

Retinoblastoma Outcomes Based on the 8th Edition American Joint Committee on Cancer Pathological Classification in 1411 Patients

Vijitha S. Vempuluru, MD,¹ Carol L. Shields, MD,² Jesse L. Berry, MD,^{3,4} Swathi Kaliki, MD,¹ on behalf of the High-Risk Retinoblastoma Collaborative Study Group

Purpose: To evaluate the outcomes of retinoblastoma (RB) based on the 8th edition of the American Joint Committee on Cancer (AJCC) pathological classification in a global cohort of patients.

Design: Retrospective, multicenter, intercontinental, collaborative study.

Participants: A total of 1411 patients.

Intervention: Primary enucleation with or without adjuvant chemotherapy or radiotherapy.

Main Outcome Measures: Orbital tumor recurrence, tumor-related metastasis, and tumor-related death.

Results: According to the 8th edition AJCC pathological classification, 645 eyes (46%) belonged to pathological T (pT)1, 164 (11%) to pT2, 493 (35%) to pT3, and 109 (8%) to pT4 categories. At a mean follow-up of 38 months (median, 35 months; < 1–149 months), orbital tumor recurrence was seen in 8 (1%), 5 (3%), 22 (4%), and 25 (23%) of pT1, pT2, pT3, and pT4 ($P < 0.001$) categories, respectively; tumor-related metastasis was seen in 7 (1%), 5 (3%), 40 (8%), and 46 (43%) of pT1, pT2, pT3, and pT4 ($P < 0.001$) categories, respectively; tumor-related death was seen in 12 (2%), 7 (4%), 64 (13%), and 64 (59%) of pT1, pT2, pT3, and pT4 ($P < 0.001$) categories, respectively. Multivariate Cox proportional hazards analysis of outcomes revealed pT category and adjuvant therapy as independent predictors of outcomes. Categories pT3b ($P = 0.005$), pT3c ($P < 0.001$), pT3d ($P < 0.001$), and pT4 ($P < 0.001$) had a greater hazard for orbital recurrence; categories pT2a ($P = 0.015$), pT3a ($P < 0.001$), pT3b ($P < 0.001$), pT3c ($P < 0.001$), pT3d ($P < 0.001$), and pT4 ($P < 0.001$) had a greater hazard for tumor-related metastasis; and categories pT2a ($P = 0.068$), pT2b ($P = 0.004$), pT3a ($P < 0.001$), pT3b ($P < 0.001$), pT3c ($P < 0.001$), pT3d ($P < 0.001$), and pT4 ($P < 0.001$) had a greater hazard for tumor-related death when compared with the pT1 category. Patients who did not receive adjuvant therapy had greater hazards of orbital tumor recurrence in categories pT3b ($P = 0.005$), pT3c ($P = 0.003$), and pT4 ($P = 0.002$); greater hazards of tumor-related metastasis in categories pT3a ($P = 0.001$), pT3b ($P = 0.01$), pT3c ($P = 0.001$), and pT4 ($P = 0.007$); and tumor-related death in categories pT3a ($P < 0.001$), pT3b ($P = 0.009$), pT3c ($P = 0.018$), and pT4 ($P < 0.001$) when compared with those who received adjuvant therapy.

Conclusions: The 8th edition AJCC pathological classification predicts outcomes in patients undergoing primary enucleation for RB, and adjuvant therapy is associated with a lower risk of orbital recurrence, tumor-related metastasis, and tumor-related death in the pT3 and pT4 categories.

Financial Disclosure(s): The author(s) have no proprietary or commercial interest in any materials discussed in this article. *Ophthalmology* 2025;132:317–326 © 2024 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.

Despite significant advances in the treatment of retinoblastoma (RB) over the last few decades, primary enucleation remains the foremost treatment option in select cases of advanced RB.¹ It is the only form of treatment available for RB in some centers worldwide for saving the lives of children affected by RB.² One main advantage of primary enucleation is that it provides an unaltered picture of tumor pathology, which aids in prognostication.³ Studies have analyzed the outcomes of RB based on histopathological features leading to the evolution of high-

risk histopathological features (HRHFs) and post-enucleation adjuvant therapy in RB.^{4–10}

It is well known that there is remarkable heterogeneity in the accepted definitions of HRHF across various RB treatment centers worldwide.¹⁰ Given this heterogeneity in the grouping, risk stratification, and management of RB,¹ using the American Joint Committee on Cancer (AJCC) Classification pathological staging provides a uniform medium for reporting the outcomes after primary enucleation for RB.¹¹ The current 8th edition of the AJCC

Classification was proposed in 2017, and, for RB, changes were made to the definitions of pT1 to pT4, among other changes.¹¹ Some studies analyzed tumor-related outcomes of RB after primary enucleation^{12–26} but only a few have considered the AJCC pathological staging system,^{23,25} which makes the results difficult to generalize across different treatment centers. To bridge this void in the literature, the High-Risk Retinoblastoma Collaborative Study Group presents this report of outcomes based on the 8th edition AJCC pathological tumor category in a global cohort of patients.

Methods

Retinoblastoma treatment centers worldwide were invited to study the histopathological features of RB, and those who agreed to participate formed the High-Risk Retinoblastoma Collaborative Study Group. The study adhered to the tenets of the Declaration of Helsinki and aligned with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.²⁷ Participating centers located in the United States adhered to the Health Insurance Portability and Accountability Act regulations. Institutional Review Board approval was obtained from the appropriate institutions. Informed consent was obtained from the parents/guardians of all the patients included in this study.

The inclusion criterion was patients with RB who underwent primary enucleation between 2011 and 2020. Records of patients with inadequate histopathological details were excluded. Data collected included demographic features, clinical features at presentation, tumor group by the International Classification of Retinoblastoma,²⁸ International Intraocular Retinoblastoma Classification,²⁹ 8th edition AJCC clinical T category,¹¹ histopathological features (growth pattern, tumor differentiation, local invasion, optic nerve invasion, and extraocular invasion), 8th edition AJCC pathological T (pT) category,¹¹ and details of adjuvant treatment and outcomes.

Outcomes were defined as orbital tumor recurrence, tumor-related metastasis, and tumor-related death. Coded, deidentified data from different centers were entered in Microsoft Excel. One author (S.K.) was responsible for compiling and verifying all the data from different centers. Two authors (V.S.V. and S.K.) verified the pT category against histopathological features of all records to ensure assignment accuracy as per the 8th edition AJCC pathological T (pT) category.

Statistical Analysis

The statistical analysis was performed using IBM SPSS Statistics (version 29.0.2.0 [20]). Demographics, clinical features, histopathological features, treatment, and outcomes were compared based on the pT categories 1, 2, 3, and 4. Continuous data were expressed as mean, median, and range. Shapiro–Wilk and Kolmogorov–Smirnov tests were used to check the normality of the distribution of continuous data. Continuous variables were analyzed using the Kruskal–Wallis test. Categorical data were expressed as proportions. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify predictors (age, race, symptom duration, pT category, and adjuvant therapy) of orbital tumor recurrence, tumor-related metastasis, and tumor-related death. Cox proportional hazard regression analysis was used to assess the hazards of outcomes without adjuvant therapy within each pT category. A *P* value of < 0.05 was

considered statistically significant. Kaplan–Meier analysis was performed to estimate the cumulative incidence of orbital tumor recurrence, tumor-related metastasis, and tumor-related death in the overall cohort based on the pT categories and subgroups with and without adjuvant therapy. The mean survival times were calculated for each pT category and within their subgroups by Kaplan–Meier analysis.

Results

A total of 1411 primarily enucleated eyes from 1411 patients were included in the study, and these were grouped under pT1 (*n* = 645, 46%), pT2 (*n* = 164, 11%; pT2a: 137, 9%; pT2b: 27, 2%), pT3 (*n* = 493, 35%; pT3a: 151, 11%; pT3b: 283, 20%; pT3c: 52, 4%; pT3d: 7, <1%), and pT4 (*n* = 109, 8%) categories as per criteria defined by the 8th edition AJCC classification system for pathological staging (Table S1, available at www.aaojournal.org), based on the presence and extent of involvement of choroid, optic nerve, sclera, iris, trabecular meshwork, and Schlemm's canal. There were 4 eyes with isolated focal invasion of the ciliary body. These eyes were classified as pT1 category, considering that the ciliary body and choroid form the posterior uveal tissue, and isolated focal choroidal invasion is defined as pT1.

Demographics and Clinical Features

The mean age of presentation was 30 months (median, 26 months; range, <1–143 months). The mean age increased from the pT1 category to the pT4 category (*P* < 0.001). The male-to-female ratio was 53:47 in the entire cohort, which was not significantly different among the 4 categories. The mean duration of symptoms showed a gradual increase from pT1 to pT4 categories (*P* < 0.001). A majority of the tumors belonged to group E by the International Classification of Retinoblastoma²⁸ (85%), IIRC (80%), and International Intraocular Retinoblastoma Classification²⁹ (75%) systems. By the 8th edition AJCC clinical T staging system, 45% of eyes were classified as cT2, 51% as cT3, and 4% as cT4 categories.¹¹ The clinical features are listed in detail in Table 2.

Histopathological Features

Endophytic growth was the most common pattern, and moderately differentiated tumors were the most common in the primarily enucleated eyes. In eyes from categories pT1, pT2, and pT3, endophytic growth was the most common pattern (55%, 55%, and 41%, respectively), whereas pT4 eyes showed a predominance (52%) of mixed growth pattern (*P* < 0.001). Moderately differentiated tumors comprised a majority in the pT1 (33%) and pT2 (39%) categories, and poorly differentiated tumors in the pT3 (41%) and pT4 (51%) categories (*P* < 0.001). The proportion of eyes with anterior chamber seeds followed an increasing trend with the advancing pT category (*P* < 0.001) (Table 3).

Table 2. Retinoblastoma Based on the 8th Edition AJCC Pathological Staging in a Global Study of 1411 Patients: Demographics and Clinical Features

Parameter	Total N = 1411 n (%)	pT1 N = 645 n (%)	pT2 N = 164 n (%)	pT3 N = 493 n (%)	pT4 N = 109 n (%)	P Value
Mean age at presentation, mos, (median, range)	30 (26, < 1–143)	27 (26, < 1–109)	28 (24, < 1–112)	33 (30, < 1–143)	38 (35, 4–127)	< 0.001
Sex						
Male	750 (53)	334 (52)	84 (51)	269 (55)	63 (58)	0.546
Female	661 (47)	311 (48)	80 (49)	224 (45)	46 (42)	
Heredity pattern						
Sporadic	1334 (94)	603 (94)	159 (97)	464 (94)	108 (99)	0.051
Familial	77 (5)	42 (6)	5 (3)	29 (6)	1 (1)	
Tumor laterality						
Unilateral	1191 (84)	549 (84)	140 (86)	405 (82)	97 (89)	0.260
Bilateral	220 (16)	96 (16)	24 (14)	88 (18)	12 (11)	
Presenting complaint						
Leukocoria	1159 (82)	525 (84)	135 (78)	398 (81)	91 (80)	0.349
Strabismus	1099 (78)	548 (86)	125 (72)	368 (75)	58 (51)	< 0.001
Red eye	119 (8)	24 (5)	17 (10)	52 (11)	16 (14)	0.001
Decreased vision	89 (6)	35 (6)	13 (8)	30 (6)	11 (10)	0.333
Proptosis	92 (6)	6 (1)	5 (3)	39 (8)	42 (37)	< 0.001
Painful blind eye	65 (5)	12 (2)	5 (3)	28 (6)	20 (18)	< 0.001
Others	167 (12)	58 (9)	28 (17)	59 (12)	22 (19)	0.228
None	5 (< 1)	1 (< 1)	2 (< 1)	2 (< 1)	0 (0)	0.666
Mean duration of symptoms, mos (median, range)	4 (2, < 1–51)	3 (1, < 1–36)	3 (1, < 1–25)	4 (2, < 1–51)	6 (4, < 1–24)	< 0.001
Mean horizontal corneal diameter, mm (median, range)	12 (12, 8–15)	11 (12, 10–14)	11 (11, 9–14)	12 (12, 8–15)	12 (12, 11–14)	< 0.001
Mean intraocular pressure, mmHg (median, range)	19 (13, 1–65)	17 (15, 2–62)	20 (16, 1–65)	20 (14, 1–56)	22 (12, 10–56)	< 0.001
Megalocornea	87 (8)	22 (3)	10 (6)	45 (10)	10 (9)	0.003
Secondary glaucoma	354 (33)	106 (23)	53 (42)	164 (40)	31 (37)	< 0.001
Anterior chamber seeds	137 (10)	27 (4)	21 (13)	61 (12)	28 (26)	< 0.001
Neovascularization of iris	350 (25)	125 (20)	47 (29)	144 (29)	34 (32)	< 0.001
Hyphema	67 (5)	24 (4)	8 (5)	25 (5)	10 (9)	0.090
Ectropion uveae	157 (11)	51 (8)	17 (10)	77 (16)	12 (11)	< 0.001
Cataract	68 (5)	23 (4)	11 (7)	28 (6)	7 (6)	0.223
Orbital pseudocellulitis	50 (3)	17 (3)	4 (2)	22 (5)	7 (6)	0.112
ICRB (Philadelphia) (n = 1398)						
Group C	2 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	< 0.001
Group D	209 (15)	131 (21)	28 (17)	46 (9)	4 (4)	
Group E	1189 (85)	493 (79)	135 (83)	446 (91)	105 (96)	
ICLoR (CHLA) (n = 1298)						
Group C	2 (<1)	2 (<1)	0 (0)	0 (0)	0 (0)	< 0.001
Group D	264 (20)	181 (30)	30 (20)	49 (11)	4 (4)	
Group E	1032 (80)	424 (70)	116 (80)	403 (89)	89 (96)	
AJCC 8 th edition T stage (n = 1281)						
cT2	571 (45)	325 (56)	63 (39)	158 (36)	25 (25)	< 0.001
cT3	649 (51)	257 (44)	90 (59)	259 (59)	43 (43)	
cT4	58 (4)	1 (<1)	0 (0)	35 (6)	31 (31)	

AJCC = American Joint Committee on Cancer; CHLA = Children's Hospital of Los Angeles; ICLoR = International Classification of Intraocular Retinoblastoma; ICRB = International Classification of Retinoblastoma; pT = pathological T.

After applying the Bonferroni correction, a *P* value of < 0.002 was considered statistically significant.

*Others = African + Indigenous Australian.

Treatment

Based on the individual RB center's definition of HRHFs, 702 were considered high-risk RB, and 709 were not regarded as high-risk RB. A total of 698 patients (50%) received adjuvant chemotherapy, and 56 patients (4%) received adjuvant chemotherapy (details elaborated

subsequently) and external beam radiotherapy (mean dose of 45 Gy; median, 45 Gy; range, 30–50 Gy).

Patients received a mean of 6 cycles of chemotherapy (median, 6; range, 1–12), using a combination of vincristine, etoposide, and carboplatin in 656 patients, other regimens in 90 patients, a combination of both in 4 patients, and no chemotherapy details were mentioned in 4 cases. Of the

Table 3. Retinoblastoma Based on the 8th Edition AJCC Pathological Staging in a Global Study of 1411 Patients: Histopathological Features, Treatment, and Outcomes

Parameter	Total N = 1411 n (%)	pT1 N = 645 n (%)	pT2 N = 164 n (%)	pT3 N = 493 n (%)	pT4 N = 109 n (%)	P Value
Growth pattern (n = 1395)						
Endophytic	664 (48)	339 (55)	90 (55)	201 (41)	34 (31)	
Exophytic	295 (21)	168 (30)	22 (13)	90 (18)	15 (14)	
Mixed	391 (28)	96 (15)	48 (29)	190 (39)	57 (52)	
Diffuse infiltrating	37 (3)	19 (3)	4 (2)	11 (2)	4 (4)	< 0.001
Tumor differentiation (n = 1389)						
Well differentiated	259 (19)	179 (29)	21 (13)	58 (12)	1 (1)	
Moderately differentiated	514 (37)	206 (33)	64 (39)	197 (40)	47 (43)	
Poor differentiation	485 (35)	181 (29)	45 (27)	203 (41)	56 (51)	
Undifferentiated	129 (9)	56 (9)	34 (21)	34 (7)	5 (5)	< 0.001
Anterior chamber seeds	182 (13)	28 (4)	33 (20)	77 (16)	44 (40)	< 0.001
Iris infiltration	112 (8)	0 (0)	23 (14)	56 (11)	33 (30)	< 0.001
Trabecular meshwork infiltration	68 (5)	0 (0)	14 (8)	39 (8)	15 (14)	< 0.001
Schlemm's canal infiltration	45 (3)	0 (0)	4 (2)	27 (6)	15 (13)	< 0.001
Ciliary body infiltration	95 (7)	8 (1)	13 (8)	53 (11)	21 (19)	< 0.001
Choroidal invasion	660 (47)	53 (8)	145 (88)	371 (75)	91 (83)	< 0.001
<3 mm, minor	281 (20)	53 (8)	145 (88)	65 (13)	18 (17)	< 0.001
≥3 mm, major	379 (27)	0 (0)	0 (0)	306 (62)	73 (67)	< 0.001
Optic nerve invasion	947 (67)	261 (40)	152 (93)	426 (86)	108 (99)	< 0.001
Up to prelaminar	363 (67)	186 (29)	104 (63)	73 (15)	0 (0)	< 0.001
Up to laminar	219 (45)	87 (14)	68 (41)	62 (13)	2 (2)	< 0.001
Up to retrolaminar	348 (25)	0 (0)	0 (0)	313 (63)	35 (32)	< 0.001
Up to transected end	85 (6)	0 (0)	0 (0)	0 (0)	85 (78)	< 0.001
Combined prelaminar/laminar optic nerve and minor: choroidal invasion (< 3 mm)	341 (24)	0 (0)	143 (87)	181 (36)	17 (16)	< 0.001
Combined prelaminar/laminar optic nerve and minor: iris/trabecular meshwork/ciliary body invasion (< 3 mm)	47 (3)	0 (0)	4 (2)	23 (5)	20 (18)	< 0.001
Scleral invasion						
Up to partial thickness	117 (8)	0 (0)	0 (0)	52 (11)	8 (9)	
Up to full thickness	11 (1)	0 (0)	0 (0)	7 (1)	4 (5)	< 0.001
Extra scleral extension	44 (3)	0 (0)	0 (0)	0 (0)	44 (40)	< 0.001
Type of adjuvant therapy						
Intravenous chemotherapy	698 (50)	96 (15)	104 (63)	439 (89)	59 (54)	
Intravenous chemotherapy (+) external beam radiotherapy	56 (4)	3 (<1)	3 (2)	21 (4)	29 (27)	< 0.001
Mean follow-up, mos (median, range)	38 (35, < 1–149)	42 (34, < 1–149)	46 (39, < 1–125)	34 (27, < 1–143)	25 (14, < 1–98)	< 0.001
Orbital tumor recurrence	60 (4)	8 (1)	5 (3)	22 (4)	25 (23)	< 0.001
Tumor-related metastasis	98 (7)	7 (1)	5 (3)	40 (8)	46 (43)	< 0.001
Tumor-related death	147 (11)	12 (2)	7 (4)	64 (13)	64 (59)	< 0.001

AJCC = American Joint Committee on Cancer; pT = pathological T.

After applying the Bonferroni correction, a P value of < 0.002 was considered statistically significant.

Table 6. Retinoblastoma Based on the 8th Edition AJCC Pathological Staging in a Global Study of 1411 Patients: Cox Proportional Hazards Analysis of Outcomes

	Univariate		Multivariate	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Orbital tumor recurrence				
Age	1.014 (1.004–1.025)	0.006	1.009 (0.998–1.02)	0.127
Lag time from symptom onset	1.04 (1.007–1.075)	0.016	1.014 (0.971–1.059)	0.516
pT stage				
pT1	Reference			
pT2a	2.658 (0.869–8.125)	0.086	2.652 (0.867–8.108)	0.087
pT2b	0 (0–3.733E+274)	0.974	0 (0–7.138E+274)	0.975
pT3a	0.55 (0.069–4.398)	0.573	0.529 (0.066–4.238)	0.549
pT3b	3.804 (1.575–9.186)	0.003	3.542 (1.46–8.593)	0.005
pT3c	9.487 (3.289–27.365)	< 0.001	8.62 (2.963–25.078)	< 0.001
pT3d	36.985 (7.833–174.629)	< 0.001	36.682 (7.731–174.047)	< 0.001
pT4	25.925 (11.666–57.61)	< 0.001	23.007 (10.173–52.03)	< 0.001
Adjuvant therapy	0.79 (0.471–1.325)	0.372	–	–
Tumor-related metastasis				
Age	1.01 (1.002–1.019)	0.021	1.005 (0.996–1.014)	0.311
Lag time from symptom onset	1.056 (1.034–1.079)	< 0.001	1.033 (1.004–1.064)	0.024
pT stage				
pT2a	2.63 (0.86–8.04)	0.09	4.046 (1.312–12.47)	0.015
pT2b	0 (0–2.314E+157)	0.96	0 (0–3.194E+159)	0.964
pT3a	3.333 (1.156–9.609)	0.026	8.249 (2.664–25.548)	< 0.001
pT3b	7.327 (3.303–16.254)	< 0.001	18.37 (7.508–44.947)	< 0.001
pT3c	7.759 (2.537–23.726)	< 0.001	19.386 (5.868–64.042)	< 0.001
pT3d	36.588 (7.756–172.598)	< 0.001	96.803 (19.239–487.086)	< 0.001
pT4	45.936 (21.593–97.723)	< 0.001	91.569 (40.133–208.929)	< 0.001
Adjuvant therapy	0.566 (0.368–0.87)	0.009	3.384 (2.054–5.575)	< 0.001
Tumor-related death				
Age	1.008 (1.001–1.015)	0.019	1.001 (0.994–1.009)	0.74
Lag time from symptom onset	1.041 (1.02–1.063)	< 0.001	1.013 (0.984–1.042)	0.391
pT stage				
pT2a	2.776 (0.783–9.839)	0.114	2.657 (0.93–7.588)	0.068
pT2b	4.068 (0.49–33.793)	0.194	9.61 (2.099–44)	0.004
pT3a	5.18 (1.741–15.418)	0.003	10.969 (4.645–25.901)	< 0.001
pT3b	11.987 (4.999–28.745)	< 0.001	18.873 (9.078–39.236)	< 0.001
pT3c	10.549 (3.219–34.573)	< 0.001	27.187 (10.952–67.488)	< 0.001
pT3d	24.082 (2.898–200.104)	0.003	69.344 (14.747–326.063)	< 0.001
pT4	40.608 (16.839–97.927)	< 0.001	92.902 (47.231–182.735)	< 0.001
Adjuvant therapy	0.514 (0.361–0.733)	< 0.001	3.227 (2.141–4.863)	< 0.001

AJCC = American Joint Committee on Cancer; CI = confidence interval; pT = pathological T.

702 patients with HRHF, 55 received no form of adjuvant therapy. The reasons included treatment refusal by parents ($n = 3$), a default of treatment ($n = 5$), logistics of travel from another country ($n = 1$), and lack of fitness for chemotherapy because of coexistent systemic disease ($n = 1$). No reason was mentioned in 45 patients. Of the 709 who did not have high-risk RB, 101 received adjuvant chemotherapy, and 5 received adjuvant chemotherapy with external beam radiotherapy. Indications for adjuvant therapy despite the absence of HRHF included bilateral disease ($n = 53$), anterior chamber infiltration ($n = 1$), and metastatic disease ($n = 2$), and the reason was not mentioned in 47 patients.

Outcomes

The mean follow-up was 38 months (median, 35 months; < 1–149 months). Orbital tumor recurrence, tumor-related

metastasis, and tumor-related death were seen in 60 (4%), 98 (7%), and 147 (11%) of all patients, respectively. Of all patients with tumor-related deaths, 83 were confirmed deaths, and 64 were likely deaths based on their general condition and disease status at the last visit. All 3 outcomes showed an increasing trend with increasing pT category ($P < 0.001$), which were statistically significant (Table 3).

The 10-year Kaplan–Meier estimates revealed cumulative incidence rates of 6% for orbital recurrence, 10% for tumor-related metastasis, and 14% for tumor-related death for the entire cohort (Figure 1). The Kaplan–Meier analysis at 1, 3, 5, and 10 years showed an increase in the estimated cumulative incidence in outcomes with advancing pT category (Table S4, available at www.aaojournal.org). Kaplan–Meier estimates of cumulative incidence of events without adjuvant therapy versus with adjuvant therapy was higher for orbital tumor recurrence in pT2a (6% vs. 3% at 10 years), pT3a (8% vs. 0% at 10 years), pT3b (30%

Table 7. Retinoblastoma Based on the 8th Edition AJCC Pathological Staging: Cox Regression Analysis of Outcomes Based on Adjuvant Therapy

pT stage	Orbital Tumor Recurrence		Tumor-Related Metastasis		Tumor-Related Death		P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
	Hazard Ratio (95% CI)		P Value		Hazard Ratio (95% CI)						
1	0.331 (0.079–1.387)		0.131		0.484 (0.094–2.496)		0.386		0.397 (0.12–1.319)		0.131
2a	2.516 (0.42–15.058)		0.312		6.724 (0.751–60.164)		0.088		6.547 (0.732–58.579)		0.093
2b*	–		–		–		–		8.756 (0.544–140.845)		0.126
3a	1106559.696 (0–1.122E+277)		0.965 [†]		14.164 (2.85–70.377)		0.001		9.723 (3.079–30.704)		<0.001
3b	6.483 (1.748–24.044)		0.005		4.129 (1.405–12.132)		0.01		3.493 (1.36–8.972)		0.009
3c	14.648 (2.564–83.673)		0.003		28.122 (3.789–208.722)		0.001		6.843 (1.392–33.649)		0.018
3d	1137.517 (0–288876424686204000)		0.678 [‡]		1137.517 (0–288876424686204000)		0.678 [‡]		1137.517 (0–288876424686204000)		0.678 [‡]
4	3.691 (1.625–8.382)		0.002		2.477 (1.274–4.817)		0.007		2.871 (1.671–4.932)		<0.001

AJCC = American Joint Committee on Cancer; CI = confidence interval; pT = pathological T.

Reference for all stages was no adjuvant therapy.

*There were no orbital recurrences or recorded tumor-related metastasis in the entire pT2b cohort.

†There were no recurrences in the pT3a group who received adjuvant therapy.

‡There was only 1 patient in the pT3d stage who did not receive adjuvant chemotherapy, and that patient had orbital recurrence, tumor-related metastasis, and tumor-related death.

vs. 8% at 10 years), pT3c (67% vs. 7% at 1 year), pT3d (100% vs. 25%), and pT4 (57% vs. 22% at 5 years) cohorts; for tumor-related metastasis in pT2a (8% vs. 1% at 10 years), pT3a (30% vs. 3% at 10 years), pT3b (44% vs. 13% at 10 years), and pT3c (67% vs. 5% at 1 year), pT3d (100% vs. 25%), and pT4 (71% vs. 49% at 5 years) cohorts; and for tumor-related mortality in pT2a (8% vs. 1% at 10 years), pT2b (33% vs. 5% at 5 years), pT3a (50% vs. 6% at 10 years), pT3b (50% vs. 14% at 10 years), pT3c (67% vs. 19% at 1 year), pT3d (100% vs. 25%), and pT4 (100% vs. 57% at 5 years) cohorts. No orbital tumor recurrence occurred in the pT2b and pT3a cohorts without adjuvant therapy, and no tumor-related metastasis occurred in the pT2 cohort. Only 1 patient in the pT3d cohort developed orbital tumor recurrence, tumor-related metastasis, and tumor-related death within 1 year of follow-up (Table S5, available at www.aaojournal.org).

Multivariate Cox regression analysis of outcomes based on pT category with age, lag times, and adjuvant therapy as covariates revealed statistically significant differences in outcomes based on pT category and adjuvant chemotherapy (Table 6). When compared with the pT1 category, categories pT3b and beyond had greater hazards of orbital tumor recurrence (3.5 times for pT3b, 8.6 times for pT3c, 36.7 times for pT3d, and 23.0 times for pT4), all categories but pT2b had greater hazards of tumor-related metastasis (4.0 times for pT2a, 8.2 times for pT3a, 18.4 times for pT3b, 19.4 times for pT3c, 96.8 times for pT3d, and 91.6 times for pT4), and categories pT2b category and beyond had greater hazards of tumor-related death (9.6 times for pT2b, 10.9 times for pT3a, 18.8 times for pT3b, 27.2 times for pT3c, 69.3 times for pT3d, and 2.9 times for pT4) (Table 6). Within each pT category, the risk of outcomes without adjuvant therapy was assessed. The hazards were significantly greater for orbital tumor recurrence in pT3b, pT3c, and pT4 categories, and for tumor-related metastasis and tumor-related death in pT3a, pT3b, pT3c, and pT4 categories in patients who did not receive adjuvant therapy compared with those who received adjuvant therapy (Table 7).

The mean survival times were estimated by Kaplan–Meier analysis for each pT category (Figure 2, Tables S8, available at www.aaojournal.org). Except for the pT2b cohort with the lowest numbers, the mean overall survival times decreased from 145 months in the pT1 category to 44 months in the pT4 category. The survival times were lower for patients who did not receive adjuvant therapy than for those who did in all cohorts. The categories pT3a, pT3b, and pT3c benefited the most in terms of overall survival with adjuvant therapy.

Within the pT4 category, no patients survived without adjuvant treatment. In the same cohort, survival estimates were 35% with adjuvant chemotherapy alone and 60% with adjuvant chemotherapy and radiotherapy, and the mean survival times were 14 months, 46 months, and 52 months, respectively. The hazard ratios for death were 4.406 (95% confidence interval, 2.089–9.294; $P < 0.001$) in patients who did not receive adjuvant therapy and 1.856 (95% confidence interval, 0.939–3.665; $P = 0.075$) in those who received adjuvant chemotherapy alone without radiotherapy.

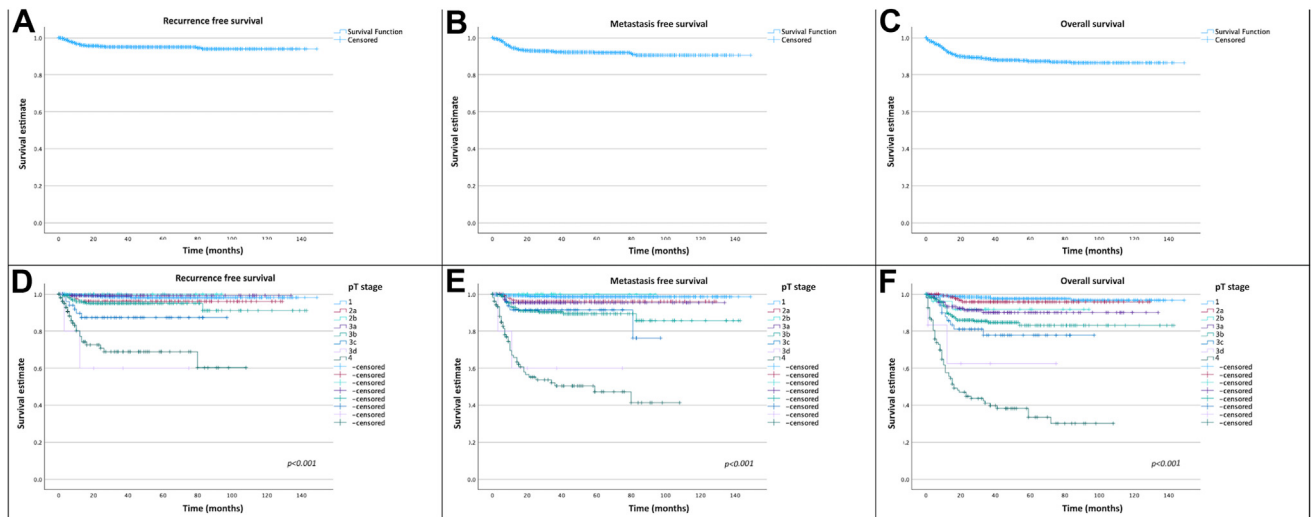


Figure 1. Kaplan–Meier curves for recurrence-free survival, metastasis-free survival, and overall survival in the entire cohort (A–C) and based on the 8th edition American Joint Committee on Cancer (AJCC) pathological category (D–F).

when compared with patients who received both adjuvant chemotherapy and radiotherapy.

Discussion

Assessment of histopathological features after primary enucleation is crucial for decision-making on additional treatment and for predicting outcomes of tumor recurrence, tumor-related metastasis, and tumor-related death from RB.^{6–9} The 8th edition AJCC classification categorizes tumors into pathological T categories. Category pT1 is assigned for tumors without any local invasion, with focal choroidal invasion (≤ 3 mm), or with isolated prelaminar or lamellar invasion. Category pT2 is assigned for tumors with local invasion, pT2a for combined focal choroidal and pre/laminar optic nerve invasion, and pT2b for tumors with invasion into iris stroma, trabecular meshwork, or Schlemm canal. Category pT3 includes tumors with significant local invasion, pT3a includes choroidal invasion of > 3 mm in diameter as single or multiple foci, pT3b includes tumors with retrolaminar optic nerve invasion at the optic nerve head not reaching the transected end, pT3c scleral involvement is limited to the inner two-thirds, and pT3d includes tumors invading full-thickness sclera or invasion of emissary channels. Category pT4 is assigned to tumors beyond the sclera into the orbit/adnexa and tumors that involve the transected end of the optic nerve.¹¹

The rationale for this is supported by studies that provide evidence that isolated choroidal invasion of ≤ 3 mm (tumor-related event incidence of 1% at 5 years) and isolated optic nerve invasion up to the lamina cribrosa (0% tumor-related events) had a low risk for tumor-related events; patients with massive choroidal invasion of > 3 mm (tumor-related event incidence of 6% at 5 years) or postlaminar optic nerve invasion not reaching the transected end (tumor-related event incidence of 14% at 5 years) were considered to have intermediate risk; and patients with postlaminar optic

invasion of the transected end of the optic nerve had a higher risk for tumor-related events (30%, with adjuvant treatment).^{8,12–14} The classification of anterior chamber tumor invasion, iris stromal invasion, ciliary body invasion, and concomitant focal choroidal invasion and optic nerve invasion up to the lamina cribrosa was variable in the older literature,^{8,12} but the 8th edition AJCC takes into consideration concomitant focal choroidal invasion and optic nerve invasion up to the lamina cribrosa and iris stromal invasion, and assigns to pT category of 2a and 2b, respectively. Isolated anterior chamber seeds and isolated ciliary body invasion are not defined explicitly.

Only 2 studies have analyzed the outcomes of RB after primary enucleation based on the pT category of the 8th edition AJCC classification, and, together, these included data from Germany, Austria, and China.^{23,25} Diarra et al²⁵ reported outcomes of 184 patients after primary enucleation for RB. They categorized the pathological T categories into low-risk patients who received no adjuvant therapy, intermediate risks 1 and 2, and high-risk groups to tailor adjuvant therapy. Low risk comprised pT1 and pT2a, who received no adjuvant treatment; intermediate risk group 1 (pT2b, pT3a), who received 3 cycles of adjuvant chemotherapy; intermediate risk group 2 (pT3b, pT3c, pT3d), who received 6 cycles of adjuvant chemotherapy; and high-risk group (pT4), who received adjuvant chemotherapy $\pm$ proton beam radiotherapy or orbital brachytherapy with I¹²⁵ seeds. With this treatment, the overall 5-year survival estimate was 100% in the pT1 to pT3 categories. Among 5 patients categorized as pT4, 2 had progressive disease, of whom 1 died.²⁵

Zhao et al²³ included data from 20 RB treatment centers in China and included a total of 700 patients who underwent primary enucleation.²³ Adjuvant chemotherapy was administered in 28% of patients in the pT1/pT2 (n = 436) categories and 90% in the pT3/pT4 (n = 264) categories, as per the respective institute's treatment protocol. In addition, 14% of pT4 patients received external beam

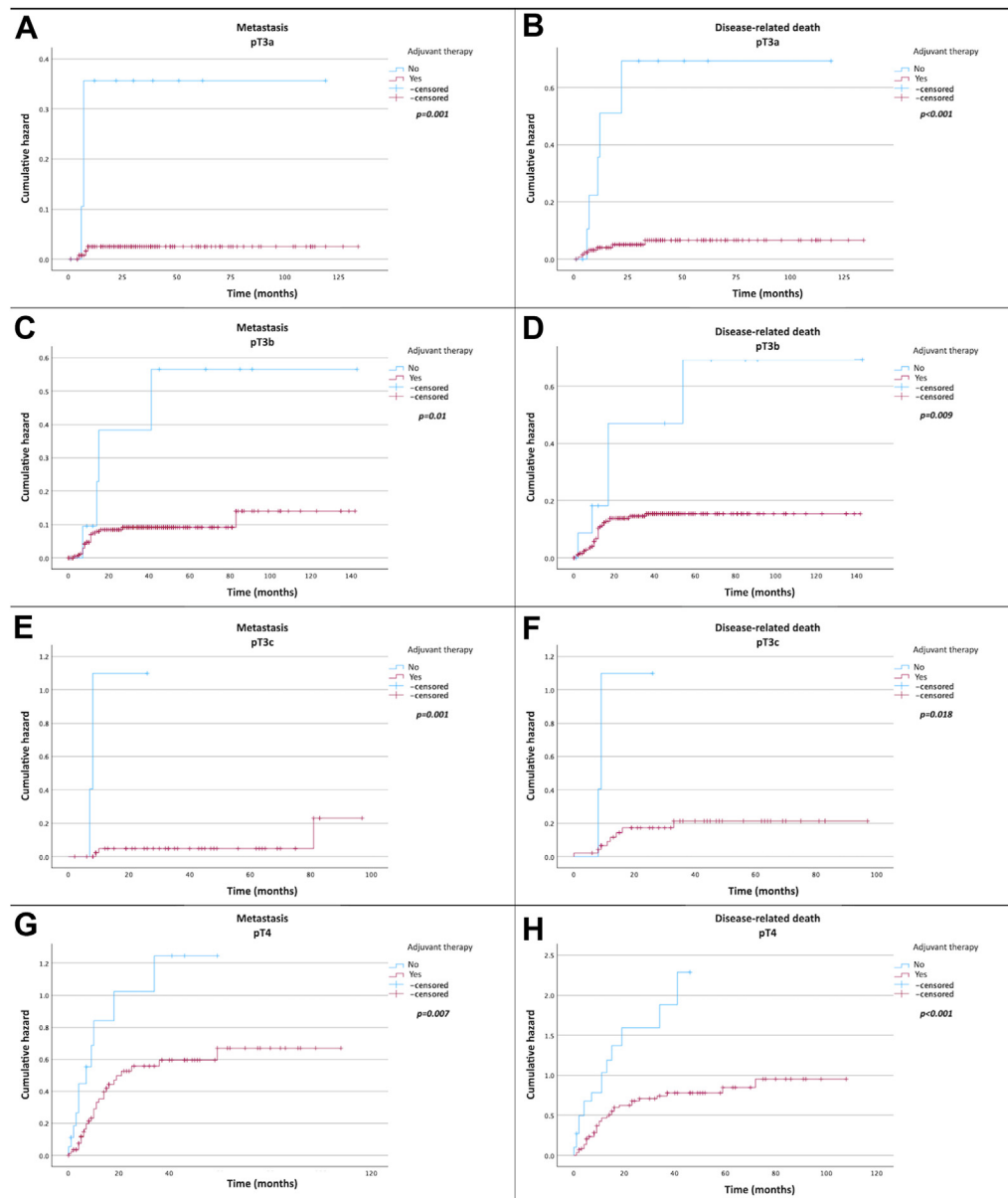


Figure 2. Kaplan—Meier curves cumulative hazards of tumor-related metastasis and tumor-related deaths in categories pathological T (pT)3a (A, B), pT3b (C, D), pT3c (E, F), and pT4 (G, H) with and without adjuvant chemotherapy.

radiotherapy. The 5-year survival rates were 99% in pT1, 96% in pT2a, 100% in pT3a, 93% in pT3b, 92% in pT3c/d, and 41% in pT4 categories. Patients fared better in the pT3 and pT4 categories with 6 cycles of chemotherapy than those who received < 6 cycles.²³

In our cohort, the 5-year overall survival estimates were 87% in the entire cohort, 98% in pT1, 96% in pT2a, 92% in pT2b, 90% in pT3a, 83% in pT3b, 88% in pT3c, 62% in pT3d, and 44% in pT4 cohorts. The overall survival estimates within each pT category were

comparable to the estimates reported by Zhao et al.²³ There was heterogeneity in the administration of adjuvant therapy in our study cohort due to various factors such as treatment protocols at individual centers, treatment refusal by parents, default of treatment, travel logistics, and poor systemic condition. Although adjuvant chemotherapy with external beam radiotherapy is recommended for patients with the pT4 category, 81% of them received chemotherapy, and only 27% received chemotherapy and external beam radiation

therapy. However, this heterogeneity in treatment allowed comparisons based on receipt of adjuvant therapy. Not receiving adjuvant therapy was associated with significantly greater hazards of tumor-related death in the pT3a, pT3b, pT3c, and pT4 categories.

Ocular oncologists have long debated the need for adjuvant therapy for patients with pT2 disease. In a global survey of ocular oncologists, only 41% of the respondents considered a combination of prelaminar and laminar optic nerve infiltration and minor (≤ 3 mm) choroidal invasion to be high risk. Likewise, 52% considered anterior chamber seeds, 63% considered iris infiltration, and 67% regarded trabecular meshwork invasion as high-risk features.¹⁰ In the present study, we noted that pT2a had a significantly higher risk for metastasis, and pT2b had increased hazards for tumor-related death than pT1. Although the mean survival times were better with adjuvant chemotherapy, the lack of it did not seem to significantly increase the hazards of tumor-related death in the pT2a and pT2b categories.

Study Strengths and Limitations

The strength of this study is its large sample size with international collaboration, which allowed comparison between the pT categories and subgroups based on adjuvant therapy. The limitations include its retrospective nature, the nonavailability of certain data, such as treatment refusal, and

the lower numbers within the pT2a and pT2b categories. In bilateral cases, another factor that could influence the outcomes was the tumor status in the contralateral eye. For this study, it was presumed that the worse eye, which was enucleated, would have a greater role to play in the development of tumor-related events.

Conclusions

In this multicentric global cohort of patients who underwent primary enucleation, the pT category was predictive of orbital tumor recurrence, tumor-related metastasis, and tumor-related death. Adjuvant therapy was associated with significantly improved survival in the pT3a, pT3b, pT3c, and pT4 categories and is recommended. Adjuvant treatment for the pT1, pT2a, and pT2b categories was not associated with any benefit. However, the risk was not 0% for these groups: Low-risk categories pT1, pT2a, and pT2b also had a cumulative incidence of tumor-related deaths of 2%, 4%, and 8%, respectively, at 5 years. Thus, the importance of follow-up should be emphasized to the caregivers. Although prophylactic adjuvant chemotherapy was not associated with significantly improved outcomes in pT2a and pT2b, the outcomes differ from the pT1 category and justify its separation from the latter in the AJCC classification.

Footnotes and Disclosures

Originally received: July 10, 2024.

Final revision: August 22, 2024.

Accepted: August 22, 2024.

Available online: September 7, 2024. Manuscript no. OPHTHA-D-24-01396.

¹ The Operation Eyesight Institute for Eye Cancer, LV Prasad Eye Institute, Hyderabad, India.

² Ocular Oncology Service, Wills Eye Hospital, Philadelphia, Pennsylvania.

³ Children's Hospital Los Angeles & USC Roski Eye Institute, Los Angeles, California.

⁴ Keck School of Medicine, Los Angeles, California.

Disclosure(s):

All authors have completed and submitted the ICMJE disclosures form.

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

Support was provided by The Operation Eyesight Universal Institute for Eye Cancer (S.K.) and Hyderabad Eye Research Foundation (S.K.), Hyderabad, India. The funders had no role in preparing, reviewing, or approving the manuscript.

HUMAN SUBJECTS: Human subjects were included in this study. Participating centers located in the United States adhered to the Health Insurance Portability and Accountability Act regulations. All research adhered to the tenets of the Declaration of Helsinki and aligned with the Strengthening the Reporting of Observational Studies in Epidemiology

guidelines. Institutional Review Board approval was obtained from the appropriate institutions. Informed consent was obtained from the parents/guardians of all the patients included in this study.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Kaliki

Data collection: High-risk Retinoblastoma Collaborative Study Group

Analysis and interpretation: Vempuluru, Shields, Berry, Kaliki

Obtained funding: Kaliki

Overall responsibility: Vempuluru, Shields, Berry, Kaliki

Abbreviations and Acronyms:

AJCC = American Joint Committee on Cancer;

HRHF = histopathological feature; **pT** = pathological T;

RB = retinoblastoma.

Keywords:

AJCC, American Joint Committee on Cancer Classification, Global Study, High-risk histopathological features, Retinoblastoma.

Correspondence:

Swathi Kaliki, MD, The Operation Eyesight Universal Institute for Eye Cancer, L.V. Prasad Eye Institute, Hyderabad, Telangana 500034, India.

E-mail: kalikiswathi@yahoo.com.

References

- Vempuluru VS, Maniar A, Kaliki S. Global retinoblastoma studies: a review. *Clin Exp Ophthalmol*. 2024;52(3):334–354.
- Kaliki S, Vempuluru VS, Mohamed A, et al. Global Retinoblastoma Study Group. Retinoblastoma in Asia: clinical presentation and treatment outcomes in 2112 patients from 33 countries. *Ophthalmology*. 2024;131(4):468–477.
- Appukuttan B, Biswas J, Khetan V. Enucleation in retinoblastoma: pros and cons. *Expert Rev Ophthalmol*. 2013;8(4):351–353.
- Tomar AS, Finger PT, Gallie B, et al; American Joint Committee on Cancer Ophthalmic Oncology Task Force. High-risk pathologic features based on presenting findings in advanced intraocular retinoblastoma: a multicenter, international data-sharing American Joint Committee on Cancer Study. *Ophthalmology*. 2022;129(8):923–932.
- Loya A, Ayaz T, Gombos DS, Weng CY. Association of choroidal invasion with retinoblastoma survival rates. *J AAPOS*. 2023;27(1):32.e1–32.e8.
- Eagle Jr RC. High-risk features and tumor differentiation in retinoblastoma: a retrospective histopathologic study. *Arch Pathol Lab Med*. 2009;133:1203–1209.
- Honavar SG, Singh AD, Shields CL, et al. Postenucleation adjuvant therapy in high-risk retinoblastoma. *Arch Ophthalmol*. 2002;120(7):923–931.
- Sullivan EM, Wilson MW, Billups CA, et al. Pathologic risk-based adjuvant chemotherapy for unilateral retinoblastoma following enucleation. *J Pediatr Hematol Oncol*. 2014;36(6):e335–e340.
- Kaliki S, Shields CL, Shah SU, et al. Postenucleation adjuvant chemotherapy with vincristine, etoposide, and carboplatin for the treatment of high-risk retinoblastoma. *Arch Ophthalmol*. 2011;129(11):1422–1427.
- Kaliki S, Shields CL, Cassoux N, et al. Defining high-risk retinoblastoma: a multicenter global survey. *JAMA Ophthalmol*. 2022;140(1):30–36.
- Mallipatna AC, Gallie BL, Chévez-Barrios P, et al. Amin MB, Edge SB, Greene FL, et al., ed. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.
- Chantada GL, Dunkel IJ, de Dávila MT, Abramson DH. Retinoblastoma patients with high risk ocular pathological features: who needs adjuvant therapy? *Br J Ophthalmol*. 2004;88(8):1069–1073.
- Chantada GL, Gutter MR, Fandiño AC, et al. Treatment results in patients with retinoblastoma and invasion to the cut end of the optic nerve. *Pediatr Blood Cancer*. 2009;52(2):218–222.
- Bosaleh A, Sampor C, Solernou V, et al. Outcome of children with retinoblastoma and isolated choroidal invasion. *Arch Ophthalmol*. 2012;130(6):724–729.
- Aerts I, Sastre-Garau X, Savignoni A, et al. Results of a multicenter prospective study on the postoperative treatment of unilateral retinoblastoma after primary enucleation. *J Clin Oncol*. 2013;31(11):1458–1463.
- Yousef YA, Hajja Y, Nawaiseh I, et al. A histopathologic analysis of 50 eyes primarily enucleated for retinoblastoma in a tertiary cancer center in Jordan. *Turk Patoloji Derg*. 2014;30(3):171–177.
- Yannuzzi NA, Francis JH, Marr BP, et al. Enucleation vs ophthalmic artery chemosurgery for advanced intraocular retinoblastoma: a retrospective analysis. *JAMA Ophthalmol*. 2015;133(9):1062–1066.
- Berry JL, Kogachi K, Aziz HA, et al. Risk of metastasis and orbital recurrence in advanced retinoblastoma eyes treated with systemic chemoreduction versus primary enucleation. *Pediatr Blood Cancer*. 2017;64(4). <https://doi.org/10.1002/psc.26270>.
- Chévez-Barrios P, Eagle Jr RC, et al. Study of unilateral retinoblastoma with and without histopathologic high-risk features and the role of adjuvant chemotherapy: a Children's Oncology Group Study. *J Clin Oncol*. 2019;37(31):2883–2891.
- Lu JE, Francis JH, Dunkel IJ, et al. Metastases and death rates after primary enucleation of unilateral retinoblastoma in the USA 2007–2017. *Br J Ophthalmol*. 2019;103(9):1272–1277.
- Zhao J, Feng ZX, Wei M, et al. Impact of systemic chemotherapy and delayed enucleation on survival of children with advanced intraocular retinoblastoma. *Ophthalmol Retina*. 2020;4(6):630–639.
- Dittner-Moormann S, Reschke M, Abbink FCH, et al. Adjuvant therapy of histopathological risk factors of retinoblastoma in Europe: a survey by the European Retinoblastoma Group (EURbG). *Pediatr Blood Cancer*. 2021;68(6):e28963.
- Zhao J, Feng Z, Leung G, Gallie BL. Retinoblastoma survival following primary enucleation by AJCC staging. *Cancers (Basel)*. 2021;13(24):6240.
- Sunwoo Y, Choi JY, Park HJ, et al. Twenty-year retrospective study of post-enucleation chemotherapy in high-risk patients with unilateral retinoblastoma. *Children (Basel)*. 2022;9(12):1983.
- Diarra Y, Brockmeyer C, Fischhuber K, et al. Adjuvant therapy for children treated by enucleation at diagnosis of retinoblastoma. *EJC Paediatr Oncol*. 2023;1:100004.
- Feng ZX, Zhao J, Zhang N, et al. Adjuvant chemotherapy improves survival for children with massive choroidal invasion of retinoblastoma. *Invest Ophthalmol Vis Sci*. 2023;64(11):27.
- Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18(6):805–835.
- Shields CL, Mashayekhi A, Au AK, et al. The International Classification of Retinoblastoma predicts chemoreduction success. *Ophthalmology*. 2006;113(12):2276–2280.
- Murphree AL. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clin North Am*. 2005;18(1):41–53. viii.