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Original Article

Radiation tolerance of the optic pathway in patients treated with proton and photon radiotherapy

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ABSTRACT

Introduction: Radiation-induced optic neuropathy (RION) is a complication of radiation therapy (RT) that causes blindness. We aimed to define the tolerance of the anterior optic pathway to fractionated RT and identify risk factors for RION.

Materials/methods: Patients with chordoma or chondrosarcoma of the skull base treated with proton and photon therapy between 1983 and 2013, who received a minimum of 30 Gy (relative biologic effectiveness [RBE]) to the anterior optic pathway were assessed. Optic neuropathy with radiographic correlation occurring ≥6 months after completion of RT in the absence of tumor recurrence or other probable cause was diagnosed as RION.

Results: Of 514 patients, 17 developed RION. With median follow-up of 4.8 years, cumulative incidence of RION was 1% among patients receiving <59 Gy (RBE) and 5.8% among patients receiving ≥60 Gy (RBE) to the optic pathway. Higher maximum point dose to the optic pathway (subhazard ratio [SHR] = 1.2, 95% CI 1.05–1.2, $p = 0.001$), older age (SHR = 1.1, 95% CI 1.02–1.08, $p < 0.0005$), and female sex (SHR = 16.3, 95% CI 2.2–122.4, $p = 0.007$) were statistically significant risk factors for RION in multivariate analysis.

Conclusion: In our study cohort, rates of RION were very low with conventionally fractionated RT up to 59 Gy. At doses ≥60 Gy, there is an increased risk of RION, with greater risk for women and older patients.
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Radiation-induced optic neuropathy (RION) is a rare complication of radiation therapy, causing impairment of vision in one or both eyes in the months to years following radiation therapy to the optic system. The peak incidence occurs within two years [1] after irradiation of the optic nerves and/or optic chiasm and is thought to be due to free radical-induced damage to endothelium and neuroglial cell progenitors leading to vaso-occlusion, demyelination, and neuronal degeneration [2]. Treatment with systemic corticosteroids, anticoagulation, and hyperbaric oxygen, which have demonstrated some efficacy in cerebral radionecrosis and radiation osteonecrosis have been largely unsuccessful in reversing or even halting loss of vision [3–5]. Anti-vascular endothelial growth factor (VEGF) therapies are potentially beneficial but as yet unproven [6,7]. Without an effective therapeutic option for treating RION, it is imperative to prevent the injury if possible. The risk of radiation-induced optic neuropathy (RION) is thought to increase with increasing age, co-morbid diabetes, concurrent chemotherapy, pre-existing optic nerve compression, and higher doses of radiation [8–11]. Previous studies have provided evidence that the optic nerve and chiasm can withstand 10–12 Gy single-fraction therapy [12,13] and up to 60 Gy with fractionated external beam radiotherapy [14–16] with fraction sizes of 1.9 Gy or less [17,18]. For fractionated radiation treatments, NRG Oncology protocols currently recommend a dose limit of 55 Gy. The 10-year actuarial risk of RION for patients treated at doses 50–60 Gy and 61–78 Gy, with median of 2 Gy per fraction, have been reported as 5% and 30%, respectively [19].

Patients with cranial base chordoma and chondrosarcoma are routinely treated to doses in the range of 70 Gy and higher, with significant incidental irradiation to the optic chiasm and nerves [20,21]. Previous studies indicate that the rate of RION ranges from 0 to 58% in patients with skull base tumors treated with photon and charged ion therapy with follow up of up to 4 years [15,22]. Proton therapy has been adopted as the preferred therapeutic radiation modality because of its superior dose localization properties as compared to photon radiation, such that higher doses of radiotherapy can be delivered to the tumor while minimizing dose and subsequent potential injury to nearby structures. Radiation

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tolerance is thought to be comparable between photon and radiobiologically corrected proton radiation therapy. A small trial in 2008 demonstrated no cases of radiation-induced optic neuropathy in 16 patients with chordoma or chondrosarcomas treated with proton therapy to 50–70 Gy (relative biologic effectiveness [RBE]) delivered at 1.8 Gy (RBE) per fraction [23]. Most data to date either result from similarly small clinical series or provide a wide range of doses with variable rates of injury [24], and fail to provide a clear confidence of long term safety. Using a large clinical database of patients with skull base chordoma or chondrosarcoma treated postoperatively with a combination of proton and photon radiation therapy, we sought to better define the tolerance of the anterior optic pathway to fractionated irradiation and to identify risk factors for RION. To date, this is one of the largest studies evaluating RION with one of the longest follow-up periods.

Materials and methods

Study cohort and treatment

This retrospective, single institution study included patients >18 years of age with chordoma or chondrosarcoma of the cranial base treated with proton therapy at Harvard Cyclotron Laboratory (HCL) or Massachusetts General Hospital (MGH) between 1983 and 2013, who received a minimum of 30 Gy (RBE) to any part of the anterior optic pathway, defined as the chiasm or either optic nerve. This study was approved by the Institutional Review Board. Patients underwent primary surgery, either craniotomy or endoscopic approach, at MGH or at an outside institution. Pathology in all patients was reviewed at MGH, following established histopathologic criteria [25].

Radiation planning was performed utilizing fusion of high-resolution, contrast-enhanced CT and MRI, when available, and a 3D treatment planning system with conformal shaping of proton and photon beams. The anterior optic pathway was carefully contoured in a collaboration between an experienced anatomist and the treating physician. Treatment planning was overseen by a senior proton dosimetrist. The optic tracts were not contoured or subject to dose constraints. Doses exceeding standard optic pathway dose constraints were allowed, with patient consent, to optimize tumor coverage and control and in some cases under a study protocol. Radiation treatment was delivered with proton radiation alone in 48 patients and a combination of proton and photon therapy in 466 patients. Among the 466 patients receiving combination treatment, the proportion of dose delivered using proton therapy ranged from 23% to 98% (median 71%). Use of mixed radiation therapies was chosen for logistical considerations and superior skin sparing with partial photon therapy as compared to proton therapy alone. Proton radiation was delivered with a fixed 164 MeV proton beam at HCL until November 2001 and with the 235 MeV gantry-based proton beam at MGH thereafter. 3D-conformal photon radiation therapy was given with 4, 6, or 10 MV photons on a linear accelerator. Patients were immobilized in the recumbent position using a thermoplastic head mask. Patients were treated on consecutive weekdays with daily doses between 1.46 and 2.0 Gy (RBE) except four patients who received some treatments on a 1.2 Gy (RBE) twice daily schedule.

Dose calculations

Summation plans and dose–volume histograms (DVHs) were available for every patient. Dose to the optic chiasm and nerves was extracted from DVHs. Terminal range uncertainties associated with proton radiation were not felt to be relevant at the optic pathway given the purposeful use of multiple beam arrangements to dilute this effect and keeping optic structures away from the field end margin for this reason. Relative biological effectiveness (RBE) of 1.1 was used for initial planning. Proton doses were defined in terms of Gy(RBE) = proton Gy $\times$ 1.1, as previously described [26,27]. Four representative patients with RION and four age, sex, and optic pathway dose-matched patients without RION were identified. Linear energy transfer (LET) calculations were performed for these patients using Monte Carlo simulations, as previously described [28]. The physical dose and LET distributions were then used to calculate variable-RBE-weighted dose distributions, using the model by McNamara et al. [29] We used alpha/beta ratio value of 10 Gy for the targets and 1.6 Gy for the optic structures. Dose-data were corrected to a radiobiologically effective dose (BED) in 1.8 or 2 Gy per fraction using the linear-quadratic model and an alpha/beta ratio of 1.6 Gy [19].

Evaluation of vision

RION was diagnosed clinically in consultation with a neuro-ophthalmologist. RION was defined as any combination of loss of visual acuity, visual field, color vision, optic chiasm or nerve enhancement on MRI, and/or pallor of optic discs on fundoscopy occurring $\geq$6 months after radiation therapy in the absence of tumor recurrence and other probable competing clinical causes. Patients were scored as definitive versus possible RION based upon the available evidence. Visual acuity loss or improvement was defined as change of 2 lines or more of best-corrected vision. Visual fields were examined using the Goldmann or automated perimeter when available, or estimated using finger confrontation testing. Color vision was assessed by Ishihara tests.

Statistical analyses

Analysis was performed by patient, not by eye, to align with clinical practice. Actuarial incidence of RION was estimated using competing risks method with death competing with development of RION. The association of treatment and patient-related factors was assessed for prognostic significance with respect to the actuarial complication using Gray's test. Wilcoxon rank-sum test was used for comparing distribution of maximum doses. For actuarial analysis of toxicity, local recurrence and death without toxicity were considered competing risks. A two-sided P value <0.05 was considered statistically significant. All calculations were performed with Stata (StataCorp 2011. Stata Statistical Software: Release 14. College Station, TX).

Results

Table 1 summarizes the baseline characteristics of the 514 patients in the study population. Median age was 43.8 years (range: 18.1–87.8), 259 patients (50.4%) were male, and 263 patients (51.2%) had chordoma. Median prescribed total dose was 75.2 Gy(RBE) for patients with chordoma and 70.0 Gy(RBE) for patients with chondrosarcoma (range: 56.0–83.6) delivered in a median of 37 fractions (range: 28–63). Median tumor target volume was 15.0 cc (range: 0.7–282.0). Median follow-up time was 4.8 years. Median maximum radiation point dose to the optic chiasm was 61.3 Gy(RBE) (range: 18.1–70.0), and median dose was 54.3 Gy(RBE) (range: 9.6–63.8). Median maximum radiation point dose to either optic nerve was 58.0 Gy(RBE) (range: 2.9–77.3), and median dose was 16.6 Gy(RBE) (range: 0.3–72.0).

Following radiation therapy, 22 eyes in 17 patients (3.3% of 514 patients) developed RION and an additional eye in one patient was suspicious for RION, but available data were inadequate for diagnosis. Median time to first symptom among these patients was 1.0 year (range: 0.6–6.8). Left and right eyes were equally vulnera-

Table 1
Patient characteristics.

	Patients*	Eyes†	Range	%
Number	514	1021		
Age: median	43.8		18.1–87.8	
Sex				
Male	259			50.4
Female	255			49.6
Comorbidities				
Diabetes mellitus	21			4.1
Hypertension	84			16.3
Vascular disease	33			6.4
Hyperlipidemia	30			5.8
Smoking history				
Non-smoker	276 (of 501)			55.1
Former or current smoker	225 (of 501)			44.9
Pre-RT KPS: median	90 (among 498)		50–100	
Diagnosis				
Chordoma	263			51.2
Chondrosarcoma	251			48.8
Abutment or compression/displacement of optic pathway	120 (of 510)			23.5
Radiotherapy factors, median				
Total dose (Gy[RBE])	70.0		56.0–83.6	
Length of treatment (days)	52		38–68	
Number of fractions‡	37		28–63	
Target volume (cc)	15.0		0.7–282.0	
Surgical factors				
Months from surgery to radiation: median	5.1		0.1–210.9	
Number of surgeries: median	1		0–10	
Incomplete resection	425			82.7
Chemotherapy	28			5.4
Ophthalmic diseases				
Corneal disease		40 (of 881)		4.5
Retinal disease		30 (of 881)		3.4
Cataracts		50 (of 881)		5.7
Glaucoma		9 (of 881)		1.0
Other		32 (of 881)		3.6
Multiple diseases		34 (of 881)		3.9
Evidence of radiation injury in other brain locations	76 (of 468)			16.2
Tumor recurrence	118			23.0
Years to local recurrence: median	3.6 (among 94)		0.2–20.3	
Deceased at last follow up	68			13.2
Years to death: median	4.5 (among 66)		0.6–18.8	
Years of total follow up: median	4.8		0.2–28.2	

Abbreviations: RT: radiation therapy; KPS: Karnofsky Performance Status.
* 514 total patients unless otherwise indicated.
† 1021 eyes unless otherwise indicated.
‡ All patients received conventionally-fractionated radiation therapy with daily doses of 1.46–2.0 Gy(RBE) except for 4 patients who received a component of hyperfractionated 1.2 Gy(RBE) twice daily schedule.

ble to RION. Characteristics of patients who developed RION are shown in Table 2.

Vision improved in 4.1% of patients (28 eyes in 21 patients) following radiation treatment. Patients recovered visual acuity, visual field, and/or experienced improved vision subjectively at a median of 9.4 months (range: 1.4–76.5). Seventy-nine patients (15.4%) were found to have worsening visual parameters attributed to causes other than RION at a median of 33.9 months (range: 0–165.7). Local tumor recurrence or progression affected 41 of 79 patients (51.9%) that lost vision. Forty of 79 patients (50.6%) were afflicted by ophthalmic diseases known to compromise vision, including diseases of the cornea (more common in this population given concurrent trigeminal nerve injuries secondary to tumor compression), retinal diseases, cataracts, and glaucoma. One patient was thought to suffer from vision loss due to optic nerve compression from tumor and surrounding brain parenchyma edema two weeks following completion of radiation therapy, earlier than would be expected for development of RION. He improved with steroids. Radiation-induced sarcoma causing compression of the optic nerve was found in one patient. One patient was diagnosed with radiation-induced retinopathy.

Higher doses to the anterior optic pathway significantly increased the risk of RION (Table 3). Patients who developed RION received, on average, 3.8 Gy(RBE) more maximum point radiation to the optic pathway than patients who did not, with maximum doses causing RION ranging from 59.4 to 71.1 Gy(RBE) (Fig. 1). Among treatment variables, maximum radiation dose to the optic nerves was the most statistically significant for increasing risk of RION in univariate analysis, and was correlated with shorter time to RION (Subhazard ratio [SHR] = 1.2, $p < 0.0005$). Given lower calculated fraction size at the optic chiasm and nerves than at the target, equivalent maximum optic structure dose was calculated for 1.8 and 2.0 Gy fraction sizes at the optic chiasm and nerves (Table 2). In patients receiving <60 Gy(RBE), the actuarial risk of RION peaked at 1.0% (95% CI 0.1–6.9%). In patients receiving ≥60 Gy(RBE) to the optic pathway, the 5-, and 10-year cumulative incidence of RION were 4.1% (95% CI 2.4–7.0%), and 5.8% (95% CI 3.3–10.3%), respectively (Fig. 2). Higher total prescribed dose (SHR = 1.1, $p = 0.04$) was statistically significant on univariate analysis, likely reflecting its close correlation with maximum radiation dose delivered to the optic pathway. Length of treatment time, hyperfractionation, proportion of dose delivered using proton

Table 2
Characteristics of patients with radiation-induced optic neuropathy (RION), ordered by age.

Patient No.	Eye No.	Age (years)	Sex	Year of RT	Prescribed dose (Gy [RBE])	No. frx	Max optic structure dose (Gy[RBE])	Max optic structure equivalent dose at 2 Gy (RBE) per fraction	Max optic structure equivalent dose at 1.8 Gy (RBE) per fraction	Pre-RT VA[§]	Pre-RT VF cut	Pre-RT subjective vision loss	Pre-RT color vision loss	Pre-RT optic atrophy or pallor	Optic nerve enhancement	Months to RION
1	1	37.4	F	2010	78	39	62.3	55.3	58.6	Good					Ipsi nerve	10.1
2	2	40.8	F	2001	69.1	37	63.1	57.9	61.3	Good			N/A		Ipsi nerve	11.4
3	3	42.7	F	1999	69.3	37	70.9	69.2	73.3	Good		X		X		80.1
4	4	44.7	F	1993	68.4	38	62.6	56.5	59.8	Good					Chiasm & Ipsi nerve	8.8
4	5	44.7	F	1993	68.4	38	62.6	56.5	59.8	Good					Chiasm	9.9
5	6	45.4	F	2001	75.2	40	64.2	57.2	60.5	Good			N/A			7.3
6	7	50.9	F	1998	69.6	37	61.7	56.0	59.3	Good						9.1
7	8	55.8	F	1998	75.5	40	61.9	54.1	57.3	Good	X		N/A		Chiasm & nerves	11.0
7	9	55.8	F	2002	75.5	40	61.9	54.1	57.3	Good	X		N/A		Chiasm & nerves	7.6
8	10	55.9	F	2002	69.6	37	71.1	69.6	73.6	Good					Ipsi nerve	47.2
9	11	57.6	F	2010	76	38	60.4	53.5	56.7	Good			N/A		Ipsi nerve	14.4
10	12	61.4	F	2010	76.0	38	65.8	60.9	64.5	Good			N/A		Chiasm	12.4
10	13	61.4	F	2010	76.0	38	65.8	60.9	64.5	Good			N/A		Chiasm	12.4
11	14	62.9	F	2002	70	35	60.6	56.1	59.4	Mod	X				Nerves	17.8
11	15	62.9	F	2002	70	35	62.8	59.2	62.7	Good					Nerves	13.8
12	16	66.4	F	2007	70	35	59.4	54.4	57.6	Good		X		X		24.2
13	17	68.3	F	1998	75	40	61.7	53.9	57.0	Good						10.1
14	18	69.0	F	1996	79.2	44	63.5	53.7	56.8	Good	X		X		Chiasm	16.8
14	19	69.0	F	1996	79.2	44	63.5	53.7	56.8	Good	X		X		Chiasm	10.8
15	20	70.5	F	1995	79.2	44	62.9	52.9	56.0	Good	X				Nerves	22.2
15	21	70.5	F	1995	79.2	44	62.9	52.9	56.0	Good					Nerves	22.2
16	22	73.2	M	1993	72	40	61.1	53.1	56.2	Good	X					12.5
17	23	81.5	F	2003	69.6	35	71.5	72.4	76.6	Good			N/A		Nerve	10.5

Abbreviations: No. = number, F = female, M = male, RBE = relative biologic effectiveness, max = maximum, frx = fraction, RT = radiotherapy, VA = visual acuity, VF = visual field, Mod = moderate, X = indicates presence of deficit, N/A = not available, Ipsi = ipsilateral.
[§] Good is >20/40, moderate is 20/50–20/200.

Table 3
Univariate Competing Risks Regression Analysis for Risk Factors for RION.

	Subhazard Ratio	95% CI	*P*-value
Older age (years)	1.1	1.04–1.11	<0.0005
Female sex	16.9	2.2–127.0	0.006
Comorbidities			
Diabetes mellitus	NE		1.0
Hypertension	3.2	1.2–8.8	0.02
Vascular disease	NE		1.0
Hyperlipidemia	NE		1.0
Pre-RT Visual field defect	3.3	1.2–9.0	0.02
Other brain injury	4.5	0.9–22.0	0.06
Smoking history	0.5	0.2–1.5	0.2
Pre-RT KPS	1.02	0.95–1.09	0.6
Abutment or compression/displacement of optic pathway	1.7	0.6–4.6	0.3
Radiotherapy factors			
Prescribed dose (Gy(RBE))	1.1	1.0–1.2	0.04
Maximum optic pathway dose(Gy(RBE))	1.2	1.1–1.3	<0.0005
Equivalent dose at 2Gy(RBE) per frx	1.1	1.04–1.2	<0.0005
Equivalent dose at 1.8Gy(RBE) per frx	1.1	1.04–1.2	<0.0005
Length of treatment (days)	1.08	1.0–1.2	0.08
Number of fractions[¶]	1.04	0.9–1.1	0.4
Proportion of dose delivered using protons	1.01	1.00–1.03	0.18
Target volume (cc)	1.0	0.98–1.01	0.8
Surgical factors			
Months from surgery to radiation	1.0	0.98–1.1	0.5
Number of surgeries	1.4	1.1–1.9	0.02
Incomplete resection	1.5	0.3–6.6	0.6
Chemotherapy	1.1	0.4–2.8	0.9

Abbreviations: CI = confidence interval, NE = not estimable, RBE = relative biologic effectiveness, frx = fraction, cc = cubic centimeters.
[¶] While not significant in univariate analysis, total number of fractions (HR = 1.2, $p = 0.01$) and dose per fraction (HR = 1.1, $p = 0.003$) were statistically significant risk factors for RION when jointly considered in a multivariate analysis.

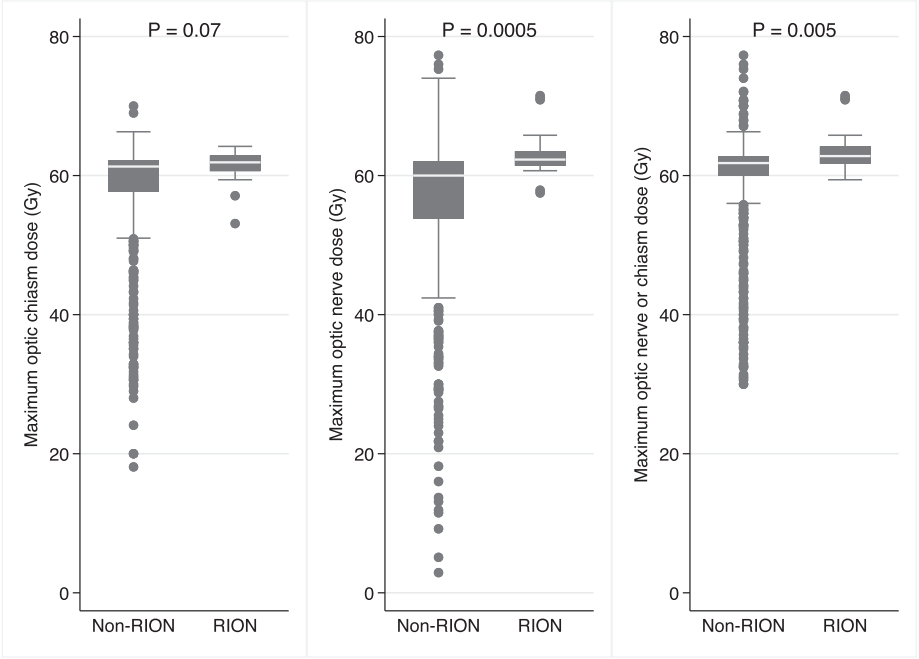

Fig. 1. Comparison of radiation doses that did and did not lead to development of RION. The box shows the interquartile range with a segment to represent the median. The whiskers indicate maximum and minimum doses and circles indicate outliers.

therapy, and target volume were not associated with development of RION (Table 3). Decade of treatment was not associated with the development of RION.

While assuming a constant RBE of 1.1 in all tissues is still standard practice in the clinic, there is increasing evidence that a variable RBE more accurately estimates effective dose, particularly in late-reacting tissues [30]. To address this issue, we calculated variable RBE-weighted doses for a representative group of patients who developed RION and matched patients who did not. When accounting for variable RBE, similarly increased mean and maximum doses to the optic structures were estimated for both groups (Supplementary Table 1). The small sample size precludes rigorous

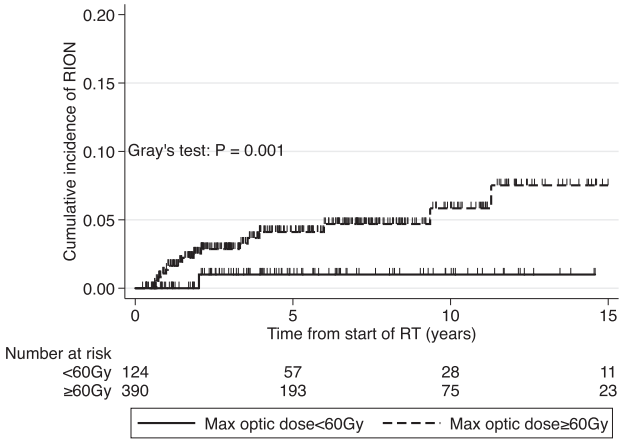

Fig. 2. Actuarial cumulative risk of RION for patients stratified by low (<60 Gy (RBE)) and high (≥60 Gy(RBE)) radiation dosage. The cumulative incidence of RION peaked at 1.0% (95% CI 0.1–6.9%) for patients receiving low dosage and 5.8% (95% CI 3.3–10.3%) for patients receiving high dosage at 10 years.

statistical testing; however, in this limited cohort, we did not see any suggestion of correlation between elevated variable RBE-based dose and RION.

The number of pre-radiation surgeries (SHR = 1.4, $p = 0.02$) was associated with increased RION risk, but neither the extent of surgical resection nor time to most recent surgery were significant risk factors (Table 3). Systemic therapy including chemotherapy (pre- or post-irradiation) was not observed to significantly increase risk of RION. However, this analysis was limited by the low prevalence of systemic therapy and lack of concurrent systemic therapy administration in this cohort.

Among patient characteristics, the most statistically significant risk factors for RION were older age and female sex in univariate analysis (Table 3). Older age increased the risk of RION by a sub-hazard ratio of 1.1 ($p < 0.001$), with median age at 57.6 years for patients with RION versus 43.3 years for patients without RION. Women were at higher risk of RION (SHR = 16.3, $p = 0.007$ when adjusted for age and optic pathway dose), with 6.3% of women (16 of 255 women) developing RION versus 0.4% of men (1 of 259 men).

To further investigate the relationship between sex and development of RION, we queried for any correlation between RION and increased or decreased hormonal states in women, including parity, gravidity, and menopause status. None of these approached statistical significance, suggesting that increased radiation sensitivity in the optic neural tissue of women was not linked to the hormonal status in women.

On univariate analysis, hypertension (SHR 3.2, $p = 0.02$) was the only comorbidity associated with increased risk of RION in this study (Table 3). Conditions including diabetes mellitus, vascular diseases, hyperlipidemia, smoking history (concurrent or prior to radiotherapy), and pre-irradiation Karnofsky performance status (KPS) were not statistically significant risk factors.

Pre-irradiation visual field defect (SHR = 3.5, $p = 0.01$) was found to be associated with increased risk of RION, while pre-irradiation abutment or tumor displacement of optic nerve or chiasm alone and prior optic nerve pallor or atrophy alone were not associated with increased risk of RION (Table 3). These data suggest that only optic nerve injuries causing measurable visual field deficits were a risk factor for RION. Prior visual acuity or subjective visual deficit, ophthalmic disease diagnosed prior to developing RION (pre- or post-irradiation), and cranial nerve neuropathies were not significantly correlated with development of RION.

Correlations were found between development of RION and other radiation-induced brain injury ($p < 0.001$), defined as symptomatic or asymptomatic MRI enhancement of irradiated brain parenchyma. There was no significant association between development of RION and recurrence ($p = 0.2$) or death ($p = 0.5$).

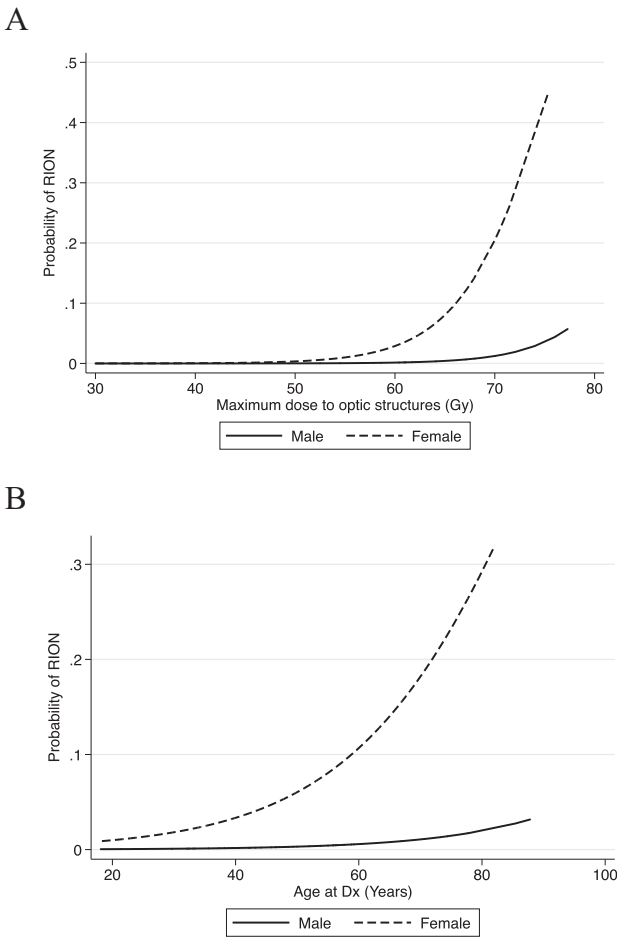

Fig. 3. Dose–response (A) and age-responsive (B) curves, projected based on multivariate model. The reference age for Fig. 3A is 44 years, the median age in the cohort. The reference maximum optic pathway dose for Fig. 3B is 62 Gy(RBE), the median dose in the cohort. Multivariable competing risks analysis showed older age, female sex, and higher optic pathway dose were statistically significantly associated with RION.

On multivariable competing risks analysis, older age (SHR = 1.1, 95% CI 1.02–1.08, $p < 0.0005$), female sex (SHR 16.3, 95% CI 2.2–122.4, $p = 0.007$), and higher optic pathway dose (SHR 1.2, 95% CI 1.05–1.2, $p = 0.001$) were statistically significantly associated with RION. The variables were selected for the inclusion in the multivariable model using all subsets approach and Akaike Information Criterion. Dose–response and age–response curves, based on the multivariable logistic model of RION with age, sex, and optic pathway dose as covariates, are shown in Fig. 3. The multivariable competing risks prediction model for RION has high discriminating power with Harrell's C concordance statistic of 0.90. For non-actuarial multivariable logistic regression model with the same covariates, the area under the ROC curve is 0.90.

Discussion

RION is a radiation dose-limiting toxicity. Using a large, robust clinical database of patients with long follow up, this study establishes the radiation tolerance of the optic pathway and risk factors for RION. Our findings may help to identify potential strategies for treatment and prevention of RION, aiding the ability of physicians

to tailor treatments for patients in an age of individualized medicine.

RION remains a low but real risk among patients receiving >59 Gy(RBE) to the optic pathway, with higher doses causing increased risk of RION. For 1.8 and 2.0 Gy fraction sizes at the optic pathway, equivalent maximum optic structure dose tolerances were calculated to be 57 Gy and 55 Gy, respectively. These dose tolerances are consistent with prior data [15–17,19], though the actuarial risk was much lower in our cohort. This may reflect higher doses per fraction and use of older imaging and treatment technologies in some of these studies, as well the more conformal radiation treatment achieved with protons in our study. Our study also advocates for careful planning with support from an experienced anatomist. After proton irradiation, some patients can experience vision improvement, suggesting that radiation does not impair healing after procedures such as decompressive surgery.

In addition to higher radiation dose, older age and female sex were found to significantly elevate risk of RION. Increased susceptibility to optic nerve injury with increasing age is consistent with prior reports [9,14,31]. It is unclear why female neural tissue may be more sensitive to radiation than its male counterpart. Our finding that RION rates were not affected by varied hormonal states in women suggests that the underlying mechanism is not hormonally mediated. The strong statistical correlation between radiation changes in other brain locations and RION provides evidence that some patients may have increased sensitivity to radiation due to intrinsic qualities. One of these intrinsic qualities may be sex-related. Reports on sex-specific differences in response to radiation are common, but show mixed results. Women have been observed to experience increased toxicity and response to chemoradiation for rectal cancer [32] and lung cancer [33,34]. On the other hand, men have been reported to develop more cataracts [35] and cauda myelopathy [36] following radiation therapy. To our knowledge, this is the first report of female predisposition for neural toxicity.

In a limited evaluation of variable RBE, we found higher effective doses delivered compared to those calculated using a constant RBE but did not find evidence to support a correlation between elevated variable RBE-weighted dose and RION. A similar difference between constant and variable RBE-weighted doses was observed for patients of both groups. We believe physical dose and patient-specific variables that determine radiosensitivity are likely more significant factors than LET in contributing to patient injury but cannot exclude the possibility that variable RBE-based dose indices are stronger predictors of RION than fixed RBE-based dose indices. To more comprehensively address this possibility, variable RBE-weighted dose analyses could be performed for all patients in the study. Such an undertaking is beyond the scope of this study but may be valuable future research. Still, any conclusions drawn from such data must acknowledge the significant uncertainties inherent in any variable RBE model and with alpha/beta values.

The small number of RION events limited the statistical power of this study in analyzing potential risk factors for RION. For example, diabetes, hyperfractionation, and systemic therapies were not found to be risk factors in this study though this may merely reflect their low prevalence in our cohort. RION is a rare condition because of careful practices in radiation planning and delivery, and a larger similar study is not likely to become available. Nevertheless, interpretation of these results should be approached with caution. Another limitation of this study is the heterogeneity of the neuro-ophthalmology follow up data. Many of the patients in the study were referred from and ultimately followed at outside institutions, thus contributing to heterogeneity of data available and making standardization for cross-comparison challenging. We attempted to decrease noise by excluding patients without clinical follow up, applying a higher threshold for what constituted visual change, loss or gain of $\geq$2 lines of visual acuity, and following multiple parameters, including visual field, color vision, and optic disc appearance. All RION cases were also reviewed in detail by an experienced neuro-ophthalmologist. We feel that evaluation of vision using a combination of metrics is a strength of this study. We have provided a set of criteria for diagnosis of RION utilizing these metrics and suggest that these should be regularly evaluated in any patient at risk for RION.

In summary, our study, the largest of its kind, supports optic pathway radiation tolerance to be up to 59 Gy at standard fractionation if careful planning and conformal radiation therapy technique are utilized. With doses to the optic pathway exceeding 59 Gy, the cumulative incidence of RION at 10 years was 5.8% (95%CI 3.3–10.3%). For tumors adjacent to the optic pathway, in which dose per fraction approaches 1.8–2 Gy, a more conservative equivalent maximum optic structure dose tolerance should be employed. Higher maximum radiation dose to the anterior optic pathway, older age, and female sex are associated with increased risk for RION. In addition to confirming these findings, future studies should investigate the role of variable RBE-based dose indices and alpha/beta ratio of proton radiotherapy in optic pathway toxicity. The genetic and epigenetic qualities that dictate radiation tolerance of tissues also merit further study. Such research will help guide future strategies for preventing and treating a variety of radiation toxicities.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.12.007.

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