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High-risk Pathologic Features Based on Presenting Findings in Advanced Intraocular Retinoblastoma:

A Multicenter, International Data-Sharing American Joint Committee on Cancer Study

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Abstract

Purpose: To determine the value of clinical features for advanced intraocular retinoblastoma as defined by the eighth edition of the American Joint Committee on Cancer (AJCC) cT3 category and AJCC Ophthalmic Oncology Task Force (OOTF) Size Groups to predict the high-risk pathologic features.

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

Participants: Eighteen ophthalmic oncology centers from 13 countries over 6 continents shared evaluations of 942 eyes enucleated as primary treatment for AJCC cT3 and, for comparison, cT2 retinoblastoma.

Methods: International, multicenter, registry-based data were pooled from patients enrolled between 2001 and 2013. High-risk pathologic features were defined as AJCC categories pT3 and pT4. In addition, AJCC OOTF Size Groups were defined as follows: (1) less than half, (2) more than half but less than two thirds, (3) more than two thirds of globe volume involved, and (4) diffuse infiltrating retinoblastoma.

Main Outcome Measures: Statistical risk of high-risk pathologic features corresponding to AJCC cT3 subcategories and AJCC OOTF Size Groups.

Results: Of 942 retinoblastoma eyes treated by primary enucleation, 282 (30%) showed high-risk pathologic features. Both cT subcategories and AJCC OOTF Size Groups ($P < 0.001$ for both) were associated with high-risk pathologic features. On logistic regression analysis, cT3c (iris neovascularization with glaucoma), cT3d (intraocular hemorrhage), and cT3e (aseptic orbital cellulitis) were predictive factors for high-risk pathologic features when compared with cT2a with an odds ratio of 2.3 ($P = 0.002$), 2.5 ($P = 0.002$), and 3.3 ($P = 0.019$), respectively. Size Group 3 (more than two-thirds globe volume) and 4 (diffuse infiltrative retinoblastoma) were the best predictive factors with an odds ratio of 3.3 and 4.1 ($P < 0.001$ for both), respectively, for high-risk pathologic features when compared with Size Groups 1 (i.e., < 50% of globe volume).

Conclusions: The AJCC retinoblastoma staging clinical cT3c–e subcategories (glaucoma, intraocular hemorrhage, and aseptic orbital cellulitis, respectively) as well as the AJCC OOTF Size Groups 3 (tumor more than two thirds of globe volume) and 4 (diffuse infiltrative retinoblastoma) both allowed stratification of clinical risk factors that can be used to predict the presence of high-risk pathologic features and thus facilitate treatment decisions.

Keywords

AJCC; Multicenter; Pathology; Retinoblastoma; Staging

The major goals in managing retinoblastoma are to preserve life, the globe, and vision.[1] Over the last 2 decades, newer treatment methods, including intra-arterial and intravitreal chemotherapy, have improved globe salvage rates[2–5]; however, the clinical question of whether eye salvage treatments result in an increased risk of extraocular dissemination of advanced retinoblastoma remains unanswered.[6] Some studies have suggested that high-risk clinical features, such as neovascularization of the iris, glaucoma, and buphthalmos, are associated with high-risk pathologic features and, thus, an increased risk of metastatic disease and death.[7–11]

Herein, we explore which eyes with advanced retinoblastoma were most likely to show high-risk pathologic features after primary enucleation. Both studies used the same international, multicenter-derived dataset and staging criteria from the eighth edition of the American Joint Committee on Cancer (AJCC) Tumor, Node, Metastasis, Heredity (TNMH) retinoblastoma staging system. The AJCC staging system is based on international, multicenter consensus and has been adopted universally by the Union for International Cancer Control and the College of American Pathologists and thus is recommended for retinoblastoma staging around the world.[1,12–15]

According to TNMH retinoblastoma staging, higher T categories include eyes with clinically defined significant retinal detachment (cT2a), seeding (vitreous, subretinal, or both; cT2b), phthisis bulbi (cT3a), anterior segment tumor invasion (cT3b), iris neovascularization with glaucoma (cT3c), intraocular hemorrhage (hyphema, massive vitreous hemorrhage, or both; cT3d), and aseptic orbital cellulitis (cT3e). The AJCC high-risk pathologic features corresponding to the pT3 category were defined as histopathologic evidence of massive choroidal invasion, postlaminar invasion of the optic nerve head with or without a positive margin, and scleral invasion, and those corresponding to the pT4 category were defined as extraocular extension. The clinical evidence that magnetic resonance imaging and computed tomography alone can predict high-risk pathologic features is limited.[16,17] Hence, high-risk clinical features are the best adjunct to guide management of primary advanced retinoblastoma, specifically deciding between globe-salvage attempt and primary enucleation.

In this study, we chose AJCC TNMH staging because the prior international retinoblastoma staging systems consolidated many of the high-risk clinical features of advanced retinoblastoma into 2 groups (D and E).[18,19] In addition, we chose AJCC TNMH staging because prior staging offered competing definitions of group E, resulting in confusion and preventing standardized outcome comparisons.[12,20]

In this study, we examined the strength of the association of high-risk clinical features with high-risk pathologic features. They could serve as an essential tool to assist decision making for these critical cases. Therefore, we used 2 parameters of advanced intraocular retinoblastoma, AJCC retinoblastoma cT subcategories and new AJCC Ophthalmic

Oncology Task Force (OOTF) Size Groups, to investigate their predictive value for high-risk pathologic features in eyes primarily enucleated because of retinoblastoma.

Methods

This international registry–based study was conducted in collaboration with 18 retinoblastoma centers from 13 countries on 6 continents. This study adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996. Each participating center procured internal institutional review board approval as appropriate. Because no patient identifiers were collected, the Princess Margaret Cancer Center determined and all centers approved that individual patient consent was not required. A retrospective chart review was performed for all patients diagnosed with retinoblastoma between January 5, 2001, and December 31, 2013. The AJCC OOTF committee formulated the registry data fields. Then, anonymized data were entered into a secure online database. The database and security measures are described in detail in prior registry publications.[12,13,21]

Definitions

Only internationally recognized ophthalmic oncology subspecialty sites were included. Patients were managed in accordance with best practices defined by each center. Clinical data were collected after retrospective record review, including demographic and clinical information comprising size and location of the intraocular retinoblastoma, presence of prephthisis or phthisis bulbi, anterior segment tumor invasion, and presence of iris neovascularization, glaucoma, buphthalmos, hyphema, vitreous hemorrhage, and aseptic orbital cellulitis. Primary enucleation was defined as the removal of a treatment-naive retinoblastoma eye. Removal of an eye after an attempt at eye salvage, regardless of the reason for enucleation (significant residual disease, recurrent tumor, etc.), was defined as secondary enucleation.

The eighth edition of the AJCC Cancer Staging Manual was used to define the primary tumor extent and high-risk pathologic features.[1] The high-risk clinical features for advanced retinoblastoma are stratified in cT3a-e (Table 1). Registry data were available for all necessary subcategories except the involvement of pars plana and ciliary body (a component of cT3b). All eyes of cT2 categories (Table 1) were chosen as a comparison base to assess the increased risk associated with each cT3 subcategory increase. Thus, high-risk pathologic features were evaluated in all cT2 and cT3 eyes that underwent primary enucleation, whereas cT1 and cT4 eyes were not considered.

AJCC OOTF Size Group Definitions

No uniform size criteria exist for intraocular retinoblastoma associated with a high risk of the presence of high-risk pathologic features. The AJCC seventh edition retinoblastoma staging system used a two-thirds fill of the ocular volume.[22] The Wills Eye Hospital used tumor filling of > 50% of globe volume to define group E, and the Children's Hospital of Los Angeles defined group E as diffuse infiltrating retinoblastoma.[18,19] Diffuse infiltrating retinoblastoma was defined as the presence of diffuse intraretinal and vitreal

growth without a defined tumoral mass. For the present study, the AJCC OOTF divided intraocular tumor size into 4 groups to estimate risk for high-risk pathologic features after primary enucleation: Size Group 1, less than one half of globe volume involved; Size Group 2, more than one half but less than two thirds of globe volume involved; Size Group 3, more than two thirds of globe volume filled with tumor; and Size Group 4, diffuse infiltrating retinoblastoma.

Exclusion criteria were as follows: if any key variable, such as clinical variables essential for retinoblastoma classification (tumor location, size, extent), treatment data (date and type of treatment), and outcome, were missing or inconsistent, the eye was excluded. The eyes that were enucleated secondarily were excluded from the analysis of high-risk pathologic features because the treatment may have downstaged those eyes. The cT1 category eyes also were excluded because they were candidates for globe-conserving therapies. Finally, cT4 eyes were excluded because these eyes are associated with orbital retinoblastoma extension, and thus globe salvage typically was not a treatment option.

The registry contained completed data for 2854 eyes from 2190 patients. Of these, 1334 eyes (46.7%) were assigned stage cT2, and 802 eyes (28.1%) were assigned stage cT3. The number of eyes treated with primary enucleation was 464 eyes (34.8%) with cT2 staging and 478 eyes (59.6%) with cT3 staging (Fig 1).

Statistical Analysis

The data are summarized per the AJCC eighth edition retinoblastoma staging system and AJCC OOTF Size Groups. Median, range, and interquartile range are used to describe continuous variables, and frequencies and proportions are reported for categorical variables. Contingency tables were constructed, and the chi-square test was used for categorical variables. Logistic regression analysis was used to test whether cT3 subcategories and AJCC OOTF Size Groups were associated independently with high-risk pathologic features. The statistical analysis was performed using SPSS software, version 26.0 (IBM). Statistical significance was set at $P < 0.05$.

Results

Clinical Features

Enucleated eyes were staged with clinical cT and pathologic pT categories such that 464 eyes with cT2b staging (with intraocular seeding [78.0%]) and 478 eyes with cT3c staging (iris neovascularization and glaucoma [49.4%]) were the most common subcategories (Tables 2 and 3). The AJCC pathologic pT categories for 942 primarily enucleated eyes were 302 eyes (32.1%) with pT1 staging, 358 eyes (38.0%) with pT2 staging, 236 eyes (25.1%) with pT3 staging, and 46 eyes (4.9%) with pT4 staging (Table 3). Of these, high-risk pathologic features were identified in 282 eyes (29.9%; Table S1, available at www.aaojournal.org).

The AJCC OOTF tumor Size Group data were available for 903 of 942 eyes. According to Size Groups, 125 eyes (13.8%) were in Group 1 (less than one half of volume), 172 eyes (19%) were in Group 2 (more than one half but less than two thirds of volume), 495 eyes

(54.8%) were in Group 3 (more than two thirds of volume), and 111 eyes (12.4%) were in group 4 (diffuse infiltrating retinoblastoma; Table 2; Fig 1).

Treatment Outcomes: Predictors of High-risk Pathologic Features

Clinical Features by AJCC cT Subcategory.—The median age at diagnosis of 282 eyes with high-risk pathologic features was 24.0 months versus 22.0 months for eyes with no high-risk pathologic features ($P = 0.064$; Fig S1, available at www.aaojournal.org). The percentages of eyes with high-risk pathologic features were similar by heritable trait and laterality ($P > 0.66$). Of the 464 eyes with cT2 staging treated with primary enucleation, high-risk pathologic features were found in 84 eyes (18.1%). Subgroup analysis revealed that these eyes more frequently had cT2a staging (23.5%) than cT2b staging (16.6%; Table S1). High-risk pathologic features were present in 198 of 478 eyes (41.4%) with cT3 staging, with a comparable frequency in eyes with cT3a staging (phthisis; 4/8 [50%]), eyes with cT3c staging (glaucoma; 103/236 [43.6%]), eyes with cT3d staging (intraocular hemorrhage; 63/136 [46.3%]), and eyes with cT3e staging (orbital cellulitis; 10/21 [47.6%]); however, only approximately half that frequency of high-risk pathologic features was seen in cT3b eyes (anterior chamber involvement; 18/77 [23.4%]).

On logistic regression (Tables 4 and 5), cT3c (glaucoma), cT3d (intraocular hemorrhage), and cT3e (orbital cellulitis) staging were significant predictive factors, with odds ratios (ORs) of 2.3 (95% confidence interval [CI], 1.3–3.9; $P = 0.002$), 2.5 (95% CI, 1.4e4.5; $P = 0.002$), and 3.3 (95% CI, 1.2–8.7; $P = 0.019$) for high-risk pathologic features compared with cT2a staging. The registry had too few cases to exclude an OR of 3.3 (95% CI, 1.2–8.7) in cT3e eyes (orbital cellulitis) as a significant predictor. The estimated ORs of 0.6 (95% CI, 0.4–1.1) for cT2b eyes, 3.3 (95% CI, 0.8–14.6) for cT3a (phthisis), and 0.9 (95% CI, 0.4–1.8) for cT3b eyes (anterior segment involvement) were not confirmed to be different from the reference cT2a eyes (OR, 1.0, by definition).

Tumor Size Group.—Of the 903 eyes with retinoblastoma for which tumor size data were available, 265 eyes (29.3%) showed high-risk pathologic features (Supplemental Table 1). According to AJCC OOTF Size Group, high-risk pathologic features were seen in 17 of 125 eyes in Group 1 (less than one half of volume; 13.6%), in 33 of 172 eyes in Group 2 (more than one half but less than two thirds of volume; 19.2%), and more commonly in 171 of 495 eyes in Group 3 (more than two thirds of volume; 34.5%) and in 44 of 111 eyes in Group 4 (diffuse infiltrating retinoblastoma; 39.6%; Table S1). On logistic regression analysis (Tables 6 and 7), the OR increased with increasing tumor size grouping (OR, 1.5–4.1). As compared with Size Group 1 (less than one-half tumor volume), the OR was significantly larger for Size Group 3 (more than two thirds of globe volume filled with tumor) and Size Group 4 (diffuse infiltrating retinoblastoma; $P < 0.001$ for both).

A sensitivity analysis was performed by merging the Size Groups to probe the effect of the existing discrepancies in tumor size cutoffs between the international classifications. When Size Groups 2 and 3 were merged (less than one half vs. more than one half of globe volume), a difference was noted in the frequency of high-risk pathologic features (Table S2, available at www.aaojournal.org); however, the OR increased with increasing category from

1.0 to 2.7 and 4.1 ($P < 0.001$ for Group 1 [less than one half tumor volume] vs. Groups 2 plus 3 (more than one half tumor volume) and for Groups 1 versus 4 (diffuse infiltrating retinoblastoma; Table S2). The logistic regression model explained 4.4% (Nagelkerke R^2) of the variance and correctly classified 70.7% of cases. The area under the receiver operating characteristic curve was 0.572 (95% CI, 0.532–0.612; $P = 0.001$).

In contrast, an analysis after merging Size Groups 1 and 2 (less than two thirds vs. more than two thirds of globe volume) showed a significant difference in frequency of high-risk pathologic features among all Size Groups (Table S3, available at www.aaojournal.org). The OR again increased with increasing category from 1.0 to 2.6 and 3.2 ($P < 0.001$ for Groups 1 plus 2 [less than two thirds tumor volume] vs. Group 3 [more than two thirds tumor volume] and for Groups 1 plus 2 vs. 4 [diffuse infiltrative retinoblastoma]; Table S3). The model explained 6.3% (Nagelkerke R^2) of the variance and also correctly classified 70.7% of cases. Area under the receiver operating characteristic curve was 0.608 (95% CI, 0.568–0.647; $P < 0.001$).

Discussion

Our study used a multicenter, international, internet-based registry to assess the association of high-risk pathologic features (defined as AJCC stages pT3 and pT4) with high-risk clinical features (AJCC clinical cT subcategories) and AJCC OOTF Size Group at diagnosis. Specifically, we found a 2.3-fold risk in cT3c eyes (raised intraocular pressure with neovascularization, buphthalmos, or both) and 2.5-fold risk with cT3d (presence of hyphema, massive vitreous hemorrhage, or both) when compared with cT2a eyes. The AJCC OOTF size grouping was associated significantly with the presence of high-risk pathologic features, with a 2.6-fold risk for Size Group 3 (tumor involving more than two thirds of globe volume) and 3.2-fold risk for Size Group 4 (diffuse infiltrating retinoblastoma) as compared with Size Groups 1 plus 2 (tumor involving less than two thirds of globe volume).

Other studies have investigated the risk of orbital recurrence and systemic dissemination after enucleation by looking for the presence of high-risk pathologic features.[7,8,23] Despite some conflicting opinions, massive choroidal invasion, optic nerve involvement beyond the lamina cribrosa, scleral invasion, and extraocular extension generally are considered to be features of advanced disease that warrant adjuvant therapy[11,24,25]; however, not all eyes with advanced intraocular retinoblastoma are enucleated at presentation. Because prior chemotherapy may obscure high-risk pathologic features and may bias evaluation at the time of secondary enucleation, identification of clinical features associated with high-risk pathologic features at initial tumor staging is paramount.[26,27] Otherwise, the patient might be deprived of the necessary follow-up and adjuvant treatment to prevent local tumor recurrence and systemic disease.[6] Nowhere is this more important than in developing nations, where advanced retinoblastoma has been shown to be the most common presenting stage and whose children show the highest retinoblastoma-associated mortality.[21,28,29]

Before AJCC retinoblastoma staging, high-risk clinical features were clustered within a single, international classification group (group E). Putting all these high-risk features together gave the false impression that all these features share the same or similar risk

for high-risk pathologic features and metastatic disease.[12,20] In contrast, our study used the AJCC clinical cT3 subcategories and AJCC OOTF Size Groups, which segregated the clinical features of advanced intraocular retinoblastoma for analysis.[1]

For example, our study revealed that raised intraocular pressure resulting from iris neovascularization with or without buphthalmos and hyphema or massive vitreous hemorrhage are important clinical predictors of high-risk pathologic features. Although the estimated OR for sterile orbital inflammation (stage cT3e) was comparable with the former predictors, the subcategory included a small sample size. Thus, a future study with larger sample size is more appropriate to include or exclude sterile orbital inflammation (stage cT3e) as an additional predictor for high-risk pathologic features.

Our study revealed new information about intraocular retinoblastoma tumor size, which long has been a factor in the decision to enucleate. Our initial analysis for the eighth edition AJCC retinoblastoma staging showed no difference in the probability of avoiding enucleation or external beam radiation for eyes with tumor of more than one half and tumor more than two thirds of the globe volume[1]; however, further analysis in this study revealed that tumor more than two thirds of globe volume and diffuse infiltrating retinoblastoma were predictors of high-risk pathologic features. Sensitivity analysis showed that tumor more than two-thirds globe volume is a more accurate risk factor for high-risk pathologic features than tumor more than one-half globe volume.

The limitations of this study are related to its retrospective design. The registry did not include clinical data fields on pars plana and ciliary body involvement, probably resulting in lower numbers of cT3b eyes (anterior chamber involvement).

The strengths of our study include that our analysis was restricted to clinical features determined at the time of diagnosis and thus before interventions that have affected high-risk pathologic features. Our study is multicenter and international, and therefore, its data should be considered an accurate representation of what occurs throughout the world. This registry-based analysis used a single, widely accepted AJCC Union for International Cancer Control retinoblastoma staging system, thus allowing rapid clinical implementation. Our large sample size for this rare cancer allowed subgroup analyses, which provided significant medical evidence that can be used to support improved retinoblastoma management.

In conclusion, AJCC retinoblastoma clinical high-risk features as defined by their cT categories and AJCC OOTF Size Groups were found to predict the presence of high-risk pathologic features in eyes with advanced intraocular retinoblastoma after primary enucleation. These features can serve as a guide to estimate retinoblastoma prognosis at presentation, to discuss treatment plans with parents, and thus to improve outcomes for children with high-risk retinoblastoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations and Acronyms:

AJCC	American Joint Committee on Cancer
CI	confidence interval
OOTF	Ophthalmic Oncology Task Force
OR	odds ratio
TNMH	Tumor, Node, Metastasis, Heredity

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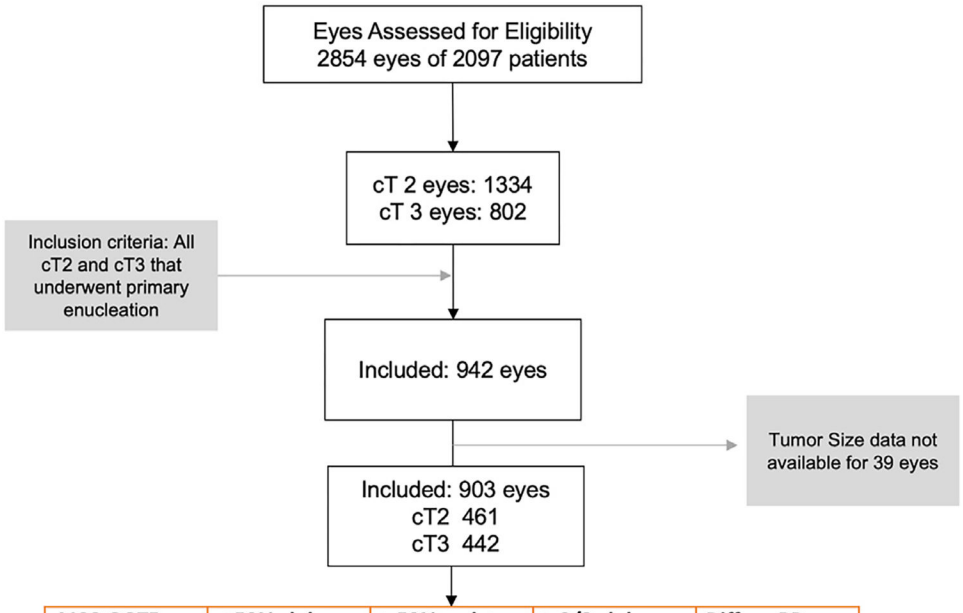

AJCC-OOTF size groups	< 50% globe involved	> 50% and < 2/3 globe involved	> 2/3 globe involved	Diffuse RB
cT2	89	119	248	5
cT3	36	53	247	106
Total	125	172	495	111

Figure 1.

Consolidated Standards for Reporting Trials flow diagram showing all eyes with advanced retinoblastoma (RB) treated with primary enucleation. AJCC = American Joint Committee on Cancer; OOTF = Ophthalmic Oncology Task Force.

Table 1.

Definitions from the Eighth Edition of American Joint Committee on Cancer Staging Used in the Present Study[1]

American Joint Committee on Cancer Category	Description
Clinical Retinoblastoma	
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, subretinal seeding, or both
cT3	Advanced intraocular tumor(s)
cT3a	Phthisis or prephthisis bulbi
cT3b	Tumor invasion of the pars plana, ciliary body, lens, zonules, iris, or anterior chamber
cT3c	Raised intraocular pressure with neovascularization, buphthalmos, or both
cT3d	Hyphema, massive vitreous hemorrhage, or both
cT3e	Aseptic orbital cellulitis
Pathologic Retinoblastoma	
pTX	Unknown evidence of intraocular tumor
pT0	No evidence of intraocular tumor
pT1	Intraocular tumor(s) without any local invasion, focal choroidal invasion, or prelaminar or intralaminar involvement of the optic nerve head
pT2	Intraocular tumor(s) with local invasion
pT2a	Concomitant focal choroidal invasion and prelaminar or intralaminar involvement of the optic nerve head
pT2b	Tumor invasion of stroma of iris, trabecular meshwork, Schlemm's canal, or a combination thereof
pT3	Intraocular tumor(s) with significant local invasion
pT3a	Massive choroidal invasion (>3 mm in largest diameter, 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, invasion into or around emissary channels, or both
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

c = clinical; p = pathologic; T = tumor.

*Clinically undetected for the purpose of this study.

Table 2.

Eighth Edition American Joint Committee on Cancer Clinical T Category and American Joint Committee on Cancer Ophthalmic Oncology Task Force Size Groups for 942 Eyes with Retinoblastoma That Underwent Primary Enucleation

Clinical American Joint Committee on Cancer Subcategory	American Joint Committee on Cancer Ophthalmic Oncology Task Force Size Group					
	1	*2*	*3*	*4*	*Data Not Available* *	Total
cT2a						
Count	8	7	83	1	3	102
Clinical subcategory (%)	7.8	6.9	81.4	1.0	2.9	100.0
Size Groups (%)	6.4	4.1	16.8	0.9	7.7	10.8
Total (%)	0.8	0.7	8.8	0.1	0.3	10.8
cT2b						
Count	81	112	165	4	0	362
Clinical subcategory (%)	22.4	30.9	45.6	1.1	0.0	100.0
Size Groups (%)	64.8	65.1	33.3	3.6	0.0	38.4
Total (%)	8.6	11.9	17.5	0.4	0.0	38.4
cT3a						
Count	0	0	5	0	3	8
Clinical subcategory (%)	0.0	0.0	62.5	0.0	37.5	100.0
Size Groups (%)	0.0	0.0	1.0	0.0	7.7	0.8
Total (%)	0.0	0.0	0.5	0.0	0.3	0.8
cT3b						
Count	12	10	32	16	7	77
Clinical subcategory (%)	15.6	13.0	41.6	20.8	9.1	100.0
Size Groups (%)	9.6	5.8	6.5	14.4	17.9	8.2
Total (%)	1.3	1.1	3.4	1.7	0.7	8.2
cT3c						
Count	18	28	156	30	4	236
Clinical subcategory (%)	7.6	11.9	66.1	12.7	1.7	100.0
Size Groups (%)	14.4	16.3	31.5	27.0	10.3	25.1
Total (%)	1.9	3.0	16.6	3.2	0.4	25.1
cT3d						

Clinical American Joint Committee on Cancer Subcategory	American Joint Committee on Cancer Ophthalmic Oncology Task Force Size Group					
	1	*2*	*3*	*4*	*Data Not Available* *	**Total**
Count	6	15	47	58	10	136
Clinical subcategory (%)	4.4	11.0	34.6	42.6	7.4	100.0
Size Groups (%)	4.8	8.7	9.5	52.3	25.6	14.4
Total (%)	0.6	1.6	5.0	6.2	1.1	14.4
cT3e						
Count	0	0	7	2	12	21
Clinical subcategory (%)	0.0	0.0	33.3	9.5	57.1	100.0
Size Groups (%)	0.0	0.0	1.4	1.8	30.8	2.2
Total (%)	0.0	0.0	0.7	0.2	1.3	2.2
Total						
Count	125	172	495	111	39	942
Total (%)	13.3	18.3	52.5	11.8	4.1	100.0

* Tumor size could not be assessed because of media opacity (vitreous hemorrhage, anterior chamber bleeding, buphthalmos, phthisis, etc.).

Table 3.

Eighth Edition American Joint Committee on Cancer Pathologic pT Category in 942 Eyes with Retinoblastoma That Underwent Primary Enucleation

	Pathologic American Joint Committee on Cancer Subcategory				
Clinical American Joint Committee on Cancer Subcategory	***pT1***	***pT2***	***pT3***	***pT4***	**Total**
cT2a					
Count	45	33	18	6	102
Clinical subcategory (%)	44.1	32.4	17.6	5.9	100.0
Pathologic category (%)	14.9	9.2	7.6	13.0	10.8
Total (%)	4.8	3.5	1.9	0.6	10.8
cT2b					
Count	153	149	56	4	362
Clinical subcategory (%)	42.3	41.2	15.5	1.1	100.0
Pathologic category (%)	50.7	41.6	23.7	8.7	38.4
Total (%)	16.2	15.8	5.9	0.4	38.4
cT3a					
Count	2	2	2	2	8
Clinical subcategory (%)	25.0	25.0	25.0	25.0	100.0
Pathologic category (%)	0.7	0.6	0.8	4.3	0.8
Total (%)	0.2	0.2	0.2	0.2	0.8
cT3b					
Count	27	32	16	2	77
Clinical subcategory (%)	35.1	41.6	20.8	2.6	100.0
Pathologic category (%)	8.9	8.9	6.8	4.3	8.2
Total (%)	2.9	3.4	1.7	0.2	8.2
cT3c					
Count	40	93	93	10	236
Clinical subcategory (%)	16.9	39.4	39.4	4.2	100.0
Pathologic category (%)	13.2	26.0	39.4	21.7	25.1
Total (%)	4.2	9.9	9.9	1.1	25.1
cT3d					
Count	28	45	43	20	136

	Pathologic American Joint Committee on Cancer Subcategory				
Clinical American Joint Committee on Cancer Subcategory	***pT1***	***pT2***	***pT3***	***pT4***	**Total**
Clinical subcategory (%)	20.6	33.1	31.6	14.7	100.0
Pathologic category (%)	9.3	12.6	18.2	43.5	14.4
Total (%)	3.0	4.8	4.6	2.1	14.4
cT3e					
Count	7	4	8	2	21
Clinical subcategory (%)	33.3	19.0	38.1	9.5	100.0
Pathologic category (%)	2.3	1.1	3.4	4.3	2.2
Total (%)	0.7	0.4	0.8	0.2	2.2
Total					
Count	302	358	236	46	942
Total (%)	32.1	38.0	25.1	4.9	100.0

Table 4.

Assessment of Risk for High-risk Pathologic Features Based on Clinical Features and Eighth Edition American Joint Committee on Cancer Clinical cT Subcategories in 942 Primarily Enucleated Eyes with Retinoblastoma

Features	High-risk Pathologic Features Absent (n = 660)*	High-risk Pathologic Features Present (n = 282)	*P* Value
Median age at diagnosis (mos), mean (IQR)	22.0 (24.7 to 11–32)	24.0 (27.2 to 15–34)	0.064
Laterality, no. (%)			
Unilateral	521 (78.9)	219 (77.7)	0.66
Bilateral	139 (21.1)	63 (22.3)	
Heritable trait, no. (%)			
H0	516 (78.2)	217 (77.0)	0.68
H1	144 (21.8)	65 (23.0)	
cT, no. (%)			
cT2	380 (57.6)	84 (29.8)	<0.001*
cT2a	78 (11.8)	24 (8.5)	
cT2b	302 (45.8)	60 (21.3)	
cT3	280 (42.4)	198 (70.2)	
cT3a	4 (0.6)	4 (1.4)	
cT3b	59 (8.9)	18 (6.4)	
cT3c	133 (20.2)	103 (36.5)	
cT3d	73 (11.1)	63 (22.3)	
cT3e	11 (1.7)	10 (3.5)	

IQR = interquartile range.

*Chi-square test for trend.

Table 5.

Logistic Regression Analysis: Predictors of High-risk Pathologic Features by Eighth Edition American Joint Committee on Cancer Clinical cT Subcategories in 942 Primarily Enucleated Eyes with Retinoblastoma

Variable	B (Standard Error)	*P* Value	Odds Ratio	95% CI
Bivariate analysis *				
Tumor size				
cT2a	Reference		1.0	
cT2b	−0.539 (0.277)	0.051	0.6	0.4–1.1
cT3a	1.201 (.756)	0.11	3.3	0.8–14.6
cT3b	−0.134 (0.360)	0.71	0.9	0.4–1.8
cT3c	0.830(0.271)	0.002	2.3	1.3–3.9
cT3d	0.921 (0.294)	0.002	2.5	1.4–4.5
cT3e	1.183 (0.503)	0.019	3.3	1.2–8.7
Age (mos)				
<8.0	Reference			
8.0–17.0	0.401 (0.274)	0.14	1.5	0.9–2.6
17.0–29.0	0.632 (0.257)	0.014	1.9	1.1–3.1
>29.0	0.656 (0.260)	0.012	1.9	1.1–3.2
Constant	−1.600 (0.300)		0.268	
Univariable analysis				
Tumor size †				
cT2a	Reference		1.0	
cT2b	−0.437 (0.273)	0.11	0.6	0.4–1.1
cT3a	1.179 (0.745)	0.11	3.3	0.8–14.0
cT3b	−0.009 (0.356)	0.98	0.9	0.5–2.0
cT3c	0.923 (0.268)	0.001	2.5	1.5–4.2
cT3d	1.031 (0.290)	<0.001	2.8	1.6–5.0
cT3e	1.083 (0.495)	0.029	3.0	1.1–7.8
Constant	−1.179 (0.233)		0.268	
Age (mos) ‡				

Variable	B (Standard Error)	*P* Value	Odds Ratio	95% CI
<8.0	Reference			
8.0–17.0	0.281 (0.255)	0.27	1.3	0.8–2.2
17.0–29.0	0.587 (0.235)	0.012	1.8	1.1–2.9
>29.0	0.527 (0.235)	0.025	1.7	1.1–2.7
Constant	−1.270 (0.200)		0.281	

CI = confidence interval.

[*] The logistic regression model explained 11.8% (Nagelkerke R^2) of the variance and correctly classified 70.1% of eyes. Area under the receiver operating characteristic curve was 0.652 (95% CI, 0.612–0.691; $P < 0.001$).

[†] The logistic regression model explained 11.3% (Nagelkerke R^2) of the variance and correctly classified 70.1% of eyes. Area under the receiver operating characteristic curve was 0.652 (95% CI, 0.612–0.691; $P < 0.001$).

[‡] The logistic regression model explained 1.2% (Nagelkerke R^2) of the variance and correctly classified 70.1% of eyes. Area under the receiver operating characteristic curve was 0.545 (95% CI, 0.506–0.584; $P = 0.028$).

Table 6.

Frequency of High-risk Pathologic Features Based on American Joint Committee on Cancer Ophthalmic Oncology Task Force Size Group in 903 Primarily Enucleated Eyes with Retinoblastoma

American Joint Committee on Cancer Ophthalmic Oncology Task Force Size Group		High-risk Pathologic Features Absent (n = 660)	High-risk Pathologic Features Present (n = 282)	*P* Value
1	Less than one half of globe involved	108 (16.4)	17 (6.0)	<0.001 *
2	More than one half and less than two thirds of globe involved	139 (21.1)	33 (11.7)	
3	More than two thirds of globe involved	324 (49.1)	171 (60.6)	
4	Diffuse infiltrating retinoblastoma	67 (10.2)	44 (15.6)	
Tumor size data not available †		22 (3.3)	17 (6.0)	

Data are presented as no. (%), unless otherwise indicated.

* Chi-square test for trend.

† Tumor size could not be assessed because of media opacity (vitreous hemorrhage, anterior chamber bleed, buphthalmos, phthisis, etc.).

Table 7.

Logistic Regression Analysis: Predictors of High-Risk Pathology by AJCC OOTF Size Group in 903 Primarily Enucleated Eyes with Retinoblastoma

Variable	B (Standard Error)	*P* Value	Odds Ratio	95% CI
Bivariate analysis *				
AJCC OOTF Size Group				
1, Less than one half of globe involved	Reference		1.0	
2, More than one half and less than two thirds of globe involved	0.405 (0.325)	0.22	1.5	0.8–2.9
3, More than two thirds of globe involved	1.184 (0.278)	<0.001	3.3	1.9–5.8
4, Diffuse infiltrating retinoblastoma	1.400 (0.326)	<0.001	4.1	2.2–7.9
Age (mos)				
<8.0			1.0	
8.0–17.0	0.235 (0.266)	0.37	1.3	0.8–2.2
17.0–29.0	0.442 (0.245)	0.071	1.6	0.9–2.6
>29.0	0.424 (0.244)	0.083	1.5	0.9–2.6
Constant	−2.160 (0.323)	<0.001	0.1	
Univariate analysis †				
AJCC OOTF Size Group				
1, Less than one half of globe involved	Reference		1.0	
2, More than one half and less than two thirds of globe involved	0.411 (0.325)	0.206	1.5	0.8–2.9
3, More than two thirds of globe involved	1.210 (0.278)	<0.001	3.3	1.9–5.8
4, Diffuse infiltrating retinoblastoma	1.428 (0.325)	<0.001	4.1	2.2–7.9
Constant	−1.849 (0.261)	<0.001	0.16	

AJCC = American Joint Committee on Cancer; CI = confidence interval; OOTF = Ophthalmic Oncology Task Force.

*The logistic regression model explained 6.5% (Nagelkerke R^2) of the variance and correctly classified 70.7% of cases. Area under the receiver operating characteristic curve was 0.611 (95% CI, 0.572–0.650; $P < 0.001$).

†The logistic regression model explained 5.9% (Nagelkerke R^2) of the variance and correctly classified 70.7% of cases. Area under the receiver operating characteristic curve was 0.611 (95% CI, 0.572–0.650; $P < 0.001$).