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Pattern of Presentation of Retinoblastoma in North India: A Teaching Hospital Survey

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***Abstract*:** **Retinoblastoma is the most common, curable intraocular malignancy of childhood. Aim of this study was to analyse the epidemiology and presentation pattern of retinoblastoma. In this hospital based observational study 76 patients diagnosed with retinoblastoma were enrolled. Patients demographic data, mode of presentation, laterality, tumor staging, treatment options and survival were analysed. The result of 76 patients (82eyes) shows male to female ratio 1.2:1. The mean age of presentation was 21±16.8 months. Majority of patients belonged to lower socioeconomic status (58.0%) and rural background (63.2%). Six patients had bilateral retinoblastoma. 43.9% eyes had advanced intraocular disease and 29.3% eyes had extraocular disease. Leukocoria (65.9% eyes), proptosis (25.6% eyes) and fungating mass (19.5%) were common presentation. 9.8% patient had intracranial extension and 13.2% had lymph node metastasis. 60.5% had delayed reporting. 92.1% received treatment, primary treatment was chemoreduction (34.2%) followed by enucleation (42.1%) and exenteration (15.8%). Mean follow-up was 24.45±26.25 months. Recurrence was seen in 10.5% and death in 6.6 % children. The mean survival was 20±18.98 months. Since majority of patients presented late in advanced stage and had poor survival. Hence retinoblastoma awareness campaign, early screening, timely appropriate intervention are recommended to save life and sight of children.**

Index terms: **Retinoblastoma, leukocoria, delayed diagnosis, demography, presentation pattern.**

I. INTRODUCTION

Retinoblastoma (RB) is one of the most frequent malignant neoplasm of infancy and childhood, accounting for 4.0% of all childhood cancer and 8000 new cases annually. The incidence of retinoblastoma is approximately 1 in every 16,000 live birth worldwide (Dimaras et al,2015). RB is highly aggressive cancer and almost fatal if left untreated but early detection and recent treatment advancement have made RB a potentially curable cancer (Musa et al,2017 & Singh G et al, 2016).

The overall 5-year survival rate is seen 83%-97% in developed countries (MacCarthy et al. 2009, Saw et al 2000 & Leal-Leal et al 2004) but much less (20-48%) in developing countries (Swaminathan et al. 2008). Poor prognosis and low patient survival in developing countries can be attributed to delay in the diagnosis and referral to appropriate centre. In developing countries majority of patients reported late in advanced stage when extraocular dissemination has already occurred (Canturk et al. 2010, Chawla et al 2016, Sitorus et al. 2009, and Sachdeva et al. 2010). Lack of knowledge/awareness, low alertness of parents as well as physicians and poor socioeconomic condition are an important factors contributing for delayed presentation (Zhao et al. 2011). The prognosis and outcome of RB depends upon the age of patient at diagnosis, stage of

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disease, histopathological differentiation & histopathological high risk features (HHRF), time elapsed between onset of disease and treatment and consistancy in treatment and follow up. To reduce the mortality rate, developing countries need to identify the prognostic factors.

The available information's regarding demography, epidemiology and clinical presentation of RB in developing countries like India is relatively few, hence this study was carried out to explore the epidemiology/demography of patients, clinico-radiological presentations and factors responsible for delayed presentation and poor prognosis. It will help to plan an intervention for improvement in survival.

II. MATERIALS AND METHODS

A.SLECTION OF AREA AND SAMPLE

A five year prospective, hospital based observational study of all patients diagnosed with retinoblastoma at Regional Institute of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, U.P., India from March 2015 to February 2019 was carried out. Patients who treated elsewhere or who had follow-up period < 6 month were excluded from the study.

B. *TOOLS AND TECHNICHS*

All the patients were asked for detailed history regarding demographic profile of patients like age at onset, age at presentation, sex, residence rural/urban/semi-urban, literacy level of parents, per capita income and socioeconomic status and clinical characteristics such as presenting complaints with duration, family history of RB, laterality of the disease. Patient who presented us > 2 weeks after initial complaint were counted as delayed diagnosis & referral. All children were subjected to detailed clinical examination of ocular adnexa, anterior segment via Slit-lamp Biomicroscopy and fundus examination under mydriasis with both direct and indirect ophthalmoscope. The clinical sign including leukocoria, vitreous seeding, strabismus and proptosis were noted. The tumour size, number and location were also recorded. Visual acuity, extraocular movement and intraocular pressure were measured. The USG, C.T. Scan or MRI imaging of the orbit and brain were advised to look for optic nerve invasion, calcifications, brain and spinal cord metastasis and for primary tumour of pineal gland. The diagnosis of RB was based on clinical findings, results of slit-lamp examinations, indirect ophthalmoscopy and radio-imaging.

Tumours were classified/staged according to the International Classification of RB (Table-1) and clinical TNM staging (Table-2). Tumour were grossly divided into unilateral and bilateral disease, and further classified as intraocular and extraocular category according to clinical and radiological presentation. We adopted tumor staging TNMH (8^{th} edition) system. Disease with stage cT2 or cT3 (intraocular) at least in one eye and cT4 (extraocular) considered as advanced disease .For localised unilateral intraocular tumour (group A-C), focal therapies such as laser photocoagulation or cryotherapy was performed. All bilateral cases underwent for neoadjuvent combination chemotherapy, enucleation of eye with advanced intraocular tumour (group D & E). Extraocular disease was treated by neo-adjuvant chemotherapy /chemoreduction (Vincristine 0.05 mg/kg on D1,Etoposide 5 mg/kg on D1 &D2 and Carboplatin 18.6 mg/kg on D1) followed by secondary enucleation/exenteration, external beam radiation and adjuvant chemotherapy (Maurya RP et al 2021). Patients were followed-up regularly. The outcome was defined in terms of globe salvage rate, alive, death and recurrence. Recurrence was defined as progression in tumour size/reappearance of new lesion 3 months after completion of primary treatment. Treatment defaulter were those patients who left out midway.

C. *STATISTICAL ANALYSIS*

All data used in this study was collected and entered in Standardized Microsoft Excel 2007. Statistical analysis was done using Statistical Package for Social Sciences (SPSS, IBM, verson 21.0 Armcan NY, USA). Patients survival was calculated using the Kaplan-Meier method. Descriptive statistics were represented as mean ± standard deviation. Categorical variables were compared using the Chi Square or Fisher's exact test. A p value <0.05 was considered statistically significant.

III. RESULTS AND DISCUSSION

A. Demographic Profile of Study Subjects :

Table 3 represents demographic profile of study subjects. Among the 76 patients with diagnosis of retinoblastoma 42(55.3%) were males and 34(44.7%) were females. The mean age of patients at presentation was 21± 6.8 months (range 4-65 months).Majority of the patients were in the age group 2-4 years (51.3%). In our study maximum patients (73.7%) were Hindus and only 23.7% were coming from Muslim community. While Ghosh et al 2018 reported maximum retinoblastoma cases from Muslim community. Forty eight (63.2%) patients belonged to rural background while 13.2% were from urban area. In majority of cases (54.0%) their parents were illiterate. 44 patients (58.0%) were below poverty line (family income <0.43 USD in rural India and about 0.53 USD in urban India).Singh Usha et al 2018 reported 13% RB patients were below poverty line.

B. Clinico-radiological Profile of Study Subjects:

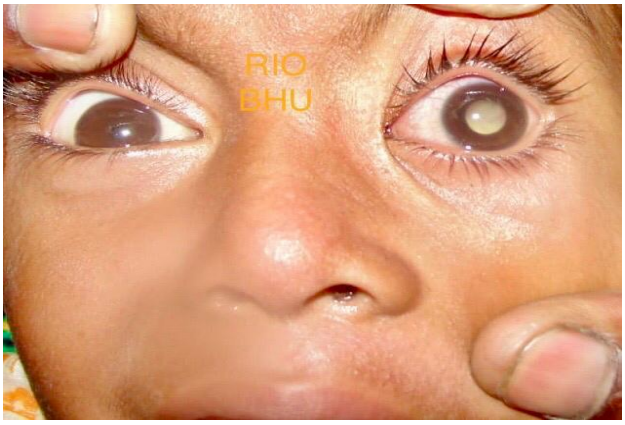

Figure 1:Clinical photograph of a 2 year old male patient with retinoblastoma showing left eye white pupillary reflex (leukocoria).

Table 4 demonstrates clinical presentations of the patients. In present study retinoblastoma was bilateral only in 6 (7.9%) patients and unilateral in 70 (92.1%) patients (31; 40.8 % in the right eye and 39; 51.3% in left eye). 60.5% patient had delayed reporting & diagnosis (> 2 week after initial complaint) most of them were belonged to rural background and below poverty line. Similar delayed presentation (in 58% patients) was reported by Soliman et al 2017.

Leukocoria (65.9%) (Figure 1) ,red eye (39.0%) and proptosis (25.6%) were the common presenting features in this study.19.5% eyes with proptosis also had fungating tumor mass (Figure 2). Strabismus was present in 17% eyes. Similar pattern of clinical presentation were reported by Reddy et al2010,Peterson et al 2000,Chang et al 2006.

10(13.2%) patients had lymph node metastasis (Figure 3). Growth pattern of retinoblastoma was endophytic type in 43.9% eyes, exophytic type in 22.0% eyes while 26.8% eyes had mixed type of tumor growth. At presentation ,36 (43.9%) eyes had features of advanced intraocular disease (Group D disease in 19.5% eyes and Group E disease in 24.4% eyes). While extraocular RB was seen in 24(29.3%) eyes. Most common tumor stage at the time of presentation was stage T4 (24 eyes;29.3%) followed by T1 (22 eyes;26.8%), stage T3 (21eyes;25.6%) and stage T2(15 eyes;18.3%). Retinoblastoma was familial in 2 cases (2.6%) and sporadic in 74 (97.4%) cases.

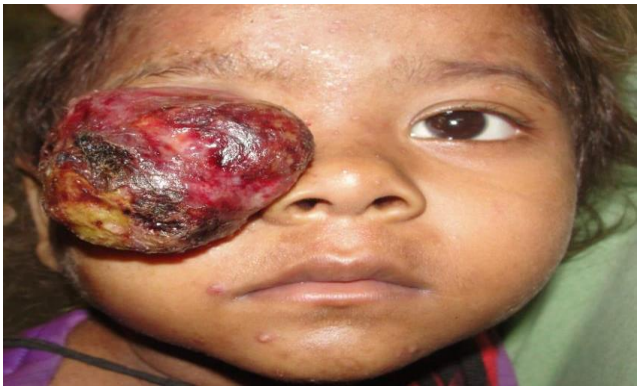

Figure 2: Clinical photograph of a 3 year old girl having right eye extraocular extension of retinoblastoma.

Figure 3: Extraocular extension of retinoblastoma in 13 month old male showing right eye large fungating mass with multiple lymph node metastasis.

Table 5 depicted radiological findings (tumor spread). Most common radiological finding was calcification (Figure 4 & 5). MRI /CT scan showed optic nerve thickening /invasion in 46 eyes (56.1%). The direct intraocular intracranial extension was noticed in 8 eyes (9.8%) where as orbital extension was present in 24 eyes (29.3%).Osteolytic lesions were observed in skull bone in 3 (3.9%) patients.

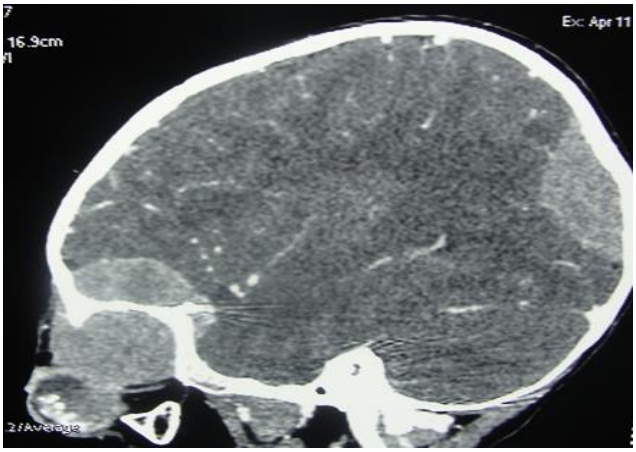

Figure 4: CT Scan (sagittal view) showing intracranial extension & metastasis of left eye retinoblastoma.

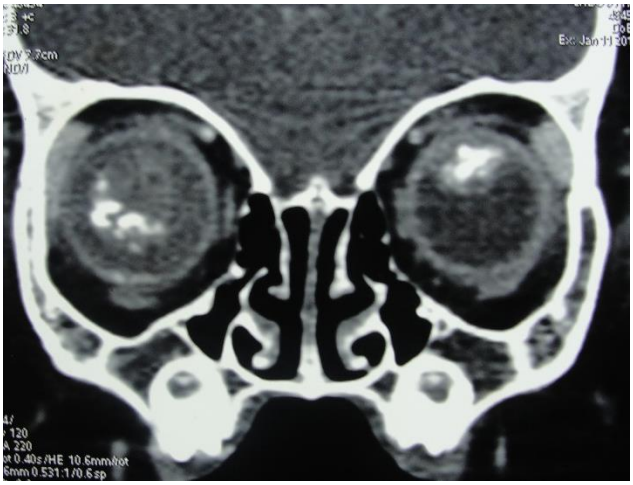

Figure 5: CT Scan of a 4 month old male patient having bilateral retinoblastoma showing intraocular calcification.

C. Mode of Treatment:

Seventy patients (72 eyes) received treatment while 6 patients refused any kind of treatment. All patients of Group D &E were first treated by neo-adjuvant systemic chemotherapy to salvage the globe. Enucleation was considered for non-responders and for extraocular disease (after 2-3 cycle of systemic chemotherapy). Exenteration was done in 12 cases of orbital disease.7.9% patients received palliative chemotherapy. External beam radiotherapy was delivered in 10.5% patients. Mean follow-up period was 24.45 ± 26.25 months.42.0% patient had complete response and no response was observed in 32.9% patient (disease was progressive). Recurrence was seen in 10.5% patients and 5 (6.6%) children of RB with intracranial spread/ metastasis died due to delayed reporting & diagnosis. In this study mean survival rate was 20.0 ± 18.98.

CONCLUSION

In conclusion retinoblastoma in northern India is diagnosed late at advanced stage and has low survival & globe preservation rate. Delay in diagnosis and high default rate are mainly due to illiteracy, poor socioeconomic condition & lack of awareness in people of rural background, poor accessibility to health care, seeking alternative non-reliable treatment options and social taboo of enucleation. On the basis of findings of our study we recommend health education and awareness campaign to general public, school teachers & health care providers , to make strategy of early and cheaper means of screening & diagnosis .Building strong referral network and development of retinoblastoma center of excellence with multidisciplinary team is highly required. Government should start a national retinoblastoma program to save eye, vision and life of children.

REFERENCES

Dimaras H, Corson TW, Cobrinik D, White A, Zhao J, Munier FL, Abramson DH, Shields CL, Chantada GL, Njuguna F, Gallie BL. Retinoblastoma. Nat Rev Dis Primers. 2015 Aug 27;1:15021. Doi: 10.1038/nrdp.2015.21.

Musa KO, Aribaba OT, Oluleye TS, Olowoyeye AO, Akinsete AM. Challenges of retinoblastoma management in a Nigerian tertiary eye care facility. J Clin Sci 2017;14:182-7.

Singh G, Daniels AB. Disparities in Retinoblastoma Presentation, Treatment, and Outcomes in Developed and Less-Developed Countries. Semin Ophthalmol. 2016;31(4):310-6. Doi: 10.3109/08820538.2016.1154177.

MacCarthy A,Birch JM, Draper GJ, et al, (2009). Retinoblastoma in Great Britain 1963-2002. Br J Ophthalmol, 93, 33-7.

Saw SM, Tan N, Lee SB, Au Eong KG, Chia KS. Incidence and survival characteristics of retinoblastoma in Singapore from 1968-1995. J Pediatr Ophthalmol Strabismus. 2000 Mar-Apr;37(2):87-93.

Leal-Leal C, Flores-Rojo M, Medina-Sansón A, Cerecedo-Díaz F, Sánchez-Félix S, González-Ramella O, Pérez-Pérez F, Gómez-Martínez R, Quero-Hernández A, Altamirano-Alvarez E, Alejo-González F, Figueroa-Carbajal J, Ellis-Irigoyen A, Tejocote-Romero I, Cervantes-Paz R, Pantoja-Guillén F, Vega-Vega L, Carrete-Ramírez F. A multicentre report from the Mexican Retinoblastoma Group. Br J Ophthalmol. 2004 Aug;88(8):1074-7. Doi: 10.1136/bjo.2003.035642.

Swaminathan R, Rama R, Shanta V. Childhood cancers in Chennai, India, 1990-2001: incidence and survival. Int J

Cancer. 2008 Jun 1;122(11):2607-11. Doi: 10.1002/ijc.23428.

Canturk S, Qaddoumi I, Khetan V, Ma Z, Furmanchuk A, Antoneli CB, Sultan I, Kebudi R, Sharma T, Rodriguez-Galindo C, Abramson DH, Chantada GL. Survival of retinoblastoma in less-developed countries impact of socioeconomic and health-related indicators. Br J Ophthalmol. 2010 Nov;94(11):1432-6. Doi: 10.1136/bjo.2009.168062.

Chawla B, Hasan F, Azad R, Seth R, Upadhyay AD, Pathy S, Pandey RM. Clinical presentation and survival of retinoblastoma in Indian children. Br J Ophthalmol. 2016 Feb;100(2):172-8. Doi: 10.1136/bjophthalmol-2015-306672.

Sitorus RS, Moll AC, Suhardjono S, Simangunsong LS, Riono P, Imhof S, Völker-Dieben HJ. The effect of therapy refusal against medical advice in retinoblastoma patients in a setting where treatment delays are common. Ophthalmic Genet. 2009 Mar;30(1):31-6. Doi: 10.1080/13816810802464320.

Sachdeva S. Trend of reported cases of retinoblastoma under five hospital based cancer registries. Indian J Cancer. 2010 Oct-Dec;47(4):473-4. Doi: 10.4103/0019-509X.73554.

Zhao J, Li S, Shi J, Wang N. Clinical presentation and group classification of newly diagnosed intraocular retinoblastoma in China. Br J Ophthalmol. 2011 Oct;95(10):1372-5. Doi: 10.1136/bjo.2010.191130.

Maurya RP, Prajapat MK, Singh VP, Roy M, Todi R, Bosak S, Singh SK, Chaudhary S Kumar A, Morekar S. Serum malonialdehyde as biomarkers of oxidative stress in patients with primary ocular carcinoma: impact on response to chemotherapy. Clinical Ophthalmol 2021;15:871-879,doi.org/10.2147/OPTH.S287747.

Ghosh D,Mondal B, Basu A, Mondal J, Gangopadhyay. Retinoblastoma lessons learned about patterns of care and contributory factors from 5 years experience in a tertiary care center in Eastern India. J Cancer Tum Int.2018;8(2): 1-11.Article no.JCTI..46642

Singh U, Katoch D, Kaur S, Dogra MR, Bansal D, Kapoor R.Retinoblastoma: A sixteen year review of the presentation,treatment and outcome from a tertiary care institute in Northern India. Ocul Oncol Pathaol.2018;4:2332.DOI:10.1159/000477408

Soliman SE, Eldomiaty W, Goweida M B, Dowidar A. Clinical presentation of retinoblastoma in Alexandria : A step toward earlier diagnosis. Saudi J Ophthalmol.2017;31:80-85.

Reddy SC, Anusya S. Clinical presentation of retinoblastoma in Malaysia: a review of 64 patients. Int J Ophthalmol.2010; 3(1):64-68.

Peterson RA. Retinoblastoma. In Albert DM.Jakobic FA (eds)Practice and Principle of Ophthalmology.2nd ed.Vol 6.WB Saunders. Philadelphia 2000.5096.

Chang CY, Chiou TJ, Hwang B, Bai LY, Hsu WM, Hsieh YL. Retinoblastoma in Taiwan: survival rate and prognostic factors. Jpn J Ophthalmol. 2006 May-Jun;50(3):242-9. Doi: 10.1007/s10384-005-0320-y. PMID: 16767380.

Table 1: International Classification of Retinoblastoma (ICRB)

GROUP A	Intraretinal Tumor <3mm in size ,3 mm away from the foveola and 1.5 mm from optic nerve
GROUP B	Tumor >3mm,any location,small cuff of subretinal fluid
GROUP C	Tumor with focal subretinal or vitreous seeding within 3mm of tumor
GROUP D	Tumor with diffuse subretinal or vitreous seeding > 3mm from tumor
GROUP E	Tumor occupying > 50% of globe with or without NVG,hemorrage, extension upto optic nerve or AC.

Table 2: Clinical Tumor-Node-Metastasis Staging [cTNM])

Primary tumor (T)
TX: primary tumor cannot be assessed.
T0: no evidence of primary tumor.
T1: tumors no more than two-thirds the volume of the eye with no vitreous or subretinal seeding.

- T1a: no tumor in either eye is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea (coinciding with IIRC Group A).
- T1b: at least 1 tumor is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea. No retinal detachment or subretinal fluid beyond 5 mm from above the base of the tumor (coinciding with IIRC Group B).

- T1c: at least 1 tumor is greater than 3 mm in largest dimension or located closer than 1.5 mm to the optic nerve or fovea, with retinal detachment or subretinal fluid beyond 5 mm from the base of the tumor (coinciding with IIRC Group C).

T2: tumors no more than two-thirds the volume of the eye with vitreous or subretinal seeding. Can have retinal detachment.

- T2a: minimal tumor spread to vitreous and/or subretinal space. Focal vitreous and/or subretinal seeding of fine aggregates of tumor cells is present, but no large clumps or "snowballs" of tumor cells (coinciding with IIRC Group C).
- T2b: massive tumor spread to the vitreous and/or subretinal space. Massive vitreous and/or subretinal seeding is present, defined as diffuse clumps or "snowballs" of tumor cells (coinciding with IIRC Group D).

T3: severe intraocular disease.

- T3a: tumor fills more than two-thirds of the eye (coinciding with IIRC Group D).
- T3b: 1 or more complications present, which may include tumor-associated neovascular or angle closure glaucoma, tumor extension into the anterior segment, hyphema, vitreous hemorrhage, or orbital cellulitis (coinciding with IIRC Group E).

T4: extraocular disease (detected by imaging studies).
T4a: invasion of optic nerve.
T4b: invasion into the orbit.
T4c: intracranial extension not past chiasm.
T4d: intracranial extension past chiasm.
Regional lymph nodes (N)
NX: regional lymph nodes cannot be assessed.
N0: no regional lymph node involvement.
N1: regional lymph node involvement (preauricular, submandibular, or cervical).
N2: distant lymph node involvement.
Distant metastasis (M)
M0: no distant metastasis.
M1: systemic metastasis.

- M1a: single lesion to sites other than CNS.
- M1b: multiple lesions to sites other than CNS.
- M1c: prechiasmatic CNS lesion(s).
- M1d: postchiasmatic CNS lesion(s).
- M1e: leptomeningeal and/or CSF involvement.

Table 3: Demographic characteristics of the study cohort.

Characteristics		**Number**	**%**
Total No Patients		76	100.0
Sex	Male	42	55.3
	Female	34	44.7
Age (years)	< 2	27	35.5
	2-4	39	51.3
	>4	10	13.2
Religion	Hindu	56	73.7
	Muslim	18	23.7
	Others	2	2.6
Residence	Rural	48	63.2
	Semi-urban	18	23.8
	Urban	10	13.2
Educational status of parents	Illiterate	41	54.0
	Primary school	24	31.6
	>Secondary school	11	14.4
Family Income	Low	44	58.0
	Average	21	27.6
	High	11	14.4

Table 4: Clinical characteristics of patients.

Characteristics		**Number** (76 patients)	**%**
Family History	Yes	2	2.6
	No	74	97.4
Laterality	Unilateral	70	92.1
	Bilateral	6	7.9
Main Complain (82 Eyes) *Some patients had >1 signs*	Leukocoria	54	65.9
	Proptosis	21	25.6
	Redness of eyes	32	39.0
	Squint	14	17.1
	Hyphema /Hypopyon	8	9.8
	Orbital cellulitis	16	19.5
Lymph node metastasis		10	13.2
Distant Metastasis		4	5.3
Type of Tumor *(82 Eyes)*	Endophytic	36	43.9
	Exophytic	18	22.0
	Mixed type	22	26.8
cTNM Staging *(82 Eyes)*	T1	22	26.8
	T2	15	18.3
	T3	21	25.6
	T4	24	29.3
IRCB Classification *(82 Eyes)*	A	5	6.1
	B	8	9.8
	C	9	11.0
	D	16	19.5
	E	20	24.4
	Extraocular disease	24	29.3

Table 5: Radiological Findings.

CT / MRI Findings	Number of Eyes (n=82)	%
Calcification	60	73.2
Optic nerve thickening	46	56.1
Orbital extension	24	29.3
Intracranial Extension / Metastasis	8	9.8
Distant Metastasis	4	4.9

(In some patients >1 signs present at the time of presentation)

Table 6: Distribution of study subjects according to treatments and treatment outcome

		Number	%
Treatment Modalities *(Some patients received >1 mode of treatment)*	Neoadjuvant Chemotherapy (IV)	26	34.2
	Enucleation	32	42.1
	Exenteration	12	15.8
	Palliative Chemotherapy	6	7.9
	External Beam Radiotherapy	8	10.5
Outcome	Cured	32	42.1
	Progressive disease	25	32.9
	Recurrence	8	10.5
	Death	5	6.6
	Refused Treatment	6	7.9

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