Primary Enucleation for Intraocular Unilateral Retinoblastoma Can Save Life in Lower-income Settings

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Abstract

Children with retinoblastoma (Rb) from lower-income settings are known to have a poor prognosis. We report the treatment outcomes in a prospective analysis including 191 treatment-naïve children with unilateral intraocular Rb from 11 centers and 10 countries that underwent primary enucleation in 2019, coupled with adjuvant systemic chemotherapy as needed. Three-year survival rate was 95.0% for the entire cohort and 87.5%, 96.6%, 93.2%, and 100% for children residing in low-, lower-middle, upper-middle and high-income countries, respectively. Early diagnosis while the tumor remains intraocular can be life-saving, particularly in low-resource settings where primary enucleation and adjuvant chemotherapy can cure Rb.

Retinoblastoma (Rb) is the most common primary intraocular cancer found within children.[1] A global analysis of treatment-naïve children diagnosed with Rb in 2017, and followed for three years, demonstrated that outcomes varied significantly depending on the child's country of residence.[2] In high-income countries (HIC), the disease was largely curable, with a survival rate of 99%, compared to just 57% in low-income countries (LIC). Extraocular tumor at time of diagnosis was most prevalent in LICs, likely due to delayed presentation, and was identified as an independent risk factor for poor outcomes.[3]

Despite recent advancements in Rb management that emphasize globe salvage, enucleation remains a mainstay treatment modality among the clinician's armamentarium, especially when treating advanced intraocular disease as well as eyes that have failed conservative management.[4,5] Furthermore, enucleation may be the preferred treatment modality in developing countries due to lack of capacity and resources, and in select cases, cure unilateral disease.[2,5]

In this prospective, multinational study, metastasis and survival rates were assessed in treatment-naïve children with advanced intraocular Rb that presented to 11 Rb centers from 10 countries - Ethiopia, India, Peru, France, Bangladesh, United States, Russia, China, United Kingdom, and Pakistan - from January 1 to December 31, 2019. Only children with unilateral intraocular Rb [8th American Joint Committee on Cancer (AJCC) cT2 and cT3][6] who underwent primary enucleation were included for analysis. High-risk histopathology features (HRHF) were previously detailed by Kaliki et al,[7] and children's countries of origin were classified as LIC, lower middle-income (LMIC), upper middle-income (UMIC), or HIC based on the United Nations World population prospects 2017 revision.[8]

During the study period, 692 children were diagnosed with Rb in the participating treatment centers and enrolled in the study (**Figure 1**). Of these, 191 children (27.6%) with unilateral AJCC cT2 and cT3 Rb underwent primary enucleation. The analysis included 24 (12.6%) children from LICs, 89 (46.6%) from LMICs, 59 (30.9%) from UMICs, and 19 (9.9%) resided in HICs (**Table 1**). Mean age at presentation was 29.5 ± 20.0 months [range: 1.3-134.2], and 82 children (42.9%) were female. Eighty-one (42.4%) children were classified as AJCC cT2 and 110 (57.6%) as cT3. According to histopathology analysis of the enucleated eyes, 110 (57.6%) children [41 cT2 (37.3%), 69 cT3 (62.7%)] were found to have HRHF,[7] of which 102 (92.7%) were treated with adjuvant intravenous chemotherapy. Children from LICs had a higher prevalence of HRHF compared to HICs ($p < 0.01$). During a mean follow-up time of 28.2 ± 32.0 months (range: 0.2 – 49.0 months), 10 (5.2%) children developed systemic metastasis and 9 (4.7%) expired.

On Kaplan-Meier analysis, three-year survival rate was 95.0% for the entire cohort (**Figure 2A**). Stratified by economic grouping of residence, 1-year survival rates were 87.5%, 98.9%, 96.6%, and 100%, and 3-year survival rates were 87.5%, 96.6%, 93.2% and 100% for LIC, LMIC, UMIC and HIC, respectively. On comparative analysis, significant differences existed in survival curves between LIC vs. LMIC, and LMIC vs. UMIC ($p \leq 0.05$). Residing in a lower-income country was associated with more systemic metastasis and poorer survival at 3-year follow up ($p \leq 0.05$). Moreover, 1-year survival rate for children with HRHF was 95.5% and dropped to 92.7% at 3-year follow-up (**Figure 2B**).

Among children who developed systemic metastasis, 9 (90%) had HRHF including: 5 post-laminar optic nerve invasion, 4 anterior segment invasion, 3 massive choroidal invasion ≥ 3 mm, 1 prelaminar/laminar optic nerve invasion with minor choroidal invasion ≤ 3 mm, and 1

scleral invasion. Of these 9 children with HRHF, 7 (77.7%) received adjuvant systemic chemotherapy.

Rb management is complex, with major differences globally in treatment facilities and healthcare infrastructure.[3] Nevertheless, basic resources are required for a rudimentary service that can provide essential treatment for children with Rb. To this day, enucleation remains a relatively inexpensive, simple and available treatment able to cure Rb in select cases.[5]

The overall 3-year survival of the present multinational group of children with unilateral advanced intraocular Rb was 95%, indicating a positive treatment response to primary enucleation in this economically diverse group of countries. Furthermore, children from lower-income level countries exhibited an encouraging three-year survival of 87.5% (LIC) and 96.6% (LMIC), despite demonstrating more HRHF compared to HIC. A majority of children that demonstrated HRHF were treated with adjuvant chemotherapy, leading to favorable survival rates for this cohort of advanced intraocular disease, independent of economic status in the presence of high-risk features.

The Global Rb Study demonstrated that enucleation and systemic chemotherapy can be performed in nearly all countries.[2] Moreover, the three-year survival rate for children from LIC was 57.3%, with 42.9% presenting with extra-ocular disease.[2,3] These findings underscore the significance of early diagnosis while the tumor remains intraocular. The combination of enucleation and chemotherapy, when indicated, for early diagnosed Rb, is critical for improving survival outcomes, particularly in LIC, where it can translate to a curable disease.

A weakness of the study includes the use of different management strategies and adjuvant chemotherapy protocols post-enucleation, which were determined by center. A strength of the study is its prospective design, conducted by a collaborative group of centers from all economic

groupings worldwide, resulting in one of the largest cohorts of children with a rare malignancy. This allowed for an accurate clinical assessment of affected children as well as pathological examination of Rb eyes without being influenced by recall and selection bias. Lastly, only primary enucleated eyes were included in the final analysis to prevent misinterpretation of neoadjuvant treated eyes.

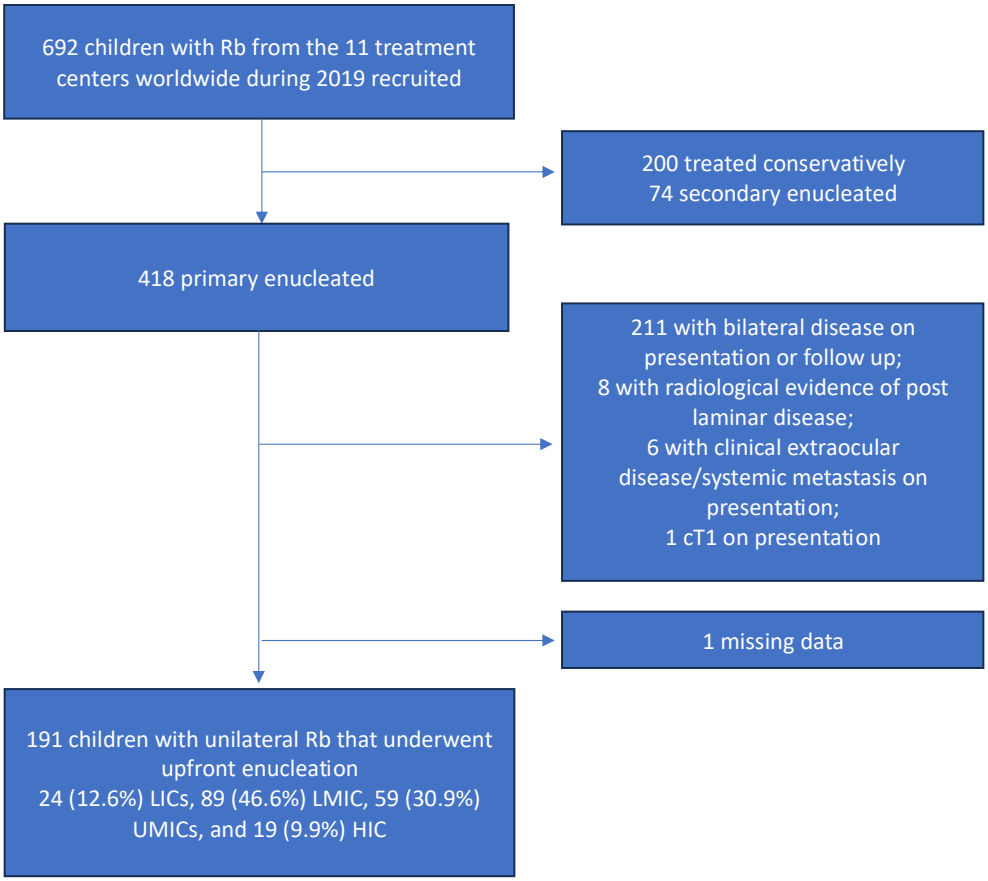
In this cohort of children with Rb from various economic backgrounds, primary enucleation for advanced intraocular AJCC cT2 and cT3 Rb followed up adjuvant chemotherapy, when deemed appropriate, significantly narrowed the socioeconomic survival gap evident in previous studies.[2,9,10] The overall 3-year survival reached 95.0% for all participants, with 87.5% and 96.6% for children from lower-income and lower-middle income centers, respectively. Efforts to establish Rb services that enhance early diagnosis, as well as provide enucleation and chemotherapy, especially in low-resource countries, are vital to improving survival rates and achieving curable disease.

Table 1. Patient demographics, clinical presentation, histopathological analysis and follow up data of a multinational cohort of 191 patients with unilateral retinoblastoma that underwent primary enucleation

Characteristic	Low-income countries (n, %)	Lower-middle income countries (n, %)	Upper-middle income countries (n, %)	High-income countries (n, %)	Total (n, %)
Countries (# children)	Ethiopia (24, 12.6)	Bangledesh, India, Pakistan (89, 46.6)	Peru, Russia, China (59, 39.9)	United States, United Kingdom, France (19, 9.9)	191
Age at presentation (months), n ± SD; range	38.9 ± 24.2; 14.3 - 134.2	27.4 ± 17.7; 1.3 - 84.7	29.0 ± 20.2; 2.3 - 81.2	35.3 ± 23.0; 9.3- 104.5	29.5 ± 20; 1.3 - 134.2
Female sex	10 (41.6)	39 (43.8)	24 (30.7)	9 (47.3)	82 (42.9)
Familial Rb	0 (0)	0 (0)	1 (1.2)	1 (5.2)	2 (1)
AJCC cT2	12 (50.0)	31 (34.8)	31 (52.5)	7 (36.8)	81 (42.4)
AJCC cT3	12 (50.0)	58 (65.2)	28 (47.5)	12 (63.2)	110 (57.6)
HRHF	11 (45.8)	52 (58.4)	42 (71.2)	5 (26.3)	110 (57.6)
Adjuvant chemotherapy	13 (54.2)	57 (64)	75 (96.1)	4 (21.0)	149 (78)
Metastasis	3 (12.5)	1 (1.1)	5 (6.4)	1 (5.2)	10 (5.2)
Death	3 (12.5)	1 (1.1)	5 (6.4)	0 (0)	9 (4.7)

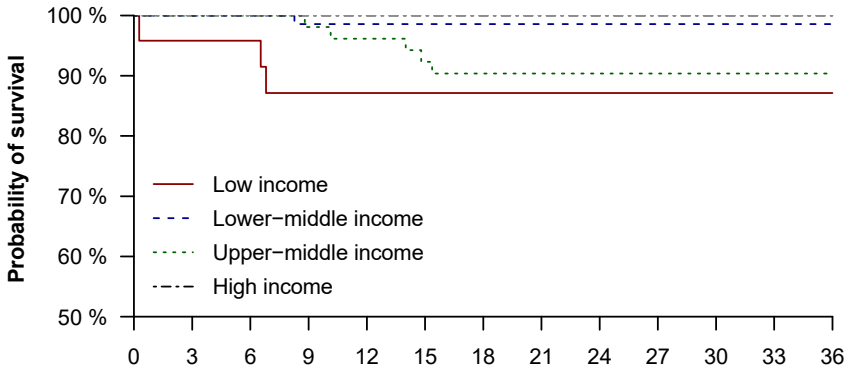
Note. Rb = retinoblastoma; AJCC = American Joint Committee on Cancer; c = clinical classification; HRHF = high-risk histopathological features; SD = standard deviation

Figure 1. Flow chart of cohort selection.



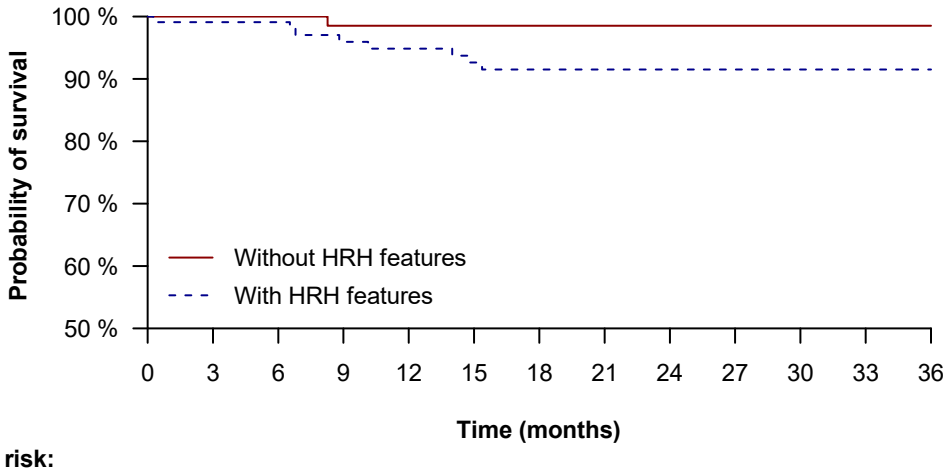
Note. Rb = retinoblastoma

Figure 2. Kaplan – Meier survival analysis of entire multinational cohort of 191 children that underwent primary enucleation for unilateral retinoblastoma A) categorized by economic grouping B) describing impact of High-Risk Histopathological features (HRHF) on Survival



Number at risk:

Low income	24	23	22	20	19	19	19	19	19	16	15	10	4
Lower−middle income	89	85	77	69	63	62	60	59	58	45	39	26	18
Upper−middle income	59	56	53	51	50	48	46	45	45	44	44	41	36
High income	19	18	18	18	18	18	18	18	17	17	15	9	6



Number at risk:

Without HRH features	75	71	67	66	61	61	59	58	57	52	49	32	23
With HRH features	110	107	99	88	86	83	81	80	79	67	61	52	39

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