6% (16)	2.2% (12)	0.9
Lymphoma	10.2% (46)	10.3% (57)	1.0
Neuroblastoma	7.6% (34)	7.2% (40)	0.93
Solid bone tumor	5.3% (24)	4.7% (26)	0.75
Soft-tissue sarcoma	6.9% (31)	7.8% (43)	0.69
Renal tumor	7.6% (34)	8.5% (47)	0.68
Others	1.8% (8)	1.4% (8)	0.87
Age of diagnosis	5.6 ± 4.2	5.5 ± 4.3	0.91
Treatment			
Anthracyclines	75.9% (334)	74.6% (402)	0.69
Cyclophosphamide	63.0% (283)	60.4% (334)	0.43
Ifosfamide	21.4% (96)	24.1% (133)	0.36
Vinca alkaloids	72.2% (324)	73.6% (407)	0.66
Platine derivate	10.0% (45)	10.5% (58)	0.89
Methotrexate	57.7% (259)	57.0% (315)	0.87
Asparaginase	43.7% (196)	41.2% (228)	0.48
Cardiac directed radiation	12.0% (54)	13.7% (76)	0.48
Cranial directed radiation	40.8% (183)	47.4% (262)	**0.04**
Cranial and neck directed radiation	41.2% (185)	47.9% (265)	**0.04**

CVSS, cardiac and vascular late sequelae in long-term survivor of childhood cancer; ICCC3, International Classification of Childhood Cancer.

In the subcategory "others" are carcinoma ($n = 3$) and hepatic tumor ($n = 5$) summarized.

The *P* values in bold represent statistical significance.

[a]Not all participants had available data von visual field testing: of 449 participants with pRNFL measurements 313 had visual field testing; of 553 participants without pRNFL measurements 380 had visual field testing.

0.001), neuroblastoma (B estimate = −4.3 µm, 95% CI = −7.56 to −0.95, *P* value = 0.01), and malignant bone tumor (B estimate = −4.22 µm, 95% CI = −7.68 to −0.75, *P* value = 0.01). No association was found for leukemia, germ cell tumor, soft-tissue sarcoma, renal tumor, and others (Supplementary Table S2).

With respect to treatment modality in the CVSS study, linear regression analysis of CCS with any tumor type showed that platin derivates (B estimate

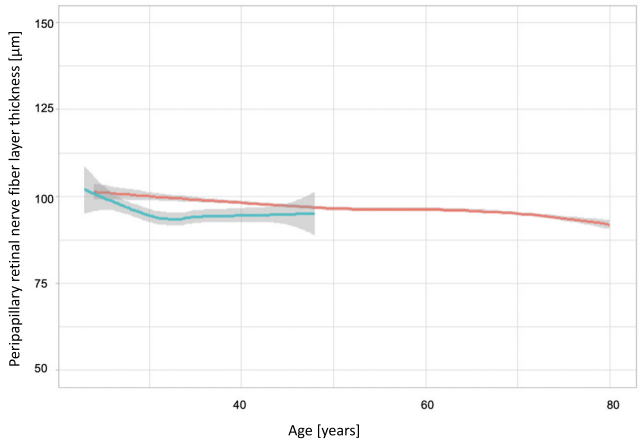

Figure 2. Retinal nerve fiber layer thickness in childhood cancer survivors and the general German population. The peripapillary retinal nerve fiber layer thickness (pRNFL) was examined with spectral-domain OCT in the CVSS Study (n = 449) and is displayed in *blue*. The pRNFL of participants of the population-based Gutenberg-Health Study is displayed in *red* and is representative for the general population. CVSS, cardiac and vascular late sequelae in long-term survivor of childhood cancer. Right eyes are illustrated.

= −2.66 µm, 95% CI = −4.96 to −0.36, P value = 0.02) and cranial and neck directed radiation (B estimate = −1.97 µm, 95% CI = −3.61 to −0.33, P value = 0.02) both were associated with a thinner pRNFL in the multivariable analysis (Table 3). A marginally positive association after treatment with anthracyclines (B estimate = 3.3 µm, 95% CI = 0.32–6.27, P value = 0.03), cyclophosphamides (B estimate = 2.58 µm, 95% CI = 0.33–4.84, P value = 0.03), or methotrexate (B estimate = 2.53 µm, 95% CI = 0.06–5.0, P value = 0.04) was found in both the univariable and multivariable (adjustment for age, sex, and spherical equivalent) model. No association was found for ifosfamide vinca alkaloids and asparaginase, and cardiac directed radiation in the multivariable model.

Analysis of the largest subgroup, CCS with prior leukemia, confirmed a negative effect of cranial and neck directed radiation on pRNFL thickness (leukemia: B estimate = −2.8 µm, 95% CI = −4.87 to −0.81, P value = 0.006). Platin derivates were not used in patients with leukemia, which is why they were excluded from this analysis. Cyclophosphamides still had a positive effect (leukemia: B estimate = 7.03 µm, 95% CI = 1.11–12.95, P value = 0.02), however, anthracyclines and methotrexate had a significant negative effect on the pRNFL in the leukemia subgroup (anthracyclines: B estimate = −22.24 µm, 95% CI = −19.06 to −15.43, P value < 0.001; methotrexate: B estimate = −6.67 µm, 95% CI = −11.83 to −1.54, P value = 0.01; details in Supplementary Table S3).

Furthermore, we analyzed the effect of different treatment methods on the six different sectors of the pRNFL (temporal, temporal superior, nasal superior, nasal, nasal inferior, and temporal inferior sector). Only radiation of the head and neck did

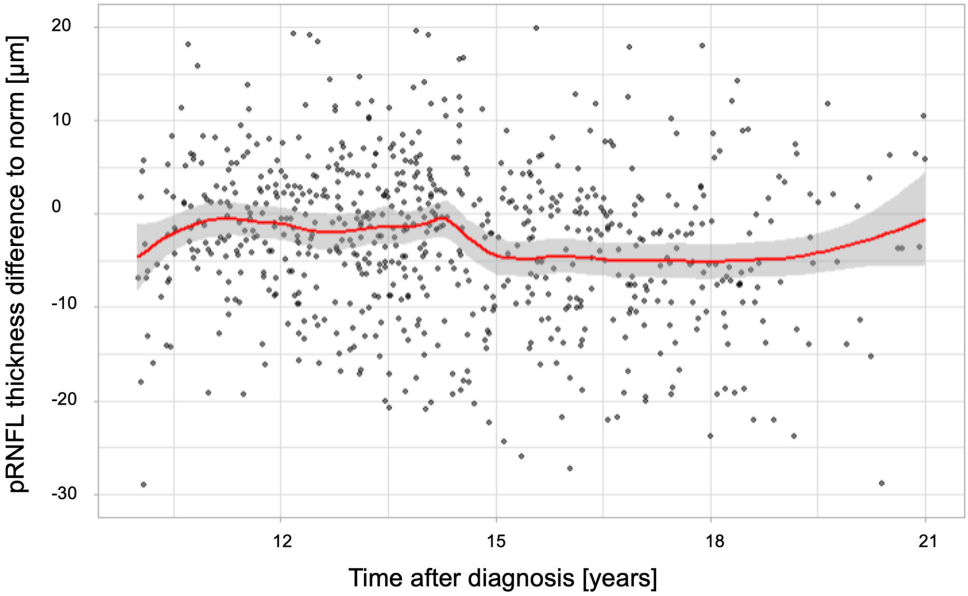

Figure 3. Retinal nerve fiber layer thickness in childhood cancer survivors' difference to norm depending on the time after diagnosis. The peripapillary retinal nerve fiber layer thickness (pRNFL) was examined with spectral-domain OCT in the CVSS Study (n = 449). CVSS, cardiac and vascular late sequelae in long-term survivor of childhood cancer.

Table 2. Associations of Previous Childhood Cancer Entity and pRNFL in Long-Term Childhood Cancer Survivors

	Univariable (Model 1)			Multivariable (Model 2)[a]		
pRNFL, µm	B Estimate	95% CI	*P* Value	B Estimate	95% CI	*P* Value
Central nervous system tumor	−10.32	−13.51 to −7.12	**<0.001**	−9.76	[−14.34 to −7.99]	**<0.001**
Leukemia	−2.1	[−3.16 to −1.08]	**<0.001**	−2.08	[−4.16 to −1.22]	**<0.001**
Germ cell tumor	−1.01	[−5.19 to 3.16]	0.63	−4.0	[−8.01 to −0.02]	0.054
Lymphoma	−1.03	[−3.6 to 1.54]	0.43	−0.03	[−3.31 to 1.64]	0.98
Neuroblastoma	−3.98	[−6.33 to −1.63]	**<0.001**	−4.39	[−7.56 to −2.23]	**<0.001**
Malignant bone tumor	−4.81	[−7.66 to −1.96]	**<0.001**	−3.56	[−7.68 to −2.38]	**0.004**
Soft-tissue sarcoma	−2.39	[−4.51 to −0.28]	**0.03**	−3.05	[−5.38 to −1.63]	**0.003**
Renal kidney tumor	−3.04	[−5.93 to −0.15]	**0.04**	−4.27	[−7.97 to −1.62]	**0.004**
others	0.21	[−4.73 to 5.14]	0.93	−2.17	[−8.28 to 0.65]	0.35
GHS		Reference			Reference	

GHS, Gutenberg Health Study; pRNFL, peripapillary retinal nerve fiber layer thickness.

GHS subjects are the reference (controls). Data from the CVSS study ($n = 449$) and Gutenberg Health Study ($n = 1796$). Multivariable linear regression analysis with generalized estimating equations was computed with adjustment for age, sex, and spherical equivalent.

The *P* values in bold represent statistical significance.

[a]Adjusted for age, sex, and spherical equivalent.

Table 3. Associations of Treatment Status of Childhood Cancer With Global pRNFL

	Univariable (Model 1)			Multivariable (Model 2)[a]		
pRNFL, µm	B Estimate	95% CI	*P* Value	B Estimate	95% CI	*P* Value
Anthracyclines	4.1	[1.76 to 6.44]	**<0.001**	3.3	[0.32 to 6.27]	**0.03**
Cyclophosphamide	3.51	[1.66 to 5.35]	**<0.001**	2.58	[0.33 to 4.84]	**0.03**
Ifosfamide	0.23	[−1.44 to 1.89]	0.79	−1.38	[−3.35 to 0.58]	0.17
Vinca alkaloids	3.15	[0.98 to 5.33]	**0.0045**	1.13	[−1.4 to 3.65]	0.38
Platine derivate	−1.8	[−3.95 to 0.35]	0.1	−2.66	[−4.96 to −0.36]	**0.02**
Methotrexate	2.93	[1.23 to 4.62]	**<0.001**	2.53	[0.06 to 5.0]	**0.04**
Asparaginase	2.14	[0.59 to 3.69]	**0.0068**	−2.3	[−4.82 to 0.28]	0.08
Cardiac directed radiation	−1.92	[−4.04 to 0.2]	0.076	0.74	[−1.47 to 2.95]	0.51
Cranial and neck directed radiation	−0.81	[−2.37 to 0.75]	0.31	−1.97	[−3.61 to −0.33]	**0.02**

Data from the CVSS study ($n = 449$). Linear regression analysis with generalized estimating equations was computed with adjustment for age, sex, and spherical equivalent.

The *P* values in bold represent statistical significance.

[a]Adjusted for age, sex, and spherical equivalent.

show a consistent effect on the pRNFL thickness with an effect on five of the six sectors (only the temporal-inferior sector was not significantly associated). Treatment with anthracyclines had a significant effect on all temporal sectors (temporal, temporal superior, and temporal inferior) with thicker pRNFL but not in nasal sectors. Other treatment options did not show a consistent association (Supplementary Table S4).

In CCS, central macular thickness was thinner (222.56 ± 38.77 µm) compared to GHS subjects (232.55 ± 19.72 µm). Linear regression analysis revealed that central macular thickness was –9.98 µm (95% CI = −15.74 to −4.23, $P = 0.0001$) thinner in CCS than GHS subjects after adjustment for sex, age, and spherical equivalent. CCS previously having leukemia (B estimate = −10.85, 95% CI = −17.39 to −4.30, *P* value = 0.001) or lymphoma (B estimate = −16.53, 95% CI = −27.20 to −5.85, *P* value = 0.002) had a thinner central macular thickness after adjustment for age, sex, and spherical equivalent. All other, less frequent tumor entities were not significantly associated with alterations in the central macular thickness in the multivariable analysis. No treatment modal-

ity had a significant effect on central macular thickness in the multivariable analysis.

Discussion

To this date, data about long-term CCS and the effect of tumor entity and/or treatment on the eye is rare and studies mostly focus either on one tumor entity or one treatment method. However, in real life, the group of CCS is heterogenic with various tumors which often require a combination of treatment modalities.

In this study, we were able to analyze pRNFL in CCS with different tumor entities and therapies. We detected a thinner pRNFL and central macular thickness in CCS compared to the general population (sample from GHS population) in an age, sex, and spherical equivalent matched setting. The pRNFL was thinner in CCS with prior central nervous system tumors, leukemia, renal tumors, neuroblastoma, soft-tissue sarcoma, and malignant bone tumor, whereas not different in CCS with prior lymphoma, germ cell tumor, and other rare tumor entities like hepatoblastoma. Central macular thickness was thinner in CCS previously having leukemia or lymphoma, but not any other entities.

History of a central nervous system tumor had the strongest impact on pRNFL thickness. This supports the idea that the tumor itself can promote neurodegenerative damage. Reduction of RNFL in patients with a tumor of the central nervous system might be a result of retrograde degeneration due to axon injury.[32] Axon injury is driven by either direct disruption of conduction of the axon, impairment of axoplasmic flow, demyelination with impaired signal conduction, or compressive ischemia.[33] This can not only occur in malignant tumor entities. A significant thinner RNFL was also reported for juvenile and pediatric craniopharyngioma, which is a benign tumor and most commonly suprasellar located.[34] Additionally, surgical resection, which is often needed in patients with tumors, can cause axon injury as well.[33] Germ cell tumors can also occur intracranially,[35] whereas other tumor entities might have intracranial metastasis or subsequent malignant neoplasms occur in the brain.[36]

Yalcinbayir et al.[37] did not find a significant reduction of the RNFL in CCS with leukemia. However, this is potentially due to the small number of studied patients ($n = 27$) set against our larger study sample and smaller effects on the RNFL of leukemia compared with CNS tumors. RNFL thinning in patients with leukemia might be a result of direct impact on the brain or eye. Leukemic infiltration of the retina, optic nerve, and brain are known.[38–40] Effects on central macular thickness were only significantly detectable in the subgroups of participants with previous leukemia and lymphoma, which were the largest subgroups. Other tumor entities might have an effect on central macular thickness, but effects could have been mitigated due to group size.

Next to the possible direct impact of the malignant disease on the pRNFL the treatment regime might play an important role in the pathogenesis of RNFL thinning.

We found treatment with platin derivates to be negatively associated with pRNFL thickness, whereas anthracyclines, cyclophosphamides, and methotrexate in the treatment scheme showed a positive association with pRNFL. Chemotherapy-related neurotoxicity is a rising medical concern. However, its pathomechanism is rarely understood. Anderson et al.[41] reported in a review including six small studies ($n = 13–30$) that platin derivates result in RNFL thinning and potentially impairment of the visual pathway, which is conclusive with our findings. Neurotoxic effects of anthracyclines, cyclophosphamides, and methotrexate are described as well but even less data about effects on the eye or the retina are available.[42–45] The positive effect of anthracyclines, cyclophosphamides, and methotrexate on the pRNFL in the total CCS cohort is not as expected when looking at reported neurotoxic effects. Potentially the use of chemotherapeutics prevents spreading of the malignant disease, which is why over all tumor entities a beneficial effect is detectable. However, the more detailed look at the leukemia subgroup revealed a significantly thinner pRNFL in patients treated with anthracyclines or methotrexate. A potential explanation of the thinner RNFL after methotrexate might be the common intrathecal application since 1986 to reduce the risk for tumor relapse and treatment of meningeosis leucaemica. This direct exposition of the brain to methotrexate is known to potentially trigger leukoencephalopathy and in high dosage can cause acute neurological deficits.[42]

Furthermore, this study revealed a negative association of pRNFL and cranial radiation. This confirms previous reports of neurotoxic effects. For example, Orksi et al.[46] detected a reduction in RNFL in a prospective study including 34 adult patients after robotic fractionated radiotherapy of benign tumors of the parasellar region. We found this negative association in the pRNFL globally and in five of six sectors. For central macular thickness, no direct effects of different treatment regimens were detectable.

Our findings indicate that CCS with thinner pRNFL and central macular thickness compared to

the general population might have a higher risk for ocular neurodegenerative diseases, such as glaucoma. That matches the findings of Whelan et al.[28] who reports an increased risk of self-reported glaucoma 5+ years after cancer treatment in CCS. Previous childhood cancer with antineoplastic treatment might indicate screening for such disease in the future. Furthermore, our data suggest the pRNFL could serve as a potential monitoring parameter in trials for childhood cancer and treatments like in clinical trials for multiple sclerosis monitoring and treatment.[47] The pRNFL can be examined in a cost-effective, noninvasively manner and could serve as a marker for toxicity of different treatment modalities.

There are some limitations of our study. First, recruitment of the CVSS study is based in Germany, whereas the GHS is located in the region of Mainz and Mainz-Bingen. Nevertheless, both samples are population-based. As treatment patterns for childhood cancer are consistent over Germany, the results can be generalized to the German population. In addition, the CCS have a selection bias: in such studies, early mortality will result in a larger proportion of better treatable cancer types. Subjects with severe mental or physical impairment are further less likely to participate. Unfortunately, OCT imaging was not conducted in all subjects due to later inclusion in the study protocol, but item-non-responder analysis revealed that subjects without OCT imaging were not different to those being included in the analysis.

In summary, this study shows a thinner pRNFL in CCS with most common tumor entities, except lymphoma and germ cell tumors for the first time. Cranial radiation and platin derivates had negative and cyclophosphamide positive effects on the pRNFL thickness, whereas the effects on other chemotherapeutics differed between tumor subgroups. Furthermore, a thinner central macular thickness in CCS in the most common tumor entities (leukemia and lymphoma) was observed, but no effects of treatments were detectable.

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