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Retinoblastoma Outcomes in the Americas: a prospective analysis of 491 children with retinoblastoma from 23 American countries

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Short Title: Retinoblastoma in Americas

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ABSTRACT

Purpose:

Globally, disparities exist in retinoblastoma treatment outcomes between high- and low-income countries, but independent analysis of American countries is lacking. We report outcomes of American retinoblastoma patients and explore factors associated with survival and globe salvage.

Design:

Subanalysis of prospective cohort study data.

Methods:

Multicenter analysis at 57 American treatment centers in 23 countries of varying economic levels (low income=LIC, lower-middle=LMIC, upper-middle=UMIC, high=HIC) of 491 treatment-naïve retinoblastoma patients diagnosed in 2017 and followed through 2020. Survival and globe salvage rates analyzed with Kaplan-Meier analysis and Cox proportional hazard models.

***Results*:**

Of patients, 8 (1.6%), 58 (11.8%), 235 (47.9%) and 190 (38.7%) were from LIC, LMIC, UMIC and HIC, respectively. Three-year survival rates in LICs were 60.0% (95% CI, 12.6-88.2) compared to 99.2% (94.6-99.9) in HICs. Death was less likely in patients older than four years (vs. four or younger, HR=0.45 [95% CI, 0.27 – 0.78], P=0.048). Patients with more advanced tumors (e.g., cT3 vs. cT1, HR= $4.65x10^{9}$ [95% CI, $1.25x10^{9}$ – $1.72x10^{10}$], P<0.001) and females (vs. males, HR=1.98 [1.27-3.10], P=0.04) were more likely to die. Three-year globe salvage rates were 13.3% (95% CI, 5.1-25.6) in LMICs and 46.2% (38.8-53.3) in HICs. At three years, 70.1% of cT1 eyes (95% CI, 54.5-81.2) versus 8.9% of cT3 eyes (5.5-13.3) were salvaged. Advanced tumor stage was associated with higher enucleation risk (e.g., cT3 vs. cT1, SHR=4.98 [95% CI, 2.36-10.5), P<0.001).

Conclusions:

Disparities exist in survival and globe salvage in American countries based on economic level and tumor stage demonstrating a need for childhood cancer programs.

INTRODUCTION

The prognosis of retinoblastoma, the most common primary pediatric eye cancer, is dependent on early diagnosis and treatment.[1-3] Treatment largely aims to cure, while also prioritizing ocular salvage and vision preservation.[3] Many patients in the Americas present with advanced intraocular disease that requires chemotherapy, adjunctive consolidative therapy and rarely even radiation to save the eye.[3] Enucleation may be done primarily, or secondarily when efforts to save the eye have failed – for advanced unilateral Group E eyes, enucleation is the most common primary therapy.[3] Success of therapy is highly related to disease burden.[4] Early diagnosis to facilitate treatment is therefore integral for globe preservation and survival.

Studies have shown disparities in treatment outcomes worldwide between high- and low-income countries (HIC and LIC, respectively).[2,3,5-7] Notably, data have shown higher mortality rates and globe loss among children diagnosed with retinoblastoma in LICs than in HICs.[2,3] In HICs, there is nearly a 100% disease-free survival rate for retinoblastoma.[8] Further, studies have shown a 9-to-10-fold higher risk of metastasis-related death in LICs than HICs.[2] It should be noted, however, that systemic disease confers virtually equal mortality risk in LICs and HICs, highlighting the importance of early treatment regardless of income status.[2]

An initial Global Retinoblastoma Outcomes study followed 4064 children from 149 countries for three years after retinoblastoma diagnosis and explored outcomes associated with survival and globe salvage.[8] Globally, patients from low-income countries experienced higher rates of death and enucleation.[8] The present study is a sub-analysis that explores disparities in retinoblastoma treatment outcomes in the Americas, through analysis of 491 children from 23 countries. This is the first study to assess retinoblastoma treatment outcomes specifically in the Americas.

METHODS

This study adheres to the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement, as well as to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[9,10] This study is a sub-analysis of patients from the Americas included in the Global Retinoblastoma Outcome Study, a 3-year prospective analysis of retinoblastoma outcomes in treatment-naïve patients; as such, the analysis methods closely followed those in the Global Study.[8] In brief, retinoblastoma treatment centers across the world were invited to participate in a cross-sectional study of all treatment-naïve patients who presented between January 1, 2017 and December 31, 2017. Next, a prospective analysis was conducted on these patients, as well as patients from additional treatment centers that were not part of the initial cross-sectional study. Data on primary and additional treatments, duration of follow-up, metastasis, globe salvage, survival outcome, and the impact of COVID-19 were collected.[8] As in the Presentation Study, national income level classifications were obtained from the 2017 World Population Prospects.[5,11] The study was approved by the London School of Hygiene & Tropical Medicine Observational Ethics Committee. Participating centers received local ethics approval.

Statistical Analysis

Statistical analyses were conducted using Stata/SE software (version 14.2; College Station, TX, USA). Survival analysis was used to examine both all-cause mortality and enucleation. Time to death was summarized using Kaplan-Meier estimates. Association of time to death with risk or protective factors was examined using Cox proportional hazard models. Time to enucleation was evaluated

using Fine and Gray proportional sub-hazard models adjusted for the competing risk of death.[12] In cases of bilateral globe loss, only the first event was included. Factors in both models included the economic group of the nation where the patient's clinic was located; primary tumor stage (cT) and hereditary category (H) based on the AJCC Staging system,[13] sex, disease laterality, family history of retinoblastoma, and age at diagnosis (fit using linear splines). Analyses were clustered by treatment center and weighted based on the inverse probability of having missing outcome data. P-values less than 0.05 were considered statistically significant after Bonferroni correction. Additional details on the global study and analysis methods are found in the **Supplement**.

RESULTS

The cohort included 491 treatment-naïve patients from 23 American countries, who presented to 57 treatment centers in 2017 and received or were offered treatment for retinoblastoma (**Table 1A**). Of these patients, 49 had missing dates of birth, and 40 had last follow-up dates missing. Of the study cohort, 1.6% (8/491) of patients were from LICs, 11.8% (58/491) were from lower-middle income countries (LMICs), 47.9% (235/491) were from upper-middle income countries (UMICs), and 38.7% (190/491) were from HICs. All countries represented in the data, identified by income level, are summarized in **Supplemental Figure 1** as well as the expected number of retinoblastoma cases per country based on crude birth rates.[11] The most represented countries were the USA (32.4%, 159/491), a HIC; Peru (14.9%, 73/491), an UMIC; Brazil (11.4%, 56/491), an UMIC; and Guatemala (7.5% (37/491), a LMIC.

Clinical Characteristics at Presentation

Of the cohort, 67.4% of patients (331/491) presented with unilateral disease and 32.6% (160/491) with bilateral disease. The median age at diagnosis was 28.4 months (IQR 0.3 – 140.1 months) for patients presenting with unilateral disease (331/491, 67.4%) and 13.2 months (IQR 0.07 - 48.2 months) for patients presenting with bilateral disease (160/491, 32.6%). 47.3% of patients (232/491) were female and 7.1% (35/490) had familial retinoblastoma. By cTNMH category, 47.9% of patients were cT3 (232/484), 78.1% of patients were N0 (379/485), and 95.1% were M0 (461/485). In terms of heritable trait or the presence of an *RB1* germline mutation, 50.6% (246/486) were HX (mutation unknown), 11.3% (55/486) were H0 (normal *RB1* allele), and 38.1% (185/486) were H1 (bilateral/trilateral retinoblastoma, positive family history, or germline blood *RB1* mutation). Presentation data were available in at least 98.6% of patient cases. The clinical characteristics at presentation, reported by national income level, and data availability, are shown in **Table 1B**.

Treatment

Enucleation surgery was available for all patients, and intravenous chemotherapy for 99.2% (487/491) of patients (eTable 1 in the **Supplement**). Detailed treatment data were available on 486 patients (eTable2 in the **Supplement**). Of those who received treatment, 36.0% (175/486) received intravenous chemotherapy, 13.6% (66/486) received intra-arterial chemotherapy, and primary enucleation was performed in 48.8% (235/486) of cases for 36.6% (238/651) of eyes included in analysis. Treatment refusal was reported in 4.7% (23/486) of patients and palliative treatment was reported in 1.0% (5/486) of patients.

For new tumors or tumor recurrence, additional treatments were represented as follows: 29.6% (144/486) of patients received intravenous chemotherapy, 14.8% (72/486) received intra-arterial chemotherapy, 11.3% (55/486) received intravitreal chemotherapy, 21.8% (106/486) underwent secondary enucleation/exenteration, and 32.7% (159/486) received laser or cryotherapy. Radiotherapy was given to 9.4% (46/486) of patients. Transformation to palliative therapy was reported in 0.4% (2/486) of children, and treatment abandonment was reported in 1.4% (7/486) of patients.

Outcomes

The median follow-up time was 34.7 months (IQR, 26.6-39.8), based on 90.8% (448/491) of reports (**Table 1C**). No patients who presented with unilateral retinoblastoma were reported to develop bilateral disease.

Survival

Death was reported in 8.8% (43/491) of the patient cohort. The mortality rate by country level is as follows: 37.5% (3/8) of patients from LICs, 22.4% (13/58) from LMICs, 10.2% (24/235) from UMICs, and 1.6% (3/190) from HICs (**Table 1C**). Of the 43 total deaths in the patient cohort, 86.0% (37/43) were from retinoblastoma with 5.4% (2/37) of these deaths from trilateral disease. Treatment-related complications were the cause of 7.0% (3/43) of deaths, and 2.3% (1/43) were reported as being from other causes; in 4.7% (2/43) of cases, the cause of death was not indicated. 88.4% (38/43) followed a diagnosis of metastatic spread.

Figure 1 shows the Kaplan-Meier survival estimates for the entire cohort (**1A**), stratified by national income level (**1B**), and by clinical stage at presentation (**1C**). For all patients, the one, two and three-year survival rates were 95.1% (95% CI, 92.5-96.8), 92.6% (89.6-94.7) and 91.4% (88.3-93.8) (**Figure 1A**), respectively. When considering national income level, the survival rate in LICs was 60.0% at one year (95% CI, 12.6-88.2); this rate was maintained at three years. In LMICs, the survival rate declined from 84.7% (95% CI, 71.6-92.0) at one year to 74.2% (59.7-84.2) at three years, and in UMICs survival rate dropped from 94.3% (89.9-96.8) at one year to 89.8% (84.4-93.4) at three years (**Figure 1B**). In comparison, for HICs the survival rate was 100% at one year, and remained 99.2% (95% CI, 94.6-99.9; Figure 1B) at three years. At three-year follow up, 22.4% of LMIC patients had died, and 10.2% of UMIC patients had died, while only 1.6% of HIC patients had died (**Table 1C, Figure 1B**). In examining AJCC stage, the survival rate for cT1-cT3 was >93.5% at three years, whereas for cT4 the survival rate was much lower at 48.1% (95% CI, 30.3-63.9) at one year, declining to 32.2% (15.9-49.7) at three years (**Figure 1C**).

Table 2 summarizes the weighted Cox proportional hazard model results for survival. National income level was not significantly associated with survival (P values>0.05), although hazard estimates reflected global results, with decreasing risk of death as a function of increasing income level.[8] In adjusted analyses based on hazard ratios, children from LICs carried 3.4 times higher risk of death compared to children from HICs (**Figure 1B**). Similarly, age at diagnosis was not significantly associated with risk of death in patients age four years and younger (P=0.56), although the hazard model showed a trend of increasing risk with increasing year of life at diagnosis until age 4.
In patients diagnosed after age four, risk of death significantly decreased with each additional year of life (HR=0.45 [95% CI, 0.27–0.78], P=0.048 for change in slope). Compared to least advanced

disease by AJCC staging (cT1), more advanced stage at diagnosis (cT2, cT3, or cT4) was found to be significantly associated with all-cause mortality, with a graded increase in risk across most categories (cT2 vs. cT1, [HR= $1.1x10^9$ (95% CI, $1.46x10^8$ – $8.26x10^9$), P<0.001]; cT3 vs. cT1, [HR=$4.65x10^9$ ($1.25x10^9$ – 1.72×10^{10}), P<0.001]; cT4 vs. cT1, [HR= $5.98x10^{10}$], P>0.05). The mortality rate was highest for patients with extraocular cT4 disease (54.8%), while no cT1s died (P<0.0001 from Fisher's exact test). Female sex was also found to be associated with an increased hazard of all-cause mortality (vs. male, HR=1.98 [95% CI, 1.27 – 3.10], P=0.04). Familial retinoblastoma history was not significantly associated with survival after model adjustment (HR=11.1 [95% CI, 1.66 – 74.8], P=0.16). Disease laterality and heritability (defined as bilateral or trilateral retinoblastoma, or positive blood *RB1* mutation) did not have significant associations with survival. As outlined in the methods, sensitivity analyses were performed, which showed little change in risk estimates from primary analyses.

Metastasis

Distant metastasis at three-year follow-up was reported in 10.2% (50/491) of patients, 36% of these patients were diagnosed with cT3 disease (18/50). Of the patients with metastatic disease, 10.0% (5/491) were confirmed alive at three years. The median time of primary tumor diagnosis to metastasis was 10 months (IQR 0–57 months) based on 44.0% (22/50) of patients. Average time between diagnosed metastases and most recent follow up was 36 months (± 4.95 months) based on 40.0% (2/5) of those surviving patients with metastatic disease.

Enucleation

Of the study cohort, 68.6% (337/491) underwent enucleation (**Table 1C**). Both eyes were enucleated in 3.7% (18/491) of patients. For all patients with available follow-up data, the one-, two-, and three-year cumulative incidence of enucleation was 67.6% (95% CI, 63.2-71.9), 71.2% (66.9-75.3), and 72.8% (68.6-77.0), respectively. Enucleation was the primary form of treatment for 48.8% (237/486) of patients and was secondarily performed in 20.6% (100/486) of patients.

Figure 2 shows the cumulative incidence of enucleation obtained from adjusted models for the entire cohort (**2A**), stratified by national income level (**2B**), and by clinical stage at presentation (**2C**). When considering national income level for patients with available follow-up data, the enucleation rate at three years was 77.8% (95% CI, 38.5-99.0) for LIC patients, 86.7% (74.4-94.9) for LMIC patients, 85.7% (80.5-90.1) for UMIC patients, and 53.8% (46.7-61.2) for HIC patients. By AJCC stage, the enucleation rate at three years was 29.9% (95% CI, 18.8-45.4) for cT1 disease, 59.0% (51.3-66.9) for cT2 disease, 91.1% (86.7-94.5) for cT3 disease, and 88.1% (64.3-98.8) for cT4 disease.

Table 3 summarizes the clustered and weighted Fine and Gray proportional sub-hazard model for enucleation, which also accounts for the competing risk of death. More advanced primary tumor category was associated with increased hazard of enucleation, reflecting global results (e.g., cT3 vs. cT1 Subhazard ratio, SHR=4.98 [95% CI, 2.36-10.5], P<0.001). Children with bilateral retinoblastoma were less likely to have enucleation than children with unilateral disease (SHR=0.62 [95% CI, 0.46-0.84], P=0.02). Although eyes of patients from HICs were less likely to be enucleated (vs. LICs, SHR=0.37 [95% CI, 0.18-0.76], P=0.08), this effect was not significant after adjustment for multiple predictors. Other parameters including sex, familial history, hereditary status, and age at diagnosis were not significant.

Impact of the COVID-19 Pandemic on Survival and Globe Salvage

None of the deaths known to have occurred during 2020 (10%, 4/40) and none of the enucleations known to have been performed during this period (2.1%, 9/335) were associated with the pandemic or a pandemic-related delay in treatment.

DISCUSSION

Similar to the global study of retinoblastoma,[8] this sub-analysis of outcomes in the Americas demonstrates a disparity in patient survival rates based on the income level of their resident country. The largest gap in survival was seen between children from LICs (60% alive at three-year follow up) and children from HICs (99.2% alive at three years); in adjusted analyses, children from LICs carried 3.4 times higher risk of death compared to children from HICs (**Figure 1B, converted from HR**). This disparity is smaller than what was reported globally, but this may be due to the nature of the Americas sample. Outcomes for LIC children are based on limited data from a single treatment center in Haiti, where restricted healthcare access may cause disparities in outcomes and reporting.[14] Nevertheless, mortality risk was significantly reduced with increasing income level. For example, at three-year follow up, 22.4% of LMIC patients had died, and 10.2% of UMIC patients had died, compared to only 1.6% of HIC patients (**Table 1C, Figure 1B**).

Mortality was strongly associated with primary tumor stage at diagnosis, which also varied based on the income level of a patient's home country. In the Americas, 67% of patients from LICs and 24% of patients from LMICs presented with extraocular cT4 disease at diagnosis, while less than 1% of HIC patients presented with advanced cT4 disease (**Table 1B**). The mortality rate was highest for patients with extraocular cT4 disease (54.8%), while no cT1s died (P<0.0001 from Fisher's exact test). However, similar to the global analysis, lower income status remained a major risk factor for death independent of the stage at diagnosis. This disparity may exist due to multiple factors including limited availability of certain treatments in LICs.[5,8] Limited follow-up data on patients from LICs also impacts survival estimates and interpretability of some model comparisons (e.g., very large HR estimates for all AJCC stages compared to cT1).

Age at diagnosis only predicted survival in older children, which differs from what was seen globally.[8] In the Americas sample, a non-significant effect of increasing risk of death was seen for each year until age four, followed by a significant decrease in risk for each additional year older (P=0.048; **Table 2**). The trend of increasing risk of death in the youngest patients, who were surviving with advanced disease, was seen in both studies, although limited study power reduced significance in the Americas data.[8] The trend of decreasing risk in older patients was also seen in both studies, although differences in the number of age categories assessed led to variations in how both studies report this effect.[8] Globally, risk of death was stable from ages three to seven (P=0.01), and then decreased (non-significantly) after age seven, while in the Americas risk decreased significantly after age four.[8] As was hypothesized in the global study,[8] patients who were diagnosed at an older age may have had lesions which existed in the benign retinoma stage for longer than those lesions diagnosed in

younger patients which may explain this finding. Notably, age at diagnosis was unrelated to enucleation risk in the Americas, although this trend was observed globally.

Female sex (HR=1.98, P=0.04) was associated with increased risk of all-cause mortality in the Americas, unlike the global study, which showed no effect. Mortality risk associated with female sex has been reported in other studies of retinoblastoma outcomes by our research team,[15] where the increased risk to females may be associated with preferential treatment of male children in some countries as opposed to a biological mechanism. Further studies examining impact of sex on mortality in retinoblastoma patients are warranted globally.

Overall, 68.6% of patients in the Americas required enucleation; 48.8% primarily and 20.6% secondarily. Disparities in enucleation rates as a function of income were observed in the Americas, as illustrated by three-year salvage rates of 13.3% (95% CI, 5.1-25.6) in LMICs and 46.2% (38.8-53.3) in HICs **(Figure 2B and 2D)**. Yet, the effect of income was not statistically significant in hazard models of enucleation globally or in this sub-analysis after adjustment for multiple predictors.[8] Lack of access to care and treatment abandonment, especially among indigenous communities in Central American LMICs, may explain this disparity.[7,16] Additional data from patients from LICs in the Americas are needed to produce stable estimates of mortality and enucleation hazard in this group.

In the larger global analysis, eyes at the lowest AJCC stage (cT1) were far less likely to be enucleated, and risk was highest for cT3 eyes, followed by cT4 and then cT2.[8] Data collected from the Americas showed the same pattern, where all clinical status levels showed an increased risk for enucleation compared to cT1 (vs. cT2: HR=2.57 [95% CI, 0.46-1.27]; vs. cT3: HR=4.98 [0.53-1.02];

vs. cT4: HR=2.14) [0.18-0.76], although only the comparison between cT1 and cT3 was statistically significant after adjustment (P<0.001). AJCC stage cT3 eyes were the least likely to be salvaged (8.9% [95% CI, 5.5-13.3]), much like what was observed globally. In the Americas, eyes with stage cT4 disease (salvage rate, 11.9% [95% CI, 1.2-35.7], after one year) showed significantly reduced incidence compared to cT3 (P=0.007, unadjusted Wald test). Due to small sample size and limited follow-up data, globe salvage rates of cT4 eyes did not significantly differ from cT1 (70.1% [54.5-81.2] salvaged at three years) or cT2 cases (41.0% [33.1-48.7] salvaged at three years).

This study has many strengths. This sub-analysis is important because it is the first study of this magnitude to assess retinoblastoma outcomes specifically in the Americas. As such, these results have the unique ability to inform future clinical practices within these particular regions. Further sub-analyses of individual regions in the Americas are ongoing. This prospective study employed the same clustering and weighting methodology utilized in the analysis of global data, and many of the same sensitivity analyses were conducted, suggesting our findings are robust with respect to American retinoblastoma patients. However, limited data from LICs, which were represented by only eight patients from one country, suggest that additional data may be needed to reliably estimate risk for the most vulnerable patients. Although some hazard ratios were not statistically significant (**Table 2, 3**), trends in overall survival and enucleation data by national income level mirrored those of the global analysis (**Figure 1, 2**).[8] Cohort size and geographical spread may have impacted the data, collection of treatment data was limited to treatment type or refusal, and COVID-19 impact data was limited to a caregiver survey.

In conclusion, major inequities exist in survival and globe salvage rates for retinoblastoma patients based on income status in the Americas. Overall, enucleation remains the most frequent treatment for retinoblastoma. Retinoblastoma patients from LICs are more likely to present with extraocular disease and have 3 times higher risk of death than those from HICs. Successful globe salvage is also three times more likely in HICs than LICs; cT1 eyes are five times more likely to be salvaged than cT3 eyes. Trends in this sub-analysis mirror those of the larger global study. Unique to this sub-analysis, females in the Americas with retinoblastoma are at 2 times higher risk of death compared to males. Our study reinforces the importance of international support in building high-quality childhood cancer programs for lower income American countries to ensure early diagnosis and treatment.

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Global Retinoblastoma Study Group Author List

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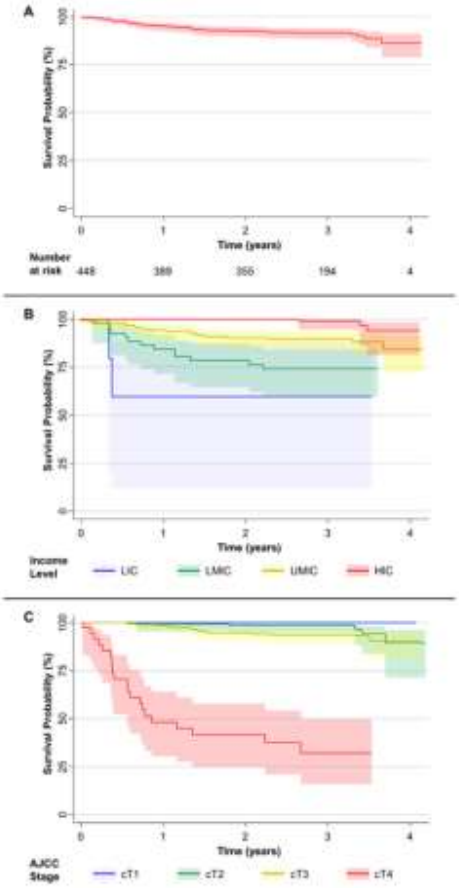
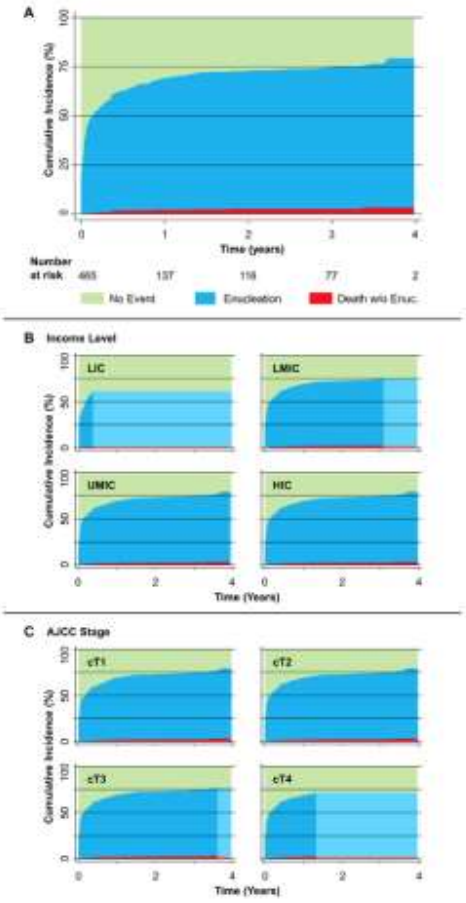


D

	Time (mo)	Survival Rate (%)	SE	Lower 95% CI	Upper 95% CI
National Income Level					
Low	12	60.0	0.22	12.6	88.2
	24	60.0	0.22	12.6	88.2
	36	60.0	0.22	12.6	88.2
Lower middle	12	84.7	0.05	71.6	92.0
	24	78.6	0.06	64.7	87.6
	36	74.2	0.06	59.7	84.2
Upper middle	12	94.3	0.02	89.9	96.8
	24	90.4	0.02	85.2	93.9
	36	89.8	0.02	84.5	93.4
High	12	100	–	–	–
	24	100	–	–	–
	36	99.2	0.008	94.6	99.9
Clinical Stage					
cT1	12	100	–	–	–
	24	100	–	–	–
	36	100	–	–	–
cT2	12	99.3	0.007	95.3	99.9
	24	98.6	0.01	94.5	99.7
	36	98.6	0.01	94.5	99.7
cT3	12	98.4	0.009	95.2	99.5
	24	94.6	0.02	90.3	97.1
	36	93.5	0.02	88.8	96.2
cT4	12	48.1	0.09	30.3	63.9
	24	41.7	0.09	24.7	57.9
	36	32.2	0.09	15.9	49.7

Figure 1. Survival analysis for the full study cohort, by national income level, and by clinical stage. (A) Kaplan-Meier survival plot for the entire cohort. (B) Kaplan-Meier survival plot by income group. Income Groups: LIC (Low Income Country); LMIC (Lower-Middle Income Country); UMIC (Upper-Middle Income Country); HIC (High Income Country). (C) Kaplan-Meier survival plot by AJCC tumor stage (cT1-cT4). 95% confidence intervals indicated by shaded regions. (D) Table showing one, two, and three year survival by income group and AJCC tumor stage.



D

	Time (mo)	Salvage Rate (%)	SE	Lower 95% CI	Upper 95% CI
National Income Level					
Low	12	0	–	–	–
	24	0	–	–	–
	36	0	–	–	–
Lower middle	12	13.3	0.05	5.1	25.6
	24	13.3	0.05	5.1	25.6
	36	13.3	0.05	5.1	25.6
Upper middle	12	21.1	0.03	15.9	26.9
	24	16.6	0.03	11.9	22.0
	36	14.3	0.02	9.9	19.6
High	12	50.8	0.04	43.4	57.8
	24	47.5	0.04	40.1	54.5
	36	46.2	0.04	38.8	53.3
Clinical Stage					
cT1	12	83.7	0.05	70.1	91.5
	24	77.4	0.06	62.9	86.8
	36	70.1	0.07	54.5	81.2
cT2	12	46.5	0.04	38.4	54.2
	24	42.6	0.04	34.7	50.2
	36	41.0	0.04	33.1	48.7
cT3	12	12.5	0.02	8.5	17.4
	24	9.4	0.02	5.9	13.9
	36	8.9	0.02	5.5	13.3
cT4	12	10.6	0.09	1.1	33.1
	24	10.6	0.09	1.1	33.1
	36	10.6	0.09	1.1	33.1

Figure 2. Cumulative incidence of enucleation and competing risk of death for the full cohort, by income level, and by clinical stage. (A) Stacked cumulative incidence plot for entire cohort. (B) Stacked cumulative incidence plots by income group. Income Groups: LIC (Low Income Country); LMIC (Lower-Middle Income Country); UMIC (Upper-Middle Income Country); HIC (High Income Country). (C) Stacked cumulative incidence plots by AJCC tumor stage (cT1-cT4). Note: Lighter color regions (e.g., LIC incidence in 2B before 1 year; cT4 incidence in 2C after 1 year) denote rates that are estimated using the last known values per group, reflecting limited follow-up data. (D) Table showing one-, two-, and three-year enucleation by income group and AJCC tumor stage.

Country	Income Group	No. of Centers	No. of Patients	Expected Cases
Canada	HIC	3	25	23
Chile	HIC	2	5	15
Puerto Rico	HIC	1	1	2
Uruguay	HIC	1	1	3
USA	HIC	22	159	235
Argentina	UMIC	1	31	45
Brazil	UMIC	3	56	182
Colombia	UMIC	1	4	46
Cuba	UMIC	1	7	8
Dominican Republic	UMIC	1	1	13
Ecuador	UMIC	2	2	20
Jamaica	UMIC	1	1	3
Mexico	UMIC	2	32	144
Panama	UMIC	1	2	5
Paraguay	UMIC	2	8	8
Peru	UMIC	5	74	38
Venezuela	UMIC	1	16	37
Bolivia	LMIC	2	6	15
El Salvador	LMIC	1	6	7
Guatemala	LMIC	1	37	25
Honduras	LMIC	1	4	12
Nicaragua	LMIC	1	5	8
Haiti	LIC	1	8	16

Supplemental Figure 1. The 23 American countries and associated number of patients and treatment centers included in analysis, categorized by income level (red= low income, orange= lower-middle income, blue= upper-middle income, green= high income). Estimated cases determined based on crude birth rate per each country's population and retinoblastoma incidence of 1 in 17,000.[11] Color map generated using mapchart.net (www.mapchart.net/americas.html).

Table 1: Clinical diagnostic characteristics and treatment outcomes for 491 patients from 57 centers in 23 American countries

Table 1A. Participating countries and treatment centers by national income level					
	National Income Level				
n (%)	**Low**	**Lower-Middle**	**Upper-Middle**	**High**	**Total**
Number of countries	1 (4%)	5 (22%)	12 (52%)	5 (22%)	23
Number of centers	1 (1.8%)	6 (10.5%)	21 (36.8%)	29 (50.9%)	57

Table 1B. Clinical characteristics at diagnosis by national income level	
	National Income Level

n/N (%)	Low	Lower-Middle	Upper-Middle	High	Total
Age at diagnosis (months)					
Median (IQR)	32.7 (27.6-46.0)	21.7 (10.8-39.0)	21.7 (9.1-32.3)	15.3 (6.1-25.1)	19.4 (8.3-31.9)
Data available[a]	6/8 (75%)	58/58 (100%)	226/235 (96.2%)	152/190 (80%)	442/491 (90%)
Laterality at presentation[b]					
Unilateral	6/8 (75%)	40/58 (69%)	174/235 (74%)	111/190 (58.4%)	331/491 (67.4%)
	6/331 (1.8%)	40/331 (12.1%)	174/331 (52.6%)	111/331 (33.5%)	
Bilateral	2/8 (25%)	18/58 (31%)	61/235 (26%)	79/190 (41.6%)	160/491 (32.6%)
	2/160 (1.3%)	18/160 (11.3%)	61/160 (38.1%)	79/160 (49.4%)	
Sex[b]					
Female	3/8 (37.5%)	35/58 (60.3%)	119/235 (50.6%)	75/190 (39.5%)	232/491 (47.3%)
	3/232 (1.3%)	35/232 (15.1%)	119/232 (51.3%)	75/232 (32.3%)	
Male	5/8 (62.5%)	23/58 (39.7%)	116/235 (49.4%)	115/190 (60.5%)	259/491 (52.7%)
	5/259 (1.9%)	23/259 (8.9%)	116/259 (44.8%)	115/259 (44.4%)	
Family history of retinoblastoma					
Yes	0	0	12/235 (5.1%)	23/189 (12.2%)	35/490 (7.1%)
	0	0	12/35 (34.3%)	23/35 (65.7%)	
No	8/8 (100%)	58/58 (100%)	223/235 (94.9%)	166/189 (87.8%)	455/490 (92.9%)
	8/455 (1.8%)	58/455 (12.7%)	223/455 (49%)	166/455 (36.5%)	
Data available[a]	8/8 (100%)	58/58 (100%)	235/235 (100%)	189/190 (99.5%)	490/491 (99.8%)

Table 1B (Continued)

	National Income Level				
n/N (%)	**Low**	**Lower-Middle**	**Upper-Middle**	**High**	**Total**
Clinical Tumor, Node, Metastasis, Heredity 8th Edition Staging					
Primary tumor					
cT1	1/6 (16.7%)	1/58 (1.7%)	17/231 (7.4%)	32/189 (16.9%)	51/484 (10.5%)
	1/51 (2%)	1/51 (2%)	17/51 (33.3%)	32/51 (62.7%)	
cT2	0	10/58 (17.2%)	59/231 (25.5%)	91/189 (48.1%)	160/484 (33.1%)
	0	10/160 (6.3%)	59/160 (36.9%)	91/160 (56.9%)	
cT3	1/6 (16.7%)	33/58 (56.9%)	134/231 (58%)	64/189 (33.9%)	232/484 (47.9%)
	1/232 (0.4%)	33/232 (14.2%)	134/232 (57.8%)	64/232 (27.6%)	
cT4	4/6 (66.7%)	14/58 (24.1%)	21/231 (9.1%)	1/189 (0.5%)	40/484 (8.3%)
	4/40 (10%)	14/40 (35%)	21/40 (52.5%)	1/40 (2.5%)	
Retinoma	0	0	0	1/189 (0.5%)	1/484 (0.2%)
	0	0	0	1/1 (100%)	

Data available[a]	6/8 (75%)	58/58 (100%)	231/235 (98.3%)	189/190 (99.5%)	484/491 (98.6%)
Regional lymph node					
NX	1/6 (16.7%)	5/58 (8.6%)	22/231 (9.5%)	65/190 (34.2%)	93/485 (19.2%)
	1/93 (1.1%)	5/93 (5.4%)	22/93 (23.7%)	65/93 (69.9%)	
N0	2/6 (33.3%)	48/58 (82.8%)	204/231 (88.3%)	125/190 (65.8%)	379/485 (78.1%)
	48/379 (12.7%)	204/379 (53.8%)	125/379 (33%)	1/93 (1.1%)	
N1	3/6 (50%)	5/58 (8.6%)	5/231 (2.2%)	0	13/485 (2.7%)
	3/13 (23.1%)	5/13 (38.5%)	5/13 (38.5%)	0	
Data available[a]	6/8 (75%)	58/58 (100%)	231/235 (98.3%)	190/190 (100%)	485/491 (98.8%)
Distant metastasis					
M0	3/6 (50%)	50/58 (86.2%)	218/231 (94.4%)	190/190 (100%)	461/485 (95.1%)
	3/461 (0.7%)	50/461 (10.8%)	218/461 (47.3%)	190/461 (41.2%)	
cM1	3/6 (50%)	4/58 (6.9%)	7/231 (3%)	0	14/485 (2.9%)
	3/14 (21.4%)	4/14 (28.6%)	7/14 (50%)	0	
pM1	0	4/58 (6.9%)	6/231 (2.6%)	0	10/485 (2.1%)
	0	4/10 (40%)	6/10 (60%)	0	
Data available[a]	6/8 (75%)	58/58 (100%)	231/235 (98.3%)	190/190 (100%)	485/491 (98.8%)
Hereditary trait					
HX	5/7 (71.4%)	40/58 (69%)	163/231 (70.6%)	38/190 (20%)	246/486 (50.6%)
	5/246 (2%)	40/246 (16.3%)	163/246 (66.3%)	38/246 (15.4%)	
H0	0	0	1/231 (0.4%)	54/190 (28.4%)	55/486 (11.3%)
	0	1/55 (1.8%)	54/55 (98.2%)	5/246 (2%)	
H1	2/7 (28.6%)	18/58 (31%)	67/231 (29%)	98/190 (51.6%)	185/486 (38.1%)
	2/185 (1.1%)	18/185 (9.7%)	67/185 (36.2%)	98/185 (53%)	
Data available[a]	7/8 (87.5%)	58/58 (100%)	231/235 (98.3%)	190/190 (100%)	486/491 (99%)

Table 1C. 3-year outcomes by national income level					
	National Income Level				
n/N (%)	**Low**	**Lower-Middle**	**Upper-Middle**	**High**	**Total**
Enucleation *					
Yes	4/8 (50%)	45/58 (77.6%)	184/235 (78.3%)	104/190 (54.7%)	337/491 (68.6%)
	4/337 (1.2%)	45/337 (13.4%)	184/337 (54.6%)	104/337 (30.9%)	
No	4/8 (50%)	13/58 (22.4%)	50/235 (21.3%)	82/190 (43.2%)	149/491 (30.3%)
	4/149 (2.7%)	13/149 (8.7%)	50/149 (33.6%)	82/149 (55.0%)	
Unknown	0	0	1/235 (0.4%)	4/190 (2.1%)	5/491 (1.0%)
	0	0	1/5 (20.0%)	4/5 (80.0%)	
Metastasis *					
Yes	5/8 (62.5%)	12/58 (20.7%)	30/235 (12.8%)	3/190 (1.6%)	50/491 (10.2%)

	5/50 (10%)	12/50 (24%)	30/50 (60%)	3/50 (6%)	
No	2/8 (25%)	39/58 (67.2%)	172/235 (73.2%)	172/190 (90.5%)	385/491 (78.4%)
	2/385 (0.5%)	39/385 (10.1%)	172/385 (44.7%)	172/385 (44.7%)	
Unknown	1/8 (12.5%)	7/58 (12.1%)	33/235 (14%)	15/190 (7.9%)	56/491 (11.4%)
	1/56 (1.8%)	7/56 (12.5%)	33/56 (58.9%)	15/56 (26.8%)	
Survival Status *					
Dead	3/8 (37.5%)	13/58 (22.4%)	24/235 (10.2%)	3/190 (1.6%)	43/491 (8.8%)
	3/43 (7%)	13/43 (30.2%)	24/43 (55.8%)	3/43 (7%)	
Alive	2/8 (25%)	40/58 (69%)	183/235 (77.9%)	178/190 (93.7%)	403/491 (82.1%)
	2/403 (0.5%)	40/403 (9.9%)	183/403 (45.4%)	178/403 (44.2%)	
Unknown	3/8 (37.5%)	5/58 (8.6%)	28/235 (11.9%)	9/190 (4.7%)	45/491 (9.2%)
	3/45 (6.7%)	5/45 (11.1%)	28/45 (62.2%)	9/45 (20%)	
Cause of Death					
Retinoblastoma	3/3 (100%)	13/13 (100%)	18/24 (75%)	3/3 (100%)	37/43 (86%)
	3/37 (8.1%)	13/37 (35.1%)	18/37 (48.6%)	3/37 (8.1%)	
Tx complication	0	0	3/24 (12.5%)	0	3/43 (7%)
	0	0	3/3 (100%)	0	
Other causes	0	0	1/24 (4.2%)	0	1/43 (2.3%)
	0	0	1/1 (100%)	0	
Data missing	0	0	2/24 (8.3%)	0	2/43 (4.7%)
	0	0	2/2 (100%)	0	
Follow-up time (months)					
Median (IQR)	11.0 (2.6-39.8)	30.5 (13.7-34.9)	35.8 (24.5-40.7)	35.2 (30.1-39.9)	34.7 (26.6-39.8)
Data available[a]	6/8 (75%)	55/58 (94.8%)	203/235 (86.4%)	184/190 (96.8%)	448/491 (90.8%)

Data are n/N (%), except where indicated otherwise. Percentages within the national income level and within the evaluated variable are shown.

*Entire cohort has data available

[a]The number of individuals for whom data were available.

[b]Inclusion criterion: 100% reporting.

Abbreviations: IQR - interquartile range; Tx – Retinoblastoma Treatment

Table 2. Summary of the clustered and weighted Cox proportional hazard model for survival*

	Coefficient	**Robust standard error**	**Z score**	**P value** Unadjusted (Corrected†)	**HR (95% CI)**
Income level of residence					
Low	Ref	–	–	–	1.00

Lower-middle	-0.18	0.22	-0.82	0.41 (1.00)	0.83 (0.54 – 1.29)
Upper-middle	-0.69	0.62	-1.11	0.27 (1.00)	0.50 (0.15 – 1.69)
High	-1.25	0.76	-1.64	0.10 (1.00)	0.29 (0.06 – 1.27)
All ages‡					
HR per month	0.03	0.02	1.81	0.07 (0.56)	1.03 (1.00 – 1.07)
HR per year	0.41	0.23	1.81	0.07 (0.56)	1.51 (0.96 – 2.35)
Age > 4 years					
HR per month	-0.07	0.02	-2.89	**0.004 (0.048)**	0.94 (0.90 – 0.98)
HR per year	-0.79	0.27	-2.89	**0.004 (0.048)**	0.45 (0.27 – 0.78)
Laterality					
Unilateral	Ref	–	–	–	1.00
Bilateral	0.52	0.36	1.46	0.14 (1.00)	1.68 (0.84 – 3.38)
Primary tumor					
cT1	Ref	–	–	–	1.00
cT2	20.8	1.03	20.2	**<0.001 (<0.001)**	$1.10x10^9$ ($1.46x10^8$ – $8.26x10^9$)
cT3	22.3	0.67	33.3	**<0.001 (<0.001)**	$4.65x10^9$ ($1.25x10^9$ – 1.72×10^{10})
cT4	24.8	–	–	–	$5.98x10^{10}$ (No CI)
Sex					
Male	Ref	–	–	–	1.00
Female	0.69	0.23	3.02	**0.003 (0.04)**	1.98 (1.27 – 3.10)
Family history of retinoblastoma					
Negative	Ref	–	–	–	1.00
Positive	2.41	0.97	2.48	0.01 (0.16)	11.10 (1.66 – 74.8)
Hereditary retinoblastoma§					
H0	Ref	–	–	–	1.00
H1	0.26	0.45	0.58	0.56 (1.00)	1.30 (0.54 – 3.13)

HR= hazard ratio *Overall, 43 observations were dropped from survival analysis because of missing observation time. †Corrected using Bonferroni method (multiplied by 12 for each model term). ‡Age included in analysis as a continuous variable. §Hereditary refers to bilateral or trilateral retinoblastoma, positive family history, or positive blood *RB1* mutation. H0= non-hereditary, H1= hereditary

Table 3: Summary of the clustered and weighted Fine and Gray proportional subhazard model for enucleation*

	Coefficient	**Robust standard error**	**Z score**	**P value** Unadjusted (Corrected†)	**SHR (95% CI)**
Income level of residence					
Low	Ref	–	–	–	1.00

Lower-middle	-0.27	0.26	-1.04	0.30 (1.00)	0.76 (0.46-1.27)
Upper-middle	-0.31	0.17	-1.85	0.06 (0.77)	0.73 (0.53-1.02)
High	-0.98	0.36	-2.71	**0.007 (0.08)**	0.37 (0.18-0.76)
All ages‡					
HR per month	-0.27	0.26	-1.04	0.66 (1.00)	1.00 (0.99-1.01)
HR per year	0.03	0.06	0.44	0.66 (1.00)	1.03 (0.91-1.17)
Age > 4 years					
HR per month	-0.01	0.01	-1.34	0.18 (1.00)	0.99 (0.97-1.01)
HR per year	-0.15	0.11	-1.34	0.18 (1.00)	0.86 (0.69-1.07)
Laterality					
Unilateral	Ref	–	–	–	1.00
Bilateral	-0.48	0.15	-3.08	**0.002 (0.02)**	0.62 (0.46-0.84)
Primary tumor					
cT1	Ref	–	–	–	1.00
cT2	0.94	0.39	2.42	0.02 (0.19)	2.57 (1.20-5.51)
cT3	1.60	0.38	4.22	**<0.001 (<0.001)**	4.98 (2.36-10.5)
cT4	0.76	0.39	1.95	0.05 (0.61)	2.14 (1.00-4.58)
Sex					
Male	Ref	–	–	–	1.00
Female	-0.09	0.15	-0.56	0.58 (1.00)	0.92 (0.68-1.24)
Family history of retinoblastoma					
Negative	Ref	–	–	–	1.00
Positive	-0.92	0.36	-2.57	0.01 (0.12)	0.40 (0.20-0.80)
Hereditary retinoblastoma§					
H0	Ref	–	–	–	1.00
H1	-0.18	0.32	-0.57	0.57 (1.00)	0.83 (0.45-1.56)

SHR= Subhazard ratio *Overall, 26 observations were dropped from survival analysis because of missing observation time. †Corrected using Bonferroni method (multiplied by 12 for each model term). ‡Age included in analysis as a continuous variable. §Hereditary refers to bilateral or trilateral retinoblastoma, positive family history, or positive blood *RB1* mutation. H0= non-hereditary, H1= hereditary

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SUPPLEMENTARY TEXT:

Methods

Background on Global Retinoblastoma Outcome Study

As summarized in the Global Retinoblastoma Outcome Study,[8] between the years 2017-2018, all known retinoblastoma centers across the world were contacted to form a global network. The Presentation Study was a 1-year cross-sectional analysis that included all treatment-naïve retinoblastoma patients that presented to participating centers from January 1, 2017 to December 31, 2017, and who were treated or offered treatment for retinoblastoma.[5] Following the Presentation study, the centers were invited to participate in a prospective analysis to report the 3-year outcome of patients from the original sample, and the following additional information was provided: primary and additional treatments, duration of follow-up, metastasis, globe salvage, survival outcome, and the impact of COVID-19. All data were combined with the presentation data.[5]

Additional treatment centers that had not previously participated in the Presentation Study were asked to submit the presentation and the outcome data for qualifying patients. Participating centers were asked to complete forms in early 2020; however, due to the COVID-19 pandemic, the first form was received on July 3, 2020, and the last on March 31, 2021. For each form received, data quality assurance was performed.[5]

Statistical Analysis

Statistical analyses mirrored the approach of the larger global study. Survival analysis was used to examine both all-cause mortality and enucleation. Time to death was summarized using Kaplan-Meier estimates. Analyses that considered time to enucleation (or exenteration) were adjusted for the competing risk of death using proportional hazard regression models proposed by Fine and Gray, as those patients who died with eyes intact must be censored differently than patients alive with eyes intact at their last follow-up care visit.[12] For time to enucleation, cumulative incidence curves were calculated. In cases where globe loss was bilateral, only the first event was included in survival analysis.

Adjustments for Nonlinear Association of Age and Risk

Smoothing splines were initially fit for age at diagnosis, a continuous variable known to have a non-linear association with risk of death or enucleation; these were replaced with linear splines with knots placed at smoothing spline inflection points to simplify data reporting. Analyses were clustered by treatment center, and robust standard errors based on clustering were used to calculate all P values and 95% confidence intervals. Schoenfeld residuals were examined to confirm that both models adhered to the proportionality assumption (i.e., risk is constant over time). Missing values for risk and protective factors were imputed using the most common value for categorical variables, and the median value for continuous variables within a given patient's economic group.

Weighting and Missing Data

Because patients with a known successful outcome at last follow-up (survival or intact eyes) and patients with an unknown outcome are categorized similarly in hazard models, inverse probability weighting (IPW) was used in hazard models, where data from patients with known outcomes are

weighted more heavily than those with unknown outcomes. The probability of outcome missingness was estimated in probit regression models using the same risk and protective factors described above. For these probit models, missing categorical factor data were not imputed, but instead were entered as another category (missing), accounting for the frequent co-occurrence of missing predictor and outcome data; missing age at diagnosis was imputed as the median global age, and another categorical variable was used to indicate age missingness. Patients with successful or unknown outcomes with no follow-up data were treated as missing the outcome in survival models. Sensitivity analyses were conducted with and without IPW, and with imputed data versus deleted data; models using IPW that imputed data demonstrated superior fit and are presented. To reduce Type I error, P values reported for coefficients in both mortality and enucleation models were adjusted for the number of terms within each model using the Bonferroni method, where each P value is divided by the number of terms in the model (twelve).

Role of the Funding Source

The source of funding had no role in study design, data collection, analysis, interpretation, or manuscript preparation. The corresponding author had full access to all data and final responsibility for the decision to publish.

eTable 1. Interventions available by national income level

	National Income Level				
Treatment n (%)	**Low (n=8)**	**Lower-Middle (n=58)**	**Upper-Middle (n=235)**	**High (n=190)**	**Total (N=491)**
Genetic Testing	0	0	89 (37.9%)	177 (93.2%)	266 (54.2%)
CT only	8 (100%)	13 (22.4%)	2 (0.9%)	4 (2.1%)	27 (5.5%)
MRI only	0	0	113 (48.1%)	83 (43.7%)	196 (39.9%)

CT + MRI	0	45 (77.6%)	120 (51.1%)	103 (54.2%)	268 (54.6%)
Pathology	8 (100%)	58 (100%)	235 (100%)	185 (97.4%)	486 (99.0%)
Laser therapy	0	52 (89.7%)	218 (92.8%)	188 (98.9%)	458 (93.3%)
Cryotherapy	0	52 (89.7%)	197 (83.8%)	187 (98.4%)	436 (88.8%)
Enucleation/ Exenteration	Available for all patients				
Intravenous chemotherapy	8 (100%)	58 (100%)	232 (98.7%)	189 (99.5%)	487 (99.2%)
Intra-ophthalmic artery chemotherapy	0	9 (15.5%)	189 (80.4%)	164 (86.3%)	362 (73.7%)
Intravitreal chemotherapy	0	9 (15.5%)	190 (80.6%)	188 (98.9%)	387 (78.8%)
Plaque brachytherapy	0	9 (15.5%)	43 (18.3%)	156 (82.1%)	208 (42.4%)
External beam radiotherapy	0	58 (100%)	219 (93.2%)	178 (93.7%)	455 (92.7%)

eTable 2. Treatments given by national income level

	National Income Level				
Treatment[a] n (%)	**Low (n=8)**	**Lower-Middle (n=58)**	**Upper-Middle (n=234)**	**High (n=186)**	**Total (n=486)**
Primary treatment for patient[b]					
Intravenous chemotherapy	2 (25%)	22 (37.9%)	81 (34.6%)	70 (37.6%)	175 (36%)
Intra-ophthalmic artery chemotherapy	0	0	24 (10.3%)	42 (22.6%)	66 (13.6%)
Enucleation[c]	3 (37.5%)	34 (58.6%)	125 (53.4%)	75 (40.3%)	237 (48.8%)
Focal laser or cryotherapy	0	3 (5.2%)	10 (4.3%)	20 (10.8%)	33 (6.8%)
Plaque brachytherapy	1 (12.5%)	0	0	0	1 (0.2%)
External beam radiotherapy	0	0	1 (0.4%)	0	1 (0.2%)
Vitrectomy	0	0	0	1 (0.5%)	1 (0.2%)
Palliative therapy[d]	2 (25%)	1 (1.7%)	2 (0.9%)	0	5 (1%)
Observation	0	0	0	1 (86.3%)	1 (0.2%)
Primary treatment refusal	2 (25%)	6 (10.3%)	12 (5.1%)	3 (1.6%)	23 (4.7%)
Additional treatment for patient[e]					

Intravenous chemotherapy	2 (25%)	20 (34.5%)	75 (32.1%)	47 (25.3%)	144 (29.6%)
Intra-ophthalmic artery chemotherapy	0	2 (3.4%)	29 (12.4%)	41 (22%)	72 (14.8%)
Intravitreal chemotherapy	0	0	24 (10.3%)	31 (16.7%)	55 (11.3%)
Enucleation/ Exenteration[c]	2 (25%)	12 (20.7%)	61 (26.1%)	31 (16.1%)	106 (21.8%)
Focal laser or cryotherapy	0	10 (17.2%)	54 (23.1%)	95 (51.1%)	159 (32.7%)
Plaque brachytherapy	0	0	8 (3.4%)	8 (4.3%)	16 (3.3%)
External beam radiotherapy	1 (12.5%)	8 (13.8%)	19 (8.1%)	2 (1.1%)	30 (6.2%)
Vitrectomy	0	0	1 (0.4%)	3 (1.6%)	4 (0.8%)
Palliative therapy	0	1 (1.7%)	0	1 (0.5%)	2 (0.4%)
Treatment refusal after primary	0	0	5 (2.1%)	2 (1.1%)	7 (1.4%)

[a] Per patient; bilateral cases are counted twice if the eyes were treated differently.
[b] First and main treatment. If both enucleation and chemotherapy were combined, both were counted as primary. If enucleation/chemotherapy was combined with an additional therapy, the other therapies were not counted.
[c] Primary and secondary enucleation or exenteration do not match totals in text, because bilateral cases are counted twice on this table (per eye), and once in the text (per patient).
[d] Palliative therapy, including oral chemotherapy.
[e] Additional treatment for tumor relapse or new tumors.

TOC Statement

This study followed treatment-naïve retinoblastoma patients diagnosed in American countries over three years to assess disparities in treatment outcomes by national income level. Patients from low-income countries were more likely to present with advanced cancer, had a greater risk of death, and were more likely to receive enucleations compared to patients from high-income countries. This study reinforces the need for high-quality childhood cancer programs in the Americas, especially in lower income countries.

Declaration of Interest Statement

We declare no competing interests relevant to the present study.