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Evaluation of high risk histopathology features in primary and secondary enucleated retinoblastoma-study of 136 cases in tertiary eye hospital

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ABSTRACT

Background: Retinoblastoma is a childhood malignant intraocular tumor, necessitates a comprehensive treatment approach. Chemotherapy plays a crucial role in managing retinoblastoma. This study aims to evaluate and analyze high-risk histopathological features (HRF) in retinoblastoma cases initially treated with enucleation and those undergoing secondary enucleation after chemotherapy in a tertiary centre in western India.

Materials and Methods: This retrospective study was carried out in the pathology department, encompassing a total of 136 cases with enucleated eyes, spanning the period from Jan 2017 to Mar 2023. In the present study, all slides were retrieved and examined to gather information on demographics, laterality, choroid invasion, optic nerve invasion, anterior chamber invasion, tumor discrimination, chemotherapy effects, and tumor regression.

Result: In this study, the predominant presenting complaint was leukocoria (90%), with a slight female preponderance (53%), in comparison to males (47%). Unilateral cases accounted for 96%, while bilateral presentations were observed in 4% of cases. The mean age was 38 months, with 43% of eyes exhibiting significant choroid invasion and 27% showing invasion beyond the post-laminar optic nerve or resection margin. 76 patients (56%) underwent primary enucleation and 60 (44%) had secondary enucleation after chemotherapy. Out of the 60 patients with secondary enucleation, only 21 patients (35%) had HRF.

Conclusion: We found late age of presentation of retinoblastoma in developing country like India. Higher incidence of HRFs in primary enucleated eyes than secondary enucleated eyes. Higher number of cases shows complete regression of tumor after chemotherapy.

1. Introduction

Retinoblastoma (RB) stands out as the common primary intraocular malignancy of childhood.[1] It manifests in two distinct clinical presentations: a heritable form (25% of all cases) characterized by bilateral or multifocal involvement, marked by the presence of a germline mutation in the Rb1 tumor suppressor gene. The remaining 75% of cases exhibit a nonhereditary, unilateral, or unifocal form, with the mean age at diagnosis being 13 months.

The investigations reported prevalence of retinoblastoma is about 1 in 16,000-18,000 live births, contributing to 7,000-8,000 new cases annually on a global scale and representing 3% of all pediatric cancers.[2,3] Developed countries witness the diagnosis of 250-300 new cases each year.[4] In India, a minimum of 1,000 children is affected

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by retinoblastoma annually.[5] Despite progress in diagnosis and management, retinoblastoma remains a significant challenge, particularly in developing countries like India. This challenge stems from delayed diagnosis, advanced presentation, and incomplete treatment, often attributed to a lack of education.

According to, International Classification of Retinoblastoma (ICRB), anticipate globe outcome after chemoreduction.[6–9] Tumors are categorized from A to E based on their size and the existence of tumor seeds in the subretinal space and vitreous cavity. Employing a comprehensive multidisciplinary therapeutic approach, including chemotherapy, thermal therapy, cryotherapy, and radiotherapy, facilitates the preservation of the eye in cases falling within group A to group C. However, for group E tumors (and group D in unilateral cases), enucleation continues to be the preferred treatment method.[6–9]

High-risk histopathology features (HRF) in enucleated eyes are related with a higher incidence of local recurrence, distant metastasis, and death. Consequently, supplementary interventions such as adjuvant chemotherapy and external beam radiation are deemed essential.

HRF is defined as tumor penetration into the anterior chamber, iris, ciliary body, significant choroid invasion (greater than 3 mm), infiltration into the sclera, post-laminar invasion of the optic nerve, a combination of focal choroid invasion and optic nerve invasion, and extra-ocular extension of the tumor into the orbit.[10–16] There are reports of higher incidences of HRF in developing country in eye enucleated for retinoblastoma as compared with studies reported in the developed country.[17–20]

The purpose of this research was to discuss and evaluate the epidemiology, demographic profile, clinical characteristics, and high risk histopathology features in retinoblastoma patients presenting to our institute, one of the largest regional tertiary eye centres in west India.

2. Materials and Methods

This retrospective study was conducted at M&J Western Regional Institute of Ophthalmology, a prominent tertiary eye care institution in western India affiliated with B.J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India. Spanning from January 2017 to March 2023, the study focused on individuals clinically diagnosed with intraocular retinoblastoma, confirmed through histopathological examination following both primary and secondary enucleation procedures. The Institutional Review Board approved the study protocol.

In this investigation, we included patients' eyes detected with intraocular retinoblastoma based on pathological criteria. The initial treatment involved enucleation, with or without pre-operative chemotherapy. The exclusion criterion for the study was the presence of intraocular diseases other than retinoblastoma. A retrospective analysis was performed on a total of 136 enucleated or exenterated eye specimens.

Patient medical records and pathology slides were selected for retrieval and review. The collected data encompassed details such as the patient's age, gender, laterality, clinical presentation, radiology findings, pre-operative chemotherapy (if administered), and the initial ICRB group.

Hematoxylin and eosin (H&E) stained slides were created from formalin-fixed, paraffin-embedded slices of the complete eyeball. Examination included two standard pupil–optic nerve sections and one transverse section of the optic nerve at the resected margin. Histopathology findings of high risk features(HRF) includes, presence of massive choroid invasion (more than 3mm), level of optic nerve invasion (prelaminar, intralaminar, retrolaminar), association of the resected margin, anterior chamber, iris, ciliary body invasion, scleral and extra-scleral extension, tumor differentiation, histological grade, pTNM(AJCC-8^{th} edition) stage.[21] Those eye where upfront chemotherapy were taken, evaluated for histopathology features like regression of tumor, necrosis, calcifications, gliosis/retinocytoma like area & HRF features if any were also reviewed.

Endophytic growth is defined as expansion from the inner retinal surface into the vitreous cavity. Exophytic tumors, on the other hand, grow primarily from the retina's outer surface and spread into the subretinal area and choroid. The aforementioned two growth patterns are combined to form the mixed type.

The parameters were taken into account while calculating the histologic grade represented as follows:

G1 tumors have retinocytoma-predominant regions, with fleurettes or neuronal differentiation accounting for more than half of the tumor;

G2 tumors have a significant presence of rosettes (Flexner-Wintersteiner or Homer Wright rosettes account for more than half of the tumor);

G3 tumors have occasional rosettes (Flexner-Wintersteiner or Homer Wright rosettes account for less than half of the tumor); and

G4 (tumor with poorly differentiated cells lacking rosettes and/or significant regions of anaplasia [greater than half of tumor]).

3. Result

The present retrospective study was performed at M&J Western Regional Institute of Ophthalmology, a prominent tertiary eye care institution in western India affiliated with B.J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India. The duration of the present study from January 2017 and March 2023, in which approximately, 136 eyeball specimens of patients received as for primary & secondary treatment for intraocular retinoblastoma. Out

of 136 specimens, one was exenteration, rest eyes were of enucleation. Table 1 shows all the demographic and other relevant details of all the cases.(Figure 1)

There were 64 males (47%) and 72 females (53%). Furthermore, investigations reported that, there were 131 (96%) unilateral and 5 (4%) bilateral cases. The mean age of study participants at the time of enucleation was 36 months (mean: 38 months, range: 3–144 months) for the whole group. (Table 1)

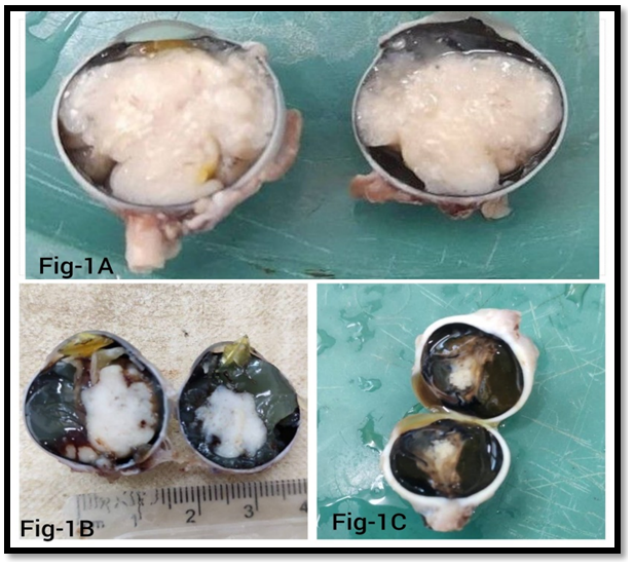

Figure 1: A): Gross photograph of retinoblastoma showing the white mass filling almost entire globe. **B):** Gross photograph of retinoblastoma showing the white mass filling almost half of the globe & multiple small mass in viterous also seen. **C)**: Gross photograph of retinoblastoma showing the residual white mass after pre operative chemotherapy.

Out of 136 cases of Retinoblastoma, 60 patients (44%) had taken neo-adjuvant chemotherapy and 76 patients (56%) had not taken neo-adjuvant chemotherapy. Table 2 shows, HRF categorized in primary and secondary enucleation of retinoblastoma cases.(Figure 2). Table-3 shows, HRF according to ICRB group classification of retinoblastoma. Table 4 shows, histopathology features in Post chemotherapy eye ball. (Figure 3)

4. Discussion

RB stands as the most prevalent intraocular cancer, with over 40% of cases identified in Asia-Pacific nations.[22]

As per existing literature, retinoblastoma typically manifests with leukocoria (30–98%) and strabismus (6–24%) as the most frequently reported presenting complaints.[23] While study from Africa & Asian country have shown eyes with fungating mass(29-46%) as advanced disease at presentation or proptosis (55–85%).[24] In our study of 136 cases, Leukocoria was the predominant

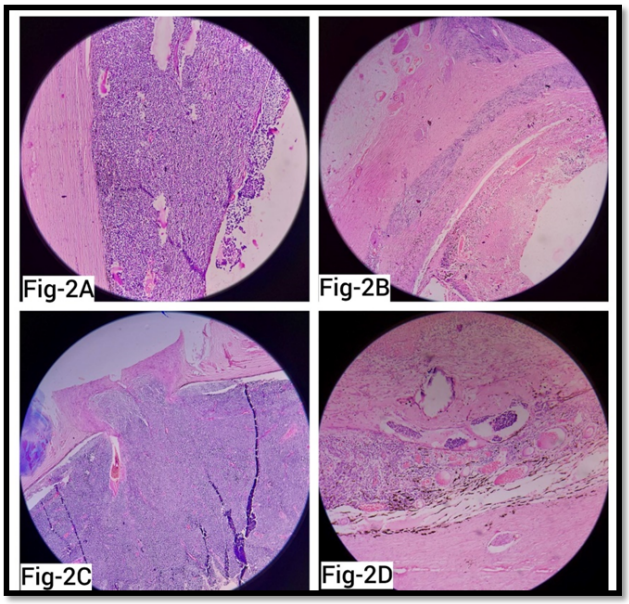

Figure 2: A): Hematoxylin & eosin stain (H&E, 40X) shows massive choroidal invasion by retinoblastoma tumor cells. **B)**: Hematoxylin & eosin stain (H&E, 40X) shows tumor cells invading sclera & extrascleral tissue. **C)**: Hematoxylin & eosin stain (H&E, 40X) shows retrolaminar optic nerve invasion by retinoblastoma tumor cells. **D)**: Hematoxylin & eosin stain (H&E, 40X) shows massive choroidal invasion by retinoblastoma tumor cells, calcification & vitreous seeding.

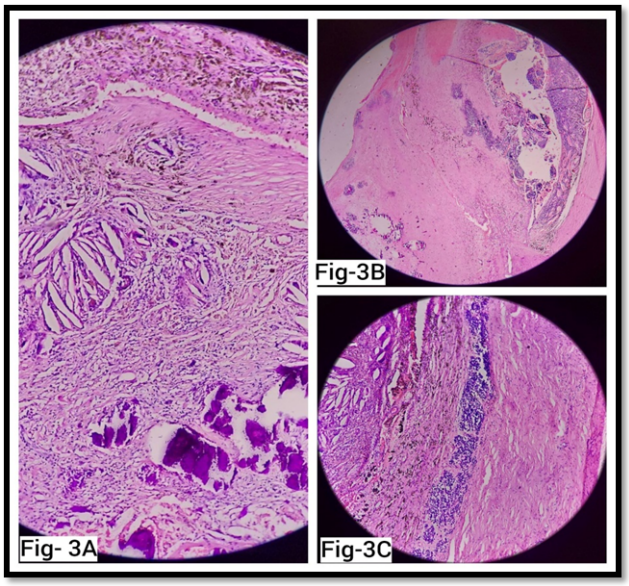

Figure 3: A): Hematoxylin & eosin stain (H&E, 40X), Post chemotherapy enucleated eye ball shows calcification, cholesterol cleft & chronic inflammation. **B)**: Hematoxylin & eosin stain (H&E, 40X), Post chemotherapy enucleated eye ball shows residual tumor cells & areas of hyalinization. **C)**: Hematoxylin & eosin stain (H&E, 40X), Post chemotherapy enucleated eye ball shows residual tumor cells invading choroid & treatment induced changes.

Table 1: Demographics and other features of 136 eye specimen enucleated for retinoblastoma

		Total number of specimens (136)	Pre-operative chemotherapy taken (60cases) 44%	Pre-operative chemotherapy not taken (76 cases) 56%
Enucleation		135	60	75
Exenteration		1	0	1
Gender	Male	64(47%)	31(52%)	33(43%)
	Female	72(53%)	29(48%)	43(57%)
Age in months (Mean)		38	34	40
Age in months (Median)		36 (3-144 months)	36	36
Laterality	Unilateral	131(96%)	56(93%)	75(99%)
	Bilateral	5(4%)	4(7%)	1(1%)
Clinical features	Leucocoria	123(90%)	55(91%)	68(89%)
	Proptosis or strabismus	1(1%)	1(2%)	0(0%)
	Diminished vision	5(4%)	1(2%)	4(5%)
	Cataract	4(3%)	2(3%)	2(3%)
	Pthisis bulbi	3(2%)	1(2%)	2(3%)
ICRB group	ICRB group D	9(7%)	3(5%)	6(8%)
	ICRB group E	72 (53%)	37(62%)	35(46%)

Table 2: Histopathological findings in 136 eye specimen enucleated for retinoblastoma

Histopathology		**Eyes, no (136) (%)**	**Chemotherapy Taken (60 cases)**	**Chemotherapy Not Taken (76 cases)**
Tumor growth pattern				
Endophytic		85 (62%)	43(72%)	42(55%)
Exophytic		50 (37%)	17(28%)	33(44%)
Combined		1 (1%)	0(0%)	1(1%)
Tumor differentiation				
Poorly differentiated		82 (60%)	45(75%)	37(49%)
Well/moderately Differentiated		54 (40%)	15(25%)	39(51%)
Choroid invasion				
None		47 (35%)	31(52%)	16(21%)
Focal		30 (22%)	13(22%)	17(22%)
Massive		59 (43%)	16(26%)	43(57%)
Optic Nerve invasion				
None		73(54%)	47(78%)	26(34%)
Pre-laminar		26(19%)	5(8%)	21(28%)
Intra & retro-laminar optic-nerve		19(14%)	4(7%)	15(20%)
Resection margin		18(13%)	4(7%)	14(18%)
Anterior chamber &ciliary body involvement		17(12%)	8(13%)	9(12%)
Neovascularisation of the iris		2 (1%)	0(0%)	2(3%)
Scleral invasion		12(9%)	4(7%)	8(10%)
Extra-ocular extension		5(4%)	2(3%)	3(4%)
	G1	26(19%)	17(28%)	9(12%)
	G2	23(17%)	11(19%)	12(15%)
Histological grade	**G3**	55(40%)	17(28%)	38(50%)
	G4	28(21%)	13(22%)	15(20%)
	Gx	4(3%)	2(3%)	2(3%)
	pT1	34(25%)	22(37%)	12(16%)
	pT2	22(16%)	9(15%)	13(17%)
AJCC pTNM staging	**pT3**	52(38%)	15(25%)	37(49%)
	pT4	16(12%)	5(8%)	11(14%)
	Not available	12(9%)	9(15%)	3(4%)

Table 3: Correlation between ICRB group and HRF

		ICRB group D (9)	ICRB group E (72)
Tumor differentiation	Well/Moderate	3(33%)	30(42%)
	Poor	6(67%)	42(58%)
Optic Nerve invasion	Pre- laminar	2(22%)	10(14%)
	Post-laminar	0(0%)	13(18%)
Choroid invasion	Focal	1(11%)	11(15%)
	Massive	1(11%)	34(47%)
Anterior chamber & ciliary body involvement		2(22%)	4(6%)
Scleral invasion		0(0%)	9(13%)
Extraocular invasion		0(0%)	4(6%)
AJCC pTNM staging	pT1	5(56%)	19(26%)
	pT2	3(33%)	9(13%)
	pT3	1(11%)	32(44%)
	pT4	0(0%)	8(11%)
	Not available	0(0%)	4(6%)

Table 4: Evaluation of histopathology features in Post chemotherapy eye ball

Histopathology findings in post chemotherapy eye ball	Post chemotherapy eye ball (60 cases)
Tumor status	
Complete regression Seen	33(55%)
Complete regression not seen	27(45%)
Retinocytoma like area	
Present	22(37%)
Absent	38(63%)
Calcification & necrosis	
Extensive	1(2%)
Moderate	2(3%)
Minimal	48(80%)
None	9(15%)

presenting complaint in 90% of cases, followed by proptosis or strabismus (1%) and cataract (3%). When comparing our study to others conducted studies in India, leukocoria emerged as the most common presenting complaint, aligning with findings from similar studies.[20,23] Our investigation revealed a slight predominance of females (53%) as opposed to males (47%). While large study done by Kaliki S et al, showed slight male preponderance (56%) compared to female (44%).[25]

According to literature, unilateral cases (61%) were more than bilateral cases (39%).[26] This study observed a unilateral tumor, presentation in 96% of cases and a bilateral occurrence in 4% of cases. Western literature suggests that, on average, retinoblastoma is typically diagnosed at around 18 months of age.[1] Similarly, another study done on retinoblastoma conducted by Kaliki S et al, observed that, the average age of total presentation cases, bilateral cases and unilateral cases were reported with 29 months, 21 months and 34 months respectively. This aligns with the present study, where the mean age was 38 months, unilateral cases presented at 35 months, and bilateral cases at 31 months.[25] The findings propose delayed referral and a lack of awareness about the disease in India when compared to Western countries..

In developed nations, the tumor primarily manifests as intraocular, and the occurrence of extraocular tumor extension during presentation is exceptionally uncommon. In one of the largest studies on retinoblastoma in India, 91% of tumors were intraocular, with only 9% demonstrating extraocular tumor extension. In the current study, 96% of tumors were intraocular, and 4% exhibited extraocular extension, alinig with the findings of the study conducted by Kaliki S. et al.[25]

In this study, the histopathology of 136 eyes subjected to enucleation for retinoblastoma was scrutinized. Among the eyes in our study, 101 exhibited some level of tumor infiltration into the choroid, optic nerve, sclera, or anterior chamber. In a study conducted in a developing country, a increased prevalence of primitive tumors (up to 80%) was observed, likely attributable to delayed age of diagnosis and treatment.[10,17,18] Additional findings of the present study shows, 60% tumors were diagnosed with poorly differentiated and 40% tumors were well/moderately differentiated. These results were concordance with similar study done by Kashyap S, and colleagues. In their study researches reported that, 73% & 26% tumour cases were

poorly differentiated & well differentiated respectively.[10] In our study, we observed a higher incidence of HRF in conjunction with poorly differentiated tumors.

In this study, substantial choroid invasion was observed in 43% of eyes, and 27% exhibited invasion beyond the post-laminar optic nerve or resection margin. These results are consistent with findings reported in the developing world and surpass those documented in the developed world.[10,11,20,27,28] In cases where secondary enucleation followed chemotherapy, 26% of eyes displayed massive choroidal invasion(MCI), while 7% showed invasion beyond the post-laminar optic nerve.

In a recent study, it was found that, MCI and post-laminar invasion, including the cut end of the optic nerve, were identified as independent and influential predictors of metastasis and mortality in retinoblastoma.[29]

The ICRB classification for intraocular retinoblastoma serves as a valuable tool for predicting tumor response to chemotherapy and the likelihood of high-risk histopathology features (HRF).[11] Wilson et al. analyzed 67 eyes and discovered that, 50% of enucleated group E eyes exhibited HRF, in contrast to only 15% of group D eyes (p=0.005).[11] Yousef Y et al.'s study demonstrated that, 17% and 4% of eyes in group D exhibited massive choroid invasion and post-laminar optic nerve invasion, respectively, while 28% and 33% of eyes in group E showed the same features.[26] In the present study, it was observed that, 11% of eyes in group D exhibited massive choroid invasion, and none of the patients in this group had post-laminar optic nerve invasion. Additionally, 47% and 18% of eyes in group E demonstrated massive choroid invasion and post-laminar optic nerve invasion, respectively.

In present study, 76 patients (56%) underwent primary enucleation and 60 (44%) had secondary enucleation after chemotherapy. Out of the 60 patients of secondary enucleation, only 21 patients (35%) had high-risk pathology. Study done by Luna-Fineman S et al. showed 59 patients who had secondary enucleation after chemotherapy, only two (3.5%) had high-risk pathology.[30] This suggests after pre-operative chemotherapy there was reduced chances to develop high- risk pathology. In a study done by, Feng ZX et al, found that, adjuvant chemotherapy significantly decreased the risk of tumor relapse, improve survival and death for children with pathological MCI.[31]

Treatment modalities for retinoblastoma encompass transpupillary thermotherapy, argon laser photocoagulation, and cryotherapy for smaller tumors. Solid tumors may be addressed through systemic chemotherapy, intra-arterial chemotherapy, and plaque radiotherapy. Vitreous seeds may be managed with intravitreal chemotherapy, periocular chemotherapy, or external beam radiotherapy. Advanced intraocular disease may necessitate enucleation, while orbital extension of retinoblastoma may be approached through multimodal treatment.[13,16,25] This study revealed that, primary enucleation (56%) was the most common primary treatment modality, followed by upfront chemotherapy with subsequent secondary enucleation (44%). In developed countries, survival rates often exceed 95%, whereas in developing countries, due to advanced disease at presentation, cure rates were observed to be up to 50%.

Chemotherapy plays a crucial role in reducing tumor size, enabling effective local treatments such as cryotherapy and laser therapy. This not only aids in controlling the tumor but also mitigates the risk of metastasis after enucleation, especially in high-risk patients. Various administration routes, including intravenous, intravitreal, intra-arterial, and subconjunctival, are employed for chemotherapy.[32] Standard systemic chemotherapy agents, such as Vincristine, Etoposide, and Carboplatin, are preferred due to their effective intraocular penetration.

Evaluating the tumor status post-chemotherapy is crucial for assessing viable tumor extent and the presence of HRFs. In our study, we examined chemotherapy response and identified HRFs to inform future treatment strategies for retinoblastoma patients. A recent study done by Yaqoob N et al, rosette formation occurred in 33.3% of cases, extensive necrosis in 52.3%, extensive calcification in 33.3%, MCI in 19%, and optic nerve invasion in 52.3%.[33] In our study, secondary enucleation cases revealed tumor regression (55%), extensive necrosis and calcification (2%), retinocytoma-like areas (37%), massive choroid invasion (26%), and optic nerve invasion (22%). Additional histopathological findings included gliosis, foamy histiocytes, hemosiderin-laden macrophages, fibrosis, foreign body-type giant cells, and hemorrhage.

5. Conclusion

This retrospective analysis of a large number of eyes treated with primary and secondary enucleation in India reveals distinctive features compared to the developed world, including delayed age of presentation and a higher incidence of HRFs. Poorly differentiated retinoblastomas, presenting later, are associated with significantly more HRFs than well/moderately differentiated tumors. Secondary enucleation post-chemotherapy indicates variable tumor regression and reduced HRF. Pathologic findings underscore the predictive value of the ICRB staging system for HRF probability after enucleation. Correlation with long-term follow-up may enhance our understanding of retinoblastoma's biological behavior and progression.

6. Source of Funding

None.

7. Conflict of Interest

None.

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Author biography

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