Objective: To present a simplified approach to management of retinoblastoma using basic clinical features.

Design: In a prospective, nonrandomized, single-center clinical trial, 158 eyes of 103 patients with retinoblastoma were managed with 6 cycles of chemoreduction (vincristine sulfate, etoposide, and carboplatin). The eyes were classified according to the Reese-Ellsworth classification and were also grouped on the basis of clinical features as follows: group 1, tumor only; group 2, tumor plus subretinal fluid; group 3, tumor plus local seeds (3a, local subretinal seeds; 3b, local vitreous seeds); group 4, tumor plus diffuse seeds (4a, diffuse subretinal seeds; 4b, diffuse vitreous seeds); and group 5, neovascular glaucoma or invasive retinoblastoma.

Main Outcome Measure: Treatment success (avoidance of enucleation and external beam radiotherapy).

Results: According to the Reese-Ellsworth classification, chemoreduction was successful in 100% of group Ia, 100% of group Ib, 86% of group IIa, 100% of group IIb, 91% of group IIIa, 100% of group IIIb, 50% of group IVa, 77% of group IVb, 50% of group Va, and 27% of group Vb. There was erratic correlation of the Reese-Ellsworth classification with treatment success. In contrast, the simplified grouping system displayed a smooth, nonerratic correlation for treatment success, with 100% success for group 1, 91% for group 2, 59% for group 3, and 12% for group 4 (group 5 always managed by primary enucleation). When all 6 subcategory groups were analyzed, there was consistent correlation for treatment success of 100% for group 1, 91% for group 2, 68% for group 3a, 54% for group 3b, 17% for group 4a, and 11% for group 4b.

Conclusion: This practical approach to retinoblastoma using basic clinical features is predictive of treatment success for eyes in which modern conservative therapy for retinoblastoma is used.

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The management of retinoblastoma is complex and includes enucleation and nonenucleation (conservative) techniques. Currently, the most popular conservative technique is chemoreduction. Chemoreduction involves intravenous chemotherapy to reduce the tumor size, followed by focal consolidation with cryotherapy or thermotherapy to permanently devitalize each retinoblastoma. Chemoreduction is most successful for tumors without associated subretinal fluid or tumor-related seeding. Success, defined as globe salvage, is found in 85% of treated patients by 5 years when the tumor is less advanced (Reese-Ellsworth groups I to IV) and 47% when the retinoblastoma is more advanced (Reese-Ellsworth group V).

Despite these informative results regarding therapy, most clinicians have difficulty applying Reese-Ellsworth classification to their practice, as it is complex and few ophthalmologists are able to recall its 10 categories. Reese and Ellsworth formulated this classification approximately 40 years ago as a method of predicting globe salvage after external beam radiotherapy. In a subsequent publication, Ellsworth stated that the Reese-Ellsworth classification was a "purely arbitrary scheme" with the intention to quantify tumor during an era when eyes with advanced retinoblastoma were being saved. This classification may no longer be so useful in predicting globe salvage.

New and improved methods of therapy for retinoblastoma, such as cryotherapy, laser photocoagulation, thermotherapy, chemothermotherapy, chemoreduction, and custom-designed plaque radiotherapy, have subsequently been developed. External beam radiotherapy currently is used far less often because of long-term radiation complications and the...
success of the newer methods. Current therapies have allowed eyes, previously judged by the Reese-Ellsworth classification as probable failures, to be uncomplicated successes. For example, an eye previously classified as group IIIa (any lesion anterior to the equator) would be “doubtful” for globe salvage by the Reese-Ellsworth classification, but current therapies such as cryotherapy, chemoreduction, or plaque radiotherapy would likely salvage the eye, resulting in a more favorable outcome. The doubtful prognosis for Reese-Ellsworth group IIIa eyes stemmed from failure of external beam radiotherapy to effectively treat tumors anterior to the equator and was not an inherent quality of retinoblastoma located anterior to the equator. The doubtful prognosis was related to the specific method of treatment, external beam radiotherapy, but since this therapy is used much less often today, there is a need to use other criteria for judging success of treatment.

On the basis of extensive clinical experience with retinoblastoma and its complexities and current management, we have developed a practical approach for grouping eyes with retinoblastoma, and this approach may be applicable to future classifications of retinoblastoma. Chemoreduction is currently the leading conservative treatment modality for retinoblastoma; in this study, we applied our grouping to a large cohort of patients with retinoblastoma treated with chemoreduction and evaluated its predictive value for treatment success.

### METHODS

All new patients with retinoblastoma who were treated with initial chemoreduction (institutional review board approval [The Children’s Hospital of Philadelphia] 582) on the Ocular Oncology Service, Wills Eye Hospital, Thomas Jefferson University, Philadelphia, Pa, in conjunction with the Division of Oncology at The Children’s Hospital of Philadelphia were identified. Patients eligible for treatment with chemoreduction were children with retinoblastoma in whom either eye would ordi

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**Table 1. Reese-Ellsworth Classification for Conservative Treatment of Retinoblastoma**

<table>
<thead>
<tr>
<th>Group</th>
<th>Likelihood of Globe Salavage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Very favorable</td>
<td>a. Solitary tumor, &lt;4 disc diameters, at or behind equator &lt;br&gt;b. Multiple tumors, none &gt;4 disc diameters, at or behind equator</td>
</tr>
<tr>
<td>II</td>
<td>Favorable</td>
<td>a. Solitary tumor, 4-10 disc diameters, at or behind equator &lt;br&gt;b. Multiple tumors, 4-10 disc diameters, behind equator</td>
</tr>
<tr>
<td>III</td>
<td>Doubtful</td>
<td>a. Any lesion anterior to equator &lt;br&gt;b. Solitary tumors &gt;10 disc diameters behind equator</td>
</tr>
<tr>
<td>IV</td>
<td>Unfavorable</td>
<td>a. Multiple tumors, some &gt;10 disc diameters &lt;br&gt;b. Any lesion extending anteriorly to ora serrata</td>
</tr>
<tr>
<td>V</td>
<td>Very unfavorable</td>
<td>a. Massive tumors involving more than half of retina &lt;br&gt;b. Vitreous seeding</td>
</tr>
</tbody>
</table>

Abbreviations: DS, diffuse seeds; FS, focal seeds; SRF, subretinal fluid; SRS, subretinal seeds; T, tumor; VS, vitreous seeds.

*Refers to chances of salvaging the affected eye and not systemic prognosis.

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**Table 2. Practical Grouping System of Retinoblastoma Based on General Clinical Features**

<table>
<thead>
<tr>
<th>Group</th>
<th>Abbreviation</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>T</td>
<td>Tumor only*</td>
</tr>
<tr>
<td>2</td>
<td>T + SRF</td>
<td>Tumor plus subretinal fluid</td>
</tr>
<tr>
<td>3</td>
<td>T + FS</td>
<td>Tumor plus focal seeds a. SRS &gt;3 mm from tumor b. VS &gt;3 mm from tumor</td>
</tr>
<tr>
<td>4</td>
<td>T + DS</td>
<td>Tumor plus diffuse seeds a. SRS &gt;3 mm from tumor b. VS &gt;3 mm from tumor</td>
</tr>
<tr>
<td>5</td>
<td>High risk</td>
<td>Tumor plus (any one) Neovascular glaucoma Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space Invasion of postlaminar optic nerve, choroid (&gt;2 mm), sclera, orbit, anterior chamber</td>
</tr>
</tbody>
</table>

Abbreviations: DS, diffuse seeds; FS, focal seeds; SRF, subretinal fluid; SRS, subretinal seeds; T, tumor; VS, vitreous seeds.

*Regardless of tumor number, size, or location.
ocular outcome, need for enucleation or external beam radiotherapy (failure) or no need for enucleation or external beam radiotherapy (success), was recorded at the date of most recent examination. The predictive value for success in treatment with chemoreduction by means of the Reese-Ellsworth classification and our simplified grouping was compared.

RESULTS

During the 62-month period of this study, there were 364 retinoblastomas in 158 eyes of 103 patients enrolled in the chemoreduction protocol. The Reese-Ellsworth clas-
sification and our grouping of each eye are listed in Table 3. The mean follow-up was 26 months (median, 20 months; range, 1-83 months). The success rate was then calculated on the basis of the Reese-Ellsworth classification and our grouping (Figure 2 and Figure 3). When the eyes were assessed by means of the 5 major Reese-Ellsworth groups, there was a general decreasing correlation of success with each higher group, with the exception that group III fared slightly better than group II (Figure 2A). When the 10 subcategory groups of the Reese-Ellsworth classification were assessed, the success for each group was as follows: 100% success for group Ia, 100% for group Ib, 86% for group IIa, 100% for group IIb, 91% for group IIIa, 100% for IIIb, 50% for IVa, 50% for Va, and 27% for Vb. As is evident, there was erratic correlation, as groups IIb and IIIb fared as well as Ia and Ib; group IVb fared better than IVa; and group Va fared the same as IVa (Figure 2B). Reese-Ellsworth groups Ia, Ib, IIb, and IIIb showed 100% success.

In contrast, the 4 major groups in our system showed a consistent progressive decrease in success rate with increasing group number as follows: 100% success for group 1, 91% for group 2, 59% for group 3, and 12% for group 4 (Figure 3A). Group 5 eyes were not eligible for chemoreduction and were managed by primary enucleation in all cases. With the use of the 6 subcategory groups of our system, there was a consistent general decreasing trend for success with higher group number without exception as follows: 100% success for group 1, 91% for group 2, 68% for group 3a, 54% for group 3b, 17% for group 4a, and 11% for group 4b (Figure 3B).

**COMMENT**

More than 40 years ago, Reese and Ellsworth presented their classification of retinoblastoma at the 67th annual...
session of the American Academy of Ophthalmology.\(^\text{14}\) For the first time, they proposed a scheme for grouping eyes with retinoblastoma according to quantity and location of tumor(s) as well as associated features such as vitreous seeding (Table 2). Their goal was to create guidelines to predict success of external beam radiotherapy for retinoblastoma. They tested their classification scheme on 164 patients with retinoblastoma treated with “x-ray and TEM [chemotherapy]” between 1953 and 1960 and found success (globe salvage) in 85% of group I patients, 60% of group II, 52% of group III, 68% of group IV, and 23% of group V.\(^\text{14}\) In the discussion of their paper, Bettman stated that “it should be crystal clear that the basic therapy for retinoblastoma is irradiation with x-ray” and further queried why the Reese-Ellsworth classification failed with regard to group IV, which fared better than group III, contrary to its presumed value. Ellsworth replied in the discussion that he acknowledged this deficiency and would like to improve the classification and could reliably predict treatment success (avoidance of enucleation and external beam radiotherapy), without factoring in visual or systemic outcome.

Table 4. Essen Classification for Conservative Sight-Saving Treatment of Retinoblastoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Likelihood of Globe Salvage</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Very favorable</td>
<td>Tumor(s) up to 4 disc diameters and 4 diopeters elevation except tumors near macula or adjacent to disc</td>
</tr>
<tr>
<td>II</td>
<td>Favorable</td>
<td>Moderate-size tumor(s) of 8-10 disc diameters if not belonging in groups III-V for other reasons</td>
</tr>
<tr>
<td>III</td>
<td>Doubtful</td>
<td>Tumor near the macula, even if small</td>
</tr>
<tr>
<td>IV</td>
<td>Unfavorable</td>
<td>Extensive tumor growth with or without limited seeding or retinal detachment</td>
</tr>
<tr>
<td>V</td>
<td>Very unfavorable</td>
<td>Massive tumor growth up to half of retina with or without diffuse vitreous seeding</td>
</tr>
</tbody>
</table>

In 1983, Hopping\(^\text{17}\) presented the Essen classification of retinoblastoma (Table 4). This accounted for newer methods of clinical examination such as binocular ophthalmoscopy and newer treatments such as light coagulation, cryocoagulation, and cobalt and rhenium applicators.\(^\text{18}\) An evaluation of 273 eyes staged by the Essen classification, de Sutter et al\(^\text{18}\) found globe salvage for 97% of group 1, 99% of group 2, 100% of group 3, 69% of group 4, and 27% of group 5. Thus, this classification showed favorable but identical results for groups 1, 2, and 3, reducing its predictive power. This thoughtful classification was elegant in its detail, but was also difficult to recall or apply to clinical practice. Vague words without precision were used, such as “tumors near the macula, even if small,” “moderately sized tumors,” and “limited seeding.” The definition of macula, details of proximity of tumor to the macula, exact tumor size, and quantification of seeding were not provided. In addition, it appeared that the Essen classification, primarily designed to predict globe salvage, attempted to consider visual outcome to some extent, as a tumor near the macula, even if small, was categorized as group 2 rather than group 1. The blending of 2 outcomes may have decreased the predictive power for a single outcome. One advantage of our current grouping is that it is based on the single outcome of treatment success (avoidance of enucleation and external beam radiotherapy), without factoring in visual or systemic outcome.

Our practical grouping system was created to provide a simple approach that could be easily remembered and could reliably predict treatment success (avoidance of enucleation and external beam radiotherapy). This approach arose during the past decade and evolved during patient treatment as it became apparent that eyes with tumor alone were successfully treated with chemoreduction, no matter the size, number, or location of the tumor(s). In fact, an eye with tumor alone was found to have 100% success, so that the tumor size, number, or location became irrelevant (Figure 3).

Before layout of the grouping system, we first performed a MEDLINE search for all published reports on retinoblastoma and selected for review those that provided statistical analysis for success of chemoreduction in large groups of patients with retinoblastoma.\(^\text{5-9,13}\) We found that the most relevant clinical features that were predictive of chemoreduction failure (need for enucleation or external beam radiotherapy) included the presence of subretinal fluid, subretinal tumor seeds, and vitreous tumor seeds at the initial examination.\(^\text{26}\) Thus, we based our grouping on these predictive factors. It should be noted that the Reese-Ellsworth classification did not account for subretinal fluid or subretinal seeds. When analyzing our grouping system with regard to treatment success, we found impressive predictive power, with treatment success in 100% of group 1 eyes, 91% of group 2 eyes, 59% of group 3 eyes, and 12% of group 4 eyes (Figure 3A). Further subdivision into 6 groups allowed for more refinement in predictive ability (Figure 3B). In contrast, the Reese-Ellsworth classification showed erratic correlation with treatment success, as 100% of eyes were successes in groups 1a, 1b, 1b, and 1b, decreasing its predictive power; in addition, group IVb fared better than...
group IVa and groups IVa and Va fared the same (Figure 2B).

We suspect that eyes with subretinal seeds and vitreous seeds showed greater risk of recurrence and treatment failure owing to inadequate exposure to chemotherapy because of deficient blood supply to the seeds. We suspect that patients with tumor plus subretinal fluid (group 2) showed greater failure than those with tumor alone (group 1) because of possible subclinical subretinal tumor seeds within the fluid, accounting for a higher rate of tumor recurrence.

There are limitations to this grouping system. First, it is designed to predict success (avoidance of enucleation and external beam radiotherapy) with current conservative (nonenucleation) therapies, especially chemoreduction. It was created to predict globe prognosis, not life or visual prognosis. Concerning success of treatment, group 1 eyes showed complete success, with continued decreasing success with each group to approximately 10% success in group 4 eyes (Figure 3). Group 5 eyes were always managed with primary enucleation. Second, our evaluation of the applicability of the grouping system in this report was directed to eyes treated with initial chemoreduction and not any of the other less commonly used conservative methods (plaque radiotherapy, cryotherapy, laser photocoagulation, and thermotherapy).10,19 but we believe that it will apply to all methods. Third, because of the simplicity of this grouping, there may be details that are not included but may be useful in predicting globe outcome. Our grouping system is based on clinical factors identified by previous studies to be predictive of treatment failure (subretinal fluid, subretinal seeds, and vitreous seeds).6-8 Although larger tumors are generally more likely to be associated with poor prognostic factors like subretinal fluid or seeds, we did not find that tumor features alone, such as size, location, or number, were specifically predictive of failure. In fact, all patients with tumor alone (group 1) showed success, despite variations in size, location, or number per eye (Figure 3). Fourth, we tested this grouping in 158 eyes, but a larger cohort of patients might be useful to better assess its predictive power.

In summary, we have used an innovative, practical method to group eyes with retinoblastoma on the basis of expected success of conservative treatments such as chemoreduction and focal therapies. We hope that this information will be beneficial to the design of future retinoblastoma classifications.30 This grouping system is concise and easy to recall, provides prediction for treatment success, and, we hope, will be useful for clinicians to estimate outcomes of management for retinoblastoma.

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