Comparison of Staging Systems for Extraocular Retinoblastoma

Analysis of 533 Patients

Differing staging systems for extraocular retinoblastoma have been proposed, but they have not been validated in large cohorts. Extracocular retinoblastoma at presentation accounts for less than 5% of patients with retinoblastoma in developed countries, but it is more frequent in developing nations, accounting for more than half of the cases in many regions. Until recently, children with extracocular retinoblastoma were usually managed in single institutions using diverse staging systems. However, cooperative groups were recently created in developing countries, so the need for a common staging system became critical for evaluating and comparing results. Therefore, following an international initiative for grouping of intraocular retinoblastoma, a new consensus International Retinoblastoma Staging System (IRSS) was developed for extracocular disease with the input of different specialists from many world regions. That initiative resulted in the publication of a proposal for a consensus staging system, and many groups adopted it. However, it was later realized that some pathological definitions were necessary to obtain a reproducible patient stratification, and a second consensus for obtaining uniform processing of enucleated eyes and for using similar definitions for pathological examination was obtained. A few years later, the American Joint Committee on Cancer TNM staging system was updated, includ-
ing the same consensus pathological definitions, and some groups adopted it for their studies. None of these systems were validated in large cohorts or were compared with the existing systems, and questions about their applicability in settings with high proportions of extracocular cases remain unanswered.

Therefore, we performed this study to evaluate the following questions: (1) Do stages of extraocular retinoblastoma proposed by each system accurately predict outcome? (2) Are there any omissions or ambiguities in the definition of significant risk factors? (3) Are there significant differences in outcome among substages?

METHODS

PATIENTS

All patients with retinoblastoma registered at our hospital from January 1, 1988, to December 31, 2009, were included. During that time, 4 institutional review board–approved prospective studies were performed using the Grabowski-Abramson (GA) system for staging in the first 3 protocols (1988-2009) and using the IRSS for the fourth. The procedure for processing enucleated eyes was previously reported, and all enucleated eyes from 2009 onward were processed under the guidelines of the IRSS. All pathology slides of enucleated eyes were reviewed for this analysis, and each case was reclassified according to the different staging systems. Clinical data were obtained from our database, but imaging studies were not reviewed. All cases with more than 12 months of follow-up data that could be adequately staged at our hospital were included. The treatment guidelines were previously published. In brief, children with unilateral retinoblastoma and no overt extracocular dissemination initially underwent enucleation except when conservative therapy was attempted (6.1% of patients). Adjuvant therapy was administered to most children with postlaminar optic nerve involvement (PLONI) and to all those with scleral invasion and tumor at the resection margin of the optic nerve. The latter also received orbital radiation therapy. Children with isolated choroidal or anterior segment invasion were not given adjuvant therapy in any protocol.

In addition, children with overt extracocular retinoblastoma received neoadjuvant therapy (followed by secondary enucleation) and adjuvant therapy (followed by consolidation with autologous stem cell rescue for metastatic disease from 2002 onward). These guidelines are summarized elsewhere.

Furthermore, children with bilateral disease were treated with enucleation of the most severely affected eye and with external beam radiation therapy to the remaining eye from 1988 to 1994 and with chemoreduction and focal therapy from 1995 onward. Children seen with glaucoma or anterior segment invasion initially underwent enucleation. The same criteria were used for adjuvant therapy as for unilateral disease.

EXTENT OF DISEASE EVALUATION

In the first 3 protocols, all children underwent brain and orbit contrast-enhanced computed tomography or magnetic resonance (MR) imaging, which was replaced by MR imaging in the fourth protocol. Bone marrow and cerebrospinal fluid examination was performed in the first protocol in all patients and was limited to high-risk patients from the second protocol onward.

STAGING SYSTEMS

The following staging systems were evaluated (Table 1 and Table 2): the IRSS, the TNM (version 2009) staging system, the GA clinicopathological classification system, and the modified St Jude Children’s Research Hospital (SJCRH) staging system. All children were assigned a stage and a substage based on the disease extent at diagnosis according to each staging system. Invasion to the choroid, optic nerve, anterior chamber, or sclera was considered only when documented pathologically after review. For children with bilateral retinoblastoma, information from the most affected eye was obtained for staging. Because we considered the staging information present at diagnosis, children treated conservatively in both eyes that were later enucleated were analyzed according to their stage at diagnosis. Hence, they were considered to have stage 0 using the IRSS, stage Ia using the GA system, and stage I using the SJCRH system. Using the TNM system, these patients are assigned a clinical group at diagnosis, and a pathological substage was assigned if they later underwent enucleation. When more than 1 pathological feature was present, patients were assigned the highest possible stage or substage.

A critical analysis of each classification was performed to detect ambiguities and missing prognostic information. The following pathological features were considered unequivocally high risk, whose omission may cause potential substaging, leading to undertreatment of affected children: (1) massive choroidal invasion, (2) PLONI with or without invasion to the resection margin, and (3) scleral invasion. Pathologically confirmed anterior chamber invasion, prelaminar optic nerve involvement, and focal choroidal invasion were considered controversial risk factors because the published evidence is inconclusive about their role as predictors of extraocular relapse.

### Table 1. Staging Systems Reported for Retinoblastoma

<table>
<thead>
<tr>
<th>Variable</th>
<th>International Retinoblastoma Staging System</th>
<th>AJCC TNM Staging System</th>
<th>Grabowski-Abramson Staging System</th>
<th>Modified St Jude Children’s Research Hospital Staging System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion of data from fundoscopy</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No. of stages</td>
<td>5</td>
<td>Stages are not considered</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>No. of substages</td>
<td>7</td>
<td>16</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Pathological definitions specified</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Imaging definitions specified</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Abbreviation: AJCC, American Joint Committee on Cancer.

Ophthalmological evaluation is not included, but this staging system was designed specifically to link with another consensus grouping system developed for that aim.10
### Table 2. Description and Patient Distribution in the Different Staging Systems

<table>
<thead>
<tr>
<th>Grabowski-Abramson Staging System</th>
<th>Modified St Jude Children’s Research Hospital Staging System</th>
<th>International Retinoblastoma Staging System</th>
<th>AJCC TNM Staging System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not included</td>
<td>Not included</td>
<td>Patients treated conservatively</td>
<td>Nonenucleated patients are given a clinical TNM group (n = 54)</td>
</tr>
<tr>
<td>Intraocular disease (n = 341, pDFS = 0.98)</td>
<td>Tumor confined to the retina (n = 161, pDFS = 0.98)</td>
<td>Eye enucleated, completely resected histologically (n = 365, pDFS = 0.96)</td>
<td>Stage I</td>
</tr>
<tr>
<td>a: Retinal tumor, single or multiple (n = 158, pDFS = 0.98)</td>
<td>a: Overt orbital tumor (n = 45, pDFS = 0.98)</td>
<td>pT1: Tumor confined to the eye with no optic nerve or choroidal invasion (n = 81, pDFS = 1.00)</td>
<td>pT1: Tumor confined to the eye with no optic nerve or choroidal invasion (n = 81, pDFS = 1.00)</td>
</tr>
<tr>
<td>b: Extension to the lamina cribrosa (n = 29, pDFS = 0.96)</td>
<td>b: Extends to choroid (n = 74, pDFS = 0.98)</td>
<td>pT2: Tumor with minimal optic nerve and/or choroidal invasion (n = 169, pDFS = 0.98)</td>
<td>pT2: Tumor with minimal optic nerve and/or choroidal invasion (n = 169, pDFS = 0.98)</td>
</tr>
<tr>
<td>c: Uveal extension (n = 154, pDFS = 0.98)</td>
<td>b1: Extends to choroid (n = 74, pDFS = 0.98)</td>
<td></td>
<td>pT2a: Tumor superficially invades optic nerve head but does not extend past lamina cribrosa, or tumor exhibits choroidal invasion (n = 115, pDFS = 0.97)</td>
</tr>
<tr>
<td></td>
<td>b2: Invasion to the optic nerve past the cut end of optic nerve (including subarachnoid) (n = 12, pDFS = 0.95)</td>
<td>pT2b: Tumor superficially invades optic nerve head but does not extend past lamina cribrosa and tumor exhibits focal invasion (n = 54, pDFS = 1.00)</td>
<td></td>
</tr>
<tr>
<td>Orbital disease (n = 167, pDFS = 0.88)</td>
<td>Tumor confined to globe/extraretinal (n = 277, pDFS = 0.97)</td>
<td>Eye enucleated, microscopic residual tumor (n = 45, pDFS = 0.86)</td>
<td>Stage II</td>
</tr>
<tr>
<td>a1: Scattered episcleral cells (n = 9, 5 alive)</td>
<td>a: Extends to optic nerve head (n = 43, pDFS = 0.97)</td>
<td>pT3: Tumor with significant optic nerve and/or choroidal invasion (n = 169, pDFS = 0.91)</td>
<td>pT3: Tumor with significant optic nerve and/or choroidal invasion (n = 169, pDFS = 0.91)</td>
</tr>
<tr>
<td>a2: Orbital invasion (n = 8, 8 alive)</td>
<td>b1: Extends to choroid (n = 74, pDFS = 0.98)</td>
<td>pT3a: Tumor invades optic nerve past lamina cribrosa but not to surgical resection line, or tumor exhibits massive choroidal invasion (n = 122, pDFS = 0.91)</td>
<td>pT3a: Tumor invades optic nerve past lamina cribrosa but not to surgical resection line, or tumor exhibits massive choroidal invasion (n = 122, pDFS = 0.91)</td>
</tr>
<tr>
<td>b1: Invasion to the optic nerve up to the cut end (n = 112, pDFS = 0.93)</td>
<td>b2: Extends to choroid with replacement (n = 16, pDFS = 1.00)</td>
<td>pT3b: Tumor invades optic nerve past lamina cribrosa but not to surgical resection line and exhibits massive choroidal invasion (n = 47, pDFS = 0.89)</td>
<td>pT3b: Tumor invades optic nerve past lamina cribrosa but not to surgical resection line and exhibits massive choroidal invasion (n = 47, pDFS = 0.89)</td>
</tr>
<tr>
<td>b2: Invasion to the optic nerve beyond the cut end (n = 38, pDFS = 0.80)</td>
<td>C: Anterior chamber involvement (n = 9, pDFS = 1.00)</td>
<td>pT4: Tumor invades optic nerve to surgical resection line or exhibits extracocular extension elsewhere (n = 35, pDFS = 0.84)</td>
<td>pT4: Tumor invades optic nerve to surgical resection line, but no extracocular extension identified (n = 32, pDFS = 0.86)</td>
</tr>
<tr>
<td></td>
<td>b: Extension to the lamina cribrosa but not to surgical resection line, or tumor exhibits massive choroidal invasion (n = 81, pDFS = 0.98)</td>
<td></td>
<td>pT4a: Tumor invades optic nerve to resection line, but no extracocular extension identified (n = 3, 1 alive)</td>
</tr>
<tr>
<td>Intracranial metastasis (n = 9, 0 alive)</td>
<td>Tumor confined to globe/extraretinal (n = 277, pDFS = 0.97)</td>
<td>Eye enucleated, microscopic residual tumor (n = 45, pDFS = 0.86)</td>
<td>Stage III</td>
</tr>
<tr>
<td>a: Positive CSF alone (n = 3)</td>
<td>a: Extends to optic nerve head (n = 43, pDFS = 0.97)</td>
<td>pT5: Tumor invades optic nerve to surgical resection line, with no extracocular extension identified (n = 32, pDFS = 0.86)</td>
<td>pT5: Tumor invades optic nerve to surgical resection line, with no extracocular extension identified (n = 32, pDFS = 0.86)</td>
</tr>
<tr>
<td>b: CNS mass (n = 6)</td>
<td>b1: Extends to choroid (n = 74, pDFS = 0.98)</td>
<td></td>
<td>pT5b: Tumor invades optic nerve to surgical resection line, but exhibits extracocular extension (n = 32, pDFS = 0.86)</td>
</tr>
<tr>
<td></td>
<td>b2: Invasion to the optic nerve past the cut end of optic nerve (including subarachnoid) (n = 12, pDFS = 0.95)</td>
<td></td>
<td>pT5b: Tumor invades optic nerve to surgical resection line, but exhibits extracocular extension (n = 32, pDFS = 0.86)</td>
</tr>
<tr>
<td>Hematogenous metastasis (n = 16, pDFS = 0.25)</td>
<td>Extrachoroidal extension (n = 72, pDFS = 0.80)</td>
<td>Regional extension (n = 11, pDFS = 0.70)</td>
<td>Stage IV</td>
</tr>
<tr>
<td>a: Positive bone marrow alone (n = 5, 1 alive)</td>
<td>A: Extends to emissaries (n = 22, pDFS = 0.80)</td>
<td>a: Overt orbital disease (n = 8, pDFS = 0.57)</td>
<td>pM1: Metastasis to sites other than central nervous system (n = 5, 1 alive)</td>
</tr>
<tr>
<td>a: Focal bone lesions with or without bone marrow invasion (n = 2, 0 alive)</td>
<td>B: Extends beyond cut end of optic nerve (including subarachnoid) (n = 7, pDFS = 1.00)</td>
<td>b: Preauricular or cervical lymph node extension (n = 3, pDFS = 1.00)</td>
<td>pM1a: Single lesion (n = 4, 1 alive)</td>
</tr>
<tr>
<td>b: Other organ involvement (n = 9, 3 survivors who had preauricular adenopathy as their only metastatic site)</td>
<td>C: Extends through sclera into orbit (n = 12, pDFS = 0.83)</td>
<td></td>
<td>pM1b: Multiple lesions (n = 1, 0 alive)</td>
</tr>
<tr>
<td></td>
<td>D: Extends to choroid (1 or 2) and beyond cut end of optic nerve (including subarachnoid) (n = 19, pDFS = 0.70)</td>
<td>pM1c: CNS metastasis</td>
<td>pM1c: CNS metastasis</td>
</tr>
<tr>
<td></td>
<td>E: Extends through sclera and cut end of optic nerve (n = 12, pDFS = 0.81)</td>
<td></td>
<td>pM1d: Discrete masses without leptomeningeal and/or CSF involvement (n = 10, 0 alive)</td>
</tr>
<tr>
<td></td>
<td>pM1e: Leptomeningeal and/or CSF involvement (n = 3, pDFS = 1.00)</td>
<td></td>
<td>pM1e: Leptomeningeal and/or CSF involvement (n = 3, 1 alive)</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; CNS, central nervous system; CSF, cerebrospinal fluid; pDFS, probability of disease-free survival.

a The TNM system does not propose formal stages, and for that staging system substages were allocated to comparable stages in other staging systems for comparison.
b Difference among substages is not significant.
c Significant difference between stages IIb1 and IIb2 (P = .001).
d No significance tests were performed because of few patients.

MAIN OUTCOME MEASURE

No analysis was performed for eye salvage. Disease-free survival (DFS), considering only extraocular relapse as an event, was calculated at 3 years, with the aim of excluding the effect of secondary malignant neoplasms in the survival estimates. Only subgroups with more than 10 cases were analyzed for DFS by the Kaplan-Meier method. Survival status was updated through June 2012. Survival curve comparison was performed with the log-rank test.

RESULTS

In total, 536 consecutive patients (197 bilateral) with a median follow-up of 78 months (range, 15-256 months) were evaluated. Three patients with unilateral retinoblastoma were excluded because they received 1 cycle of preenucleation chemotherapy after their families temporarily refused enucleation. The 3-year DFS for the whole cohort was 0.91 (95% CI, 0.89-0.93). The site of extraocular relapse (n = 45) included the central nervous system (CNS) (with or without other sites) in 36 patients, systemic metastasis without CNS invasion in 5 patients, and isolated orbital relapse in 4 patients. Only 4 relapsed children achieved a long-lasting second complete remission. The patient distribution according to stage and substage in the different staging systems is given in Table 2. The DFS according to stage in the different systems is summarized in Table 2 and in the Figure.

VALUE OF STAGE TO PREDICT OUTCOME

The DFS was correlated with stage in the SJCRH system and the IRSS but not in the GA system (Figure), in which children with stage IV fared better than those with stage III. The TNM system does not assign stages, so this analysis was not performed. However, children with nodal involvement (N1) did not fare worse than those without nodal involvement.

AMBIGUOUS DEFINITIONS

Ambiguous terms in the 4 staging systems were defined. These are listed in Table 3.

OMISSION OF RISK FACTORS

Unequivocal Pathological Risk Factors

The SJCRH system does not recognize PLONI with resection margin free of tumor, and the GA system does
not recognize massive choroidal invasion. Only the IRSS (in its update) and the TNM system provide definitions for the degree of choroidal invasion that could provide an unequivocal identification of patients with massive choroidal invasion. The TNM system does not include invasion to the sclera for staging. All other systems include it, albeit with different definitions. The IRSS classifies it as intrascleral invasion and transscleral invasion, the GA system identifies only 1 category of “scattered episcleral cells,” and the SJCRH system includes evaluation of the emissary veins.

### Controversial Risk Factors

Only the SJCRH system assigns a separate substage to children with anterior chamber invasion. Prelaminar optic nerve involvement was considered in all staging systems, albeit defined differently for the SJCRH system (Table 3). Children with focal choroidal invasion could be accurately identified only using the IRSS and the TNM system.

All systems except for the GA system include information about invasion to regional lymph nodes for stage assignment. All staging systems propose substaging for children with metastatic disease, distinguishing CNS from systemic metastasis and separating a single lesion vs multiple ones. All systems recognize as a separate substage those children with leptomeningeal dissemination other than a CNS mass. No system mentions trilateral retinoblastoma.

### EFFECT OF OMISSION OF UNEQUIVOCAL RISK FACTORS IN NONMETASTATIC PATIENTS

#### Omission of Scleral Involvement in 51 Patients by the TNM System

The 51 patients with omission of scleral involvement by the TNM system could be assigned a substage because they had at least massive choroidal invasion. Therefore, 19 were staged as pT3a, and their DFS was 0.77 (95% CI, 0.50-0.90), whereas the DFS for the 103 remaining children with stage pT3a and no scleral invasion was 0.95 (95% CI, 0.98-0.89) (P < .01). Of 20 children with scleral invasion who were assigned a pT3b stage, the DFS was 0.85 (95% CI, 0.61-0.94) vs 0.96 (95% CI, 0.77-0.99) for those with stage pT3b and no scleral invasion (P = .10). Twelve patients with scleral invasion had concomitant tumor invasion to the optic nerve beyond the resection margin; they were staged as pT4a, and their DFS was 0.72 (95% CI, 0.47-0.89), whereas the DFS was 0.94 (95% CI, 0.67-0.99) for children with pT4a without scleral invasion (P = .10). In 2 patients, scleral invasion could not be assessed because of the effects of preoperative chemotherapy (no extraocular relapse occurred).

#### Omission of Massive Choroidal Invasion in 97 Patients by the GA System

In total, 154 children had isolated choroidal invasion at diagnosis (stage Ic). Among them, 33 had massive choroidal invasion, and their DFS was 0.94 (95% CI, 0.76-0.98) compared with 0.99 (95% CI, 0.93-1.00) for children with focal choroidal invasion (P = .04). Ninety-eight children had PLONI (stage IIb1) and choroidal invasion, and the DFS for 46 of them with associated massive choroidal invasion was 0.91 (95% CI, 0.79-0.96) compared with 0.94 (95% CI, 0.82-0.98) for 53 of them with focal choroidal invasion and PLONI (P = .55). For children with tumor at the resection margin of the optic nerve (stage IIb2), the DFS for 18 patients with concomitant massive choroidal invasion was 0.75 (95% CI, 0.53-0.89) compared with 0.84 (95% CI, 0.63-0.94) for 20 patients without massive choroidal invasion (P = .50).

#### Omission of PLONI by the SJCRH System in 115 Patients

Fifteen patients who had PLONI and no other pathological risk factor could not be accurately staged by the SJCRH system because it did not include PLONI for staging; and they were assigned to stage Ila. No events occurred. Seventy-seven children were considered stage 2d because of concomitant choroidal invasion, and their DFS was 0.94 (95% CI, 0.86-0.97) vs 0.96 (95% CI, 0.86-0.98) for the remaining 56 children at this stage without PLONI (P = .72). Twenty children had PLONI and concomitant scleral invasion (13 stage IIIa and 7 stage IIIc).

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### Table 3. Ambiguous Definitions in the 4 Staging Systems

<table>
<thead>
<tr>
<th>Staging System/Stage</th>
<th>Ambiguous Term</th>
<th>Definition of ot is not provided.</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Retinoblastoma Staging System/Ila</td>
<td>Overt orbital disease</td>
<td></td>
</tr>
<tr>
<td>Modified St Jude Children’s Research Hospital staging system/Ila</td>
<td>Invasion to the optic nerve head</td>
<td>The limits of the optic nerve head cannot be defined histologically. Relationship to the lamina cribrosa is preferred. Patients were assumed to correspond to prelaminar involvement.</td>
</tr>
<tr>
<td>Modified St Jude Children’s Research Hospital staging system/Iib2</td>
<td>Extend to choroid with replacement</td>
<td>Degrees of replacement are not specified. Patients were assumed to have complete replacement.</td>
</tr>
<tr>
<td>AJCC TNM staging system/pT4</td>
<td>Extraocular extension</td>
<td>It is not clarified if it is microscopic or macroscopic.</td>
</tr>
<tr>
<td>AJCC TNM staging system/cT4a and cT4b</td>
<td>Optic nerve extension (cT4a), orbital extension (cT4b)</td>
<td>Contradiction that patients seen with macroscopic optic nerve enlargement in imaging studies qualify for both cT4a and cT4b.</td>
</tr>
<tr>
<td>Grabowski-Abramson staging system/IIa1</td>
<td>Scattered episcleral cells</td>
<td>Definition of scattered is not provided.</td>
</tr>
</tbody>
</table>

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### Abbreviation: AJCC, American Joint Committee on Cancer.
There was 1 event among 13 children with stage IIIa and PLONI and 4 events among 9 children with stage IIIa without PLONI. However, in our protocol we considered PLONI an indication for a higher-intensity chemotherapy regimen, so the events that occurred in children without PLONI occurred in the group receiving less intensive chemotherapy. Seven children had concomitant transscleral involvement (stage IIIC), and 2 events occurred. No events were noted among the remaining children in stage IIIC without PLONI. Two additional patients were considered stage I because a conservative approach was taken, and PLONI was detected at secondary enucleation. No events occurred. One other patient had optic nerve enlargement in the imaging studies and no evidence of extrascleral invasion and no metastatic disease. This patient had PLONI at secondary enucleation and could not be assigned a stage using this system.

**DIFFERENCES IN OUTCOME ACCORDING TO SUBSTAGES**

The DFS of each substage and the statistical significance were evaluated. The results are summarized in Table 2.

**DISCUSSION**

The analyzed staging systems differ in many respects. The SJCRH system and the GA system were developed by single institutions, whereas the IRSS and the TNM system were the result of a consensus among many centers, including developing countries, as well as different specialties in the IRSS and ophthalmologists and ocular pathologists from developed countries in the TNM system. The GA system and the IRSS focused on extraocular extension and risk of extraocular relapse, while the TNM system and the SJCRH system attempted to encompass the whole spectrum of the disease, including information from fundoscopy to assess the likelihood of eye preservation. No single staging system gained uniform acceptance worldwide, and centers may prefer different systems depending on the prevalence of extraocular extension. However, each stage must ideally predict incrementally a higher risk of treatment failure, and only the IRSS and the SJCRH system accomplish this goal. The TNM system does not assign a stage, but children with nodal invasion who may have a higher stage than those without nodal invasion fared better than others with orbital invasion alone.

Staging systems are essential to guide physicians for assigning treatment based on risk estimation. However, all staging systems in use presented omissions or ambiguities in the definition of significant risk factors potentially associated with implications for treatment. In this regard, our study reports solid information about children with microscopically disseminated disease based on the many patients treated consistently. Conversely, our cohort of children with more advanced stages is smaller. According to our data, for children with microscopically disseminated disease, only the IRSS identified accurately all high-risk patients because at least 1 of the unequivocally high-risk factors was omitted by the other staging systems analyzed. Omissions significantly associated with poorer DFS included isolated massive choroidal invasion by the GA system and scleral invasion by the TNM system. Both were previously identified as risk factors for extraocular relapse. PLONI was also identified as an unequivocal risk by some groups, but it is omitted by the SJCRH system for staging. The effect of this omission in our population was less evident because we used the presence of PLONI as an indication for adjuvant chemotherapy, which led to excellent survival in our population. So, it was impossible to determine their natural history, in whom the probability of relapse would be as high as 40% without adjuvant treatment based on historical reports. Hence, despite not reaching statistical significance, we believe that invasion to the PLONI should be considered for staging retinoblastoma.

Our series confirmed in a large cohort that other pathological risk factors, such as anterior chamber invasion, prelaminar involvement, or focal choroidal involvement are not significantly associated with poor outcome. All staging systems recognize most of them, and some (eg, the SJCRH system and the TNM system) assign different substages to children manifesting combinations of these risk factors. In addition, some treatment groups based their indication for adjuvant chemotherapy on these associations (eg, the presence of prelaminar optic nerve and focal choroidal invasion). No significant differences in DFS were found in these subgroups. The GA system, the TNM system, and the IRSS do not include invasion to the anterior chamber for staging, but it did not seem to add any prognostic implication because all these patients survived without adjuvant therapy. Because pathological risk factors are not used for substaging in a hierarchical fashion, it is possible with the IRSS to assess their effect alone or in combination. However, some categories included by the IRSS (eg, prelaminar optic nerve and focal choroidal invasion alone or in combination) are not associated with any increased risk, so they may not be needed for staging. Practically, it would be desirable to keep the number of substages to a minimum, so an ideal staging system should include only those substages necessary to significantly predict outcome or to dictate a change in therapy. Therefore, according to our series analyzed together, 99.5% of 217 children initially undergoing enucleation who were without PLONI, massive choroidal invasion, or any degree of scleral invasion survived without any treatment other than enucleation. Hence, focal choroidal invasion, prelaminar optic nerve, and anterior chamber invasion could be safely omitted for staging.

The excess of substages also affected the advanced staging, but our population was too small to make definitive recommendations. No substaging seems necessary for children with CNS metastasis because they all died of disease. On the other hand, children with distant metastatic disease now achieve 90% to 70% DFS when the CNS is not involved, so distinguishing between those patients with and without CNS metastasis would be important. The IRSS also adds substages to children with macroscopic regional extension, so children with preauricular nodal involvement are analyzed in a separate substage. These patients
do not fare worse than those with orbital invasion alone. For children with macroscopic orbital extension, it may be important to discriminate between those with optic nerve enlargement and the others. On the other hand, MR imaging for categorizing invasion to the optic nerve or other ocular coats has limited sensitivity and was not used for staging in our series.27 A recent publication shows that children with enlarged optic nerves on MR imaging have a poor prognosis.28 In our population, too few patients were included to reach a conclusion. These patients with macroscopic optic nerve invasion showing an enlarged optic nerve on MR imaging should be distinguished from those seen with normal-size optic nerves and presumed microscopic optic nerve invasion detectable only by high-resolution MR imaging. The former are not adequately identified in any staging system because definitions of orbital extension were divergent. The IRS recognizes children with overt orbital disease as a separate stage (stage III), and the TNM system also assigns them to a different clinical category (cT4a and cT4b). However, no systems provide definitions for invasion to the optic nerve as seen on imaging studies.29 Strictly, these patients could be staged as cT4b (invasion into the orbit) or as cT4a, a substage given for optic nerve invasion (Table 3). It is impossible to accurately stage these children in the SJCRH system because only those with orbital extension via the sclera are considered. Therefore, all systems fail to identify these high-risk children, and consensus definitions for categorization of macroscopic orbital disease, especially about the imaging involvement of the optic nerve, are needed.

We conclude that only the IRS and the SJCRH system allowed for grouping of patients with increasing risk of extracocular relapse for stage assignment. For lower stages, only the IRS considers all unequivocal pathologic prognostic factors. For higher stages, all systems had redundant information, resulting in an excess of sub-stages, and consensus definitions are needed for imaging evaluation.

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