The Evolution of Radiation Therapy for Retinoblastoma: The MD Anderson Cancer Center Experience

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Abstract

Purpose: The role of radiation therapy (RT) for retinoblastoma (Rb) has significantly evolved from first-line to salvage therapy. The objectives of our study were to evaluate efficacy of proton RT (PRT) and other advanced RT techniques for Rb and to observe evolving trends in RT use.

Materials and Methods: An analysis of patients with Rb who received RT between 1990 and 2012 was conducted. Thirty-nine patients with 70 affected eyes were identified. Of these, 47 eyes were treated with RT with photon or electron RT (ERT), PRT, or brachytherapy (BRT). The clinical history, treatment details, and tumor outcomes were reviewed for all patients.

Results: Radiation therapy was first-line treatment in 14 eyes, second-line in 4, postoperative in 4, and salvage in 25. Median length of follow-up was 8 years for all patients, and 10, 3, and 5 years for ERT, PRT, and BRT, respectively. Overall survival was 97.4%. In total, 16 (34.0%) eyes required enucleation after RT. Median PRT dose was 36 Gy (RBE) (range, 36-45 Gy [RBE]), ERT dose was 45 Gy (range, 36-46 Gy), and BRT dose was 45 Gy (range, 36-45 Gy). A higher proportion of PRT patients (93.8%) than ERT patients (51.9%) were treated in the salvage setting ($P < .01$). Among patients with International Classification for Intraocular Retinoblastoma stage D and E disease, 6 of 11 (54.5%) ERT patients required enucleation and 5 of 13 (38.5%) PRT patients required enucleation.

Conclusion: This study represents a large series of patients treated with PRT, ERT, and BRT for Rb and reports favorable efficacy and toxicity. Patients treated with salvage PRT are typically heavily pretreated and have advanced disease. Despite more advanced disease, patients treated with PRT with lower RT doses achieve comparable salvage and enucleation-free rates to ERT. Chemoreduction followed by focal treatments should be standard of care when clinically feasible, with PRT considered in the salvage setting.

Keywords: retinoblastoma; proton therapy; salvage
Introduction

Retinoblastoma (Rb) is the most common intraocular malignancy of childhood. It affects 1 in 18,000 children each year and approximately 300 new cases are diagnosed every year in the United States alone [1, 2]. Roughly 60% of tumors are sporadic and 40% are hereditary cases due to germline mutations in the biallelic \(RB1\) tumor-suppressor gene [3]. Patients with a germline \(RB1\) mutation present at earlier age, are at higher risk of developing bilateral disease, and are more likely to develop a secondary malignant tumor. In comparison, patients with sporadic Rb often present with unilateral, more advanced disease at diagnosis [4].

Early detection is of paramount importance for overall survival and ocular preservation. In the United States, early detection efforts and better treatment options have improved the prognosis from 30% overall survival in the 1930s to nearly 95% in the 1990s [5, 6]. The primary goals of treatment are to eradicate disease in order to save the patient’s life, preserve as much vision as possible, and reduce the risk of late effects of treatment, such as secondary malignancies [7].

Local therapy options for management of intraocular disease include enucleation, radiation therapy (RT), cryotherapy, and laser therapy. Historically, external beam radiation therapy (EBRT) was the preferred vision-preserving mode of therapy with very good tumor control and vision preservation in patients, based on the Reese-Ellsworth (RE) staging system, which stratifies patients on the probability of vision preservation after RT [8–11]. Over time, owing to concerns of RT-related morbidities in this vulnerable population, the role of EBRT in the primary management of Rb has diminished. Instead, chemotherapeutic regimens, including intra-arterial, intravitreal, and subconjunctival methods in conjunction with non–EBRT-based local therapies have become first-line therapies. In response to the development of these new therapies, the International Classification of Intraocular Retinoblastoma (ICIR) was developed in 2003 to better predict which patients with intraocular Rb were likely to be cured without the need for enucleation or EBRT [7, 12]. External beam RT is now reserved for advanced cases and for patients with refractory or progressive disease after chemotherapy [6, 7, 13–15].

Advances in RT technology, such as intensity-modulated radiation therapy and proton radiation therapy (PRT) allow for more conformal RT options for patients with Rb [16–18]. The unique dosimetric properties of PRT have the potential to reduce the injury to uninvolved structures while attaining appropriate tumor coverage and may lead to an improved therapeutic index with respect to tumor control and toxicity [17, 19–21]. However, PRT has only become widely available in the past decade and as such, PRT is commonly used as a salvage therapy. Given the evolution in RT techniques and practice changes in the use of RT, we sought to evaluate the clinical outcomes of patients treated for Rb with proton therapy (PRT), photon or electron RT (ERT), or brachytherapy (BRT) during a 22-year period at our institution.

Methods

Patient Selection Criteria

We performed an institutional review board–approved retrospective analysis of all patients with Rb treated with radiation (RT) at our institution between April 1990 and December 2012. Patients were stratified by radiation treatment type, including PRT, ERT, or BRT. One patient that was treated with ERT and then with PRT for salvage therapy was sorted in the ERT group since ERT was the initial RT treatment.

Patient Characteristics and Patient Outcomes

Patient demographic information, disease burden, treatment information, and outcomes data were collected for all patients identified. Patients were stratified by the ICIR system, the presence or absence of bilateral disease, and the presence or absence of extraocular disease. To assess treatment information, we assessed radiation type and dose. The treatment was classified as first-line, second-line, postoperative, or salvage. Outcome assessments included enucleation-free survival (EnFS), 5-year local control, overall survival, and other complications related to radiation toxicity. Overall survival time was calculated from the end of RT to death from any cause or last follow-up date. Enucleation-free survival was calculated from the end of RT to enucleation date for patients who received enucleation and from last follow-up date for patients who did not. Complications were grouped into acute toxicities and long-term toxicities. Long-term toxicities assessed included cataracts, retinopathy, vitreous hemorrhage, orbital hypoplasia, strabismus, and changes in visual acuity.
Treatment Details

All patients underwent 2-dimensional or 3-dimensional computed tomography–based radiation planning before the start of RT. Patients were treated with ERT (XRT 1990-2007, ERT 2003-9), BRT (2004-9), or PRT (2008-12). The target volume was defined through collaboration between the ophthalmologist and the treating radiation oncologist. Brachytherapy was performed with either an I-125 plaque or Ru-106 plaques depending on plaque availability, tumor height, and patient age. The plaque was sutured in place over the area of the tumor by the ophthalmologist and generally a dose of 45 Gy was delivered at a rate of 40 to 60 cGy/h to the tumor apex. The treatment volume for BRT contained the tumor plus a 2-mm margin for patients with localized disease. The patients remained hospitalized for the duration of the treatment [22]. For all other eyes treated with ERT or PRT, the anterior chamber was spared if the vitreous was not involved; otherwise, the treatment volume encompassed the whole eye. For patients with larger tumors or disease that included vitreous seeding, larger volumes of the vitreous and retina were included in the treatment field.

In general, RT was delivered with the assistance of anesthesia owing to patients’ young age. Eyelid position during simulation and treatment was dependent on disease presentation and RT treatment modality and included eyes taped closed, eyes opened with retractors (to minimize dose build-up at the surface), and a generally neutral position. An aquaplast mask was used to immobilize the head. No specific globe repositioning techniques were used for the fractionated treatments though the eye remained neutral while under sedation. XRT was delivered by using 2-dimensional or 3-dimensional planning techniques, with either a lateral beam, using a D cone or with left and right anterior oblique and vertex beams. Patients treated via ERT were treated with an appositional field with skin collimation (Figure 1A). Proton RT was delivered by using a passive scatter technique with either an appositional field or a combination of left and right anterior oblique beams and a vertex beam (Figure 1B and 1C), as described previously [20]. One patient was treated to the pineal region for a trilateral Rb (Figure 1D). Patients were all initially followed up at our institution after delivery of RT and were ultimately seen in coordination with the referring pediatric hospital and patients’ local pediatric and/or primary care offices.

Statistical Analysis

The Fisher exact test and unpaired t tests were used to assess differences in treatment characteristics and treatment outcomes. Mean, median, and standard deviations were calculated. All P values are based on a 2-sided hypothesis, and a value of less than .05 was considered statistically significant. Kaplan-Meier curves were created to evaluate survival and EnFS, with differences between groups evaluated by using the log-rank test. Data analysis was performed with Microsoft Excel (Microsoft, Redmond, WA) and Stata/MP 14.0 (StataCorp, College Station, TX).

Results

Patient, Tumor, and Treatment Characteristics

We identified 39 patients who received RT for Rb between 1990 and 2012 (Table 1). The median age at diagnosis was 11.4 months, with a range of 0.2 months to 8.9 years. Of the 39 patients, 8 (20.5%) patients had unilateral disease, 30 (76.9%) patients had bilateral disease, and 1 (2.6%) patient had trilateral disease, for a total of 70 affected eyes. Of the 70 eyes diagnosed with Rb, 47 (67.1%) were treated with RT. Of the 47 eyes treated with RT, none were group A; 8 (17.0%) were group B; 4 (8.5%) were group C; 20 (42.6%) were group D; 7 (14.9%) were group E; 5 (10.6%) had extraocular disease; and 3 (6.4%) were not staged by the ICIR system.

Of the 47 eyes, 27 (57.4%) received ERT, 16 (34%) received PRT, and 4 (8.5%) received BRT. Radiation therapy was first-line treatment in 14 (29.8%) eyes, second-line in 4 (8.5%), postoperative in 4 (8.5%), and salvage in 25 (53.2%).

Most patients (28 of 39, 71.8%) treated with RT received chemotherapy, and nearly half of those patients received multiple regimens (13 of 28, 46.4%). A variety of chemotherapy regimens were used; the most common agents used included etoposide, carboplatin, and vincristine. Of the patients who received chemotherapy, all 28 (100%) received systemic chemotherapy; 9 (32.1%) received subtenon chemotherapy, 3 (10.7%) received intra-arterial chemotherapy, and 2 (7.1%) received intravitreal chemotherapy. Most patients (24 of 39, 61.5%) were also treated with focal therapies such as laser photocoagulation and/or cryotherapy.
Tumor and Treatment Characteristics by Treatment Type

Patients treated with PRT trended toward having more advanced-stage disease with need for salvage therapy. Only 1 (6.3%) of the 15 staged PRT eyes had ICIR stage A-C disease and 9 (36.0%) of the 25 staged ERT eyes had ICIR stage A-C disease ($P = .06$). Fifteen of the 16 eyes (93.8%) treated with PRT were treated in the salvage setting. Comparatively, 14 of 27 eyes (51.9%) treated with ERT were in the salvage setting ($P < .01$). The median ERT dose was 45 Gy (range, 36-46 Gy), median PRT dose was 36 Gy (RBE) (range, 36-45 Gy [RBE]), and median BRT dose was 45 Gy (range, 36-45 Gy). The mean dose for PRT, at 38.7 Gy, was significantly lower than the mean dose for ERT at 42.3 Gy ($P < .01$). The median patient ages at time of ERT, PRT, and BRT were 17 months (range, 3-125 months), 23 months (range, 11-51 months), and 21 months (range, 10-59 months), respectively.

Treatment Outcomes

The median length of follow-up was 8 years (range, 1 month-24 years). The median length of follow-up for ERT, PRT, and BRT was 10, 3, and 5 years, respectively. Of the 39 patients treated with RT, 38 (97.4%) were alive at last follow-up (Figure 2A). Sixteen of 47 (34.0%) eyes ultimately required enucleation. Reasons for enucleation included local disease progression,
intraocular hemorrhage, painful glaucoma, or other factors leading to inability to examine the eye. By RT type, 8 of the 27 (29.6%) ERT eyes required enucleation, 6 of the 16 (37.5%) PRT eyes required enucleation, and 1 of the 4 (25.0%) BRT eyes required enucleation. Among patients with stage D and E disease, 6 of 11 (54.5%) ERT patients required enucleation and 5 of 13 (38.5%) PRT patients required enucleation (Figure 2B). The overall median time to enucleation from the end of salvage RT was 11.5 months (range, 4.0-64.7 months).

Local failure after RT, as documented by ophthalmology, was similar between the PRT and ERT groups (56.3% versus 59.3%, \( P = 1.0 \)). The median number of days to local failure among patients with stage D and E disease treated with ERT and PRT was 235 days and 135 days (\( P = .20 \)), respectively.

Acute toxicities included immediate effects of RT, such as erythema of the skin (n = 33), hyperpigmentation (n = 8), erythema of the conjunctiva (n = 5), and loss of eyelashes (n = 4). Patients treated with PRT had a similar rate of acute toxicities, compared to patients treated with ERT (93.8% versus 74.1%, \( P = .22 \)).

Long-term toxicity data (Table 2) were inconsistently reported in follow-up but included late effects of radiation such as cataracts (n = 15), vitreous hemorrhage (n = 7), radiation retinopathy (n = 5), isolated changes in visual acuity (n = 4), strabismus (n = 3), and several less common toxicities. Overall, of the 27 eyes treated with ERT, 15 (55.6%) developed at least 1 long-term side effect; and during the available follow-up period, of the 16 PRT treated eyes, 10 (62.5%) developed at least 1 long-term side effect (\( P = .75 \)). No long-term toxicities were significantly associated with any single modality of treatment. Additional follow-up regarding secondary malignancies and late toxicities may have been limited in this study owing to continued follow-up care for patients at outside centers.

| Table 1. Patient and treatment characteristics. |
|-----------------------------------------------|
| Patient and treatment characteristics         | Variables |
| No. of patients                               | 39         |
| Female                                        | 20 (51.3%) |
| Male                                          | 19 (48.7%) |
| Median age at diagnosis (range), mo           | 11.4 (0.2-106.7) |
| Race                                         |            |
| White                                         | 20 (51.3%) |
| Hispanic                                      | 17 (43.6%) |
| Black                                         | 1 (2.6%)   |
| Asian                                         | 1 (2.6%)   |
| Type of disease                               |            |
| Unilateral disease                            | 8 (20.5%)  |
| Bilateral disease                             | 30 (76.9%) |
| Trilateral disease                            | 1 (2.6%)   |
| No. of eyes treated with RT                   | 47         |
| ERT                                           | 27 (57.4%) |
| PRT                                           | 16 (34.0%) |
| BRT                                           | 4 (8.5%)   |
| International Classification System stage     |            |
| B                                             | 8 (17.0%)  |
| C                                             | 4 (8.5%)   |
| D                                             | 20 (42.6%) |
| E                                             | 7 (14.9%)  |
| Extraocular disease                           | 5 (10.6%)  |
| Stage unknown                                 | 3 (6.4%)   |
| Treatment setting                             |            |
| First-line                                    | 14 (29.8%) |
| Second-line                                   | 4 (8.5%)   |
| Postoperative                                 | 4 (8.5%)   |
| Salvage                                       | 25 (53.2%) |

**Abbreviations**: RT, radiation therapy; ERT, electron radiation therapy; PRT, proton therapy; BRT, brachytherapy.
Discussion

In our retrospective review of 39 patients treated for Rb during a 22-year period, we have reported outcomes of patients treated with ERT, PRT, and BRT in the primary, secondary, or salvage settings. Overall, our results show that the role of RT has evolved significantly over time and that all 3 RT modalities offer favorable efficacy and toxicity profiles.

We observed a shift in treatment strategy over time in this series of patients. Patients were initially treated with primary ERT for early and advanced ocular pathologic processes. This approach shifted in the mid 1990s to a chemoreduction approach with alternative non–RT-based focal therapies in an attempt to decrease the incidence of secondary malignancies in patients with an otherwise long projected overall survival. Radiation therapy, in the form of electrons, 3D-conformal RT, or intensity-modulated RT, was used in the salvage setting. The increasing availability of PRT, however, has introduced the potential to maintain efficacy but further reduce the incidence of secondary malignancies by improving dosimetric sparing of surrounding normal tissue [21].

Consistent with the trend toward primary chemoreduction for globe conservation, patients treated with PRT in our series typically had more advanced, refractory, and heavily pretreated disease when PRT was used in the salvage setting. Despite these risk factors, our early results with patients treated with PRT show comparable salvage and EnFS rates to ERT. One patient, treated with ERT in our series, died of disease. All patients treated with PRT are alive at this time, with 8 of 13 (61.5%) patients with stage D and E disease preserving the treated eye at last follow-up. In other studies of patients with stage D disease treated with ERT, ERT can raise the salvage rate to nearly 70%, compared to a salvage rate of approximately 45% with chemoreduction alone [23–25].

| Table 2. Long-term complications of RT. |

| Long-term RT complications | All treatment modalities, No. of eyes (% of total) | Proton therapy, No. of eyes (% of total) |
|----------------------------|-----------------------------------------------|----------------------------------------|
| Cataracts                  | 15 (31.9)                                    | 5 (31.3)                               |
| Vitreous hemorrhage        | 7 (14.9)                                     | 3 (18.8)                               |
| Radiation retinopathy      | 5 (10.6)                                     | 2 (12.5)                               |
| Change in visual acuity    | 4 (8.5)                                      | 0 (0)                                  |
| Strabismus                 | 3 (6.4)                                      | 1 (6.3)                                |

Abbreviation: RT, radiation therapy.
Other studies of patients treated with PRT have achieved similar outcomes to those from our experience, but with higher median doses of 44 Gy (RBE) [17, 21]. Although our follow-up data are limited, our study suggests that a lower dose (36 Gy) can be used for patients undergoing PRT in the salvage setting. This lower dose suggests that favorable outcomes can still be achieved in patients through the routine use of lower-dose PRT in the salvage setting.

In a large series of patients followed up after treatment for Rb, the rate of developing secondary malignancies was relatively linear for 50 years following the end of radiation treatment, with a cumulative incidence of developing a second cancer at 38.2% [26]. Secondary malignancies are the most common cause of death in patients with hereditary Rb, accounting for a long-term mortality of 26% [26, 27]. In another large study of 816 patients treated for Rb, there were more secondary tumors within the field of radiation but no significant difference in the incidence of tumors outside the field of radiation between patients who were treated with ERT and those who were not [28]. Proton RT, which offers the ability to further reduce the irradiated volume in patients with Rb, has the potential to further reduce the risk of secondary malignancies by limiting the field of radiation and reducing the overall integral dose [19].

The 22-year period of this study may introduce differences in outcomes that reflect a heterogeneous patient population who underwent a variety of different treatment regimens, other than radiation. Further, because most cases of Rb are referred to specialized cancer centers, regular follow-up to evaluate late side effects and track outcomes remains a significant challenge. Even other large academic centers often refer patients to this institution for PRT, with all subsequent follow-up care continued at the referring institution. In our study, the median length of follow-up for patients treated with PRT was 3 years compared to 10 years for ERT, which leads to difficulty in making definitive conclusions regarding long-term outcomes, such as the occurrence of secondary malignancies. We intend to follow up the PRT group for a longer period of time to determine additional late effects. We encountered limited long-term follow-up data owing to limited interoperability of electronic health records, paper records at other institutions, and a lack of regular follow-up data collection when care was completely transferred to other centers.

With more and more children surviving to older ages, many of these patients will seek care through multiple doctor groups in potentially geographically separated places during their lifetime. In addition, although current recorded follow-up outcomes focus on goals such as EnFS and overall survival, long-term outcomes data do not adequately describe other important outcome measures such as function in school, patient satisfaction with outcome/appearance, endocrine problems, and other quality measures. The weakness in our collected data reflects the lack of a consistent, unified, and comprehensive set of outcome metrics for patients with Rb specifically and pediatric cancers generally [29–31]. The shift toward quality reporting and value-based health care may necessitate the development of more comprehensive outcomes for Rb to drive patient-centered treatment decisions [32].

Conclusions
This study reports favorable efficacy and toxicity profiles for PRT and highlights its current role as a salvage treatment. Consistent with the trend toward primary chemoreduction for globe conservation, the role of RT has evolved and patients treated with salvage PRT are typically heavily pretreated and have advanced disease. Further study is required to improve RT techniques, dose, and toxicity estimation within the scope of new treatment paradigms that will affect RT tolerance. Despite these challenges, PRT with lower RT doses achieves comparable salvage and EnFS rates to ERT. Chemoreduction followed by focal treatments should be standard of care when clinically feasible, with PRT considered in the salvage setting.

**ADDITIONAL INFORMATION AND DECLARATIONS**

**Conflicts of Interest:** The authors have no conflicts of interest to disclose.

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