


Survival outcomes of unilateral retinoblastoma based on pathological risk stratification-experience at a tertiary care centre in Pakistan

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Abstract

Retinoblastoma (RB) is the most common childhood intraocular malignancy. In high-income countries over the past decade, upfront enucleation for unilateral RB is least favoured due to other alternatives that can help in globe preservation, but in low-middle income countries it is still the preferred option due to lack of resources and expertise. The treatment of RB after enucleation is tailored based on the histopathological risk features, as adjuvant chemotherapy with high-risk features reduces the risk of metastasis. The aim of our study was to analyse the survival outcomes of adjuvant therapy based on histopathological risk stratification in patients who underwent upfront enucleation for unilateral RB with advanced disease. A retrospective study was carried out at Shaukat Khanum Memorial Cancer Hospital and Research Centre, Pakistan. A total 113 patients (aged 3 months till 16 years) diagnosed with unilateral RB who had upfront enucleation from July 2009 till January 2019 were included in this study. The mean age of diagnosis was 37.4 months (± 24.5) and male-to-female ratio of 1.3:1. The most common clinical presentation was leukocoria (74.3%). Patients who underwent enucleation had advanced disease; group D present in 62.8% followed by group E (32.7%). Histopathology revealed high-risk features in 29 patients (25.7%) and intermediate risk in 54 patients (47.8%). Disease progression and relapse was seen in patients with high-risk histopathological features. The 4-year over-all survival and EFS observed for this cohort was 74% and 71%. Awareness about the early symptoms among the general population and health care personnel at a nationwide level is needed to facilitate early detection and lessen disease related morbidity and mortality.

Keywords: *children, enucleation, retinoblastoma, pathology*

Introduction

Retinoblastoma (RB) is the most common intraocular malignancy in childhood and accounts for about 2% of all childhood cancers [1]. The incidence of RB ranges from 1 case per 15,000–20,000 live births worldwide [2]. RB occurs due to germline or somatic

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ecancer 2022, 16:1360
<https://doi.org/10.3332/ecancer.2022.1360>

Published: 01/03/2022

Received: 26/08/2021

Publication costs for this article were supported by ecancer (UK Charity number 1176307).

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Table 1. Patient and tumour characteristics (n = 113).

Patient characteristics	n (Percentages %)
Mean age at presentation	37.4 ± 24.5 months
Gender	
Male	65 (57.5%)
Female	48 (42.5%)
Presenting signs ^a	
Leukocoria	84 (74.3%)
Proptosis	11 (9.7%)
Red eye	6 (5.3%)
Vision loss	7 (6.2%)
Squint	3 (2.7%)
Ptosis	1 (0.9%)
IIRC Group	
Group C	5 (4.4%)
Group D	68 (60.2%)
Group E	40 (35.4%)
Pathology	
Anterior segment invasion	38 (33.6%)
Ciliary body invasion	16 (14.1%)
Massive choroidal invasion	20 (17.7%)
Scleral invasion	12 (10.6%)
Pre-laminar invasion	15 (13.3%)
Post-Laminar invasion	33 (29.2%)
Optic nerve cut end invasion	29 (25.7%)
4-year OS	74%
4-year EFS	71%

^a One patient had strong family history, had upfront enucleation despite having Group C

Table 2. Outcomes of disease regarding histopathological risk stratification.

Risk group based on histopathological features (n = 113)	Outcomes					p value
	Complete response	Disease relapse	Disease progression	Death	Abandonment	
Low risk	29	1	0	0	0	<0.05
Intermediate risk	43	6	1	1	3	
High risk	11	5	6	3	4	

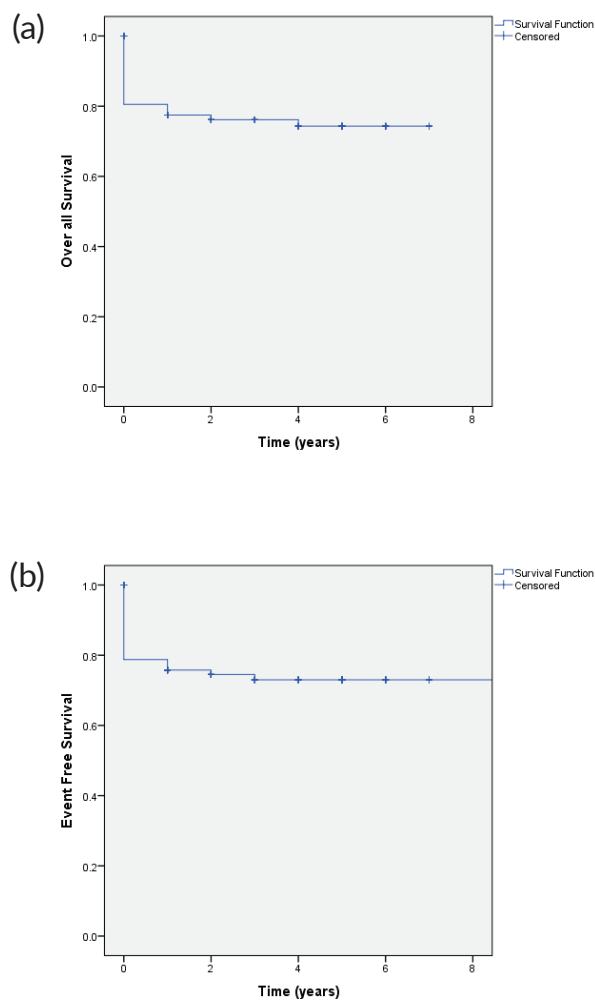


Figure 1. (a): OS and (b): EFS.

The 4-year OS and EFS observed for this cohort was 74% and 71%, respectively (Figure 1). OS of patients with group C at 4 years was 80%, group D 82.4%, and group E was 65%, respectively. The event-free survival in group C, D and E was 80%, 79%, and 59%, respectively (Figure 2).

The 4-year OS survival based on histopathological risk stratification in low-risk group was 96.7%, in intermediate risk group 79.6% and 43% in high-risk group, whereas 4-year EFS in low-risk group was 96%, 76% in intermediate risk and 41% in high-risk group respectively (Figure 3).

Discussion

Asia-pacific region of the world contributes significantly to the diagnosis of RB, Pakistan is among the top ten countries of the regions that shares significant burden of this disease [21]. The clinical presentation of the RB is variable including leukocoria, strabismus, vision loss or painful eye [22]. Leukocoria was the most common clinical presentation (74.3%) seen in our patients followed by proptosis, comparable to

other LMICs [23]. Along with leukocoria, proptosis and vision loss were the usual presenting clinical signs associated with advanced group disease D and E (p value 0.002). The mean age of presentation among our cohort was 37.4 months, which is higher than our neighbouring countries where it was reported to be 20 months [24]. This may reflect delay in diagnosis and referral of our study population to the cancer treatment centre. A male predominance was seen in our patients, other studies from Asia have reported similar results, although no sex pre-dilection has been seen in RB and the differences mainly can be due to gender discrimination [25, 26].

The advanced group D and E disease among our patients had high-risk histopathological features and required adjuvant chemotherapy. Optic nerve cut end invasion termed as high-risk feature was present in 25.7% of patients and they received radiation therapy along with adjuvant chemotherapy. Globe salvage is being promoted for group D eyes with the introduction of the new treatment modalities like intra-arterial chemotherapy (IAC), but disease relapse can still not be ignored. However, for group E disease primary enucleation is still the treatment of choice [27]. Unfortunately, in our setting we lack the expertise of administration of IAC.

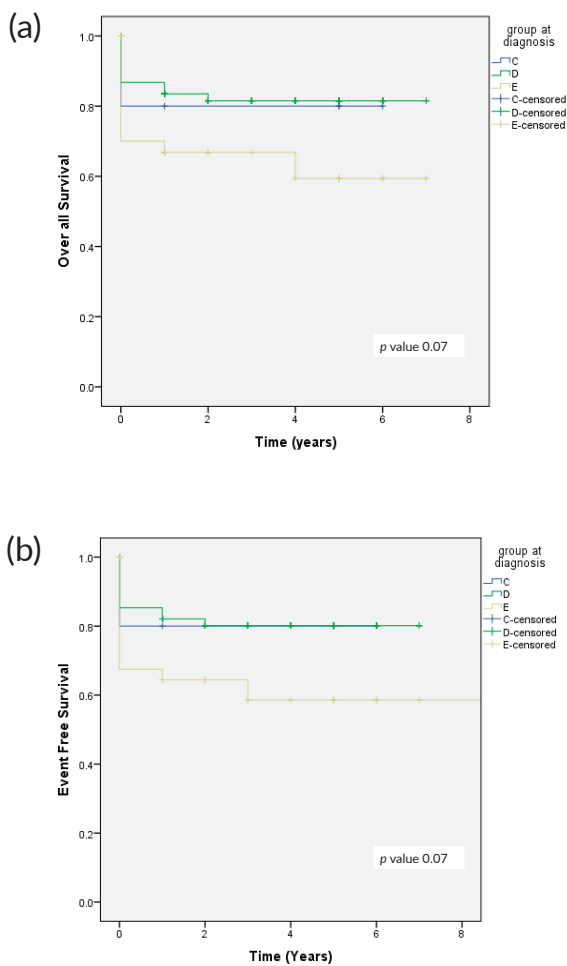


Figure 2. (a): OS in relation to clinical group and (b): EFS in relation to clinical group.

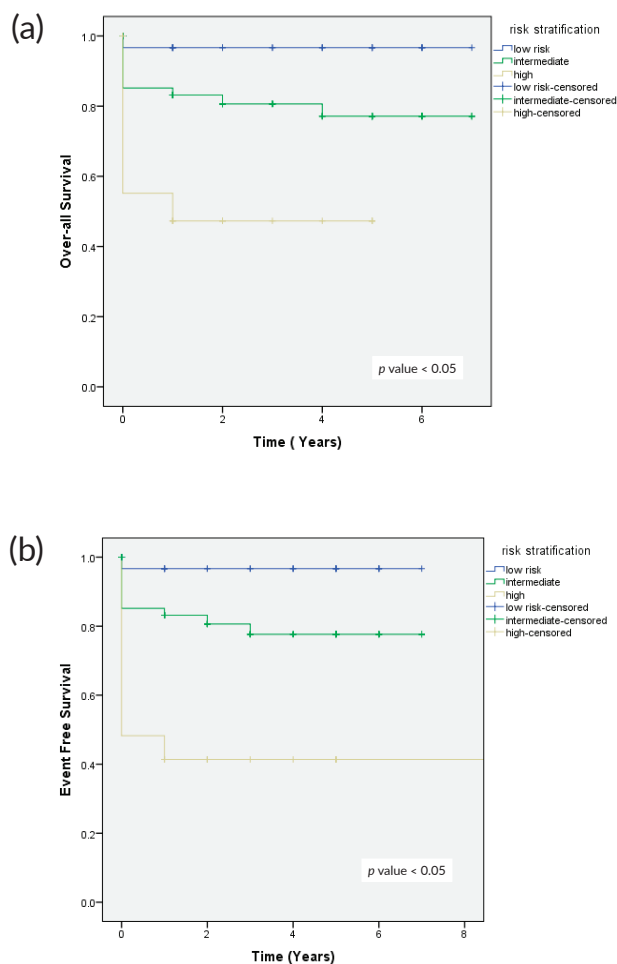


Figure 3. (a): OS as per risk stratification and (b): EFS as per risk stratification.

Previous study has shown that timely enucleation followed by adjuvant chemotherapy in high-risk histopathology reduces the risk of metastatic disease [28]. In our data, 15 patients had disease progression and metastasis in intermediate and high-risk group who received adjuvant chemotherapy after 2 weeks of enucleation. When we analysed the outcomes based on initiation of adjuvant chemotherapy, the patients who received chemotherapy within 2 weeks of enucleation had better survival compared to those who received after 2 weeks (94.1% versus 64.1%, p -value 0.02) (Figure 4).

The histopathological feature of RB plays major role in predicting outcome of the disease [29]. On microscopic level, RB reveals small hyperchromatic cells with high nuclear to cytoplasmic ratio, the tumour is differentiated into well differentiated to poorly differentiated (based on the Homer–Wright rosettes) [30]. In our data, 62 patients (54.8%) with poorly and moderately differentiated histology had high risk features and were given adjuvant chemotherapy. Disease relapse and progression was also seen among these patients, although statistically it was not significant (p value- 0.26). Kashyap *et al* [31] reported that poorly differentiated tumours are associated with multiple high-risk features, as compared to well differentiated tumours (p value of <0.001).

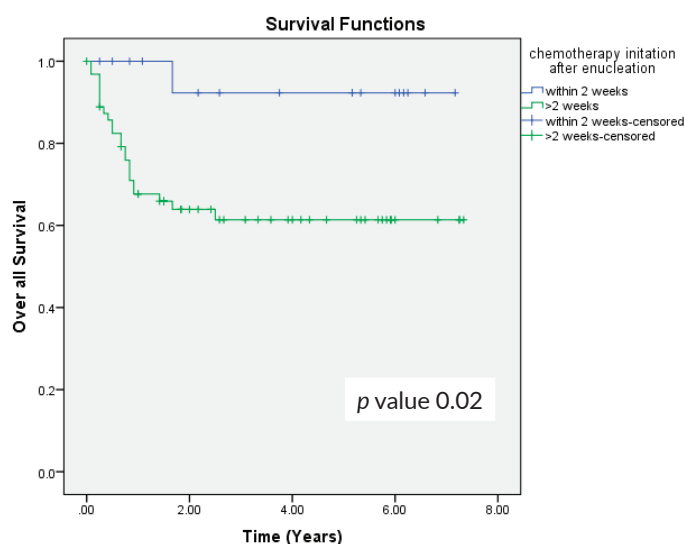


Figure 4. OS in relation to the initiation of chemotherapy after enucleation.

Early diagnosis and treatment can improve outcomes in RB. In our cohort, disease progression was seen in 6.2% patients while on treatment, which is within the estimated range for LMICs [32]. Slightly better outcomes were seen in patients who had enucleation at our facility as compared to those who had at outside facility (EFS 75.3% versus 70%).

Five patients (4.4%) in our study had group C disease on EUA, but they underwent upfront enucleation (at an outside facility). Majority of our patients (72.6%) that presented with advanced disease belonged to urban areas. Due to lack of expertise and limited resources in our country, novel therapies for globe salvage could not be offered, it can be speculated that the treatment option of upfront enucleation can be one of the risk factors that lead to advanced disease presentation. Since it is retrospective study exact risk factors that lead to advanced disease could not be assessed.

In our report, seven patients (5.3%) abandoned treatment, even though free of cost therapy was offered at our centre. Abandonment had always been a challenge when treating oncology patients, high rate of abandonment has been seen in RB patients in LMICs, intensive chemotherapy regimens and mutilating surgical procedures such as enucleations and prolong follow up can be considered as a risk factor [33]. In the central American Association of Pediatric Hematology Oncology II trial, 102 patients ($n = 161$) received upfront enucleation and 59 patients underwent delayed enucleation. Although they were successful in reducing the abandonment in patients with advanced disease, the children with upfront enucleation had better outcomes as compared to those with delayed enucleation (5-year OS 94% versus 74%: p value < 0.001) [34].

This study is retrospective with some inherited limitations, as data was collected through online electronic media and majority of our patients were referred after enucleation, the exact onset of symptoms could not be determined. Secondly, to determine the intraocular disease group in children, we relied on the examination done by referring ophthalmologist. In resource limited setting, patients with advanced unilateral disease (group D or E) without treatment modalities for globe salvage upfront enucleation can be considered. RB awareness programs for early recognition and referrals, multiple disciplinary team (MDT) meetings with experts or telemedicine clinics are the ways through which management of RB could be implemented in LMICs, resulting in early recognition and reducing mortality rates [35]. We have started similar program as National RB MDT under guidance of Pakistan Society of Pediatric Oncology (PSPO) where difficult and complex cases are being discussed. Recently, for uniformity of staging and treatment we have proposed nationwide protocol of RB under leadership of PSPO which is to be adopted by all oncology centres and ophthalmologists of the country, the results of which are yet to be determined.

Conclusion

Risk stratification based on histopathological features of the enucleated eye is an effective way of tailoring adjuvant therapy. Significant number of patients avoided chemotherapy with very low risk of relapse. Globe salvage in advanced disease is possible with the introduction of newest modalities like IAC, but it has limited availability due to cost effectiveness and lack of expertise in resource limited setting. Hence, in advanced unilateral RBs, we recommend upfront enucleation for risk stratification and treatment accordingly in our setting.

Conflicts of interest

The authors declare no conflict of interest.

Disclosure

The abstract was presented as an e-poster at SIOP 2021.

Funding

None.

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