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Scientific Article

Analysis of patient outcomes following proton radiation therapy for retinoblastoma

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Abstract

Purpose: Proton radiation therapy (PRT) is used to treat patients with retinoblastoma (RB) and has the potential to minimize exposure of normal tissue to radiation and thus decrease the risk of

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toxicity and second malignancies. However, comprehensive analyses of long-term patient outcomes are not available.

Methods and materials: Patients with RB who were treated with PRT at our institution between 1986 and 2012 were invited to participate in a study that was designed to assess long-term outcomes. Patients who were enrolled in the study underwent a comprehensive analysis that included oncologic, ophthalmic, endocrine, cephalometric, and quality of life (QOL) assessments.

Results: A total of 12 patients were enrolled in this study. The average length of follow-up was 12.9 years (range, 4.8-22.2 years). All study patients had bilateral disease, and the disease and visual outcomes were similar to the outcomes for all patients with RB who were treated with PRT over the same time period at our institution. An analysis of endocrine-related test results revealed no growth abnormalities or hormonal deficiencies across the cohort. Magnetic resonance imaging scans and external cephalometry showed that PRT was associated with less facial hypoplasia than enucleation. Patient and parent-proxy QOL assessments revealed that treatment for RB did not appear to severely affect long-term QOL.

Conclusions: In addition to providing an opportunity for long-term disease control and functional eye preservation, PRT does not appear to be associated with unexpected late visual, endocrine, or QOL effects in this cohort of patients with RB.

Introduction

Approximately 300 cases of retinoblastoma (RB) are diagnosed each year in the United States, which makes this disease the most common intraocular childhood malignancy.[1] Sporadic and inherited forms of the disease exist, and patients typically present with symptoms of leukocoria or strabismus during the first few years of life.[2] Patients with the inherited form of the disease often develop tumors earlier in childhood and are at risk for bilateral eye involvement.

The majority of retinoblastoma cases are confined to the globe at the time of diagnosis; therefore, treatment success depends on effective local control. Radiation therapy (RT) has a long history of use in RB treatment; for many decades, RT was the only available eye-sparing treatment modality.[3-5] Although RT has been associated with high rates of disease control and vision preservation in many settings, concerns about RT-related toxicities (eg, growth abnormalities, secondary malignancies) have led to an increased use of systemic or intra-arterial chemotherapy and focal therapies (eg, cryoablation, laser photocoagulation), especially for the treatment of early stage tumors.[6-9]

Proton radiation therapy (PRT) is a unique form of RT that has been used to treat RB at our institution for nearly 30 years. Due to the physical properties of the proton beam, exposure of normal (non-tumor) tissue can be minimized compared with traditional photon-based RT techniques. We recently reported on long-term disease outcomes for patients with RB who were treated with PRT.[10] Tumor control rates are similar to historical series, and side effects appear to be limited. Importantly, PRT should reduce the risk of radiation-induced malignancies compared with patients who were treated with modern photon-based techniques.[11,12]

Despite the high cure rates that can be achieved with current treatment techniques, little is known about the long-term effects of treatment on survivors of RB. Given the increasing use of PRT in the treatment of childhood malignancies, prospective data are needed to understand disease and patient outcomes. Here, we report on the functional and quality of life (QoL) outcomes for patients with RB who were treated with PRT.

Methods and materials

Patient identification and enrollment

Institutional review board approval was obtained prior to the enrollment of patients (IRB protocol DFCI #07-166). We identified all patients who received PRT for RB at our institution between 1986 and 2012 (N = 61). Treatment details for this cohort have been described previously: all eyes were treated using a single lateral or posterior-lateral field. Patients with optic nerve involvement were excluded.[10,12] Eligible patients were contacted via telephone, and those who were interested in participating were mailed additional information including a copy of the approved protocol. For most patients, the decision to participate was made by a parent with assent or by the patients themselves if they were capable of providing consent. Direct patient consent without parental consent was obtained from patients aged ≥18 years at the time of contact. The costs for travel to our institution and accommodation for a 2-day period were offered to the patient and a guardian. For patients who were already

followed at our institution, study participation was coordinated with regularly scheduled follow-up visits.

Patient testing

Each patient was examined by a radiation oncologist (H.A.S. or T.I.Y.) who reviewed relevant portions of the patient's medical history and coordinated additional follow-up visits as needed. At the beginning of the first visit, the purpose of the study was reviewed with and written consent was obtained from the patient (or a legal guardian if the patient was aged 18 years). Each patient also underwent a comprehensive ophthalmologic evaluation by a retinal specialist (S.M.).

A gadolinium-enhanced magnetic resonance imaging (MRI) scan was obtained for 9 of 12 patients. General anesthesia was available but not required for patients in the cohort. Orbital measurements were made by a medical team that included a radiation oncologist and neuro-radiologist on the T1 post-gadolinium sequence with Vitrea software (Vital Images; Minnetonka, MN). Orbital width was measured from the inner table of the frontal bone medially to the inner table of the zygomatic bone laterally. Orbital height was measured from the inner table of the frontal bone superiorly to the inner table of zygomatic bone inferiorly. External cephalometric measurements were performed by 1 of 2 oculoplastic surgeons (A.F., S.K.F.) and an accompanying oculoplastic surgery fellow (D.D.) with the use of calipers. Measurements included orbital height (measured from superior orbital rim to inferior orbital rim), palpebral width (measured from inner canthal angle to lateral canthal angle), and maxillary depth (measured from subnasion to tragus).[13-15]

Each patient was also examined by 1 of 2 pediatric endocrinologists (M.K., M.M.). Eleven of 12 patients consented to provide blood and urine samples. The following serum values were tested: insulin-like growth factor 1, insulin-like growth factor binding protein 3, thyroid stimulating hormone, free thyroxine, morning cortisol, prolactin, follicle-stimulating hormone, luteinizing hormone, estradiol (female patients only), testosterone (male patients only), sodium, and osmolality. For patients with an equivocal morning cortisol value, a low-dose adrenocorticotropic hormone stimulation test was performed by administering cosyntropin (1 mcg/m^2) and measuring plasma cortisol levels at 0, 30, and 60 minutes. Urine sodium and osmolality values were also measured.

In addition, each patient and the patient's family met with a study coordinator to discuss QoL assessment tools. Patients and family members were allowed to complete the questionnaires unsupervised and without time pressure. For participants aged <18 years, the general core and cancer modules of the Pediatric Quality of Life Inventory (PedsQL) Version 4.0 were used.[16,17] For children aged 5 to 7 years, the questionnaire was administered by a study staff member to control for differences in reading ability. The parents of study participants were asked to complete the PedsQL parent proxy report and the Caregiver Reaction Assessment.[18] For patients ≥ 18 years of age, the Functional Assessment of Cancer Therapy (FACT)-Brain, FACT-Fatigue, and frontal systems behavior tools were used.[19,20]

Statistical analysis

The length of follow-up was calculated from the date of PRT initiation to the date of study participation. Enucleation-free survival was calculated from the date of PRT initiation to the date of enucleation and censored at the date of study participation for non-enucleated eyes. Enucleation-free survival was estimated with the Kaplan-Meier method. Height, weight, and body mass index (BMI) percentiles were compared with distributions of the general population with use of a Wilcoxon signed-rank test, and a two-sided alternative was tested versus the 50th percentile that was expected under the null hypothesis.[21] One-sample t tests were used to assess the one-sided hypothesis that participants' PedsQL Core scores were significantly worse than the child and parent proxy mean values in the normal population. Data analysis was performed with SAS 9.4 (SAS Institute, Cary, NC).

Results

Patient characteristics and disease outcomes

A total of 61 patients underwent PRT for RB at our institution between 1986 and 2012, and we recently reported on the disease and toxicity outcomes for the majority of these patients.[10] To gather patients for the current study, multiple attempts were made to contact each patient who was treated with PRT. Twelve patients ultimately returned for study participation (Table 1).

The median age at the time of diagnosis for the 12 patients who were enrolled was 3.0 months (range, 0.75-19.5 months). The majority of these patients (10 of 12, 83%) presented symptomatically with either leukocoria (7 of 10) or strabismus (3 of 10), and 2 cases (17%) were identified by screening. Three patients had a family history of RB in a first-degree relative, including the 2 patients who were identified by screening. Interestingly, all patients in this cohort had bilateral disease at the time of initial diagnosis; however, only 2 patients (17%) underwent bilateral PRT. The majority of patients (8 of 12, 67%) had enucleation of 1 eye prior to PRT to the remaining eye. In 2 patients (17%), the eye that was not treated with PRT was treated with cryotherapy and/or laser photocoagulation instead.

Ten of 14 eyes that were treated with PRT (71%) had a group A or B disease according to the International Classification for Intraocular Retinoblastoma system, and

Table 1 Patient and treatment characteristics

No. of patients	12
Female	3
Male	9
Median age at diagnosis, mo (range)	3.0 (1-20)
Presenting symptom	
None (diagnosed by screening)	2
Leukocoria/abnormal pupil appearance	7
Strabismus/head tilt	3
ICIR group at diagnosis of PRT-treated eyes (n = 14)	
Group A-B	10
Group C-D	4
No. patients with positive family history	3
No. patients with bilateral disease	12
Bilateral PRT	2
Contralateral enucleation	8
No contralateral enucleation/PRT	2
No. patients who received chemotherapy	9/12
No. patients with previous RT	1/12
Median age at PRT start, mo (range)	11 (4-32)
Median PRT dose, Gy (RBE) (range)	44.0 (40-49)
Median length of follow-up, y (range)	12.9 (5-22)
Median age at last follow-up, y (range)	13.8 (5-23)
No. eyes treated with PRT that were enucleated	3/14
Group A-B	2/14
Group C-D	1/14
Median time from PRT end to enucleation, mo (range)	10 (8-19)
Non-enucleative ocular complications that required procedure	1
No. patients with metastatic disease	0
No. patients with second malignancy	0

ICIR, International Classification for Intraocular Retinoblastomal; PRT, proton radiation therapy; RBE, relative biological effectiveness; RT, radiation therapy.

4 patients (29%) had a group C or D disease. Nine of 12 patients (75%) received systemic chemotherapy in addition to PRT, and all but 1 (8 of 9) received chemotherapy prior to PRT. One patient received chemotherapy for tumor progression after PRT.

The median age at the start of PRT was 11.3 months (range, 3.6-31.9 months), and the median PRT dose was 44 Gy (relative biological effectiveness [RBE]; range, 40-48.6). All PRT was delivered in 1.8 to 2.0 Gy (RBE) fractions with 4 or 5 treatments per week. One patient received previous bilateral photon-based radiation therapy and bilateral ruthenium plaque brachytherapy; however, no other patients had radiation treatment prior to PRT.

The median length of follow-up for this cohort was 12.9 years (range, 4.8-22.2 years; Table 1). Seven of 12 patients (58%) had at least 1 follow-up visit at our institution between completion of PRT and study participation, and 5 patients (42%) returned for the first time since completing PRT. Many patients who were seen at our institution in the interim also reported follow-up by their local providers. The median age at the time of study participation was 13.8 years (range, 5.4-22.7 years).

Three of 14 eyes that were treated with PRT (21%) required enucleation for disease progression between completion of RT and study participation (Fig 1). The median time from the end of PRT to enucleation was 10 months (range, 8-19 months). Two of these patients had group A-B tumors and 1 had a group C-D tumor. None of the enucleations was performed at our institution.

Visual outcomes

A formal ophthalmologic evaluation was performed for 10 of the 11 non-enucleated eyes that were treated with PRT. Visual acuity outcomes were scored as no or mild impairment (20/70 visual acuity or better), moderate impairment (visual acuity worse than 20/70 but better than or equal to 20/200), severe impairment (visual acuity worse than 20/200 but better than or equal to 20/400), and no useful vision (visual acuity worse than 20/400). Seven of 10 non-enucleated eyes treated with PRT had no or mild visual impairment (70%), 1 eye had moderate visual impairment (10%), and 2 eyes had no useful vision (20%). Although not formally tested, the majority of these patients were noted to have apparent visual deficits at the time of diagnosis, and all 3 patients with severe visual impairment or no useful vision at the time of study participation had documented macula or fovea involvement at the time of diagnosis. One patient who was treated for advanced disease developed a cataract in an eye that was treated with PRT, which was successfully removed prior to enrollment in this study. No other ophthalmologic complications that required a procedure were noted in the cohort.

Endocrine outcomes

All study participants were evaluated by a pediatric endocrinologist. Height, weight, and BMI percentiles for

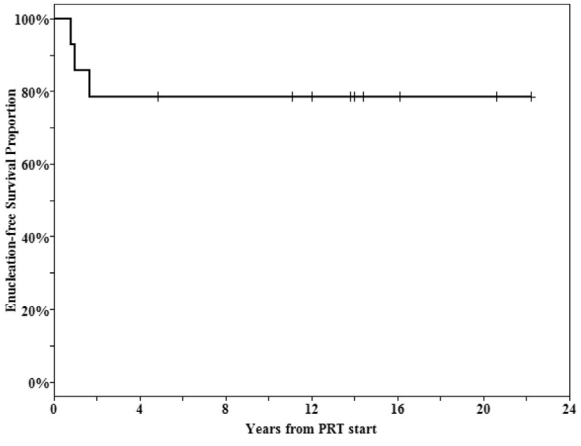

Fig. 1 Enucleation-free survival for study participants.

patients are shown in Table 2, and these values did not differ significantly from the respective distributions of the general age-matched population ($P = .867$, .264, and .137 for height, weight, and BMI, respectively). Of the patients who were younger than 20 years of age and who had more than 1 previous set of measurements at our institution (n = 5), none had a >50% increase or decrease in height or weight percentile during follow-up.

Eleven of 12 patients consented to provide blood and urine samples for endocrine evaluation. None of the patients showed abnormalities in reproductive hormone levels, and age-appropriate sexual development was noted for all patients. One patient had a borderline low morning cortisol level, but a subsequent low-dose adrenocorticotropic hormone stimulation test result was normal. One patient had an elevated thyroid stimulating hormone level and tested positive for thyroid peroxidase antibody, which is suggestive of chronic lymphocytic thyroiditis. No other endocrine abnormalities were suspected on the basis of laboratory test results or physical examinations.

Magnetic resonance imaging volumetrics

A gadolinium-enhanced MRI of the orbits was obtained for 9 of 12 patients. Orbital width and height were measured on axial and sagittal images, respectively (Table 3). Only 2 patients (patient 4 and patient 8) had unilateral PRT without enucleation of the other eye. In 1 case (patient 8), long-term disease control was achieved with PRT, and the height and width differences between the orbit that was treated with PRT and the unirradiated contralateral orbit were small (<1 mm). Patient 4 underwent enucleation of the eye that was treated with PRT 10 months after completing PRT (at 43 months of age); in this case, the orbital height and width of the side that was treated with PRT was notably smaller than the unirradiated, non-enucleated side (3.8 mm and 6.5 mm difference in height and width, respectively). In 4 cases, enucleation of 1 eye preceded PRT to the other eye (patients 3, 6, 9, and 12), and in 3 of these cases, the orbital height and/or width was >1 mm smaller on the enucleated side than on the side that was treated with PRT. Patient 11 had bilateral PRT, and patient 2 had bilateral photon-based RT prior to unilateral PRT; in both cases, the height and width differences between the orbits were small (<1 mm).

External cephalometrics

To further investigate the effects of PRT on facial symmetry, all study participants underwent a cephalometric analysis that was performed by an oculoplastic surgeon (Table 3). We did not observe a systematic pattern of asymmetry in any of the recorded metrics on the basis of treatment (PRT, enucleation, both, or neither). However, there were individual examples of asymmetry that may be related to treatment. For example, patient 4 underwent PRT on the left side, followed by enucleation 10 months later (at 43 months of age), and the orbital dimensions on the left side were notably smaller than those on the right (unirradiated, non-enucleated) side (3.0 mm and 1.3 mm for height and width, respectively). For this patient, asymmetry was apparent by both MRI and cephalometry. However, the MRI scans and cephalometry measurements were discordant for other patients. For example, patient 9 underwent enucleation on the right side, followed by PRT on the left side. MRI scans showed that both the orbital height and width were smaller on the right side (4.6 mm and 1.6 mm smaller, respectively), whereas both the orbital height and fissure length were smaller on the left side when measured by cephalometry (3.3 mm and 6 mm, respectively). Mid-facial growth can also be affected by RB treatment; however, only 1 patient (patient 8) had a difference of >2 mm in maxillary depth, and in this case, the side that was treated with PRT was larger than the untreated side.

Table 2 Height, weight, and BMI

Patient No.	Age at PRT (mo)	Age at Visit (y)	Height Percentile	Weight Percentile	BMI Percentile
1	7	5.4	3	36	85
2	22	7.2	31	16	19
3	5	11.5	55	34	25
4	32	11.7	96	73	42
5	25	13.2	94	98	96
6	16	13.4	86	73	52
7	4	14.2	59	71	75
8	15	15.7	36	88	86
9	25	16.1	27	89	94
10	4	16.4	6	20	71
11	4	20.9	78	83	76
12	6	22.7	11	18	33

BMI, body mass index; PRT, proton radiation therapy.

Table 3 MRI and external cephalometric measurements

Patient No.	OD Event 1	OD Event 1 Age (Mo.)	OD Event 2	OD Event 2 Age (Mo.)	OS Event 1	OS Event 1 Age (Mo.)	OS Event 2	OS Event 2 Age (Mo.)	Age at Visit (Yrs)	MRI Measurements						External Cephalometry Measurements								
										Orbital Width (mm)			Orbital Height (mm)			Horizontal Palpebral Distance (mm)			Orbital Height (mm)			Maxillary Depth (mm)		
										OD	OS	OD-OS	OD	OS	OD-OS	OD	OS	OD-OS	OD	OS	OD-OS	OD	OS	OD-OS
1	Enuc	7	-	-	PRT	7	-	-	5.4	NA	NA	NA	NA	NA	NA	30.0	25.0	5.0	25.0	30.0	−5.0	110.0	110.0	0
2	RT	10	Enuc	19	RT	10	PRT	22	7.2	29.6	29.9	−0.3	27.8	28.2	−0.4	25.0	22.5	2.5	15.0	15.0	0	120.0	120.0	0
3	PRT	5	-	-	Enuc	2	-	-	11.5	32.5	31.9	0.6	31.9	29.2	2.7	30.8	30.5	0.3	23.1	23	0.1	116.1	115.4	0.6
4	Other	-	-	-	PRT	32	Enuc	43	11.7	34.4	30.6	3.8	34.8	28.3	6.5	26.9	23.9	3.0	24	22.7	1.3	117.1	117.1	0
5	PRT	25	Enuc	34.0	Enuc	19.5	-	-	13.2	31	30.8	0.2	28.7	30.5	−1.8	31.6	32.2	−0.6	26.4	27.6	−1.2	141.2	141.4	−0.2
6	Enuc	12	-	-	PRT	16	-	-	13.4	28	30.1	−2.1	28.8	32.6	−3.8	24.7	28.4	−3.7	29.5	25.4	4.1	111.9	111.9	0
7	PRT	4	-	-	PRT	4	-	-	14.2	NA	NA	NA	NA	NA	NA	28.0	29.0	−1.0	23.0	25.0	−2.0	135.0	137.0	−2.0
8	Other	-	-	-	PRT	15	-	-	15.7	33.2	32.4	0.8	34.9	35.2	−0.3	25.0	26.0	−1.0	25	23	2.0	135.0	140.0	−5.0
9	Enuc	18	-	-	PRT	25	-	-	16.1	30.4	32	−1.6	27.8	32.4	−4.6	32.6	26.6	6.0	25.6	22.4	3.3	124.6	123.1	1.5
10	PRT	4	-	-	Enuc	2	-	-	16.4	NA	NA	NA	NA	NA	NA	22.4	30.2	−7.8	20.2	25.4	−5.2	140.0	140.0	0
11	PRT	4	-	-	PRT	4	-	-	20.9	31.5	32.4	−0.9	29.8	30.6	−0.8	32.5	32.5	0	25.0	30.0	−5.0	160.0	160.0	0
12	PRT	6	-	-	Enuc	5	-	-	22.7	33.9	34.5	−0.6	31.2	31.4	−0.2	30.0	28.6	1.4	18.7	18.7	0	116.8	116.8	0

Enuc, enucleation; MRI, magnetic resonance imaging; NA, not applicable; OD, right; OS, Other, laser ablation and/or cryotherapy; left; PRT, proton radiation therapy; RT, photon radiation therapy.

Table 4 Quality of life outcomes

Patient No.	PedsQL				Caregiver Reaction	FACT			FrSBe	
	Core		Cancer							
	Child	Parent	Child	Parent		Fatigue	General	Brain	Self	Family
1	NA	NA	NA	NA	NA					
2	87	92.4	96.2	95.2	58/120					
3	93.5	87	96.3	85.2	52/115					
4	97.8	94.6	NA	NA	NA					
5	79.6	88	94.4	100	48/120					
6	84.8	82.6	88	75.9	NA					
7	92.4	98.9	83.3	96.3	64/120					
8	93.5	89.1	89.8	86.1	71/120					
9	97.8	96.7	96.2	88.5	44/105					
10	68.2	67.1	47	50.9	75/120					
11	NA	NA	NA	NA	NA	47/52	99/108	167/184	48 (42%)	37 (10%)
12	NA	NA	NA	NA	NA	46/52	93/108	160/184	48 (42%)	37 (10%)
Mean	88.3	88.5	86.4	84.8	58.9					
95% CI	68.9-107.7	69.5-107.5	53.2-119.6	53.4-116.2	35.1-82.7					

FACT, Functional Assessment of Cancer Therapy; FrSBE, frontal systems behavior; NA, not available; PedsQL, Pediatric Quality of Life Inventory.

Health-related quality of life

Participants and parents were asked to complete health-related QoL questionnaires at the time of their visit. The core and cancer modules of the PedsQL 4.0 tool were administered to participants aged ≤17 years and their parents (Table 4). For the core module, the average child and parent scores were similar at 88.3 (range, 68.2-97.8) and 88.5 (range, 67.1-98.9), respectively. Interestingly, these values were slightly higher than the average scores from a healthy population (79.6 and 80.9 for child and parent scores, respectively), but no significant differences were noted ($P = .986$ and .978 for child and parent scores, respectively).[22] The mean caregiver reaction score was 58.9 (95% confidence interval, 35.5-82.3). Two participants were at least 18 years of age at the time of participation in the study. Both patients completed the FACT-Brain, FACT-Fatigue, and frontal systems behavior questionnaires (FrSBe); in both cases, FACT scores were somewhat higher than the average scores from patients with brain tumors (Table 4).[19,23]

Discussion

We report the results from a study on the long-term functional and QoL outcomes for patients with RB who were treated with PRT. All patients with RB who were treated with PRT at our institution between 1986 and 2012 were invited to participate in the study, and 12 of 61 patients who were eligible (19.6%) returned for study participation. There were no significant differences in the clinical characteristics of patients who participated in the study and those who did not. In addition, the disease outcomes of patients who participated in the study were similar to those of patients who did not. Among the patients who enrolled in the study, 3 of 14 eyes that were treated with PRT required enucleation (21%), but the enucleation rate among all patients with RB who were treated at our institution was 18% during the same time period.[10] Although we cannot rule out that differences were not detected due to a lack of power, the patients who were enrolled in this study appear to be representative of the larger population of patients with RB who were treated at our institution during the same time period.

The majority of non-enucleated eyes that were treated with PRT had no or mild (70%) or moderate (10%) visual impairment after PRT. These outcomes were similar to the outcomes that were observed in the larger population of patients who did not participate in the study but were treated at our institution during the same time period.[10] In our institutional cohort and in published experiences from other institutions, the best long-term visual outcomes are achieved in patients with early-stage tumors that do not involve the optic disc, macula, or fovea.[24-26]

Traditional RT techniques for RB expose the hypothalamus and pituitary to significant doses of radiation, and studies have shown that survivors are at an increased risk for a variety of growth and metabolic defects that stem from endocrine dysfunction.[27,28] PRT eliminates the radiation dose to midline structures including the hypothalamus–pituitary axis and would therefore be predicted to be associated with much lower rates of endocrinopathies. Indeed, we did not observe any growth or endocrine abnormalities among the patients in this study. Therefore, in addition to being associated with a lower risk of radiation-induced malignancies, PRT can reduce the risk of radiation-related endocrine dysfunction.[12]

Radiation for RB and other pediatric tumors of the head and neck can lead to severe craniofacial abnormalities from impaired growth and development that result from damage to the osteogenic precursors and surrounding vasculature.[29,30] Among very young patients with RB, orbital and maxillary hypoplasia can also occur after enucleation but the use of a large implant or dermis fat graft may decrease this risk.[31] Because changes in growth patterns can be multifactorial and often take years to manifest, quantifying the long-term effects of RB treatment on growth and development is challenging. In our previous report on the disease outcomes of all patients with RB who were treated with PRT at our institution, facial asymmetry was subjectively noted during follow-up for 15 of 49 patients; however, hypoplasia was not quantitatively assessed in any of these patients, and the relative contribution of enucleations and PRT to the subjective assessment of hypoplasia was not specified.

All patients in the current study had bilateral disease at the time of diagnosis, and the majority (10 of 12 patients) underwent bilateral treatment with either enucleation and/or PRT. Therefore, it was not possible to compare the effect of PRT with a contralateral untreated eye in the majority of cases. Only 1 patient underwent PRT alone to 1 eye and had neither PRT nor enucleation of the other eye, and the differences in orbital height and width between the sides were <1 mm. Rates of facial asymmetry after photon-based RT for RB and pediatric head and neck rhabdomyosarcomas vary widely, but some degree of asymmetry is noted in a majority of reported cases.[29,32,33] However, many of the patients in these studies were treated using older radiation techniques, and it is likely that the rates of hypoplasia are lower with intensity modulated radiation therapy (IMRT)-based techniques.[34,35] For example, in a recent study of 13 patients who were treated with chemotherapy and IMRT for head and neck rhabdomyosarcoma, 7 patients developed facial hypoplasia.[36] In all PRT cases in this study, a single lateral or lateral-oblique field was used, thus exposing only a limited volume of the lateral orbit to radiation. Additional studies are needed to assess the long-term craniofacial outcomes among patients with RB who were treated with contemporary photon- and proton-based techniques.

The interpretation of MRI scans and external cephalometry data was more complicated for patients who underwent enucleation of 1 eye and received PRT to the other eye. However, anecdotally, MRI-based orbital heights and widths were typically at least 1 mm smaller on the enucleated side than on the side that was treated with PRT, which suggests that PRT may affect orbital development less than enucleation in this cohort.

The correlation between MRI and external cephalometry was mixed in our study. Although these differences may simply reflect the practical limits of resolution for each technique, the 2 techniques also provide slightly different types of information. MRI measurements (as performed in this study) reflect only the differences in bone growth, whereas external cephalometry includes contributions from both bone and soft tissues. Further work is needed to understand how to accurately interpret and integrate data that are collected with each technique.

Given that more than 95% of patients with RB in the United States are cured using current treatment approaches, understanding the long-term QoL effects of RB treatment will become increasingly important as efforts seek to minimize treatment-associated physical and psychosocial sequelae. In this study, there was no evidence that QoL outcomes were worse among survivors of RB compared with a non-cancer population. Although the numbers are small, this is in agreement with other QoL studies of patients with RB. For example, a recent study of 470 survivors of RB who were treated between 1932 and 1994 revealed that this population did not appear to have significantly worse psychosocial functioning compared with a matched cohort of subjects without cancer.[37] Similarly, few cognitive or social attainment deficits were noted among a cohort of adult survivors of RB, although patients who were diagnosed at >1 year of age or received photon-based RT had worse outcomes than younger patients or patients who were not treated with RT.[38] These data highlight the importance of patient-reported QoL metrics rather than relying on provider- or observer-based metrics.

PRT is associated with less normal tissue exposure than photon-based RT and with improved QoL outcomes compared with photon-based RT in cohorts of survivors of pediatric brain tumors.[39,40] In this study, the first QoL study to prospectively enroll patients with RB who were treated with PRT, we did not observe a difference between child- or parent proxy-reported QOL outcomes and those of the general population. However, results must be interpreted carefully because the cohort reported here includes a relatively small number of patients from a larger institutional cohort treated over the same time period. Despite these important limitations, these data provide evidence that PRT-based treatment of patients with RB can be associated with favorable long-term functional and QoL outcomes. Given the high cure rates that are achievable with current RB treatment approaches, comprehensive QoL studies in populations with RB who are treated with contemporary techniques including PRT, IMRT, and chemotherapy-based approaches, are needed to more fully understand the impact of treatments on QoL outcomes.

References

1. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975-2004. *Br J Ophthalmol*. 2009;93:21-23.
2. Ortiz MV, Dunkel IJ. Retinoblastoma. *J Child Neurol*. 2016;31:227-236.

3. Cassady JR, Sagerman RH, Tretter P, Ellsworth RM. Radiation therapy in retinoblastoma. An analysis of 230 cases. *Radiology*. 1969;93:405-409.
4. Blach LE, McCormick B, Abramson DH. External beam radiation therapy and retinoblastoma: Long-term results in the comparison of two techniques. *Int J Radiat Oncol Biol Phys*. 1996;35:45-51.
5. Schipper J, Tan KE, van Peperzeel HA. Treatment of retinoblastoma by precision megavoltage radiation therapy. *Radiother Oncol*. 1985; 3:117-132.
6. Sagerman RH, Cassady JR, Tretter P, Ellsworth RM. Radiation induced neoplasia following external beam therapy for children with retinoblastoma. *Am J Roentgenol Radium Ther Nucl Med*. 1969;105: 529-535.
7. Schipper J, Alberti W. Late effects of radiation on surviving retinoblastoma patients. *Ophthalmology*. 1985;92:60A-63A.
8. Jairam V, Roberts KB, Yu JB. Historical trends in the use of radiation therapy for pediatric cancers: 1973-2008. *Int J Radiat Oncol Biol Phys*. 2013;85:e151-e155.
9. Yu CL, Tucker MA, Abramson DH, et al. Cause-specific mortality in long-term survivors of retinoblastoma. *J Natl Cancer Inst*. 2009; 101:581-591.
10. Mouw KW, Sethi RV, Yeap BY, et al. Proton radiation therapy for the treatment of retinoblastoma. *Int J Radiat Oncol Biol Phys*. 2014; 90:863-869.
11. Chung CS, Yock TI, Nelson K, Xu Y, Keating NL, Tarbell NJ. Incidence of second malignancies among patients treated with proton versus photon radiation. *Int J Radiat Oncol Biol Phys*. 2013;87: 46-52.
12. Sethi RV, Shih HA, Yeap BY, et al. Second nonocular tumors among survivors of retinoblastoma treated with contemporary photon and proton radiotherapy. *Cancer*. 2014;120:126-133.
13. Farkas LG, Katic MJ, Forrest CR, et al. International anthropometric study of facial morphology in various ethnic groups/races. *J Craniofac Surg*. 2005;16:615-646.
14. Farkas LG, Hreczko TM, Katic MJ, Forrest CR. Proportion indices in the craniofacial regions of 284 healthy North American white children between 1 and 5 years of age. *J Craniofac Surg*. 2003;14: 13-28.
15. Farkas LG, Katic MJ, Forrest CR. Surface anatomy of the face in Down's syndrome: Anthropometric proportion indices in the craniofacial regions. *J Craniofac Surg*. 2001;12:519-524. discussion 525-526.
16. Varni JW, Burwinkle TM, Seid M, Skarr D. The PedsQL 4.0 as a pediatric population health measure: feasibility, reliability, and validity. *Ambul Pediatr*. 2003;3:329-341.
17. Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer*. 2002;94:2090-2106.
18. Given CW, Given B, Stommel M, Collins C, King S, Franklin S. The caregiver reaction assessment (CRA) for caregivers to persons with chronic physical and mental impairments. *Res Nurs Health*. 1992;15:271-283.
19. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA. The Functional Assessment of Cancer Therapy (FACT) scale. Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. *Cancer*. 1995;75:1151-1161.
20. Stout JC, Ready RE, Grace J, Malloy PF, Paulsen JS. Factor analysis of the frontal systems behavior scale (FrSBe). *Assessment*. 2003;10:79-85.
21. Kuczmarski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. Advance data from vital and health statistics; no. 314. Hyattsville, Maryland: National Center for Health Statistics. 2000.
22. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care*. 2001;39:800-812.
23. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570-579.
24. Batra A, Pushker N, Venkatesh P, Arora T, Tewari R, Bakhshi S. Long-term visual outcomes in intraocular retinoblastoma with eye preservation. *Clin Transl Oncol*. 2016;18:1034-1038.
25. Orman A, Koru-Sengul T, Miao F, Markoe A, Panoff JE. The modern role of radiation therapy in treating advanced-stage retinoblastoma: long-term outcomes and racial differences. *Int J Radiat Oncol Biol Phys*. 2014;90:1037-1043.
26. Suzuki S, Yamane T, Mohri M, Kaneko A. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. *Ophthalmology*. 2011;118:2081-2087.
27. Pomarede R, Czernichow P, Zucker JM, et al. Incidence of anterior pituitary deficiency after radiotherapy at an early age: Study in retinoblastoma. *Acta Paediatr Scand*. 1984;73:115-119.
28. Brauner R, Rappaport R, Prevot C, et al. A prospective study of the development of growth hormone deficiency in children given cranial irradiation, and its relation to statural growth. *J Clin Endocrinol Metab*. 1989;68:346-351.
29. Gevorgyan A, La Scala GC, Neligan PC, Pang CY, Forrest CR. Radiation-induced craniofacial bone growth disturbances. *J Craniofac Surg*. 2007;18:1001-1007.
30. Paulino AC, Simon JH, Zhen W, Wen BC. Long-term effects in children treated with radiotherapy for head and neck rhabdomyosarcoma. *Int J Radiat Oncol Biol Phys*. 2000;48:1489-1495.
31. Ji Y, Ye F, Zhou H, Xie Q, Ge S, Fan X. Bony orbital maldevelopment after enucleation. *J Anat*. 2015;227:647-653.
32. Denys D, Kaste SC, Kun LE, Chaudhary MA, Bowman LC, Robbins KT. The effects of radiation on craniofacial skeletal growth: a quantitative study. *Int J Pediatr Otorhinolaryngol*. 1998; 45:7-13.
33. Guyuron B, Dagys AP, Munro IR, Ross RB. Effect of irradiation on facial growth: A 7- to 25-year follow-up. *Ann Plast Surg*. 1983;11: 423-427.
34. Reisner ML, Viegas CM, Grazziotin RZ, et al. Retinoblastoma—comparative analysis of external radiotherapy techniques, including an IMRT technique. *Int J Radiat Oncol Biol Phys*. 2007; 67:933-941.
35. Eldebawy E, Parker W, Abdel Rahman W, Freeman CR. Dosimetric study of current treatment options for radiotherapy in retinoblastoma. *Int J Radiat Oncol Biol Phys*. 2012;82:e501-e505.
36. Owosho AA, Brady P, Wolden SL, et al. Long-term effect of chemotherapy-intensity-modulated radiation therapy (chemo-IMRT) on dentofacial development in head and neck rhabdomyosarcoma patients. *Pediatr Hematol Oncol*. 2016;33:383-392.
37. Ford JS, Chou JF, Sklar CA, et al. Psychosocial outcomes in adult survivors of retinoblastoma. *J Clin Oncol*. 2015;33:3608-3614.
38. Brinkman TM, Merchant TE, Li Z, et al. Cognitive function and social attainment in adult survivors of retinoblastoma: A report from the St. Jude Lifetime Cohort Study. *Cancer*. 2015;121:123-131.
39. Kuhlthau KA, Pulsifer MB, Yeap BY, et al. Prospective study of health-related quality of life for children with brain tumors treated with proton radiotherapy. *J Clin Oncol*. 2012;30:2079-2086.
40. Yock TI, Bhat S, Szymonifka J, et al. Quality of life outcomes in proton and photon treated pediatric brain tumor survivors. *Radiother Oncol*. 2014;113:89-94.