Original Article

Pattern and Ocular Trend of Retinoblastoma and Treatment Option in Our Hospital

Asad Aslam Khan,[1] **Riffat Mehboob,**[2] **Mulazim Hussain Bukhari**[3]

Abstract

Objective: The study was conducted to see the pattern and ocular trend of Retinoblastoma and treatment option in our hospital.

Study Design: Analytical Descriptive.

Study Population: Patients with Retinoblastoma who visited the Institute of Ophthalmology from 2006 to 2011.

Study Settings: Patients who came to Ophthalmology Department, Mayo Hospital, King Edward Medical University, Lahore. The study plan was approved by ethical committee of King Edward Medical University.

Material and Methods: This was a retrospective descriptive analytical study. The records of the Institute of Ophthalmology, King Edward Medical University / Mayo hospital, Lahore: Pakistan January 2006- Dec 2011 was analyzed. Five years biopsies (June 2006 to June 2012) of the retinoblastoma, from the Pathology department, ware retrieved to see optic nerve involvement in all the retrieved specimens.

Results: There were 909 cases of Primary orbital lesions and out of these 262/909 (29%) lesions were of primary orbital neoplasms. There were 65/262 (36%) cases of malignant neoplasms (62/65:95% case of Retinoblastoma and 3/65:5% cases of melanoma), the remaining 197/262 (64%) cases were benign tumors. There were 52 cases of Retinoblastoma with complete record and their blocks and data were retrieved from the previous record (2007 – 2011) of Ophthalmology and Pathology Department of Mayo Hospital/ King Edward Medical University, Lahore. There were 15 cases of bilateral retinoblastoma and 37 cases with unilateral neoplasms. The age range of bilateral tumors was 2 – 6 years while the range in unilateral tumor was 1 – 10 years. There 32 female and 20 males suffering from Retinoblastoma and male to female ratio was 1:1.5. Male were 38% and females were 61.5%. On clinical examinations, 28 (53.8%) patients presented with proptosis, 20 (38.5%)cases presented with leucocoria eye was the second most common presenting sign, accounting for about 38.5% of cases), 3 cases (5.8%) with strabismus. Retinoblastoma caused secondary changes in the eye, including glaucoma and 1 case (1.9%) presented with sec glaucoma. The clinical findings in all the stages of retinoblastoma were numerous and varied. Surgical removal of the tumor was used as a standard management of very unfavorable retinoblastoma cases. Enucleation was performed when there was no chance of preserving useful vision in an eye. It was done in 21/52 (40.4%) cases. Exenteration was also performed when extension of the tumor into the surrounding areas was considerable. It was performed in 31/52. Cryotherapy was used in bila-

Khan A.A.[1]
Prof. of Ophthalmology, KEMU, Lahore

Mehboob R.[2]
Asstt. Professor of Biomedical Sciences, KEMU, Lahore

Bukhari M.H.[3]
Associate Professor of Pathology, KEMU, Lahore

teral involvement in second eye with small tumors located remote from the disc and macula. It was also used for recurrence after radiation therapy. 6/52 (11.5%) cases were treated with cryotherapy, 5 (9.6%) cases on right side and one case (1.9%) on left side.

Conclusion: The most common pattern of retinoblastoma was exophytic while the optic nerve and extra ocular involvement was one of the most prognostic factors for distance affecting the treatment. Patients suffering from optic nerve invasion and extra ocular extension or invasion of surrounding tissue with distance metastasis were referred to Oncology Department.

Introduction

Retinoblastoma , a rapidly developing cancer which arises from the immature neural retinal cells of retina.[1] Irrespective of the gender and race the mean age – adjusted incidence of RB in the USA is 11.8 per million children aged 0 – 4 years.[2]

Retinoblastoma appears as a white mass with many calcifications. The tumor can spread in different directions. Three patterns of tumor growth can be distinguished: endophytic, exophytic and diffuse infiltrating growth. The cellular infiltration in the anterior eye segment (pseudohypopyon) mimics inflammation, making the diagnosis a challenge.[3,4]

Among all pathological risk factors, optic nerve involvement is one of the most predictor for distance metastasis as is generally agreed that the risk for metastasis from retinoblastoma increases with degree retinoblastoma invasion to optic nerve and orbital extension.[5]

The clinical presentation depends upon the pattern of this tumor. Optic nerve invasion by Retinoblastoma beyond the lamina cribrosa is associated with a greater metastatic risk. Large exophytic retinoblastoma with secondary glaucoma is at highest risk for optic nerve invasion.[6]

It has best cure rates of all childhood cancers (95 – 98%) with nine of ten sufferers surviving into adulthood. Research, education of survivors and families and early detection and referral by advanced practice nurses, play key role in the visual outcome and survival.[1,7-12] At early stage the usual presentation is with white pupil (Leucocoria), however patients may present with strabismus, inflamed or painful red eye. Presentation of late cases varies from proptosis to fungating mass with secondaries.[13] The growth pattern is not prognostic for survival but can have implications for management. The important histopathogical progostic factors for RB are the optic nerve invasion, extraocular extension and choroidal invasion. Ten percent mortality has been reported with superficial invasion of the nerve head, 29 percent with involvement of the lamina, 42 percent with extension posterior to the lamina, and 78 percent with tumor cells to the surgical resection line.[14,15]

Successful treatment of retinoblastoma depends upon its early detection and intervention. Different treatment options available to treat a case of retinoblastoma are laser photocoagulation, cryotherapy, radioactive plaques, external beam radiotherapy, chemotherapy and surgery. The surgical options include enucleation or exentration, depending the stage at which the child presents. All the treatment options can be used alone or in combinations.[16]

The study was conducted to see the pattern and ocular trend of Retinoblastoma and treatment option in our hospital.

Material and Methods

This was a retrospective descriptive analytical study. The records of the Institute of Ophthalmology, King Edward Medical University / Mayo hospital, Lahore. Pakistan, for more than 909 cases of orbital lesions January 2006 – December 2011 was analyzed. Five years biopsies of the retinoblastoma, from the Pathology department, were retrieved to see optic nerve involvement in all the retrieved specimens. In addition the evaluation of slides for invasion of the anterior chamber, iris, ciliary body, choroid, sclera and extraocular extension were done.

Study Design: Analytical Descriptive.

Study Population: Patients with Retinoblastoma who visited the Institute of Ophthalmology from 2007 to 2011.

Study Settings: Patients who came to Ophthalmology Department, Mayo Hospital, King Edward Medical University, Lahore. The study plan was approved by ethical committee of King Edward Medical University.

All collected data was entered in SPSS version 17 and data was analyzed by using the same software. The qualitative data was presented in form of frequency table (%) and appropriate graphs. The quantitative data was presented in form of mean ± S.E. We used Standard Deviation to see the variability of the quantitative data.

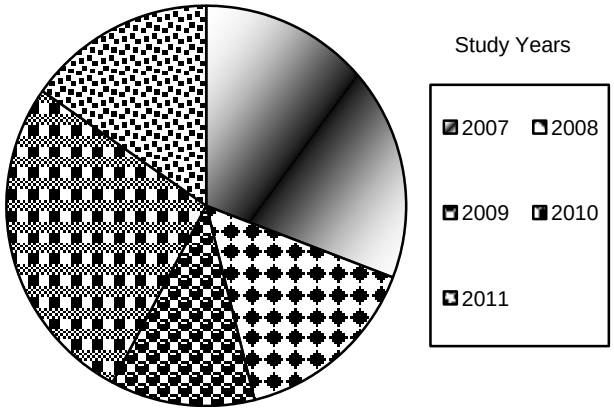
We calculated prevalence for descriptive study design and Chi-square analysis was used to see the association between qualitative data. Fisher exact test was used when expected count was less than 5.

Results

There 909 cases of Primary orbital lesions and out of these 262/909 (29%) lesions were of primary orbital neoplasms. There were 65/262 (36%) cases of malignant neoplasms (62/65:95% case of Retinoblastoma and 3/65:5% cases of melanoma), the remaining 197/262 (64%) cases were benign tumors (Table 1).

Table 1: Data showing total number Retinoblastoma (n = 62) from total Primary Orbital Tumors (262) of the Orbital lesions from 2006-2011 (Total orbital Lesion = 909).

Lesions		Number	Percentage
Orbital Tumors		262	29%
Benign		197	64%
Malignant		65	36%
Malignant Lesions	Retinoblastoma	62	95%
	Melanoma	3%	5%



Graph 1: Showing statistical data of frequency of cases studied in different years

There were 52 cases of Retinoblastoma with complete record and their blocks and data were retrieved from the previous record (2007 – 2011) of Ophthalmology and Pathology Department of Mayo Hospital / King Edward Medical University, Lahore (table 2 and

Graph 1).

The minimum age was 1 year while maximum age was 10 years (Age Range 1 – 10 years) while the mean age was 3.54 ± 1.686 years. The maximum numbers of cases with Retinoblastoma eye were of 3 years 18/52 (34.6%) while one case was found with seven years and 10 years group (Table 3).

Table 2: Number of cases studied in different years (2007–2011).

	Frequency	% age
2007	16	30.8
2008	8	15.4
2009	6	11.5
2010	14	26.9
2011	8	15.4
Total	52	100.0

There were 15 (28.2%) cases of bilateral retinoblastoma and 37 (71.8%) cases with unilateral neoplasms. The age range of bilateral tumors was 2 – 6 years while the range in unilateral tumor was 1 – 10 years. There were 32 (61.5%) female and 20 (38%) males suffering from Retinoblastoma with male to female ratio of 1:1.5 (Table 3).

On radiological examination of patients suffering from retinoblastoma by B – Scan (Ultrasound), there were 33 (63.5%) cases with exophytic presentation while 18 (34.6%) cases showed endophytic morphology. One Patient (1.9%) suffering with recurrence retinoblastoma did not present ant specific morphology (Table 5 – 6 and Graph 2).

On clinical examinations, 28 (53.8%) patients presented with proptosis, 20 (38.5%) cases presented with leucocoria, 3 cases (5.8%) with strabismus and 1 case (1.9%) presented with sec glaucoma. The clinical findings in all the stages of retinoblastoma were numerous and varied (Table 7).

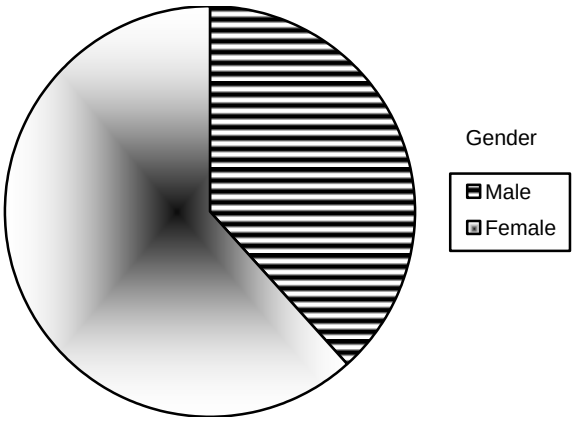
Surgical removal of the tumor was used as a standard management of very unfavorable retinoblastoma cases. Enucleation was performed when there was no chance of preserving useful vision in an eye. It was done in 21/52 (40.4%) cases. We performed enucleation in Patients those who presented with total retinal

Table 3: Descriptive statistical ana-lysis of all cases of Retino-blastoma Eye studied 2007-2011.

Years of Ages Age (Years) (1 – 10 years)	Frequency of Cases in Different Age Groups (Number of cases: 52)	Percent of Cases in Different Years	Mean Age with Std. Deviation	
1 Year	3	5.8	1	1.9
2 Years	11	21.2	1	1.9
3 Years	18	34.6	3.54	1.686
4 Years	5	9.6	10	19.2
5 Years	3	5.8		
6 Years	1	1.9		
7 Years	1	1.9		
10 Years	1	1.9		
Total	52	100.0		

Table 4: Age Distribution of Unilateral and Bilateral Retinoblastoma.

Laterality		Age (Mean Age in Years)		Average
		Male (20)	Female (32)	
Unilateral: 37 (Male: 13) (Female: 24)	Range	1 – 10	1 – 6	1 – 10
	Mean	3.7 ± 2.5	3.37 ± 1.34	3.5 ± 1.80
Bilateral: 15 (Male = 7) (Female = 8)	Range	2 – 4	2 – 6	2 – 6
	Mean	3.42 ± 1.27	3.87 ± 1.55	3.6 ± 1.4



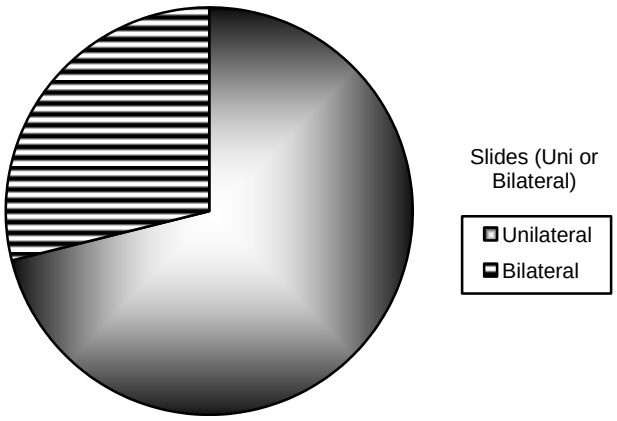
Graph 2: Gender wise distribution of 52 cases of Retinoblastoma Eye.

detachments and/or the posterior segment was full of the tumor, in which case it was clear the patient cannot retain any form of useful vision. Exenteration was also performed when extension of the tumor into the surrounding areas was considerable. It was performed in 31/52 (59.6) (Table 8).

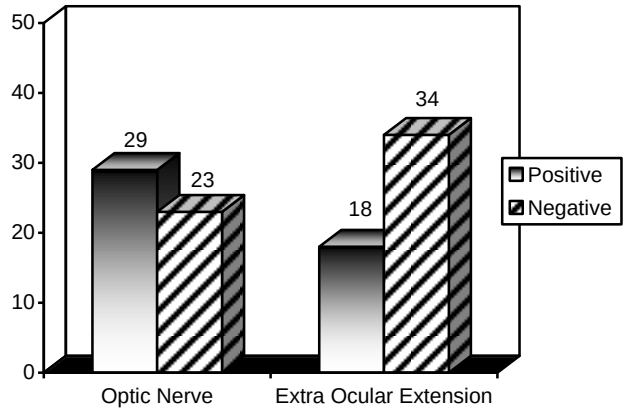
Table 5: Distribution of Retinoblastoma in both eyes (Side Involvement).

Side of Involvement	Frequency	% age
Unilateral	37	71.2
Bilateral	15	28.8
Right Eye	20	38.5
Left Eye	17	32.7
Both Eye	15	28.8
Total	52	100.0

Cryotherapy was used in bilateral involvement in the second eye for tumors located remote from the disc and optic nerve. It was also used for recurrence after radiation therapy. Cryotherapy was performed in 6/52 (11.5%) cases, 5 (9.6%) cases on right side and one case (1.9%) on left side (Table 8). Patients suffering from optic nerve and optic disc involvement or invasion of surrounding tissue with distance metastasis were referred to Oncology Department. Oncology therapy was directed toward complete control of the tumor to save the life of patients from recurrence. Treatment was usually individualized to the specific patient. Thirty four cases were referred to Oncology Department after surgically removal of tumor while 18 were not sent to oncology for further treatment depending upon the stage of tumor (Table 8).



Graph 3: Anatomical distribution of Retinoblastoma eye. (Unilateral and Bilateral).



Graph 4: Optic Nerve involvement with Retinoblastoma and extra ocular extension of Disease.

29/52 (56%) cases after surgery and histological confirmation of optic nerve involvement were referred to oncology department for further management. and 28/52 (54%) cases of retinoblastoma were involving retinal disc, while 18/52 (60%) cases showed extension of tumor is surrounding tissue (Graph 4).

Table 6: B – Scan (Ultrasound) Evaluation of Morphological Presentation of Retinoblastoma eye (Exophytic / Endophytic).

	Frequency	%age
Exophytic	33	63.5
Endophytic	18	34.6
Recurrence	1	1.9
Total	52	100.0

Table 7: Clinical Presentation of the patients suffering from Retinoblastoma eye and Surgical management of patients suffering from Retinoblastoma.

Presentation (n = 52)	Frequency	Percent
Proptosis	28	53.8
Leucocoria	20	38.5
Strabismus	3	5.8
Sec Glaucoma	1	1.9
Enucleation	21	40.4
Exenteration	31	59.6
Cryotherapy of fellow eye	6	11.5

Regarding surgical procedure for patients with optic nerve invasion (ONI), 21/52 patients were performed enucleation (15/21 cases with *ONI* negative and 6/21 patients with *ONI* positive) while 31/52 patients (8/31 cases with *ONI* negative and 23/31 patients with *ONI* positive) were performed exentration. A strong association was seen with patients lesions and surgical procedures (p = 0.001), while the cryotherapy was performed in only 6 patients, there was also no association cryotherapy was seen with *ONI* (p = 0.076). 25/34 cases with *ONI* were referred to oncology Department for chemotherapy and radiotherapy. There was strong association of *ONI* and mode of treatment of the patients in oncology Department (0.000) (Table 5.15).

Regarding surgical procedure for patients with ***EOE***, 3/52 patients were performed enucleation, 18/52 exentration and 6/52 were performed cryotherapy (second eye in Bilateral tumors) as compared to 18/52 cases were performed enucleation, 16/52 exentration showing no ***EOE*** (Table 9).

Discussion

In our study amongst 52 cases, 37 (71.2%) had unilateral Retinoblastoma and 15 (28.28%) patients were with bilateral disease. In Unilateral cases, 20 (38.5%) patients had disease in the right eye and 17 (32.7) cases in left eye. In one study in United State of America, the proportion of bilateral cases (26.7%) versus unilateral cases (71.9%) is stable over the 30 – year period,[2] which is consistent with our study.

In a study in China, the frequency of bilateral retinoblastoma were greater than our study, it was found that bilateral retinoblastoma was present in 150 (32%) of the patients. Bilateral retinoblastoma as compared with unilateral retinoblastoma was diagnosed at a significantly ($p < 0.001$) younger mean age (1.25 years versus 2.5 years).[17] The findings are not consistent with our results both in laterality and incidence of age. The findings are consistent with Arif and Islam (2010), who found 64.51% had unilateral tumours and 35.4% presented with bilateral disease.

Table 8: Surgical Treatment of right and Left eye with second eye treated with Cryotherapy.

Right eye	Frequency	Percent
NA	37	71.2
Enucleation	4	7.7
Exenteration	6	11.5
Cryotherapy of fellow eyes	5	9.6
Total	52	100.0
Left Eye treated with Cryotherapy	Frequency	Percent
NA	37	71.2
Enucleation	2	3.8
Exenteration	12	23.1
Cryotherapy of fellow eye	1	1.9
Total	52	100.0

Table 9: Optic Nerve involvement and treatment option of the Patients.

Optic Nerve	Surgical Treatment			Referred to Oncology Department
	*Enuc	*Exen	*Cryo	
No	15	8	4	10
Yes	6	23	2	24
Total	21	31	6	34
*(p = 0.001), **(0.076), *** (0.004)				
Extra-Orbital Extension				
No	18	16	10	19
Yes	3	15	6	15
Total	21	31	16	34
* (p = 0.017), **(0.068), *** (0.035)				

Key: Enuc: enucleation, Exent: exentration, Cryo: Cryotherapy

On radiological examination of patients suffering from retinoblastoma by B – Scan (Ultrasound), there were 33 (63.5%) cases with exophytic presentation while 18 (34.6%) cases showed endophytic morphology. One Patient (1.9%) suffering with recurrence retinoblastoma did not present any specific morphology. Our findings vary from two other studies, one study[18] showing endophytic retinoblastoma (181 cases;

61%) more often than exophytic (116 cases;39%)(18). and another study in India revealing endophytic growth pattern more common in 118 (51%) of the eyes.

On clinical examinations, 28 (53.8%) patients presented with proptosis of, 20 (38.5%) cases presented with leukocoria eye (white pupillary reflex or cat's eye reflex, 3 cases (5.8%) with strabismus and 1 (1.9%) case presented with painful red eye due to secondaary glaucoma. The clinical findings in all the stages of retinoblastoma were numerous and varied. In a study by Balasubramanya et al (2004), the clinical presentation of their patients were different from our patients, it was found that out of a total of 392 cases of retinoblastoma were reviewed; 72.2% of the patients had leukocoria, 13% had proptosis, 10% had strabismus, 1.5% were asymptomatic (detected on screening), 3.3% had atypical presentations and (0.76%), secondary glaucoma (0.76%).[19] These clinical findings are not consistent from our data. In our patients proptosis (53.8% vs 13) was more common presenatation as compared to leukocoria (38.5% vs 72.2%). Our findings are consistent with Arif and Islam, a Pakistani study, who found that 83/176 (47.3%) presented with proptosis and fungating mass and 41 (30.14%) presented with leukocoria.[9] In another study of 360 eye ***RB*** with median age of two years, glaucoma was the most common clinical finding at presentation apart from leucocoria.[20]

Depending upon the mode of presentation, involvement of optic nerve, secondaries and involvement of fellow eye, different treatment methods adopted were enucleation or exentration. If the involvement of optic nerve was confirmed on histopathology or there were secondaries, the cases were referred to Oncology department for further management. In cases with bilateral involvement, the fellow eye with early stage of the disease were treated with cryotherapy. Enucleation was performed when there was no chance of preserving useful vision in an eye mainly in those who presented with total retinal detachments, proptosis and/or the posterior segment was full of the tumor..Exenteration was done in 31/52 (59.6) cases mainly in those cases where extension of the tumor into the surrounding areas was considerable (Table 5.7 and Graph 5.7). Cryotherapy was performed in 6/52 (11.5%) cases in that eye of a bilateral cases where a small sized tumour was located, remote from the disc and macula. Cryotherapy was also used for recurrence after radiation therapy. This treatment was in 5 (9.6%) cases on right side and one case (1.9%) on left side. Patients suffering from optic nerve and optic disc involvement or invasion of surrounding tissue with distance metastasis were referred to Oncology Department. Oncology therapy was directed toward complete control of the tumor to save the life of patients from recurrence. Treatment was usually individualized to the specific patient. 34 cases were referred to Oncology Department after surgically removal of tumor while 18 were not sent to oncology for further treatment depending upon their stage of tumor. 29/52 (56%) cases after surgery and histological confirmation of optic nerve involvement were referred to oncology department for further management. and 28/52 (54%) cases of retinoblastoma were involving retinal disc, while 18/52 (60%) cases showed extension of tumor is surrounding tissue. Our treatment options were different from Gunalp et al where enucleation was more as compared to exentration.[21] While similar procedures option was found in a study by Abdu et al. They performen exentration in thirty – one patients (74%) and enucleation in 11 patients (26%).[22] Shah has described chemoreduction followed by laser or cryotherapy is the treatment of choice. Sub-tenon carboplatin injection is also an accepted treatment modality for vitreous seeds, along with systemic chemotherapy. Transient periocular edema, optic neuropathy and fibrosis of orbital tissues are the known side effects of sub-teneon carboplatin injection.[23] In our study Cryotherapy was performen in 6/52 (11.5%) cases in that eye of a bilateral cases where a small sized tumour was located , remote from the disc and macula. Cryotherapy was also used for recurrence after radiation therapy. This treatment was in 5 (9.6%) cases on right side and one case (1.9%) on left side. High – risk histopathological features that are an indication for adjuvant chemotherapy include massive uveal invasion and retrolaminar optic nerve invasion. Eye – sparing therapies including brachyradiotherapy and systemic and intra-arterial chemotherapy have reduced the number of eyes with retinoblastoma requiring enucleation in recent years.[24] In our study, patients suffering from optic nerve and with optic disc involvement or extraorbital extension, invasion of surrounding tissue and distance metastasis were referred to Oncology Department for further management by chemotherapy or radiation therapy or both. Our treatment plan was consistent with that of Cuenca et al (2009) who adopted chemotherapy and radiation for tumors with optic nerve, optic disc, surrounding tissues invasions and extra orbital extension.[25]

Regarding Optic nerve Invasion ***(ONI)*** prognostic factors of the lesion, 29/52 (55.7%) patients showed involvement of ***ONI***, 17/52 (32.7%) were from 1 – 3 years

age and 12/52 (23%) were from 4 – 6 years. Therefore age is not related to ***ONI***. Statistically there was no difference in the involvement of *ONI* with the age of patients (p = 0.217). In a study, Fifty – five of 297 ***RB*** (18.5%) had high – risk features with optic nerve invasion in 31 (10.4%).[26] In another study, ***ONI*** was significantly associated with time rather than age; "the median time from diagnosis to enucleation was 11 months. Co-existing retinal detachment and vitreous hemorrhage significantly increased the likelihood of optic nerve invasion (P = 0.014 and P = 0.011, respectively). Prolonged time to enucleation was significantly associated with the likelihood of choroidal (P = 0.010) and ciliary body (P = 0.021) invasion as well as invasion of multiple sites".[27] Our study is also consistent with Shields et al who found no association of age with ***ONI.***[5] Our findings are also consistent with Arif and Islam (2010), who found no correlation with age and laterality as potential factors in metastasis. There was also no statistical difference seen in gender for *ONI* (p = 0.578). In our study, as 11 males and 18 females showed ***ONI.*** Statistically no significance was determined for *ONI* with respect to side of origin as 11 patient with right eye involvement 9 with involvement of the left side and 9 bilateral cases showed optic nerve involvement (Table 5.13). However 9/15, bilateral lesions showed *ONI* as compared to 20/37 unilateral lesions showed *ONI*. Our study is consistent with Shields et al who found no association of sex with ***ONI* and concludes that "**Factors not predictive for invasion included the age, race, and sex of the patient and the tumour laterality, inheritance, size, and growth pattern" which is consistent to our study.[5]

A strong to strongest association was seen with patient's presentation, symptoms and size of the tumors and *ONI*. 21/52 endophytic and 7/52 exophytic lesions showed association of ***ONI.*** It was found that ***ONI*** was found significantly more often in patients who had exophytic retinoblastoma than in those who had endophytic retinoblastoma (p = 0.041). Our findings are consistent with Palazzi et al (1990) and Abouzeid (2012) who found similar association in their patients.[18,20]

Greater the size of tumor, more the ONI and extra ocular extension (p = 0.005). Our study is consistent with an Indian study of Chawla et al (2012) who found tumor volume showed a significant association with optic nerve invasion (P = 0.023).[29] A strong association of ***EOE***, was seen with patients lesions and surgical procedures (p = 0.017). While the cryotherapy was performed in only 6 patients, No association of cryotherapy was seen with ***EOE*** (p = 0.068). 15/52 cases with ***EOE*** were referred to oncology department for chemotherapy and radiotherapy. There was positive association of ***EOE*** and mode of treatment of the patients in oncology Department (0.035).

Conclusion

The most common pattern of retinoblastoma was exophytic, while the optic nerve and extra ocular involvement were prognostic factors for the treatment. Patients suffering from optic nerve invasion and extra ocular extension or invasion of surrounding tissue with distance metastasis were referred to Oncology Department.

Acknowledgement

We are thankful for Dr Samina Qamar, Dr Saqib Hussain and Shamia Zeeshan for helping us is PCR and sequencing the type of mutation.

Conflict of Interest

The manuscript is the real aspect of PhD Project of Asad Aslam Khan (Gene based study of prognostic evaluation of retinoblastoma of eye) and authors have no conflict of interest.

Author Contribution

Khan AA, conceived of the study, analyzed the data and participated in the redaction of the manuscript, conducted pathological analyses. Mahboob R gave analytical support for all the analysis. Bukhari MH, Supervised the research project, read the article and made possible language changes. All authors read and approved the final manuscript.

References

1. Yun J, Li Y, Xu CT, Pan BR. Epidemiology and Rb1 gene of retinoblastoma. Int J Ophthalmol. 2011; 4 (1): 103-9.
2. Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975 – 2004. The British journal of ophthalmology. 2009 Jan; 93 (1): 21-3.
3. Bhatnagar R, Vine AK. Diffuse infiltrating retinoblastoma. Ophthalmology. 1991 Nov; 98 (11): 1657-61.

4. Longmuir SQ, Syed NA, Boldt HC. Diffuse anterior retinoblastoma without retinal involvement. Ophthalmology. 2010 Oct; 117 (10): 2034-8.
5. Shields CL, Shields JA, Baez KA, Cater J, De Potter PV. Choroidal invasion of retinoblastoma: metastatic potential and clinical risk factors. Br J Ophthalmol. 1993 Sep; 77 (9): 544-8.
6. Shields CL, Shields JA, Baez K, Cater JR, De Potter P. Optic nerve invasion of retinoblastoma. Metastatic potential and clinical risk factors. Cancer. 1994 Feb 1; 73 (3): 692-8.
7. Aligbe JU, Igbokwe UO, Akang EE. Histopathology of orbito-ocular diseases seen at University of Benin Teaching Hospital, Benin City. Niger Postgrad Med J. 2003 Mar; 10 (1): 37-41.
8. Ud-Din N, Mushtaq S, Mamoon N, Khan AH, Malik IA. Morphological spectrum of ophthalmic tumors in northern Pakistan. J Pak Med Assoc. 2001 Jan; 51 (1): 19-22.
9. Arif M, Islam Z. Retinoblastoma: postenucleation orbital recurrence. Can J Ophthalmol. 2010 Dec; 45 (6): 606-9.
10. Lee V, Subak – Sharpe I, Hungerford JL, Davies NP, Logani S. Exposure of primary orbital implants in postenucleation retinoblastoma patients. Ophthalmology. 2000 May; 107 (5): 940-5; discussion 6.
11. Dimaras H, Dimba EA, Gallie BL. Challenging the global retinoblastoma survival disparity through a collaborative research effort. The British journal of ophthalmology. 2010 Nov; 94 (11): 1415-6.
12. Lohmann D. Retinoblastoma. Advances in experimental medicine and biology. 2010; 685: 220-7.
13. Du W, Pogoriler J. Retinoblastoma family genes. Oncogene. 2006 Aug 28; 25 (38): 5190-200.
14. Harbour W. Retinoblastoma: Pathogenesis and Diagnosis. In: Char DH, editor. Tumours of the eye and ocular adenexa, American cancer society, Atlas of clinical oncology. London publisher: BC Decker Inc Hamilton; 2001: p. 253.
15. Muhammad MH V, No. 4, P: 111. A statistical analysis of 581 primary Orbital tumours in Pakistan. Pakistan Journal of Ophthalmology. 1987; 3 (4): 111-14.
16. Arora RS, Eden TO, Kapoor G. Epidemiology of childhood cancer in India. Indian journal of cancer. 2009 Oct. – Dec.; 46 (4): 264-73.
17. Zhao J, Li S, Shi J, Wang N. Clinical presentation and group classification of newly diagnosed intraocular retinoblastoma in China. The British journal of ophthalmology. 2011 Oct; 95 (10): 1372-5.
18. Palazzi M, Abramson DH, Ellsworth RM. Endophytic vs exophytic unilateral retinoblastoma: is there any real difference? J Pediatr Ophthalmol Strabismus. 1990 Sep. – Oct; 27 (5): 255-8.
19. Balasubramanya R, Pushker N, Bajaj MS, Ghose S, Kashyap S, Rani A. Atypical presentations of retinoblastoma. J Pediatr Ophthalmol Strabismus. 2004 Jan – Feb; 41 (1): 18-24.
20. Kashyap S, Meel R, Pushker N, Sen S, Bakhshi S, Sreenivas V, et al. Clinical predictors of high risk histopathology in retinoblastoma. Pediatric blood & cancer. 2012 Mar; 58 (3): 356-61.
21. Gunalp I, Gunduz K, Arslan Y. Retinoblastoma in Turkey – treatment and prognosis. Jpn J Ophthalmol. 1996; 40 (1): 95-102.
22. Abdu L, Malami S. Clinicopathological pattern and management of retinoblastoma in Kano, Nigeria. Ann Afr Med. 2011 Jul – Sep; 10 (3): 214-9.
23. Shah PK, Kalpana N, Narendran V, Ramakrishnan M. Severe aseptic orbital cellulitis with subtenon carboplatin for intraocular retinoblastoma. Indian J Ophthalmol. 2011 Jan – Feb; 59 (1): 49-51.
24. Eagle RC, Jr. The pathology of ocular cancer. Eye (Lond). 2012 Nov. 16.
25. Cuenca A, Giron F, Castro D, Fandino A, Guitter M, de Davila MT, et al. Microscopic scleral invasion in retinoblastoma: clinicopathological features and outcome. Archives of ophthalmology. 2009 Aug; 127 (8): 1006-10.
26. Eagle RC, Jr. High – risk features and tumor differentiation in retinoblastoma: a retrospective histopathologic study. Archives of pathology and laboratory medicine. 2009 Aug; 133 (8): 1203-9.
27. Mukhopadhyay S, Ghosh S, Chattopadhyay D, Dutta SK. An observational study on retinoblastoma cases attending a medical college in Calcutta. J Indian Med Assoc. 2006 Feb; 104 (2): 67-70.
28. Abouzeid H, Balmer A, Moulin AP, Mataftsi A, Zografos L, Munier FL. Phenotypic variability of retinocytomas: preregression and postregression growth patterns. The British journal of ophthalmology. 2012 Jun; 96 (6): 884-9.
29. Chawla B, Sharma S, Sen S, Azad R, Bajaj MS, Kashyap S, et al. Correlation between clinical features, magnetic resonance imaging, and histopathologic findings in retinoblastoma: a prospective study. Ophthalmology. 2012 Apr; 119 (4): 850-6.