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Ocular Late Effects in Childhood and Adolescent Cancer Survivors: A Report from the Childhood Cancer Survivor Study[a]

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Abstract

Introduction—Approximately 80% of children currently survive 5 years following diagnosis of their cancer. Studies based on limited data have implicated certain cancer therapies in the development of ocular sequelae in these survivors.

Procedure—The Childhood Cancer Survivor Study (CCSS) is a retrospective cohort study investigating health outcomes of 5+ year survivors diagnosed and treated between 1970 and 1986 compared to a sibling cohort. The baseline questionnaire included questions about the first occurrence of 6 ocular conditions. Relative risks (RR) and 95% confidence intervals (CI) were calculated from responses of 14,362 survivors and 3,901 siblings.

Results—Five or more years from the diagnosis, survivors were at increased risk of cataracts (RR:10.8; 95% CI: 6.2–18.9), glaucoma (RR: 2.5; 95% CI: 1.1–5.7), legal blindness (RR: 2.6;

[a]Other investigators and institutions participating in the Childhood Cancer Survivor Study are listed in Appendix.

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Conflict of Interest
The authors have none to declare.

95% CI: 1.7–4.0), double vision (RR:4.1; 95% CI: 2.7–6.1), and dry eyes (RR: 1.9; 95% CI: 1.6–2.4), when compared to siblings. Dose of radiation to the eye was significantly associated with risk of cataracts, legal blindness, double vision, and dry eyes, in a dose-dependent fashion. Risk of cataracts were also associated with radiation 3000+ cGy to the posterior fossa (RR: 8.4; 95% CI: 5.0–14.3), temporal lobe (RR: 9.4; 95% CI: 5.6–15.6), and exposure to prednisone (RR:2.3; 95% CI:.1.6–3.4)

Conclusions—Childhood cancer survivors are at risk of developing late occurring ocular complications, with exposure to glucocorticoids and cranial radiation being important determinants of increased risk. Long-term follow-up is needed to evaluate potential progression of ocular deficits and impact on quality of life.

Keywords

late effects of cancer therapy; radiation therapy; chemotherapy

Introduction

With improvements in multi-modality therapies and supportive care over the past three decades, almost 80% of all children diagnosed with a malignancy will become long-term survivors (1–3). At present, it is estimated that there are over 300,000 survivors of childhood cancer in the United States and by 2010 an estimated 1 of every 570 young adults will be a childhood cancer survivor (4–6). The combined modality therapies that led to such improvements in survival also place survivors at risk of developing late effects of treatment (7). Studies have found that approximately two-thirds of childhood cancer survivors report at least one chronic medical condition related to their diagnosis and/or therapy (4–5).

Neurosensory complications affecting the auditory, ocular, olfactory, or speech systems are commonly reported by survivors. A prospective study by Lackner et al. (8) found that 22% of childhood cancer survivors reported auditory or ocular late effects during the first decade following treatment. Ocular sequelae observed in childhood cancer survivors include cataracts, keratoconjunctivitis sicca, and vision loss. Treatment-related factors, specifically radiation and glucocorticoids, are established risk factors for the development of eye-related complications (9–10). Although multiple studies have investigated ocular late effects and treatment associations, many are hampered by small sample sizes, lack of a comparison group, or vague treatment details.

This study reports the results of an analysis of the long-term ocular-related outcomes in a large cohort of survivors of childhood cancer diagnosed between 1970–1986. Our primary aims were 1) to describe the risk of specific ocular complications with respect to survivors' at 5 years since diagnosis; 2) to compare the occurrence of these ocular complications among survivors to their occurrence among a sibling control group; and 3) to evaluate the effect of specific cancer treatments on the risk of developing late ocular complications five or more years post-diagnosis.

Methods

Patient Selection and Contact

The Childhood Cancer Survivor Study (CCSS) is a multi-institutional collaborative study of individuals who survived at least 5 years after diagnosis of cancer during childhood or adolescence and who met the following criteria: 1) diagnosis of leukemia, kidney tumor, bone tumor, soft tissue sarcoma, neuroblastoma, Hodgkin disease, non-Hodgkin lymphoma, or primary central nervous system malignancy of any histologic subtype; 2) diagnosis and

treatment at 1 of 26 collaborating institutions; 3) diagnosis date between January 1, 1970 and December 31, 1986; 4) age less than 21 years old at diagnosis (11).

The CCSS research protocol and subject contact documents were approved by the Human Subjects Committees at each participating institution. At study entry, a 24-page self-administered baseline questionnaire was sent to eligible study participants. This questionnaire contained queries pertaining to demographic variables, medical conditions, surgical procedures, and other health outcomes. A copy of the baseline survey can be found at: www.stjude.org/ccss.

Of the 20,688 eligible 5-year survivors, 3,123 (15.6%) were lost to follow-up, and therefore could not be contacted for participation. Of the remaining 17,565 cases, 14,362 (81.8%) completed the baseline questionnaire and 3,203 (18.2%) declined to participate. Of the participants, 13,247 (92.2%) gave consent to abstract information from their medical records. Excluding participants on active cancer treatment at the time of the baseline questionnaire and those with incomplete medical records resulted in 12,480 survivors for the current analysis. Nearest age siblings of randomly selected participants were invited to participate as the control population. Of the 4,855 siblings sent a questionnaire, 3901 (80.4%) completed the baseline questionnaire. Comparison analysis is based on these 3901 siblings.

Data Collection

Ocular deficits considered in this analysis included the following: legally blind in one or both eyes, cataracts, glaucoma, double vision, retinal conditions, and very dry eyes requiring drops or ointment. The questions were introduced with the phrase "Have you ever been told by a doctor or other health care professional that you have, or have had… " Possible responses were “yes”, “no”, and “not sure”. If the respondent answered “yes”, they were asked to indicate the *age* at first occurrence of the condition. Information abstracted from medical records included their initial therapy, salvage therapy for recurrent disease, and bone marrow transplant preparative regimens (if applicable). Detailed qualitative information was obtained on 42 chemotherapeutic agents. For this analysis, glucocorticoid drugs were defined as receiving either prednisone or dexamethasone. The medical record abstraction form is available at www.stjude.org/ccss.

Radiation Dosimetry

Within the CCSS, 8,507 patients were documented to have been treated with radiation therapy. Cut-off dates for exposure to radiation were set at 5 years from the diagnosis date of the primary cancer. To quantify radiation exposure, right and left eye doses were calculated for all patients. Doses were based on measurements in a water phantom with corrections made for eye blocking (12). The eye was assumed to be blocked for patients treated with whole brain irradiation. In addition, maximum radiation doses were estimated for the posterior fossa and temporal lobe (which encompasses part of the optic nerve) segment of the brain (9). A brain segment was considered in the radiation field if at least half of the segment was included in the primary radiation volume. For those that received radiotherapy to the brain, radiation exposure to each segment was categorized as either less than 3000 cGy or greater than or equal to 3000 cGy.

Data Analysis

Outcomes were evaluated within two time periods: diagnosis to the 5 year anniversary of the original diagnosis (Period 1), and 5 or more years post-diagnosis (Period 2). In the event that a survivor or sibling reported a condition but did not report the age at first occurrence, multiple-imputation methodology for event time imputation was performed using a slightly

modified version of the technique of Taylor et al. (13–14) to create ten imputed values for each missing age. Age, gender, primary diagnosis, and therapy were used to model the rate of development of each ocular condition, with effects of therapy allowed to change across the two time periods. Therapies included specific radiation fields and two glucocorticoid drugs: dexamethasone and prednisone. The imputation method for siblings did not include diagnosis and therapy information. In analyses run on a data set with complete case data (ages not imputed), estimates for were within the 95% confidence intervals from the imputed analyses.

The relative risk (RR) for developing each ocular condition in the time period ≥ 5 years post-diagnosis, comparing the survivors to the siblings, was estimated by Poisson regression (15), adjusting for gender, and with a cubic spline function for age. Potential within-family correlation was accounted for using generalized estimating equations (16).

The prevalence ratio (PR) at study entry was estimated by dividing the observed count of the condition among survivors by an expected count for the years from diagnosis to 5 years based on an outcome rate from the age and gender- matched siblings. Statistical inference was based on bootstrap samples.

Multivariable Poisson probability models, adjusted for age and gender, were used among survivors to evaluate the impact of eye or brain segment radiation and glucocorticoid drugs on the risk of developing each ocular condition ≥ 5 years post-diagnosis. Busulfan was excluded from the final models as too few cases were exposed (n=47). Cumulative incidence curves, starting with the 5-year anniversary of the primary cancer diagnosis, were constructed using the method described in Gooley et al. (17).

RESULTS

The slight male predominance in the survivor group was not noted in the sibling comparison group (53.7% compared with 48.1%, see Table I). Survivors were younger than siblings, with 77% less than 30 years old at initial contact versus 63% of siblings. More than 60% were younger than 10 years old at diagnosis. Leukemia was the most common diagnosis, accounting for about one-third of the survivor cohort.

Reported Occurrence of Ocular Conditions and Relative Risk Compared to Siblings

For all ocular conditions other than glaucoma, the prevalence of the condition among survivors at 5 years post-diagnosis, relative to siblings, was 2 to 5 fold higher than the rate ratio reported five or more years post-diagnosis (table II). During the period 5+ years post-diagnosis, the risk among survivors was significantly higher (p value <0.05) relative to siblings for all conditions other than retinal condition. We looked at possible correlations between reports of multiple ocular conditions. Among 438 survivors who reported dry eyes 5+ years post-diagnosis, 29 survivors (7%) also reported double vision and 26 (6%) also reported cataracts. At 5 or more years post- diagnosis, 815 survivors (5.67%) reported a first occurrence of an ocular late effect. Two ocular conditions were reported in 96 survivors (0.67%) and only 19 survivors (0.13%) reported 3 or more ocular complications (data not shown in table).

Diagnosis and Treatment Related Factors for Specific Conditions Occurring ≥ 5 Years Post-Diagnosis

Dry eyes requiring drops or ointments were associated with prior treatment with dexamethasone (RR: 1.8; 95% CI: 1.3–2.6, Table III). Eye radiation doses greater than 500 cGy were associated with a statistically significant increased risk of dry eyes (RR: 6.4; 95% CI: 3.4–12.0, for greater than 4000 cGy, Table IV) compared to those with no radiation to

the eye. In addition, radiation doses greater than or equal to 3000 cGy to the temporal lobe demonstrated an increased risk of dry eyes (RR 1.8; 95% CI: 1.3–2.6, Table V). The median time from diagnosis to the onset of very dry eyes was 7.2 years with a range of 0.0–26.7 years. In analyzing the effect of diagnosis on the risk of dry eyes, it was found that the cumulative incidence at 20 years post-diagnosis was greatest for leukemia survivors (cumulative incidence= 5.1%; 95% CI 4.1–6.1, Table VI) and primary CNS malignancy survivors (cumulative incidence= 5.3%; 95% CI 3.8–6.8). The cumulative incidence of self-reported dry eyes, which required treatment, continued to increase up to 25 years after diagnosis for survivors who received > 500 cGy of radiation to the eye (Fig 1, D).

Survivors who received radiation doses greater than 500 cGy to the eye reported an increased risk of double vision (RR: 4.3; 95% CI: 2.6–7.1 for 501–1200 cGy). An increased risk was also seen for radiation doses ≥3000 cGy to the temporal lobe or posterior fossa (RR: 5.7; 95% CI: 3.7–8.7 and RR: 6.5; 95% CI: 4.2–10.1, respectively). The median time from diagnosis to the onset of double vision was 2.2 years with a range of 0.0–26.5 years. At 20 years post-diagnosis, those diagnosed with a primary CNS malignancy had the greatest cumulative incidence of double vision (cumulative incidence= 5.7%; 95% CI 4.1–7.3). Among those who received > 500 cGy radiation to the eye, the cumulative incidence of reported double vision continued to increase up to 20 years after diagnosis (Fig 1, C). A statistically significant decrease in the risk of double vision was present among those exposed to prednisone (RR: 0.6; 95% CI: 0.4–1.0).

Radiation was associated with an increased risk of legal blindness. Specifically, radiation doses greater than 500 cGy to the eye (RR: 5.3; 95% CI: 2.8–10.2 for 501–1200 cGy), any radiation to the posterior fossa, and radiation doses > 3000 cGy to the temporal lobe (RR: 5.7; 95% CI: 3.2–10.1) were associated with a statistically significant increased risk of reporting being legally blind in 1 or both eyes. The median time from diagnosis to the onset of legal blindness was 1.0 year with a range of 0.0–23.5 years. Legal blindness at 20 years post-diagnosis was more common in survivors who were treated for soft tissue sarcomas (cumulative incidence=1.9%; 95% CI 1.0–2.9) and primary CNS tumors (cumulative incidence= 1.8%; 95% CI 1.1–2.6). Cumulative incidence of legal blindness continued to increase up to 20 years post-diagnosis for those treated with radiation to the eye at doses >500 cGy (Fig 1A). Prednisone was inversely associated with legal blindness (RR: 0.6; 95% CI: 0.3–0.9). Further analysis of the 107 survivors reporting late onset legal blindness revealed that the majority were diagnosed with solid tumors (26 primary CNS tumor, 18 soft tissue sarcoma, 4 Ewing sarcoma, 1 osteosarcoma, 9 neuroblastoma, 10 Hodgkin's lymphoma, and 9 kidney tumors) and were not treated with prednisone. Furthermore, out of the 31 survivors who were treated with prednisone and reported late onset legal blindness, 24 also received brain or total body irradiation.

An increased risk of cataracts was reported in survivors who had been treated with prednisone (RR: 2.3; 95% CI: 1.6–3.4) and radiation. This increased risk was present at radiation doses greater than 200 cGy to the eye (RR: 3.2; 95% CI: 2.0–5.2 for 201–500 cGy), and all doses to the posterior fossa and temporal lobe (e.g. RR: 9.4 95% CI: 5.6–15.6 for ≥3000 cGy to the temporal lobe). The median time from diagnosis to the onset of cataracts was 4.7 years with a range of 0.0–24.1 years. At 20 years post-diagnosis, those diagnosed with leukemia (cumulative incidence= 3.5%; 95% CI 2.9–4.2) and a primary CNS malignancy (cumulative incidence= 2.1%; 95% CI 1.3–3.0) had the greatest cumulative incidence of cataracts. Cumulative incidence of cataracts continued to increase up to 20 years after diagnosis for those who received radiation to the eye (doses >500 cGy) (Fig 1B).

Risk of self-reported retinal conditions was not associated with exposure to prednisone or dexamethasone (Table III). The only increase in risk due to radiation was present among

survivors who received radiation doses to the eye of greater than 2000 cGy (RR: 6.3; 95% CI: 1.8–22.3 for radiation doses greater than 4000 cGy). Analysis of risk of retinal conditions based on diagnosis revealed low cumulative incidences at 20 years post diagnosis, with the greatest incidence being seen in survivors of Hodgkin lymphoma (cumulative incidence= 1.3%; 95% CI 0.7–2.0). Analyses of diagnosis or treatment-related risks or for glaucoma did not provide any statistically significant associations. The median time from diagnosis to the onset of retinal conditions was 6.9 years (range 0.0–24.2 years) and the median time to the onset of glaucoma was 10.3 years (range 0.0–23.8).

DISCUSSION

Previous studies have investigated the prevalence of ocular complications in childhood cancer survivors, often targeting specific disease populations (18–23). The current study adds new information by providing risk estimates for the occurrence of eye-related late effects 5 or more years post-diagnosis, with follow-up spanning up to 25 years. The availability of detailed treatment information, including radiation dosimetry to the eye and optic nerve, allowed for investigation of treatment-related risk factors, which can directly inform guideline-based recommendations for long-term follow-up.

The large size, prolonged follow-up period, and diverse diagnosis and treatment characteristics of the CCSS cohort provide a unique opportunity to characterize and quantify the risk of ocular late effects. With the large number of survivors in the cohort it was necessary to rely upon self-reported ocular outcomes. While well-defined ocular outcomes were selected for inclusion in the questionnaire, and self-reported data from survivors were compared to self-reported data from the sibling cohort, it is important to acknowledge that the potential exists for misclassification (I.e., either under- or over-reporting) of outcomes.

The lens is the most sensitive structure of the eye to the effects of ionizing radiation (21). Early studies in adults found that a single dose of 200 cGy or multiple, fractionated doses of radiation at a minimum total dose of 400 cGy could lead to cataract formation (10,21). We found that even low doses of radiation to the eye resulted in an increased risk of cataract formation, which increased with increasing dose. Previous reports have found that latency period and severity of cataracts after total body irradiation is also influenced by other factors, such as steroid treatment for graft versus host disease (GVHD) (18–20). The mechanism triggering the formation of posterior subcapsular cataracts due to chronic high doses glucocorticoid use is controversial (24–25). One opinion is the oxidation of lens proteins and changes to lens hydration by steroids will induce cataract formation. Other theories include glucocorticoid receptor activation leading to changes in transcription of specific genes, such as RGC32 protein, which has been reported to induce cellular proliferation (24–25). While our study found that prednisone was associated with cataract formation, we found no increased risk of cataracts in survivors treated with dexamethasone, possibly due to the small number of survivors in the CCSS cohort exposed to dexamethasone.

A known complication of radiation to the orbit is severe dry eyes, also known as keratoconjunctivitis sicca, with symptoms increasing when the dose to the eye is > 4000 cGy (26–28). Radiation may damage the lacrimal apparatus through various mechanisms, including scarring of the canaliculi and puncta and failure of the lacrimal pump due to decreased eyelid mobility (10). This complication was observed in our survivors with as little as 500 cGy radiation to the eye. Other factors within CCSS survivors could also account the increased risk of severe dry eyes. For example, 6.8% of CCSS survivors who reported late onset dry eyes had received total body irradiation, presumably as part of a preparative regimen for a bone marrow transplant. This subset would be at risk for the

development of chronic GVHD, which frequently affects the eye and manifests as keratoconjunctivitis sicca (22). Specific information on type of transplant was not collected for the original CCSS cohort, but will be available for the CCSS cohort expansion that is currently underway and may provide more insight into the risk of ocular complications after transplant.

Our analysis identified two associations that require further investigation. The first is the reported late onset of diplopia. Double vision may be secondary to ocular and brain conditions, including cataracts, retinal detachment, cranial nerve palsies, astigmatism, or uncorrected refractory errors (29). We found a modest correlation between diplopia and other reported ocular conditions, with 6% of survivors with cataracts also reporting double vision. Second, is the risk of reported late-onset legal blindness. A small percentage of survivors with late onset blindness also reported cataracts, which may have contributed to vision loss in 22 out of 107 survivors. In addition, 20 survivors who reported a recurrence of their primary CNS malignancy or developed a second malignant neoplasm located in the CNS reported vision loss occurring 5 or more years after initial diagnosis. The underlying etiology of the reported blindness however, is not clear.

Glucocorticoids appear to have a protective effect against development of some ocular conditions, such as legal blindness or diplopia. Other studies have noted the beneficial anti-inflammatory effects of steroids with respect to some eye-related conditions such as keratitis and macular degeneration (30–31). This finding may be reflective of the underlying cancer diagnosis, and should be pursued in future research endeavors.

We found no increase in risk of glaucoma among survivors treated with glucocorticoid therapy. Some reports suggest an increased risk of open angle glaucoma after steroid use due to alterations in the trabecular meshwork, resulting in impaired aqueous outflow (32). Other studies have found that increased intraocular pressure after prolonged oral glucocorticoid therapy is rare (22). It is possible we may have underestimated the true incidence of glaucoma in survivors, as it is often an asymptomatic condition, difficult to diagnose unless routine eye exams include measuring intraocular pressure. Additional follow-up may uncover increased risk of glaucoma in childhood cancer survivors treated with steroid therapy

In summary, survivors of childhood cancer are at increased risk for ocular late effects, related to both glucocorticoid and radiationx exposure. This analysis demonstrates that self-reported eye-related complications continue to manifest more than 5 years after diagnosis. While some of these effects have a minor impact on survivors' quality of life, others, such as blindness and cataracts, may have significant consequences. Continued medical follow-up of survivors is essential for early detection to minimize the effects of ocular complications, and to optimizing survivors' quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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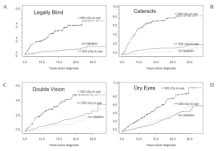

Figure 1.
Cumulative incidence (%) of select ocular conditions and radiation exposure >500 cGy to eye: >500 cGy to eye, some to brain segments; Brain segment: <=500 cGy to eye, some to brain segments; No radiation: Zero cGy to eye and brain

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Table I

Demographics of Survivors and Siblings

Characteristic		Survivor		Sibling	
		N	%	N	%
Gender	Female	6645	46.3	2026	51.9
	Male	7717	53.7	1875	48.1
Age at baseline(yrs)*	<18	3959	27.6	816	20.9
	18–29	7165	49.9	1652	42.3
	30–39	2906	20.2	1117	28.6
	40–49	332	2.3	304	7.8
	49+	0	0	12	0.3
Vital Status	Alive	12602	87.7	3901	100
	Dead	1760	12.3	0	0
Age at diagnosis	0–4	5756	40.1	NA	NA
	5–9	3200	22.3	NA	NA
	10–14	2915	20.3	NA	NA
	15–20	2491	17.3	NA	NA
Year of diagnosis	1970–1973	1923	13.4	NA	NA
	1974–1977	2913	20.3	NA	NA
	1978–1981	3758	26.2	NA	NA
	1982–1986	5768	40.2	NA	NA
Diagnosis	Leukemia	4833	33.7	NA	NA
	Hodgkin’s Disease	1926	13.4	NA	NA
	CNS Tumor	1877	13.1	NA	NA
	Kidney Tumor	1257	8.8	NA	NA
	Soft Tissue Sarcoma	1245	8.7	NA	NA
	Bone Tumor	1188	8.3	NA	NA
	NHL	1082	7.5	NA	NA
	Neuroblastoma	954	6.6	NA	NA
Radiation: Post Fossa	zero dose	4137	33.5	NA	NA
	1cGy−<30 Gy	7106	57.6	NA	NA

Characteristic		Survivor		Sibling	
		N	%	N	%
Radiation: Temporal Lobe	30+ Gy	1092	8.9	NA	NA
	zero dose	4137	33.5	NA	NA
	1cGy– <30 Gy	6821	55.3	NA	NA
Radiation: Eye	30+ Gy	1376	11.1	NA	NA
	zero dose	4143	34	NA	NA
	0.1–200 cGy	3761	30.9	NA	NA
	201–500 cGy	3135	25.7	NA	NA
	501–1200 cGy	848	7	NA	NA
	1201–2000 cGy	127	1	NA	NA
	2001–4000 cGy	78	0.6	NA	NA
	>4000 cGy	98	0.8	NA	NA
Chemotherapy: Busulfan	No	12529	99.6	NA	NA
	Yes	47	0.4	NA	NA
Dexamethasone	No	11561	91.9	NA	NA
	Yes	1015	8.1	NA	NA
Prednisone	No	6704	53.3	NA	NA
	Yes	5872	46.7	NA	NA

NA: not applicable;

* p value <0.0001;

NHL: Non Hodgkin's Lymphoma

Table II

Reported Ocular Conditions in Survivors- Prevalence Ratios Compared to Sibling Cohort

	No.		Diagnosis to 5 years post diagnosis		5+ years post diagnosis		
Ocular Condition	**No**[a]	**Yes**[b]	**Yes**	**Prevalence Ratio (95% CI)**	**Yes**	**Incidence Rate*** **(95% CI)**	**Relative Risk**** **(95% CI)**
Dry Eyes	13574	788	278	4.6 (3.5–6.1) [d]	438	3.9 (3.3–4.5)	1.9 (1.6–2.4) [d]
Double Vision	13765	597	325	14.5 (9.5–22.1) [d]	200	1.5 (1.2–1.9)	4.1 (2.7–6.1) [d]
Legally Blind	13782	580	383	12.4 (8.5–18.1) [d]	107	0.8 (0.6–1.1)	2.6 (1.7–4.0) [d]
Cataracts	13854	508	248	23.1 (12.6–42.3) [d]	215	1.2 (0.9–1.5)	10.8 (6.2–18.9) [d]
Retinal Condition	14213	149	52	3.4 (1.9–5.8) [d]	78	0.5 (0.3–0.6)	1.3 (0.9–2.0)
Glaucoma	14303	59	20	----	33	0.2 (0.1–0.3)	2.5 (1.1–5.7) [c]

* among survivors, per 1000 person-years;

** adjusted for age at baseline completion; ---: not estimable; 95% CI: 95% confidence interval;

[a] the “No” column also contains counts for “not sure” and missing;

[b] the “Yes” column includes those who developed the condition before diagnosis and those who were unsure of when the condition first occurred;

[c] p value<0.05;

[d] p value< 0.01

Table III

Glucocorticoid Exposure and Relative Risk of Late Ocular Conditions ≥5 Years Post-Diagnosis

	Chemotherapy Relative Risk* (95% CI)	
Ocular Condition	**Prednisone**	**Dexamethasone**
Dry Eyes	1.1 (0.9–1.5)	1.8 (1.3–2.6)*b*
Double Vision	0.6 (0.4–1.0) *a*	1.4 (0.8–2.6)
Legally Blind	0.6 (0.3–0.9) *a*	1.0 (0.4–2.5)
Cataracts	2.3 (1.6–3.4) *b*	1.2 (0.8–1.9)
Retinal Condition	0.7 (0.4–1.2)	1.6 (0.6–4.1)
Glaucoma	0.6 (0.2–1.6)	---

*Models adjusted for age, gender, and radiation to the eye; 95% CI: 95% confidence interval; ---: not estimable;

a p value <0.05;

b p value <0.01

Table IV

Radiation Dose to Eye (maximum dose) and Risk of Late Ocular Conditions ≥ 5 Years Post-Diagnosis

	Relative Risk* (95% CI)					
Ocular Condition	**1–200 cGy**	**201–500 cGy**	**501–1200 cGy**	**1201–2000 cGy**	**2001–4000 cGy**	**>4000 cGy**
Dry Eyes	0.8 (0.6–1.0)	1.0 (0.7–1.4)	2.0 (1.4–2.9) *b*	3.2 (1.3–7.5) *b*	3.4 (1.3–9.3) *a*	6.4 (3.4–12.0) *b*
Double Vision	1.4 (0.9–2.2)	1.8 (1.1–2.9)*a*	4.3 (2.6–7.1) *b*	5.0 (1.8–14.1) *b*	3.5 (0.9–13.7)	3.8 (1.3–10.7) *a*
Legally Blind	1.1 (0.6–2.0)	1.5 (0.7–3.1)	5.3 (2.8–10.2) *b*	9.2 (3.1–27.2) *b*	15.8 (5.1–48.5) *b*	26.6 (11.2–62.9) *b*
Cataracts	0.6 (0.3–1.3)	3.2 (2.0–5.2) *b*	10.7 (6.2–18.4) *b*	52.2 (28.6–95.3) *b*	28.2 (10.9–73.3) *b*	17.9 (6.0–53.6) *b*
Retinal Condition	1.4 (0.8–2.7)	1.6 (0.8–3.3)	1.4 (0.5–3.9)	---	7.3(1.7–31.8) *b*	6.3 (1.8–22.3) *b*
Glaucoma	1.6 (0.6–4.4)	1.4 (0.4–5.5)	2.5 (0.6–10.2)	---	---	---

*Models adjusted for age, gender, dexamethasone, and prednisone; 95% CI: 95% confidence interval; ---: not estimable;

a p value <0.05;

b p value <0.01

Table V

Radiation Dose to Various Regions of the Brain and Risk of Late Ocular Conditions ≥5 Years Post-Diagnosis

	Relative Risk* (95% CI)			
	Posterior Fossa		Temporal Lobe	
Ocular Condition	**<3000 cGy**	**≥3000 cGy**	**<3000 cGy**	**≥3000cGY**
Dry Eyes	1.0 (0.8–1.3)	1.4 (1.0–2.1)	1.0 (0.7–1.2)	1.8 (1.3–2.6) *b*
Double Vision	1.3 (0.9–1.9)	6.5 (4.2–10.1) *b*	1.2 (0.8–1.8)	5.7 (3.7–8.7) *b*
Legally Blind	1.8 (1.1–3.1) *a*	3.6 (1.9–7.0) *b*	1.4 (0.8–2.4)	5.7 (3.2–10.1) *b*
Cataracts	2.9 (1.9–4.7) *b*	8.4 (5.0–14.3) *b*	2.7 (1.7–4.3) *b*	9.4 (5.6–15.6) *b*
Retinal Condition	1.5 (0.8–2.6)	2.1 (0.9–4.9)	1.5 (0.8–2.6)	2.0 (0.9–4.5)
Glaucoma	1.7 (0.6–4.3)	3.0 (0.8–10.8)	1.6 (0.6–4.2)	3.0 (0.8–10.6)

*Models adjusted for age, gender, dexamethasone, and prednisone; 95% CI: 95% confidence interval;

a p value <0.05;

b p value <0.01

Table VI

Cumulative Incidence (%) and 95% C.I. for Ocular Conditions at 20 Years Post-Diagnosis by Diagnosis Group

	Diagnosis							
Ocular Condition	**Leukemia**	**CNS Tumor**	**Hodgkins Disease**	**NHL**	**Kidney Tumor**	**Neuroblastoma**	**Soft Tissue Sarcoma**	**Bone Tumor**
Dry Eyes	5.1(4.1–6.1)	5.3(3.8–6.8)	3.6(2.5–4.6)	3.6(1.9–5.3)	4.3(2.5–6.1)	3.9(2.1–5.6)	3.9(2.5–5.3)	4.1(2.5–5.7)
Double Vision	1.2(0.7–1.6)	5.7(4.1–7.3)	1.9(1.2–2.7)	1.1(0.3–1.9)	1.4(0.6–2.2)	0.8(0.1–1.5)	1.8(0.8–2.8)	1.3(0.4–2.1)
Legally Blind	0.9(0.5–1.2)	1.8(1.1–2.6)	0.6(0.2–1.0)	0.1(0.0–0.3)	0.9(0.2–1.5)	1.1(0.2–2.0)	1.9(1.0–2.9)	0.5(0.0–1.0)
Cataracts	3.5(2.9–4.2)	2.1(1.3–3.0)	0.1(0.0–0.3)	1.5(0.7–2.3)	0.4(0.0–1.0)	0.7(0.0–1.4)	1.3(0.6–2.0)	0.2(0.0–0.5)
Retinal Condition	0.6(0.2–0.9)	0.7(0.1–1.3)	1.3(0.7–2.0)	0.7(0.0–1.4)	1.2(0.2–2.3)	0.6(0.0–1.4)	0.8(0.2–1.3)	0.7(0.0–1.5)
Glaucoma	0.2(0.0–0.3)	0.8(0.2–1.4)	0.4(0.0–0.8)	0.3(0.0–0.6)	0.2(0.0–0.7)	0.1(0.0–0.3)	0.7(0.0–1.5)	0.0(0.0–0.0)

95% CI: 95% confidence interval; NHL: Non-Hodgkins Lymphoma