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ORIGINAL ARTICLE

Retinoblastoma in Jordan, 2003–2013: Ocular Survival and Associated Factors

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ABSTRACT

Purpose: To determine ocular survival and factors affecting globe survival in patients diagnosed with retinoblastoma at King Hussein Cancer Center (KHCC).

Methods: A retrospective review of medical records of 71 Jordanian patients (45 males and 26 females) diagnosed with retinoblastoma (114 eyes) between June 2003 and May 2013 was conducted. Patient sociodemographic and relevant characteristics were collected from records. Patients with bilateral retinoblastoma were treated with chemoreduction and focal consolidation. Lens-sparing radiation therapy and enucleation were reserved for eyes that failed chemoreduction combined with focal therapy. In cases of unilateral retinoblastoma, primary enucleation was recommended for eyes with advanced unilateral disease (Reese-Ellsworth classification groups IV and V). Kaplan-Meier survival and Cox regression multilevel analysis were used to analyze the data.

Results: Median age at diagnosis was 12 months. The follow-up period ranged from 0.25–160 months (mean 26.9 months). The Kaplan–Meier estimate of globe survival of the 114 eyes was 68.0% at 1 year, 63.3% at 2 years, and 62.1% at 5 years. The mean survival time was 101.6 months (95% confidence interval, CI, 87.6–115.6 months). In multivariable-adjusted analysis, advanced stage of the disease (hazard ratio, HR, 5.1, 95% CI 2.3–11.6), unilateral disease (HR 3.3, 95% CI 1.4–8.1), and delay in diagnosis (HR 2.4, 95% CI 1.1–5.5) were significantly associated with increased hazard of enucleation.

Conclusion: The overall ocular survival rate for eyes with retinoblastoma was close to regional and international figures. Disease stage, laterality, and delay in diagnosis were significant predictors of enucleation.

Keywords: Enucleation, Jordan, ocular, retinoblastoma, survival

INTRODUCTION

Retinoblastoma, the most common malignant intraocular tumor in children, has an incidence of one case in16,000–18,000 live births.[1,2] In developed countries, survival rates of more than 90% have been reported, but remain much lower in developing countries, primarily due to late presentation.[3] The use of chemoreduction and focal modalities of treatment have been associated with increased survival as well as better ocular preservation.[4]

In Jordan, incidence of retinoblastoma has been reported to be 9.32 cases per million children per year for children aged 0–5 years,[5] which is close to estimates from other countries worldwide. There are very few ocular survival analysis studies on retinoblastoma in the Middle East. In the present report, we study ocular survival and factors affecting outcome in patients diagnosed with retinoblastoma between 2003 and 2013 at King Hussein Cancer Center (KHCC), a tertiary oncology center and the sole referral center in Jordan for the management of retinoblastoma.

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MATERIALS AND METHODS

In this retrospective study, we reviewed the medical records of 71 consecutive Jordanian patients diagnosed with retinoblastoma between June 2003 and May 2013. Ethical approval was obtained from the Institutional Review Board at the KHCC and the study was conducted in adherence to the guidelines of the Declaration of Helsinki.

All patients were referred to KHCC in Amman, Jordan, which has been the exclusive center for the management of retinoblastoma cases in Jordan. Examination and treatment of these cases was carried out by a multidisciplinary team consisting of a pediatric ophthalmologist, vitreoretinal ophthalmologist, oculoplastic surgeon, pediatric oncologist, and radiation oncologist. Patients were examined under general anesthesia and RetCam fundus photography (Clarity Medical Systems, Pleasanton, CA, USA) was obtained in all cases.

All patients had magnetic resonance imaging (brain and orbit) at time of diagnosis. Patients with Reese-Ellsworth classification group V tumors at diagnosis and eyes that showed high risk pathological features after enucleation had lumbar puncture and bone marrow biopsy to look for metastasis.

Patient sociodemographic data and relevant characteristics were collected, and included information on age at diagnosis, sex, family history of retinoblastoma, presenting symptoms, duration between presenting symptom and time of diagnosis, laterality of the disease, globe salvage, presence of extraocular spread or metastatic disease, survival, and duration of follow-up. Stage of the disease was recorded in the records according to the Reese-Ellsworth classification.[6] Pathologic confirmation of all enucleated eyes was available. We defined eye survival as having no enucleation or radiation, and defined the delay of diagnosis as the time from the appearance of first ocular symptoms as reported by parents to time of first examination under anesthesia that documented a diagnosis of retinoblastoma.

The treatment protocol at KHCC is described in detail elsewhere.[7] In summary, chemoreduction consisted of carboplatin (18 mg/kg/day for children <36 months old or 560 mg/m^2 for children ≥36 months old × 1 day) and vincristine (0.05 mg/kg/day or 1.5 mg/m^2 × 1 day) given every 4 weeks. For patients with advanced disease, etoposide was added (5 mg/kg per day or 150 mg/m^2 × 2 days). For high-risk pathologic features after enucleation (e.g. massive choroidal invasion or retro-laminar optic nerve invasion), four cycles of the above regimen were alternated with five cycles of doxorubicin (1 mg/kg or 30 mg/m^2 × 1 day), cyclophosphamide (25 mg/kg or 750 mg/m^2 × 1 day; followed by mesna), and vincristine (same dose as above) administered every 4 weeks. For advanced unilateral retinoblastoma (Reese-Ellsworth groups IV and V), primary enucleation was recommended. For bilateral retinoblastoma, chemoreduction and focal consolidation (cryotherapy, transpupillary thermotherapy, subconjuctival carboplatin for selected patients with advanced intraocular disease) was used. Lens-sparing radiation therapy and enucleation were reserved for eyes that failed chemoreduction combined with focal therapy.

Data were analyzed using SPSS software version 20 (IBM Corp, Armonk, NY, USA). Data were described using mean, medians, and percentages wherever appropriate. Difference in median age at diagnosis between unilateral and bilateral cases was tested using the Mann-Whitney U test. Independent t test was used to compare the mean delay in diagnosis between patients with a family history of the disease and those with no family history. The Kaplan-Meier survival curve was used to demonstrate the cumulative globe survival rate for eyes with retinoblastoma, with censoring at the time of last contact. A multilevel survival analysis was performed using generalized estimating equations (GEE) with interval-censored survival as a link function. The analysis specified binomial as the distribution and complementary log-log as the link function. The variable ''laterality'' was considered as a within-subject variable.

Cox regression analysis was used to determine the predictors of enucleation of the affected eyes. Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. A p value <0.05 was considered statistically significant.

RESULTS

Ocular survival analysis was performed for 114 eyes with retinoblastoma belonging to 71 patients (45 males and 26 females). The median age of patients at diagnosis was 12 months with a mean of 21.7 months (SD 35.5 months). Of all patients, 39.4% had retinoblastoma in one eye (unilateral) and 60.6% had retinoblastoma in both eyes (bilateral). The median age at presentation was significantly higher for patients with unilateral disease compared to those with bilateral disease (24.0 months vs 11.0 months, $p < 0.001$). About one fifth (19.7%) of patients had a family history of retinoblastoma. Those with and without a family history of retinoblastoma did not differ in age of presentation. The delay in diagnosis reached a maximum of 9 weeks with a mean delay of 1.7 weeks (SD 1.9 weeks). The mean delay was significantly shorter ($p = 0.010$) for patients with family history of the disease compared to those with no family history (1.0 weeks vs 2.0 weeks). Moreover, the mean delay in diagnosis was shorter for eyes with stage Ia–IVb retinoblastoma compared to eyes with stage V retinoblastoma (1.4 weeks vs 2.2

weeks; $p = 0.039$). The delay was not significantly different between unilaterally and bilaterally affected eyes.

The follow-up period ranged from 0.25–160 months (mean 26.9). One patient died after 9 months of follow-up because of extraocular spread. Leukocoria was the most common presenting sign (54.4%) followed by strabismus (22.8%). Demographic and clinical characteristics of the 71 patients with retinoblastoma are shown in Table 1.

Of the 114 eyes with retinoblastoma, 42 were enucleated (36.8%; seven eyes with retinoblastoma stage Ia–IVb and 35 eyes with stage V). The Kaplan–Meier estimate of globe survival of the 114 eyes was 68.0% at 1 year, 63.3% at 2 years, and 62.1% at 5 years. Mean survival time was 101.6 months (95% CI 87.6–115.6 months). The survival distribution of globes differed significantly according to laterality ($p < 0.005$; Figure 1). Mean survival time was 37.2 months (95% CI 18.2–56.3 months) for unilaterally diseased eyes and 117.9 months (95% CI 103.2–132.6 months) for bilaterally diseased eyes. On the other hand, mean survival time was 139.8 months (95% CI 125.9–153.8 months) for eyes with stage Ia–IVb retinoblastoma and 50.5 months (95% CI 35.9–65.1 months) for eyes with stage V retinoblastoma (Figure 2). The adjusted number of eyes at risk of enucleation and the cumulative number of eyes enucleated at specific time points are shown in Table 2.

In the multilevel survival analysis, seven variables were entered in the model: age, sex, side of the affected eye, laterality, family history, stage of the disease, and diagnosis delay (Table 3). The only variables that were significantly associated with globe survival were stage of the disease, laterality, and delay in diagnosis. HR was 5.1 (95% CI 2.3–11.6) for eyes with stage V disease compared to eyes with disease of lower stages. Unilaterally affected eyes were 3.3 times more likely to be enucleated than when both eyes were affected. Delay in diagnosis of more than 1 month was associated with increased hazard of enucleation (HR 2.4).

TABLE 1. Demographic and clinical characteristics of 71 patients with retinoblastoma, Jordan.

Characteristic	Patients with retinoblastoma
Age in months, mean, (range)	21.7 (1.0–276.0)
Male/female, *n*	45/26
Positive family history, *n* (%)	14 (19.7)
Laterality, *n* (%)	
Unilateral	28 (39.4)
Bilateral	43 (60.6)
Presenting symptom/sign, %	
Leukocoria	54.4
Strabismus	22.8
Proptosis	1.8
Family screening for retinoblastoma	10.5
Combination	2.6
Other	7.9

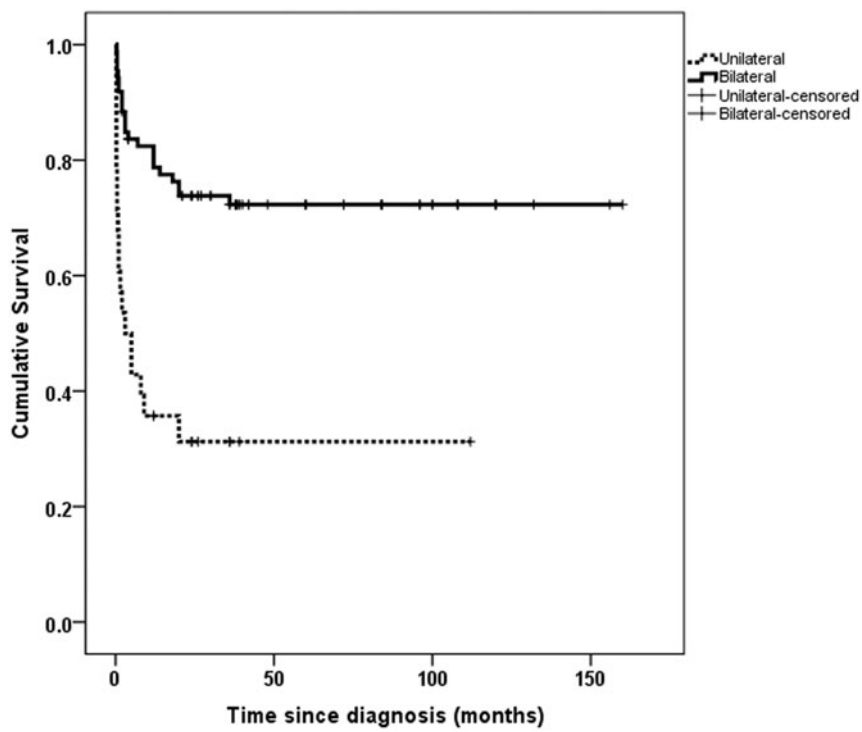

FIGURE 1. Kaplan–Meier estimate of retinoblastoma globe survival distribution according to laterality, Jordan.

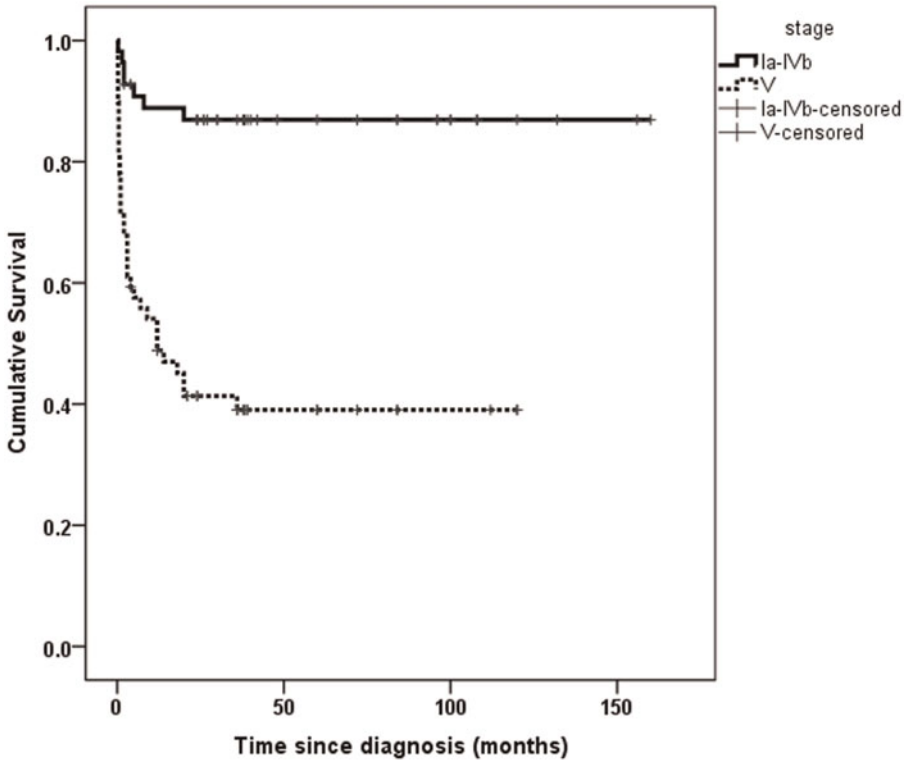

FIGURE 2. Kaplan–Meier estimate of retinoblastoma globe survival distribution according to stage of disease, Jordan.

TABLE 2. The adjusted number of eyes at risk of enucleation and the cumulative number of eyes enucleated at specific time points.

		Time				
Stage	Number	0	3 months	6 months	1 year	2 years
Ia-IVb	At risk*	55	50	47	46	45
	Already enucleated	–	4	5	6	7
V	At risk*	59	40	33	31	20
	Already enucleated	–	23	25	30	34

*Number of eyes at risk of enucleation adjusted for the number withdrew (“censored”) during the interval.

DISCUSSION

In recent years, survival rates of nearly 95% have been achieved in retinoblastoma patients.[8] Therefore, more consideration is being given to globe salvage and preservation of visual function. This has been associated with a significantly reduced rate of primary enucleation, which is still relatively high in developing countries due to late presentation, delay in diagnosis or lack of appropriate treatment with globe saving strategies.[9]

This study describes the 5-year globe survival rate of retinoblastoma patients referred to a major oncology center in Jordan from 2003 to 2013. It is the first study on globe survival in the country and therefore, cannot describe a trend or change in ocular survival. The 5-year globe survival rate was 62.1%, which is comparable to those reported in other developing countries[10,11] as well as developed countries.[12,13] In the present study, factors that were associated with globe survival were stage of the disease, laterality, and delay in diagnosis. The most common presenting stage was stage V (49%) and 66% of all eyes were classified as either stage IV or V, indicating that most patients still present with more advanced disease.[14]

Bilateral cases accounted for 60.6% of patients and were associated with a lower enucleation rate compared to unilateral cases, consistent with more aggressive treatments to preserve at least one eye in bilateral cases.[15] In addition, different protocols were used for enucleation in unilateral cases compared to bilateral cases, and this may explain the difference in globe survival between both groups. Bilateral cases also presented at a younger age compared to unilateral cases, which may also explain the better globe survival. The ratio of unilateral to bilateral cases is variable among different studies describing larger numbers of patients, but the higher percentage of bilateral cases in our patients is yet to be explained.

The average delay in diagnosis was 1.7 weeks, a duration much shorter than those reported in other developing countries.[10,16] About 20% of patients had positive family history of retinoblastoma compared to 10–15% reported in the literature.[15] Those patients had shorter delay in diagnosis, apparently because of early screening by ophthalmologists and subsequent

TABLE 3. Factors associated with globe survival in multivariable-adjusted survival analysis for 114 eyes with retinoblastoma, Jordan.

Variable	*n*	Enucleation, *n* (%)	Adjusted hazard ratio	95% confidence interval	*p* Value
Age, months					
≥12	44	24 (54.5)	1.2	(0.6–2.7)	0.636
<12	70	18 (25.7)	1		
Sex					
Male	72	25 (34.7)	1.4	(0.8–2.7)	0.265
Female	42	17 (40.5)	1		
Stage					
V	59	35 (59.3)	5.1	(2.3–11.6)	<0.001
Ia–IVb	55	7 (12.7)	1		
Side					
Right	58	24 (41.4)	1.3	(0.7–2.6)	0.392
Left	56	18 (32.1)	1		
Laterality					
Unilateral	28	19 (67.9)	3.3	(1.4–8.1)	0.008
Bilateral	86	23 (26.7)	1		
Family history					
Yes	26	4 (15.4)	1.2	(0.4–3.3)	0.735
No	88	38 (43.2)	1		
Diagnosis delay					
<1 month	49	12 (24.5)	1		
≥1 month	65	30 (46.2)	2.4	(1.1–5.5)	0.041

urgent referral. Previous experience with retinoblastoma in older siblings would also contribute to more rapid referral. Patients with positive family history also tended to present at a younger age, but this was not significant ($p = 0.28$). Abramson and colleagues[15] demonstrated that positive family history of retinoblastoma was associated with better ocular survival in a large series of patients. In the present study, positive family history was associated with better ocular survival in univariate analysis but this was not shown in the multivariable-adjusted model. As described above, positive family history was associated with shorter delay in diagnosis (thus earlier stage of disease), and earlier age at diagnosis. Adjustment by age at diagnosis and stage of disease makes the association become non-significant in the multivariable-adjusted analysis.

Leukocoria was the most common presenting symptom followed by strabismus, with both accounting for more than 77% of presenting signs. This is consistent with previous reports.[15,17] Contrary to many reports where leukocoria was associated with poor ocular survival,[15,17] there was no association between leukocoria and ocular survival ($p = 0.43$).

The average age at diagnosis was 21.7 months (35.4 months for unilateral cases vs 12.8 months for bilateral cases). The ratio of unilateral to bilateral cases in a particular community would affect the average age of the total number of cases, hence, the mean age is expected to be different from that reported in other studies. There was no significant association between mean age and ocular survival in the present study.

It is important to consider several issues when comparing total ocular survival rates among different studies. Ocular survival may vary depending on the ratio of unilateral to bilateral cases included in a particular population, where more bilateral cases would favor better ocular salvage rates. It is also clearly affected by the stage of the disease and the delay in diagnosis, both of which are related to socioeconomic, cultural, and compliance factors.

Ocular survival in the present study mainly describes the preservation of the eye regardless of visual function. Therefore, there is a need to assess visual function in the long term, which also takes into consideration ocular side effects of focal treatment. One limitation of the present study is the retrospective nature of the study design. Since retinoblastoma is a rare disease, a prospective design is not always possible, and the sample size tends to be small. This limitation applies to most studies on retinoblastoma.

Other therapeutic interventions are being assessed to improve globe salvage rates while reducing toxicity from systemic chemotherapy such as intra-arterial, periocular, and intravitreal chemotherapy.[18] Their indications depend on laterality and tumor stage.

In conclusion, the overall ocular survival rate for eyes with retinoblastoma in Jordan treated with systemic chemoreduction and focal therapy is close to regional and international figures. There is a need for longer follow-up periods to assess visual function in the preserved eyes. Newer modalities of treatment which can improve the outcome while avoiding systemic side effects should be adopted in the future.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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