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

Part II: Treatment Success and Globe Salvage

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Purpose: To evaluate the ability of the American Joint Committee on Cancer (AJCC) 8th edition to predict local tumor control and globe salvage for children with retinoblastoma (RB).

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

Participants: A total of 2854 eyes of 2097 patients from 18 ophthalmic oncology centers from 13 countries over 6 continents.

Methods: International, multicenter, registry-based data were pooled from patients enrolled between January 2001 and December 2013. All RB eyes with adequate records to allow tumor staging by the AJCC 8th edition criteria and follow-up to ascertain treatment outcomes were included.

Main Outcome Measures: Globe-salvage rates were estimated by AJCC clinical (cTNMH) categories and tumor laterality. Local treatment failure was defined as use of enucleation or external beam radiation therapy (EBRT), with or without plaque brachytherapy or intra-arterial chemotherapy (IAC).

Results: Unilateral RB occurred in 1340 eyes (47%). Among the 2854 eyes, tumor categories were cT1 to cT4 in 696 eyes (24%), 1334 eyes (47%), 802 eyes (28%), and 22 eyes (1%), respectively. Of these, 1275 eyes (45%) were salvaged, and 1179 eyes (41%) and 400 eyes (14%) underwent primary and secondary enucleation, respectively. The 2- and 5-year Kaplan–Meier cumulative globe-salvage rates without the use of EBRT by cTNMH categories were 97% and 96% for category cT1a tumors, 94% and 88% for cT1b tumors, 68% and 60% for cT2a tumors, 66% and 57% for cT2b tumors, and 32% and 25% for cT3 tumors, respectively. Risk of local treatment failure increased with increasing cT category ($P < 0.001$). Cox proportional hazards regression analysis confirmed a higher risk of local treatment failure in categories cT1b (hazard ratio [HR], 3.5; $P = 0.004$), cT2a (HR, 15.1; $P < 0.001$), cT2b (HR, 16.4; $P < 0.001$), and cT3 (HR, 45.0; $P < 0.001$) compared with category cT1a. Use of plaque brachytherapy and IAC improved local tumor control in categories cT1a ($P = 0.031$) and cT1b ($P < 0.001$).

Conclusions: Multicenter, international, internet-based data sharing validated the 8th edition AJCC RB staging to predict globe-salvage in a large, heterogeneous, real-world patient population with RB. *Ophthalmology 2020;127:1733-1746 © 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/).*

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Cancer classification systems provide a universal language for determining disease extent, planning treatment strategies, and estimating prognosis.[1] A standardized system of cancer staging enhances communication among eye cancer specialists, pediatric oncologists, radiologists, radiation therapists, ophthalmic pathologists, geneticists, and

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researchers who treat patients with retinoblastoma (RB). Classifications for RB have evolved over the last few decades as a result of the development of new treatment modalities used to improve local tumor control and globe salvage.[2-5] These rates have improved considerably from 26% to 43%[6-9] in the early chemotherapy era to 67% to 80%[9-11] with primary and rescue intra-arterial chemotherapy (IAC), intravitreal chemotherapy, use of plaque brachytherapy, and other focal treatments.[12,13] Treatment success rates differ in various parts of the world, especially in the lower-income countries where patients present with advanced disease.[14]

Reese and Ellsworth[3] developed a classification system to predict globe salvage after external beam radiotherapy (EBRT) as primary treatment.[3] Then, as systemic chemotherapy replaced EBRT, the International Intraocular Retinoblastoma Classification (IIRC), also termed as "Murphree's Children's Hospital of Los Angeles" (CHLA) classification,[4] and the International Classification for Retinoblastoma (ICRB), also termed as "Shield's Wills Eye Hospital" (WEH) classification,[5] emerged to predict globe salvage after chemotherapy. These classification systems were formulated by single-center experience or small-group consensus and still lack published multicenter validation.[15] More importantly, both CHLA and WEH grouping systems use the same group names such as group A to E, but each group definition contains key differences that hinder the ability to collate evidence that predict treatment success and to compare clinical outcomes in centers across the world.[16-18] The lack of a universal RB cancer classification has harmed both research and clinical care.[17]

An evidence-based accurate staging of the eye and child with RB would serve to predict which eyes are safe to be salvaged and provide a quantitative risk for salvage failure, the need for secondary enucleation, and the risk for extraocular relapse. The 8th edition American Joint Committee on Cancer (AJCC) RB staging system was created by 18 RB specialist centers from 13 countries on 6 continents. Global consensus was derived from the Ophthalmic Oncology Task Force (OOTF).[2] More comprehensive than previous editions, the resultant TNMH staging system defined anatomic stages of growth of the primary tumor (T), with regional lymph node (N), and systemic metastasis (M) framework, and uniquely includes heritability (H) as an independent category. It was adopted by the Union for International Cancer Control (UICC) and has been accepted by multiple ophthalmology, medical oncology, radiation oncology, and medical journals around the world.[19-21]

Multicenter international data collection to enroll a global spectrum of cases was used to evaluate the ability of the AJCC 8th edition classification to predict outcomes with respect to eye salvage and long-term tumor control.

Methods

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 (OOTF) Retinoblastoma Registry at Princess Margaret Cancer Center (Toronto, Ontario, Canada). All centers agreed that individual patient consent was not required because there were no patient identifiers collected. Each site was an ophthalmic oncology subspecialty center. Patients with RB were diagnosed and treated according to the best practices defined by each institute. Patient records were excluded from analysis if key variables, such as demographic data, clinical variables essential for RB classification (tumor location, size, and extent), treatment data (date and type of treatment), and outcome (globe salvage, primary, or secondary enucleation) were missing or inconsistent. This study adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996.

The Registry

Internet-based, retrospective registry was created to evaluate the staging system for RB in the AJCC Cancer Staging Manual.[2] Through a consensus process, OOTF committee members (primarily ophthalmic oncologists and pathologists) developed the epidemiologic, clinical, and pathological data fields.

Internet Database and Security

International standards for patient privacy protection and statistical analysis were used. 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 web page accessing). Access to the online survey required user accounts issued by the coordinating center. Each center could only access their patient records. When documentation of the local ethics approval was received by the coordinating center, unique login passwords were provided to initiate patient entry. Each center created a random alphanumeric identifier for each patient.

Definitions

Primary enucleation: removal of treatment naive RB eyes.

Secondary enucleation: removal of an eye after an attempt at eye salvage, irrespective of the reason for enucleation (significant residual disease, recurrent tumor).

CHLA/IIRC classification: termed CHLA for the purpose of this study to avoid any confusion regarding the 2 similar sounding but distinct classification systems IIRC and ICRB.

WEH/ICRB classification: termed WEH for the purpose of this study.

Each center used its own best 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 size and location of intraocular tumor, presence of glaucoma, presence and type of vitreous seeds, subretinal seeds, and macroscopic anterior chamber seeds, and neovascularization of the iris. Reese-Ellsworth, CHLA, WEH, and cTNMH staging of RB were noted for each eye. Treatment details were noted. The eyes with substantial residual or recurrent disease after chemotherapy and focal consolidation were treated with further focal laser, cryotherapy, plaque brachytherapy, IAC, EBRT, or enucleation. Local treatment failure after conservative treatment was defined as the need for EBRT or secondary enucleation. Plaque brachytherapy and IAC are standard in multimodal treatment for globe salvage, but they are not universally available. To assess the difference among the success rates of different main treatment

modalities, the second criterion for treatment failure was defined as the need for plaque brachytherapy, IAC, EBRT, or secondary enucleation. The latter criterion was formulated purely as a statistical tool to study the impact on globe salvage if plaque brachytherapy and IAC were not available. Their use should not be considered as treatment failure, quite the opposite. Based on these 2 definitions, failure-free globe salvage refers to eye conservation without need of above listed modalities.

TNMH Retinoblastoma Staging

In contrast to CHLA and WEH, the 8th edition AJCC RB classification included more complex information focusing not only on the patient's primary tumor but also on regional lymph node spread, metastatic disease, and heritable trait (Table 1). In that the registry data fields and collection predated 2013, we used the raw clinical data to classify all the tumors accurately by AJCC 8th edition. Data were available for all necessary fields except for the involvement of pars plana and ciliary body (cT3b) by the tumor.

Statistical Analysis

Continuous variables were described using medians, ranges, and interquartile ranges (IQRs), and categoric variables were described using frequencies and proportions. Kaplan–Meier plots with log-rank test for trend were implemented to test whether tumor category is related to treatment success. All the eyes with intraocular RB that were not primarily enucleated were analyzed for local failure-free globe salvage analysis. Eyes were censored at the time of the last follow-up. Cumulative proportion of local failure-free globe salvage estimates at 1, 2, 5, and 10 years were tabulated. SPSS (version 23.0, IBM, Armonk, New York, NY) 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

Eighteen eye cancer specialty centers from 13 countries over 6 continents successfully entered data online into an internet-based

Table 1. American Joint Committee on Cancer 8th Edition TNM Classification for Retinoblastoma[2] Definitions for AJCC Primary Tumor Staging (cT)

cTX		Unknown evidence of intraocular tumor
cT0		No evidence of intraocular tumor
cT1		Intraocular tumor(s) with subretinal fluid ≤5 mm from the base of any tumor
	cT1a	Tumors ≤3 mm and >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	Increased 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 central nervous system 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

CNS = central nervous system; RB = retinoblastoma.

registry to evaluate the predictive value of the 8th edition AJCC TNMH staging system for globe salvage after RB treatment. Between January 2001 and December 2013, 2905 eyes of 2097 RB patients were enrolled. Because of incomplete data, 51 eyes were excluded, leaving 2854 (98.2%) complete records for analysis.

Patient Features

The median age at diagnosis was 17.0 months (mean, 21.6; SD, 20.9; IQR, 8−29; range, 1−365 months). Of the 2854 eyes, RB was unilateral in 1340 eyes (47%) and bilateral in 1514 eyes (53%). Among patients with unilateral RB, the right eye was involved in 688 (51.3%).

Classifications

Comparative staging was performed using the Reese-Ellsworth, CHLA, and WEH systems. The Reese-Ellsworth classification[3] was reported in 1250 eyes; 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%); and 746 were in group V (59.9%).

The CHLA[4] was reported in 2835 eyes as follows: 176 eyes were in group A (6.2%); 476 eyes were in group B (16.8%); 208 eyes were in group C (7.3%); 1101 eyes were in group D (38.9%); and 874 eyes were in group E (30.8%) (Table 2).

The WEH[5] was reported in 2835 eyes as follows: 188 eyes were in group A (6.6%); 600 eyes were in group B (21.2%); 40 eyes were in group C (1.4%); 277 eyes were in group D (9.8%); and 1730 eyes were in group E (61.0%) (Table 2). The largest disparity between CHLA and WEH can be seen in group E classified eyes.

AJCC Clinical Classification

In 2854 eyes, the AJCC clinical T category that indicates the anatomic extent of the primary tumor (cT) was in 696 eyes with cT1 (24.4%), in 1334 eyes with cT2 (46.7%), in 802 eyes with cT3 (28.1%), and in 22 eyes with cT4 (0.8%) (Table 2). Regional lymph node involvement (cN) was demonstrated in 12 patients (0.6%) as cN1. The involved lymph nodes were preauricular, cervical, or submandibular. Twenty-five (1.2%) of 2085 patients presented with distant metastasis (cM), including 13 with cM1a (0.6%, including 3 with distant lymph nodes) and 12 with central nervous system (CNS) metastasis, cM1b (0.6%). Trilateral RB in the AJCC system is classified as a brain tumor and thus does not influence the cM category.

Table 2. Classification of Retinoblastoma Eyes with Local Treatment Outcomes

Group	No. of Eyes by CHLA Classification (%)	Treatment Outcome	N (%)	No. of Eyes by WEH Classification (%)	Treatment Outcome	N (%)
A	N = 176 (6.2%)	Globe salvage	174 (98.8%)	N = 188 (6.6%)	Globe salvage	184 (97.9%)
		Primary enucleation	1 (0.6%)		Primary enucleation	2 (1.1%)
		Secondary enucleation	1 (0.6%)		Secondary enucleation	2 (1.1%)
B	N = 476 (16.8%)	Globe salvage	425 (89.3%)	N = 600 (21.2%)	Globe salvage	534 (89%)
		Primary enucleation	22 (4.6%)		Primary enucleation	30 (5.0%)
		Secondary enucleation	29 (6.1%)		Secondary enucleation	36 (6.0%)
C	N = 208 (7.3%)	Globe salvage	155 (74.5%)	N = 40 (1.4%)	Globe salvage	25 (62.5%)
		Primary enucleation	30 (14.4%)		Primary enucleation	7 (17.5%)
		Secondary enucleation	23 (11.1%)		Secondary enucleation	8 (20.0%)
D	N = 1101 (38.9%)	Globe salvage	388 (35.2%)	N = 277 (9.8%)	Globe salvage	122 (44.0%)
		Primary enucleation	498 (45.2%)		Primary enucleation	102 (36.8%)
		Secondary enucleation	215 (19.5%)		Secondary enucleation	53 (19.1%)
E	N = 874 (30.8%)	Globe salvage	116 (13.2%)	N = 1730 (61.0%)	Globe salvage	400 (23.1%)
		Primary enucleation	626 (71.6%)		Primary enucleation	1030 (59.5%)
		Secondary enucleation	132 (15.1%)		Secondary enucleation	300 (17.3%)
Data Not Available	N = 19			N = 19		

Tumor Category		No. of Eyes	Treatment Outcome	N (%)
cT1	cT1a	N = 230 (8.1%)	Globe salvage	201 (87.4%)
			Primary enucleation	23 (10.0%)
			Secondary enucleation	6 (2.6%)
	cT1b	N = 466 (16.5%)	Globe salvage	423 (90.8%)
			Primary enucleation	14 (3.0%)
			Secondary enucleation	29 (6.2%)
cT2	cT2a	N = 280 (9.9%)	Globe salvage	116 (41.3%)
			Primary enucleation	119 (42.5%)
			Secondary enucleation	45 (16.0%)
	cT2b	N = 1054 (37.2%)	Globe salvage	428 (40.6%)
			Primary enucleation	430 (40.8%)
			Secondary enucleation	196 (18.6%)
cT3		N = 802 (28.3%)	Globe salvage	100 (12.5%)
			Primary enucleation	587 (73.2%)
			Secondary enucleation	115 (14.3%)

AJCC = American Joint Committee on Cancer; CHLA = Children's Hospital of Los Angeles; WEH = Wills Eye Hospital.

Table 3. Kaplan–Meier Cumulative Proportion of Avoiding Local Treatment Failure Based on Different Retinoblastoma Classifications

Local Treatment Failure Defined as Need for EBRT or Enucleation					
		Kaplan–Meier Point Estimates (95% CI) %			
Classification	*Variable*	*1 Yr*	*2 Yrs*	*5 Yrs*	*10 Yrs*
	All patients (n = 1574)	78 (77–79)	75 (74–76)	68 (67–69)	42 (38–46)
CHLA Classification (n =1556)	A (n = 168)	100	100	98 (96–100)	98 (96–100)
	B (n = 438)	96 (95–97)	94 (93–95)	89 (87–91)	59 (50–68)
	C (n = 167)	89 (86–92)	87 (85–89)	86 (83–89)	69 (62–76)
	D (n = 563)	66 (64–68)	61 (59–63)	49 (46–52)	16 (11–21)
	E (n = 220)	39 (35–43)	29 (25–33)	23 (19–27)	15 (10–20)
WEH Classification (n =1563)	A (n = 179)	99 (98–100)	99 (98–100)	98 (96–100)	98 (96–100)
	B (n = 555)	96 (95–97)	94 (93–95)	89 (87–91)	63 (56–70)
	C (n = 32)	73 (65–81)	73 (65–81)	73 (65–81)	65 (54–76)
	D (n = 164)	71 (67–75)	68 (64–72)	56 (51–61)	15 (8–22)
	E (n = 633)	56 (54–58)	49 (47–51)	39 (36–42)	15 (10–20)
AJCC cT size category (n =1574)	cT1a (n = 200)	97 (96–98)	97 (96–98)	96 (94–98)	96 (94–98)
	cT1b (n = 436)	96 (95–97)	94 (93–95)	88 (86–90)	59 (50–68)
	cT2a (n = 144)	74 (70–78)	68 (64–72)	60 (55–65)	38 (29–47)
	cT2b (n = 592)	70 (68–72)	66 (64–68)	57 (54–60)	25 (20–30)
	cT3 (n = 202)	39 (35–43)	32 (28–36)	25 (20–30)	17 (12–22)

For CHLA Classification				
Overall Comparison: Log-Rank test, P < 0.001				
Pairwise Comparison:				
	A	*B*	*C*	*D*
A				
B	<0.001			
C	<0.001	0.005		
D	<0.001	<0.001	<0.001	
E	<0.001	<0.001	<0.001	<0.001

For WEH Classification				
Overall Comparison: Log-Rank test, P < 0.001				
Pairwise Comparison:				
	A	*B*	*C*	*D*
A				
B	0.001			
C	<0.001	<0.001		
D	<0.001	<0.001	0.429	
E	<0.001	<0.001	0.009	<0.001

For cT Category				
Overall Comparison: Log-Rank Test, P < 0.001				
Pairwise Comparison:				
	cT1a	*cT1b*	*cT2a*	*cT2b*
cT1a				
cT1b	0.035			
cT2a	<0.001	<0.001		
cT2b	<0.001	<0.001	=0.584	
cT3	<0.001	<0.001	<0.001	<0.001

Local Treatment Failure Defined as Need for Plaque Brachytherapy, IAC, EBRT, or Enucleation					
		Kaplan–Meier Point Estimates (95% CI), %			
Classification	*Variable*	*1 Yr*	*2 Yrs*	*5 Yrs*	*10 Yrs*
	All patients (n = 1574)	76 (75–77)	72 (71–73)	61 (59–63)	25 (22–28)

(*Continued*)

Table 3. (Continued.)

Local Treatment Failure Defined as Need for Plaque Brachytherapy, IAC, EBRT, or Enucleation					
		Kaplan–Meier Point Estimates (95% CI), %			
Classification	*Variable*	*1 Yr*	*2 Yrs*	*5 Yrs*	*10 Yrs*
CHLA/IIRC Classification (n = 1556)	A (n = 168)	98 (97–99)	96 (94–98)	88 (84–92)	62 (50–84)
	B (n = 438)	93 (92–94)	89 (87–91)	78 (76–80)	30 (23–37)
	C (n = 167)	88 (85–91)	85 (82–88)	78 (74–82)	33 (24–42)
	D (n = 563)	64 (62–66)	59 (57–61)	42 (39–45)	12 (8–16)
	E (n = 220)	39 (35–43)	29 (25–33)	23 (19–27)	15 (10–20)
WEH/ICRB Classification (n = 1563)	A (n = 179)	98 (97–99)	95 (93–97)	88 (82–92)	61 (50–72)
	B (n = 555)	93 (92–94)	90 (89–91)	78 (76–80)	32 (26–38)
	C (n = 32)	73 (65–81)	69 (60–78)	63 (53–73)	27 (11–43)
	D (n = 164)	68 (64–72)	65 (61–69)	48 (43–53)	12 (7–17)
	E (n = 633)	55 (53–57)	48 (46–50)	36 (33–39)	12 (8–16)
AJCC cT size category (n = 1574)	cT1a (n = 200)	95 (93–97)	93 (91–95)	87 (84–90)	62 (51–73)
	cT1b (n = 436)	93 (92–94)	89 (87–91)	78 (76–80)	29 (22–36)
	cT2a (n = 144)	72 (68–76)	64 (60–68)	47 (42–52)	21 (14–28)
	cT2b (n = 592)	69 (67–71)	65 (63–67)	51 (48–54)	16 (12–20)
	cT3 (n = 202)	39 (35–43)	32 (28–36)	25 (20–30)	17 (12–22)

For CHLA Classification

Overall Comparison: Log-Rank Test, P < 0.001

Pairwise Comparison:

	A	*B*	*C*	*D*
A				
B	=0.003			
C	<0.001	0.100		
D	<0.001	<0.001	<0.001	
E	<0.001	<0.001	<0.001	<0.001

For WEH Classification

Overall Comparison: Log-Rank test, P < 0.001

Pairwise Comparison:

	A	*B*	*C*	*D*
A				
B	0.002			
C	<0.001	=0.001		
D	<0.001	<0.001	0.459	
E	<0.001	<0.001	0.012	<0.001

For cT Category

Overall Comparison: Log-Rank Test, P < 0.001

Pairwise Comparison:

	cT1a	*cT1b*	*cT2a*	*cT2b*
cT1a				
cT1b	0.031			
cT2a	<0.001	<0.001		
cT2b	<0.001	<0.001	=0.983	
cT3	<0.001	<0.001	<0.001	<0.001

Comparison between the Kaplan–Meier Curves Stratified by cT Categories Using 2 Different Definitions of Local Treatment Failure

Pairwise Comparison:

	P Value
cT1a	0.031
cT1b	<0.001

Table 3. (Continued.)

Comparison between the Kaplan–Meier Curves Stratified by cT Categories Using 2 Different Definitions of Local Treatment Failure	
Pairwise Comparison:	
	P Value
cT2a	0.387
cT2b	0.535
cT3	No difference

AJCC = American Joint Committee on Cancer; CHLA = Children's Hospital of Los Angeles; CI = confidence interval; EBRT = external beam radiotherapy; IAC = intra-arterial chemotherapy; RB = retinoblastoma; WEH = Wills Eye Hospital.

Treatment Outcomes

Treatment protocols were defined by each subspecialty center. Modalities included enucleation, systemic chemotherapy with focal consolidation, plaque brachytherapy, IAC, and EBRT. Focal treatment included laser (532 or 810 nm) and cryotherapy. Additionally, intravitreal, intracameral, and periocular chemotherapy were used for treatment of vitreous or subretinal seeds.

Of the 2854 eyes, local tumor control was achieved in 1275 eyes (44.7%) and enucleation was performed in 1579 eyes (55.3%). Primary enucleation was performed in 1179 eyes (41.3%). Secondary enucleation was performed in 400 eyes (14.0%, 23.9% of 1675 eyes that were not primarily enucleated). Of the 2854 eyes, EBRT was used for 91 (3.2%), plaque brachytherapy for 130 (4.6%), and IAC for 116 (4.1%). Treatment outcomes based on the different classification systems are described in Table 2.

Cumulative Proportion of Avoiding Local Treatment Failure According to Initial Tumor Classification

Of the 2854 eyes, 1675 had an attempt at globe salvage. Of these, 1574 had complete data for globe salvage analysis, as included in this section (Consort Flow Diagram available online at www.aaojournal.org). Secondary enucleation was required for 344 eyes at a median time (from diagnosis) of 8.0 months (mean, 12.4; SD, 12.2; IQR, 5.0–16.0, range, 1–74 months).

Local Treatment Failure Defined as Need for External Beam Radiotherapy or Secondary Enucleation

A total of 434 (27.6%) of 1574 eyes were treated by EBRT or enucleation for RB control. According to the AJCC criteria, of these eyes, 6 (1.4%) had cT1a, 48 (11.1%) had cT1b, 49 (11.3%) had cT2a, 217 (50.0%) had cT2b, and 114 (26.3%) had cT3. Tables 3 and 4 show their distribution based on different classification systems. The 2- and 5-year Kaplan–Meier cumulative proportions of avoiding local treatment failure by clinical cTNMH categories were 97% (95% confidence interval [CI], 96–98) and 96% (95% CI, 94–98) for cT1a tumors, 94% (95% CI, 93–95) and 88% (95% CI, 86–90) for cT1b tumors, 68% (95% CI, 64–72) and 60% (95% CI, 55–65) for cT2a tumors, 66% (95% CI, 64–68) and 57% (95% CI, 54–60) for cT2b tumors, and 32% (95% CI, 28–36) and 25% (95% CI, 20–30) for cT3 tumors, respectively. Category cT4 includes tumors with orbital disease and hence were not included in globe salvage analyses. Increasing

Table 4. Proportion of Retinoblastoma Eyes with Local Treatment Failure Based on Two Different Criteria

Classification	No. of Eyes	Local Treatment Failure Defined as Need for EBRT or Secondary Enucleation	Percentage of All Eyes	Local Treatment Failure Defined as Need for Plaque Brachytherapy, IAC, EBRT, or Secondary Enucleation	Percentage of All Eyes
CHLA-A	168	1	0.6%	16	9.5%
CHLA-B	438	48	11%	102	23.3%
CHLA-C	167	27	16.2%	44	26.3%
CHLA-D	563	233	41.4%	263	46.7%
CHLA-E	220	124	56.4%	124	56.4%
WEH-A	179	2	1.1%	18	10.1%
WEH-B	555	61	11%	131	23.6%
WEH-C	32	9	28.1%	13	40.6%
WEH-D	164	69	42.1%	81	49.4%
WEH-E	633	292	46.1%	306	48.3%
cT1a	200	6	3.0%	23	11.5%
cT1b	436	48	11.0%	102	23.4%
cT2a	144	49	34.0%	65	45.1%
cT2b	592	217	36.7%	246	41.6%
cT3	202	114	56.4%	114	56.4%

AJCC = American Joint Committee on Cancer; CHLA = Children's Hospital of Los Angeles; EBRT = external beam radiotherapy; IAC = intra-arterial chemotherapy; WEH = Wills Eye Hospital.

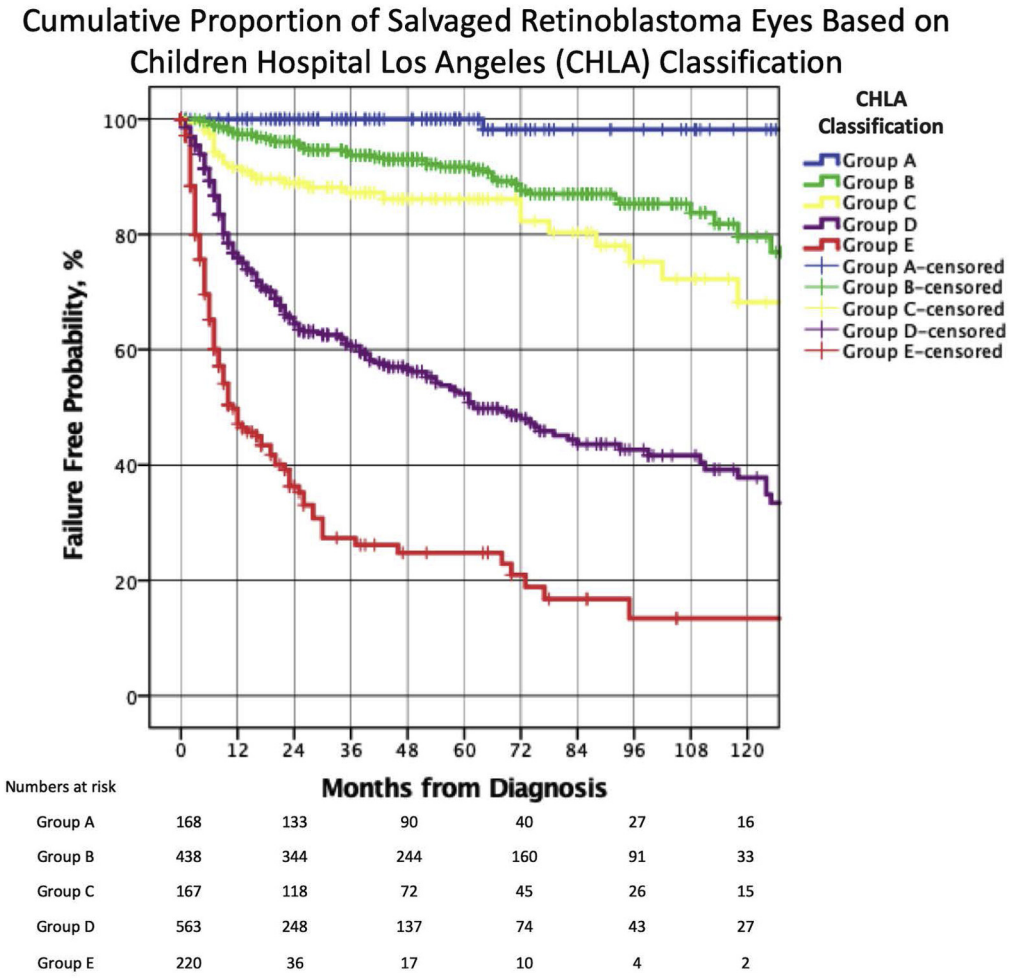

Figure 1. Kaplan–Meier curve of the cumulative proportion of salvaged eyes with retinoblastoma (RB) without the need for external beam radiation therapy (EBRT), classified by the Children's Hospital of Los Angeles (CHLA).

cT category translated to increased risk of local treatment failure and less frequent globe salvage ($P < 0.001$, log-rank test for trend). Pairwise comparison showed a significant difference between all categories except cT2a and cT2b (Table 3 and Figs 1–3).

Cox proportional hazard regression analysis revealed that patients with unilateral disease (hazard rate [HR], 2.7; 95% CI, 2.2–3.2; $P < 0.001$) had a greater risk relative to those with bilateral disease, and patients with cT1b (hazard ratio [HR], 3.5; 95% CI, 1.5–8.2; $P = 0.004$), cT2a (HR, 15.1; 95% CI, 6.5–35.2; $P < 0.001$), cT2b (HR, 16.4; 95% CI, 7.3–36.9; $P < 0.001$), and cT3 (HR, 45.0; 95% CI, 19.8–102.5; $P < 0.001$) had a greater risk of local treatment failure (need for EBRT or enucleation) compared with those with cT1a (Table 5).

Local Treatment Failure Modelled by Need for Plaque Brachytherapy, Intra-Arterial Chemotherapy, External Beam Radiotherapy or Enucleation

A total of 550 (34.9%) of 1574 eyes needed IAC, plaque brachytherapy, EBRT, or enucleation for RB control. According to the AJCC criteria applied to these eyes, 23 (4.2%) were cT1a, 102 (18.6%) were cT1b, 65 (11.8%) were cT2a, 246 (44.7%) were cT2b, and 114 (20.7%) were cT3. Tables 3 and 4 provide their distribution based on different classification systems. The 2- and 5-year Kaplan–Meier cumulative proportions of avoiding local treatment failure by clinical tumor categories were by cTNMH categories were 93% (95% CI, 91–95) and 87% (95% CI, 84–90) for category cT1a tumors, 89% (95% CI, 87–91) and 78% (95% CI, 76–80) for cT1b tumors, 64% (95% CI, 60–68) and 47% (95% CI, 42–52) for cT2a tumors, 65% (95% CI, 64–68) and 51% (95% CI, 48–54) for cT2b tumors, and 32% (95% CI, 28–36) and 25% (95% CI, 20–30) for cT3 tumors, respectively. Increasing tumor category translated to increased risk of local treatment failure ($P < 0.001$, log-rank test for trend). Pairwise comparison showed a significant difference between all categories except cT2a and cT2b (Table 3).

Cox proportional hazard regression analysis revealed that patients with unilateral disease (HR, 2.4; 95% CI, 2.1–2.9; $P < 0.001$) had a greater risk relative to those with bilateral disease, and patients with cT1b (HR, 1.9; 95% CI, 1.2–3.0; $P = 0.005$), cT2a (HR, 5.4; 95% CI, 3.3–8.7; $P < 0.001$), cT2b (HR, 5.0; 95% CI, 3.3–7.6; $P < 0.001$), and cT3 (HR, 13.0; 95% CI, 8.3–20.4; $P < 0.001$) had a greater risk of treatment failure (need for enucleation or EBRT) compared with those with cT1a (Table 5).

Figure 4 illustrates a comparison between eyes with treatment failure defined by the 2 aforementioned criteria. The solid lines denote treatment failure with need for EBRT or enucleation, and

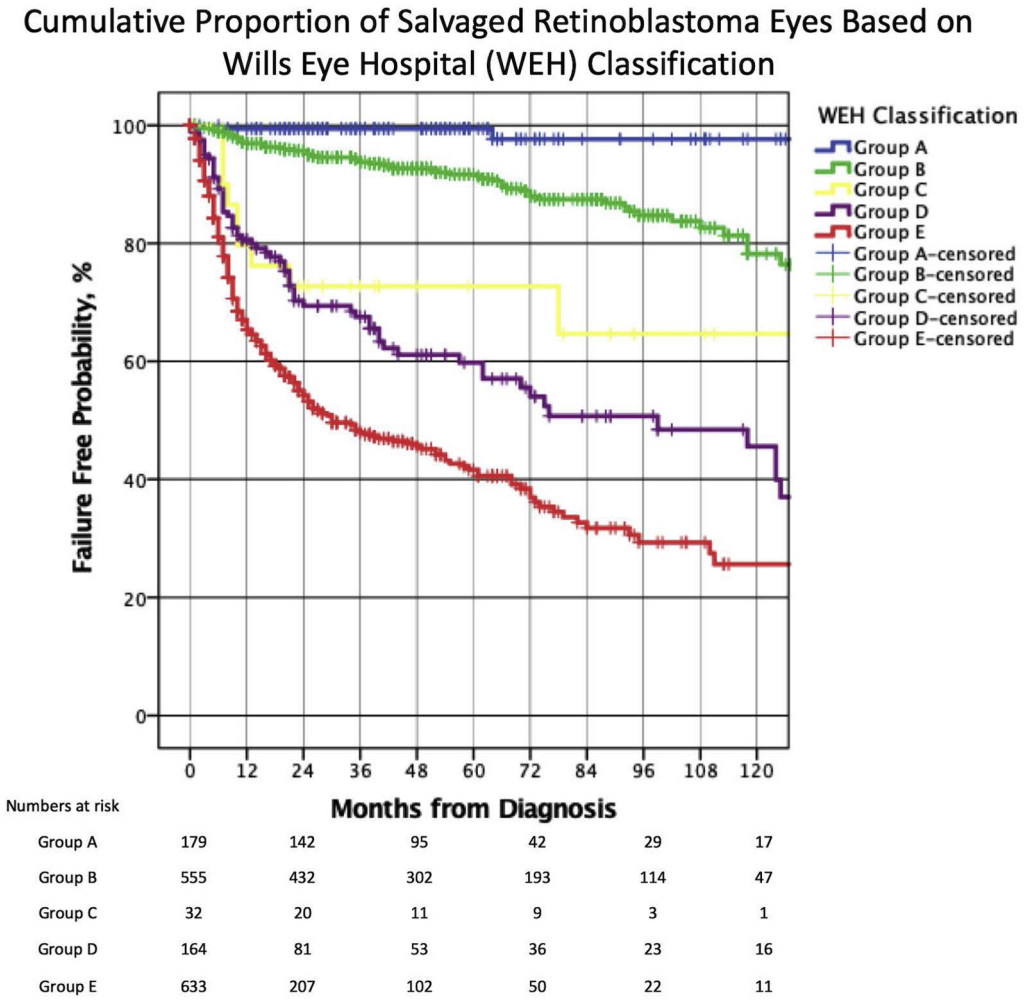

Figure 2. Kaplan–Meier curve of cumulative proportion of salvaged retinoblastoma (RB) eyes without the need for external beam radiation therapy (EBRT), classified by Wills Eye Hospital (WEH) classification.

the dotted lines represent treatment failure with need for IAC, plaque brachytherapy, EBRT, or enucleation. Kaplan–Meier survival curves showed a significant pairwise difference for cT1a ($P = 0.031$) and cT1b ($P < 0.001$) but not for cT2a ($P = 0.390$) and cT2b ($P = 0.530$). For example, cT1b, the divergent green lines (1 solid, 1 broken), represents the difference in globe salvage results, which is statistically significant. If IAC and plaque brachytherapy are not available, the globe salvage curve would shift from a solid to a dotted line.

Discussion

We present a multicenter, international, internet-based registry to study the ability of the 8th edition of AJCC RB Staging System to predict globe salvage without the need for EBRT. We found that increasing AJCC cT category was significantly related to increasing risk of local treatment failure as defined by need for EBRT or enucleation. Specifically, as the T-categories increased from cT1a to cT3, the hazard of treatment failure increased. We found a 3.5-fold risk for cT1b, 15.1-fold risk for cT2a, 16.4-fold risk for cT2b, and 45.0-fold risk for cT3 compared with cT1a.

This study included patients from 18 international RB subspecialty centers from 13 countries in 6 continents. Their participation allowed for the inclusion of an unusually diverse real-world sample sampling of patients from around the globe. The numbers of enrolled patients with RB were large enough to obtain statistically significant results.

The existence of multiple RB classification systems has led to confusion and miscommunication.[16-18] The CHLA and WEH classification systems were designed to predict treatment success using a combination of systemic chemotherapy and focal consolidation. Both had the same "A" to "E" categories with subtle but significant criteria differences, leading to non-comparable results.[16] The most clinically relevant discrepancy is the size criteria for advanced tumors, which essentially classifies large CHLA group D tumors to group E tumors in the WEH system.[17] This disparity was evident in our study, in which the same cohort had 30.8% eyes classified in group E as per CHLA and 61.0% per WEH classification (Table 2). Compared with the 8th edition AJCC cTNMH classification, cT3 most closely resembles CHLA group E and includes 28.3% of all eyes. With most literature using either of the

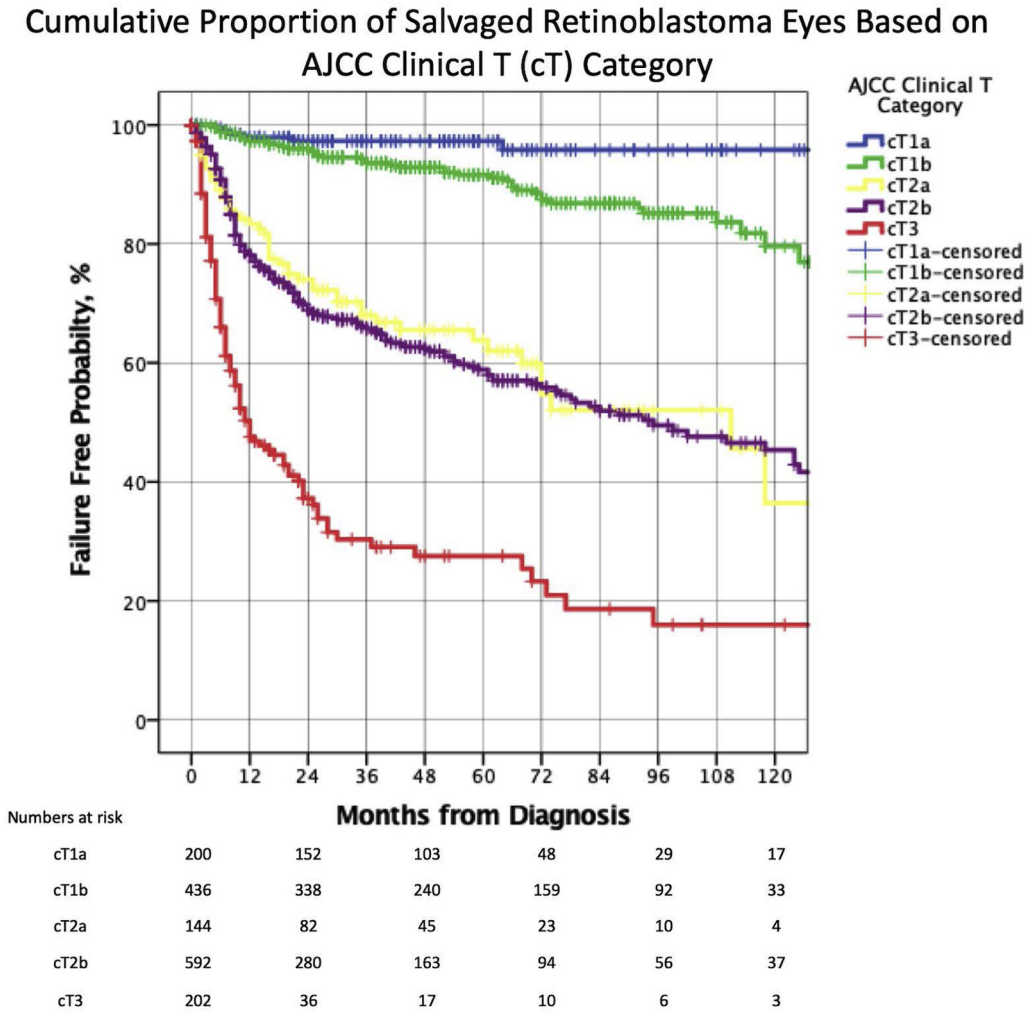

Figure 3. Kaplan–Meier curve of cumulative proportion of salvaged retinoblastoma (RB) eyes without the need for external beam radiation therapy (EBRT), classified by American Joint Committee on Cancer (AJCC) Clinical Tumor (cT) category.

2 partly dissimilar classification systems, accurate treatment prediction outcome has become impossible.[18] In addition to the use of the intrinsically different CHLA and WEH grouping classifications, the variety of chemotherapy protocols (in terms of agents and number of cycles) makes comparison between clinical and research studies more difficult.

That said, major studies with at least 2-year mean follow-up claim an overall tumor control of 70% to 100% for smaller tumors (group A to C) and 23% to 64% for advanced tumors (group D or E).[9,11,17] In comparison, this study revealed that a cumulative proportion of globe salvage without the need for EBRT declines from cT1a (96%) to cT3 (25%) tumor category at 5 years follow-up. This data supports the use of the 8th edition AJCC staging system to predict globe salvage.

In contrast to the existing classification systems, AJCC RB classification is a comprehensive staging that incorporates intraocular and extraocular RB, with the power to predict both globe and life salvage. Worldwide use by both the AJCC and UICC, allows the AJCC classification system to serve as a common language and thus a foundational element for communication between different specialties at multi-modality healthcare systems around the world.[1,22] The AJCC-RB staging is not radically different in terms of stratification from CHLA or WEH. Therefore, clinicians can easily adapt AJCC RB-staging to day-to-day clinical practice.

We noted that unilateral RB had a higher rate of enucleation compared with bilateral RB. This likely relates to clinical risk-to-benefit analysis on whether to keep a unilaterally affected eye, requiring multiple significant invasive treatments compared with sparing some useful vision when both eyes are at risk.

We defined treatment failure in 2 ways. Thus, we examined the significance of adjunctive plaque brachytherapy and IAC for controlling local tumor recurrences for globe salvage (Tables 3 and 4). We note that the difference in local treatment failure rates was significant in less advanced tumors (cT1a and cT1b) compared with cT3, again similar to group E in CHLA classification, but in variance with group E in WEH classification. Studies from more developed countries have revealed a high globe salvage rate that remains stable over 20 years.[11] In contrast, our results reflect real-world, global

Table 5. Cox Proportional Hazard Regression Models

Cox Proportional Hazards Regression Model for Association of Retinoblastoma Eyes Based on CHLA Classification with Local Treatment Failure

Variable	*Eyes in Group, No. (%) (N = 1556)*	*Reference*	*Local Treatment Failure Defined as Need for EBRT or Secondary Enucleation*		*Local Treatment Failure Defined as Need for Plaque Brachytherapy, IAC, EBRT, or Secondary Enucleation*	
			Hazard Ratio (95% CI)	*P Value*	*Hazard Ratio (95% CI)*	*P Value*
Group B	438 (28.1%)	Group A	17.9 (2.5–129.5)	0.004	2.4 (1.4–4.0)	0.001
Group C	167 (10.7%)	Group A	29.0 (3.9–213.8)	0.001	2.9 (1.7–5.2)	<0.001
Group D	563 (36.2%)	Group A	102.9 (14.4–733.8)	<0.001	7.6 (4.6–12.6)	<0.001
Group E	220 (14.1%)	Group A	252.4 (35.2–1807.5)	<0.001	17.6 (10.4–29.6)	<0.001

Cox Proportional Hazards Regression Model for Association of Retinoblastoma Eyes Based on WEH Classification with Local Treatment Failure

Variable	*Eyes in Group, No. (%) (N = 1563)*	*Reference*	*Local Treatment Failure Defined as Need for EBRT or Secondary Enucleation*		*Local Treatment Failure Defined as Need for Plaque Brachytherapy, IAC, EBRT, or Secondary Enucleation*	
			Hazard Ratio (95% CI)	*P Value*	*Hazard Ratio (95% CI)*	*P Value*
Group B	438 (28.1%)	Group A	9.6 (2.4–39.1)	0.002	2.3 (1.4–3.7)	0.001
Group C	167 (10.7%)	Group A	30.7 (6.6–142.3)	0.001	5.1 (2.5–10.3)	<0.001
Group D	563 (36.2%)	Group A	45.7 (11.2–186.4)	<0.001	6.0 (3.6–10.0)	<0.001
Group E	220 (14.1%)	Group A	77.8 (19.4–312.7)	<0.001	9.8 (6.1–15.8)	<0.001

Cox Proportional Hazards Regression Model for Association of Retinoblastoma Eyes Based on AJCC Clinical Tumor (cT) Classification with Local Treatment Failure

Variable	*Eyes in Group, No. (%) (N = 1574)*	*Reference*	*Local Treatment Failure Defined as Need for EBRT or Secondary Enucleation*		*Local Treatment Failure Defined as Need for Plaque Brachytherapy, IAC, EBRT or Secondary Enucleation*	
			Hazard Ratio (95% CI)	*P Value*	*Hazard Ratio (95% CI)*	*P Value*
cT1b	436 (27.7%)	cT1a	3.5 (1.5–8.2)	0.004	1.9 (1.2–3.0)	0.005
cT2a	144 (9.1%)	cT1a	15.1 (6.4–35.2)	<0.001	5.4 (3.3–8.7)	<0.001
cT2b	592 (37.6%)	cT1a	16.4 (7.3–36.9)	<0.001	5.0 (3.2–7.6)	<0.001
cT3	202 (12.8%)	cT1a	45.0 (19.8–102.5)	<0.001	13.0 (8.3–20.3)	<0.001

Cox Proportional Hazards Regression Model for Association of Tumor Laterality with Retinoblastoma Local Treatment Failure

Variable	*Eyes in Group, No. (%) (N = 1574)*	*Reference*	*Local Treatment Failure Defined as Need for EBRT or Secondary Enucleation*		*Local Treatment Failure Defined as Need for Plaque Brachytherapy, IAC, EBRT or Secondary Enucleation*	
			Hazard Ratio (95% CI)	*P Value*	*Hazard Ratio (95% CI)*	*P Value*
Unilateral RB	425 (27%)	Bilateral RB	2.7 (2.2–3.2)	<0.001	2.4 (2.0–2.9)	<0.001

AJCC = American Joint Committee on Cancer; CHLA = Children's Hospital of Los Angeles; EBRT = external beam radiotherapy; IAC = intra-arterial chemotherapy; WEH = Wills Eye Hospital.

RB perspective. The disparity in treatment success rates between the high- and low-income countries is considered to be due to advanced disease at presentation, lack of availability of newer treatment modalities, and more limited possibilities for adequate follow-up after conservative treatment.[14]

Limitations of our study are based on the inherent nature of data entry from 2001 to 2013. The last decade has witnessed significant advancements in globe salvage associated with the use of IAC and intravitreal chemotherapy.[12,13] Our retrospective design, which used locally defined diagnostic and treatment modalities, limits subgroup analysis. Although no data were available on patient sex or ethnic/racial backgrounds, the data were collected from 6 continents and thus sourced from a diverse, worldwide group of patients. Visual acuities were not measured and thus prevented us from assessing the visual outcomes after globe salvage. It is significant that 1179 eyes, 39.2% of the total, underwent primary enucleation and were thus excluded from this analysis. A detailed subgroup analysis, histopathologic correlation in enucleated eyes, and effect of neoadjuvant chemotherapy were beyond the scope of this study.

In conclusion, the 8th edition AJCC classification for RB was derived from the AJCC Ophthalmic Oncology Task

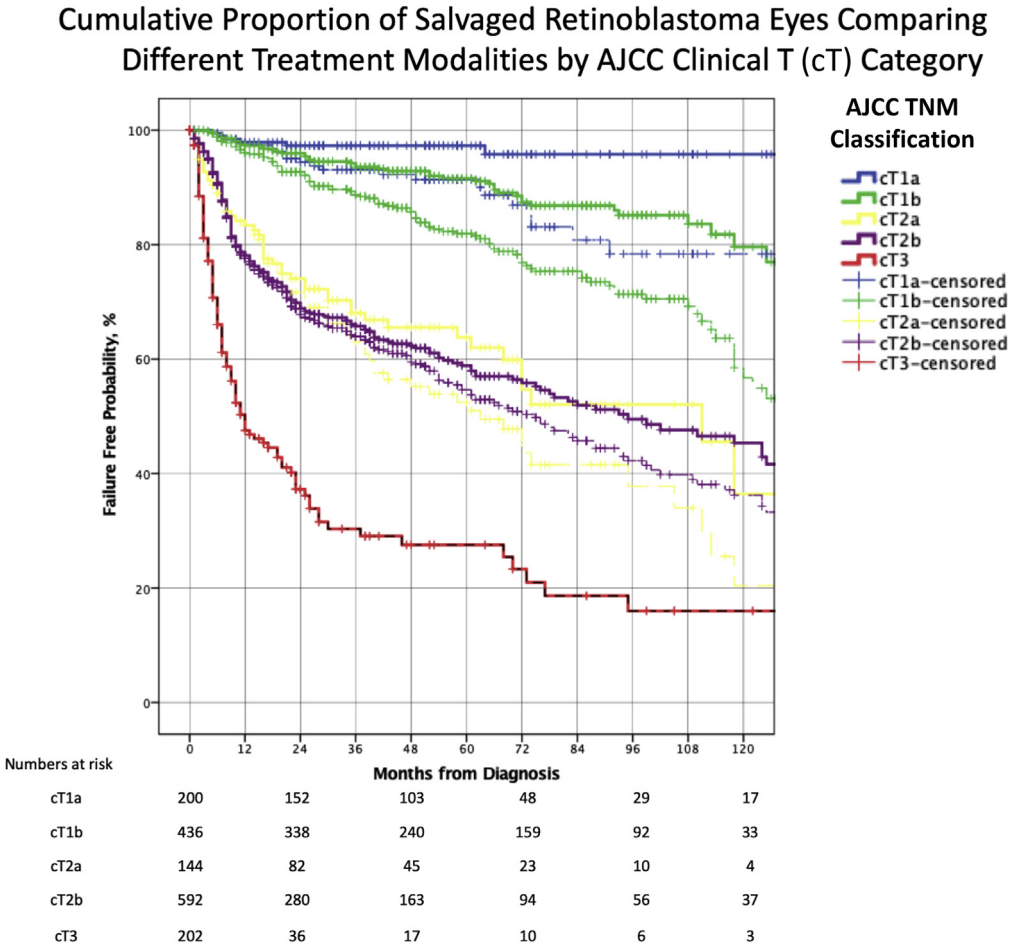

Figure 4. Kaplan–Meier curves of cumulative proportion of salvaged retinoblastoma (RB) eyes, with comparison between different treatment modalities, classified by American Joint Committee on Cancer (AJCC) Clinical Tumor (cT) category. The **solid lines** denote treatment failure with need for external beam radiation therapy (EBRT) or enucleation, and the **dotted lines** represent treatment failure modeled by need for intra-arterial chemotherapy (IAC), plaque brachytherapy, EBRT, or enucleation. For example, see cT1b, the divergent green lines (1 solid, 1 broken) represents the difference in globe salvage results, which are statistically significant. If IAC and plaque brachytherapy are not available, the globe salvage curve would shift from a **solid** to a **dotted line**.

Force, which was tasked to only use evidence-based data and to form an international consensus.[2] Universal adoption of this classification system will clarify outcome reporting and improve research and multispecialty patient care.[1,22] Our recommendation for the use of AJCC RB classification over the CHLA and WEH systems are based on the following factors:

- AJCC RB staging is a comprehensive classification system that can be used to predict both risk of metastasis and globe salvage.
- AJCC RB stages both intraocular and extraocular RB extension.
- AJCC RB staging is a dynamic, ever-evolving classification system in which multicenter international committees of subspecialists periodically convene to modify AJCC RB staging based on current medical evidence.
- AJCC RB staging defines the TNM, which is the most commonly used world cancer terminology.

This study demonstrates that international, multicenter, registry-based studies of rare cancers can be performed using internet-based data sharing. In this study, the 8th edition AJCC classification for RB was used to accurately estimate treatment success and globe salvage.

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Abbreviations and Acronyms:
AJCC = American Joint Committee on Cancer; **CHLA** = Children's Hospital of Los Angeles; **CI** = confidence interval; **EBRT** = external beam radiotherapy; **HR** = hazard ratio; **IAC** = intra-arterial chemotherapy; **ICRB** = International Classification for Retinoblastoma; **IIRC** = International Intraocular Retinoblastoma Classification; **IQR** = interquartile range; **OOTF** = Ophthalmic Oncology Task Force; **RB** = retinoblastoma; **WEH** = Wills Eye Hospital.

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