

AMERICAN ACADEMY  
OF OPHTHALMOLOGY®

# A Multicenter, International Collaborative Study for American Joint Committee on Cancer Staging of Retinoblastoma

## Part I: Metastasis-Associated Mortality

Ankit Singh Tomar, MD,<sup>1</sup> Paul T. Finger, MD,<sup>1</sup> Brenda Gallie, MD,<sup>2</sup> Ashwin Mallipatna, MBBS, MS,<sup>11</sup> Tero T. Kivelä, MD,<sup>3</sup> Chengyue Zhang, MD,<sup>4</sup> Junyang Zhao, MD,<sup>4</sup> Matthew W. Wilson, MD,<sup>5,6</sup> Jonathan Kim, MD,<sup>7</sup> Vikas Khetan, MBBS, MS,<sup>8</sup> Suganeswari Ganesan, MBBS, MS,<sup>8</sup> Andrey Yarovoy, MD,<sup>9</sup> Vera Yarovaya, MD,<sup>9</sup> Elena Kotova, MD,<sup>9</sup> Yacoub A. Yousef, MD,<sup>10</sup> Kalle Nummi, MD,<sup>3</sup> Tatiana L. Ushakova, MD,<sup>12,13</sup> Olga V. Yugay, MD,<sup>12</sup> Vladimir G. Polyakov, MD,<sup>12,13</sup> Marco A. Ramirez-Ortiz, MD, MPH,<sup>14</sup> Elizabeth Esparza-Aguilar, MD,<sup>14</sup> Guillermo Chantada, MD,<sup>15</sup> Paula Schaiquevich, MD,<sup>15</sup> Adriana Fandino, MD,<sup>16</sup> Jason C. Yam, MD,<sup>17</sup> Winnie W. Lau, MD,<sup>17</sup> Carol P. Lam, MD,<sup>17</sup> Phillipa Sharwood, MBBS,<sup>18</sup> Sonia Moorthy, MD,<sup>19</sup> Quah Boon Long, MD,<sup>19</sup> Vera Adobea Essuman, MD,<sup>20</sup> Lorna A. Renner, MD,<sup>21</sup> Jaume Català, MD,<sup>22</sup> Genoveva Correa-Llano, MD,<sup>23</sup> for the American Joint Committee on Cancer Ophthalmic Oncology Task Force\*

**Purpose:** To evaluate the ability of the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual to estimate metastatic and mortality rates for children with retinoblastoma (RB).

**Design:** International, multicenter, registry-based retrospective case series.

**Participants:** A total of 2190 patients from 18 ophthalmic oncology centers from 13 countries over 6 continents.

**Methods:** Patient-specific data fields for RB were designed and selected by subcommittee. All patients with RB with adequate records to allow tumor staging by the AJCC criteria and follow-up for metastatic disease were studied.

**Main Outcome Measures:** Metastasis-related 5- and 10-year survival data after initial tumor staging were estimated with the Kaplan–Meier method depending on AJCC clinical (cTNM) and pathological (pTNM) tumor, node, metastasis category and age, tumor laterality, and presence of heritable trait.

**Results:** Of 2190 patients, the records of 2085 patients (95.2%) with 2905 eyes were complete. The median age at diagnosis was 17.0 months. A total of 1260 patients (65.4%) had unilateral RB. Among the 2085 patients, tumor categories were cT1a in 55 (2.6%), cT1b in 168 (8.1%), cT2a in 197 (9.4%), cT2b in 812 (38.9%), cT3 in 835 (40.0%), and cT4 in 18 (0.9%). Of these, 1397 eyes in 1353 patients (48.1%) were treated with enucleation. A total of 109 patients (5.2%) developed metastases and died. The median time (n = 92) from diagnosis to metastasis was 9.50 months. The 5-year Kaplan–Meier cumulative survival estimates by clinical tumor categories were 100% for category cT1a, 98% (95% confidence interval [CI], 97–99) for cT1b and cT2a, 96% (95% CI, 95–97) for cT2b, 89% (95% CI, 88–90) for cT3 tumors, and 45% (95% CI, 31–59) for cT4 tumors. Risk of metastasis increased with increasing cT (and pT) category ( $P < 0.001$ ). Cox proportional hazards regression analysis confirmed a higher risk of metastasis in category cT3 (hazard rate [HR], 8.09; 95% CI, 2.55–25.70;  $P < 0.001$ ) and cT4 (HR, 48.55; 95% CI, 12.86–183.27;  $P < 0.001$ ) compared with category cT1. Age, tumor laterality, and presence of heritable traits did not influence the incidence of metastatic disease.

**Conclusions:** Multicenter, international, internet-based data sharing facilitated analysis of the 8th edition AJCC RB Staging System for metastasis-related mortality and offered a proof of concept yielding quantitative, predictive estimates per category in a large, real-life, heterogeneous patient population with RB. *Ophthalmology* 2020;127:1719–1732 © 2020 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Supplemental material available at [www.aaojournal.org](http://www.aaojournal.org).

Retinoblastoma (RB) is one of the childhood cancers for which survival of almost all affected children is possible. However, timely diagnosis and prompt treatment must be available.<sup>1</sup> Disease-specific mortality has significantly decreased over the past few decades.<sup>2</sup> However, a significant global disparity exists in regional mortality rates, with rates in Asia and Africa as high as 40% to 70% compared with 3% to 5% in Europe, Canada, and the United States.<sup>3-7</sup> Delays in diagnosis, poor access to eye cancer specialists, ophthalmic pathology, genetic testing, and socioeconomic factors contribute to RB-related loss of life.

In addition, the lack of a universally accepted classification system prevents accurate medical communication among eye cancer specialists, pediatric oncologists, radiation therapists, ophthalmic pathologists, and research workers. The impact of collaboration among international research groups using a uniform staging system was exemplified by the Children's Oncology Group study of rhabdomyosarcoma, in which cooperative research and pooled analyses both increased knowledge about the disease and improved cure rates.<sup>8,9</sup>

Classification systems for RB have evolved from changes in treatment options.<sup>10-12</sup> For example, the earliest, the Reese-Ellsworth staging system, predicted globe salvage after external beam radiation therapy.<sup>13</sup> Then, with the advent of systemic chemotherapy and adjuvant eye and vision conserving therapies, newer classification systems were introduced. These included the International Intraocular Retinoblastoma Classification (IIRC) or Children's Hospital of Los Angeles (CHLA) classification and the International Classification for Retinoblastoma (ICRB), also known as the "Wills Eye Hospital" (WEH) classification.<sup>10,11</sup> Each of these last 2 classification systems originated from a single institution and lack published multicenter validation. These classifications have been widely used to predict globe salvage from chemotherapy-based treatments, not to predict prognosis for life. In addition, significant differences exist, despite many shared features. The lack of uniformity in worldwide RB eye classification has been a hindrance for both research and clinical care.<sup>14,15</sup> In addition, the International Retinoblastoma Staging System (IRSS) was developed for extraocular disease.<sup>12</sup> To date, not one of these systems has been validated using large international multicenter cohorts nor are they universally accepted.

To gain both international consensus and thus widespread acceptance, writing of the 8th edition American Joint Committee on Cancer (AJCC) RB staging system involved 18 RB specialist centers from 13 countries on 6 continents.<sup>16</sup> The resultant AJCC cancer staging system not only brings RB care into the mainstream of ophthalmic and pediatric oncology but also provides a standardized primary tumor (T), regional lymph node (N), systemic metastasis (M) framework for RB communication worldwide. The AJCC system has been adopted by the Union for International Cancer Control and is thus accepted by medical oncology, radiation oncology, and medical journals around the world.<sup>17-20</sup>

The AJCC staging systems serve to standardize data reporting, case-to-case prognostication, and selection of the most suitable treatments.<sup>16</sup> In addition, the AJCC RB staging system not only provides TNM information but also uniquely adds a new AJCC category heritable trait (H). Based on medical evidence and thus accepted by the AJCC, the H designation includes the presence of a germline mutation as a risk factor for cancer-related mortality. The AJCC Cancer Staging Manual, 8th edition staging for RB serves as a complete intraocular, extraocular, and systemic disease classification system that simplifies outcome reporting. In contrast to the prior classification systems, it was constructed to predict metastatic risk and patient survival. We present a foundational multicenter, international study to evaluate the potential of the 8th edition of the AJCC Cancer Staging System to predict metastasis-related mortality based on tumor category. In addition, we compared AJCC RB staging with prior existing RB classifications for metastatic risk and patient survival. Comparisons for local treatment efficacy and globe salvage can be found in Part II of this series.

## Methods

Patients were diagnosed with RB from January 5, 2001, to December 31, 2013. Data were collected and entered into a secure online database. This study adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996.

All participating centers obtained internal institutional review board approval to perform retrospective medical record reviews and contribute de-identified data to the AJCC Ophthalmic Oncology Task Force Retinoblastoma Registry. The Princess Margaret Cancer Center determined, and all centers agreed that individual patient consent was not required because there were no patient identifiers collected in this retrospective study. Each participating site was an ophthalmic oncology subspecialty center, and the patients were diagnosed and treated as per the best practices defined by each institute. Patient records were excluded from analysis if key variables, such as demographic data, presenting clinical variables, treatment data, and outcome, were missing or inconsistent.

## The Registry

An internet-based, retrospective registry was created to evaluate the staging system for RB in the 8th edition of the AJCC Cancer Staging Manual.<sup>16</sup> Through a consensus process, retinoblastoma AJCC Ophthalmic Oncology Task Force committee members (primarily ophthalmic oncologists and pathologists) developed epidemiological, clinical, and pathological data fields. The scope of the present study was limited to the evaluation of 8th edition AJCC TNMH staging with regard to the risk of metastasis and RB-related mortality.

## Internet Database and Security

Secure data storage met international standards for patient privacy protection and statistical analysis. Security measures included the lack of personal patient identifiers, Secure Sockets Layer encryption, protection against Structured Query Language injection, variable and session management, record locking, and trail auditing (e.g., failed login attempts and webpage accessing). In addition, access to the online survey required user accounts issued by the

Table 1. The American Joint Committee on Cancer 8th Edition TNM Classification for Retinoblastoma<sup>16</sup>

Definitions for Primary Tumor Staging (cT)	
cTX	Unknown evidence of intraocular tumor
cT0	No evidence of intraocular tumor
cT1	Intraocular tumor(s) with subretinal fluid $\leq 5$ mm from the base of any tumor
cT1a	Tumors $\leq 3$ mm and farther than 1.5 mm from the disc and fovea
cT1b	Tumors $> 3$ mm or closer than 1.5 mm to the disc and fovea
cT2	Intraocular tumor(s) with retinal detachment, vitreous seeding, or subretinal seeding
cT2a	Subretinal fluid $> 5$ mm from the base of any tumor
cT2b	Tumors with vitreous seeding or subretinal seeding
cT3	Advanced intraocular tumor(s)
cT3a	Phthisis or pre-phthisis bulbi
cT3b	Tumor invasion of the pars plana, ciliary body, lens, zonules, iris, or anterior chamber
cT3c	Raised intraocular pressure with neovascularization or buphthalmos
cT3d	Hyphema or massive vitreous hemorrhage
cT3e	Aseptic orbital cellulitis
cT4	Extraocular tumor(s) involving the orbit, including the optic nerve
cT4a	Radiologic evidence of retrobulbar optic nerve involvement or thickening of the optic nerve or involvement of the orbital tissues
cT4b	Extraocular tumor clinically evident with proptosis and orbital mass
Definitions for Regional Lymph Node Staging (cN)	
cNX	Regional lymph nodes cannot be assessed
cN0	No regional lymph node involvement
cN1	Evidence of preauricular, submandibular, and cervical lymph node involvement
Definitions for Distant Metastasis Staging (M)	
cM0	No signs or symptoms of intracranial or distant metastasis
cM1	Distant metastasis without microscopic confirmation
cM1a	Tumor(s) involving any distant site (e.g., bone marrow, liver) on clinical or radiologic tests
cM1b	Tumor involving the CNS on radiologic imaging (not including trilateral RB)
pM1	Distant metastasis with microscopic confirmation
pM1a	Histopathologic confirmation of tumor at any distant site (e.g., bone marrow, liver, or other)
pM1b	Histopathologic confirmation of tumor in the cerebrospinal fluid or CNS parenchyma
Definitions for Heritable Trait Staging (H)	
HX	Unknown or insufficient evidence of a constitutional RB1 gene mutation
H0	Normal RB1 alleles in blood tested with demonstrated high sensitivity assays
H1	Bilateral RB, RB with an intracranial CNS midline embryonic tumor (i.e., trilateral RB), patient with family history of RB, or molecular definition of constitutional RB1 gene mutation
Definitions for Pathological Tumor Staging (pT)	
pTX	Unknown evidence of intraocular tumor
pT0	No evidence of intraocular tumor
pT1	Intraocular tumor(s) without any local invasion, focal choroidal invasion, or pre- or intralaminar involvement of the optic nerve head
pT2	Intraocular tumor(s) with local invasion
pT2a	Concomitant focal choroidal invasion and pre- or intralaminar involvement of the optic nerve head
pT2b	Tumor invasion of stroma of iris or trabecular meshwork or Schlemm's canal
pT3	Intraocular tumor(s) with significant local invasion
pT3a	Massive choroidal invasion ( $> 3$ mm in largest diameter, or multiple foci of focal choroidal involvement totaling $> 3$ mm, or any full-thickness choroidal involvement)
pT3b	Retrolaminar invasion of the optic nerve head, not involving the transected end of the optic nerve
pT3c	Any partial-thickness involvement of the sclera within the inner two-thirds
pT3d	Full-thickness invasion into the outer third of the sclera or invasion into or around emissary channels
pT4	Evidence of extraocular tumor: tumor at the transected end of the optic nerve, tumor in the meningeal spaces around the optic nerve, full-thickness invasion of the sclera with invasion of the episclera, adjacent adipose tissue, extraocular muscle, bone, conjunctiva, or eyelids

CNS = central nervous system; RB = retinoblastoma.

coordinating center. Each center could only access records pertinent to their site. When documentation of approval from the local ethics committee was received by the coordinating center, unique

login passwords were provided to initiate patient entry. All data were deidentified at the local center, where a random study identifier was generated for each patient.

## Definitions

Each center used its own diagnostic and therapeutic methods. Data collected included date of diagnosis, age at diagnosis (months), hereditary pattern (familial, sporadic), laterality (unilateral, bilateral), and the eye involved (right, left). The clinical information included intraocular pressure, presence of macroscopic anterior chamber seeding, and neovascularization of the iris. Reese-Ellsworth, CHLA (IIRC), WEH (ICRB), IRSS, and TNMH staging of RB were noted for each eye. The terms “CHLA” and “WEH” were preferred in this study instead of IIRC and ICRB, respectively, to prevent any ambiguity in these 2 similar-sounding but distinct classification systems and to avoid confusion for the readers. For bilateral RB (by AJCC convention), the worse eye tumor category was attributed to the overall clinical (cT) and pathological (pT) category for survival analysis. A similar approach was used for CHLA and WEH, where the worse eye group (A to E) was attributed to the patient for survival analysis. This analysis was performed for comparative statistical analysis and does not suggest use of these prior classifications when predicting patient survival.

Treatment details were noted. Information regarding the outcome included the occurrence of metastasis, date of detection of metastasis, and site of metastasis. The final patient outcome (alive without metastasis, alive with metastasis, alive with second malignant neoplasm, dead with metastasis, dead with second malignant neoplasm, dead because of other causes, or lost to follow-up), the date of the last follow-up, and the duration of follow-up were noted. All patients with central nervous system metastasis who were lost to follow-up were considered deceased and included in the metastasis-related mortality analysis. The patients whose treatment was discontinued by request of their guardians and were lost to follow-up and eventually were noted to have died of the disease were also included in metastasis-related mortality. All other non-metastasis-related deaths were noted but censored from the analysis.

## TNMH Retinoblastoma Staging

The primary tumor extent, node, metastasis, and heritable trait, as well as the anatomic and prognostic groups, were defined in accordance with the 8th edition of the AJCC Cancer Staging Manual on RB (Table 1).<sup>16</sup> The registry data fields and collection predated AJCC 8th edition. Thus, we used the raw clinical data to

classify all the cases accurately by AJCC 8th edition. Data were available for all necessary fields except the following: (1) involvement of pars plana and ciliary body (cT3b); (2) distinction between cT4 subcategories (radiologic vs. overt orbital involvement); and (3) data regarding pT2b (anterior segment involvement) were not recorded.

## Statistical Analysis

Continuous variables were described using medians, ranges, and interquartile ranges (IQRs), and categorical variables were described using frequencies and proportions. Log-rank tests for trend, Kaplan–Meier plots, and Cox proportional hazards regression models were implemented to test for evidence suggesting that tumor category is related to metastasis. Cumulative proportions of surviving patient estimates at 1, 5, and 10 years were tabulated. SPSS Version 23.0 (SPSS Inc., Chicago, IL) was used to generate Kaplan–Meier plots and to perform all other statistical analyses. Statistical significance was set at  $P < 0.05$ , and no adjustments were made for multiple tests.

## Results

In this study, 2190 patients were enrolled between January 2001 and December 2013. Eighteen eye cancer specialty centers from 13 countries in more than 6 continents successfully entered data online into our internet-based registry. A total of 105 patients were excluded because of incomplete data. Thus, complete records for analysis were available for 2085 patients (95.2%) and 2905 RB-affected eyes.

## Patient Features

The median age at diagnosis was 17.0 months (mean, 21.6; standard deviation [SD], 20.9; IQR, 8–29; range, 1–365 months). Of the 1928 patients, 1260 (65.4%) had unilateral RB and 668 (35.6%) had bilateral RB. Among the patients with unilateral RB, the right eye was involved in 734 (51.9%). As expected, the patients with unilateral RB were older at presentation than the bilateral RB. The number of patients who presented at an age of less than 12 months was 826 (39.6%), less than 36 months was 1770 (84.9%), and more than 8 years was 18 (0.80%) (Fig 1). A genetic test for RB1 pathogenic variant was

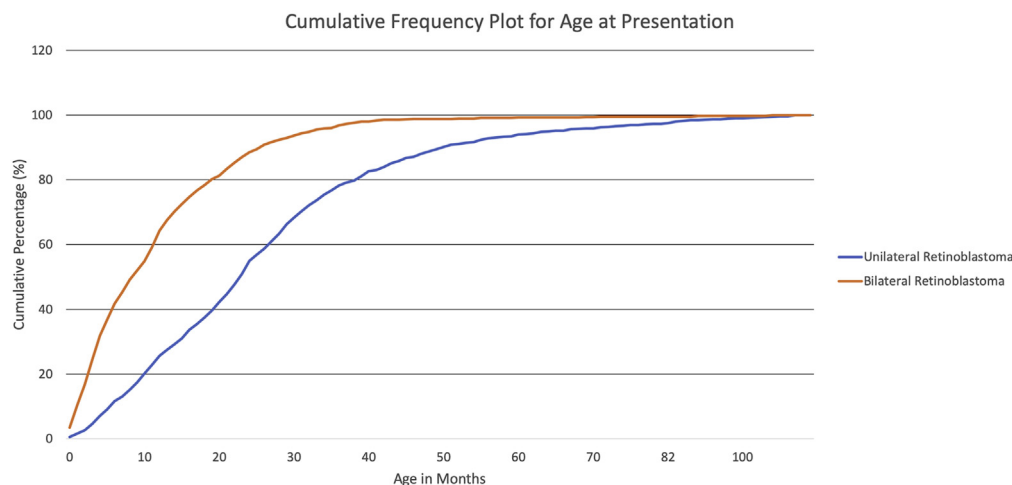


Figure 1. Cumulative frequency plot for age at presentation for 2085 patients with retinoblastoma.

Table 2. Classification of Eyes and Patients Based on Different Retinoblastoma Classification Systems

Reese-Ellsworth Classification (N = 1262 eyes) <sup>13</sup>	Number	% of Total
Data not available	1462	
Group Ia: <4 disk diameters behind equator; solitary tumor	102	8.1%
Group Ib: <4 disk diameters behind equator; multiple tumor	66	5.3%
Group IIa: 4–10 disk diameters behind equator; solitary tumor	61	4.9%
Group IIb: 4–10 disk diameters behind equator; multiple tumor	58	4.6%
Group IIIa: any tumor anterior to equator	89	7.0%
Group IIIb: solitary tumor >10 disk diameters behind equator	37	2.9%
Group IVa: multiple tumors, some more >10 disk diameters	48	3.8%
Group IVb: any tumor anterior to ora serrata	43	3.4%
Group Va: massive tumors seeding more than half the retina	312	24.7%
Group Vb: vitreous seeding	446	35.3%
<b>International Intraocular Retinoblastoma Classification (Children's Hospital of Los Angeles) (N = 2866 eyes)<sup>11</sup></b>		
Data not available	19	
Group A	176	6.1%
Group B	476	16.5%
Group C	212	7.3%
Group D	1119	38.8%
Group E	903	31.3%
<b>International Classification of Retinoblastoma (Wills Eye Hospital) (N = 2866 eyes)<sup>10</sup></b>		
Data not available	19	
Group A	188	6.5%
Group B	602	20.8%
Group C	40	1.4%
Group D	281	9.7%
Group E	1775	61.6%
<b>International Retinoblastoma Staging System (N = 958 patients)<sup>12</sup></b>		
Data not available	1127	
0, Patient treated conservatively	287	30.0%
I, Eye enucleated; tumor completely resected	605	63.2%
II, Eye enucleated; microscopic residual tumor	35	3.7%
IIIa, Overt orbital disease	11	1.1%
IIIb, Preauricular or cervical node tumor	2	0.2%
IVa1, Hematogenous metastasis without CNS disease, single lesion	2	0.2%
IVa2, Hematogenous metastasis without CNS disease, multiple lesion	3	0.3%
IVb1, CNS disease (± other metastasis); prechiasmatal	3	0.3%
IVb2, CNS disease (± other metastasis); CNS mass	2	0.2%
IVb3, CNS disease (± other metastasis); leptomeningeal and CSF	8	0.8%

CNS = central nervous system; CSF = cerebrospinal fluid.

performed on 44 patients (2.1%), and 14 (31%) of them were found positive.

## Classifications

The proportions of the same registry eyes staged by the different classifications/staging schema illustrate the different features of the 5 schemas. The Reese-Ellsworth classification<sup>13</sup> was reported in 1262 eyes as follows: A total of 168 eyes were in group I (13.3%); 119 eyes were in group II (9.4%); 126 eyes were in group III (10.0%); 91 eyes were in group IV (7.3%); 758 eyes were in group V (60.0%). Data were not available for 1643 eyes (Table 2).

The CHLA (IIRC)<sup>11</sup> was reported in 2886 eyes as follows: A total of 176 eyes were in group A (6.1%); 476 eyes were in group B (16.5%); 212 eyes were in group C

(7.3%); 1119 eyes were in group D (38.8%); 903 eyes were in group E (31.3%). Data were not available for 19 eyes (Table 2).

The WEH (ICRB)<sup>10</sup> was reported in 2886 eyes as follows: A total of 188 eyes were in group A (6.5%); 602 eyes were in group B (20.8%); 40 eyes were in group C (1.4%); 281 eyes were in group D (9.7%); 1775 eyes were in group E (61.6%). Data were not available for 19 eyes (Table 2).

The IRSS<sup>12</sup> was reported in 958 patients as follows: A total of 287 had stage 0 (30.0%); 605 had stage 1 (63.2%); 35 had stage 2 (3.7%); 11 had stage 3A (1.1%); 2 had stage 3B (0.2%); 2 had stage 4A1 (0.2%); 3 had stage 4A2 (0.3%); 3 had stage 4B1 (0.3%); 2 had stage 4B2 (0.2%); 11 had stage 4B3 (0.8%). Data were unavailable for 1127 patients (Table 2).



Table 3. Classification of Eyes and Patients per American Joint Committee on Cancer 8th Edition TNM Classification for Retinoblastoma<sup>16</sup>

Primary Tumor (cT)		
<i>N</i> = 2905 eyes	<i>N</i>	%
Data not available	0	
cT1a	232	8.0%
cT1b	466	16.0%
cT2a	284	9.8%
cT2b	1071	36.9%
cT3a	28	1.0%
cT3b	125	4.3%
cT3c	414	14.3%
cT3d	211	7.3%
cT3e	52	1.8%
cT4	22	0.8%
<i>N</i> = 2085 patients	<i>N</i>	%
cT1a	55	2.6%
cT1b	168	8.1%
cT2a	197	9.4%
cT2b	812	38.9%
cT3a	22	1.1%
cT3b	166	8.0%
cT3c	389	18.7%
cT3d	203	9.7%
cT3e	51	2.4%
cT4	18	0.9%
Regional Lymph Nodes (cN)		
<i>N</i> = 2085 patients	<i>N</i>	%
cNX	1358	65.1%
cN0	715	34.3%
cN1	12	0.6%
Distant Metastasis (M)		
<i>N</i> = 2085 patients	<i>N</i>	%
cMX	1378	66.1%
cM0	682	32.7%
cM1a	13	0.6%
cM1b	12	0.6%
Pathological Tumor (pT)		
<i>N</i> = 1353 patients	<i>N</i>	%
0	0	
pT1	491	36.3%
pT2a	466	34.4%
pT2b	Data not available	
pT3a	106	7.8%
pT3b	156	11.5%
pT3c	50	3.7%
pT3d	11	0.8%
pT4	73	5.4%
Heritable trait (H)		
<i>N</i> = 2085 patients	<i>N</i>	%
H0	1329	63.7%
H1	756	36.3%

## American Joint Committee on Cancer Classification

Compared with the aforementioned classification systems, the 8th edition AJCC Classification includes more complex information about the patients' primary tumor, regional lymph node spread, metastatic disease, and heredity.<sup>16</sup> These are described next.

## American Joint Committee on Cancer Clinical Classification

The eye-level clinical tumor category (cT) in 2905 eyes was as follows: cT1 in 698 (24.0%); cT2 in 1355 (46.6%); cT3 in 830 (28.6%); cT4 in 22 (0.8%). The patient-level clinical tumor category (cT) for 2085 patients were as follows: cT1a in 55 (2.6%); cT1b in 168 (8.1%); cT2a in 197 (9.4%); cT2b in 812 (38.9%); cT3 in 835 (40.0%); cT4 in 18 (0.9%) (Table 3).

## American Joint Committee on Cancer Pathological Classification

Of the 2905 eyes, 1397 eyes (48.1%) of 1353 patients were treated with enucleation. Of these, 44 patients had bilateral enucleation (0.1%). The patient-level pathological tumor category (pT) in 1353 patients was as follows: pT1 in 491 (36.3%); pT2 in 466 (34.4%); pT3 in 323 (23.9%); pT4 in 73 (5.4%) (Table 3).

## American Joint Committee on Cancer Nodes, Metastasis, and Heritable Trait

According to the regional lymph node involvement classification (cN), 12 patients (0.6%) were reported as cN1. The lymph nodes involved were preauricular, cervical, or submandibular. According to the distant metastasis classification (cM) of the 2085 patients, 13 were cM1a (0.6%), including 3 patients with distant lymph nodes and 12 patients with central nervous system metastasis and thus cM1b (0.6%) at presentation.

According to the AJCC rules, we classified heritable trait (H) by considering bilateral disease, family history of RB, presence of pinealoblastoma, and presence of pathogenic RB variant on genetic testing. Thus, of the 2085 patients, heritable trait was seen in 756 (36.3%) (Table 3).

An additional 84 patients developed metastasis over the median follow-up period of 48.0 months (mean, 53.80; SD, 41.50; IQR, 20–79 months). The median time to metastasis in 92 patients was 9.5 months (mean, 13.7; SD, 13.6; IQR, 4–19.8 months). The different sites to metastasis were distant lymph nodes, bone, bone marrow, and central nervous system (including cerebrospinal fluid, leptomeninges, pre- and postchiasmatic central nervous system sites). Multiorgan metastasis was seen in 34 of 109 patients (31.2%).

Table 4. Kaplan-Meier Cumulative Proportion of Surviving Patients for AJCC Clinical T Category, CHLA, and WEH Classification for 2085 Patients with Retinoblastoma

Classification	Variable	Kaplan–Meier Point Estimates (95% CI), %		
		1 Yr	5 Yrs	10 Yrs
CHLA Classification (n = 2085)	All patients (n = 2085)	95 (94–96)	95 (94–96)	93 (92–94)
	A (n = 27)	100	100	100
	B (n = 178)	100	98 (97–99)	97 (95–99)
	C (n = 112)	99 (98–100)	99 (98–100)	99 (98–100)
	D (n = 904)	98	97 (96–98)	97 (96–98)
WEH Classification (n = 2080)	E (n = 864)	90 (89–91)	88 (87–89)	88 (87–89)
	A (n = 29)	100	100	100
	B (n = 240)	100	100	99 (98–100)
	C (n = 26)	100	100	100
	D (n = 195)	100	100	100
AJCC cT size category (n = 2085)	E (n = 1590)	94 (93–95)	91(90–92)	91 (90–92)
	cT1a (n = 55)	100	100	100
	cT1b (n = 168)	100	98 (97–99)	96 (94–98)
	cT2a (n = 197)	99 (98–100)	98 (97–99)	98 (97–99)
	cT2b (n = 812)	98 (97–99)	96 (95–97)	96 (95–97)
	cT3 (n = 835)	91 (90–92)	89 (88–90)	89 (88–90)
	cT4 (n = 18)	63 (51–75)	45 (31–59)	Not available

For CHLA classification.  
Overall comparison: Wilcoxon  $P < 0.001$ .

Pairwise Comparison	A	B	C	D
A				
B	0.559			
C	0.621	0.904		
D	0.400	0.228	0.312	
E	0.064	<0.001	=0.001	<0.001

For WEH classification  
Overall comparison: Wilcoxon  $P < 0.001$

Pairwise Comparison	A	B	C	D
A				
B	0.787			
C	N/A	0.625		
D	N/A	0.317	N/A	
E	0.117	<0.001	0.126	<0.001

For cT category  
Overall comparison: Wilcoxon  $P < 0.001$

Pairwise Comparison	cT1a	cT1b	cT2a	cT2b	cT3
cT1a					
cT1b	0.343				
cT2a	0.368	0.880			
cT2b	0.198	0.182	0.250		
cT3	0.011	<0.001	<0.001	<0.001	
cT4	<0.001	<0.001	<0.001	<0.001	<0.001

Kaplan–Meier Cumulative Proportion of Surviving Patients for AJCC Pathological T Category for 1353 Patients with Retinoblastoma

Variable	Kaplan–Meier Point Estimates, % (95% CI)		
	1 Yr	5 Yrs	10 Yrs
All patients (N = 1353)	96 (95–97)	94 (95–96)	94 (93–95)
pT1 (N = 491)	99	99	98 (97–99)
pT2 (N = 466)	99	98 (97–99)	98 (97–99)
pT3 (N = 323)	94 (93–95)	91 (89–93)	91 (89–93)

(Continued)

Table 4. (Continued.)

Variable	Kaplan–Meier Point Estimates, % (95% CI)		
	1 Yr	5 Yrs	10 Yrs
pT4 (N = 73)	61 (55–67)	48 (41–55)	48 (41–55)
Overall comparison: $P < 0.001$			
Pairwise comparison (P value)	pT3a	pT3b	pT3c
pT3a			
pT3b	$P = 0.109$		
pT3c	$P = 0.403$	$P = 0.645$	
pT3d	$P < 0.001$	$P = 0.004$	$P = 0.008$

AJCC = American Joint Committee on Cancer 8th edition; CHLA = Children’s Hospital of Los Angeles; CI = confidence interval; N/A = not available; WEH = Wills Eye Hospital.

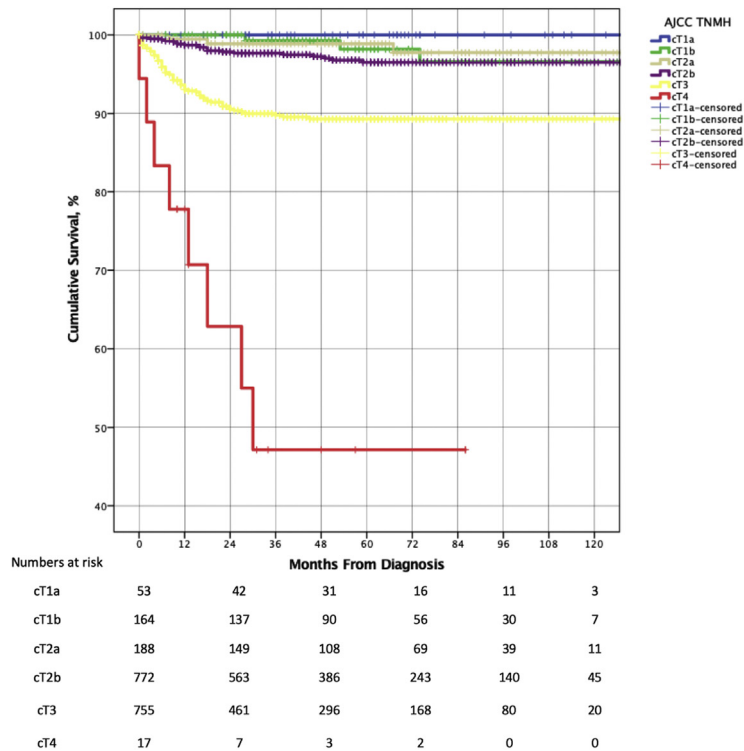
**Multiple Cancers**

Twenty-one patients with RB (1.0%, 19 patients with bilateral and 2 patients with unilateral) were noted to have multiple cancers at diagnosis or during follow-up. The tumors were pineal (trilateral RB) tumor in 15 patients (0.8%, 71% of other cancers) and olfactory neuroblastoma, acute myeloid leukemia, acute lymphoid leukemia, osteosarcoma, rhabdomyosarcoma, and palate and maxillary sinus sarcoma in 1 patient each.

**Cumulative Proportion Estimates of Survival According to Initial cTNM**

Of the 2085 patients, 109 (5.2%) developed metastatic disease and eventually died of the disease. The median time from presentation to development of metastasis in 92 patients was 9.50 months (mean, 13.7; SD, 13.6, IQR, 4.0–19.8). According to the AJCC criteria, of the 109 patients who developed metastasis, 3 (2.7%) were cT1b, 3 (2.7%) were cT2a, 22 (20.2%) were cT2b, 73 (67.0%) were

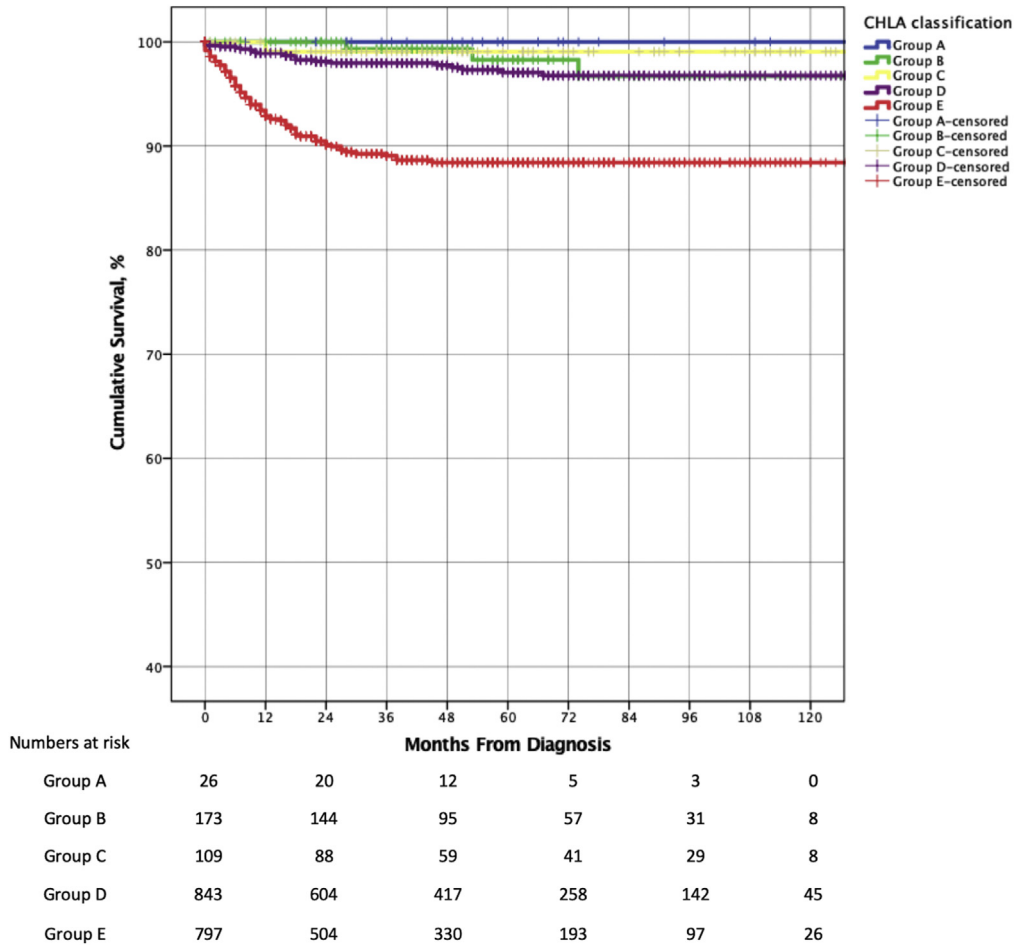
**Cumulative Survival of Retinoblastoma Patients Based on AJCC Clinical T (cT) Category**



**Figure 2.** Kaplan–Meier curves of cumulative survival estimates for 2085 patients, classified by American Joint Committee on Cancer (AJCC) Clinical Tumor (cT) category for retinoblastoma.



## Cumulative Survival of Retinoblastoma Patients Based on Children Hospital Los Angeles Classification (CHLA)



**Figure 3.** Kaplan–Meier curves of cumulative survival estimates for 2085 patients, classified by Children Hospital Los Angeles (CHLA) classification for retinoblastoma.

cT3, and 8 (7.3%) were cT4. The 5-year Kaplan–Meier cumulative survival estimates by clinical tumor categories were 100% for category cT1a, 98% (95% confidence interval [CI], 97–99) for cT1b and cT2a, 96% (95% CI, 95–97) for cT2b, 89% (95% CI, 88–90) for cT3, and 45% (95% CI, 31–59) for cT4. Increasing tumor category translated to increased risk of metastasis-related mortality and decreased survival ( $P < 0.001$ , log-rank test for trend). Pairwise comparison showed a significant difference between all categories except between cT1 and cT2 (Table 4 and Figs 2–4).

### Cumulative Proportion Estimates of Survival According to Initial pTNM

Of the 1353 patients who underwent enucleation, 69 (5.1%) developed metastatic disease and eventually died of the disease. According to the AJCC criteria, of the 69 patients who developed metastasis, 4 (5.8%) had pT1, 9 (13%) had pT2, 24 (34.8%) had pT3, and 32 (46.4%) had pT4. The 5- and 10-year Kaplan–Meier cumulative survival estimates

by tumor categories were 99% and 98% (95% CI, 97–99) for pT1 tumors, 98% (95% CI, 97–99) (both 5 and 10 years) for pT2 tumors, 91% (95% CI, 89–93; both 5 and 10 years) for pT3 tumors, and 48% (95% CI, 41–55; both 5 and 10 years) for pT4 tumors, respectively. Increasing tumor category was consistent with increased risk of metastasis-related mortality and decreased survival ( $P < 0.001$ ), log-rank test for trend (Table 4 and Fig 5).

### Cox Proportional Hazards Regression Analysis

In this study, age (hazard ratio [HR], 1.09; 95% CI, 1.01–1.16;  $P = 0.016$ ), tumor laterality (HR, 1.09; 95% CI, 0.74–1.61;  $P = 0.661$ ), and presence of heritable trait (HR, 1.06; 95% CI, 0.72–1.57;  $P = 0.750$ ) did not influence the incidence of metastatic disease on Cox proportional hazard regression analysis. Patients with cT3 (HR, 8.09; 95% CI, 2.55–25.70;  $P < 0.001$ ) and cT4 categories (HR, 48.55; 95% CI, 12.86–183.27;  $P < 0.001$ ) had greater risk of metastasis compared with those with cT1 (Table 5).

### Cumulative Survival of Retinoblastoma Patients Based on Wills Eye Hospital Classification (WEH)

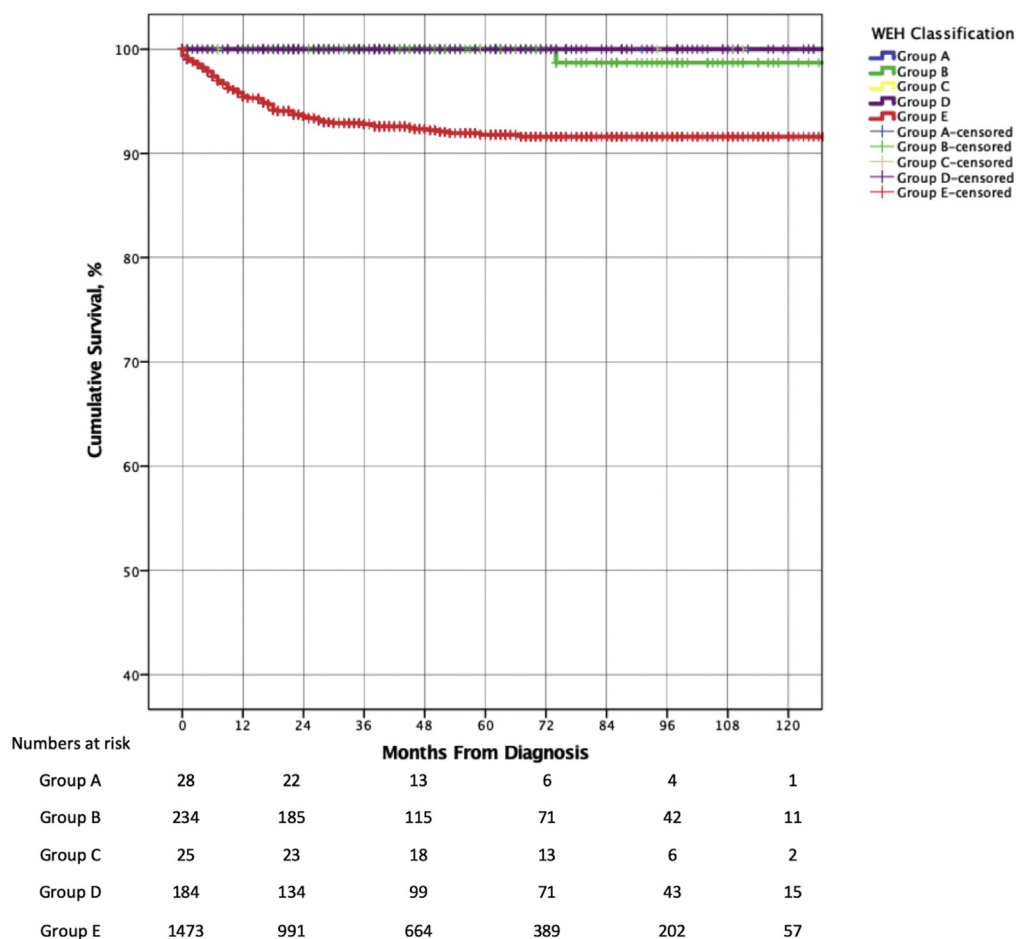


Figure 4. Kaplan–Meier curves of cumulative survival estimates for 2085 patients, classified by Wills Eye Hospital (WEH) classification for retinoblastoma.

Likewise, patients with pT3 (HR, 9.76; 95% CI, 3.38–28.13;  $P < 0.001$ ) and pT4 categories (HR, 77.26; 95% CI, 27.28–218.77;  $P < 0.001$ ) had significantly higher risk of metastasis compared with those with pT1 (Table 5).

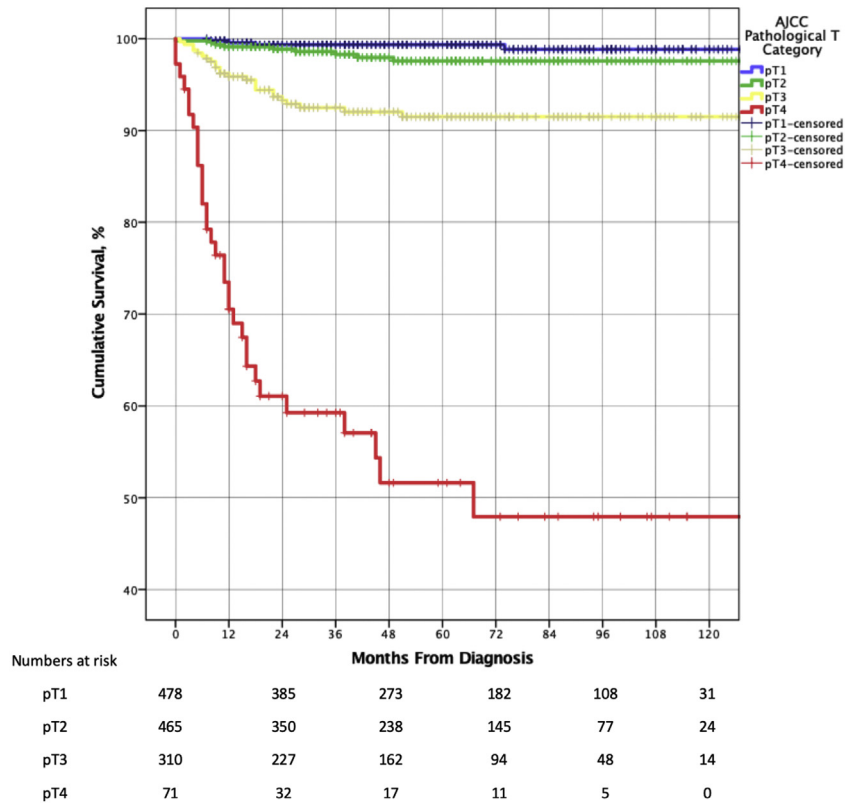
### Discussion

This study included patients from many of the largest international RB subspecialty centers and smaller national and regional referral RB centers. Their participation allowed for inclusion of worldwide data and thus an unusually diverse sampling of patients. These numbers were large enough to obtain statistically significant results. We used the multicenter, international, internet-based registry to retrospectively validate the 8th edition of the AJCC Cancer Staging Manual system for RB. That is, we confirm that

increasing AJCC cT and pT categories were significantly related to increased risk of metastasis-related mortality. Specifically, as the tumor category increased from cT1 to cT4, the odds of metastasis increased exponentially. This study revealed an 8.09-fold risk for cT3 and a greater than 48.55-fold risk for cT4 compared with cT1. As found in enucleated eyes, the presence of the high-risk features categorized as pT3 or pT4 was associated with higher risks of metastasis and should prompt metastasis screening.

Classification for a disease is necessary for appropriate management strategies and predicting prognosis. But the use of multiple classification systems has led to confusion and miscommunication that undermine RB research and patient care.<sup>15</sup> For example, the Reese-Ellsworth classification, introduced to stage the results of external beam radiation therapy, became rarely used as that modality waned. Likewise, the CHLA and WEH classifications were primarily introduced to predict globe salvage after systemic

## Cumulative Survival of Patients Based on AJCC Pathological T (pT) Category



**Figure 5.** Kaplan–Meier curves of cumulative survival estimates for 1353 patients, classified by American Joint Committee on Cancer (AJCC) pathological tumor (pT) category for retinoblastoma.

chemotherapy and not to calculate metastatic risk and life prognosis. Both had the same “A” to “E” classification scheme with subtle but significant criteria differences, leading to non-comparable results.<sup>10,11</sup>

Although helpful for treatment-specific outcome prediction, these classification systems were developed by single centers and largely based on a single author’s experience or small group consensus. They have not been validated by published large multicenter studies. The disparity between them is elucidated in our results in which the same cohort had 31.3% eyes classified in group E as per CHLA classification and 61.6% as per WEH classification (Table 2). When comparing these with the TNM classification, cT3 resembles most closely group E and includes 39.9% of all eyes. Unfortunately, the majority of studies stratifying globe salvage rates by WEH or CHLA classification fail to specify which version was used.<sup>15</sup>

To focus on patients with RB with extraocular extension, the IRSS emphasizes the presence and risk of extraocular relapse.<sup>12</sup> In contrast, the AJCC TNMH classification encompasses the whole spectrum of RB disease and is thus multifunctional. To include these aspects, the lead authors of the IRSS were invited to participate in writing the 8th edition AJCC RB staging system.

The regional epidemiology of RB has been discussed in multiple studies.<sup>21–23</sup> However, ours is the first multicenter

study, with patients from all 6 continents who have been uniformly classified within a single classification system, that provides an assessment of the risk of metastasis and loss of life. The finding that the cumulative survival proportion with respect to tumor categories showed a steep decline from cT1a (100%) to cT4 (45%) and from pT1 (99%) to pT4 (48%) at the 5-year follow-up supports the validity of the 8th edition AJCC staging system. When compared with CHLA and WEH, the AJCC TNMH classification shows a better tumor stratification in terms of risk for metastasis-related mortality. Therefore, this study shows that AJCC-TNMH is superior for predicting RB metastasis and thus provides evidence that clinical and research groups should switch from CHLA and WEH to AJCC staging.

In this study, we show that a drastic increase in the risk of metastasis was associated with increased tumor volume and presence of extraocular disease. For example, in an eye treated with enucleation, risk of metastatic RB is maximum with pT3d (50-fold) and pT4 (77-fold) compared with an intraocular tumor without any local invasion (pT1). Clearly, prognosis of patients with RB worsens drastically once RB breaches the ocular coats.<sup>24</sup> Other risk factors hypothesized for increasing the metastatic risk include lower age at diagnosis, tumor laterality, presence of heritable trait, and trilateral RB.<sup>24,25</sup> In contrast, Cox proportional hazards

Table 5. Cox Proportional Hazard Regression Models

Cox Proportional Hazards Regression Model for Association of Age, Tumor Laterality, and H Category with Metastatic Mortality				
Variable	Patients in Category, No. (%) (N =2085)	Reference	HR (95% CI)	P Value
Age	2085 (100.0%)	1-yr increment	1.09 (1.01–1.16)	0.016
Bilateral	748 (35.9%)	Unilateral	1.09 (0.74–1.61)	0.661
H1	756 (36.3%)	H0	1.06 (0.72–1.57)	0.750
Cox Proportional Hazards Regression Model for Association of AJCC Clinical T (cT) Category with Metastatic Mortality				
Variable	Patients in Category, No. (%) (N =2085)	Reference	HR (95% CI)	P Value
cT2	1010 (48.4%)	cT1	2.05 (0.62–6.80)	0.24
cT3	831 (39.9%)	cT1	8.09 (2.55–25.70)	<0.001
cT4	18 (0.9%)	cT1	48.55 (12.86–183.27)	<0.001
Cox Proportional Hazards Regression Model for Association of AJCC Pathological T (pT) Category with Metastatic Mortality				
Variable	Patients in Category, No. (%) (N =1353)	Reference	HR (95% CI)	P Value
pT2	466 (34.4%)	pT1	2.42 (0.75–7.87)	0.140
pT3	323 (23.9%)	pT1	9.76 (3.38–28.13)	<0.001
pT4	73 (5.4%)	pT1	77.26 (27.28–218.77)	<0.001
Cox Proportional Hazards Regression Model for Association of AJCC Pathological T3 Subcategory (pT) Category with Metastatic Mortality				
Variable	Patients in Category, No. (%) (N =1353)	Reference	HR (95% CI)	P Value
pT3a	106 (7.8%)	pT1	4.89 (1.22–19.56)	0.020
pT3b	156 (11.5%)	pT1	10.90 (3.55–33.44)	<0.001
pT3c	50 (3.7%)	pT1	8.12 (1.82–36.28)	0.006
pT3d	11 (0.8%)	pT1	49.74 (12.44–198.9)	<0.001

AJCC = American Joint Committee on Cancer 8th edition; CI = confidence interval; HR = hazard ratio.

regression analysis showed that younger age, laterality, and presence of heritable traits do not significantly influence the risk of metastasis.

Limitations of our study are based on the inherent nature of data entry from 2001 to 2013 (before the 8th edition TNMH RB staging). The retrospective design of the study is also a limitation. Although we did not ask for data regarding patient sex and ethnic/racial backgrounds, the data were collected from 6 continents and thus sourced from a diverse group of patients. The data fields did not include the pars plana and ciliary body involvement, which may have resulted in the depreciation of the cT3b subcategory. Another limitation was that cT4a and cT4b were not differentiated, which prevented that specific analysis for those TNM prognostic stage groups. Furthermore, genetic testing was performed on a small cohort of patients. This likely reflected the timing of data collection and the local availability of genetic services. Therefore, our H-status data may not accurately represent the presence of heritable traits in patients with unilateral RB. This bias could have led to an underestimation of its significance with respect to metastatic disease. The data regarding pT2b (anterior segment involvement) were not recorded, preventing analysis of anterior segment involvement as a risk factor for metastatic disease. The

data fields for IRSS data were incomplete for 1127 patients (54%); therefore, a meaningful comparison between AJCC and IRSS could not be performed. In that trilateral RB is classified separately in the AJCC system, it was not specifically registered in our study. Although mentioned as additional information in some reports, some of the trilateral tumors could have developed during later follow-up.

In review of the literature, a meta-analysis has suggested that the incidence of trilateral RB is 3.8% (among patients with bilateral RB).<sup>26</sup> Applied to our study, this would translate to approximately 25 patients. However, in our study, there were 668 bilaterally affected patients, and only 15 (2.2%) were found to have trilateral disease.

In conclusion, the 8th edition AJCC classification for RB was derived from evidence-based data and international consensus. This retrospective data analysis provided significant evidence that AJCC-RB staging can be used for predicting metastasis-associated mortality. However, a future independent prospective study could provide a more powerful independent validation of the AJCC-TNM staging system. We believe that the universal adoption of this classification system will clarify outcome reporting and improve research and patient care. We show that

international, multicenter, registry-based studies of rare cancers can be performed using internet-based data sharing. The 8th edition AJCC classification for RB was used to accurately estimate mortality related to metastatic disease.

## References

- Dimaras H, Corson TW, Cobrinik D, et al. *Retinoblastoma*. Nat Rev Dis Primer. 2015;1:15021.
- Young JL, Smith MA, Roffers SD, et al. Retinoblastoma. In: Ries LA, Smith MA, Gurney GJ, eds. Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995. NIH Publication No. 99-4649. Bethesda, MD: National Cancer Institute, SEER Program; 1999.
- Dimaras H, Kimani K, Dimba EAO, et al. Retinoblastoma. *Lancet Lond Engl*. 2012;379:1436–1446.
- Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol*. 2009;93:1129–1131.
- MacCarthy A, Draper GJ, Steliarova-Foucher E, Kingston JE. Retinoblastoma incidence and survival in European children (1978-1997). Report from the Automated Childhood Cancer Information System project. *Eur J Cancer Oxf Engl* 1990. 2006;42:2092–2102.
- Nyamori JM, Kimani K, Njuguna MW, Dimaras H. The incidence and distribution of retinoblastoma in Kenya. *Br J Ophthalmol*. 2012;96:141–143.
- Leal-Leal C, Flores-Rojo M, Medina-Sansón A, et al. A multicenter report from the Mexican Retinoblastoma Group. *Br J Ophthalmol*. 2004;88:1074–1077.
- Malempati S, Hawkins DS. Rhabdomyosarcoma: review of the Children's Oncology Group (COG) Soft-Tissue Sarcoma Committee experience and rationale for current COG studies. *Pediatr Blood Cancer*. 2012;59:5–10.
- Oberlin O, Rey A, Lyden E, et al. Prognostic factors in metastatic rhabdomyosarcomas: results of a pooled analysis from United States and European cooperative groups. *J Clin Oncol*. 2008;26:2384–2389.
- Shields CL, Mashayekhi A, Au AK, et al. The International Classification of Retinoblastoma predicts chemoreduction success. *Ophthalmology*. 2006;113:2276–2280.
- Linn Murphree A. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clin North Am*. 2005;18:41–53. viii.
- Chantada G, Doz F, Antoneli CBG, et al. A proposal for an international retinoblastoma staging system. *Pediatr Blood Cancer*. 2006;47:801–805.
- Reese AB, Ellsworth RM. The evaluation and current concept of retinoblastoma therapy. *Trans Am Acad Ophthalmol Otolaryngol*. 1963;67:164–172.
- Novetsky DE, Abramson DH, Kim JW, Dunkel IJ. Published international classification of retinoblastoma (ICRB) definitions contain inconsistencies—an analysis of impact. *Ophthalmic Genet*. 2009;30:40–44.
- Scelfo C, Francis JH, Khetan V, et al. An international survey of classification and treatment choices for group D retinoblastoma. *Int J Ophthalmol*. 2017;10:961–967.
- Mallipatna A, Gallie BL, Chévez-Barrios P, et al. Retinoblastoma. In: Amin MB, Edge SB, Greene FL, eds. *AJCC Cancer Staging Manual*. 8th ed. New York, NY: Springer; 2017:819–831.
- AJCC Ophthalmic Oncology Task Force. International Validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma. *JAMA Ophthalmol*. 2015;133:376–383.
- Finger PT; 7th Edition, AJCC-UICC Ophthalmic Oncology Task Force. The 7th edition AJCC staging system for eye cancer: an international language for ophthalmic oncology. *Arch Pathol Lab Med*. 2009;133:1197–1198.
- Jain P, Finger PT, Damato B, et al. Multicenter, International Assessment of the Eighth Edition of the American Joint Committee on Cancer Staging Manual for Conjunctival Melanoma. *JAMA Ophthalmol*. 2019;137:905–911.
- Ophthalmic Oncology Task Force. Local recurrence significantly increases the risk of metastatic uveal melanoma. *Ophthalmology*. 2016;123:86–91.
- Committee for the National Registry of Retinoblastoma. The National Registry of Retinoblastoma in Japan (1983-2014). *Jpn J Ophthalmol*. 2018;62:409–423.
- Wongmas P, Jetsrisuparb A, Komvilaisak P, et al. Incidences, trends and long term outcomes of retinoblastoma in three cancer registries, Thailand. *Asian Pac J Cancer Prev*. 2015;16:6899–6902.
- Chawla B, Hasan F, Azad R, et al. Clinical presentation and survival of retinoblastoma in Indian children. *Br J Ophthalmol*. 2016;100:172–178.
- Finger PT, Harbour JW, Karcioğlu ZA. Risk factors for metastasis in retinoblastoma. *Surv Ophthalmol*. 2002;47:1–16.
- de Jong MC, Kors WA, de Graaf P, et al. Trilateral retinoblastoma: a systematic review and meta-analysis. *Lancet Oncol*. 2014;15:1157–1167.
- de Jong MC, Kors WA, de Graaf P, et al. The incidence of trilateral retinoblastoma: a systematic review and meta-analysis. *Am J Ophthalmol*. 2015;160:1116–1126.e5.

## Footnotes and Financial Disclosures

Originally received: February 10, 2020.

Final revision: May 4, 2020.

Accepted: May 29, 2020.

Available online: June 6, 2020.

Manuscript no. D-20-00261.

<sup>1</sup> Department of Ocular Tumor and Orbital Disease, The New York Eye Cancer Center, New York, New York.

<sup>2</sup> The Eye Cancer Clinic, Princess Margaret Cancer Centre, Toronto, Ontario, Canada.

<sup>3</sup> Ocular Oncology Service, Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.

<sup>4</sup> Pediatric Oncology Center, Beijing Children's Hospital, Beijing, China.

<sup>5</sup> Department of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center, College of Medicine, Memphis, Tennessee.

<sup>6</sup> Department of Surgery, St. Jude Children's Research Hospital, Memphis, Tennessee.

<sup>7</sup> USC Roski Eye Institute, Keck Medical School of the University of Southern California, Los Angeles, California; The Vision Center at Children's Hospital Los Angeles, Los Angeles, California.

<sup>8</sup> Department of Vitreoretina Services, Sankara Nethralaya, Chennai, Tamil Nadu, India.

<sup>9</sup> Ocular Oncology Department, The S.N. Fyodorov Eye Microsurgery Federal State Institution, Moscow, Russian Federation.



<sup>10</sup> Department of Surgery (Ophthalmology), King Hussein Cancer Center, Amman, Jordan.

<sup>11</sup> Department of Ophthalmology and Vision Sciences, Hospital for Sick Children, Toronto, Canada.

<sup>12</sup> SRI of Pediatric Oncology and Hematology of N.N. Blokhin National Medical Research Center Oncology of Russian Federation, Moscow, Russian Federation.

<sup>13</sup> Medical Academy of Postgraduate Education, Moscow, Russian Federation.

<sup>14</sup> Department of Ophthalmology, Hospital Infantil de México Federico Gómez, Mexico City, Mexico.

<sup>15</sup> Precision Medicine Coordination Hospital JP Garrahan and CONICET, National Scientific and Technical Research Council, Buenos Aires, Argentina.

<sup>16</sup> Ophthalmology Service Hospital JP Garrahan, Buenos Aires, Argentina.

<sup>17</sup> Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Kowloon, Hong Kong.

<sup>18</sup> Save Sight Institute, Discipline of Ophthalmology, Sydney Medical School, University of Sydney, Sydney, Australia.

<sup>19</sup> KK Women's and Children's Hospital, Singapore.

<sup>20</sup> Ophthalmology Unit, Department of Surgery, School of Medicine and Dentistry, College of Health Sciences, University of Ghana, Accra, Ghana.

<sup>21</sup> Department of Child Health, University of Ghana Medical School, Accra, Ghana.

<sup>22</sup> Retinoblastoma Unit, Department of Ophthalmology, Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain.

<sup>23</sup> Retinoblastoma Unit, Department of Oncology, Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain.

\*The AJCC Ophthalmic Oncology Task Force members are listed in the Supplemental Appendix (available at [www.aajournal.org](http://www.aajournal.org)).

Financial Disclosure(s):

The author(s) have no proprietary or commercial interest in any materials discussed in this article.

T.T.K.: Received a governmental grant from the Helsinki University Hospital Research Fund.

A.S.T.: Received an ophthalmic oncology fellowship grant to study with Dr. Finger (from The Eye Cancer Foundation).

Supported by The Myrna and John Daniels Charitable Trust, the Paul Finger Fund (Canada), and The Helsinki University Hospital Research Fund (Finland). The Eye Cancer Foundation (USA) provided monetary support to the Princess Margaret Cancer Centre's Internet Technology Program, which has (in turn) participated in the design, construction, and maintenance of this RB registry. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Yuliya Gavrylyuk, MD, MHA, Princess Margaret Cancer Centre, Toronto, Ontario, Canada, assisted with multicenter institutional review board, ethics committee, privacy, and other contractual

relationships. Rachel C. Brenna, MD, and Michala Burges, BS, Department of Ophthalmology, Hamilton Eye Institute, University of Tennessee Health Science Center, College of Medicine, Memphis, Tennessee, Ekaterina Semenova, MD, Department of Ocular Tumor and Orbital Disease, The New York Eye Cancer Center, New York, New York, and Elisa Carreras, MD, Retinoblastoma Unit, Department of Oncology, Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain, assisted with data collection.

Writing Committee: Ankit S. Tomar, MD, Paul T. Finger, MD, Brenda Gallie, MD, Aswhin Mallipatna, MD, and Tero Kivelä MD. All authors participated in critical review of the manuscript before publication.

HUMAN SUBJECTS: Human subjects were included in this study. All research adhered to the tenets of the Declaration of Helsinki. All participating centers obtained internal Institutional Review Board approval to perform retrospective medical record reviews and contribute de-identified data to the AJCC Ophthalmic Oncology Task Force Retinoblastoma Registry. All participants provided informed consent.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Finger, Gallie

Data collection: Tomar, Finger, Gallie, Mallipatna, Kivelä, Zhang, Zhao, Wilson, Kim, Khetan, Ganesan, Yarovoy, Yarovaya, Kotova, Yousef, Nummi, Ushakova, Yugay, Polyakov, Ramirez-Ortiz, Esparza-Aguiar, Chantada, Schaiquevich, Fandino, Yam, Lau, Lam, Sharwood, Moorthy, Long, Essuman, Renner, Català, Correa-Llano

Analysis and interpretation: Tomar, Finger, Gallie, Mallipatna, Kivelä, Zhang, Zhao, Wilson, Kim, Khetan, Ganesan, Yarovoy, Yarovaya, Kotova, Yousef, Nummi, Ushakova, Yugay, Polyakov, Ramirez-Ortiz, Esparza-Aguiar, Chantada, Schaiquevich, Fandino, Yam, Lau, Lam, Sharwood, Moorthy, Long, Essuman, Renner, Català, Correa-Llano

Obtained funding: Each author's time contributions for data entry and manuscript review were performed as part of their regular employment or taken from their free time. No additional funding was provided for these tasks.

Overall responsibility: Tomar, Finger, Gallie, Mallipatna, Kivelä, Zhang, Zhao, Wilson, Kim, Khetan, Ganesan, Yarovoy, Yarovaya, Kotova, Yousef, Nummi, Ushakova, Yugay, Polyakov, Ramirez-Ortiz, Esparza-Aguiar, Chantada, Schaiquevich, Fandino, Yam, Lau, Lam, Sharwood, Moorthy, Long, Essuman, Renner, Català, Correa-Llano

Abbreviations and Acronyms:

**AJCC** = American Joint Committee on Cancer; **CHLA** = Children's Hospital of Los Angeles; **CI** = confidence interval; **HR** = hazard ratio; **ICRB** = International Classification for Retinoblastoma; **IIRC** = International Intraocular Retinoblastoma Classification; **IRSS** = International Retinoblastoma Staging System; **IQR** = interquartile range; **RB** = retinoblastoma; **SD** = standard deviation; **WEH** = Wills Eye Hospital.

Correspondence:

Paul T. Finger, MD, The New York Eye Cancer Center, 115 East 61st Street, 5th Floor, New York, NY 10065. E-mail: [pfinger@eyecancer.com](mailto:pfinger@eyecancer.com).