Association between Clinical and High Risk Histopathological Features of Primary Enucleated eyes at Muhimbili National Hospital.

Moshi, Neema[1] MMED, Sanyiwa, Anna[1] MMED, Mhina, Celina[1] MMED, Susan, Mosenene[1] MMED, Kisimbi, John[1] MMED Malango, Atuganile[2] MMED.

[1] Muhimbili University of Health and allied Services

[2] Muhimbili National Hospital

Disclosure of monetary grant: Ministry of Health, Community Development, Gender, Elderly and Children of Tanzania

All replies should be sent to: Phone no +255784275306 email address swetynei@gmail.com

ABSTRACT

Purpose: To associate the clinical and histopathological high risk features of primary enucleated eyes with retinoblastoma at Muhimbili National Hospital.

Method: Descriptive cross sectional study done at Muhimbili National Hospital. Consecutive sampling was used to recruit total of 66 participants from January 2018 to December 2020. Data were analyzed by statistical package for social sciences version 23. Mann Whitney test, independent T test tested, Chi squire and Fishers test confirmed statistical association which was significant when $P<0.05$.

Results: Sixty six (38.5%) patients with retinoblastoma underwent primary enucleation. Dilated pupil was commonly found in examination under anesthesia. The rate of histopathological high risk features was 64%; massive choroidal involvement predominated by 53%. The median intraocular pressure (34mm) was statistically higher in patients with high risk histopathological features by $P=0.006$. The far the place of residence, duration of symptoms, high intraocular pressure, shallow anterior chamber depth, dilated pupil, poor tumor differentiation and extensive necrosis were significantly related to histopathological high risk features at $P<0.05$.

Conclusion: The proportion of primary enucleation among patients with retinoblastoma at MNH is still low. The presence of histopathological high risk feature is still high. Dilated pupil, high intraocular pressure, shallow anterior chamber, poorly differentiated and extensively necrotic tumor are associated with histopathological high risk features. Awareness of the natural history of retinoblastoma to the general public is emphasized. Tertiary care for retinoblastoma should be established in referral hospitals to reduce patients who are coming late.

Keywords: retinoblastoma, prognostic indicators, optic nerve invasion, choroidal invasion, histopathological high risk features.

Introduction:

Retinoblastoma is the most common childhood primary intraocular malignancy. Contributes about 3% of all childhood malignancy. The incidence is 1:15000 to 1:20000[1,2]. In Muhimbili it is the 2nd most common malignance managed in paediatric oncology unity whereas in Kilimanjaro Christian Medical Collage Hospital retinoblastoma is the first histopathological diagnosis among children with cancer[3]. Retinoblastoma mostly affects children under the age of five and there is no sex predilection. It can affect one or both eyes.

The clinical features include leukocoria, raised intraocular pressure, and buphthalmos[4]. The disease is fatal if left untreated as the tumor cells invade the coats of the eyes and spread to distant organs(5,6). Routes of metastasis include the optic nerve, haematogenous through choricapillaries in the choroid, and lymphatic system through the conjunctiva[7,8].

The goal of treatment of retinoblastoma is to save life then the globe then vision. It is individualized based on the age, extent and laterality of the disease[9]

Primary enucleation is the surgical procedure of removal of the eyeball prior to any treatment. This is indicated in patients with advanced disease those in international classification of retinoblastoma group E and those with unilateral disease group D with limited hope of visual rehabilitation[10]. The enucleated eye is evaluated for histopathological high risk features. According to the consensus reached by international retinoblastoma staging working group and Child Oncology Group, histopathological high risk features are defined as massive choroidal invasion, optic nerve invasion at the cut end or post lamina, sclera invasion and combination of focal and either prelamina or lamina invasion [11,12].

Presence of these high risk histopathological feature implicate systemic metastasis after enucleation and dictate institution of post enucleation chemotherapy to limit the risk of metastasis and improve survival rate [13]. It has been reported the incidence of metastasis is 24% without chemotherapy and reduced to 4% if chemotherapy is given to patients with histopathological high risk features [14].

Some studies have shown a link between risk features in the clinical presentation of retinoblastoma and those histopathological features[15]. Neoadjuvant chemotherapy is indicated in patents with retinoblastoma who present with buphthalmos, proptosis and fungating tumor hence the evidence of histopathological high risk features may be destroyed[16]. Therefore to better define the association between the clinical and histopathological high risk features we undertook a cross-sectional study of association between these features was done on primary enucleated eyes at our hospital.

Material and methods

Approval from institutional review board and authorization to conduct the study from hospital were obtained.

Study design and area: A hospital based descriptive cross sectional study was conducted at Muhimbili national Hospital from January 2018 and December 2020. Muhimbili national Hospital is a tertiary hospital situated in Dar es Salaam. Patients with retinoblastoma are seen in pediatric eye clinic; admitted in eye paediatric ward or paediatric oncology ward and surgeries are done in eye theatre. Clinic, theatre and these wards are located in new paediatric complex building. Histology unit is in central pathology laboratory building.

Study Population: All patients with retinoblastoma seen from January 2018 to December 2020 who underwent primary enucleation procedure.

Exclusion criteria: All those patients with retinoblastoma who underwent primary enucleation but their clinical features are missing and the slides are missing from histopathology unit.

Data collection procedure: The previous collected data of patients with retinoblastoma who underwent primary enucleation was obtained from medical record from January 2018 to June 2020 together with new patients were recruited from July 2020 to December 2020. Consent was sought from new patients to enter the study, together with consent to do examination under anaesthesia and enucleation for those with criteria.

Demographics, presenting features, corneal diameter, intraocular pressure, hyphema, hypopion, iris neovasularization, iris heterochromia, iris ectropion, cataract, vitreous seeds, vitreous haemorrhage, tumor size, tumor pattern, and international classicfication of retinoblastoma grouping system[17] were all recorded as clinical features after examination under anaesthesia.

All enucleated eyes had been fixed in formalin, and submitted for routine histopathological processing with H&E stain. Calottes were removed from the globe (horizontal, vertical or oblique) in such a manner as to ensure maximum tumour volume in the pupiloptic nerve section. Calottes and pupiloptic nerve sections were submitted for processing. We reviewed the histopathological features of the enucleated eyes for tumour differentiation (rosette formation or none), optic-nerve invasion (none, prelaminar, laminar, and postlaminar), choroid involvement (none, focal or massive deep) ciliary-body involvement, iris involvement, anterior-chamber involvement, scleral involvement, calcification, neovascular glaucoma, exudative retinal detachment, vitreous seeds, subretinal seeds and extraocular extension. In this study, we defined of massive choroid invasion, sclera, postlaminar and cut end optic nerve and combination of focal choroid and either lamina or pre lamina optic nerve invasion to be high risk histopathological features. Our definition of massive choroidal involvement was in keeping with the International Retinoblastoma Staging Working Group[18]: full-thickness replacement of the choroid by tumour with basal diameter greater than 3 mm. Sclera involvement was defined as invasion of inner scleral lamella or emissary canal.

Data analysis: Statistical Package for Social Services version 23 was used for analysis. The Chi square and Fishers exact test were used to statistically determine the association between variables. Independent sample T test and Mann Whitney U test were used to compare mean horizontal cornea diameter and median intraocular pressure between the risk groups respectively. Significance was determined by $p<0.05$. Statistical charts and tables were used to represent the data.

Results

We identified 66 patients (41 females (62%) who underwent primary enucleation for retinoblastoma between January 2018 and December 2020. Majority came from upcountry 47(71%). All patients had unilateral retinoblastoma. The median age at diagnosis was 24 months. Median duration of symptoms was 4.5 months. Almost all patients 65(98%) were blind.

Table 1: Description of patients' clinical features observed on EUA (N=66 eyes)

Characteristics	
Horizontal cornea diameter (mm) Mean±SD	**11.8±0.93**
Intraocular pressure (mmHg) Median	**28.5(IQR 12.7,40)**
Staphyloma n(%)	2(3)
Shallow anterior chamber n(%)	32(49)
Hypopion n(%)	3(5)
Hyphema n(%)	6(9)
Synechia n(%)	7(11)
Iris neovascularization n(%)	15(23)
Iris heterochromia n(%)	32(49)
Iris ectropion n(%)	31(47)
Dilated pupil n(%)	48(73)
Cataract n(%)	21(32)
Massive Vitreous seeds n(%)	18(27.3)
Vitreous haemorrhage n(%)	2(3)
More than 50% tumor size n(%)	48(73)
Subretinal fluid and seeds n(%)	22(33)
Tumor growth pattern	
Endophytic n(%)	38(58)
Exophytic n(%)	20(30)
Mixed n(%)	8(12)
International classification of retinoblastoma	
Group D n(%)	1(2)
Group E n(%)	64(98)

Leucokoria was the most common complaint in 64(97%) patients. Dilated pupil and large tumor size of more than 50% of vitreous volume was the commonest clinical finding (73%) (Table 1).

Table 2: Histopathological features identified on enucleated eyes

Histology feature	**Number**
Anterior chamber seeds n(%)	15(23)
Iris invasion n(%)	4(6)
Anterior chamber Angle invasion n(%)	3(5)
Ciliary body invasion n(%)	14(21)
Optic nerve involvement n(%)	37(49)
Prelaminar n(%)	11(17)
Laminar n(%)	4(6)
Retrolaminar n(%)	9(14)
Cut end n(%)	5(8)
Choroidal invasion n(%)	43(65)
Focal n(%)	8(12)
Massive n(%)	35(53)
Intrasclera invasion n(%)	9(14)
Tumor necrosis	
Massive (>90%) n(%)	27 (41)
<90% n(%)	25(38)
Level of tumor differentiation	
Well n(%)	13(19)
Moderate n(%)	29(39)
Poor n(%)	27(41)

The proportion of the eyes with histopathological high risk feature was 64% and commonest was massive choroidal invasion by 53% (table 2)

Table 4: Association between clinical features in examination under anaesthesia and histopathological high risk features.

Clinical features			**HHRF n=42 (%)**	**NO HHRF n=24 (%)**	**Total**	**p-value**
Horizontal Cornea Diameter (mm)	Less than 10		0 (0)	1 (100)	1	**0.023**
	10-12		26 (56)	20 (44)	46	
	12 or more		16 (84)	3 (16)	19	
	Mean		**11.9SD1.05**	**11.6SD0.64**		**0.190****
Intraocular Pressure (mmHg)	Less than 22		8 (38)	13 (62)	21	**0.004**
	22-34		12 (63)	7 (37)	19	
	34 or more		22 (85)	4 (15)	26	
	Median (IQR)		**34.0(22-42)**	**16(7-30)**		**0.006***
Anterior segment findings	Dilated pupil	Yes	39 (81)	9 (19)	48	**0.000**
		No	3 (17)	15 (83)	18	
	Shallow AC	Yes	16 (47)	18 (53)	34	**0.004**
		No	26 (81)	6 (19)	32	
	Iris heterochromia	Yes	26 (81)	6 (19)	32	**0.006**
		No	15 (48)	16 (52)	31	
	Iris neovascularization	Yes	13 (87)	2 (13)	15	**0.045**
		No	28 (58)	20 (42)	48	
	Iris ectropion	Yes	24 (77)	7 (23)	31	**0.054**
		No	17 (53)	15 (47)	32	
	Cataract	Yes	14 (67)	7 (33)	21	0.727
		No	28 (62)	17 (38)	45	
	Synechia	Yes	5 (71)	2 (29)	7	1.00
		No	36 (63)	21 (37)	57	
	Hyphema	Yes	3 (50)	3 (50)	6	0.660
		No	39 (65)	21 (35)	60	
	Hypopion	Yes	3 (100)	0 (0)	3	0.295
		No	39 (62)	24 (38)	63	
Fundus Findings	Vitreous seeds	Focal	3 (50)	3 (50)	6	0.189
		Massive	15 (83)	3 (17)	18	
	Vitreous haemorrhage	Yes	2 (100)	0 (0)	2	0.789
		No	31 (63)	18 (37)	49	
	Tumor size	≤50%	0 (0)	3 (100)	3	0.062
		≥50%	33 (68)	15 (31)	48	
	Tumor pattern	Endophytic	23 (61)	15 (39)	38	0.326
		Exophytic	12 (60)	8 (40)	20	
		Mixed	7 (88)	1 (12)	8	

*Chi squire and fishers test *Mann Whitney u test **T test. Abbreviations: HHRF histopathological high risk features, AC anterior chamber.*

Discussion

We examined the histopathology of 66 eyes primarily enucleated for retinoblastoma and associated clinical with high-risk histopathological features. All eyes examined had advanced intraocular disease at diagnosis and were classified as either International classification of Group D or E[17].

The Median intraocular pressure was higher in patients with histopathological high risk feature as compared with those who did not have any risk. On the other hand mean horizontal cornea diameter was slightly higher on eyes with histopathological high risk feature but the difference was not statistically significant when compared to eyes without risk. Additional analysis showed intraocular pressure and horizontal cornea diameter were associated with histopathological high risk feature. Study done by Wilson et al in USA, IOP and HCD showed trend in causing histopathological high risk feature but it was not statistical significance[19]. This difference could be explained by higher number of patients with histopathological high risk feature in our study. Which shows in our study population, majority had advanced disease. Similarly a study done by Kim in Los Angles had the same findings, intraocular pressure was higher in patients with histopathological high risk feature[20].

Shallow anterior chamber, dilated pupil, iris heterochromia, iris neovascularisation showed strong association with histopathological high risk feature. All these features relate with either glaucoma or higher intraocular pressure. Cataract, Hyphema and hypopion showed no association with histopathological high risk feature. In previous studies cataract, hyphema, hypopion correlated with histopathological high risk feature[21–23]. This could be explained with small number of participants with such clinical characteristics in our study.

None of the fundus findings which included vitreous seedling, haemorrhage, tumor size, tumor pattern showed any association with histopathological high risk feature but majority of the eyes with massive vitreous seedling, vitreous haemorrhage, larger tumor size and mixed type of tumor pattern were high in the histopathological high risk feature. Contrary to the studies done by Ngan et al in Vietnam and Khan in Pakistan which showed correlation of vitreous seedling and larger tumor size with histopathological high risk feature[21,24]. This could be explained by small number of sample size which could not be proven by statistical analysis.

We acknowledge our study has some limitations that the number of sample size was too small to do further analysis.

In conclusion the horizontal corneal diameter, intraocular pressure of more than 34mmHg, shallow anterior chamber, dilated pupil, iris heterochromia and neovascularisation are the clinical findings that associated with histopathological high risk feature. When these features are seen a clinician should be alert of the presence of histopathological high risk feature.

Acknowledgement

I sincerely acknowledge Muhimbili University of Health and Allied Sciences and Muhimbili National Hospital staff for their assistance to make this research possible.

Ministry of health, community development, gender, elderly and children in Tanzania for supporting the study.

Reference

1. Islam F, Zafar SN, Siddiqui SN et al. Clinical course of retinoblastoma. J Coll Physicians Surg Pakistan. 2013;23(8):566–9.
2. Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. Br Med Bull. 1996;52(4):682–703.
3. Killenga S, Msuya S, Philemon R et al. Histopathological Pattern of Pediatric Malignant Tumors and Survival Rate at Kilimanjaro Christian Medical Centre , Tanzania from 2013 to 2015. J cancer tumor Int. 2016;4(2):1–8.
4. Ghassemi F, Khodabande A. Risk definition and management strategies in retinoblastoma: Current perspectives. Clin Ophthalmol. 2015;9:985–94.
5. Nyaywa M, Chipalo-Mutati G, Chintu C. Modes of presentation, management and outcome of retinoblastoma treatment at University Teaching Hospital. Medicla J Zambia. 2016;43(4):216–23.
6. Shifa, Jemal Zeberga Gezmu AM. Presenting signs of retinoblastoma at a tertiary level teaching hospital in Ethiopia. Pan Afr Med J. 2017;8688:1–5.
7. Kim JW, Kathpalia V, Dunkel IJ et al. Orbital recurrence of retinoblastoma following enucleation. Br J Ophthalmol. 2009;93(4):463–7.
8. Chen X, Wang J, Cao Z et al. Invasiveness and metastasis of retinoblastoma in an orthotopic zebrafish tumor model. sciantific reports. 2015;5:1–11.
9. Balmer A, Zografos L, Munier F. Diagnosis and current management of retinoblastoma. Oncogene. 2006;25:5341–9.
10. Fabian ID, Stacey AW, Johnson KC et al. Primary Enucleation for Group D Retinoblastoma in the Era of Systemic and Targeted Chemotherapy: The Price of Retaining an Eye. Br J Ophthalmol. 2018;44(0):1–18.
11. Cuenca A, Giron F, Castro D et al. Microscopic Scleral Invasion in Retinoblastoma. Arch Ophthalmol. 2009;127(8):1006–10.
12. Chantanda GL, Dunkel IJ, DeDavila MTG et al. Retinoblastoma patients with high risk ocular pathological features: who needs adjuvant therapy ? Br J Ophthalmol. 2004;88(8):1069–73.
13. Honavar, Santosh G, Singh, Arun D, Shields CL et al. Postenucleation Adjuvant Therapy in High-Risk Retinoblastoma. Arch Ophthalmol. 2002;120:923–31.
14. Lu JE, Francis JH, Dunkel IJ et al. Metastases and Death Rates After Primary Enucleation of Unilateral Retinoblastoma in the United States 2007-2017. Br J Ophthalmol. 2019;103(9):1272–7.
15. Yahaya JJ, Rugwizangoga B, Mremi A et al. Clinicopathological Findings of Retinoblastoma: A 10-Year Experience from a Tertiary Hospital in Kampala, Uganda. J Ophthalmol. 2019;2019:1–8.

16. Zhao J, Dimaras H, Massey C, Al E. Pre-enucleation chemotherapy for eyes severely affected by retinoblastoma masks risk of tumor extension and increases death from metastasis. J Clin Oncol. 2011;29(7):845–51.

17. Fabian ID, Reddy A, Sagoo MS. Classification and staging of retinoblastoma. Community Eye Heal J. 2018;31(101):11–3.

18. Sastre X, Chantada GL, Doz F et al. Proceedings of the Consensus Meetings from the International Retinoblastoma Staging Working Group on the pathology guidelines for the examination of enucleated eyes and evaluation of prognostic risk factors in retinoblastoma. Arch Pathol Lab Med. 2009;133(8):1199–202.

19. Wilson MW, Qaddoumi I, Billups C et al. A clinicopathological correlation of 67 eyes primarily enucleated for advanced intraocular retinoblastoma. Br J Ophthalmol. 2010;1–7.

20. Kim ME, Shah S, Zolfaghari E et al. An Intraocular Pressure Predictive of High-risk Histopathologic Features in Group E Retinoblastoma Eyes. int Ophthalmol Clin. 2019;59(2):77–86.

21. Ngan HN, Trong VP, Anh TH et al. Clinical and histopathological correlation: A study on 334 eyes with retinoblastoma from Vietnam. Asian J Ophthalmol. 2018;16(1):23–34.

22. Kashyap S, Meel R, Pushker N et al. Clinical Predictors of High Risk Histopathology in Retinoblastoma. Pediatr Blood Cancer. 2012;58:356–61.

23. Alsharif, H Helmi H, Maktabi A. Histopathological characteristics and classification for prognostic indicator. retinoblastoma-Past, Present and Future. London: IntechOpen. 2019;89–99.

24. Khan AA, Bukhari MH, Mehboob R. Association of retinoblastoma with clinical and histopathological risk factors. Nat Sci. 2013;5(4):437–44.