Objective: To describe patient and ocular outcomes following initial treatment with external beam radiotherapy (EBT) in eyes with Reese-Ellsworth group Vb retinoblastoma.

Methods: Retrospective case series (from January 1, 1979, to February 28, 2002). The Kaplan-Meier method was used to analyze survival (ocular and patient) and incidence (second cancer) data.

Results: Two hundred forty-three patients with 1 or more Reese-Ellsworth group Vb eyes were identified. Of 284 group Vb eyes, 63 (22.2%) initially received EBT, vs 172 (60.6%) that were initially enucleated. Of the 63 radiated group Vb eyes, 31 (49.2%) had no further tumor growth, 26 (41.3%) developed a recurrence, and 8 (12.7%) developed a new tumor. Of the 63 radiated group Vb eyes, 33 (52.4%) developed ocular complications. The ocular survival rate of radiated group Vb eyes was 81.4% at 1 year and 53.4% at 10 years. Twenty-eight radiated group Vb eyes survived to the last follow-up with visual acuity information. Thirteen patients developed second cancers, 11 in the field of radiation. The probability of developing a second cancer following initial EBT for group Vb disease in patients with bilateral disease was 29.7% by 10 years after diagnosis. Survival from second cancers in patients with bilateral disease initially receiving EBT for group Vb disease was 93.6% at 5 years and 52.6% at 18 1/4 years. No patient with unilateral disease developed a second cancer. Deaths due to metastatic retinoblastoma were uncommon.

Conclusions: To our knowledge, this is the first study focusing exclusively on group Vb eyes treated initially with EBT, most of which were salvaged with vision. Outcome data provided herein are clinically relevant when choosing treatment options for advanced intraocular retinoblastoma.

Arch Ophthalmol. 2004;122:1316-1323

IT HAS BEEN 100 YEARS SINCE THE first report1 of the successful treatment of intraocular retinoblastoma (RB) with radiation. Since then, there has been an abundance of articles on the subject in the ophthalmic and radiation oncology literature. Virtually every major figure in ophthalmic oncology worldwide, and every major center, has contributed to this literature.

It took more than 50 years to determine the optimal dose, dose rate, portals, fractionation scheme, and energy to correctly treat RB; as a result of these advances, more eyes with RB were salvaged and more children retained sight, in addition to being cured of their cancer. Retinoblastoma is a solid cancer of childhood that may be routinely cured with radiation alone.

In the early years of radiation therapy, the cancer was cured, but radiation-induced complications were common. Enucleations following radiation were more often because of these complications than because the treatment failed to control the tumors.2,3 For more than 30 years, however, ocular complications have been uncommon. The anterior segment complications (other than cataract) are no longer seen, and radiation vasculopathy is so rare that recent series4-8 no longer mention it as an event that occurred in treated patients. With the recognition that the orbital growth problems are minimal when radiation is withheld until the age of 6 to 12 months, even this untoward effect has become less common.9

While ocular complications following radiation have been reduced, it is known that radiation plays a role in the genesis of subsequent primary malignancies, so-called second nonocular tumors, in patients who receive external beam radiotherapy (EBT) as a treatment modality for RB. These additional malignancies are associated with germline RB gene (RB1)
defects; patients with unilateral disease who do not harbor a germline RB1 mutation do not develop these second cancers after radiation. Among the patients with a germline RB1 mutation who receive radiation, we know the following: (1) the incidence of subsequent nonocular cancers is hundreds of times more common than in the general pediatric population, (2) there is a dose-response curve for sarcomas in the field, (3) there is an increased incidence in children who undergo radiation in the first year of life, and (4) there is an alteration in the timing and location of where the cancers occur in the patient who has undergone radiation, especially in the first year of life. Without radiation, children with heritable RB develop one third of the second cancers in the field of radiation and two thirds out of the field of radiation; with radiation, they develop two thirds of the second cancers in the field of radiation and one third out of the field of radiation. Because the cancers that occur out of the field of radiation tend to occur at a later age, those who received radiation develop their cancers at a younger age overall and, therefore, have radiation-induced cancer deaths at an earlier age. In fact, in the United States, the main cause of death in RB patients is not RB—it is their second, nonocular, cancer! The overall risk of radiation-induced second cancers is about 1% per year, which is higher than that of any other cured pediatric malignancy.

The knowledge of radiation-related second cancers has been one of the main stimuli for the development of alternative strategies in the management and treatment of patients with RB. Worldwide, systemic and local chemotherapies have been used since the mid-1990s in the hope that cures for RB may be attained without an increased risk of second cancers. Chemotherapy alone seems to rarely cure intraocular RB; however, when combined with focal techniques (photocoagulation, transpupillary thermotherapy, cryotherapy, and radioactive plaques), it has proved to be a useful adjunct, often obviating the need for EBT. The success of the chemotheraphy plus focal techniques approach, however, seems related to the extent of the intraocular disease. For Reese-Ellsworth (RE) groups I, II, and III, radiation can usually be avoided. For eyes in which the tumors are larger, such as RE groups IV (multiple tumors, some >10 disc diameters, and/or lesions extending anteriorly to the ora serrata) and V (massive tumors involving more than half of the retina, with or without seeding), success rates are much lower. These children require multiagent chemotherapy, usually for 6 to 9 months, with a significant incidence of systemic toxicity, including anemia, anorexia, leukopenia, myelosuppression, neurotoxicity, neutropenia, secondary infections, and optic atrophy. The literature suggests that most of these eyes are not cured with chemotherapy alone and may still receive EBT and/or undergo enucleation. The impact of a chemotherapeutic approach on second cancers is not known, but recent evidence suggests that acute myelocytic leukemia may be induced by etoposide.

The question of deciding between multiagent chemotherapy or EBT for advanced disease would seem to be a simple weighing in of the known risks and benefits of each approach. With the many articles on radiation, it would seem that the success rates and complications for eyes with advanced disease are known and well published; however, when we reviewed the literature, we were surprised to find that there are no articles exclusively focusing on radiation for eyes with RE group Vb RB. In some series, these cases are included in the overall reports, but it is impossible to filter out exactly how often radiated group Vb eyes are cured, require subsequent enucleation, develop new intraocular tumor foci, have complications, and develop second cancers, and what the final visual outcome is for this important subset. We believe that modern-day clinicians could not make a fair and balanced decision about chemotherapy as an initial choice for eyes with group Vb RB without this information; consequently, we undertook a study to answer these questions. We limited this series to cases performed in recent times with modern dosing, fractionation, and portals; therefore, we did not include those cases treated previously by Algernon B. Reese, MD.

A retrospective medical record review was conducted for all patients who were examined by us between January 1, 1979, and February 28, 2002, at the Robert M. Ellsworth Ophthalmic Oncology Center, New York, NY, and who initially had at least one eye diagnosed as having RE group Vb RB. A diagnosis of RB was defined as the presence of 1 or more retinal tumors detected on fundoscopic examination using indirect ophthalmoscopy and scleral depression. The following clinical data were collected: sex, family history, age at diagnosis, laterality, and initial treatment modality for the group Vb eye (enucleation, EBT, or other).

For those who received EBT as the initial treatment for the RE group Vb eyes, the following clinical data were collected: age of RE group Vb eye at initial treatment, EBT variables, development of recurrent or new ocular tumors, ocular complication rate following EBT, whether additional treatment was given following initial EBT, development of additional primary neoplasms, length of follow-up, and visual acuity following EBT. Radiation therapy was administered in a fairly consistent fashion during this period. The dose prescribed to the retinal target volume ranged from 4200 to 4600 rad (4200-4600 cGy). The children were treated 5 days per week, with fractions of 180 to 200 rad/d (180-200 cGy/d).

Ocular survival was evaluated for RE group Vb eyes that received radiation as their initial treatment during the follow-up period from the date of diagnosis. For ocular survival analysis, the event variable was enucleation.

Patient survival was also evaluated during the follow-up period from the date of diagnosis for the following cohorts: all patients with RB diagnosed as having at least one RE group Vb eye, patients with bilateral RB with at least one RE group Vb eye, patients with unilateral RB with one RE group Vb eye, patients with bilateral RB with at least one RE group Vb eye treated with EBT, patients with bilateral RB with at least one RE group Vb eye treated initially with EBT, and patients with bilateral RB with at least one RE group Vb eye who were never treated with EBT.

Probability curves for the development of a second nonocular cancer were generated for the following subgroups of patients with bilateral disease who received EBT as the initial treatment for the group Vb eyes: all 43 patients from the date of diagnosis to the development of a second primary neoplasm or the date of the last follow-up for those who did not develop a second cancer, those who were diagnosed as having the disease at 12 months or younger vs older than 12 months.
RESULTS

DEMOGRAPHICS

Two hundred forty-three patients were identified as having at least one RE group Vb eye at diagnosis, with a mean follow-up of 5 years (median, 3.5 years; range, <1-20.3 years). There were 284 group Vb eyes among these 243 patients. Patient characteristics are listed in Table 1.

Table 1. Demographic Variables for the 243 Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>111 (45.7)</td>
</tr>
<tr>
<td>Female</td>
<td>132 (54.3)</td>
</tr>
<tr>
<td>Family history of retinoblastoma</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>15 (6.2)</td>
</tr>
<tr>
<td>Negative</td>
<td>219 (90.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>9 (3.7)</td>
</tr>
<tr>
<td>Laterality at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>137 (56.4)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>106 (43.6)</td>
</tr>
<tr>
<td>Laterality by number of group Vb eyes</td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>202 (83.1)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>41 (16.9)</td>
</tr>
<tr>
<td>Patient age at diagnosis, mo†</td>
<td>19.0 (1-154)</td>
</tr>
<tr>
<td>Those with unilateral disease</td>
<td>26.0 (1-154)</td>
</tr>
<tr>
<td>Those with bilateral disease</td>
<td>10.0 (1-116)</td>
</tr>
<tr>
<td>Follow-up, mo†</td>
<td>42.0 (0-243)</td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of patients unless otherwise indicated.
†Data are given as median (range).

Ocular complications observed are summarized in Table 3. The overall ocular complication rate following EBT for a group Vb eye was 52.4%, with 33 of 63 eyes developing a total of 41 ocular complications. The types of complications observed are summarized in Table 3.

Ocular Survival

Table 3 summarizes the survival for the group Vb eyes that were treated initially with EBT. Of the 63 group Vb eyes initially treated with EBT, 25 were eventually enucleated.

INITIAL TREATMENT MODALITIES

Sixty-three (22.2%) of the 284 group Vb eyes, representing 53 patients (43 with bilateral RB and 10 with unilateral RB), were initially treated with EBT. The median age at initial treatment with EBT of the RE group Vb eye was 14 months (range, 1-53 months). Twenty-seven (50.9%) of these patients were 1 year or younger at the time of EBT, while 26 (49.1%) were older than 1 year. One hundred seventy-two (60.6%) of the group Vb eyes, representing 170 patients, were treated with initial enucleation. The median age of the RE group Vb eyes initially enucleated was 23 months (range, 1-154 months). Fortynine (17.3%) of the group Vb eyes, representing 33 patients, were treated with another initial treatment modality. Information regarding the initial treatment of the RE group Vb eyes is listed in Table 2.

OCULAR OUTCOMES FOLLOWING EBT

Disease Status

Of the 63 group Vb eyes initially treated with EBT, 26 developed recurrence of intraocular RB, 8 developed a new intraocular tumor, and 2 developed recurrence and a new intraocular tumor. Thirty-one of the RE group Vb eyes initially treated with EBT developed no intraocular disease recurrence or new tumors. Table 3 lists the variables associated with ocular outcome.

Ocular Complications

The overall ocular complication rate following EBT for a group Vb eye was 52.4%, with 33 of 63 eyes developing a total of 41 ocular complications. The types of complications observed are summarized in Table 3.
ated while 38 survived to the last follow-up. Twenty-one (55.3%) of the 38 eyes that survived to the last follow-up required no additional treatment after EBT, while 17 (44.7%) required some type of salvage treatment. The 25 group Vb eyes that were eventually enucleated had a median survival of 14 months (range, 5-107 months) after treatment, while the 38 group Vb eyes that survived to the last follow-up had a median survival of 112 months (range, 3-228 months).

Figure 1 demonstrates the Kaplan-Meier curve for ocular survival for all group Vb eyes treated with initial EBT. Survival time (81.4% at 1 year, 56.4% at 5 years, and 53.4% at 10 years) is measured from the end of EBT to the date of enucleation or last follow-up.

Visual Acuity

Visual acuity information was available for 28 of the 38 eyes that survived to the last follow-up (Table 4). Of these 38 eyes, 17 (44.7%) required additional treatment and 21 (55.3%) required no additional treatment. These data represent the most recent visual acuity that was recorded for each patient. Eight eyes (21.1%) had a visual acuity of at least 20/50. No eye had a visual acuity of 20/20 following EBT. Eyes that required no additional treatment following EBT had slightly better visual acuities (9 [42.9%] of 21 with a visual acuity ≥20/200) than eyes that required additional treatment (6 [35.3%] of 17 with a visual acuity ≥20/200).

DEVELOPMENT OF NONOCULAR TUMORS

Thirteen (5.3%) of the 243 group Vb patients developed second nonocular tumors. Of these 13 patients, 12 had bilateral RB. One patient had unilateral RB (group Vb disease), but was first seen with a pineoblastoma and had a positive family history of RB. Ten patients (76.9%) received EBT as their initial therapy, while the remaining 3 (23.1%) received EBT as salvage treatment. The types of second nonocular cancers are listed in Table 5. Of 13 secondary neoplasms, 11 occurred in the field of radiation. The cumulative probability of a patient with bilateral RB developing a second nonocular cancer following initial EBT for an RE group Vb eye is shown in Figure 2. at 1 year after diagnosis, the probability is 2.3%; at 5 years, 11.2%; and at 10 years, 29.7%. If the Kaplan-Meier curves for the probability of developing a second nonocular cancer following EBT to an RE group Vb eye in a patient with bilateral disease are compared between those receiving initial EBT at 1 year or younger and those receiving initial EBT at older than 1 year, the difference is not significant ($P = .49$ and $P > .05$, respectively). Even if the comparison between the curves is defined as the
first 60 months following EBT, the probability of developing a second nonocular cancer is not significantly different between these 2 groups ($P = .09$ and $P > .05$, respectively). Overall, 7 patients with bilateral RB died of a second nonocular cancer; 6 of these patients received radiation as initial treatment for 1 or more eyes with RE group Vb disease. **Figure 3** is a Kaplan-Meier curve demonstrating, for the patients with bilateral RB diagnosed as having at least one RE group Vb eye and who received EBT as the initial treatment, freedom from the development of second cancers for 93.6% at 5 years and 10 years after diagnosis and 52.6% at 181/4 years after diagnosis.

**PATIENT SURVIVAL**

Of the 243 group Vb patients, there were 13 confirmed deaths: 6 of metastatic disease and 7 of second cancers. Figure 3 shows freedom from metastatic disease for patients with unilateral and bilateral RB diagnosed as having at least one RE group Vb eye. One patient with unilateral RB and no known family history of RB died of metastatic disease 15 months after diagnosis. The group Vb eye was treated initially by enucleation. The rate of freedom from the development of metastatic RB for patients with bilateral disease with 1 or more RE group Vb eye was 99.0% at 1 year after diagnosis and 93.3% at 5 and 90.3% at 10 years after diagnosis. Of the 5 patients with bilateral disease who died of metastatic RB, 3 (3 of 43 total patients) received radiation as the initial treatment for the group Vb eye. Two patients died following initial enucleation for the group Vb eye and recurrence following failed EBT for the other (non–group Vb) eye. The median (mean±SD) age at death for all 13 patients who died was 8.1 (8.0±4.8) years, while the median (mean±SD) age at death for the 9 patients who died and received initial EBT was 6.2 (8.1 ± 5.7) years.

**COMMENT**

The RE RB classification system is not, nor was it intended to be, a traditional cancer staging scheme. In traditional cancer schemes, the untreated cancer progresses from a lower stage to a higher stage. This progression may even occur despite treatment. The RE classification system was designed to allow clinicians worldwide to compare the results of lateral photon external beam therapy for RB. The features that most predicted failure with this technique were tumor location and size and the presence of vitreous seeds. The more anterior a tumor, the lower the success rate; and the larger the tumor, the lower the success rate with lateral photons. Thus, group V describes tumors involving more than half the retina, while group I tumors are 0 to 4 disc diameters behind the equator. A review of all subsequent articles reveals the strength of this scheme; every center has found that group V tumors are less often cured with radiation than group I, II, III, and IV tumors. In New York, 85% of RE groups I through III avoided enucleation after primary EBT.

Reese-Ellsworth group Vb represents cases with vitreous seeds. They were classified as group V because most, but not all, of the cases with vitreous seeds were associated with large retinal tumors. Group Vb represented the hardest to cure because focal techniques failed and the subsequent alternatives were global treatments: enucleation or EBT. Deciphering exactly how hard these eyes were to cure with radiation has been confusing; many researchers frequently lumped together group IV and V eyes in their analyses or reported their experience with group V eyes alone (ie, not subdividing cases with seeds vs large tumors). Cassady et al reported a 20% cure rate for groups IV and V. McCormick et al reported a 35% cure rate for groups IV and V, Foote et al reported control in 2 of 10 cases, and Eghert et al reported success in only 29% of group IV and V eyes. It was previously reported that 42% of group IV and V (together) eyes survived with the anterior lens-sparing technique, and 50% were controlled with the modified lateral beam technique after EBT. In describing his experience with only RE group V eyes, Stallard reported that treatment failed in 11 of his 20 group V eyes treated between 1948 and 1960. Cassady et al reported that only 15% of group V
eyes were locally controlled. Egbert et al reported failure in 12 of 14 cases. Foote et al reported no successes. Fontanesi et al\(^7\) reported success in only 1 of 4 cases. In the largest cohort of group V eyes described in the United States, 38\% of the irradiated eyes avoided enucleation.\(^9\)

Few published reports focus exclusively on the success or failure of radiation for group Vb eyes. In one report from China, 5 of 6 irradiated eyes were in patients with group Vb disease. Two eyes were saved. One had a visual acuity of 20/30 and the other had peripheral vision.\(^10\) Among the landmark radiation articles that have not subdivided group Vb eyes are those of Stallard,\(^17\) Abramson et al,\(^48,49\) Blach et al,\(^5\) Hernandez et al,\(^4\) Fontanesi et al,\(^8\) Cassady et al,\(^31\) Bedford et al,\(^40\) Merchant et al,\(^8\) and Amendola et al.\(^1\) Thus, we believed that the paucity of data on group Vb eyes justified this analysis of our experience with radiation for group Vb eyes. To our knowledge, our series of 53 patients who underwent radiation, with 63 group Vb eyes, represents the largest in the literature. Some of our findings were expected, while others were not.

Of the 284 eyes classified as RE group Vb at our institution between January 1, 1979, and February 28, 2002, 172 were enucleated primarily. Although we did not have a protocol in effect to determine which group Vb eyes were to be enucleated primarily, most of them were in patients with unilateral disease and/or in patients who had rubeosis, painful blind eyes, or buphthalmos or who were believed by us to have no reasonable hope of vision. While the latter category is "soft," it is important to realize that when comparing radiation with chemotherapy, the initial selection of which eyes to enucleate may significantly affect success/failure rates with chemotherapy or radiation.

As expected, there were an equal number of boys and girls affected with group Vb eyes and, overall, 90.1\% of newly diagnosed cases had no family history of RB. Also expected was the observation that the median age at diagnosis was younger for the patients with bilateral disease (10 months) than for the patients with unilateral disease (26 months) diagnosed as having group Vb eyes, and that most group Vb eyes receiving initial EBT were in patients with bilateral disease (n=43), with 10 patients with unilateral disease initially treated with EBT. It has been previously noted that EBT for patients with unilateral disease is possible, with success, but great care must be taken in choosing such patients.\(^10\) The risks and benefits must be clearly understood by the family and all treating physicians.

The ocular outcome variables we chose to analyze following initial EBT for RE group Vb disease included ocular survival, disease recurrence, new tumor growth, visual acuity, and ocular complication rate. The ocular survival for all radiated group Vb eyes was 81.4\% at 1 year, 56.4\% at 3 years, and 53.4\% at 10 years. Failures following radiation usually occur in the first or second year after treatment, and late failures following EBT of group Vb eyes are rare and usually reflect complications of treatment.

Approximately half (49.2\%) of all group Vb eyes initially treated with EBT had no recurrence and no new tumors after a single course of EBT: of 63 eyes, 26 (41.3\%) developed recurrent disease and 8 (12.7\%) developed new tumor foci after radiation. Two eyes (3.2\%) developed recurrence and new tumors. The subsequent development of new tumor foci in patients who underwent radiation has been extensively reviewed elsewhere, and is directly related to the age at which children are treated.\(^47\)

Ocular complications following initial EBT were common, observable in 52.4\% of the group Vb eyes. As expected, the most common ocular complication was a cataract. Radiation retinopathy developed in only 1 patient, and vitreous hemorrhage, in 13 eyes. One striking observation of this study is that vitreous hemorrhage seems to be more common than generally appreciated following irradiation.

The visual results of group Vb eyes initially treated with EBT are often an important measure of success for the treating physicians and the family. Thirty-eight group Vb eyes, in patients who survived to the last follow-up, had useful data: 15 (39.5\%) had a visual acuity of 20/200 or better, and 8 (21.1\%) had a visual acuity of 20/50 or better.

Our analysis of patient survival revealed that deaths due to metastatic disease were uncommon in the patient populations with unilateral and bilateral RB. Of the 243 patients with 284 group Vb eyes, 137 were diagnosed as having unilateral RB and had the unilateral diseased eye classified as RE group Vb. One hundred nineteen patients with unilateral disease had their group Vb eye treated by primary enucleation. One patient developed metastasis and died 15 months after enucleation. This patient had choroidal, optic nerve, and scleral invasion, and developed an orbital recurrence. Ten eyes in 10 patients with unilateral disease were initially treated by EBT; no metastatic events occurred.

In the patient population with bilateral disease with at least one group Vb eye (n=106), 5 patients died of metastatic disease: 3 received bilateral radiation for bilateral group Vb disease as their initial treatment and 2 underwent enucleation for the unilateral group Vb eye and radiation for the other, non–group Vb, eye as the primary treatment regimen. Both patients developed an orbital recurrence in the non–group Vb eye. No patient with a group Vb eye that was treated with only primary enucleation (for unilateral disease, or both eyes for bilateral disease) developed metastatic disease; 3 patients with bilateral group Vb disease underwent bilateral enucleation as their initial treatment, with no metastatic events occurring.

The use of radiation for group Vb disease was not associated with the development of second nonocular cancers in our study in patients with sporadic unilateral RB. No patient with sporadic unilateral disease, whether undergoing enucleation or radiation, developed a second nonocular cancer. Prior studies\(^18\) have emphasized that patients with unilateral disease who harbor the germinal mutation are at risk of developing second nonocular cancers whether they receive radiation or not. It would seem that radiation for eyes with unilateral group Vb disease in patients who do not harbor the mutation is a reasonable treatment strategy for the management of RB.

Second tumor incidence in patients with bilateral disease is usually thought to develop at 1% a year, so our observed incidence of 11.2% by 5 years and 29.7% by 10

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years in this study seemed high. Because certain features have been demonstrated to further increase the incidence of second cancers, such as higher doses of radiation (a dose-response curve exists for sarcomas\textsuperscript{48}), radiation in the first year of life, and the presence of lipomas, we looked for these markers in our patient population. On further analysis, our apparent increase above the previously reported incidence in patients with bilateral disease following radiation is not attributable to the following: (1) the age of the patient at EBT, (2) the laterality (total surface area) of the radiation, and (3) the dose of radiation. The children in our study were all treated at one institution with similar doses, so radiation dose is not the answer. Patients with bilateral disease could be bilaterally affected with group Vb disease or unilaterally affected with group Vb disease (and the other eye may have some other RE grouping). A detailed analysis of patients with bilateral disease treated with radiation in one or both eyes failed to reveal a significant difference in second cancers. Last, 27 patients with bilateral disease underwent radiation in the first 12 months of life, and 26 underwent radiation after the age of 1 year. A $\chi^2$ comparison between the 2 probability curves when the time measured is adjusted from the date of radiation revealed $P=.09$. While it is possible that some of this effect is due to age, the small numbers make it impossible to be certain.

Furthermore, when we looked at all patients with bilateral RB and group Vb disease who received any radiation throughout their treatment course ($n=84$), we found a 5.7% second cancer incidence by 5 years and a 26.3% incidence by 11 years (data not shown). Those patients with bilateral group Vb disease who never received EBT ($n=22$) developed no second cancers during the study follow-up period (data not shown). The difference between these 2 curves was not significant ($P=.16$ and $P>.05$, respectively). Perhaps our observed trend toward more second cancers may reflect a real difference, but the numbers are small and the follow-up is short. Or, it is possible that we may be observing the earlier radiation-induced second cancers rather than the later cancers known to develop in all survivors of bilateral RB following radiation. Regardless, our study suggests that the presence of vitreous seeds, in combination with EBT, is not a marker for an increased risk of second cancers.

External beam radiation as an initial treatment for selected cases of RE group Vb eyes is associated with few metastatic disease cases and deaths from RB. Most eyes can be salvaged (81.4% at 1 year and 33.4% at 10 years) with vision; yet, ocular complications are common, with vitreous hemorrhages occurring more often than generally appreciated following EBT.

A comparative study looking at the use of chemotherapy as the initial treatment for management of RE group Vb disease is necessary. Like the radiation data for group Vb eyes, few published reports focus exclusively on the success or failure of chemotherapy for group Vb eyes: groups IV and V are analyzed together as advanced disease\textsuperscript{25-28} or group V eyes are described with references to vitreous seed response.\textsuperscript{20,21,35-38} Chemotherapy for intraocular RB is still in its infancy, with dosing, agent selection, and response variables yet to be optimized; therefore, long-term consistent treatment data and follow-up data, with particular attention to local control and complication rates (ocular and systemic), are unavailable. We look forward to these future studies, which will enable clinicians to make informed risk-benefit assessments for patients with group Vb disease.

Submitted for publication August 14, 2003; final revision received January 16, 2004; accepted March 4, 2004.

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REFERENCES


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28. Turner AR, Melynk A, Clark G. MDS and acute monocytic leukemia after retino-...