Ocular complications after proton radiation for childhood brain tumors

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Abstract

Background: There is limited data regarding the incidence, timing, and risk factors for ocular complications after proton radiation (RT) for childhood brain tumors. Methods: We performed a single-institution retrospective review of children treated with protons for brain tumors. Data abstracted included demographics, radiation details and ocular complications. Results: Of 81 children treated with protons for brain tumors, from 2010-18, 42 with ophthalmology data available, were included. Median age was 8.3 years (y) (0.8 – 20.6y) and median follow- was 2.1 years. Ocular complications were detected only in patients who received craniospinal irradiation (CSI). The incidence of ocular complications was 19% (8/42 patients) overall, and 62% (8/13) after craniospinal irradiation (CSI). Bilateral cataracts were detected at a median of 3.2 y post-CSI, with an incidence of 38% (5/13). Dry eyes were detected in 23% (3/13) of patients during or soon after CSI (0.04 and 0.7y post-RT). The median radiation dose (Gray RBE) to the lenses for patients with cataract was 29.3 Gy (19.41 – 38.07), and with dry eyes was 27.93 Gy (11.98 – 28.71) (mean doses to bilateral ocular structures). Multivariable analysis identified CSI as a significant risk factor for cataract and ocular complications overall. Conclusions: Children are at risk for cataract and dry eyes after proton CSI and need ophthalmology follow-up. Larger prospective studies are needed to validate our findings, identify risk factors, and formulate strategies for risk-mitigation. Longer follow-up is needed to determine the incidence of late ocular complications and consequent functional outcomes after cranial proton radiation.

1 I INTRODUCTION

Radiation therapy (RT) has played an essential role in significantly improving outcomes for many pediatric brain tumors.[1-5]However these cures come at a cost, with significant radiation-related late effects including neurocognitive deficits,[6]second neoplasms,[7] cerebral vasculopathy and endocrinopathies,[8] even with newer modalities of radiation like protons.

The Childhood Cancer Survivor Study (CCSS) reported that when compared to their siblings, survivors of childhood cancer, more than 5 years off-therapy, had more than ten times the risk for cataracts, and more than double the risk of developing glaucoma, legal blindness and double vision.[9] There was a significant dose-associated risk for these ocular complications, with radiation to the eye. There is an increased risk of cataract with radiation to the lens, at doses as low as 50 cGy.[10] The literature describes an increased risk of ocular complications like cataract after total body irradiation (TBI) prior to bone marrow transplant,[11-16] and after

orbital radiation for other childhood cancers like sarcomas,[17] and retinoblastoma.[18]However data regarding these complications for children with brain tumors who receive radiation, is more limited. Moreover, the existing literature pertains to patients treated with "photon" radiation, treated largely prior to the advent of modern techniques which deliver radiation more precisely. There is very limited data regarding the incidence of ocular complications after treatment with protons, a newer modality of radiation, which is now widely used for the treatment of children with brain tumors, due to absence of an exit dose and the potential to spare healthy tissue that is not in the target field.[19]

The primary aim of our study was to determine the incidence, timing and risk factors for the development of ocular complications in children with brain tumors after proton radiation, to better inform screening and follow-up, as well as to devise strategies to minimize the risk of these late-effects. The secondary aim was to describe the visual function of children after the completion of treatment that included cranial radiation, for brain tumors.

2 I METHODS

This study was a retrospective review of a cohort of children, younger than 21 years of age at the time of receiving cranial proton radiation, for tumors of the central nervous system (CNS). All patients received oncology care at the Jimmy Everest Center for Cancer and Blood Disorders (University of Oklahoma Health Sciences Center), proton radiation at ProCure Proton Therapy Center, and ophthalmology follow-up for all but 1 patient, at the Dean McGee Eye Institute (DMEI) in Oklahoma City. Data was extracted from patient charts regarding demographic and clinical details, including diagnosis and treatment. Patients with ophthalmology data available were included in the final analysis. For each patient, complete details of the first and last formal eye exam, were recorded. Their ophthalmology charts were reviewed for details regarding the detection and management of 4 complications: cataract, dry eyes, retinal changes (pigmentation, scarring, mottling, hemorrhage, vaso-occlusion) and glaucoma. The severity of dry eyes was graded as mild if no treatment was needed, moderate if artificial tears were prescribed, and severe if serum tears, cyclosporine ophthalmic suspension or punctal plugs were required. For patients found to have an ocular complication, previous visit notes were reviewed to determine the time when it was first detected. Finally, visual acuity for each eye, at the first and last eye exams, were recorded and compared. Radiation treatment details documented were the planning treatment volume, radiation dose in Gy (Gray) RBE (relative biological effectiveness) in total, as well as to the lens, cornea, and lacrimal glands on each side. Patients who did not have ophthalmology data available, were excluded from the study.

Descriptive statistics were computed for all demographic and clinical variables. Patients included in the study were compared with those excluded due to lack of ophthalmology data, for differences in distribution by gender, age at radiation, tumor location and radiation volume. Multivariable analysis was performed to identify significant risk factors for the development of ocular complications after cranial proton radiation. Categorical variables such as gender, tumor location, and radiation volume were compared between groups using the Chi-square test or Fisher's Exact test, as appropriate. Continuous variables such as age at radiation start, mean dose to lens, retina, and cornea were assessed for normality using the Shapiro-Wilk test, and group comparisons were made using Student's t-test, or Wilcoxon-Mann-Whitney test, as appropriate.

3 I RESULTS

3.1 I Patient characteristics

Of 81 consecutive children treated with proton radiation for brain tumors, at a single institution, 42 patients with ophthalmology exam records available, were included in the study. There was no significant difference between included and excluded patients in distribution by gender, age at start of radiation, tumor location (supratentorial or infratentorial), and radiation volume (CSI or IFRT or WVI) (Supplementary Tables 1a and 1b).

The demographic and clinical characteristics of the study patients are summarized in Table 1. There was nearly an equal distribution of patients by gender. The median age at start of radiation was 8.3 years and

median follow-up from the end of radiation to the last ophthalmology exam, was 2.1 years. Most patients had supratentorial tumors (60%; 25/42 patients). Nearly a third of patients (31%; 13/42 patients) received CSI and most of the other patients received involved-field radiation therapy (IFRT). Median radiation dose to the lenses for the 13 patients who received CSI, was 22.68 (range 11.99 – 38.07) Gy RBE. Of the 29 patients with a radiation volume other than CSI (IFRT or WVI), only 5 patients received any radiation to their lenses, with a significantly lower dose ranging from 0.01 – 7.85 Gy RBE (values represent the mean dose to right and left lenses).

Post-radiation ocular complications occurred in 8 patients (19%; 8/42), all of whom received whole brain radiation as part of CSI (62%; 8/13). The characteristics of patients who developed ocular complications are summarized in Tables 2 and 3.

3.2 I Cataract

Five patients developed bilateral cataracts at a median duration of 3.2 years (1.2 – 5.1 years) after completion of radiation (Table 3). All these patients received CSI for embryonal tumors (4 medulloblastoma, 1 primitive neurectodermal tumor/PNET). The incidence of cataract was 12% (5/42) in the cohort overall, and 38% (5/13) for those who received CSI. Four patients had posterior sub-capsular cataracts, with details not available for 1 patient who died due to disease, a few months after cataract detection at an outside center. Three patients underwent cataract surgery.

Of the 5 patients with cataracts after CSI, 2 each received 23.4 and 36 Gy RBE, and 1 received 25.2 Gy RBE to the whole brain and spinal cord, with a median of 29.3 Gy to the lenses. The median radiation dose to the lens for patients with cataract was significantly higher than that for patients without cataract (Table 4).

Multivariable analysis identified CSI radiation volume, infratentorial tumor location and the use of radiosensitizer chemotherapy as significant risk factors for the development of cataract (Table 5) and ocular complications overall (cataract and dry eyes) (Supplementary Table 2). All 5 patients who developed cataract after CSI, had infratentorial tumors, and 4 received radiosensitizing chemotherapy (2 Vincristine, 1 Carboplatin and Vincristine, 1 Temozolomide and Irinotecan). Of the 13 patients in the cohort who received CSI, 12 had infratentorial tumors (10 medulloblastoma, 1 mucoid spindle sarcoma, 1 primitive neurectodermal tumor in the cervical spinal cord). All 10 patients with medulloblastoma received weekly Vincristine during radiation, and 1 received additional Carboplatin.

One patient with craniopharyngioma, with a normal eye exam prior to radiation, developed left retinal scarring 2.2 years after, and cataract 3.5 years and 4.7 years in the left and right eyes, respectively, after IFRT. She received both photon and proton radiation, and hence was excluded from analysis.

3.3 I Dry eyes

Three patients developed dry eyes after receiving CSI (Table 2). One patient had severe dry eyes requiring cyclosporine ophthalmic suspension towards the end of radiation, with subsequent resolution during follow-up. The second patient had moderate dry eyes requiring artificial tears 2 weeks after finishing radiation, and the last patient developed mild dry eyes ˜8 months post-radiation but did not need any treatment.

Amongst these 3 patients, there was no correlation of severity of dry eyes and the radiation dose to the lenses, lacrimal glands, and cornea, as the patient with mild dry eyes received higher doses to these structures. However, all 3 patients did receive significant radiation to these ocular components, with the median of the average (right and left eyes) dose to the lenses, lacrimal glands and corneas being 27.93 (11.98 – 28.71), 36.96 (25.12 – 47.49) and 30.78 (25.08 – 36.49) Gy RBE, respectively.

3.4 I Retinal changes and glaucoma

As mentioned previously, one patient with craniopharyngioma who developed scarring and pigmentation in the left retina, 2.2 years after RT, with a normal eye exam prior to radiation, but was excluded from analysis,

because she received both photon and proton radiation. Another patient was found to have retinal scarring, but on an exam prior to radiation. No patients in our cohort were found to have glaucoma.

3.5 I Visual acuity

In the cohort overall, at last ophthalmology follow-up, visual acuity (VA) in the best eye, was better than 20/60 for a majority of patients, with 17 patients (40%) having 20/20 VA, and 13 (31%) with acuity less than 20/20, but better than 20/60. Vision was severely compromised for 6 patients (14%) in the cohort, 3 with VA of 20/100 and 3 with VA 20/300 or worse. Acuity was not specified for 6 patients (14%) (4 not recorded, 2 "fix and follow").

Comparing right and left eye for each patient, visual acuity was the same or similar ($<$ 20/40 difference) in both eyes for 71% (30/42: 15 same and 15 similar) of patients, different (difference in VA $>$ 20/40 $<$ 20/120) for 10% (4/42), and very different (difference in VA $>$ 20/200) for the 2 eyes, for 10% (4/42) of patients.

Of the 13 patients with a formal eye exam prior to radiation, change in VA post-RT varied without a clear pattern. At last exam, for the right eye, acuity was worse for 5, the same for 5, and better for 3. For the left eye, VA was worse for 4, same for 7, and better for 2 patients.

4 I DISCUSSION

Our study describes the incidence of 4 ocular complications - cataract, dry eyes, retinopathy, and glaucoma, in early follow-up after cranial proton radiation. It also provides a snapshot of visual function for childhood brain tumor survivors after completion of treatment that includes proton radiation. For patients who receive whole brain radiation, as a part of CSI, the incidence of bilateral cataracts is significant, even with limited follow-up. Nearly two-thirds of patients in our cohort who received this volume of radiation, developed cataracts. In addition, nearly a quarter of these patients developed dry eyes during or shortly after CSI. Multivariable analysis identified CSI radiation volume as a significant risk factor for the development of cataract and ocular complications overall (cataract and dry eyes). In contrast, patients who did not receive whole-brain radiation, did not have ocular complications that could be attributed to radiation. Only 1 patient who received IFRT for craniopharyngioma, developed retinal scarring and bilateral cataracts, but had to be excluded due to having received both photon and proton radiation. No other patient was found to have retinal scarring, and none had glaucoma.

Infratentorial tumor location and the use of radiosensitizer chemotherapy were also found to be significant risk factors for the development of cataract and ocular complications overall. However, all patients with these 2 variables, who developed cataract or dry eyes, also received CSI radiation volume, making them likely confounding factors, although this could not be tested statistically. For whole brain radiation (CSI), the proton beam enters through the posterior aspect of the brain and ends at the eyes, to ensure adequate coverage of the planning target volume. Hence the lenses of the eyes receive some radiation. The relative biological effectiveness (RBE) for protons is postulated to be 1.1 compared to photons. However, depending on the area relative to the Bragg peak, it is possible that the RBE might be higher, with an increased linear energy transfer (LET), and potentially higher doses to tissues in the vicinity of the target volume.[20] Our finding of significantly increased risk of cataracts with whole brain radiation, is consistent with the literature. A study of long-term survivors in the Childhood Cancer Survivor Study (CCSS), reported an increased risk for cataracts with radiation dose to the lens greater than, as little as 200 cGy, with a relative risk of 3.2, compared to their siblings.[9]Steroid treatment has been described to be significantly associated with an increased risk for cataracts in leukemia survivors who received TBI, while other literature has shown a lack of significant risk in the absence of CNS irradiation.[11,21] Busulfan in the setting of conditioning for bone marrow transplant, with TBI, has also been reported to increase the risk for cataracts.[14,22]None of the patients in our cohort received Busulfan. However, all patients in our cohort who received CSI for embryonal tumors, also received dexamethasone as an anti-emetic prior to chemotherapy, making it a confounding factor.

At last follow-up, after completion of all treatment, nearly three in four patients in our cohort had a visual acuity in their best eye, better than 20/60. Only 3 patients had VA in both eyes, worse than 20/100. In the

Childhood Cancer Survivor Study (CCSS), any radiation dose to the posterior fossa, more than 3000 cGy to the temporal lobe and more than 500 cGy to the lenses, were associated with increased risk of legal blindness at a median of 1 year from cancer diagnosis.[9] However, the patients in the CCSS cohort received radiation prior to the advent of more targeted techniques like intensity modulated radiation therapy (IMRT), and the use of protons. That study also had a much larger number of patients, with more heterogeneous diagnoses and longer follow-up.

Our study had several limitations. Our study was retrospective and relied on data recorded in medical records, with missing or limited details. All patients received radiation and oncology care at a single institution, limiting the generalizability of our findings. Most patients in our cohort, did not have ophthalmology exam data from prior to radiation. Most patients' ocular complications were detected at their first formal eye exam post-radiation. Hence the true time to develop these complications could not be accurately determined, and they were presumed to have occurred after radiation. While our study provides a glimpse of ocular function in childhood brain tumor survivors after treatment, the absence of pre-treatment visual acuity data for most patients precluded the analysis of the change of visual function with treatment. Very few patients had eye exam data during or shortly after radiation, limiting the analysis of the true incidence of dry eyes, as an acute adverse effect of radiation. Parsons et al. reported a significant increase in the risk of severe dry eyes at ocular radiation doses higher than 40 Gy.[23,24] In the CCSS study, the median time to the development of dry eyes was 7.2 years, with a cumulative incidence of over 5% for survivors of primary CNS malignancies.[9] The long-term incidence of dry eyes after protons could not be elucidated in our study due to the limited duration of follow-up.

Nearly half the patients in our cohort of consecutive patients who received protons for brain tumors, did not have ophthalmology data available, which creates the potential for inclusion bias. Our statistical analysis, however, suggests the excluded patients were similar to study patients in gender, age at radiation, tumor location and volume of radiation. The ophthalmology follow-up for our cohort was relatively short, and hence our results do not provide insight into the incidence of more delayed ocular complications after radiation. In the CCSS cohort, patients who received more than 500 cGy to the lens, the incidence of cataracts continued to increase up to 20 years after diagnosis.[9] The lack of long-term follow-up also limited our analysis of the functional outcomes for patients who developed ocular complications.

Our study findings highlight the need for larger prospective, multi-institutional pediatric CNS tumor trials, to include regular, formal ophthalmology exams prior to and after radiation, with longer follow-up, to determine the true incidence of these complications and their impact on visual function for these children. This would help inform ophthalmology screening guidelines for these patients, and also radiation planning to mitigate the risk of these adverse effects when possible.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

DATA AVAILABILITY

The data used and/or analyzed in this study are available from the corresponding author on reasonable request.

REFERENCES

1. Gajjar A, Chintagumpala M, Ashley D, et al. Risk-adapted craniospinal radiotherapy followed by high-dose chemotherapy and stem-cell rescue in children with newly diagnosed medulloblastoma (St Jude Medulloblastoma-96): long-term results from a prospective, multicentre trial. *The Lancet Oncology.* 2006;7(10):813-820.

2. Packer RJ, Gajjar A, Vezina G, et al. Phase III Study of Craniospinal Radiation Therapy Followed by Adjuvant Chemotherapy for Newly Diagnosed Average-Risk Medulloblastoma. *Journal of Clinical Oncology.*2006;24(25):4202-4208.

3. Merchant TE, Li C, Xiong X, Kun LE, Boop FA, Sanford RA. Conformal radiotherapy after surgery for paediatric ependymoma: a prospective study. *The Lancet Oncology.* 2009;10(3):258-266.

4. Jensen AW, Laack NN, Buckner JC, Schomberg PJ, Wetmore CJ, Brown PD. Long-term follow-up of dose-adapted and reduced-field radiotherapy with or without chemotherapy for central nervous system germinoma.*International journal of radiation oncology, biology, physics.*2010;77(5):1449-1456.

5. Kiehna EN, Merchant TE. Radiation therapy for pediatric craniopharyngioma. 2010;28(4):E10.

6. Kahalley LS, Douglas Ris M, Mahajan A, et al. Prospective, longitudinal comparison of neurocognitive change in pediatric brain tumor patients treated with proton radiotherapy versus surgery only.*Neuro-oncology.* 2019;21(6):809-818.

7. Bavle A, Tewari S, Sisson A, Chintagumpala M, Anderson M, Paulino AC. Meta-analysis of the incidence and patterns of second neoplasms after photon craniospinal irradiation in children with medulloblastoma.*Pediatric blood & cancer.* 2018;65(8):e27095.

8. Eaton BR, Esiashvili N, Kim S, et al. Endocrine outcomes with proton and photon radiotherapy for standard risk medulloblastoma.*Neuro-oncology.* 2016;18(6):881-887.

9. Whelan KF, Stratton K, Kawashima T, et al. Ocular late effects in childhood and adolescent cancer survivors: a report from the childhood cancer survivor study. *Pediatric blood & cancer.*2010;54(1):103-109.

10. Chodick G, Sigurdson AJ, Kleinerman RA, et al. The Risk of Cataract among Survivors of Childhood and Adolescent Cancer: A Report from the Childhood Cancer Survivor Study. *Radiation research.*2016;185(4):366-374.

11. Benyunes MC, Sullivan KM, Deeg HJ, et al. Cataracts after bone marrow transplantation: long-term follow-up of adults treated with fractionated total body irradiation. *International journal of radiation oncology, biology, physics.* 1995;32(3):661-670.

12. Ferry C, Gemayel G, Rocha V, et al. Long-term outcomes after allogeneic stem cell transplantation for children with hematological malignancies. *Bone marrow transplantation.* 2007;40(3):219-224.

13. Gurney JG, Ness KK, Rosenthal J, Forman SJ, Bhatia S, Baker KS. Visual, auditory, sensory, and motor impairments in long-term survivors of hematopoietic stem cell transplantation performed in childhood: results from the Bone Marrow Transplant Survivor study. *Cancer.*2006;106(6):1402-1408.

14. Horwitz M, Auquier P, Barlogis V, et al. Incidence and risk factors for cataract after haematopoietic stem cell transplantation for childhood leukaemia: an LEA study. *Br J Haematol.*2015;168(4):518-525.

15. van Kempen-Harteveld ML, Belkacémi Y, Kal HB, Labopin M, Frassoni F. Dose-effect relationship for cataract induction after single-dose total body irradiation and bone marrow transplantation for acute leukemia.*International journal of radiation oncology, biology, physics.*2002;52(5):1367-1374.

16. Zierhut D, Lohr F, Schraube P, et al. Cataract incidence after total-body irradiation. *International journal of radiation oncology, biology, physics.* 2000;46(1):131-135.

17. Oberlin O, Rey A, Anderson J, et al. Treatment of orbital rhabdomyosarcoma: survival and late effects of treatment–results of an international workshop. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.*2001;19(1):197-204.

18. Shields CL, Shields JA, Cater J, Othmane I, Singh AD, Micaily B. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. *Ophthalmology.*2001;108(11):2116-2121.

19. Gondi V, Yock TI, Mehta MP. Proton therapy for paediatric CNS tumours — improving treatment-related outcomes. *Nature Reviews Neurology.* 2016;12(6):334-345.

20. Lühr A, von Neubeck C, Krause M, Troost EGC. Relative biological effectiveness in proton beam therapy - Current knowledge and future challenges. *Clinical and translational radiation oncology.*2018;9:35-41.

21. Alloin A-L, Barlogis V, Auquier P, et al. Prevalence and risk factors of cataract after chemotherapy with or without central nervous system irradiation for childhood acute lymphoblastic leukaemia: an LEA study. *British Journal of Haematology.* 2014;164(1):94-100.

22. Socié G, Salooja N, Cohen A, et al. Nonmalignant late effects after allogeneic stem cell transplantation. *Blood.*2003;101(9):3373-3385.

23. Parsons JT, Bova FJ, Mendenhall WM, Million RR, Fitzgerald CR. Response of the normal eye to high dose radiotherapy. *Oncology (Williston Park, NY).* 1996;10(6):837-847; discussion 847-838, 851-832.

24. Parsons JT, Bova FJ, Fitzgerald CR, Mendenhall WM, Million RR. Severe dry-eye syndrome following external beam irradiation.*International journal of radiation oncology, biology, physics.*1994;30(4):775-780.

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