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Clinical Investigation

The Modern Role of Radiation Therapy in Treating Advanced-Stage Retinoblastoma: Long-Term Outcomes and Racial Differences

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Summary

The efficacy and toxicity of external beam radiation therapy was investigated in 41 eyes of 30 patients with advanced-stage retinoblastoma. We demonstrated excellent long-term outcomes with low rates of toxicity and secondary malignancy. Unexpectedly, white patients had significantly better overall survival than did African-American patients. External beam radiation therapy continues to be an effective treatment modality for advanced retinoblastoma.

Purpose/Objective(s): To evaluate the effects of various patient characteristics and radiation therapy treatment variables on outcomes in advanced-stage retinoblastoma.
Methods and Materials: This was a retrospective review of 41 eyes of 30 patients treated with external beam radiation therapy between June 1, 1992, and March 31, 2012, with a median follow-up time of 133 months (11 years). Outcome measures included overall survival, progression-free survival, local control, eye preservation rate, and toxicity.
Results: Over 90% of the eyes were stage V. Definitive external beam radiation therapy (EBRT) was delivered in 43.9% of eyes, adjuvant EBRT in 22% of eyes, and second-line/salvage EBRT in 34.1% of eyes. A relative lens sparing (RLS) technique was used in 68.3% of eyes and modified lens sparing (MLS) in 24.4% of eyes. Three eyes were treated with other techniques. Doses $\geq$45 Gy were used in 68.3% of eyes. Chemotherapy was a component of treatment in 53.7% of eyes. The 10-year overall survival was 87.7%, progression-free survival was 80.5%, and local control was 87.8%. White patients had significantly better overall survival than did African-American patients in univariate analysis (hazard ratio 0.09; 95% confidence interval 0.01-0.84; $P = .035$). Toxicity was seen in 68.3% of eyes, including 24.3% with isolated acute dermatitis.
Conclusions: External beam radiation therapy continues to be an effective treatment modality for advanced retinoblastoma, achieving excellent long-term local control and survival with low rates of treatment-related toxicity and secondary malignancy.

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Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy in children, with 200 to 300 cases diagnosed per year in the United States (1). It is estimated that 33% of children have a germline mutation in the RB1 tumor suppressor gene (2). When compared with nonirradiated germline patients, these patients have a threefold higher risk of secondary malignancies, especially sarcomas (3, 4). In addition, 25% of germline RB survivors and 5% of nongermline RB survivors will die of a second cancer by the age of 50 (5).

The desire to eliminate treatment-related morbidity and mortality has driven advancement in chemoreductive strategies. As a result, the use of external beam radiation therapy (EBRT) in the treatment of RB has declined from approximately 35% in the late 1980s to 7% currently (6). EBRT is now reserved for only the most advanced cases, or refractory cases, or both, including intraocular tumors with subretinal or vitreal seeding, tumors extending to the extraocular structures, and residual disease after enucleation (7).

There are 2 commonly used EBRT techniques. The modified lens sparing (MLS) technique uses 2 lateral oblique photon fields and 1 lateral electron field, placing the anterior field border 2 mm to 3 mm posterior to the surgical limbus. This is done so that the posterior pole of the lens falls in the 50% to 70% isodose line (in an effort to spare the lens) and the eye is treated to the 90% to 95% isodose line (8). The second technique, the relative lens sparing (RLS) technique uses a wedged pair of photon beams, with the goal of treating the entire globe with coverage of the optic nerve to the conus (9). Radiation doses to the posterior lens are similar in both techniques (8, 9).

Historically, our institution has treated many cases of advanced RB in an ethnically and racially diverse population. We sought to evaluate the treatment variables of EBRT dose, technique, and timing, and the patient characteristics of race and ethnicity on outcomes.

Methods and Materials

This study was approved by the institutional review board of the University of Miami School of Medicine. The medical records of all patients with RB who received EBRT at any point in the course of their treatment from June 1, 1992 through March 31, 2012 at either Sylvester Comprehensive Cancer Center or Jackson Memorial Hospital, Miami, FL were reviewed.

Clinical data were summarized by mean, standard deviation, and median values for continuous variables and by frequencies and percentages for categorical variables. Differences in means or in proportions were tested either by Student's t test for continuous variables or by χ^2 or Fisher's exact test for categorical variables. We defined a dichotomous variable for EBRT dose wherein 45 Gy was chosen as a threshold because of institutional preference ($\geq$45 Gy or $<$45 Gy). Staging was performed with the Reese Ellsworth system (RE) (10).

Treatment timing was defined relative to EBRT. Definitive EBRT was given as the first modality of treatment. Adjuvant EBRT was given immediately after surgery. Second-line EBRT was given for active disease that did not respond to a definitive treatment other than surgery or radiation. Salvage EBRT was defined as radiation therapy for recurrent disease.

Outcomes of note were overall survival (OS), progression-free survival (PFS), local control (LC), eye preservation rate (EPR), and toxicity. OS time was calculated as the elapsed time between the dates of radiation treatment completion and death or last follow-up visit for living patients. PFS time was calculated as the elapsed time between completion of radiation and earliest progression (local recurrence or distant metastasis or death) or last follow-up visit for patients without recurrence. Kaplan-Meier survival analyses were used for OS and PFS wherein median survival and survival rates at 1, 2, 3, 5, and 10 years were calculated for all patients and by EBRT dose, EBRT technique, EBRT timing, race, and ethnicity, respectively. Log-rank test was used to test the differences in survival between the groups. Unadjusted and adjusted hazard ratios (HR), with their corresponding 95% confidence intervals (95% CI) and P values, were calculated from fitting several univariate models to identify significant predictors of the clinical outcomes. Univariate models were fitted to 3 dichotomous clinical outcomes; LC, eye preservation, and toxicity. Odds ratios (OR), with 95% confidence intervals (95% CI) and P values were calculated. Type I error rate was set to 5%, where P values $<.05$ were considered as statistically significant. Statistical analyses were performed by SAS version 9.3 (SAS Institute, Inc, Cary, NC).

Results

Our retrospective interventional case series included 41 eyes of 30 patients. The median follow-up time was 133 months (11 years). The median age at diagnosis was 12.5 months. The patient characteristics are shown in Table 1. The tumor and treatment characteristics by eye are shown in Table 2 according to EBRT dose ($\geq$45 Gy or $<$45 Gy) and EBRT technique (RLS, MLS, and others). Over 90% of the eyes were Reese Ellsworth stage V (10). Definitive EBRT was delivered in 43.9% of eyes, adjuvant EBRT in 22% of eyes, and second-line/salvage EBRT in 34.1% of eyes. All postoperative eyes had a positive margin at the optic nerve after enucleation as the indication for adjuvant EBRT. The RLS technique was used in 68.3% of eyes and MLS in 24.4% of eyes. Three eyes were treated with other techniques (2 with anterior-posterior mixed photon electron beams, 1 with electron). Chemotherapy was a component of treatment in 53.7% of eyes. Doses $\geq$45 Gy were used in 68.3% of eyes. Tumor or treatment