Retinoblastoma Outcomes in the Americas: a prospective analysis of 491 children with retinoblastoma from 25 American countries

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Key points:

Question: Do disparities in retinoblastoma treatment outcomes exist within the Americas?

Findings: In this prospective analysis of 491 retinoblastoma patients in 25 American countries, lower income countries were associated with a lower rate of survival and a higher rate of enucleation. More advanced disease at diagnosis was associated with an increased hazard of death and an increased hazard of enucleation.

Meaning: In the Americas, disparities in mortality and globe salvage exist based on income-level of the country of residence. Early diagnosis and treatment are imperative for improved survival and globe salvage outcomes.

Abstract

Importance:

Globally, disparities exist in retinoblastoma treatment outcomes between high- and low-income countries, but independent analysis of the Americas has not been performed.

Objective:

To report longitudinal outcomes of American retinoblastoma patients and explore factors associated with survival and globe salvage.

Design:

Clustered and weighted analysis of data collected prospectively on retinoblastoma patients diagnosed in 2017 at American treatment centers and followed for three years.

Setting:

Multicenter analysis encompassing 59 treatment centers in 25 American countries of varying economic levels (low income=LIC, lower-middle=LMIC, upper-middle=UMIC, high=HIC).

Participants:

491 treatment-naïve retinoblastoma patients diagnosed in 2017 and offered treatment at participating tertiary centers.

Main Outcome(s) and Measure(s):

Survival and globe salvage rates analyzed with Kaplan-Meier survival analysis and Cox proportional hazard models based on demographic and outcome data.

Results:

Of the study patients, 8 (1.6%), 58 (11.8%), 235 (47.9%) and 190 (38.7%) were from LIC, LMIC, UMIC and HIC, respectively. The three-year survival rate for LIC patients was 60.0% (95% CI, 12.6-88.2) compared to 99.2% (94.6-99.9) for HIC patients. Patients older than four years were less likely to experience all-cause mortality (HR=0.45 [95% CI, 0.27 – 0.78], P=0.048), while patients with more advanced tumor stage at diagnosis (cT1 vs. cT3, HR= $4.65x10^9$ [95% CI, $1.25x10^9$ – $1.72x10^{10}$], P<0.001) and female patients (vs. male, HR=1.98 [1.27-3.10], P=0.04) were more likely to die. Three-year globe salvage rates ranged from 13.3% (95% CI, 5.1-25.6) in LMICs to 46.2% (38.8-53.3) in HICs. At three years, 70.1% of cT1 eyes (95% CI, 54.5-81.2) were salvaged, compared to only 8.9% of cT3 eyes (5.5-13.3). More advanced tumor stage was associated with greater hazard of enucleation (e.g., cT1 vs. cT3, SHR=4.98 [95% CI, 2.36-10.5), P<0.001).

Conclusions and Relevance:

Disparities exist in survival and globe salvage rates in American countries based on economic level and tumor stage at diagnosis. There is a need for improved childhood cancer awareness in lower income American countries for earlier diagnosis and treatment.

INTRODUCTION

The prognosis of retinoblastoma, the most common primary pediatric eye cancer, is dependent on early diagnosis and treatment.[1-3] Treatment primarily 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 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 25 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 closely followed the analysis methods of the Global Retinoblastoma Outcome Study, a 3-year prospective analysis of retinoblastoma outcomes in treatment-naïve patients.[8] Initially, retinoblastoma treatment centers across the world were invited to participate in 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] The study was approved by the London School of Hygiene & Tropical Medicine Observational Ethics Committee. Participating centers applied for and 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.[11] 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, 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 25 American countries, who presented to 59 treatment centers in 2017 and received or were offered treatment for retinoblastoma (**Table 1A**). Of these patients, 49 had missing date 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. The country most represented in the data was the USA at 32.4% (159/491), followed by Peru at 14.9% (73/491), Brazil at 11.4% (56/491), Guatemala at 7.5% (37/491), and Argentina and Mexico both at 6.3% (31/491).

Clinical Characteristics at Presentation

The median age at diagnosis was 19.4 months (IQR, 8.3-31.9), 47.3% of patients (232/491) were female, 67.4% of patients (331/491) presented with unilateral disease, and 7.1% of patients (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 a *RB1* germline mutation, 50.6% (246/486) were HX (mutation unknown), and 38.1% (185/486) had an identified mutation. These data were available in at least 98.6% of the patients. 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 primarily. Primary enucleation was performed in 48.8% (235/486) of cases. Primary intra-arterial chemotherapy was performed in 13.6% (66/486) patients, none of whom came from LICs. Upfront treatment refusal was reported in 4.7% (23/486) 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, 21.8% (106/486) underwent secondary enucleation/exenteration, 32.7% (159/486) received laser or cryotherapy, 14.8% (72/486) received intra-arterial chemotherapy, and 11.3% (55/486) received intravitreal chemotherapy. 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) 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, 7.0% (3/43) were from retinoblastoma-related treatment complications, 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 UMIC 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. 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 (Ps>0.05), although hazard estimates reflected global results, with decreasing risk of death as a function of increasing income level.[8] Similarly, age at diagnosis was not significantly associated with risk of death in patients under four years old (P=0.56), but like global results,[8] hazard of death was estimated to increase as a function of age in younger patients. Patients over age four showed a relatively reduced risk of death, significantly decreasing with each added year (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). Female sex was also found to be associated with an increased hazard of all-cause mortality (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, of whom 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 is 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 from 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) patients and was used following other forms of therapy 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., cT1 vs. cT3 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 (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 greater 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.[12] 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 disease at diagnosis, while less than 1% of HIC patients presented with advanced extraocular 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 factors including limited availability of sophisticated treatment and more advanced disease at presentation 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, although the trend observed was similar to what was seen in global results.[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**). In both studies, death was more common in children diagnosed younger than age four, who are surviving with advanced disease. Notably, age at diagnosis was unrelated to enucleation risk in the Americas, although this 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,[13] where the increased risk to females is associated with preferential treatment of male children in some countries as opposed to a biological mechanism. Further studies examining impact of sex and gender on mortality in retinoblastoma patients are warranted globally.

Larger disparities in enucleation rates as a function of income were observed in the Americas compared to what was observed globally, 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. 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.[7,14] Additional data from patient 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), but due to small sample size and limited follow-up data 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. Most importantly, it is the first study of this magnitude to assess retinoblastoma outcomes in the Americas. This prospective study employed the same clustering and weighting methodology utilized in 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[8] (**Figure 1, 2**). 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. Survival trends in this sub-analysis mirror those of the larger global study, with higher income level being associated with lower risk of all-cause mortality, although

this risk factor also impacted enucleation rates in the Americas. Females in the Americas diagnosed with retinoblastoma are at greater risk of death compared to their male peers, although this risk is not reflected globally. Our study reinforces the importance of international support in building high-quality childhood cancer programs for lower income countries in the Americas to ensure early diagnosis and treatment.

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Author contributions:
Fabian and Berry had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fabian and Bowman.
Acquisition, analysis or interpretation of data: All co-authors.
Drafting of the manuscript: Berry, Pike, Rajagopalan, Reid.
Critical revision of the manuscript for important intellectual content: All co-authors.
Statistical analysis: Reid.
All co-authors approved the final version for publication.

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We declare no competing interests relevant to the present study.

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Data sharing:
This study follows the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER). The study data will become available online once all analyses are complete.

Additional Contributions
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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.[11] 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).

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Figure Legends:

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.

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.