External Beam Radiotherapy in Retinoblastoma

Tumor Control and Comparison of 2 Techniques

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Objective: To investigate eye conservation, local control, and complication rates among children with retinoblastoma treated with 2 different external beam radiotherapy (EBR) techniques.

Methods: Fifty-eight eyes in 42 patients received EBR as the primary treatment modality for retinoblastoma (median follow-up, 37 months). The EBR technique was relative lens-sparing (RLS) in 26 eyes and modified lateral beam (MLB) in 32 eyes. Both groups were comparable in Reese-Ellsworth retinoblastoma classification. If necessary, patients received focal salvage therapy.

Results: At 24 months, eye conservation rates were 88.5% and 89.1% among eyes treated with RLS and MLB, respectively (P = .40); tumor control rates without salvage therapy were 84.6% and 53.3% (P = .02), respectively. Among eyes with Reese-Ellsworth stage IV and V disease, eye conservation rates were 88% ± 8% and 83% ± 9% at 36 months in the RLS and MLB groups, respectively, and local tumor control rates were 81% ± 10% and 51% ± 12%. Percentages of eyes without cataract at 36 months were 83.1% and 63.0%, respectively (P = .40). Among patients observed for at least 18 months, midfacial hypoplasia developed in 38.5% and 29.4%, respectively (P = .70).

Conclusions: The EBR technique was associated with high eye conservation and local control rates. Salvage therapy was performed significantly less frequently in the RLS group compared with the MLB group, and complication rates in both groups were similar.

Retinoblastoma is the most common primary intraocular tumor in children and is second only to uveal melanoma as the most common primary intraocular malignant neoplasm overall. Traditionally, bilateral retinoblastoma has been treated by enucleating the most involved eye and administering external beam radiotherapy (EBR) to the second eye. However, after retinoblastoma was found to be an extremely radiosensitive tumor, EBR evolved into an eye-conserving treatment for children with bilateral intraocular disease. Traditionally, a single D-shaped lateral field with the anterior field border positioned at the lateral bony canthus was used. With this technique, the posterior pole of the lens was in the 30% isodose line, and the eye was generally treated to the 90% to 95% isodose line. Although this technique was believed to spare the radiosensitive lens, the anterior retina was undertreated and frequent anterior recurrences were noted. In an effort to spare the lens and treat anterior retina, a number of techniques were developed to treat the anterior eye but shield the lens with a hanging block or a shielded contact lens, these anterior lens-sparing (ALS) techniques, however, were associated with undesired shielding of the posterior retina, and because of a high incidence of local recurrences, the modified lateral beam (MLB) technique was developed. With the MLB technique, the anterior field border is positioned 2 to 3 mm posterior to the surgical limbus so that the posterior pole of the lens is in the 50% to 70% isodose line and the eye is treated to the 90% to 95% isodose line. In addition to the MLB technique, we used a relative lens-sparing (RLS) technique, which attempts to treat the entire globe with coverage of the optic nerve to the conus; radiation doses to the middle and posterior lens are similar to those with the MLB technique.

Clinicians disagree as to whether the ALS, RLS, or MLB technique is the optimal EBR modality in terms of maximizing tumor control while minimizing the risk for such complications as cataract and midfacial hypoplasia. Increasingly, primary chemotherapy has been proposed as an alternative to radiation therapy in children with retinoblastoma. To evaluate treatment results, recent outcomes of radiation therapy should be reported from separate institutions as a basis for comparison of emerg-
MATERIALS AND METHODS

The study protocol was approved by the institutional review boards of the University of Miami School of Medicine, Miami, Fla, and the University of California at San Francisco School of Medicine, San Francisco. The clinical records of all patients who received EBR as primary treatment of retinoblastoma from January 1, 1989, through December 31, 1996, were reviewed. Data collected included age at diagnosis of retinoblastoma, sex, family history of retinoblastoma, Reese-Ellsworth stage of retinoblastoma at diagnosis, presence or absence of vitreous seeds, retinal detachment, optic nerve involvement, macular involvement, technique of EBR used, total radiation dose, salvage therapy administered (including direct laser photocoagulation, transpupillary hyperthermia, and/or cryotherapy), tumor progression or recurrence, new tumor development, whether enucleation was performed, and complications (including cataract, midfacial hypoplasia, radiation retinopathy, ptosis, restrictive strabismus, secondary tumor, and metastasis). The RLS and MLB techniques included treatment to the 95% isodose line, with a total dose goal of 45 Gy at 1.8 Gy per fraction. The practice at one clinic was exclusively RLS, and the practice at the other was exclusively MLB; therefore, assignment of EBR technique was according to the clinic at which the patient received treatment. Length of follow-up was calculated from the date of the last EBR administration to the date of the most recent examination under anesthesia.

Dichotomous variables, eg, sex, family history of retinoblastoma, and midfacial hypoplasia, were compared between the RLS and MLB groups using Fisher exact tests. Categorical variables with more than 2 categories, eg, Reese-Ellsworth classification, were compared using the exact-permutation 2 categories, eg, Reese-Ellsworth classification, were compared using the Fisher exact tests. Categorical variables with more than 2 categories, eg, Reese-Ellsworth classification, were compared using the exact-permutation 2 categories, eg, Reese-Ellsworth classification, were compared using the Fisher exact tests.

The principal outcome variable in this study, time until treatment failure, was defined in the following 2 ways: time from EBR treatment until enucleation, regardless of whether salvage therapy was required to preserve the eye, and time from EBR until salvage therapy was mandated by tumor recurrence or new tumor. For the latter definition, eyes that required enucleation and received no salvage therapy were counted as eyes in which treatment failed at the time of enucleation. Time until treatment failure data for the RLS and MLB groups were summarized using Kaplan-Meier analysis and compared using the log-rank test. These methods were also used to compare the RLS and MLB groups with respect to time to cataract formation.

RESULTS

Characteristics of the 42 patients identified are shown in Table 1. Patients were observed a median of 37 months. Tumor characteristics are displayed in Table 2. More than 40% of eyes harbored Reese-Ellsworth stage V retinoblastomas, and 29% of eyes contained vitreous seeding of tumor. There were no significant differences between the RLS and MLB groups in patient or tumor characteristics. Salvage and EBR therapy administered are shown in Table 3.

The cumulative percentages of eyes not enucleated are displayed in Figure 1. Eye conservation rates were not significantly different between the RLS and MLB groups (P = .40). Figure 2 shows the cumulative percentages of eyes in which tumor control was achieved without salvage therapy. Salvage therapy was performed significantly less frequently in eyes in the RLS group compared with eyes in the MLB group (P = .02). Eye conservation and local control rates did not differ significantly by Reese-Ellsworth classification. In fact, among eyes with Reese-Ellsworth stage IV and V disease, eye conservation rates were 88% ± 8% and 83% ± 9% at 36 months in the RLS and MLB groups, respectively, and local tumor control rates were 81% ± 10% and 51% ± 12% (Figure 3). Among eyes with Reese-Ellsworth stage V disease, eye conservation rates were 82% ± 12% (n = 11) and 83% ± 11% (n = 13) in the RLS and MLB groups, respectively, and local tumor control rates were 82% ± 12% (n = 11) and 43% ± 14% (n = 13). Of the 13 eyes in the MLB group that underwent enucleation or required salvage therapy, new tumors developed in 6 eyes, tumor recurrences in 3 eyes, progressive vitreous seeds in 3 eyes, and massive posterior segment neovascularization and dense vitreous hemorrhage in 1 eye (rendering it impossible to observe the tumor). Progressive vitreous seeds developed in all 4 eyes in the RLS group that underwent enucleation or required salvage therapy.

Figure 4 displays the cumulative percentages of eyes without cataract. Cataract development rates were not significantly different between the RLS and MLB groups.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>RLS (n = 18)</th>
<th>MLB (n = 24)</th>
<th>Total (N = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis, y</td>
<td>1.2 ± 1.5</td>
<td>0.9 ± 0.7</td>
<td>1.0 ± 1.1</td>
<td>.40†</td>
</tr>
<tr>
<td>Follow-up, mo</td>
<td>40.3 ± 20.8</td>
<td>36.0 ± 18.3</td>
<td>37.9 ± 19.3</td>
<td>.48‡</td>
</tr>
<tr>
<td>No. (%) of patients with unilateral enucleation</td>
<td>2 (11)</td>
<td>3 (12)</td>
<td>5 (12)</td>
<td>.99‡</td>
</tr>
<tr>
<td>No. (%) of patients with unilateral EBR treatment</td>
<td>10 (56)</td>
<td>16 (67)</td>
<td>26 (62)</td>
<td>.53‡</td>
</tr>
</tbody>
</table>

RLS indicates relative lens-sparing radiotherapy technique; MLB, modified lateral beam radiotherapy technique; and EBR, external beam radiotherapy.

†Student t test.
‡Fisher exact test.
§Data missing for 1 patient.
not involving macula 13 (50) 10 (31) 23 (40) .19

No. (%) with optic nerve involvement 0 0 0

No. (%) with macular involvement 15 (58) 22 (69) 37 (64) .42

**Table 3. Treatment**

<table>
<thead>
<tr>
<th>RLS</th>
<th>MLB</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total radiation dose,† Gy</td>
<td>43.5 ± 3.9</td>
<td>47.5 ± 2.6</td>
<td>45.8 ± 3.8</td>
</tr>
<tr>
<td>Median (range)</td>
<td>45 (36-49)</td>
<td>48 (44-54)</td>
<td>46 (36-54)</td>
</tr>
<tr>
<td>Salvage therapy, No. of eyes‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plaque</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>2</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Photocoagulation</td>
<td>1</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*RLS indicates relative lens-sparing radiotherapy technique; MLB, modified lateral beam radiotherapy technique.

†P < .001 by Mann-Whitney test.

‡Many eyes received multiple salvage therapy modalities.

(P = .30). Among patients observed for at least 18 months, midfacial hypoplasia developed in 38.5% and 29.4% of eyes in the RLS and MLB groups, respectively (P = .70). No other complications were noted in the RLS group. In the MLB group, radiation retinopathy developed in 1 patient 19 months after EBR, bilateral ptosis in 2 patients, and restrictive strabismus in 1 patient. No second nonocular tumor developed in any of the patients in our series, although the relatively short follow-up precludes adequate analysis of this issue.

In the present study, EBR combined with focal salvage therapy was associated with 91% eye conservation at 36 months. This compares favorably with previously reported results of EBR combined with salvage therapy. Egbert et al treated 38 eyes with lateral beam EBR combined with focal salvage therapy and reported 80% ocular survival in eyes with Reese-Ellsworth stages I to III disease, but only 29% in eyes with stages IV and V disease; follow-up ranged from 2½ to 21 years. Hernandez et al reported 73.5% ocular survival in 34 eyes treated with anterior and lateral wedged EBR plus focal salvage therapy and observed for a mean of 35 months. The 73.5% ocular survival reported by Hernandez et al is lower than that of our series, despite the fact that only 13 (54%) of 24 eyes had Reese-Ellsworth stages IV or V disease in the former study compared with 36 (62%) of 58 eyes in our series. However, the eyes in the study by Hernandez et al were treated with fractions of 1.5 to 2.0 Gy/d. If most patients were treated at the lower daily dose, this might have adversely affected their outcomes. Unfortunately, survival analysis accounting for varying lengths of follow-up was not performed in the aforementioned studies and, therefore, direct comparisons with the results of our study are not possible.

Tumor control with EBR alone was achieved in 69% of eyes at 3 years in our series. Cassady et al reported local tumor control in 109 (48.9%) of 223 eyes treated via 1 or 2 lateral fields; however, the length of follow-up of eyes included in that study is unclear, and survival analysis was not performed. Hernandez et al reported tumor control with EBR alone in 15 (44%) of 34 eyes observed a mean of 35 months.

In our study, there was no significant difference in ocular survival between the RLS and MLB groups, although tumor control without salvage therapy was significantly higher in the RLS group compared with the MLB group. This may be because of a higher frequency of anterior recurrences in the MLB group that were successfully treated with salvage therapy. Because the assignment of external beam technique was not randomized and depended on the clinic at which patients were treated, the possibility of systematic differences between the patients seen at both clinics cannot be ruled out; however, we have examined both groups for risk factors that might account for the difference in salvage therapy rates and found no significant differences between the groups (Table 1). Reports by Foote et al and Schomberg et al, in which 14 eyes were treated via anterior segment-sparing lateral fields and 16 eyes via an anterior approach, provide only median follow-up data (80% ocular survival with a median follow-up of 32 months) and, therefore, cannot be directly compared with our study. However, those results are consistent with ours in that salvage treatment was more frequently required in eyes treated via the lateral beam technique (10 [71%] of 14 eyes) than in eyes treated via the anterior approach (4 [36%] of 11 eyes). In contrast, in a study by McCormick et al of 121 eyes treated with the ALS or the MLB technique, survival analysis of tumor control with EBR alone demonstrated 83% control in the MLB group com-

**Table 2. Tumor Characteristics**

<table>
<thead>
<tr>
<th>RLS</th>
<th>MLB</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of eyes treated</td>
<td>26</td>
<td>32</td>
<td>58</td>
</tr>
<tr>
<td>No. of tumors per eye†</td>
<td>2.5 ± 1.7</td>
<td>3.7 ± 2.6</td>
<td>3.1 ± 2.3</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>2 (1-7)</td>
<td>3 (1-14)</td>
<td>2 (1-14)</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Not involving macula 8/12 (67)# 6/10 (60) 14/22 (64)

Involving macula 4/12 (33) 4/10 (40) 8/22 (36) .99

§Exact x² test.

*Indicates data missing for 1 eye.

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pared with 33% in the ALS group with Reese-Ellsworth stages I to III disease, and no difference in tumor control rates for eyes with Reese-Ellsworth stage IV and V disease (35% control) at 3 years. Blach et al treated 67 eyes via an ALS technique and 113 eyes via an MLB technique. In that study, there was no significant difference between groups in ocular survival (5-year rates, 73% vs 78%, respectively). However, similar to the study by McCormick et al, the tumor control rate without salvage therapy was higher in the MLB group than the ALS group with Reese-Ellsworth stages I to III disease (5-year rates, 84% vs 37%, respectively). In the study by Blach et al, no significant difference in tumor control rates was found between the EBR groups for eyes with Reese-Ellsworth stages IV and V disease (50% vs 38%, respectively). A possible explanation for the difference in results between our study and those of Blach et al and McCormick et al (Table 4) is that in the latter studies the ALS technique was used, whereas in our study, the RLS technique was used. The ALS technique, sparing the lens, may undertreat the anterior retina and permit more frequent anterior tumor recurrences. Furthermore, in the studies by Blach et al and McCormick et al, the patients in the ALS group were treated from 1979 through 1984 and 1980 through 1984, respectively, whereas the patients in the MLB groups of both studies were treated from 1984 through 1991. In our study, both groups were treated from 1989 through 1996. Improvements in EBR techniques since 1984, eg, enhanced localization techniques using computed tomographic 3-dimensional imaging, may permit enhanced control of more posteriorly located tumors.

Figure 1. Kaplan-Meier plots of the cumulative proportion of eyes without enucleation for each external beam technique. Vertical lines indicate censoring due to nonavailability for follow-up. The relative lens-sparing (RLS) group had a significantly lower rate of salvage therapy (P = .02, log-rank test). At 48 months, the number of patients still being observed was 11 in the relative lens-sparing (RLS) group and 6 in the modified lateral beam (MLB) group.

Figure 2. Kaplan-Meier plots of the cumulative proportion of eyes without salvage therapy via external beam technique. Vertical lines indicate censoring due to loss to follow-up. The relative lens-sparing (RLS) group had a significantly lower rate of salvage therapy (P = .02, log-rank test). MLB indicates modified lateral beam.

Figure 3. Kaplan-Meier plots of the cumulative proportion of eyes without salvage therapy via external beam technique for eyes with Reese-Ellsworth stages IV and V retinoblastoma. Vertical lines indicate censoring due to unavailability for follow-up. The relative lens-sparing (RLS) group had a borderline significantly lower rate of salvage therapy (P = .09, log-rank test). MLB indicates modified lateral beam.

Figure 4. Kaplan-Meier plots of the cumulative proportion of eyes without cataract after treatment with external beam radiotherapy. Vertical lines indicate censoring due to unavailability for follow-up. There was no significant difference between groups (P = .40, log-rank test). MLB indicates modified lateral beam; RLS, relative lens-sparing.
It is interesting that in our series, RLS treatment failures generally occurred within the first year, whereas treatment failures in the MLB group continued to occur after 24 months of follow-up. This emphasizes the importance of continued vigilant follow-up. All enucleations in our series occurred secondary to progressive vitreous seeding. This appears to reflect the successful use of focal salvage therapy for eye conservation in children treated with RLS or MLB.

Similar to the study by Blach et al,19 we found no significant difference in rates of cataract between the RLS and MLB groups; however, follow-up in our study was relatively short, and differences in cataract rates may become significant with longer follow-up. By 3 years after EBR, cataracts had developed in 16.9% of patients in the RLS group and 37.0% of patients in the MLB group. These rates are comparable to the incidence of cataract development reported in the literature for patients with retinoblastoma after EBR, which range from 8% to 66%9,11,15,16,18,20-27. Rigorous comparison between studies is not possible due to the lack of standardized cataract grading.

The frequent occurrence of midfacial hypoplasia in the RLS and MLB groups emphasizes that although EBR is an effective treatment modality for retinoblastoma control, it is not a risk-free procedure. A major concern is the dramatic increase in the incidence of second tumors and tumor-related mortality associated with the use of EBR.23-28 Experimental advances in combined modality therapy have suggested the potential for a decrease in EBR dose when EBR is combined with ocular hyperthermia or chemotherapy.29,30

External beam radiotherapy combined with focal salvage therapy is associated with high eye conservation and local control rates. In our series, salvage therapy was performed significantly less frequently in the RLS group compared with the MLB group, and complication rates in both groups were similar. Use of salvage therapy was not associated with ocular complications or eye loss, and all enucleations resulted from progressive vitreous seeding.

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REFERENCES


Table 4. Cumulative Local Tumor Control Rates Without Salvage Therapy At 3-Year Follow-up*

<table>
<thead>
<tr>
<th>Tumor Control Rate, %</th>
<th>Present Study</th>
<th>Blach et al19</th>
<th>McCormick et al22</th>
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</thead>
<tbody>
<tr>
<td>Reese-Ellsworth stage I-III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS†</td>
<td>90</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td>MLB</td>
<td>58</td>
<td>84</td>
<td>83</td>
</tr>
<tr>
<td>Reese-Ellsworth stages IV and V</td>
<td></td>
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</tr>
<tr>
<td>LS†</td>
<td>81</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>MLB</td>
<td>51</td>
<td>53</td>
<td>35</td>
</tr>
</tbody>
</table>

*LS indicates lens-sparing radiotherapy technique; MLB, modified lateral beam radiotherapy technique.†Indicates anterior lens-sparing for Blach et al19 and McCormick et al22; relative lens-sparing for present study.