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Global Retinoblastoma Treatment Outcomes

Association with National Income Level

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Purpose: To compare metastasis-related mortality, local treatment failure, and globe salvage after retinoblastoma in countries with different national income levels.

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

Participants: Two thousand one hundred ninety patients, 18 ophthalmic oncology centers, and 13 countries on 6 continents.

Methods: Multicenter registry-based data were pooled from retinoblastoma patients enrolled between January 2001 and December 2013. Adequate data to allow American Joint Committee on Cancer staging, eighth edition, and analysis for the main outcome measures were available for 2085 patients. Each country was classified by national income level, as defined by the 2017 United Nations World Population Prospects, and included high-income countries (HICs), upper middle-income countries (UMICs), and lower middle-income countries (LMICs). Patient survival was estimated with the Kaplan-Meier method. Logistic and Cox proportional hazards regression models were used to determine associations between national income and treatment outcomes.

Main Outcome Measures: Metastasis-related mortality and local treatment failure (defined as use of secondary enucleation or external beam radiation therapy).

Results: Most (60%) study patients resided in UMICs and LMICs. The global median age at diagnosis was 17.0 months and higher in UMICs (20.0 months) and LMICs (20.0 months) than HICs (14.0 months; $P < 0.001$). Patients in UMICs and LMICs reported higher rates of disease-specific metastasis-related mortality and local treatment failure. As compared with HICs, metastasis-related mortality was 10.3-fold higher for UMICs and 9.3-fold higher for LMICs, and the risk for local treatment failure was 2.2-fold and 1.6-fold higher, respectively (all $P <$ 0.001).

Conclusions: This international, multicenter, registry-based analysis of retinoblastoma management revealed that lower national income levels were associated with significantly higher rates of metastasis-related mortality, local treatment failure, and lower globe salvage. *Ophthalmology 2020;■:1−14 © 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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Retinoblastoma, the most frequent primary pediatric eye cancer, has been the second most common intraocular cancer worldwide.[1−3] Patient prognosis has depended on early diagnosis and prompt treatment.[1] Advances in chemotherapy and local treatment have resulted in improved globe salvage and reductions in disease-specific mortality.[4−6] Toward that end, multispecialty management, international outreach, and cooperative research are crucial.[2,3,5−15]

Despite new retinoblastoma treatment strategies, ever-widening disparities persist with respect to access to subspecialty care, globe salvage, and mortality.[3,13,16−21] For

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example, retinoblastoma patients from high-income countries (HICs) in North America and Europe have a 3% to 5% risk of metastasis-related mortality compared with 40% and 70% in resource-poor countries in Asia and Africa, respectively.[22–30] Mortality rates have been so low in HICs that the focus of ophthalmic oncology care has shifted from metastasis to globe salvage, visual rehabilitation, and quality of life.[4] This is not the case for low-resource countries, where children with retinoblastoma have been more likely to lose their eye and die of metastatic disease.[2,31,32]

Low-resource countries suffer from a lack of retinoblastoma awareness, trained ophthalmic oncologists, pathologists, and genetic services. This has resulted in diagnostic delays, leading to loss of both eyes and life. Although socioeconomic and cultural factors remain a challenge, epidemiologic and research publications from low- and middle-income countries have been scarce.[33] In addition, the lack of a universally applied retinoblastoma classification system has hampered communication and made published results harder to compare and compile for meta-analysis.[34] A 2017 publication on global retinoblastoma based on national income group showed that children from lower- and middle-income countries sought treatment at an older age with more advanced disease.[3] However, the outcomes of metastasis-free survival and globe salvage were not presented. Herein, we used the American Joint Committee on Cancer—Ophthalmic Oncology Task Force's (AJCC-OOTF) multicenter, international retinoblastoma registry database to investigate the association between treatment outcomes and national income level.

Methods

This study was performed on data derived from a retrospective registry created by 18 retinoblastoma centers from 13 countries on 6 continents. Ophthalmic oncologists from subspecialty centers volunteered to participate; therefore, no centers were excluded or selected with bias toward geographic location or national income. Data from retinoblastoma patients diagnosed from January 5, 2001, through December 31, 2013, were collected and entered into a secure online database. Medical record reviews were performed by all participating centers after obtaining internal institutional review board approval. The Princess Margaret Cancer Centre Internal Review Board (IRB) provided study-specific application materials to each and every participating center to be amended and approved by their local IRB and Ethics Committee. This study adhered to the tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act of 1996.

The Registry

The internet-based, retrospective registry was created to evaluate the staging system for retinoblastoma in the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual.[35] By consensus, select retinoblastoma AJCC-OOTF committee members (primarily ophthalmic oncologists and pathologists) developed epidemiologic, clinical, and pathologic data fields. The scope of the present study was limited to assessing the risk of metastasis-related mortality, local treatment success, and globe salvage based on the national income of the participating countries.

Internet Database and Security

International standards were ensured for secure data storage, patient privacy protection, and statistical analysis. The security measures included the lack of personal patient identifiers, secure sockets layer encryption, protection against structured query language injection, variable and session management, record locking, and trail auditing (e.g., failed login attempts and webpage accessing). The online survey could be accessed only by the user accounts issued by the coordinating Princess Margaret Cancer Centre, and unique login passwords were provided after Princess Margaret Cancer Centre had received local ethics approval documentation. The centers could access only records submitted from their site. Princess Margaret Cancer Centre determined, and all centers agreed, that individual patient consent was not required because no patient identifiers were collected in this retrospective study. All data were de-identified at the local center, where an alphanumeric study identifier was generated for each patient. De-identified data were entered into the AJCC-OOTF Retinoblastoma Registry.

Tumor Extent, Node, Metastasis, and Heritable Trait Retinoblastoma Staging

The primary tumor extent, node status, metastasis status, and heritable trait status were defined in accordance with the eighth edition of the AJCC Cancer Staging Manual on retinoblastoma (Table S1, available at www.aaojournal.org).[35] We preferred AJCC retinoblastoma classification because it is a comprehensive classification that predicts both metastasis and globe salvage[5,6]; accounts for both intraocular and extraocular retinoblastoma extent; has been updated periodically with the latest significant medical evidence; holistically includes tumor, node, metastasis, and heritable trait; and has been adopted by the Union for International Cancer Control.

Definitions

The country classification by national income level, obtained from the 2017 World Population Prospects (United Nations, Department of Economic and Social Affairs), segregates participating centers into high-income countries (HICs), upper middle-income countries (UMICs), and lower middle-income countries (LMICs).[36] No centers from lower-income countries contributed to the AJCC-OOTF Retinoblastoma Registry. All centers used their standard diagnostic and therapeutic methods. Data collected included: date of diagnosis (month and year), age at diagnosis (months), laterality (unilateral, bilateral), and the eye involved (right or left). The clinical information included size and location of the intraocular tumor, presence of glaucoma, and iris neovascularization. Also noted was the type and location of seeds (subretinal, vitreal, anterior chamber, or a combination thereof). For bilateral retinoblastoma (by AJCC convention), the worse-eye tumor category was attributed to the overall clinical tumor (cT) and pathologic tumor (pT) category for survival analysis. According to AJCC retinoblastoma staging, we classified H based on bilateral disease, family history of retinoblastoma, and presence of trilateral retinoblastoma, as well as the presence of pathogenic retinoblastoma variant on genetic testing.[37]

Treatment details were noted as follows. First, primary enucleation was defined as removal of treatment-naïve retinoblastoma eyes. Second, secondary enucleation referred to removal of

Table 1. Geographic Characteristics at Presentation of 2085 Retinoblastoma Patients

Location	No. of Patients (%)	No. of Eyes (%)
Continent		
Asia		1356 (47.5)
Africa		43 (1.5)
North America		973 (34.1)
South America		75 (2.6)
Europe		352 (12.3)
Australia		55 (2)
Participant centers (no. of patients, % of total patients)		
High income		
1. St. Jude Children's Research Hospital, Memphis (244 [11.7%])	834 (40.0)	1171 (41.0)
2. Children's Hospital Los Angeles (213 [10.2%])		
3. SickKids Hospital, Toronto (163 [7.8%])		
4. Helsinki University Hospital, Helsinki (62 [3.0%])		
5. Hong Kong Eye Hospital, Hong Kong (48 [2.3%])		
6. The Sydney Children's Hospitals Network, Sydney (44 [2.1%)		
7. KK Women's and Children's Hospital, Singapore (34 [1.6%])		
8. Hospital Sant Joan de Deu Barcelona, Barcelona (10 [0.5%])		
9. The New York Eye Cancer Center (16 [0.8%])		
Upper middle income		
1. Beijing Tongren Hospital, Beijing (631 [30.3%])	912 (43.7)	1185 (41.5)
2. S. Fyodorov Eye Microsurgery Federal State Institute, Moscow (78 [3.7%])		
3. Hospital Infantil de Mexico Federico Gomez, Mexico City (57 [2.7%])		
4. Hospital de Pediatria Garrahan, Buenos Aires (77 [3.7%])		
5. N. N. Blokhin Cancer Research Center, Moscow (69 [3.3%])		
Lower middle income		
1. Sankara Nethralaya Eye Hospital, Chennai (128 [6.1%])	339 (16.3)	498 (17.5)
2. King Hussein Cancer Center, Amman (112 [5.4%])		
3. Narayana Nethralaya Eye Hospital, Bengaluru, India (63 [3.0%])		
4. University of Ghana Medical School, Accra, Ghana (36 [1.7%])		
Total	2085	2854

Ranked according to United Nations, Department of Economic and Social Affairs World Population Prospects List.[37]

an eye after an attempt at eye salvage, regardless of the reason for enucleation (e.g., significant residual disease, recurrent tumor). Eyes with substantial residual or recurrent disease after chemotherapy and focal consolidation were typically treated with further focal laser therapy, cryotherapy, plaque brachytherapy, intra-arterial chemotherapy, external beam radiotherapy (EBRT; not considered as initial treatment for retinoblastoma in the present time), and if necessary, enucleation. Third, local treatment failure after conservative treatment was defined as the need for EBRT or secondary enucleation.

Information regarding the survival outcome included occurrence of metastasis, date of detection of metastasis, the sites of metastases, and the final patient outcome (alive without metastasis, alive with metastasis, died with metastasis, died because of second malignant neoplasm, death related to other causes, or lost to follow-up). Date of last follow-up and the duration of follow-up were noted. All patients with central nervous system metastasis and those lost to follow-up were considered deceased and thus included in the metastasis-related mortality analysis. Patients whose treatment was discontinued by request of their guardians or who were lost to follow-up without completing treatment were recorded as having died of the disease and were included in metastasis-related mortality. All other deaths not related to metastasis were censored.

Patients were excluded if key variables, such as demographic data, clinical variables essential for retinoblastoma classification (tumor location, size, extent), treatment data (date and type of treatment), and outcome (globe salvage, primary or secondary enucleation, metastatic disease, survival) were missing or inconsistent.

Statistical Analysis

Continuous variables were described using the median, range, and interquartile range (IQR), and categorical variables were described using frequencies and proportions. Kaplan-Meier plots, the log-rank test for trend, and logistic and Cox proportional hazards regression models were implemented to test if national income level was related independently to metastasis-related mortality and local treatment failure. Cumulative proportion of surviving and of local failure-free globe salvage estimates at different intervals were tabulated using SPSS software version 23.0 (IBM, Armonk, NY) to generate Kaplan-Meier plots and perform other statistical analyses. Statistical significance was set at $P < 0.05$.

Results

A total of 2190 patients were enrolled from 18 ocular oncology centers around the world. Records with data sufficient for this study were available for 2085 patients (95.2%).

Table 2. Clinical Characteristics at Presentation of 2085 Retinoblastoma Patients by National Income Group, Logistic Regression Analysis, and Classification of Retinoblastoma Eyes

A. Clinical Characteristics at Presentation

Parameter	*National Income Level, No. of Patients (% within the National Income Level) or [% within the Evaluated Parameter]*			
	High Income	*Upper Middle Income*	*Lower Middle Income*	*Total, No. (%)*
All patients	834 [40.0]	912 [43.7]	339 [16.3]	2085 (100)
Age at diagnosis (mos), median (IQR)				
All patients	14.0 (6.0–26.0)	20.0 (9.3–30.0)	20.0 (10.0–33.0)	17.0 (8.0–29.0)
Unilateral RB	21.0 (10.0–32.0)	24.0 (14.0–33.0)	24.0 (11.0–38.0)	23.0 (12.0–34.0)
Bilateral RB	6.0 (2.0–13.0)	10.0 (4.0–18.0)	12.5 (7.0–23.8)	9.0 (4.0–17.0)
Laterality at diagnosis				
Unilateral	521 (62.6)	639 (69.8)	211 (62.5)	1371 [65.2]
Bilateral	313 (37.4)	273 (30.2)	128 (37.5)	714 [34.8]
Clinical primary tumor				
cT1	144 (17.3)	55 (6.0)	27 (8.0)	226 [10.8]
cT1a	38 (4.6)	11 (1.2)	10 (2.9)	59 [2.8]
cT1b	106 (12.7)	44 (4.8)	17 (5.1)	167 [8.0]
cT2	427 (51.2)	418 (45.8)	165 (48.7)	1010 [48.3]
cT2a	122 (14.6)	38 (4.2)	36 (10.6)	196 [9.4]
cT2b	305 (36.6)	380 (41.7)	129 (38.1)	814 [39.0]
cT3	262 (31.4)	433 (47.5)	136 (40.1)	831 [39.9]
cT3a	9 (1.1)	10 (1.1)	3 (0.9)	22 [1.1]
cT3b	84 (10.1)	62 (6.8)	20 (5.9)	166 [8.0]
cT3c	82 (9.8)	229 (25.1)	78 (23)	389 [18.7]
cT3d	61 (7.3)	112 (12.3)	30 (8.8)	203 [9.7]
cT3e	26 (3.1)	20 (2.2)	5 (1.5)	51 [2.4]
cT4	1 (0.1)	6 (0.7)	11 (3.2)	18 [0.9]
Regional lymph node				
NX	374 (44.9)	785 (85.1)	199 (58.7)	1358 [65.1]
N0	458 (54.9)	123 (14.6)	131 (38.6)	712 [34.1]
N1	2 (0.2)	4 (0.4)	9 (2.7)	15 [0.7]
Distant metastasis				
cMX	375 (45.0)	787 (86.3)	216 (63.7)	1378 [66.1]
cM0	454 (54.4)	118 (12.9)	110 (32.4)	682 [32.7]
cM1a	2 (0.2)	1 (0.1)	10 (2.9)	13 [0.6]
cM1b	3 (0.4)	6 (0.7)	3 (0.9)	12 [0.6]
Hereditary trait				
H0	516 (61.9)	633 (69.3)	211 (62.2)	1360 [65.2]
H1	318 (38.1)	279 (30.6)	128 (37.8)	725 [34.8]
Pathological primary tumor				
pT1	218 (41.1)	168 (28.8)	105 (45.3)	491 [36.5]
pT2	189 (35.7)	228 (39.0)	46 (19.8)	463 [34.4]
pT3	111 (20.9%)	142 (24.3)	66 (28.4)	319 [23.7]
pT4	12 (2.3)	46 (7.9)	15 (6.5%)	73 [5.4]

B. Logistic Regression Analysis: Predictors of Advanced Disease at Presentation*,†

Variable	*B (Standard Error)*	*P Value*	*Odds Ratio (95% Confidence Interval)*
Income level			
HIC			1.0
LMIC + UMIC	0.487 (0.095)	<0.001	1.6 (1.4–2.0)
Age (mos)			
<8.0			1.0
8.0–17.0	0.321 (0.134)	0.017	1.4 (1.1–1.8)
17.0–29.0	0.919 (0.129)	<0.001	2.5 (2.0–3.2)
>29.0	0.885 (0.130)	<0.001	2.4 (1.9–3.1)
Constant	−1.214 (0.109)	<0.001	0.3

Table 2. (Continued.)

C. Classification of Retinoblastoma Eyes by National Income Group

Tumor Category	*No. of Eyes (% of Total Eyes in Income Group)*		
	High-Income Country	*Upper Middle-Income Country*	*Lower Middle-Income Country*
cT1			
cT1a	154 (13.2)	56 (4.7)	20 (4.0)
cT1b	211 (18.0)	162 (13.7)	93 (18.7)
cT2			
cT2a	93 (7.9)	66 (5.6)	121 (24.3)
cT2b	445 (38.0)	493 (41.6)	116 (23.3)
cT3	267 (22.8)	400 (33.8)	135 (27.1)
cT4	1 (0.1)	8 (0.7)	13 (2.6)

D. Classification of Retinoblastoma Eyes with Local Treatment Outcomes by National Income Group

Tumor Category	*Treatment Outcomes*	*No. of Eyes (% of Total Eyes)*		
		High-Income Country	*Upper Middle-Income Country*	*Lower Middle-Income Country*
cT1				
cT1a	Primary enucleation	18/154 (11.7)	3/56 (5.4)	2/20 (10)
	Globe salvage	134/154 (87)	49/56 (87.5)	18/20 (90)
	Secondary enucleation	2/154 (1.3)	4/56 (7.1)	0/20 (0)
cT1b	Primary enucleation	6/211 (2.8)	8/162 (4.9)	0/93 (0)
	Globe salvage	190/211 (90)	143/162 (88.3)	90/93 (96.8)
	Secondary enucleation	15/211 (7.1)	11/162 (6.8)	3/93 (3.2)
cT2				
cT2a	Primary enucleation	52/93 (55.9)	23/66 (34.8)	44/121 (36.4)
	Globe salvage	31/93 (33.3)	31/66 (47)	54/121 (44.6)
	Secondary enucleation	10/93 (10.8)	12/66 (18.2)	23/121 (19)
cT2b	Primary enucleation	222/445 (49.9)	154/493 (31.2)	54/116 (46.6)
	Globe salvage	159/445 (35.5)	236/493 (47.9)	33/116 (28.4)
	Secondary enucleation	64/445 (14.4)	103/493 (20.9)	29/116 (25)
cT3	Primary enucleation	217/267 (81.3)	270/400 (67.5)	100/135 (74.1)
	Globe salvage	20/267 (7.5)	62/400 (15.5)	18/135 (13.3)
	Secondary enucleation	30/267 (11.2)	68/400 (17)	17/135 (12.6)

HIC = high-income country; IQR = interquartile range; LMIC = lower middle-income country; UMIC = upper middle-income country.
*The logistic regression model was statistically significant (chi-square (4) = 111.658; $P < 0.001$). The model explained 7.0% (Nagelkerke R^2) of the variance and correctly classified 62.1% of cases. Area under the receiver operating characteristic curve was 0.631 (95% confidence interval, 0.607–0.655; $P < 0.001$).
†Advanced disease is defined as cT3 and cT4.

Geographic Characteristics

Nearly half of the patients were from Asia (1016 [48.7%]), followed by North America (694 [33.2%]), Europe (218 [10.5%]), South America (77 [3.7%]), Australia (44 [2.1%]), and Africa (36 [1.7%]). Based on national income, 834 patients (40%) came from an HIC, 912 patients (43.7%) came from a UMIC, and 339 patients (16.3%) from an LMIC (Table 1).

Patient Features

Median age at diagnosis was 17.0 months (mean, 21.6 months; standard deviation [SD], 20.9 months; IQR, 8–29 months; range, 1 month–30.4 years; Table 2A). Median age at diagnosis increased as national income level decreased ($P < 0.001$) at 14.0 months for HICs (mean, 19.3 years; SD, 19.7 years; range, 1 month–30.4 years; IQR, 6.0–26.0 years), 20.0 months for UMICs (mean, 22.4 years; SD, 18.7 years; range, 1 month–13.6 years; IQR, 9.3–30.0 years), and 20.0 months for LMICs (mean, 24.9 years; SD, 27.5 years; range, 10–32 years; IQR, 10.0–33.0 years). Bilateral retinoblastoma at diagnosis was seen in 714 of 2085 patients (34.8%; 313 patients [37.4%], 273 patients [30.2%], and 128 patients [37.5%] from HICs, UMICs, and LMICs, respectively). Table 2A shows tumor features by income group. On logistic regression (Table 2B), lower national income level and older age at presentation were found to be both independent and significant predictive factors ($P < 0.001$) for advanced disease (cT3 and cT4).

American Joint Committee on Cancer Classification

The clinical tumor categories (cT) for all 2085 patients were: cT1a in 59 patients (2.8%), cT1b in 167 patients (8.0%), cT2a in 196 patients (9.4%), cT2b in 814 patients (39.0%), cT3 in 831 patients (39.9%), and cT4 in 18 patients (0.9%); Table 2A. Lymph node involvement at presentation was seen in 15 patients: 2 patients (0.2%) in HICs, 4 patients (0.4%) in UMICs, and 9 patients (2.7%) in LMICs. Synchronous metastatic disease at the time of diagnosis of the primary tumor was seen in 25 patients: 5 patients (0.6%) in HICs, 7 patients (0.8%) in UMICs, and 13 patients (3.9%) in LMICs. Heritable trait, diagnosed in 725 patients, was unrelated to national income level: 318 patients (38.1%) in HICs, 279 patients (30.6%) in UMICs, and 128 patients (37.8%) in LMICs (Table 2A).

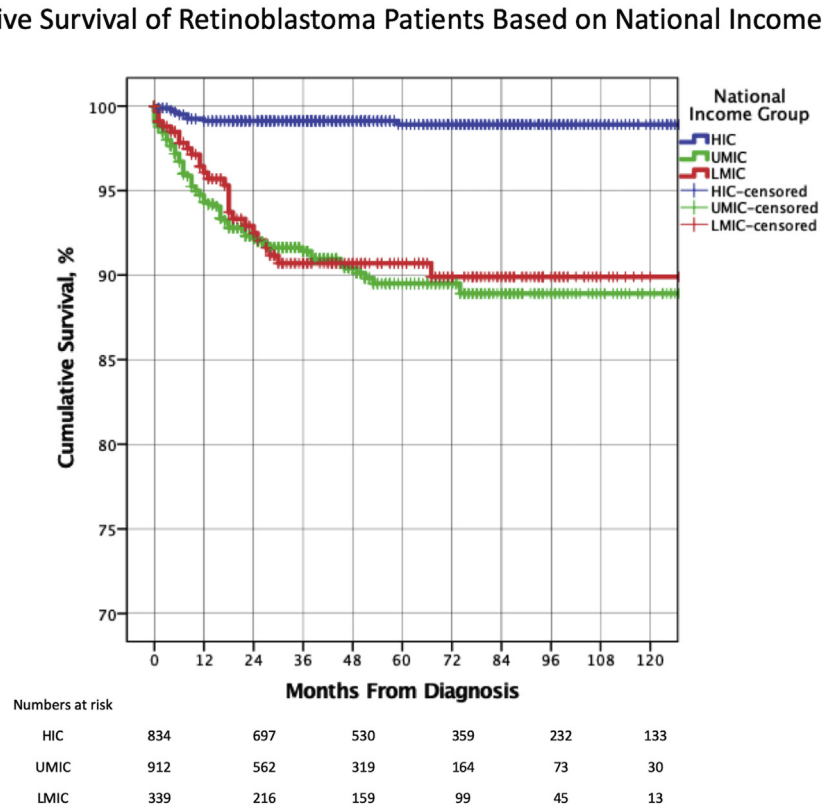

Figure 1. Kaplan-Meier curves showing cumulative survival estimates for all retinoblastoma patients by national income groups. HIC = high-income country; LMIC = lower middle-income country; UMIC = upper middle-income country.

Cumulative Proportion Estimates of Survival According to National Income

Of 2085 patients, 109 (5.2%; 95% confidence interval [CI], 4.3%−6.3%) died of metastatic disease. The other causes of death, not included in survival analysis, were chemotherapy-related adverse events in 4 patients (0.2%), trilateral retinoblastoma in 1 patient (0.1%), and non−disease-related causes in 3 patients (0.2%). The median time from presentation to development of metastasis (known for 92 patients) was 9.5 months (mean, 13.7 months; SD, 13.6 months; IQR, 4.0−19.8 months; range, 0 months−13.9 years). The risk of metastasis was associated strongly with lower national income group: 1.0% (8/826; 95% CI, 0.4%−1.9%) demonstrated metastases in an HIC, 9.0% (75/837; 95% CI, 4.2%−19.0%) demonstrated metastases in a UMIC, and 8.3% (26/313; 95% CI, 5.5%−11.9%) demonstrated metastases in an LMIC.

The 5-year Kaplan-Meier cumulative survival estimates by national income were 99% for HICs, 89% (95% CI, 88%−90%) for UMICs, and 90% (95% CI, 88%−92%) for LMICs, respectively (Fig 1; Figs S1−S3, available at www.aaojournal.org). Compared with HIC patients, the UMIC and LMIC patients showed an increased risk of metastasis-related mortality and shorter survival ($P < 0.001$, log-rank test for trend; Table 3A; Table S2, available at www.aaojournal.org). Pairwise comparison showed a significant difference between HICs and UMICs and LMICs ($P < 0.001$ for each), whereas no significant difference was found between UMICs and LMICs ($P = 0.57$). Cox proportional hazards regression estimates showed that patients in UMICs (hazard ratio [HR], 10.3; 95% CI, 5.0−21.4; $P < 0.001$) and those in LMICs (HR, 9.3; 95% CI, 4.2−20.5; $P < 0.001$) demonstrated a greater risk of metastasis-related mortality compared with those in HICs (Table 4A). Multivariate analysis revealed a higher risk of metastatic mortality with advanced age at presentation: age of 17.0 to 29.0 months (HR, 1.9; 95% CI, 1.0−3.3; $P = 0.030$) and older than 29.0 months (HR, 2.3; 95% CI, 1.3−4.1; $P = 0.006$) compared with age at presentation younger than 8.0 months as well as positive heritable trait status (HR, 1.6; 95% CI, 1.0−2.5; $P = 0.027$) compared with unknown or absence of heritable trait, Hx or H0.

Of the 1353 patients who underwent primary or secondary enucleation, 69 (5.1%; 95% CI 4.0%−6.4%) died of metastatic disease. Histopathologic analysis was undertaken, and a pT category was assigned for all eyes (Table 3; Table S3, available at www.aaojournal.org). Among these, 1.3% (7/523; 95% CI, 0.5%−2.7%) demonstrated metastasis in an HIC, 8.8% (47/537; 95% CI, 6.5%−11.5%) did so in a UMIC, and 6.9% (15/217; 95% CI, 3.9%−11.1%) did so in an LMIC.

The 5-year Kaplan-Meier cumulative survival estimates (enucleated patients) by national income were 99% (95% CI, 98%−100%) for HICs, 90% (95% CI, 89%−91%) for UMICs, and 92% (95% CI, 90%−94%) for LMICs, respectively (Fig 2; Figs S4−S6, available at www.aaojournal.org). Compared with HIC patients, UMIC and LMIC patients showed an increased risk of metastasis-related mortality and shorter survival ($P < 0.001$, log-rank test for trend; Table 3B; Table S3, available at www.aaojournal.org). Pairwise comparison showed significant differences between HICs compared with UMICs and LMICs ($P < 0.001$ for each), whereas no significant difference was found between UMICs and LMICs ($P = 0.37$). Cox proportional hazards regression analysis showed that

Table 3. Kaplan-Meier Analyses

A. Kaplan-Meier Cumulative Proportion of Surviving Patients According to National Income Group

	Kaplan-Meier Estimate, % (95% Confidence Interval)		
Variable	*1 Year*	*5 Years*	*10 Years*
All patients (N = 2085)	95 (94-96)	94 (93-95)	93 (92-94)
HIC (n = 834)	99 (98-100)	99 (98-100)	99 (98-100)
UMIC (n = 912)	92 (91-93)	89 (88-90)	89 (88-90)
LMIC (n = 339)	93 (91-95)	90 (88-92)	90 (88-92)
Overall comparison, $P < 0.001$			

	High-Income Country	**Upper Middle-Income Country**
HIC		
UMIC	$P < 0.001$	
LMIC	$P < 0.001$	$P = 0.57$

B. Kaplan-Meier Cumulative Proportion of Surviving Patients in All Enucleated Retinoblastoma Patients According to National Income Group

	Kaplan-Meier Estimate, % (95% Confidence Interval)		
Variable	*1 Year*	*5 Years*	*10 Years*
All patients (n = 2085)	95 (94-96)	94 (93-95)	93 (92-94)
HIC (n = 834)	99 (98-100)	99 (98-100)	99 (98-100)
UMIC (n = 912)	93 (92-94)	90 (89-91)	90 (88-92)
LMIC (n = 339)	94 (92-96)	92 (90-94)	92 (90-94)
Overall comparison, $P < 0.001$			

	High-Income Country	**Upper Middle-Income Country**
HIC		
UMIC	$P < 0.001$	
LMIC	$P < 0.001$	$P = 0.37$

C. Kaplan-Meier Cumulative Proportion of Avoiding Local Treatment Failure According to National Income Group

	Kaplan-Meier Estimate, % (95% Confidence Interval)			
Classification	*1 Year*	*2 Years*	*5 Years*	*10 Years*
All eyes (n = 1574)	78 (77−79)	75 (74-76)	68 (67-69)	42 (38-46)
HIC (n = 633)	84 (83−85)	83 (81-85)	77 (75-79)	48 (43-53)
UMIC (n = 682)	72 (70−74)	67 (65-69)	54 (51-57)	33 (27-39)
LMIC (n = 259)	75 (72−78)	72 (69-75)	69 (66-72)	61 (57-65)

Overall comparison, $P < 0.001$

	HIC	UMIC
HIC		
UMIC	$P < 0.001$	
LMIC	$P = 0.002$	$P = 0.15$

HIC = high-income country; LMIC = lower middle-income country; UMIC = upper middle-income country.

enucleated patients in UMICs (HR, 6.9; 95% CI, 3.1−15.3; $P < 0.001$) and LMICs (HR, 5.4; 95% CI, 2.2−13.2; $P < 0.001$) showed a greater risk of metastasis-related death compared with those in HICs (Table 4B). Multivariate analysis revealed a higher risk of metastasis-related mortality in enucleated patients with advanced age at presentation of more than 29.0 months (HR, 2.4; 95% CI, 1.0−5.6; $P = 0.044$) compared with those younger than 8.0 months, but not with those 17 to 29 months of age ($P = 0.067$) and with positive heritable trait status ($P = 0.373$).

Local Treatment Outcomes

Of the 2854 eyes, primary enucleation was performed in 1179 and 2D)(41.3%), 1675 underwent an attempt at globe salvage, and local tumor control was achieved for 1275 (44.7%). Secondary enucleation became necessary in 400 eyes (14.0%; Table 2C and 2D

Cumulative Proportion of Avoiding Local Treatment Failure by National Income

Of 1675 eyes not primarily enucleated, 1574 showed complete data for globe salvage analysis and 434 (27.6%) were treated by EBRT (90 eyes) or secondary enucleation (334 eyes) for retinoblastoma control. Analysis by national income revealed that globe salvage failed in 25.2% (110 were enucleated and 50 needed EBRT of 633) in HICs, 29.8% (172 were enucleated and 31 needed EBRT of 682) in UMICs, and 27.4% (62 were enucleated and 9 needed EBRT of 259) in LMICs. The 5-year Kaplan-Meier cumulative proportion of

Table 4. Cox Proportional Hazards Regression

Variable	No. of Patients in Category (%)	Reference	Wald Chi-Square	Hazard Ratio (95% Confidence Interval)	P Value
A. Cox proportional hazards regression model in all retinoblastoma patients for association of national income level with metastatic mortality					
Univariate analysis	(n = 2085)				
UMIC	n = 912	HIC	39.21	10.3 (5.0–21.4)	<0.001
LMIC	n = 339	HIC	30.38	9.3 (4.2–20.5)	<0.001
Multivariate analysis	(n = 2085)				
UMIC	n = 912	HIC	37.4	9.8 (4.7–20.4)	<0.001
LMIC	n = 339	HIC	27.8	8.5 (3.8–18.8)	<0.001
Age (mos)					
8.0–17.0	n = 480	Age < 8.0 mos	0.04	0.9 (0.5–1.8)	0.839
17.0–29.0	n = 532	Age < 8.0 mos	4.7	1.9 (1.0–3.3)	0.030
>29.0	n = 504	Age < 8.0 mos	7.5	2.3 (1.3–4.1)	0.006
H1	n = 725	H0	4.8	1.6 (1.0–2.5)	0.027
B. Cox proportional hazards regression model in all enucleated retinoblastoma patients for association of national income level with metastatic mortality					
Univariate analysis	(n = 1353)				
UMIC	n = 584	HIC	22.66	6.9 (3.1–15.3)	<0.001
LMIC	n = 232	HIC	13.45	5.4 (2.2–13.2)	<0.001
Multivariate analysis	n = 2085				
UMIC	n = 584	HIC	21.7	6.6 (3.0–14.7)	<0.001
LMIC	n = 232	HIC	12.4	5.1 (2.1–12.5)	<0.001
Age (mos)					
8.0–17.0	n = 280	Age < 8.0 mos	0.2	1.2 (0.5–3.2)	0.655
17.0–29.0	n = 413	Age < 8.0 mos	3.4	2.2 (1.0–4.9)	0.067
>29.0	n = 387	Age < 8.0 mos	4.1	2.4 (1.0–5.6)	0.044
H1	n = 383	H0	0.8	1.3 (0.7–2.3)	0.373
C. Cox proportional hazards regression model in retinoblastoma eyes for association of national income level with local treatment failure					
Univariate analysis	n = 1353				
UMIC	n = 682	HIC	48.07	2.2 (1.7–2.7)	<0.001
LMIC	n = 259	HIC	9.61	1.6 (1.2–2.1)	<0.001
Multivariate analysis	(n = 2085)				
UMIC	n = 682	HIC	19.0	1.7 (1.3–2.1)	<0.001
LMIC	n = 259	HIC	3.1	1.3 (1.0–1.7)	0.081
Age (mos)					
8.0–17.0	n = 413	Age < 8.0 mos	0.01	1.0 (0.8–1.2)	0.904
17.0–29.0	n = 273	Age < 8.0 mos	31.1	2.1 (1.6–2.6)	<0.001
>29.0	n = 180	Age < 8.0 mos	19.6	2.0 (1.5–2.6)	<0.001
Unilateral	n = 425	Bilateral	47.3	2.1 (1.7–2.6)	<0.001

HIC = high-income country; LMIC = lower middle-income country; UMIC = upper middle-income country.

eyes avoiding local treatment failure was 77% (95% CI, 75%–79%) for HICs, 54% (95% CI, 51%–57%) for UMICs, and 69% (95% CI, 66%–72%) for LMICs (Fig 3; Figs S6–S9, available at www.aaojournal.org). In comparison with eye in HICs, eyes in both UMICs and LMICs showed an increased risk of local treatment failure and less frequent globe salvage ($P < 0.001$, log-rank test for trend; Table 3C; Table S4, available at www.aaojournal.org). Pairwise comparison revealed a significant difference in local failure between HICs as compared with UMICs and LMICs ($P < 0.001$ for each). No significant difference existed between UMICs and LMICs ($P = 0.15$). Cox proportional hazards regression analysis showed that patients in a UMIC (HR, 2.2; 95% CI, 1.7–2.7; $P < 0.001$) and those in an LMIC (HR, 1.6; 95% CI, 1.2–2.1; $P < 0.001$) demonstrated a greater risk of local treatment failure (defined as need for EBRT or enucleation) compared with those in an HIC (Table 4C). Multivariate analysis revealed that a higher risk was found of local treatment failure with advanced age at presentation: age of 17.0 to 29.0 months (HR, 2.1; 95% CI, 1.6–2.6; $P < 0.001$) and older than 29.0 months (HR, 2.0; 95% CI, 1.5–2.6; $P < 0.001$) compared with age at presentation of younger than 8.0 months. In addition, a higher risk was found of local treatment failure for unilateral retinoblastoma (HR, 2.1; 95% CI, 1.7–2.6; $P < 0.001$) compared with bilateral retinoblastoma.

Discussion

A multicenter, international, internet-based registry was used to study retinoblastoma metastasis-related mortality, local treatment failure, and eye salvage on a global scale. Outcomes were related to the 2017 United Nations, Department of Economic and Social Affairs World Population Prospects definitions of national incomes. Forty percent of retinoblastoma patients were from HICs and 60% were from UMICs and LMICs. This study revealed that lower national income levels were related significantly to increased risk of poor treatment outcomes. Specifically, compared with patients from HICs, retinoblastoma patients

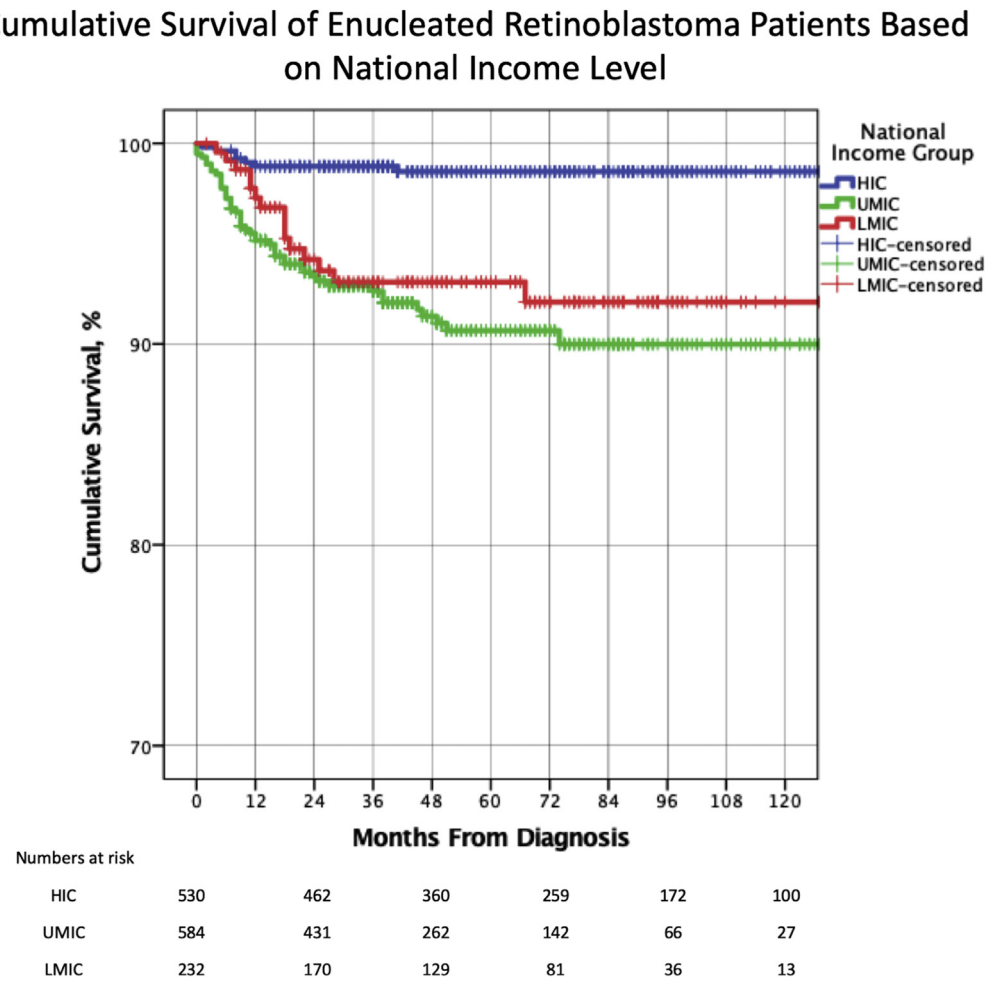

Figure 2. Kaplan-Meier curves showing cumulative survival estimates for all enucleated retinoblastoma patients by national income groups. HIC = high-income country; LMIC = lower middle-income country; UMIC = upper middle-income country.

from UMICs and LMICs showed a 10.3-fold risk and 9.3-fold risk, respectively, for metastatic mortality and a 2.2-fold risk and 1.6-fold risk, respectively, for local treatment failure.

Table 5 compares and contrasts the Global Retinoblastoma Study Group findings from 2017 with our results.[3] Our work showed identical demographic and clinical features at diagnosis. Notable similarities include the highest proportion of patients from Asia, an association between age at diagnosis and national income level, advanced intraocular tumor in one eye, and increased nodal and systemic metastasis at presentation were related to decreasing national income. Note that the difference in geographic distribution and national income were influenced by the heterogeneity of our LMIC group and lack of a lower-income country group in our registry. The greater variability in age at diagnosis and tumor stage was found among countries in the LMIC group, which may have affected outcomes in this category. Moreover, for LMICs, a comparison of these two cohorts (AJCC-OOTF and Global Retinoblastoma Study Group) suggested no improvement in age and stage at diagnosis from 2001 through 2013 to 2017 (Table 5). Both studies emphasize the need for curative frontline therapy in these resource-poor countries.

Our study revealed a higher risk of systemic metastasis and mortality on follow-up in patients with advanced age at presentation and positive heritable trait status. These children face a poorer prognosis because of the presence of germline mutation, increased tumor load, risk of secondary cancers, and often their custodian's failure to accept bilateral enucleation. Similarly, older children and those with unilateral retinoblastoma showed a higher risk of local treatment failure.

We recently published 2 validation studies of the eighth edition of the AJCC retinoblastoma staging system that revealed that it can be used to predict both globe salvage and metastasis-related mortality.[5,6] Together, the AJCC offers the first uniform comprehensive classification for retinoblastoma and a useful tool for global reporting of treatment outcomes. Our study uniquely reports real-world data on local treatment failure, eye salvage, and metastasis-related mortality stratified by national income level as well as differences in treatment outcomes from various nations by their socioeconomic status. We showed that children with retinoblastoma not only from LMICs but

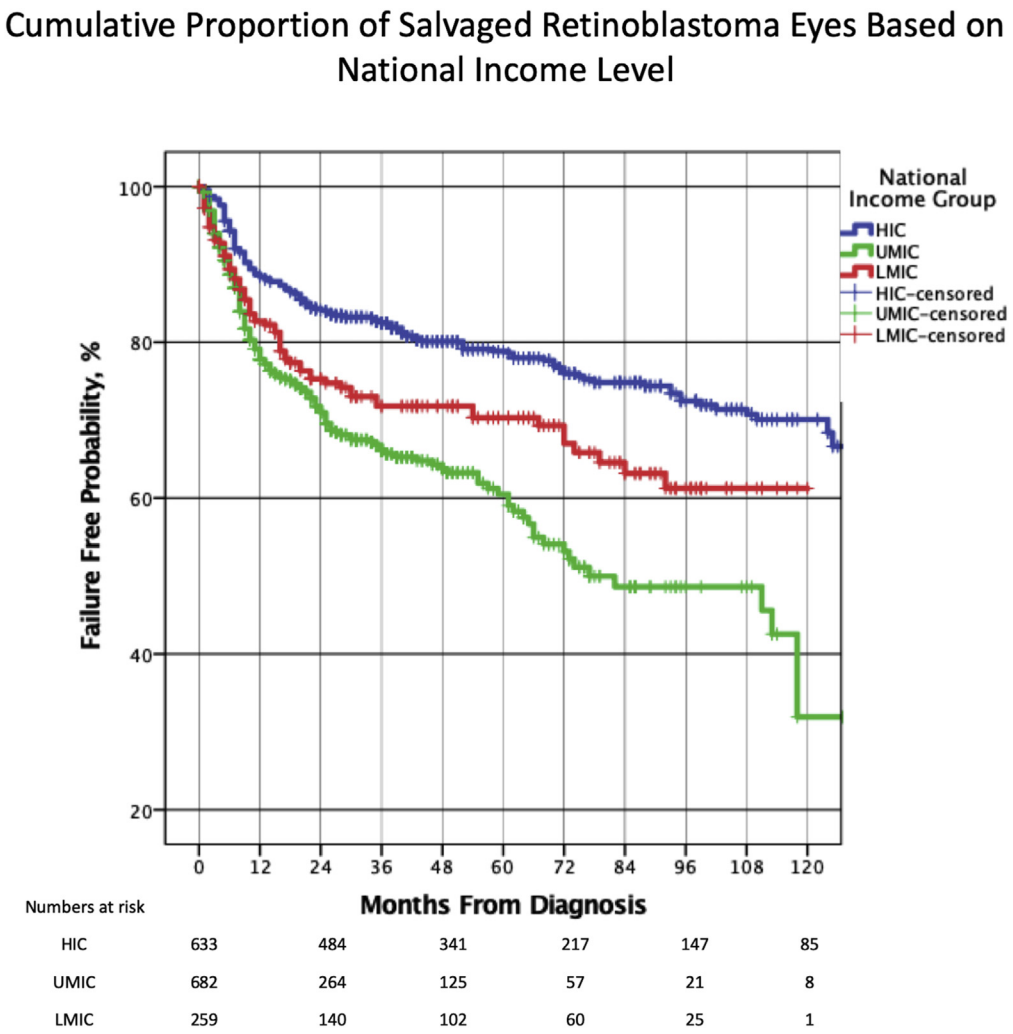

Figure 3. Kaplan-Meier curve of cumulative proportion of salvaged retinoblastoma eyes (without need for external beam radiation therapy) by national income groups. HIC = high-income country; LMIC = lower middle-income country; UMIC = upper middle-income country.

also from UMICs are at 9- to 10-fold higher risk of metastasis-related death compared with those from HICs. Poor outcomes for the world's children affected by retinoblastoma are related primarily to delay in diagnosis and abandonment of treatment.[38] Because of religious beliefs and social stigma, some families refuse to accept enucleation even for cases of unilateral retinoblastoma. Unrealistic hope for eye salvage, particularly in advanced cases, can result in multiple treatments and delay of local cure and metastatic disease.[10] These grave problems could be addressed when health ministries support clinical practice guidelines among all levels of care, led by dedicated retinoblastoma teams, with eye cancer specialists and skills transfer appropriate for lower-income countries.[39–42] Although early detection and prompt enucleation are typically life saving, the relative lack of stem-cell treatment facilities, EBRT, and salvage techniques in lower-income countries also contribute to the disparity.

Local treatment failure and globe salvage rates follow a similar pattern for both UMICs and LMICs. An important reason for contrasting eye salvage has been that many lower-income countries lack access to advanced, end-organ chemotherapy typically used in an HIC.[3,4,43,44] Eyes with high-risk pathologic features are at higher risk of extraocular retinoblastoma extension and relapse. Such cases are more frequent in developing countries, occurring in more than 50% of children, compared with developed countries, where they are seen in less than 20% of enucleated eyes.[45] Histopathologic analysis of enucleated eyes from LMICs and UMICs revealed that patients with high-risk histopathologic features (pT3 and pT4 cancers) fared worse in comparison with HICs (see Table S3).

Our analysis found that treatment outcomes were not statistically different between UMICs and LMICs. However, we may not have fully captured the variability of patients in LMICs.[3] Alternatively, national income is likely not the only metric that can be applied when gauging treatment outcomes for retinoblastoma. Others include socioeconomic and health-related indicators, including annual per capita healthcare expenditure, physician and nurse density, type of healthcare system, presence of national retinoblastoma referral centers, registries, patient

Table 5. Global Retinoblastoma Study Group[3] Compared with American Joint Committee on Cancer—Ophthalmic Oncology Task Force Retinoblastoma Study

Feature	Global Retinoblastoma Study Group[3]	American Joint Committee on Cancer—Ophthalmic Oncology Task Force
Study population	4351 patients representing 278 centers and 153 countries	2085 patients from 18 centers and 13 countries
Study design	1-year, survey-based cross sectional cohort study	13-year, registry-based retrospective case series
Geographic distribution of cases (% of patients)		
Asia	52.3	48.7
Americas	11.8	North America, 33.2 South America, 3.7
Europe	12.0	10.5
Oceania	0.4	2.1
Africa	23.5	1.7
Patient distribution by national income level (%)		
HICs	15.3	40
UMICs	27.9	43.7
LMICs	44.6	16.3
LICs	12.3	N/A
Median age at diagnosis, mos		
Global	23.5	17.0
HICs	14.0	14.0
UMICs	20.7	20.0
LMICs	24.4	20.0
LICs	30.5	N/A
Bilateral retinoblastoma (%)		
Global	30.8	34.8
HICs	35.4	37.4
UMICs	30.1	30.2
LMICs	31.7	37.5
LICs	23.5	N/A
Most common clinical tumor category at presentation (cT3; %)		
Global	47.0	39.9
HICs	34.0	31.4
UMICs	44.6	47.5
LMICs	52.4	40.1
LICs	42.6	N/A
Children with positive lymph node status (cN1) at presentation (%)		
Global	3.4	0.7
HICs	0.0	0.2
UMICs	1.9	0.4
LMICs	4.3	2.7
LICs	8.3	N/A
Children presenting with metastatic disease (cM1) at presentation (%)		
Global	5.0	1.2
HICs	0.0	0.6
UMICs	3.2	0.8
LMICs	5.8	3.9
LICs	13.1	N/A

cM = clinical metastasis; cN = clinical node; HIC = high-income country; LIC = lower-income country; LMIC = lower middle-income country; N/A = not available; UMIC = upper middle-income country.

gender, and religion. Such a comprehensive analysis could provide a more nuanced picture of worldwide retinoblastoma and could enable treatment strategies.[33] Another interesting aspect of assessment would include studying gender bias in disease presentation and choice of treatment options, community impact of awareness programs, availability of nongovernment funding for treatment and counseling, and the role of parents' organizations. Specifically, these studies should consider gender-biased treatment options, community impact of awareness programs, availability of funding for parent counseling, and the role of parents' organizations.

Limitations of our study include its retrospective design and lack of data (by design) on patient gender and ethnic

and racial backgrounds. It is also important to consider that treatment strategies are evolving, and the registry data collection was performed for 2001 through 2013. The strengths include that this is an international, multicenter, 6-continent, and, therefore, real-world registry-based analysis of retinoblastoma management using a uniform staging system across centers.

This study highlighted the persistent gap between countries for retinoblastoma stage, age at diagnosis, and treatment outcomes. We emphasized the need to improve awareness and detection of retinoblastoma, as well as access to treatment in countries where resources are limited. The World Health Organization Global Initiative for Childhood Cancer aims to raise survival for key childhood cancers (including retinoblastoma) to 60% by the year 2030.[46] This could be feasible through a coordinated global effort. Toward that aim, crucial steps include: prospective collection of uniform, multicenter, international retinoblastoma data; open-access textbooks that allow general ophthalmologists to provide care; and twinning programs that link higher-resource and lower-resource centers and funded subspecialty training programs to supply ocular oncologists for unserved and underserved countries (e.g., International Council of Ophthalmology and The Eye Cancer Foundation - 2020 Campaign).[15,47,48] With infrastructure to treat retinoblastoma in place, government-enabled social programs can educate parents, parent organizations, schools, and pediatricians about early signs of retinoblastoma (i.e., leukocoria, strabismus, etc.). These prerequisite measures can achieve early diagnosis followed by prompt intervention, which has reduced retinoblastoma morbidity and mortality effectively.

Results from both the AJCC-OOTF and the Global Retinoblastoma Study Group suggest that advanced stage of retinoblastoma at presentation was found to be dependent on national income level. In addition, we found differences in life, globe, and vision salvage in countries with lower national income. This underscores the need to improve awareness of retinoblastoma as well as access to early diagnosis and treatment through national and international effort.[15,49]

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References

1. Dimaras H, Corson TW, Cobrinik D, et al. Retinoblastoma. *Nat Rev Dis Primer*. 2015;1:15021.
2. Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol*. 2009;93(9):1129–1131.
3. Global Retinoblastoma Study Group, Fabian ID, Abdallah E, et al. Global retinoblastoma presentation and analysis by national income level. *JAMA Oncol*. 2020;6(5):685–695.
4. Munier FL, Beck-Popovic M, Chantada GL, et al. Conservative management of retinoblastoma: challenging orthodoxy without compromising the state of metastatic grace. "Alive, with good vision and no comorbidity.". *Prog Retin Eye Res*. 2019;73:100764.
5. Tomar AS, Finger PT, Gallie B, et al. A multicenter, international collaborative study for American Joint Committee on Cancer-staging of retinoblastoma: Part I: metastasis-associated mortality. *Ophthalmology*. 2020 Jun 6;S0161-6420(20)30516-9. https://doi.org/10.1016/j.ophtha.2020.05.050. Online ahead of print.
6. Tomar AS, Finger P, Gallie BL, et al. A multicenter, international collaborative study for American Joint Committee on Cancer-staging of retinoblastoma: Part II: treatment success and globe salvage. *Ophthalmology*. 2020 Jun 8;S0161-6420(20)30524-8. https://doi.org/10.1016/j.ophtha.2020.05.051. Online ahead of print.
7. Young JL, Smith MA, Roffers SD, et al. Retinoblastoma. In: Ries LA, Smith MA, Gurney GJ, eds. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975–1995. NIH Publication No. 99-4649*. Bethesda, MD: National Cancer Institute, SEER Program; 1999:73–77.
8. Krishna SM, Yu G-P, Finger PT. The effect of race on the incidence of retinoblastoma. *J Pediatr Ophthalmol Strabismus*. 2009;46(5):288–293.
9. Finger PT, Meskin SW, Wisnicki HJ, et al. High-frequency ultrasound of anterior segment retinoblastoma. *Am J Ophthalmol*. 2004;137(5):944–946.
10. 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.
11. Finger PT, Harbour JW, Karcioglu ZA. Risk factors for metastasis in retinoblastoma. *Surv Ophthalmol*. 2002;47(1):1–16.
12. Sastre X, Chantada GL, Doz F, et al. Proceedings of the consensus meetings from the International Retinoblastoma Staging Working Group on the pathology guidelines for the examination of enucleated eyes and evaluation of prognostic risk factors in retinoblastoma. *Arch Pathol Lab Med*. 2009;133(8):1199–1202.
13. Chantada GL, Doz F, Orjuela M, et al. World disparities in risk definition and management of retinoblastoma: a report from the International Retinoblastoma Staging Working Group. *Pediatr Blood Cancer*. 2008;50(3):692–694.
14. Chantada G, Doz F, Antoneli CBG, et al. A proposal for an international retinoblastoma staging system. *Pediatr Blood Cancer*. 2006;47(6):801–805.
15. Chaugule S, Honavar SG, Finger P, eds. *Surgical Ophthalmic Oncology: A Collaborative Open Access Reference*. Switzerland: Springer International Publishing; 2019:1–216.
16. Grigorovski N, Lucena E, Mattosinho C, et al. Use of intra-arterial chemotherapy for retinoblastoma: results of a survey. *Int J Ophthalmol*. 2014;7(4):726–730.
17. Ademola-Popoola DS, Opocher E, Reddy MA. Contemporary management of retinoblastoma in the context of a low-resource country. *Niger Postgrad Med J*. 2019;26(2):69–79.
18. Rajeshuni N, Whittemore AS, Ludwig CA, et al. Racial, ethnic, and socioeconomic disparities in retinoblastoma enucleation: a population-based study, SEER 18 2000–2014. *Am J Ophthalmol*. 2019;207:215–223.
19. Truong B, Green AL, Friedrich P, et al. Ethnic, racial, and socioeconomic disparities in retinoblastoma. *JAMA Pediatr*. 2015;169(12):1096–1104.

20. Orman A, Koru-Sengul T, Miao F, et al. The modern role of radiation therapy in treating advanced-stage retinoblastoma: long-term outcomes and racial differences. *Int J Radiat Oncol Biol Phys*. 2014;90(5):1037−1043.
21. Green AL, Chintagumpala M, Krailo M, et al. Correlation of insurance, race, and ethnicity with pathologic risk in a controlled retinoblastoma cohort: a Children's Oncology Group study. *Ophthalmology*. 2016;123(8):1817−1823.
22. MacCarthy A, Draper GJ, Steliarova-Foucher E, Kingston JE. Retinoblastoma incidence and survival in European children (1978−1997). Report from the Automated Childhood Cancer Information System Project. *Eur J Cancer Oxf Engl 1990*. 2006;42(13):2092−2102.
23. Park SJ, Woo SJ, Park KH. Incidence of retinoblastoma and survival rate of retinoblastoma patients in Korea using the Korean National Cancer Registry database (1993−2010). *Invest Ophthalmol Vis Sci*. 2014;55(5):2816−2821.
24. Luna-Fineman S, Barnoya M, Bonilla M, et al. Retinoblastoma in Central America: report from the Central American Association of Pediatric Hematology Oncology (AHOPCA). *Pediatr Blood Cancer*. 2012;58(4):545−550.
25. MacCarthy A, Birch JM, Draper GJ, et al. Retinoblastoma: treatment and survival in Great Britain 1963 to 2002. *Br J Ophthalmol*. 2009;93(1):38−39.
26. Nummi K, Kivelä TT. Retinoblastoma in Finland, 1964−2014: incidence and survival. *Br J Ophthalmol*. 2020 Mar 25;bjophthalmol-2019-315744. https://doi.org/10.1136/bjophthalmol-2019-315744. Online ahead of print.
27. Ueda T, Koga Y, Yoshikawa H, et al. Survival and ocular preservation in a long-term cohort of Japanese patients with retinoblastoma. *BMC Pediatr*. 2020;20(1):37.
28. 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.
29. Desandes E, Faure L, Guissou S, et al. Infant cancers in France: incidence and survival (2000−2014). *Cancer Epidemiol*. 2020;65:101697.
30. Moreno F, Sinaki B, Fandiño A, et al. A population-based study of retinoblastoma incidence and survival in Argentine children. *Pediatr Blood Cancer*. 2014;61(9):1610−1615.
31. Nyamori JM, Kimani K, Njuguna MW, Dimaras H. The incidence and distribution of retinoblastoma in Kenya. *Br J Ophthalmol*. 2012;96(1):141−143.
32. Leal-Leal C, Flores-Rojo M, Medina-Sansón A, et al. A multicentre report from the Mexican Retinoblastoma Group. *Br J Ophthalmol*. 2004;88(8):1074−1077.
33. Canturk S, Qaddoumi I, Khetan V, et al. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. *Br J Ophthalmol*. 2010;94(11):1432−1436.
34. Finger PT. Do you speak ocular tumor? *Ophthalmology*. 2003;110(1):13−14.
35. Mallipatna A, Gallie BL, Chévez-Barrios P, et al. Retinoblastoma. In: Amin MB, Edge SB, Greene FL, eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017:819−831.
36. United Nations, Department of Economic and Social Affairs. World population prospects: the 2017 revision. Volume I: comprehensive tables. https://population.un.org/wpp/Publications/Files/ WPP2017_Volume-I_Comprehensive-Tables.pdf; 2017. Accessed 13.06.20.
37. de Jong MC, Kors WA, de Graaf P, et al. The incidence of trilateral retinoblastoma: a systematic review and meta-analysis. *Am J Ophthalmol*. 2015;160(6):1116−1126.e5.
38. Luna-Fineman S, Chantada G, Alejos A, et al. Delayed enucleation with neoadjuvant chemotherapy in advanced intraocular unilateral retinoblastoma: AHOPCA II, a prospective, multi-institutional protocol in Central America. *J Clin Oncol Off J Am Soc Clin Oncol*. 2019;37(31):2875−2882.
39. Qaddoumi I, Nawaiseh I, Mehyar M, et al. Team management, twinning, and telemedicine in retinoblastoma: a 3-tier approach implemented in the first eye salvage program in Jordan. *Pediatr Blood Cancer*. 2008;51(2):241−244.
40. Wilimas JA, Wilson MW, Haik BG, et al. Development of retinoblastoma programs in Central America. *Pediatr Blood Cancer*. 2009;53(1):42−46.
41. Rodriguez-Galindo C, Wilson MW, Chantada G, et al. Retinoblastoma: one world, one vision. *Pediatrics*. 2008;122(3):e763−e770.
42. Al-Haddad C, Bashour Z, Farah L, et al. Establishment of a formal program for retinoblastoma: feasibility of clinical coordination across borders and impact on outcome. *Pediatr Blood Cancer*. 2019;66(11):e27959.
43. Yousef YA, Soliman SE, Astudillo PPP, et al. Intra-arterial chemotherapy for retinoblastoma: a systematic review. *JAMA Ophthalmol*. 2016;134(5):584−591.
44. American Brachytherapy Society—Ophthalmic Oncology Task Force. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. *Brachytherapy*. 2014;13(1):1−14.
45. Chantada GL, Qaddoumi I, Canturk S, et al. Strategies to manage retinoblastoma in developing countries. *Pediatr Blood Cancer*. 2011;56(3):341−348.
46. World Health Organization. Global initiative for childhood cancer. https://www.who.int/cancer/ childhood-cancer/en/; 2018. Accessed 13.06.20.
47. Torres-Netto EA, Gabel-Obermaier C, Gabel P, et al. Twenty years of International Council of Ophthalmology fellowships: description of the programme and the impact on more than 1100 awardees. *Br J Ophthalmol*. 2020 Aug 29;bjophthalmol-2020-316484. https://doi.org/10.1136/bjophthalmol-2020-316484. Online ahead of print.
48. The Eye Cancer Foundation. The 2020 campaign: train 20 specialists in 20 countries to treat childhood eye cancer. http://www.eyecancercure.com/news-and-events/news/65/the-2020-campaign-train-20-specialists-in-20-countries-to-treat-childhood-eye-cancer; 2020. Accessed 26.08.20.
49. Finger PT. Foundational elements for collaboration in ophthalmic oncology. *Ophthalmol Retina*. 2017;1(4):263−265.

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Abbreviations and Acronyms:
AJCC = American Joint Committee on Cancer; **AJCC-OOTF** = American Joint Committee on Cancer—Ophthalmic Oncology Task Force; **cT** = clinical tumor; **EBRT** = external beam radiation therapy; **HIC** = high-income country; **HR** = hazard ratio; **IQR** = interquartile range; **LMIC** = lower middle-income country; **pT** = pathologic tumor; **SD** = standard deviation; **UMIC** = upper middle-income country.

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