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PENTEC ORGAN SYSTEM REVIEW

Retinopathy, Optic Neuropathy, and Cataract in Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review

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Purpose: Few reports describe the risks of late ocular toxicities after radiation therapy (RT) for childhood cancers despite their effect on quality of life. The Pediatric Normal Tissue Effects in the Clinic (PENTEC) ocular task force aims to quantify the radiation dose dependence of select late ocular adverse effects. Here, we report results concerning retinopathy, optic neuropathy, and cataract in childhood cancer survivors who received cranial RT.

Methods and Materials: A systematic literature search was performed using the PubMed, MEDLINE, and Cochrane Library databases for peer-reviewed studies published from 1980 to 2021 related to childhood cancer, RT, and ocular endpoints including dry eye, keratitis/corneal injury, conjunctival injury, cataract, retinopathy, and optic neuropathy. This initial search yielded abstracts for 2947 references, 269 of which were selected as potentially having useful outcomes and RT data. Data permitting, treatment and outcome data were used to generate normal tissue complication probability models.

Results: We identified sufficient RT data to generate normal tissue complication probability models for 3 endpoints: retinopathy, optic neuropathy, and cataract formation. Based on limited data, the model for development of retinopathy suggests 5% and 50% risk of toxicity at 42 and 62 Gy, respectively. The model for development of optic neuropathy suggests 5% and 50% risk of toxicity at 57 and 64 Gy, respectively. More extensive data were available to evaluate the risk of cataract, separated into

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self-reported versus ophthalmologist-diagnosed cataract. The models suggest 5% and 50% risk of self-reported cataract at 12 and >40 Gy, respectively, and 50% risk of ophthalmologist-diagnosed cataract at 9 Gy (>5% long-term risk at 0 Gy in patients treated with chemotherapy only).

Conclusions: Radiation dose effects in the eye are inadequately studied in the pediatric population. Based on limited published data, this PENTEC comprehensive review establishes relationships between RT dose and subsequent risks of retinopathy, optic neuropathy, and cataract formation.

Introduction

Treatment for many pediatric malignancies (eg, for primary eye/brain tumors, head and neck sarcomas, and hematologic malignancies requiring total body irradiation [TBI]) involves radiation therapy (RT) to, or near, ocular structures. RT has the potential, even at only moderate doses, to injure ocular tissues and thereby compromise function with enduring complications in survivors. Because the eye is a critical sensory organ, injury or loss of function dramatically affects quality of life. A thorough understanding of RT dose-volume effects is necessary to balance our goal to optimize tumor control while decreasing ocular complications. However, limited data exist describing radiation dose-related late ocular toxicities in childhood cancer survivors who received RT. This comprehensive Pediatric Normal Tissue Effects in the Clinic (PENTEC) review aims to describe the risks of 3 ocular complications in pediatric cancer survivors who received cranial RT: retinopathy, optic neuropathy, and cataract formation (other potential complications considered could not be adequately assessed with the available data).

Clinical Significance

RT is a key component in the treatment of several pediatric tumors involving, or near, ocular structures. Typical doses prescribed for focal RT are 45 to 60 Gy; for craniospinal irradiation (not including focal boost), 18 to 36 Gy; and for TBI, 2 to 15 Gy, typically in 1.8 to 2 Gy/fraction. These doses can damage ocular structures.

Cataracts

Cataract is the most common radiation-associated ocular injury, as there is likely no minimum threshold dose for risk of cataract formation, and the risk increases as dose to the lens increases.[1] Reported risks of cataract formation vary significantly depending on the method of assessment: ophthalmologist-diagnosed cataract occurs at much higher rates than self-reported cataract, suggesting that self-reported events represent a more clinically significant injury. In patients receiving older TBI regimens (largely 8 Gy or more), 5-year risk of ophthalmologist-diagnosed cataract was ~30% to 70%.[2] For long-term survivors on the Childhood Cancer Survivor Study (CCSS), the prevalence of self-reported cataract formation at the end of follow-up (mean, 21.4 years) was 1.3% for lens exposure <0.5 Gy, 1.8% for 0.5 to <1.5 Gy, 3.5% for 1.5 to <2.5 Gy, 6.1% for 2.5 to <3.5 Gy, 8.1% for 3.5 to <5.0 Gy, 9.8% for 5.0 to <10.0 Gy, 32.2% for 10.0 to <20.0 Gy, and 40.6% for exposure of 20 to 60 Gy.[3] The median time from date of first cancer diagnosis to development of self-reported cataract was 9.6 years. Given that cataracts can occur after even low doses of RT to the lenses, and lens replacement surgery is an option, it is uncommon to limit dose to the lenses at the expense of target coverage. However, in pediatric patients, lens replacement is a much greater challenge, as there are continued changes in the refractive elements of the eye during childhood, and unequal input between the eyes during development can result in amblyopia. Thus, optical rehabilitation and postoperative supervision is much more critical and extensive for pediatric patients than adults.[4]

The current standard use of intensity modulated RT for focal RT poses an interesting shift in the risk of cataract formation compared with 3-dimensional conformal RT: while high doses to the ipsilateral lens can be reduced, there may be increased low-dose RT exposure to the contralateral lens,[5,6] which is still associated with risk of cataract formation. Thus, reducing both high- and low-dose RT exposures to the lenses should be prioritized for pediatric patients; proton therapy may be beneficial for some circumstances in maximally sparing the ocular structures.

Retinopathy and optic neuropathy

Radiation-associated retinopathy manifests as a deterioration of vision, characterized by visual distortion and decreased visual acuity (metamorphasia). Radiation-associated optic neuropathy is typically characterized by painless, monocular vision loss (dyschromatopsia), decreased visual acuity, and progressive visual field defects. Both are much less common than radiation-associated cataract formation because of the higher doses required to cause retinal or optic nerve injury. Because of difficulty repairing these injuries, radiation oncologists generally opt to underdose targets to spare the retina and optic apparatus from doses for which unacceptable risk of vision loss would be anticipated. Both radiation-associated retinopathy and optic neuropathy occur months to years after exposure. Although damage is often difficult to reverse, both injuries, particularly retinopathy, can be improved with anti−vascular endothelial growth factor injections, and photocoagulation, corticosteroids, and

hyperbaric oxygen treatment may also help minimize complications.[7-9]

Although radiation-associated optic neuropathy is a better studied endpoint in adults (vs children), as described in the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) analysis,[10] limited clinical data exist for pediatric patients for this endpoint. Radiation-associated retinopathy is less well studied for both adults and pediatric patients. Early vision loss from ocular structure damage (lens, retina, optic nerve) can affect learning, social, and psychological development.[11,12]

Other ocular toxicities

Other nonvisual acuity complications can also significantly affect quality of life, including dry eye, keratitis, conjunctivitis, and glaucoma. Severe complications can even result in enucleation. Reports describe the qualitative effect of RT on some of these outcomes, but limited data exist on the quantitative dose-effect relationship between RT and these other ocular complications. Studies of late sequelae in children treated with RT for orbital rhabdomyosarcoma describe keratoconjunctivitis in ~20% to 30%, eyelid fibrosis/atrophy in ~20%, and lacrimal fibrosis/lacrimation complications in ~15%.[13-15] Transient eyelid erythema and lash loss as well as keratoconjunctivitis have been described at 30 to 40 Gy, and permanent injury including corneal ulcer, scarring, and perforation, lacrimal atrophy/stenosis, chronic conjunctivitis, and permanent lash loss have been reported at 50 to 60 Gy.[16] A study from the CCSS noted increased risk of dry eyes at doses to the eye greater than 5 Gy (relative risk of 6.4 for doses >40 Gy).[17]

Endpoints and Toxicity Scoring

This systematic review focused on endpoints of retinopathy, optic neuropathy, and cataract in children who received RT to the eye/ocular structures.

The Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (https://ctep.cancer.gov) scores cataract, retinopathy, and optic neuropathy based on the presence of symptoms affecting visual acuity, effect on activities of daily living, and need for intervention (Table 1). However, the CTCAE has several limitations (eg, lack of characterizing partial vision loss or visual field deficit, as well as time interval to developing toxicity). Moreover, most of the reports cited in this review did not use CTCAE or any specific toxicity scoring system. Therefore, it is impossible to link definitively the risks presented in this report with a specific grade of toxicity. In this review, we included all reported events of all levels of severity.

Anatomy and Developmental Dynamics

The eye is composed of 3 major tissues: the cornea, the lens, and the retina. Retinal ganglion cells grow toward the optic stalk, and their axons form the optic nerve (Fig. 1).[18] The anterior tissues, including the cornea and lens, derive from surface ectoderm and mesenchyme, and posterior tissues, including the retina, develop from the neural tube. The lens and cornea focus and refract light onto the posterior retina, which transmits visual information via the optic nerve to the brain.[19] The macula is the central portion of the retina that surrounds the fovea centralis, the point of maximum optical resolution.

Although most eye development occurs during gestation, full development of the retina/fovea centralis occurs several months after birth in humans. Similarly, the axons of the optic nerve become myelinated beginning at the seventh month of gestation, and although at birth the optic nerve is 3 mm thick, the diameter continues to increase for 6 to 8 years after birth.[18] Human lens growth is biphasic, with gestational growth resulting in formation of an adult nuclear core by 3 months after birth and subsequent growth over most of a person's life leading to an ever-expanding cortex.[20] The majority of the lens is comprised of uniquely elongated

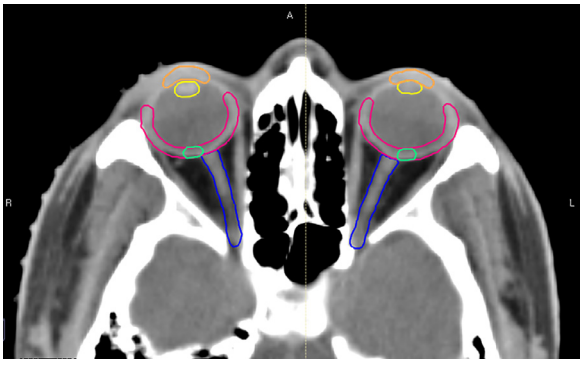

Fig. 1. Anatomy of the eye via axial computed tomography scan. Orange = cornea, yellow = lens, pink = retina, green = macula, blue = optic nerve.

Table 1 CTCAE version 5.0 toxicity scoring for cataract, retinopathy, and optic nerve disorder

CTCAE version 5.0	Grade 1 toxicity	Grade 2 toxicity	Grade 3 toxicity	Grade 4 toxicity
Cataract, retinopathy, optic nerve disorder	Asymptomatic, clinical dx only, no intervention	Symptomatic, moderate decrease in visual acuity, symptoms affecting instrumental ADL	Symptomatic with marked decrease in visual acuity, limiting self-care ADL	Best corrected visual acuity 20/200

Abbreviations: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events; dx = diagnosis.

fiber cells, which lose their organelles and cell nuclei during the final differentiation process.[18]

Based on preclinical data in zebrafish, there is no clear evidence that early x-ray irradiation affects eye development.[21] However, clinical data are lacking. Injury to ocular structures from ionizing radiation is best studied in the lens, retina, and optic nerve. The human lens has a lifespan of decades, and as lens fiber cells lack nuclei and other organelles, radiation-induced damage to macromolecules is retained because these macromolecules cannot be easily replenished. As humans age, combined lifestyle, genetic, and environmental processes result in damage to lens macromolecules, leading to cataract formation. Additional damage from radiation-induced free radical generation and oxidative stress accelerates lens aging and cataract development.[22] There are 3 primary types of cataract based on lens anatomy: nuclear (affecting the core of the lens), cortical (affecting the lens fibers surrounding the core), and posterior subcapsular (affecting the most posterior cortical layer, directly under the lens capsule). Although age-related cataracts are typically nuclear or cortical cataracts, radiation-induced cataracts are more commonly posterior subcapsular cataracts.[22] Limited histologic data on radiation-induced cataracts (from atomic bomb survivors, patients treated with RT for ocular tumors, etc) suggest the lens epithelium, particularly at the equatorial region, is most sensitive to radiation exposure.[23] Posterior subcapsular cataracts develops from posterior migration of lens epithelial cells from the equator, often due to an external stimulus, such as radiation or long-term corticosteroid use.[24,25]

The mechanisms of radiation-associated retinopathy and optic neuropathy are less clearly understood. The first sign of radiation-associated retinopathy is preferential loss of vascular endothelial cells, followed by ischemia, retinal degradation, and late-stage neovascularization. The macula, the central portion of the retina, appears to be preferentially affected, and it is proposed that the latency of radiation-associated retinopathy is related to the slow life cycle of retinal vascular endothelial cells.[26,27] Radiation-associated optic neuropathy is also thought to stem from endothelial cell damage, resulting in gradual damage to nerve fibers and retinal ganglion cells, although somatic mutations in glial cells may also result in metabolically deficient cells, which results in demyelination and neuronal degeneration. The longer latency is thought to reflect the slow turnover rate of both glial and endothelial cells.[26,28]

Defining Volumes: Pediatric Imaging Issues

The ability to contour accurately depends on imaging modality. The lens, distal optic nerves, and retina are typically well visualized on computed tomography (CT). The optic chiasm and proximal optic nerves can also be seen, but (depending on scan slice thickness) it can be challenging to visualize on CT. Depending on the level of accuracy needed, these structures can usually be better visualized with a T1-weighted magnetic resonance imaging (MRI).[29,30]

For the purpose of comparing data series or developing broad guidelines, it is critical that the relevant structures be consistently defined. To facilitate this, contouring guidelines that have been proposed for optic structures at risk, including the lens, retina, optic nerve, and optic chiasm, should be followed.[29-34] The most recent global consensus recommendations, published by the Global Harmonisation Group for Clinical Trial Quality Assurance (www.rtqaharmonization.org),[30] compiled guidelines from numerous consensus standards:

- Lens: The lens is a clearly visible biconvex, avascular structure located between the vitreous humor and the iris. The diameter measures up to 10 mm.[29,31]
- Retina: The retina is a 2- to 3-mm-thick membrane covering the posterior 5/6 of the globe. The anterior border is approximately at the insertion of the medial and lateral rectus muscles.[31]
- Macula: The macula is the central portion of the retina, measuring 5 to 6 mm in diameter and located temporally and slightly inferiorly to the center of the head of the optic nerve. The macula cannot be distinguished on CT or MRI from the rest of the retina, but a surrogate region should be delineated for avoidance purposes.[32]
- Optic chiasm: The optic chiasm is located in the subarachnoid space of the suprasellar cistern, approximately 10 mm cranial to the pituitary gland and anterior to the pituitary stalk. Laterally, the optic chiasm is bordered by the internal carotid artery and the anterior communicating artery. The contour meets the optic nerves anteriorly and includes the divergence of the optic tracts posteriorly. When contouring, the optic chiasm should be contiguous with the optic nerves. Thin-slice (<1-2 mm) MRI is essential for accurate delineation of the optic chiasm.[29,31,33]
- Optic nerve: The optic nerve is a 2- to 5-mm-diameter structure originating at the posterior aspect of the eye, passing through the bony optic canal and terminating at the optic chiasm. When contouring, the optic nerves should be contiguous with the eye and the optic chiasm.[31,33]
- Lacrimal gland: The lacrimal gland lies in the superolateral extraconal portion of the orbit, medial to the zygomatic process of the frontal bone, superior to the lateral rectus muscle, and lateral to the superior rectus muscle. Its size varies, up to 20 mm in the craniocaudal dimension, 15 mm in the anteroposterior dimension, and 5 mm in the transverse dimension.[29,31]
- Cornea: The cornea is located at the anterior portion of the eyeball, ventral to the vitreous humor, the iris, ciliary body, and lens. Using a brush of 2 to 3 mm, the cornea can be delineated on MRI and CT.[31]

Per American Society for Radiation Oncology consensus guidelines,[34] the eye (globe), lens, and optic nerves/chiasm should be contoured for brain, orbit, craniospinal irradiation,

nasopharynx, and sinonasal treatments. In addition, contouring the retina specifically should be considered for orbit treatments. The lens and eye (globe) should be contoured for treatments of the face/parotid. Contouring the lacrimal glands is recommended for orbit treatments and should be considered for brain, face/parotid, and sinonasal treatments. There are currently no consensus guidelines on indications for contouring the macula as a specific portion of the retina or for contouring the cornea, but we encourage contouring these structures for orbit and sinonasal treatments.

We strongly encourage studies to apply structure names for these organs compliant with the American Association of Physicists in Medicine Task Group-263 report on standardized nomenclature,[35] in particular, Eye_L/R, Lens_L/R, OpticChiasm, OpticNrv_L/R, Retina_L/R.

Eye motion during RT can result in variation in the position of the lens, macula, and anterior portion of the optic nerve, up to several millimeters.[36,37] For targets near these structures, we encourage use of a planning organ-at-risk volume for conventionally fractionated treatment regimens and asking the patient to look forward if they are old enough to do so. When hypofractionation is used and the effect of motion may not be averaged over a longer course of treatment, consideration should be given to methods to minimize eye motion or use an eye tracking and gating system.[38-40] If the bolus effect of a closed eyelid is not relevant, then closing the eyes more consistently minimizes eye motion.[41]

Review of Dose-Volume Response Data and Risk Factors

Search methodology

Comprehensive literature search criteria were developed to identify studies that evaluated radiation dose-volume effects on the risk of cataract, retinopathy/retinal injury, optic nerve/chiasm injury, dry eye/lacrimal gland damage, lacrimal duct damage, eyelid injury/atrophy, keratitis, conjunctivitis, and glaucoma among childhood cancer survivors. This comprehensive review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[42] PubMed and Cochrane Library searches of peer-reviewed articles written in English and published from January 1, 1980, to December 31, 2021, were conducted. Appendix E1 provides further details of the search strategy and data collection.

Ten investigators independently reviewed titles and abstracts and subsequently full texts of any article that any reviewer considered potentially eligible. For eligible studies, the same investigators independently extracted the information on study design, source of data, population characteristics, and outcomes of interest using an electronic data extraction form. Studies were included if they had quantitative or adequate qualitative data describing ocular toxicity outcomes for patients younger than age 21 years who constituted at least 50% of the study cohort. Outcomes were not limited to a specific follow-up duration. In addition, information about treated volumes and dose information as a group or individual (prescribed dose, fractionation) were required. Additional information, if available, for technique, dose distribution, and other therapies was recorded.

A total of 2947 unique references at title and abstract screening were identified. After review by task force members, 269 studies with potentially relevant information were selected. Of those, 11 studies included pertinent data that were included in our pooled analyses for retinopathy (n = 4 studies), optic neuropathy (n = 2), both retinopathy and optic neuropathy (n = 1), and cataract (n = 4). Figure 2 summarizes the selection and elimination process used to identify the eligible studies. Tables 2 to 4 summarize these studies. There were insufficient data to generate normal tissue complication probability (NTCP) models to analyze the relationship between RT exposure and endpoints of keratitis, dry eye, conjunctivitis, and glaucoma, among other ocular endpoints.

Review of historical dose-volume response data

Retinopathy

Five studies contained sufficient data to contribute to NTCP models for radiation-associated retinopathy (summarized in the following sections and in Table 2).

In the study with the most events, Coucke et al[43] reported on outcomes of 44 eyes in 38 children treated with external RT for retinoblastoma, with a minimum follow-up of 12 months (range, 14 months to 17 years). RT technique and dose fractionation varied widely, with 39 of 44 treated with lateral beam technique versus anterior or anterior/lateral beam, dose per fraction ranged from 1 to 4.5 Gy, and total dose ranged from 30 to 61.5 Gy. Clinical evidence of retinopathy (diagnosed by clinical examination and photography, eventually confirmed by angiography) was noted in 10 of 44 treated eyes, at total doses ranging from 44 to 61.5 Gy and dose/fraction of 2 to 4.5 Gy. Four of the 10 cases also had treatment with concurrent chemotherapy. The study derived a dose-response model for the risk of retinopathy, as described in the following.

Haik et al[13] described outcomes of 18 patients (15 children with mean age 6 years, 3 adults with mean age 21 years) with parameningeal rhabdomyosarcoma involving the orbit. The primary tumor received 45 to 72 Gy, and chemotherapy began with the start of RT for a total of 8 cycles. Eleven of 18 patients had a minimum follow-up of 2 years (range, 2-12 years). Of these 11 patients, retinopathy was noted in 1 patient who received 57 Gy with concurrent chemotherapy.

In a report from the Intergroup Rhabdomyosarcoma Studies II and III, Raney et al[44] studied 213 children with nonorbital soft tissue sarcoma of the head and neck who survived relapse-free for 5 or more years after diagnosis. The primary tumor received a total dose of 40 to 60.6 Gy,

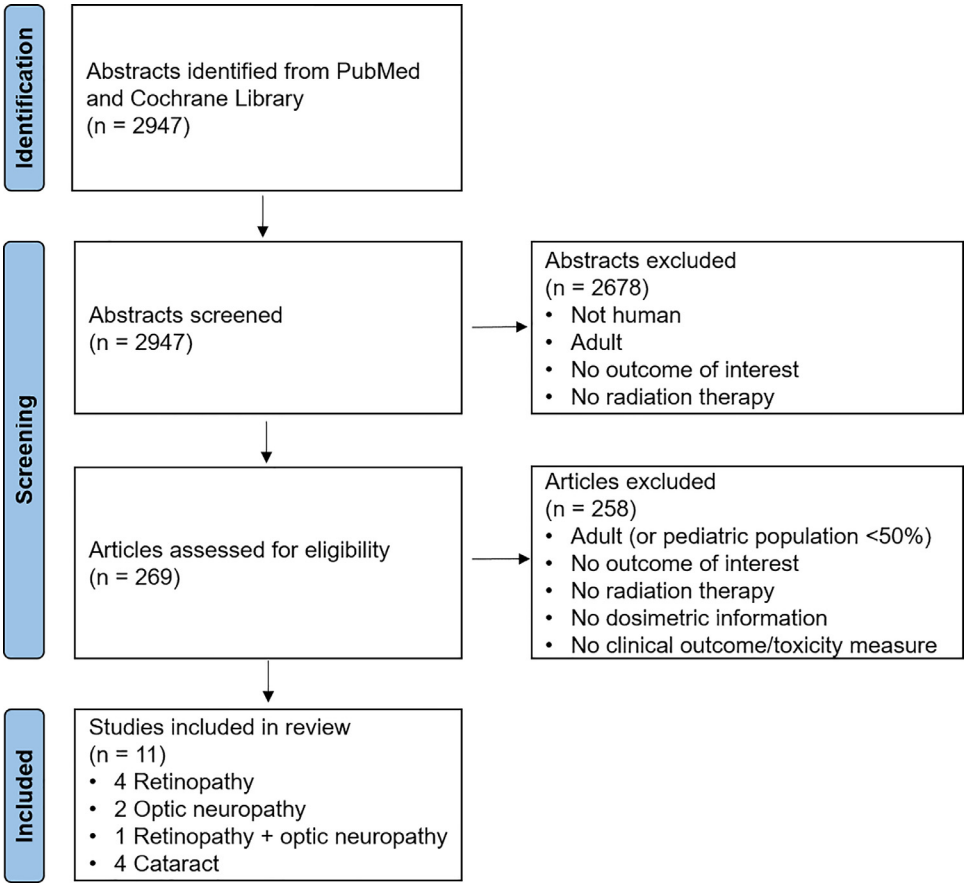

Fig. 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram summarizing process of selection and elimination of published data used in evaluation for this project.

and all patients received concurrent chemotherapy. Four patients developed retinopathy or retinal hemorrhage at estimated doses to the eye of 47 to 65.8 Gy.

Anteby et al[45] reviewed outcomes of 38 children (50 eyes) treated with RT for retinoblastoma (median follow-up, 36 months; range, 6-180 months). Patients were treated to a mean of 46 Gy (range, 45-60 Gy) with lateral fields. Retinopathy developed in 6 (12%) eyes treated to 50 to 60 Gy, at a mean of 37 months (range, 11-72 months) after RT.

In a more modern series, Lucas et al[46] evaluated 8 patients (median age, 10 years; range, 4-21 years) treated with passive scattering proton therapy for esthesioneuroblastoma, with median follow-up of 4.6 years (range, 0.8-9.4 years). The majority of patients received surgery and chemotherapy in addition to RT, with median RT dose 59.4 Gy relative biological effectiveness (RBE) (range, 54-70.2). Grade 2 retinopathy developed in 2 patients whose maximum retinal doses were 69 and 51 Gy_{RBE}.

Optic neuropathy

Three studies contained sufficient data to contribute to NTCP models for radiation-associated optic neuropathy (summarized in the following and in Table 3).

Bates et al[47] reviewed the largest series of patients, 458 children (median age, 9.6 years; range, 1.3-21.8 years) with 875 eyes at risk (received ≥30 Gy_{RBE} to 0.1 cm^3 of the ipsilateral optic nerve or optic chiasm) treated with double-scattered proton therapy for intracranial malignancy. Median follow-up was 3.1 years (range, 0.1-11.8 years). There were 17 eyes with visual acuity decline in 13 children, treated with maximum RT dose (to 0.1 cm^3) to the optic nerve or chiasm of 54.4 to 55.9 Gy_{RBE}, at a median time of 3.3 years (range, 0.5-6.3 years). The study provided a logistic regression model for risk of visual decline, as described in the following.

Habrand et al[48] reported on outcomes of 37 children (mean age, 7.4 years; range, 1-15 years) treated with RT (with or without surgical resection) for craniopharyngioma, with mean follow-up of 8.2 years (range, 1.1-22.8 years). Of 37 patients, 35 could be evaluated for quality of life after therapy. One patient had histologically documented radiation necrosis of the optic chiasm 27 months after receiving 55 Gy with ^{60}Co.

Lucas et al[46] (described in the prior section) reported grade 3 optic neuropathy in 1 patient who received a maximum of 61 Gy_{RBE} to the optic nerve.

Cataract formation

There is substantially more data on radiation-associated risk of cataract formation compared with other ocular toxicities, and we have chosen to include 3 large series as well as a

Table 2 Data used for modeling the risk of retinopathy in childhood cancer survivors treated with cranial RT

First author (publication year, institution)	Treatment period	Number of patients	Cancer diagnosis	Med. age at dx (y)	Med. FU (y)	Est. dose to retina (Gy)*	Dose uncertainty (%)†	Number of events (dose)
Haik[13] (1986, MSKCC)	1971-1983	11	Paramening. RMS involving orbit	6	6	30-57	7	1 (57 Gy)
Raney[44] (1999, CCG/POG)	1978-1987	213	Nonorbital STS head/neck	5	7	Range N/A	10	4 (47-65.8 Gy)
Coucke[43] (1993, Lausanne University)	1963-1991	38 (44 eyes treated)	Retinoblast.	1.4	2.9	30-61.5	7	10 eyes (44-61.5 Gy)
Anteby[45] (1998, Hadassah University)	1979-1995	38 (50 eyes treated)	Retinoblast.	2 (unilateral), 0.4 (bilateral)	3	45-60	7	6 eyes (50-60 Gy)
Lucas[46] (2015, MGH)	2000-2013	8	Esthesio.	10	4.6	37-69	5	2 (51, 69 Gy_{RBE})

Abbreviations: CT = computed tomography; CCG/POG = Children's Cancer Group/Pediatric Oncology Group; dx = diagnosis; est. = estimated; esthesio. = esthesioneuroblastoma; FU = follow-up; Med. = median; MSKCC = Memorial Sloan Kettering Cancer Center; MGH = Massachusetts General Hospital; paramening. = parameningeal; N/A = not applicable; RBE = relative biological effectiveness; retinoblast. = retinoblastoma; RMS = rhabdomyosarcoma; RT = radiation therapy; STS = soft tissue sarcoma.

* The Haik et al, Raney et al, Coucke et al, and Anteby et al studies used older RT techniques without CT-based planning, and as such the estimated doses to the retina likely reflect whole retinal doses. For the Lucas et al study, the estimated dose to the retina reflects maximum retinal dose.

† See the Dosimetric Uncertainties section and Appendix E2.

Table 3 Data used for modeling the risk of optic neuropathy in childhood cancer survivors treated with cranial radiation therapy

First author (publication year, institution)	Treatment period	Number of patients	Cancer diagnosis	Med. age at dx (y)	Med. FU (y)	Est. dose to optic nerve/chiasm (Gy)*	Dose uncertainty (%)†	Number of events (dose)
Habrand[48] (1999, Institute Gustave-Roussy)	1969-1992	37	Craniopharyng.	7.4 (mean)	8.2 (mean)	45-56	7+	1 (55 Gy)
Lucas[46] (2015, MGH)	2000-2013	8	Esthesio.	10	4.6	37-63	5	1 (61 Gy)
Bates[47] (University of Florida)	2006-2018	458 (875 eyes)	Multiple	9.6	3.1	30-60	2	17 eyes (54.4-55.9 Gy_{RBE})

Abbreviations: craniopharyng. = craniopharyngioma; dx = diagnosis; est. = estimated; esthesio. = esthesioneuroblastoma; FU = follow-up; Med. = median; MGH = Massachusetts General Hospital; RBE = relative biological effectiveness.

* The majority of patients in the Habrand et al study were treated with parallel-opposed beams with ~2-cm margin on the gross tumor volume, and thus the estimated dose is likely to a large portion of the optic chiasm and nerves. For the Lucas et al and Bates et al studies, the estimated dose reflects maximum optic nerve/chiasm dose.

† See the Dosimetric Uncertainties section and Appendix E2.

Table 4 Data used for modeling the risk of cataract formation in childhood cancer survivors treated with cranial RT

First author (publication year, institution)	Treatment period	Number of patients	Cancer diagnosis/ survival	Med. age at dx (y)	Med. FU (y)	Est. dose to lens (Gy)*	Dose uncertainty (%)†	Number of events (dose)
Allodji[49] (2016, Euro2K)	1945-1985	1833	5-y survivors of childhood cancer	4	32 (mean)	Mean 2.5	7-50	47 eyes (self-report)
Chodick[3] (2016, CCSS)	1970-1986	13,902	5-y survivors of childhood cancer	8.3 (mean)	21.4 (mean)	Mean 2.2 (range, 0-66)	7-50	483 (starting 0.5 Gy) (self-report)
Hall[2] (2015, multi-institutional)	1990s-2000s	1386	Multiple (treatment: TBI)	N/A	3-9 (multiple studies)	0-15.75	15	Not specified (majority ophtho dx)
Nguyen[50] (2019, CHLA)	1997-2015	61 (94 eyes)	Retinoblastoma	0.8	4.3	Median 37.5 (whole eye RT), 10 (lens-sparing RT)	10	50 eyes (3.6-47 Gy) (ophtho dx)

Abbreviations: CCSS = Childhood Cancer Survivor Study; CHLA = Children's Hospital Los Angeles; dx = diagnosis; est. = estimated; FU = follow-up; Med. = median; N/A = not applicable; ophtho = ophthalmology; RT = radiation therapy; TBI = total body irradiation.

* Estimated dose to the lens reflects maximum dose to the left or right lens in the Chodick et al and Allodji et al studies, whole lens dose in the Hall et al study, and mean lens dose in the Nguyen et al study.

† See the Dosimetric Uncertainties section and Appendix E2.

smaller but more modern series as summarized in the following and in Table 4, acknowledging this list is not comprehensive but should be very representative of other smaller studies.

Chodick et al[3] report on the largest series, reviewing risk of cataract among 13,902 5-year survivors of childhood cancer in the CCSS. Among patients treated with RT (n = 7792), the mean dose to the lens was 2.8 Gy (range, 0-66 Gy). Within the follow-up period, 483 cataract cases (3.5% of the study population) were reported by questionnaire (self-reported), with median time from first cancer diagnosis to cataract onset of 9.6 years (maximum of 37 years). Of these, 113 required cataract surgery by self-report. The unadjusted prevalence of cataract was 1.3% for patients exposed to <0.5 Gy, 6.1% for exposure to 2.5 to 3.49 Gy, 32.2% for exposure of 10 to <20 Gy, and 40.6% for exposure to 20 to 60 Gy.

Allodji et al[49] investigated the risk of cataract among 1833 5-year survivors of nonretinoblastoma solid cancer in the Euro2K cohort who completed a self-report questionnaire. Among these patients, 1175 (64%) received RT, with mean RT dose to the eyes of 2.6 Gy on the left and 2.5 Gy on the right. Over the follow-up period, 47 cataract events were self-reported in 33 patients, at a median time from cancer diagnosis to cataract diagnosis of 18 years (range, 2-55 years). On multivariable Cox proportional hazard regression analysis, patients who received RT had a 4.4-fold increased cataract risk compared with those who did not, with greater risk at higher RT doses.

Hall et al[2] performed a meta-regression of published data from hematopoietic stem cell transplantation regimens with and without TBI to model the 5-year probability of cataract development. Based on data from 1386 patients in 21 series, in which TBI was given to a total dose of 0 to 15.75 Gy with single or multifraction schedules, factors significantly associated with 5-year cataract incidence included total dose and dose times dose per fraction. In pediatric series (n = 163 patients in 6 series), the estimated 5-year cataract incidence was 28% at 0 Gy (chemotherapy-only regimens without TBI), 32% with 2 Gy TBI (1 fraction), and 60% with 12 Gy TBI (6 fractions). All pediatric series included an ophthalmologist as an author of the study.

In a more modern series, Nguyen et al[50] assessed incidence of cataracts in patients with retinoblastoma (median age at diagnosis, 10.0 months; range, 0.8-31.8 months) treated with lens-sparing versus whole-eye RT. At a median follow-up of 51.8 months, ophthalmologist-diagnosed cataract developed in 71.7% of eyes treated with whole-eye RT versus 35.3% with lens-sparing RT. The estimated 5-year probability of cataract formation in eyes receiving a mean lens dose of ~10 Gy was 35%.

Risk factors

A variety of patient-related factors (eg, age at the time of treatment, comorbidities) and treatment-related factors (eg, RT fraction size, concurrent chemotherapy) are generally believed to affect risk of radiation-associated ocular complications, but the data are mixed. For example, higher daily fraction sizes are associated with greater risks of radiation-associated retinopathy and optic neuropathy.[43,51] Bates et al[47] did not find a relationship between chemotherapy with risk of optic neuropathy, although only 34% of patients received chemotherapy pre-, during, or post-RT.

More data are available to assess the effect of these factors on radiation-associated cataract formation; however, the data are insufficient to allow quantitative evaluation. In the CCSS report by Chodick et al,[3] other than lens radiation dose, treatment with certain chemotherapy agents (cytosine arabinoside and doxorubicin) and diabetes as a comorbid condition were independently associated with cataract formation. However, patient age at the time of RT and use of corticosteroids were not found to be independent risk factors for cataract formation.[3] The Euro2K study similarly noted an increase in cataract risk in patients treated with the chemotherapeutic agent melphalan hydrochloride but did not find an effect of age at the time of RT on cataract risk.[49] In a meta-regression of hematopoietic stem cell transplantation regimens,[2] TBI dose, fractionation, and pediatric versus adult status were significantly associated with 5-year cataract incidence. Dose rate and steroid use were not significant.[2] All studies in the meta-regression, however, had dose rates <0.2 Gy/min, so extrapolation to higher dose rates may not be reliable. The results could suggest that pediatric patients have increased sensitivity to cataract development compared with adult patients, but the authors do note that all pediatric series analyzed reported regular cataract surveillance, which was not the case for all adult series analyzed.

Dosimetric Uncertainties

Because of the limited data available for this study, and the relatively high accuracy in the reported doses, the uncertainty in the dosimetric data was not incorporated into any modeling. However, to put all of the uncertainties into context, we quantified the dosimetric uncertainty associated with each study, as detailed in the following.

Dosimetric uncertainty was estimated for each study based on the study's methods to assess dose (Tables 2-4). Key examples are discussed in the following, and further details are available in Appendix E2. Although many factors were estimated, it was not possible to estimate the uncertainty introduced from all factors and therefore these estimates are likely lower limits.

For the largest radiation-associated retinopathy study,[43] the prescribed dose to the eye was taken as the dose to the retina. The uncertainty of 7% was derived from a study-reported dose heterogeneity of 5% across the eye as well as a further (independent) 5% estimated uncertainty in the accuracy of the historical dose calculation system.[52,53] The largest radiation-associated optic neuropathy study[47] reported dose from MR-CT fused images calculated in a modern

proton planning system and had an associated uncertainty of 2%.[54] However, this did not include uncertainty from setup variability near a steep gradient or for proton end-of-range RBE being potentially different from 1.1. The largest radiation-associated cataract study[3] used retrospective dose reconstruction, which had a range of uncertainties from 7% (for in-field cases, similar to Coucke et al[43]) to 20% to 50% for lenses far from the treatment field.[55]

Mathematical and Biologic Models and Epidemiologic Issues

General modeling approach

The review of dose-volume response data was separated into the 3 outcomes studied. There was substantially more data on cataract formation in pediatric patients treated with RT compared with retinopathy or optic neuropathy, and this was reflected in the number of patients represented by the studies reviewed (n = 314 for retinopathy, n = 503 for optic neuropathy, n = 17,182 for cataract). Thus, we note that the NTCP models for retinopathy and optic neuropathy in particular were developed using data from a limited number of studies, which could limit their accuracy. Dose-response models were extracted from original publications where possible and the dose-response data combined using inverse variance weighting. If raw data points were extracted by the PENTEC authors, we used a logistic dose-response model to fit extracted data according to $p = \frac{1}{1+exp\left(4\gamma_{50}(1-\frac{D}{D_{50}})\right)}$, where p is the probability of the event in question, D is the radiation dose metric studied, and γ_{50} and D_{50} represent the steepness of the function and the dose at 50% probability, respectively.

Retinopathy

Data from several sources are summarized in Fig. 3. Coucke et al[43] provided a dose response model for the risk of retinopathy versus dose based on a set of 44 eyes in 38 children treated for retinoblastoma. A model presenting the equivalent dose in 2 Gy fractions (EQD2) resulting in a given probability of retinopathy was provided in the publication as defined as $EQD_2 = \frac{4.2-ln(-lnp)}{0.074}$. The 95% confidence interval (CI) on the complication probability in Fig. 3 is calculated by propagation of error from the reported estimates and CI in Coucke et al under the assumption of zero covariance. A value of α/β = 1 Gy (this low α/β reflecting a strong sparing effect of reduced fraction size, as is commonly seen for normal nervous tissue[56,57]) was estimated and applied in the calculation of EQD2 by Coucke et al. The Coucke et al model is reproduced and serves as the primary model in Fig. 3. Further studies presenting case reports with corresponding doses are also included.[13,44] Additionally, Anteby et al[45] reported no cases below an exposure of 50 Gy. Lucas

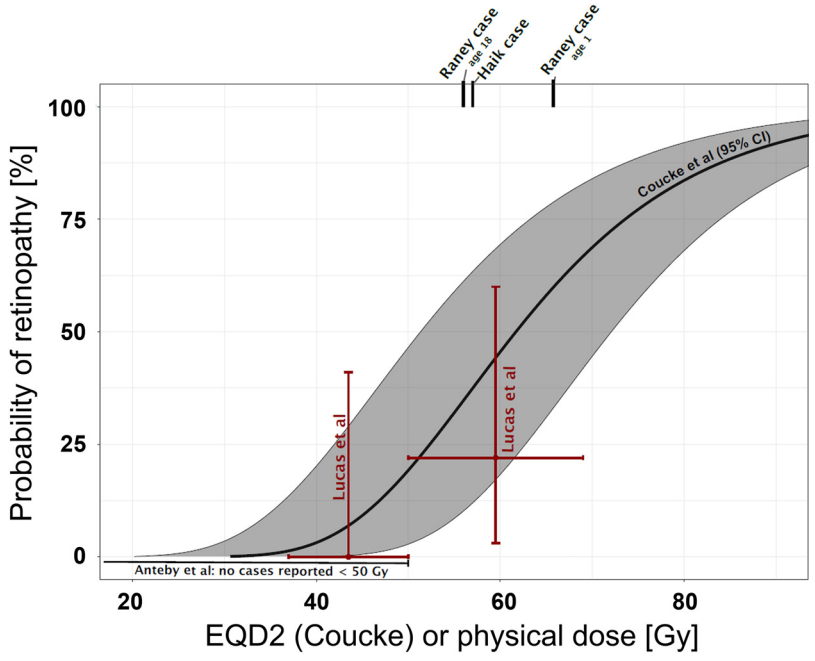

Fig. 3. Risk of retinopathy for irradiated children based on studies described in Table 2. Primary model and gray 95% confidence band reproduced from Coucke et al[43] defined as $EQD_2 = \frac{4.2-ln(-lnp)}{0.074}$, where EQD2 is at $\frac{\alpha}{\beta} = 1Gy$, yielding probability, p, of retinopathy. Other reported cases (Raney et al,[44] Haik et al[13]) and data from other studies (Anteby et al,[45] Lucas et al[46]) are included as well. Raney et al, Haik et al, and Lucas et al report physical doses only, and these are plotted directly on EQD2 axis assuming ≈ 2 Gy/fraction in these cases. *Abbreviation*: EQD2 = equivalent dose in 2-Gy fractions.

et al[46] reported individual data for the exposure to 16 eyes (8 patients) and 2 cases of grade 2 retinopathy (Table 2). These raw data were split into 2 groups according to retina maximum dose (37-50 Gy vs 50-69 Gy), and incidences were plotted with their binomial CIs (Fig. 3).

Optic neuropathy

Bates et al[47] report detailed data on the risk of optic neuropathy in pediatric patients after proton therapy. Doses associated with a risk of 1%, 5%, and 10% of optic neuropathy were 52.5, 56.1, and 58.3 Gy_{RBE}, respectively, corresponding to a logistic dose response with steepness γ_{50} = 6.3 and D_{50} = 64 Gy_{RBE}—a very steep dose response with a D_{50} in the same range as that observed in adult patients in the QUANTEC report.[10] Data points from 2 case reports[46,48] (Table 3) are also included in the figure, using physical doses because data on fractionation were uncertain. However, given the diagnoses and reported doses, these were likely delivered at ~1.8 to 2 Gy/fraction, and extrapolation beyond this range should be made with caution. These are plotted in the same format as the retinopathy data in Fig. 4. CIs were unable to be provided given the limited data set. We note that as this optic neuropathy model is largely based on data from Bates et al in which patients were treated with double-scattered protons, the modeling may not as accurately reflect risks for patients treated with photon or spot-scanning proton RT.

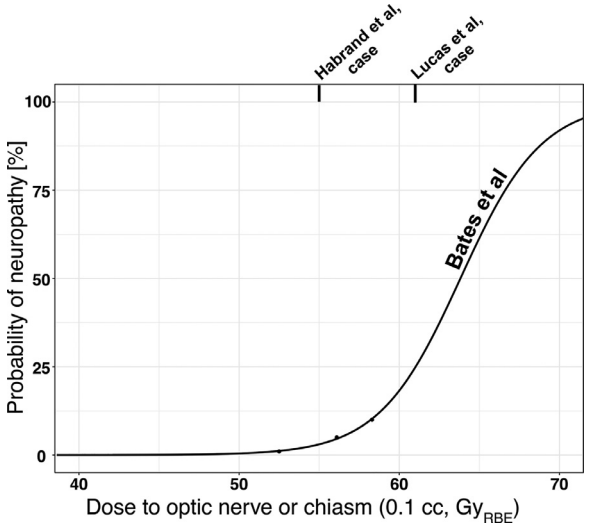

Fig. 4. Risk of optic neuropathy for children irradiated described using normal tissue complication probability models based on studies described in Table 3. Primary model based on Bates et al[47] fitted to the equation $p = \frac{1}{1+exp\left(4\gamma_{50}\left(1-\frac{D}{D_{50}}\right)\right)}$, where D is the minimum dose to 0.1 cm^3 of the most irradiated volume of the optic nerve or chiasm. Data points from 2 case reports (Habrand et al,[48] Lucas et al[46]) are included.

Cataract formation

Four studies provided dose-response information for cataract formation (Table 4). Two of these studies, Allodji et al[49] and Chodick et al,[3] used patient-reported cataract as the endpoint. Nguyen et al[50] used cataract formation as diagnosed by ophthalmologists specializing in retinoblastoma as the endpoint in a modest series of 65 patients with retinoblastoma. Hall et al[2] provided a meta-regression including both adult and pediatric data, and ophthalmologists were on the author list for 18 of 21 publications included.

We grouped these endpoints as self-reported for the Allodji et al and Chodick et al studies, which likely reflects a combination of symptomatic cataract formation as well as increased surveillance, which may pertain especially to the earlier post-RT years. Then we combined an ophthalmologist-scored group using the Nguyen et al study, as well as pediatric studies that included an ophthalmologist as an author from the Hall et al meta-regression. This group likely included a greater proportion of patients with asymptomatic cataract diagnoses compared with the self-reported cataract group, which is consistent with the greater probability of cataract development in the ophthalmologist-scored group in Fig. 5.

The Allodji et al data were extracted according to the model of excess relative risk, $ERR = (1 + \gamma D^2)$, where γ = 0.05 (95% CI, 0.01-0.09) and used the baseline observed risk of 6 of 1424 eyes for reference at 0 Gy. A logistic model was fitted to the Chodick et al actuarial

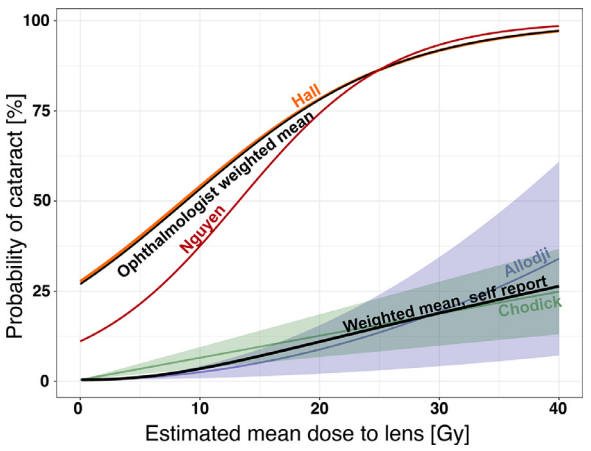

Fig. 5. Risk of cataract development for children treated with radiation therapy (and some treated without radiation therapy, with chemotherapy only, are reflected as data at 0 Gy), described using normal tissue complication probability models based on studies described in Table 4. Two studies were based on ophthalmologist-assessed cataract (Hall et al,[2] Nguyen et al[50]) and 2 based on self-reported cataract (Allodji et al,[49] Chodick et al[3]). Shaded areas represent 95% CIs, but these could not be extracted from the Nguyen et al and Hall et al studies. See Appendix E3 for details concerning modeling.

Table 5 Parameters of NTCP models for different endpoints with 95% CIs

Endpoint	NTCP model	Parameter values (95% CI)
Retinopathy	$\exp(-\exp(b_0 - b_1 \times EQD_2))$	b_0 = 4.2 (1.35-7.0) b_1 = 0.074 (0.019-0.13) α/β = 1 Gy
Optic neuropathy	$1/(1 + \exp(4 \times \gamma_{50} \times (1 - D/D_{50})))$	D_{50} = 64 Gy (N/A) γ_{50} = 6.3 (N/A)
Cataract (self-reported)*	<4% for D < 7 Gy $b_0 \times D - 0.04$ for D > 7 Gy	b_0 = 7.6e-3 (N/A)
Cataract (ophthalmology-diagnosed)	$1/(1 + \exp(4 \times \gamma_{50} \times (1 - D/D_{50})))$	D_{50} = 9 Gy (N/A) γ_{50} = 0.25 (N/A)

Abbreviations: α/β = measure of the radiation fractionation sensitivity of cells; γ_{50} = steepness of the function at 50% probability; D = radiation dose metric studied; D_{50} = dose at 50% probability; EQD_2 = equivalent dose in 2 Gy fractions; N/A = not applicable; NTCP = normal tissue complication probability.

* Because of the inverse variance weighting and functional forms, the Allodji et al[49] study gets a very high weight and low point estimate at doses <7 Gy. As this entails a potential underestimation of the risk, we choose to report less than 4% risk at less than 7 Gy in the affected dose region. This should be interpreted as an additional uncertainty, not as a threshold dose. Details concerning endpoint-specific models and methods for combining study-specific results are provided in the text and Appendix E3.

incidence data at 5 years, and the 2 studies were combined using inverse variance weighting at each dose level to yield a synthesized estimate.

In the absence of extractable variances from Hall et al and Nguyen et al, we combined these 2 studies by weighting by the number of patients. Because the Hall et al study dominated, the synthesized fit follows the logistic model of that study closely (while Hall et al formulate the logistic model differently, it can be reconciled with the conventional γ_{50}, D_{50} formalism, cf Table 5). The resulting data are depicted in Fig. 5.

Additional modeling notes

Additional notes on modeling choices and modeling details are provided in Appendix E3. An overview of the suggested models with parameter estimates is shown in Table 5. The retinopathy data are provided according to the original paper by Coucke et al, but a more conventional formalism that provides an adequate fit is given in the appendix. As a general note of caution, the synthesis of these data was challenging, often relying on relatively old data or smaller series and with limited data on time to the event. As a consequence, the uncertainty in the models should be appreciated. In the toxicity scoring recommendations and future investigations sections that follow, we provide suggestions for improvements of future work and encourage validation of the models proposed in Table 5.

Dose-Volume Recommendations

Table 6 presents our best estimates on the relationship between RT dose and risk of toxicity. A maximum retina dose of 40 Gy (which in the era of more conformal treatment planning and differential dose across the retina would best apply to the macula as opposed to the entire retina) was associated with <5% risk of late retinal toxicity. A maximum optic nerve/chiasm dose of 55 Gy in 1.8 to 2 Gy fractions was associated with <5% risk of optic neuropathy. A mean lens dose of <10 Gy was anticipated to minimize risk of clinically significant cataract. There are no good data to provide dose/outcome estimates in the setting of hypofractionation or concurrent chemotherapy in the pediatric population.

Caveats

RT plays an essential role in the definitive management of tumors around ocular structures, and consideration of the balance between tumor control and late toxicity must be weighed carefully with the patient and family. Because of difficulties reversing radiation-associated retinopathy and optic neuropathy, the planning target volume is often underdosed around the retina (and particularly the

Table 6 Doses corresponding to 5% and 50% risk of toxicity

Toxicity	Doses corresponding to 5% risk (Gy)	Doses corresponding to 50% risk (Gy)
Retinopathy	42	62
Optic neuropathy	57	64
Cataract (self-reported)	12	>40
Cataract (ophtho-diagnosed)	0*	9

Abbreviation: ophtho = ophthalmology.

* There is >5% risk of ophthalmologist-diagnosed cataract without radiation therapy (0 Gy) in these studies (patients treated with chemotherapy only).

macula) and optic nerves/chiasm to limit the risk of permanent vision loss (maintaining the coverage of the gross tumor volume as much as possible). Given that cataracts can occur after low doses of RT exposure to the lens, and the option of lens replacement surgery, it is uncommon to limit dose to the lenses at the expense of target coverage. However, as noted in the Clinical Significance section, lens replacement is a much greater challenge in pediatric patients, and minimizing both high- and low-dose RT exposure to the lenses when feasible is recommended. Regular follow-up with ophthalmology for children who receive RT near ocular structures is also a critical component of survivorship care.

Toxicity Scoring Recommendations

The challenges experienced during the current data synthesis and the consequential model uncertainties suggest the need for more detailed data series. At a minimum, the toxicity definitions should be clear, and time-to-event data (eg, Kaplan-Meier curves for toxicity) should be presented as function of dose to the critical structures. We recommend reporting CTCAE version 5.0 grade toxicity, as well as additional information on the presence of partial vision loss. Such reporting would better facilitate assessment of the effect of higher RT doses to specific portions of the retina. However, considering the relative sparsity of pediatric data, we encourage making the individual dose, outcome, and time-to-event data available to researchers, either as an online repository or on request.

Data Reporting Standards Specific to This Organ

Published data on ocular complications are rare and usually do not allow for systematic dosimetric analysis, for several reasons: dose-volume information is often not included in sufficient detail (or only for cases with complications and not for those without complications); the endpoint is rare in the case of optic neuropathy or retinopathy; the method of diagnosis for cataract is often unclear (self-reported vs ophthalmologist-diagnosed); a standard toxicity scoring system is not typically used; and complications such as corneal injury, dry eye, conjunctival injury, and glaucoma are either difficult to diagnose or underreported. Consequently, it is vital that published data sets conform to rigorous reporting standards so their results can be pooled. We propose reporting the following information in future studies:

- Patient sex and race
- Clinical indication for RT (ie, cancer diagnosis)
- Age when treated with RT
- Prescribed RT dose and dose fractionation
- RT technique (ie, photon-based 2-dimensional, 3-dimensional, intensity modulated RT, volumetric modulated arc therapy; proton therapy: passive scatter, spot scanning, intensity modulated proton therapy; treatment planning system, dose calculation algorithm)
- Organ radiation exposure (the dose-volume histogram for the relevant normal organs with 0.1 Gy dose resolution). Metrics that were used in the modeling for this report for lens, optic nerves, and retina/macula should be included. In addition, radiation exposure metrics for organs for which there were not sufficient quantitative data for NTCP modeling (lacrimal glands, cornea) should be included for future modeling.
- Mean dose to lens (left and right)
- Maximum (or D0.1cc) dose to optic nerves (left and right) and optic chiasm
- Maximum (or D0.1cc) dose to retina (left and right) and macula subvolume (left and right) (macula contoured and dose evaluated when the maximum retina dose exceeds 40 Gy)
- Mean and maximum doses to the lacrimal glands, as well as volume of lacrimal gland receiving $\geq$20 Gy[58]
- Mean and maximum doses to the cornea (left and right)
- Chemotherapy use (if yes, timing with respect to RT and agents used)
- Frequency of clinical follow-up for late complications of RT
- Whether the patient had follow-up with ophthalmology, and if so, frequency and date of last follow-up
- Outcome
- Diagnosis of cataract, optic neuropathy, retinopathy, lacrimal stenosis/atrophy/dry eye, corneal injury (ulcer, perforation, scarring) (yes/no and laterality)
- CTCAE version 5.0 grade toxicity when applicable
- Description of partial vision loss if present (quadrant-level detail)
- Age of diagnosis of ocular toxicity
- Time from completion of RT to diagnosis of toxicity or last follow-up
- For cataract: self-reported versus ophthalmologist-diagnosed, as well as whether the patient has had lens replacement surgery (if yes, age at surgery)
- Number of patients in the study, number of those with or without toxicity; dosimetric data for both those with and without toxicity

Future Investigations

We could not synthesize data on dry eye, corneal/conjunctival injury, and other ocular toxicities, so reports on these endpoints are encouraged, keeping in mind the reporting recommendations discussed previously. Likewise, we had little data to support conclusions on the effect of age at exposure on the risk of toxicity. Because the age at exposure, attained age, and latency time are intercorrelated, this is a

particular situation where careful reporting of time to event is important, and publication of individual data sets is encouraged. Potential synergistic effects of systemic therapy and radiation dose could not be analyzed in the current study and are therefore also encouraged.

For all of this, a comparison between our proposed risk models (Table 5) and observed outcome in independent external series is encouraged, and the effect of the previously mentioned factors could, in such a scenario, ideally be elucidated by depicting residuals as a function of the omitted putative risk factors in independent series.

Finally, the dosimetry in these retrospective analyses is naturally limited to the contemporary method at the time of writing the individual reports. Data on toxicity incidence with newer techniques and partial volume exposure would be of considerable value. Thin slice volumes for imaging are now trivial to manage and inherently improve structure determination and dosimetry accuracy and should be encouraged, in particular near small structures including optic nerves, the lenses, and other cranial anatomy. For example, if doses to different regions of the retina (or even optic nerves) can be accurately determined, these can be used to attempt to relate local retinal doses to changes in visual acuity in different parts of the visual field.

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