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.

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**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. 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. 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. 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.

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. 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.

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. 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 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 photoagulation 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
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](image-url) 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 \((P = .867, .264, \text{ and } .137 \text{ for height, weight, and BMI, respectively})\). 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 3 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.

| 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.
| Patient No. | OD Event Age (Mo.) | OD Event Age (Mo.) | OD Event Age (Mo.) | OD Event Age (Mo.) | OS Event Age (Mo.) | OS Event Age (Mo.) | OS Event Age (Mo.) | OS Event Age (Mo.) | 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 | 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 | 25.0 15.0 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 |
| 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 |
| 5 | PRT 25 Enuc 34.0 | 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 |
| 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 -1.2 |
| 7 | PRT 4 - - PRT 4 - - | 14.2 | NA NA NA | NA NA NA | 28.0 290 -1.0 | 23.0 25.0 -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 |
| 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 |
| 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 |
| 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 |
| 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 |

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.
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 \( \leq 17 \) 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 \( (P = .986 \text{ and } .978 \text{ for child and parent scores, respectively}) \). The mean caregiver reaction score was 58.9 (95% confidence interval, 35.1-82.7).

Table 4  Quality of life outcomes

| Patient No. | PedsQL | Caregiver Reaction | FACT | FrSBe |
|-------------|--------|--------------------|------|-------|
|             | Core   | Cancer             |      |       |
|             | Child  | Parent             | Child| Parent|
| 1           | 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    | 47/52 |
| 12          | NA     | NA                 | NA   | NA    | 46/52 |
| Mean        | 88.3   | 88.5               | 86.4 | 84.8  | 58.9  |

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

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. 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. 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. 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. 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.
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. 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. 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. 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. 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. 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 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.

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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. 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. 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. 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.

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