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Importance of Early Diagnosis and Treatment in getting better Visual Performance in Retinoblastoma: A Research Article

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KEYWORDS
Retinoblastoma, Mortality rates, Contrast sensitivity, Electrophysiological tests, Enucleation, Intra-arterial chemotherapy

ABSTRACT:
Background: Retinoblastoma is the most common paediatric cancer which occurs due to uncontrolled division of Retinoblast cells, which are precursor of photoreceptor cells. Prevalence of retinoblastoma is approximately 1 in 17,000 live births worldwide and 1 in 10,000 in India. Annually around 3,000-3,350 children are dying due to retinoblastoma. Treatment options for retinoblastoma depend on nature of tumor and patient age, which involves Focal therapy, Chemotherapy and Enucleation.
Objective: Aim of this study is to find the impact of delayed diagnosis and treatment on visual outcome of patients.
Method: A cross-sectional study of 45 eyes with regressed Retinoblastoma in 36 patients is done at Eye OPD, to find delay in treatment and its relation to visual outcome. Delay in treatment is assessed by questionnaires based history taking and reduced visual outcome is measured by assessment of Visual Acuity, Colour vision, Refraction, Contrast sensitivity, Visual fields and results of electrophysiological tests like visual evoked response (VER) and Electroretinogram (ERG). Data is statistically analyzed and presented graphically to guide Retinoblastoma management team about importance of early diagnosis and treatment in getting better visual outcomes in retinoblastoma patients.
Results: Based on research analysis of data average delay in treatment after diagnosis recorded in our study population was 19.6 ± 15.0 months. Correlation of delay in treatment to Grade of Retinoblastoma present at the time of initiation of treatment and Visual Acuity achieved after treatment in patients of our study group showed that, all 4 patients reporting with delay of < 6 months had Grade A RB(Vn.>6/12), all 10 patients reporting between 6-12 months also had Grade A RB(Vn.>6/12), 9 patient reporting between 12-18 months had 73% Grade A RB(Vn.>6/12) and 27% Grade B RB(Vn.<6/12->6/60), 5 patient reporting between 18-24 months had 71% Grade B RB(Vn.<6/12->6/60) and 29% Grade D(Vn.<3/60) RB while patient reporting with delay of >24 months had 9% Grade B RB(Vn.<6/12->6/60) and 18% Grade C RB(Vn.< 6/60->3/60), and 73% Grade D RB(Vn.<3/60). Reduced capacity of Colour vision, Contrast sensitivity, VER and ERG is recorded in study population. It is observed in study population that delay in treatment leads to poor Grade of Retinoblastoma present at the time of initiation of treatment leading to poorer Visual performance after treatment.
Conclusion: It is observed in our study tumour progression is initially slow till 18 months after that it grows exponential. Visual outcome seen in patients after treatment is related to delay in the treatment hence a higher degree of awareness in guardian and health care worker can reduce delay in treatment leading to better visual outcome and enhanced quality of life of patient

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1. INTRODUCTION

Retinoblastoma is a most common paediatric cancer [1] it occurs due to uncontrolled cell division of Retinoblast cell which are precursor cells of photoreceptor [2]. Retinoblastoma is treatable cancer if diagnosed at early stage of disease [3]. Healthcare workers and guardians often overlook the significance of early treatment, resulting in delays in diagnosing and treating patients. Consequently, this delay can lead to diminished visual performance even after treatment is administered.

1.1 Prevalence of this disease is 1 in 17 000 live births worldwide [4]. High prevalence rate is observed in India which is 1 in 10,000 [5]. Around 1500 to 2000 patients of retinoblastoma are born every year in India [6] specially in the eastern part of UP. Most common age of onset for familial or hereditary retinoblastoma is 18 months [7]. At this stage patient can`t do not express about his condition nor his parents are sure about it. Poverty and lack of education also make it worse because realisation of severity of problem comes at very late stage of disease which leads to poor visual outcome in these patients [8].

1.2 Survival Rate

Kivela highlighted that approximately 7202 and 8102 new cases of retinoblastoma are identified worldwide annually [9] out of these around 3000–3350 children fail to survive due to retinoblastoma [10]. Survival rate of patients after Retinoblastoma treatment worldwide [11] is high in developed countries like 98% in America, 96% in Japan, 95% in Europe, 80% in Latin America/Caribbean, 65 % in Asia and 30% in Africa. Survival rate of patient depends on early diagnosis and proper management [12].

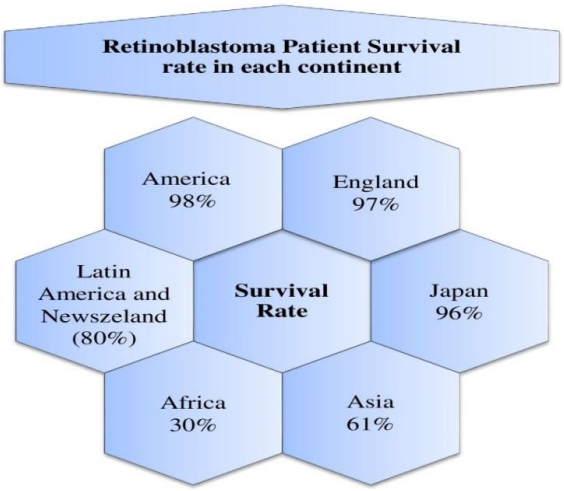

Fig 1 Retinoblastoma Patient Survival rate in each continent

1.3 Importance of early diagnosis

In an article 'Retinoblastoma: One World, One Vision [13], highlighted importance of using flier and poster for creating awareness in healthcare workers and society in 2003 in Honduras. It helped in reducing delay in retinoblastoma diagnosis from 212 to 165 days and reduced extraocular retinoblastoma from 73% to 35% [14]. Collaborative efforts between countries with advance treatment technologies and rest of the world can enhance awareness about disease and train health care workers about recent advancements in diagnosis and treatment of disease [15] leading to early diagnosis and better visual performance after treatment in patients with retinoblastoma. Retinoblastoma is a curable cancer, if detected when it is within the retina, subretinal space or vitreous [16]. Invasion into deeper ocular structures like optic nerve, choroid, or scleral invasion [17] promotes metastatic disease [18].In literature review it is identified that tumor growth can shift from Grade A to Grade C within 1 year [19]. Hence we conclude that results of retinoblastoma treatment at early stage are remarkably good in which we are able to save life and eye ball of patient with a very good visual performance after treatment [20].

1.4 International classification of retinoblastoma

The International Classification of Retinoblastoma [21] (ICRB) is based on size, location and rate of growth of tumor. It tells us about stage of disease and also guides most appropriate treatment methodology ICRB grading of retinoblastoma is given below.

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- Grade A stands for very low risk < 3 mm retinal tumor at >3mm from Fovea and spread at the distance <1.5mm from optic disc [22].
- Grade B stands for low risk >3 mm retinal tumor at < 3mm from Fovea and spread at the distance >1.5mm from optic disc [23].
- Grade C stands for moderate risk focused subretinal and Vitreous seeding tumor >3 mm in size, distance from Fovea <3 mm, spread at the distance from optic disc <3mm [24].
- Grade D stands for high risk diffused subretinal and Vitreous seeding tumor >3 mm in size, distance from Fovea <3 mm, spread at the distance from optic disc >3mm [25].
- Grade E stands for very high-risk extensive tumor spreading in > than 50% of Retina with anterior chamber and optic nerve involvement causing neovascularisation, haemorrhage and Glaucoma [26]. Therefore, Retina becomes non-functional and it shows tendency to spread into secondary organs like brain, C etc [27].

1.5 Factors causing this disease

- Retinoblastoma occurs due to uncontrolled cell division of Retinoblast cells [28]. It happens due to free and active E2f growth factor. E2f is responsible for conversion of Cycline E to Cycline A at G1 stage of cell cycle[29] This cycline A is active in S phase and produce DNA polymerase which starts the process of cell division by opening and duplication of DNA [30].
- RB regulator gene is present on the long arm of both alleles of 13th chromosomes [31]. It plays a vital role in holding E2F by producing mRNA which translates in cytoplasm producing pRb protein which binds with E2f growth factor [32]. Hence in the absence of Free and active E2f factor, uncontrolled cell division and cancer formation does not take place [33].

1.6 Progression pattern of tumor

Retinoblastoma tends to growth from intraretinal white nodules to endophytic vitreous seeding and finally into diffused exophytic, tumor [34]. Observation of progression pattern of retinoblastoma shows that it is highly aggressive at advance stage [35].

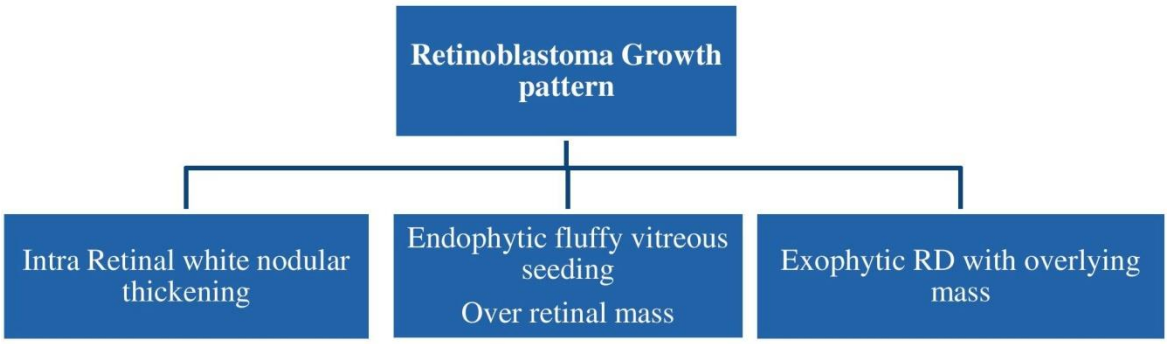

Figure 2 Progression pattern of tumor

1.7 Sign and symptoms of retinoblastoma

Most common clinical signs seen in retinoblastoma patients are painful swollen red eye with white pupil and strabismus [36] having reduced visual performance like blur vision, defected Colour vision, Contrast sensitivity, with refractive error and scotoma in visual fields, and delayed and reduced responses to electro physiological test like ERG, VER etc. Fundus examination reveals multiple white or pearly cancerous growths in vitreo-retinal region [37].

1.8 Examination of patient with retinoblastoma

Examination of patient involves [38] following procedure

- Assessment of redness, and proptosis in eye by torchlight and Slit lamp examination [39].
- Assessment of visual performance like Visual Acuity, Colour vision, Refraction, Contrast sensitivity, Visual fields etc [40]. If paediatric patient is not giving proper subjective responses, then visual performance is be assessed by using ERG and VER techniques [41].
- Assessment of IOP by applanation tonometry [42].

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- Assessment of tumor in posterior segment of eye by doing fundus examination through Direct and Indirect ophthalmoscopy [43], Picture of retina is taken by using high resolution fundus cameras [44].
- USG-B scan also helps in identification of size and location of tumor [45].
- CT scan and MRI can help to access tumor behind eye ball and in midbrain [46].

With recent advancements in intra-ocular diagnostic facilities early diagnosis is possible [47]. This early diagnosis and appropriate treatment considerably improved survival rate and visual outcome in cases having potential risk of getting retinoblastoma [48].

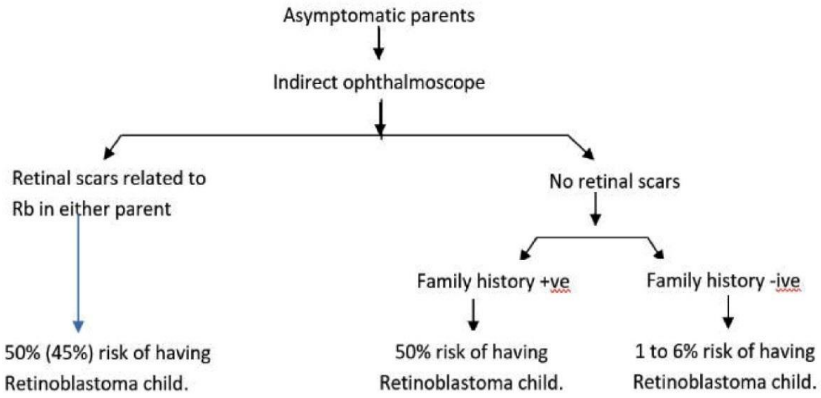

Fig. 3 Potential risk of retinoblastoma in next generation

Based on risk associated in various categories of patients we understand that high risk is seen in off springs of RB affected parents. Therefore, examination of suspected parents and their genetic counseling plays a very important role in preventing birth of child with Retinoblastoma [49].

1.9 Visual outcome is main area of concern for Retinoblastoma patient

Visual outcome and its functional parameters are Visual Acuity, Colour vision, Refraction, Contrast sensitivity, Visual fields and results of electrophysiological tests like visual evoked response (VER) and Electroretinogram (ERG) [50] Visual outcome which is one of the most important matters of concern for any patient coming for treatment specially in present scenario of customised combination therapy in which patient survival rate is high [51].

1.10 Aim of Retinoblastoma treatment

Aim is to save life, save eye and reduce loss of visual performance in patients after removal of retinoblastoma tumor [52].

1.11 Various modalities available for management of Retinoblastoma

It depends on resources available to an Eye specialist, his personal expertise and option chosen by patient [53-54].

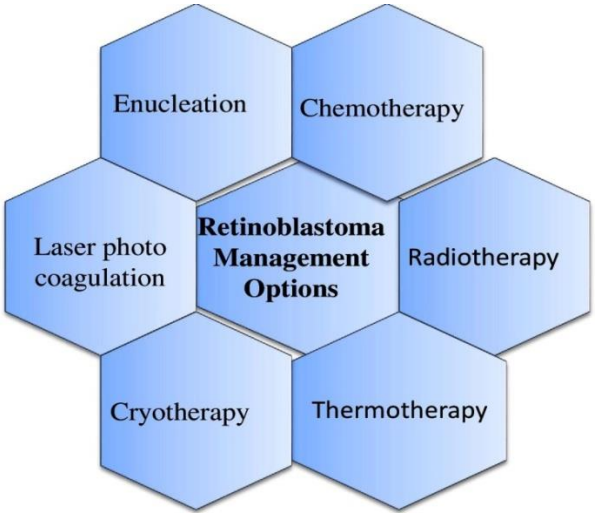

Figure 4 Treatment options in Retinoblastoma

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With the recent advances in the past couple of decades, Retinoblastoma therapy shifted towards non-enucleation modalities with protection of eyeball and vision [55]. Generally, these options are preferred by most of the retinoblastoma expert worldwide

- Cryotherapy is done in patients with small retinal tumor located anterior to equator of eye ball [56]. Touching of tumor cell by cryotherapy probe at freezing point reduces their activity and control their growth and progression [57].
- Focal radiation with thermal effect is done in patients with small retinal tumor located posterior to equator away from Macula [58]. It stops the growth of tumor by burning them [59].
- External beam radiotherapy stops the growth of tumor by burning them [60]. It side effects are risk of germline mutation and possibility of late onset of cancers [61].
- Plaque radiotherapy is done in patients with focused tumor [62]. In this process radioactive iodine material is inserted close to that cancer cell [63]. It coagulates cellular molecules specially nucleotides and proteins leading to death of cancer cells [64].
- Laser photocoagulation is done in patients with small to moderate tumor located posterior to equator away from Macula [65] It coagulates cellular molecules specially nucleotides and proteins leading to death of cancer cells [66].
- Intravenous chemotherapy (chemoreduction) is done in patients with small to moderate diffused tumor located in secondary areas [67] it involves four to six cycles of Carboplatin, Etoposide and Vincristine by intra venous route [68]. These drugs kill cancer cells. Hence it reduces tumor size and in turn reduces the dose of other therapy required [69].
- Intra-arterial chemotherapy is done in patients with focused tumor [70]. In this process cannula is inserted by catheterization in intracarotid artery to release Melphalan close to that cancer cell [71] causing reduced tumor size and lesser dose of other therapies with minimum side effects [72]
- Intravitreal chemotherapy is a process of giving chemotherapy directly near recurrent vitreous seeding following failed therapies [73]. It reduces tumor size with minimum side effects [74].
- Enucleation is done in patients with high-risk extensive tumor with tendency to spread particularly if it is unilateral [75]. In this process surgical removal of tumor in eye ball and outer portion of optic nerve is done to stops its spreading [76]. An infection resistant, light weight polymer-coated hydroxyapatite prosthetic artificial eye is given to maintain stability and socket volume [77].

1.12 Logic behind selection of treatment for Retinoblastoma

- Eye is very sensitive organs we have to be extra careful while planning treatment of tumor [78] because there is high probability of losing visual performance of eye [79]. Treatment choice depends upon stage to Retinoblastoma like size of tumor and its nature, its location in reference to macula, optic disc, choroid and sclera and its spread in other eye and secondary tissue. Other factors like general patient age and health, and the family desires [80]. Also play important role in deciding various combination of treatment modalities.

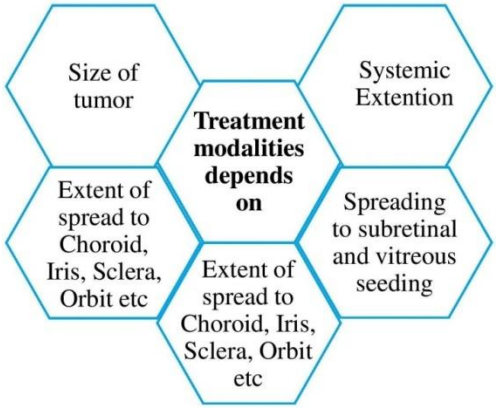

Fig 5 Logic behind selection of treatment for Retinoblastoma

1.13 Treatment option based on Size of tumor

- Early small to medium size tumor with little sub retinal fluid retinoblastoma is treated by cryotherapy, thermotherapy, plaque radiotherapy and Laser photocoagulation [81].

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- Advance larger tumors or those with multiple seeding in sub retinal fluid are treated by External beam radiotherapy, Intravenous chemo-reduction, Intra-arterial chemotherapy and Enucleation [82].
- Very large tumor, with no possibility of functional vision, is treated by enucleation [83].

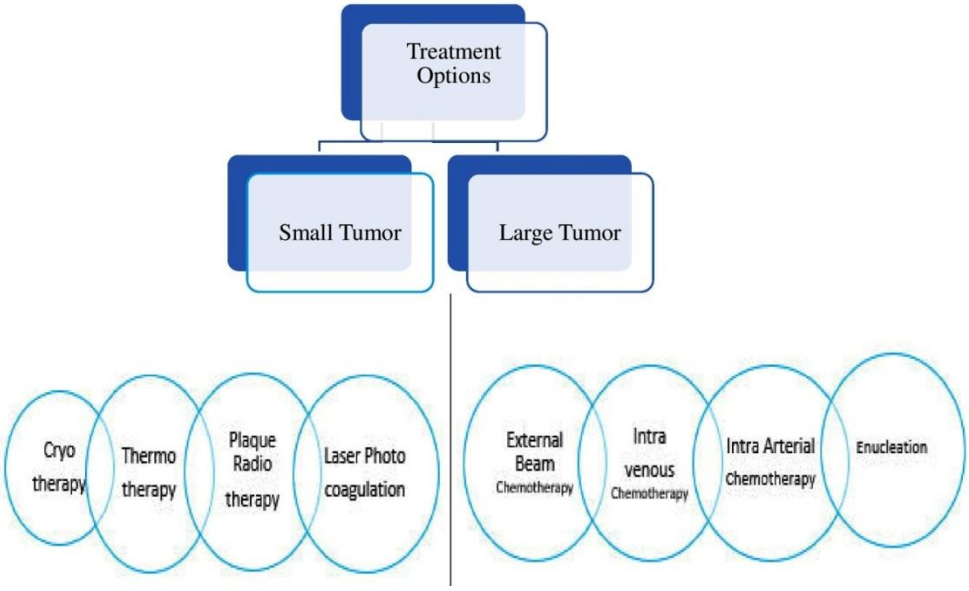

Figure 6: Treatment option based on Size of tumor

4. AIM & OBJECTIVE OF THIS STUDY

4.1 Aim of our study is to assess visual outcome achieved in patients with various Grade of regressed retinoblastoma and identify advantage of early diagnosis and treatment in getting better visual performance.

4.2 Objectives of this study are to identify the importance of early diagnosis and treatment for getting better visual performance in retinoblastoma.

By History

- Age of onset of tumor or age at which patient was first time diagnosed for the disease.
- Grade of Retinoblastoma at which treatment of patient is started.
- Assessment of delay in treatment by measuring delay in start of treatment after diagnosis of tumor.

By Examination of visual parameters

- To study the visual outcome achieved in patients with regressed retinoblastoma.
- To correlate Grade of Retinoblastoma at starting stage of treatment to delay in treatment
- To correlate visual outcome to delay in treatment.

5. RESEARCH METHODOLOGY

A cross-sectional study of 45 eyes with regressed Retinoblastoma in 36 patients is done at Eye OPD, and their visual outcome is recorded. All patients who satisfied the below mentioned inclusion and exclusion criteria are chosen for the study.

5.1. A Inclusion Criteria

- All patients have completed treatment for retinoblastoma
- No further treatment is given to them in last 6 months
- No further change in tumorigenesis is recorded
- Age more than 7 years
- Consent form is signed by their guardian and they were on regular follow ups

5.1.B Exclusion Criteria

- Patient with hazy media
- Patients not willing to get investigated
- Un cooperative patients

Focused questionnaire-based history of all patients is taken to assess chronological history of disease including treatment taken and their results. Visual outcome is assessed by complete clinical workup which includes assessment of Visual Acuity, Colour vision, Refraction, Contrast sensitivity, Visual fields and results of electrophysiological tests like visual evoked response (VER) and Electroretinogram (ERG). These were conducted for both the eyes and the results were recorded.

6. OBSERVATION & RESULT

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Our study group involves 45 eyes with regressed Retinoblastoma in 36 patients. They have completed customized chemotherapy and focal therapy treatment for retinoblastoma and no further treatment is given to them in last 6 months. Out of these 36 patients, 9 patients had regressed lesion in both eye, 23 patients had regressed lesion in one eye and other eye enucleated while 4 patients had regressed lesion in one eye and no lesion in other eye. 18 eyes had Macular lesion while 27 eyes had extra macular lesion.

DEMOGRAPHIC PROFILE

Our study involved children (Age between 7years – 12 years). Average age of patients in our study was 9.50 ± 1.95 years. Age when treatment is initialized in these 36 patients was 19.6 ± 15.0 months.

6.1 Delay in treatment recorded in study population

It is observed in study population that more than 60% patients reported after delay of more than 1 year.

Table 4: Distribution of delay in treatment

1. Delay in treatment	2. No of patients	3. Percentage of patients
4. 0-6 months	4	11%
5. 6-12 months	10	28%
6. 12-18 months	9	25%
7. 18-24 months	5	14%
8. >24 months	8	22%

6.2 Visual acuity achieved in patients with regressed retinoblastoma in our study group

It is observed in study population that 54% patients achieved Vn>6/12, 20% have Vn in the range of 6/12 – 6/60, 4% have Vn in the range of 6/60-3/60, 22% have Vn in the range of <3/60.

Table 5: Distribution of Visual Acuity

Group	Visual Acuity	No of eyes	Percentage of Eye
Group 1	>6/12	24	54%
Group 2	6/12 – 6/60	9	20%
Group 3	6/60 – 3/60	2	4%
Group 4	< 3/60	10	22%

6.3 Correlation of delay in treatment to Grade of Retinoblastoma present at the time of initiation of treatment in patients with regressed retinoblastoma in our study group

It is observed in study populations that delay in treatment leads to poor Grade of Retinoblastoma present at the time of initiation of treatment.

Table: Grade of retinoblastoma observed due to delay in the treatment

Delay in treatment	No. of Patients	Combination of Eyes		Total No. of Eyes / Grade of Retinoblastoma
		No. of Eye	Grade Achieved	
0-6 Months	4	4 Uni RB = 4	A	**24 / A**

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6-12 Months	10	2 eyes of Bi RB (B1, B2) + 1 eye of 8 Uni RB = 12	A	
12-18 Months	9	1 eye of 2 Bi RB (B3, B4) + 6 Uni RB = 8	A	
		1 eye of 2 Bi RB (B3, B4) + 1 Uni RB = 3	B	**9 / B**
18-24 Months	5	1 eye of 2 Bi RB (B5, B6) + 3 Uni 3 = 5	B	
		1 eye of 2 Bi RB (B5, B6) = 2	D	**10 / D**
> 24 Months	8	1 Uni RB = 1	B	
		1 eye of 2 Bi RB (B7, B8) = 2	C	**2 / C**
		BE of 1 Bi RB (B9) + 1 eye of 2 Bi RB (B7, B8) + Uni RB = 8	D	

6.4 **Correlation of delay in treatment to Visual Acuity achieved in patients with regressed retinoblastoma in our study group:** It is observed in study population that delays in treatment leads to poor Visual acuity after treatment.

Table 7: Visual acuity achieved due to delay in the treatment

Delay in treatment	**No. of patients**	**Combinations of eyes**	
		No. of Eyes	**Vn achieved**
0-6 months	4	4 Uni RB = 4	> 6/12
-12 months	10	2 eye of 2 Bi RB (B1,B2) + 1 eye of 8 unit RB = 12	> 6/12
12-18 months	9	1 eye of 2 Bi RB (B3, B4), + 6 Uni RB = 8	> 6/12
		1 eye of 2 Bi RB (B3, B4) + 1 Uni RB =3	6/12 – 6/60
18-24 months	5	1 eye of 2 Bi RB (B5, B6) + 3 Uni RB = 5	6/12 – 6/60
		1 eye of 2 Bi RB (B5, B6) = 2	< 3/60
>24 months	8	1 Uni RB = 1	6/12 – 6/60
		1 eye of 2 Bi RB (B7, B8) = 2	6/60 – 3/60
		BE of 1 Bi RB (B9) + 1 eye of 2 Bi RB (B7, B8) + 4 Uni RB = 8	< 3/60

6.5 **Colour vision achieved in patients with regressed retinoblastoma*:*** Colour vision was assessed using Ishihara's chart. Normal colour vision is observed in 22 patients, Dyschromatopsia is seen in 2 patients while 12 patients could not be assessed due to very poor visual acuity.

Table 8: Distribution of Colour vision

Colour vision	**No of patients**	**% of patients**
Normal	22	62%
Dyschromatopsia	2	5%
Cannot be assessed	12	33%

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6.6 Refraction achieved in patients with regressed retinoblastoma

It is observed that 6 eyes were myopia, 14 eyes were Emmetropic and 25 eyes were Hyperopic with astigmatism. An average Astigmatism of 1.66 D cylinder was seen. High hyperopia is seen probable because of younger age of study population.

Table 9: Distribution of refraction

Type of refraction	No. of eyes	% of eyes
Myopia	6	13
Emmetropia	14	31
Hyperopia	25	56

6.7 Contrast sensitivity achieved in patients with regressed retinoblastoma

The contrast sensitivity is done by Pelli-Robson chart. Reduced contrast sensitivity is due to low visual acuity. 10 eyes with Macular Retinoblastoma can`t be assessed because they have very poor visual acuity.

Table 10: Distribution of contrast sensitivity

Contrast sensitivity	No. of eyes	% of eyes
Normal	25	56
Reduced	10	22
Cannot be assessed	10	22

6.8 Visual Fields: Visual field assessment was one of the parameters included in our study, But attention required for this tests was not possible in these younger patients (Avg age - 8.57 ± 1.85 years). Hence these tests could not be performed.

6.8 Visual evoked response (VER): Over all reduced amplitude and increase in latency was seen inFlash VER. Amplitude and latency in macular lesions was 5.5 ± 3.23µv and 130.9 ± 17.91ms and in in extramacular lesion was 13.2 ± 4.58µv and 117.5 ± 20.7ms. Reduced amplitude and increased in latency was found which was less in Extra Macular lesion compare to macular lesion.

Table 11: Distribution of visual evoked response

Type of regressed lesion	Amplitude	Latency
Macular Regressed Lesion	55 ± 3.23 µv	130.9 ± 17.91 ms
Extra Macular Regressed Lesion	13.2± 4.58 µv	117.5±20.7 ms

6.9 Electroretinogram:

Reduced average amplitude is seen in standard flash electroretinogram. Reduced amplitude in macular regressed Retinoblastoma was 31.7±11.1µv, and it was lesser than that in extramacular regressed lesions with 41.8± 8.01µv ($P < 0.0001$).

Table 12: Distribution of ERG amplitude

Type of Regressed Lesion	No. of Eyes	ERG Amplitude
Macular Regressed Lesion	18	31.0±11.2 µv
Extra Macular Regressed Lesion	27	41.1±8.11µv

9. SUMMARY OF RESULTS

- Total no of patients involved in the study were 36, which included 45 eyes. Out of these 36 patients, 9 patients had regressed lesion in both eye, 23 patients had regressed lesion in one eye and other eye enucleated while 4 patients had regressed lesion in one eye and no lesion in other eye.
- Average age of patients in our study was 9.50 ± 1.95 years, Ranging between 7 to 12 yrs.
- Age when treatment was initialised was 19.6 ± 15.0 months.
- Out of 36 patients 27 (75%) patients were males and 9(25%) patients were females.
- Distribution of Visual acuity in our study group was > 6/12 in group 1 with 24(54%) eyes, 6/12 –

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6/60 in group 2 with 9(20%) eyes, 6/60 – 3/60 in group 3 with 2(4%) eyes and < 3/60 in group 4 with 10(22%) eyes.

- 18 eyes had Macular lesion with average log mar visual acuity 1.74±1.01 and 27 eyes had extramacular lesion with average log mar visual acuity 0.20± 0.19.
- Distribution of Grades of Retinoblastoma present in our study group at the time when treatment was initiated Grade A in 24(54%) eyes, Grade B in 9(20%) eyes, Grade C in 2(4%) eyes and Grade D in 10(22%) eyes.
- Average delay in treatment after diagnosis recorded in study populationwas 15 ± 12 monthes.
- Correlation of delay in treatment to Grade of Retinoblastoma present at the time of initiation of treatment in patients of our study group showed that, all 4 patients reporting with delay of < 6 monthes had Grade A RB, all 10 patients reporting between 6-12 monthes also had Grade A RB, 9 patient reporting between 12-18 monthes had 73% Grade A RB and 27% Grade B RB, 5 patient reporting between 18-24 monthes had 71% Grade B RB and 29% Grade D RB while patient reporting with delay of >24 monthes had 9% Grade B RB and 18% Grade C RB, and 73% Grade D RB
- Correlation of delay in treatment to Visual acuity achieved after treatment in patients of our study group showed that, all 4 patients reporting with delay of < 6 monthes achieved Vn >6/12, all 10 patients reporting between 6-12 monthes also achieved Vn >6/12, 9 patient reporting between 12-18 monthes achieved 73% Vn >6/12 and 27% Vn >6/60-<6/12, 5 patient reporting between 18-24 monthes achieved 71% Vn >6/60-<6/12and 29% Vn<3/60 while patient reporting with delay of >24 monthes achieved 9% Vn >6/60-<6/12 and 18% Vn >3/60-<6/60, and 73% Vn<3/60
- Distribution of colour vision present in our study group was Normal in 22(62%) patients, Dyschromatopsia in 2(5%) patients while 12(33%) patients could not be assessed due to very poor visual acuity.
- Distribution of refractive error present in our study group was Myopia in6(13%) eyes, Emmetropia in 14(31%) eyes and Hyperopic with astigmatism in 25(56%) eyes.
- Distribution of Contrast sensitivity in our study group was Normal in 25(56%) eyes, Reduced in 10(22%) eyes and rest of 10(22%) eyes can`t be assessed because they have poor visual acuity.
- Visual field assessment could not be performed because attention required for this test was not possible in our study group (Age – 7-12yrs).
- VER assessment showed reduction in amplitude and increase in latency. Amplitude and latency in Extra Macular lesion (13.2 ± 4.58µv and 117.5 ± 20.7ms) is damaged less compare to that in macular lesion(5.5 ± 3.23µv and 130.9 ± 17.91ms)
- ERG assessment showed reduction in amplitude. Amplitude in extramacular macular lesion(41.8± 8.01µv) is damaged less compare to that in macular lesion(31.7±11.1µv) with (P < 0.0001).

- Correlation of delay in treatment to Visual acuity achieved after treatment in patients of our study group showed that, all 4 patients reporting with delay of < 6 monthes achieved Vn >6/12, all 10 patients reporting between 6-12 monthes also achieved Vn >6/12, 9 patient reporting between 12-18 monthes achieved 73% Vn >6/12 and 27% Vn >6/60-<6/12, 5 patient reporting between 18-24 monthes achieved 71% Vn >6/60-<6/12and 29% Vn<3/60 while patient reporting with delay of >24 monthes achieved 9% Vn >6/60-<6/12 and 18% Vn >3/60-<6/60, and 73% Vn<3/60
- Distribution of colour vision present in our study group was Normal in 22(62%) patients, Dyschromatopsia in 2(5%) patients while 12(33%) patients could not be assessed due to very poor visual acuity.
- Distribution of refractive error present in our study group was Myopia in6(13%) eyes, Emmetropia in 14(31%) eyes and Hyperopic with astigmatism in 25(56%) eyes.
- Distribution of Contrast sensitivity in our study group was Normal in 25(56%) eyes, Reduced in 10(22%) eyes and rest of 10(22%) eyes can`t be assessed because they have poor visual acuity.
- Visual field assessment could not be performed because attention required for this test was not possible in our study group (Age – 7-12yrs).
- VER assessment showed reduction in amplitude and increase in latency. Amplitude and latency in Extra Macular lesion (13.2 ± 4.58µv and 117.5 ± 20.7ms) is damaged less compare to that in macular lesion(5.5 ± 3.23µv and 130.9 ± 17.91ms)

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➢ ERG assessment showed reduction in amplitude. Amplitude in extramacular macular lesion(41.8± 8.01μv) is damaged less compare to that in macular lesion(31.7±11.1μv) with (P < 0.0001)

10. CONCLUSION

This study highlights importance of early diagnosis and treatment of Retinoblastoma to get better visual outcome. Retinoblastoma is a most common paediatric cancer. It is observed in our study tumour progression is initially slow till 18 months after that it grows exponential. Initially it is within the retina, subretinal space or vitreous, Invasion into deeper ocular structures like optic nerve, choroid, or scleral invasion promotes metastatic disease therefore grade of retinoblastoma present at the time of initiation of treatment and visual outcome seen in patients after treatment is related to delay in the treatment hence a higher degree of awareness in guardian and health care worker can reduce delay in treatment.

Eye is very sensitive organs we have to be extra careful while planning treatment of tumor because there is high probability of losing visual performance of eye. Treatment choice depends upon stage to Retinoblastoma like size of tumor and its nature, its location in reference to macula, optic disc, choroid and sclera and its spread in other eye and secondary tissue.

Visual outcome of patient depends on early diagnosis and proper management with advance technologies. Assessment of various components of Visual outcome helps us to get these results. Correlation of delay in treatment to Grade of Retinoblastoma present at the time of initiation of treatment in patients of our study group showed that those patients who initiated early treatment had lower grade of tumor compare to those who reported with delay and higher grade of tumor. Correlation of delay in treatment to Visual acuity achieved after treatment in patients of our study group showed that, those patients who initiated early treatment had better visual outcome compare to those who reported with delay and get poor visual outcome after treatment. Contrast sensitivity and colour vision are directly related to visual acuity hence they are affected in same proportion to delay in treatment as it is affecting visual acuity. Hyperopic astigmatism is most common in our study population because they belong to young age group where this is a common finding. Damage of visual outcome due to extra macular tumor is less than the damage caused by the macular tumor in all visual outcomes specially seen in electrophysiological test like VER and ERG.

Hence we realized that higher degree of awareness about advantage of early diagnosis and treatment can lead to better visual outcome and enhance quality of life of patient.

9. RECOMMENDATIONS

➢ Based on findings of research on `Importance of early diagnosis and treatment in getting better visual performance in Retinoblastoma` following recommendations can be made:

➢ Due to limitation of resources and availability of patients our sample size was small with fewer numbers of eyes. We recommend a detailed study at large scale so that a universally acceptable data with higher degree of accuracy can be achieved.

➢ Awareness campaign for Guardians, health care worker and public about importance of early detection of Retinoblastoma.

➢ Preparation of standard diagnostic and treatment protocols of various grades of retinoblastoma

➢ Assistance to Patient and family

➢ Genomic study to treat factors causing disease can also be of great help in treatment process.

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Reference:

1. Dimaras H, Kimani K, Dimba EA, Gronsdahl P, White A, Chan HS, Gallie BL. Retinoblastoma. The Lancet. 2012 Apr 14;379(9824):1436-46.
2. Dyer MA, Cepko CL. Regulating proliferation during retinal development. Nature Reviews Neuroscience. 2001 May 1;2(5):333-42.
3. Dimaras H, Corson TW, Cobrinik D, White A, Zhao J, Munier FL, Abramson DH, Shields CL, Chantada GL, Njuguna F, Gallie BL.

Retinoblastoma. Nature reviews Disease primers. 2015 Aug 27;1(1):1-23

4. Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, Keavney BD. Global birth prevalence of congenital heart defects 1970–2017: updated systematic review and meta-analysis of 260 studies. International journal of epidemiology. 2019 Apr 1;48(2):455-63.
5. Yeole BB, Advani S. Retinoblastoma: An epidemiological appraisal with reference to a population in Mumbai, India. Asian Pac J Cancer Prev. 2002 Jan 1;3(1):17-21.
6. Jain M, Rojanaporn D, Chawla B, Sundar G, Gopal L, Khetan V. Retinoblastoma in Asia. Eye. 2019 Jan;33(1):87-96.
7. Moll AC, Imhof SM, Schouten-Van Meeteren AY, Boers M. At what age could screening for familial retinoblastoma be stopped? A register based study 1945–98. British journal of ophthalmology. 2000 Oct 1;84(10):1170-2.
8. Das V. Affliction: health, disease, poverty. Fordham Univ Press; 2015
9. Usmanov RH, Kivelä T. Predicted trends in the incidence of retinoblastoma in the Asia-Pacific region. The Asia-Pacific Journal of Ophthalmology. 2014 May 1;3(3):151-7.
10. Hashimoto R, Waldman C. Eye Care in the Low Resource Setting. InContemporary Issues in Global Medicine and Moving Toward International Healthcare Equity 2022 (pp. 168-200). IGI Global.
11. Tomar AS, Finger PT, Gallie B, Kivelä TT, Mallipatna A, Zhang C, Zhao J, Wilson MW, Brenna RC, Burges M, Kim J. Global retinoblastoma treatment outcomes: association with national income level. Ophthalmology. 2021 May 1;128(5):740-53.
12. Levin B, Lieberman DA, McFarland B, Andrews KS, Brooks D, Bond J, Dash C, Giardiello FM, Glick S, Johnson D, Johnson CD. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology. 2008 May 1;134(5):1570-95.
13. Rodriguez-Galindo C, Wilson MW, Chantada G, Fu L, Qaddoumi I, Antoneli C, Leal-Leal C, Sharma T, Barnoya M, Epelman S, Pizzarello L. Retinoblastoma: one world, one vision. Pediatrics. 2008 Sep 1;122(3):e763-70.
14. Leander C, Fu LC, Peña A, Howard SC, Rodriguez-Galindo C, Wilimas JA, Ribeiro RC, Haik B. Impact of an education program on late diagnosis of retinoblastoma in Honduras. Pediatric blood & cancer. 2007 Nov;49(6):817-9
15. World Health Organization. Global technical strategy for malaria 2016-2030. World Health Organization; 2015 Nov 4.
16. Kaliki S, Shields CL, Rojanaporn D, Al-Dahmash S, . McLaughlin JP, Shields JA, Eagle Jr RC. High-risk retinoblastoma based on international classification of retinoblastoma: analysis of 519 enucleated eyes. Ophthalmology. 2013 May 1;120(5):997-1003.
17. Maheshwari A, Finger PT. Cancers of the eye. Cancer and Metastasis Reviews. 2018 Dec 15;37:677-90.
18. Hos D, Schlereth SL, Bock F, Heindl LM, Cursiefen C. Antilymphangiogenic therapy to promote transplant survival and to reduce cancer metastasis: what can we learn from the eye?. InSeminars in cell & developmental biology 2015 Feb 1 (Vol. 38, pp. 117-130). Academic Press.
19. Epstein JI, Walsh PC, Ballantine Carter H. Dedifferentiation of prostate cancer grade with time in men followed expectantly for stage T1c disease. The Journal of urology. 2001 Nov;166(5):1688-91.
20. Goldberg I, Susanna Jr R. Glaucoma: How to save your sight. Kugler Publications; 2015 Jun 3.
21. Shields CL, Mashayekhi A, Au AK, Czyz C, Leahey A, Meadows AT, Shields JA. The International Classification of Retinoblastoma predicts chemoreduction success. Ophthalmology. 2006 Dec 1;113(12):2276-80.
22. Zafar SN, Ahmad SQ, Zafar N. Retinoblastoma in an adult. BMC research notes. 2013 Dec;6:1-3.
23. Ortiz MV, Dunkel IJ. Retinoblastoma. Journal of child neurology. 2016 Feb;31(2):227-36.
24. Dimaras H, Corson TW, Cobrinik D, White A, Zhao J, Munier FL, Abramson DH, Shields CL, Chantada GL, Njuguna F, Gallie BL. Retinoblastoma. Nature reviews Disease primers. 2015 Aug 27;1(1):1-23.
25. Kiss S, Leiderman YI, Mukai S. Diagnosis, classification, and treatment of retinoblastoma.

International ophthalmology clinics. 2008 Apr 1;48(2):135-47.
26. Wyse E, Handa JT, Friedman AD, Pearl MS. A review of the literature for intra-arterial chemotherapy used to treat retinoblastoma. Pediatric radiology. 2016 Aug;46:1223-33
27. Collins VP. Brain tumours: classification and genes. Journal of Neurology, Neurosurgery & Psychiatry. 2004 Jun 1;75(suppl 2):ii2-11.
28. Madhavan J, Ganesh A, Kumaramanickavel G. Retinoblastoma: from disease to discovery. Ophthalmic research. 2008 Apr 29;40(5):221-6.
29. Kent LN, Leone G. The broken cycle: E2F dysfunction in cancer. Nature Reviews Cancer. 2019 Jun;19(6):326-38.
30. Sclafani RA, Holzen T. Cell cycle regulation of DNA replication. Annu. Rev. Genet.. 2007 Dec 1;41:237-80.
31. Pei L, Melmed S, Scheithauer B, Kovacs K, Benedict WF, Prager D. Frequent loss of heterozygosity at the retinoblastoma susceptibility gene (RB) locus in aggressive pituitary tumors: evidence for a chromosome 13 tumor suppressor gene other than RB. Cancer research. 1995 Apr 15;55(8):1613-6.
32. Sahin F, Sladek TL. E2F-1 binding affinity for pRb is not the only determinant of the E2F-1 activity. International journal of biological sciences. 2010;6(4):382.
33. Kent LN, Leone G. The broken cycle: E2F dysfunction in cancer. Nature Reviews Cancer. 2019 Jun;19(6):326-38.
34. Ottaviani D. In-depth characterization of human retinoblastoma subtype 2 and preclinical models (Doctoral dissertation, Université Paris Saclay (COmUE)).
35. Balmer A, Zografos L, Munier F. Diagnosis and current management of retinoblastoma. Oncogene. 2006 Aug;25(38):5341-9
36. Karcioglu ZA, Abboud EB, Al-Mesfer SA, Al-Rashed W, Pilapil DH. Retinoblastoma in older children. Journal of American Association for Pediatric Ophthalmology and Strabismus. 2002 Feb 1;6(1):26-32.
37. Kumar V, Surve A, Kumawat D, Takkar B, Azad S, Chawla R, Shroff D, Arora A, Singh R, Venkatesh P. Ultra-wide field retinal imaging: A wider clinical perspective. Indian Journal of Ophthalmology. 2021 Apr;69(4):824.
38. Uusitalo MS, Van Quill KR, Scott IU, Matthay KK, Murray TG, O'Brien JM. Evaluation of chemoprophylaxis in patients with unilateral retinoblastoma with high-risk features on histopathologic examination. Archives of Ophthalmology. 2001 Jan 1;119(1):41-8.
39. Kumar NK, Yogeswari A, Prakash MV, Umamaheswari TG. Comparing Slit Lamp Exophthalmometry with Hertel's Exophthalmometry and Computed Tomography Imaging in Quantification of Axial Proptosis–A Prospective Analytical Study. tnoa Journal of Ophthalmic Science and Research. 2023 Apr 1;61(2):163-8
40. Almaliotis D, Almpanidou S, Chatzimbalis T, Nikolaidou A, Talimtzi P, Karampatakis V. Correlation between color vision, visual acuity, contrast sensitivity and photo-stress recovery in the visually impaired. A cross-sectional study. Annals of Medicine and Surgery. 2023:10-97
41. Handley SE, Šuštar M, Tekavčič Pompe M. What can visual electrophysiology tell about possible visual-field defects in paediatric patients. Eye. 2021 Sep;35(9):2354-73.
42. Bhartiya S, Bali SJ, Sharma R, Chaturvedi N, Dada T. Comparative evaluation of TonoPen AVIA, Goldmann applanation tonometry and non-contact tonometry. International ophthalmology. 2011 Aug;31:297-302.
43. Bhartiya S, Bali SJ, Sharma R, Chaturvedi N, Dada T. Comparative evaluation of TonoPen AVIA, Goldmann applanation tonometry and non-contact tonometry. International ophthalmology. 2011 Aug;31:297-302.
44. Jain AB, Prakash VJ, Bhende M. Techniques of fundus imaging. Med. Vis. Res. Found. 2015 Jun;33:100.
45. MADAN R. Evaluation of the Posterior Segment Ocular Disorders by Usg B-Scan in Rural Hospital (Doctoral dissertation, Rajiv Gandhi University of Health Sciences)
46. Dermarkarian CR, Kini AT, Al Othman BA, Lee AG. Neuro-ophthalmic manifestations of intracranial malignancies. Journal of Neuro-Ophthalmology. 2020 Sep 1;40(3):e31-48.
47. Muralidhar N, Menon V. The eye of the beholder: Catching retinoblastoma early. Indian Journal of Health and Wellbeing. 2018 Jun 1;9(6):881-5.

48. Balmer A, Zografos L, Munier F. Diagnosis and current management of retinoblastoma. Oncogene. 2006 Aug;25(38):5341-9.
49. Soliman SE, Racher H, Zhang C, MacDonald H, Gallie BL. Genetics and molecular diagnostics in retinoblastoma—an update. The Asia-Pacific Journal of Ophthalmology. 2017 Mar 1;6(2):197-207.
50. Robson AG, Nilsson J, Li S, Jalali S, Fulton AB, Tormene AP, Holder GE, Brodie SE. ISCEV guide to visual electrodiagnostic procedures. Documenta Ophthalmologica. 2018 Feb;136:1-26.
51. Zugazagoitia J, Guedes C, Ponce S, Ferrer I, Molina-Pinelo S, Paz-Ares L. Current challenges in cancer treatment. Clinical therapeutics. 2016 Jul 1;38(7):1551-66
52. Friedman DN, Chou JF, Francis JH, Sklar CA, Li Y, McCabe M, Robison LL, Kleinerman RA, Oeffinger KC, Abramson DH, Dunkel IJ. Vision-targeted health-related quality of life in adult survivors of retinoblastoma. JAMA ophthalmology. 2018 Jun 1;136(6):637-41.
53. Chawla B, Jain A, Azad R. Conservative treatment modalities in retinoblastoma. Indian journal of ophthalmology. 2013 Sep;61(9):479.
54. Teutsch C. Patient–doctor communication. Medical Clinics. 2003 Sep 1;87(5):1115-45.
55. Khurram D, Zaheer N, Sharif N. Effects of primary chemotherapy, radiotherapy plus local treatments on regression patterns of posterior pole retinoblastoma. Pakistan Journal of Ophthalmology. 2011;27(4).
56. Maheshwari A, Finger PT. Cancers of the eye. Cancer and Metastasis Reviews. 2018 Dec 15;37:677-90
57. Fraunfelder FW. Liquid nitrogen cryotherapy for surface eye disease (an AOS thesis). Transactions of the American Ophthalmological Society. 2008 Dec;106:301.
58. Shields CL, Shields JA, Cater J, Lois N, Edelstein C, Gündüz K, Mercado G. Transpupillary thermotherapy for choroidal melanoma: tumor control and visual results in 100 consecutive cases. Ophthalmology. 1998 Apr 1;105(4):581-90.
59. Abramson DH, Schefler AC. Transpupillary thermotherapy as initial treatment for small intraocular retinoblastoma: technique and predictors of success. Ophthalmology. 2004 May 1;111(5):984-91.
60. Kunkler I, James N, Maher J. Radiotherapy. Expert Review of Anticancer Therapy. 2004 Jun 1;4(3):S37-.
61. Begg AC, Stewart FA, Vens C. Strategies to improve radiotherapy with targeted drugs. Nature Reviews Cancer. 2011 Apr;11(4):239-53.
62. Shields CL, Shields JA, Cater J, Gündüz K, Miyamoto C, Micaily B, Brady LW. Plaque radiotherapy for uveal melanoma: long-term visual outcome in 1106 consecutive patients. Archives of Ophthalmology. 2000 Sep 1;118(9):1219-28.
63. Aird EG, Folkard M, Mayes CR, Bownes PJ, Lawson JM, Joiner MC. A purpose-built iodine-125 irradiation plaque for low dose rate low energy irradiation of cell lines in vitro. The British journal of radiology. 2001 Jan;74(877):56-61.
64. Fass L. Imaging and cancer: a review. Molecular oncology. 2008 Aug 1;2(2):115-52.
65. Shields JA. The expanding role of laser photocoagulation for intraocular tumors: The 1993 H. Christian Zweng Memorial Lecture. Retina. 1994 Jan 1;14(4):310-22.
66. Fisher JW, Sarkar S, Buchanan CF, Szot CS, Whitney J, Hatcher HC, Torti SV, Rylander CG, Rylander MN. Photothermal response of human and murine cancer cells to multiwalled carbon nanotubes after laser irradiation. Cancer research. 2010 Dec 1;70(23):9855-64
67. Shields CL, Meadows AT, Leahey AM, Shields JA. Continuing challenges in the management of retinoblastoma with chemotherapy. Retina. 2004 Dec 1;24(6):849-62.
68. Dobson JM, Hohenhaus AE, Peaston AE. Cancer chemotherapy. Small Animal Clinical Pharmacology 2nd ed.(Maddison, JE, Page, SW and Church, DB eds.), Saunders Elsevier, Edinburgh. 2008 Jan 1:330-66
69. Frei III E, Canellos GP. Dose: a critical factor in cancer chemotherapy. The American journal of medicine. 1980 Oct 1;69(4):585-94.
70. Nagai H, Sumino Y. Therapeutic strategy of advanced hepatocellular carcinoma by using combined intra-arterial chemotherapy. Recent Patents on Anti-Cancer Drug Discovery. 2008 Nov 1;3(3):220-6.
71. Klufas MA, Gobin YP, Marr B, Brodie SE, Dunkel IJ, Abramson DH. Intra-arterial chemotherapy as a treatment for intraocular retinoblastoma: alternatives to direct ophthalmic artery

catheterization. American journal of neuroradiology. 2012 Sep 1;33(8):1608-14.
72. Huang R, Boltze J, Li S. Strategies for improved intra-arterial treatments targeting brain tumors: a systematic review. Frontiers in Oncology. 2020 Aug 26;10:1443.
73. Yousef YA, Al Jboor M, Mohammad M, Mehyar M, Toro MD, Nazzal R, Alzureikat QH, Rejdak M, Elfalah M, Sultan I, Rejdak R. Safety and efficacy of intravitreal chemotherapy (melphalan) to treat vitreous seeds in retinoblastoma. Frontiers in Pharmacology. 2021 Jul 12;12:696787.
74. Smith SJ, Smith BD, Mohney BG. Ocular side effects following intravitreal injection therapy for retinoblastoma: a systematic review. British Journal of Ophthalmology. 2013 Nov 1.
75. Mohammad M, Shehada R, Al-Nawaiseh I, Mehyar M, AlHussaini M, Jaradat I, Sultan I, Halalsheh H, Khzouz J, Yousef YA. A comparison of high risk pathological features between primary and secondary enucleation for retinoblastoma. European Journal of Ophthalmology. 2023 Feb 9:11206721231155671.
76. Patel BC, Perry JD. Enucleation for Ocular Tumors. Clinical Ophthalmic Oncology: Orbital Tumors. 2019:231-40.
77. Baino F, Potestio I. Orbital implants: State-of-the-art review with emphasis on biomaterials and recent advances. Materials Science and Engineering: C. 2016 Dec 1;69:1410-28.
78. Gerteis M, Edgman-Levitan S, Daley J, Delbanco TL, editors. Through the patient's eyes: understanding and promoting patient-centered care. John Wiley & Sons; 2002 May 3.
79. Gragoudas E, Li W, Goitein M, Lane AM, Munzenrider JE, Egan KM. Evidence-based estimates of outcome in patients irradiated for intraocular melanoma. Archives of ophthalmology. 2002 Dec 1;120(12):1665-71
80. Almater A, Alfaleh A, Alshomar K, AlMesfer S. Retinoblastoma: update on current management. Retinoblastoma—past, present and future. 2019 Sep 19.
81. Shields CL, Shields JA, Cater J, Othmane I, Singh AD, Micaily B. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. Ophthalmology. 2001 Nov 1;108(11):2116-21.
82. HASSAN F, YASSA G, NASSEF AA, ZAKARIA A. The Role of Intra-Arterial Chemotherapy in the Manegment of Retinoblastoma in Comparison with Other Modalities. The Medical Journal of Cairo University. 2019 Sep 1;87(September):3507-17.
83. Kincaid MC. Uveal Melanoma: Enucleation has been the standard therapeutic intervention for malignant melanoma of the uveal tract, but alternative approaches offer hope for tumor control and vision preservation. Cancer Control. 1998 Jul;5(4):299-309.
84. Qi D, Gang S, Shengli S, Yuebing L, Jing Z, Jing L, Jing H, Zhiping C. Comparison of clinical outcomes of ophthalmic artery chemotherapy with systemic vein-eye artery chemotherapy for retinoblastoma in children. Chinese Journal of Experimental Ophthalmology. 2022:1071-7.
85. Huang D, Zhang Y, Zhang W, Wang Y, Zhang P, Hong L, Zhou Y, Han T, Zhi T. Study on clinical therapeutic effect including symptoms, eye preservation rate, and follow-up of 684 children with retinoblastoma. European Journal of Ophthalmology. 2013 Jul;23(4):532-8.
86. Bas Z, Dalvin LA, Tadepalli S, Rao R, Shah A, Leahey AM, Shields CL. Outcomes of intravenous chemotherapy (chemoreduction) for retinoblastoma based on patient age in 964 eyes of 554 patients. The Asia-Pacific Journal of Ophthalmology. 2021 Jul 1;10(4):373-80.
87. Shields CL, Mashayekhi A, Demirci H, Meadows AT, Shields JA. Practical approach to management of retinoblastoma. Archives of Ophthalmology. 2004 May 1;122(5):729-35.
88. Demirci H, Shields CL, Meadows AT, Shields JA. Long-term visual outcome following chemoreduction for retinoblastoma. Archives of Ophthalmology. 2005 Nov 1;123(11):1525-30.
89. Schefler AC, Cicciarelli N, Feuer W, Toledano S, Murray TG. Macular retinoblastoma: evaluation of tumor control, local complications, and visual outcomes for eyes treated with chemotherapy and repetitive foveal laser ablation. Ophthalmology. 2007 Jan 1;114(1):162-9.
90. Holbek S, Ehlers N. Long-term visual results in eyes cured for retinoblastoma by radiation. Acta Ophthalmologica. 1989 Oct;67(5):560-6.

91. Holbek S, Ehlers N. Long-term visual results in eyes cured for retinoblastoma by radiation. Acta Ophthalmologica. 1989 Oct;67(5):560-6.
92. Abramson DH, Melson MR, Servodidio C. Visual fields in retinoblastoma survivors. Archives of Ophthalmology. 2004 Sep 1;122(9):1324-30.
93. Wenzel D, Brandl U, Beck JD, Cedzich C, Albert F. Visual evoked potentials in tumors from orbita to occipital lobe in childhood. Neurosurgical review. 1988 Sep;11(3-4):279-86.
94. Lubinski W, Zajaczek S, Sych Z, Penkala K, Palacz O, Lubinski J. Electroretinographic changes in the inner retinal layers of the retained eyes of patients with sporadic unilateral retinoblastoma. Ophthalmic Genetics. 2002 Jan 1;23(2):99-107.
95. Goddard A, Kingston J, Hungerford J. Delay in diagnosis of retinoblastoma: risk factors and treatment outcome. The British journal of ophthalmology. 1999 Dec;83(12):1320.
96. Batra A, Kumari M, Paul R, Patekar M, Dhawan D, Bakhshi S. Quality of life assessment in retinoblastoma: a cross-sectional study of 122 survivors from India. Pediatric Blood & Cancer. 2016 Feb;63(2):313-7.
97. De Graaf P, Barkhof F, Moll AC, Imhof SM, Knol DL, van der Valk P, Castelijns JA. Retinoblastoma: MR imaging parameters in detection of tumor extent. Radiology. 2005 Apr; 235(1):197-207.
98. 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 genetics. 2009 Jan 1;30(1):31-6.
99. Moser DK, McKinley S, Dracup K, Chung ML. Gender differences in reasons patients delay in seeking treatment for acute myocardial infarction symptoms. Patient education and counseling. 2005 Jan 1;56(1):45-54.
100. Abramson DH, Beaverson K, Sangani P, Vora RA, Lee TC, Hochberg HM, Kirszrot J, Ranjithan M. Screening for retinoblastoma: presenting signs as prognosticators of patient and ocular survival. Pediatrics. 2003 Dec 1;112(6):1248-55.
101. Inoue M, Arakawa A, Yamane S, Kadonosono K. Long-term results of intravitreal ranibizumab for the treatment of retinal angiomatous proliferation and utility of an advanced RPE analysis performed using spectral-domain optical coherence tomography. British Journal of Ophthalmology. 2014 Mar 5
102. Filler G. AsSALTed: Saving Lives and Money by Adopting the Finnish Salt Laws. FriesenPress; 2020 Aug 28.
103. Homogenous semi-translucent, gray ,“fish-flesh” lesion
104. Vollmer S, Menssen A, Trommler P, Schendel D, Prinz JC. T lymphocytes derived from skin lesions of patients with psoriasis vulgaris express a novel cytokine pattern that is distinct from that of T helper type 1 and T helper type 2 cells. European journal of immunology. 1994 Oct;24(10):2377-82.
105. Campochiaro PA, Morgan KM, Conway BP, Stathos J. Spontaneous involution of subfoveal neovascularization. American journal of ophthalmology. 1990 Jun 1; 109(6):668
106.-75.