Original Research Article

Retinoblastoma – lessons learned about patterns of care and contributory factors from 5 years' experience in a tertiary care center in Eastern India

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Abstract

Objectives: Retinoblastoma is the most common intraocular malignancy afflicting children worldwide. Even though there are enough data about the epidemiology of retinoblastoma in western population, there are only few reports from developing countries like India. In this retrospective study, we aimed to describe the epidemiological patterns, survival characteristics and prognostic factors of retinoblastoma.

Materials & methods: From medical records, we retrospectively analyzed the data of 68 children diagnosed in our hospital between January 2013 and December 2017 as having retinoblastoma. Data on sex, religion, laterality, age at diagnosis, presenting signs, family history, lag time for treatment, cause of such lag time and spread of tumor, treatment mode, and survival time were collected.

Results: The median age of onset was 22 ± 19.73 months (range 2-92 months).The median patient age of onset of the unilateral cases was 23 ± 20.6 months, and that of the bilateral cases was 21 ±16.2 months. The median overall survival was 28.1±2.2 months. For unilateral cases, it was 30.1±2.5 months and for bilateral cases it was 19.7±2.9 months. The overall progression free survival (PFS) was 22.2±2.3 months. For unilateral cases, it was 24.18±2.7 months and for bilateral cases it was 13.9±2.9 months.

4 cases of familial retinoblastoma were reported. Among the 13 bilateral cases, 3 were found to have pinealoblastoma too. On Cox regression analysis, age of onset below 36 months, diagnostic delay of less than 5 months and delay of treatment initiation (after diagnosis) less than 2 months were found to have significant effect on OS. The former two were found to have significant effect on PFS but not the latter ($p<0.05$ and $HR>1$).

Conclusions: Almost 81% of patients presented at an advanced stage of the disease, the reason being accounted by diagnostic and therapeutic delay by virtue of a number of causes, the major one being eluded by apparently nonviolent yet ineffective alternative medicine practices. In spite of following the institutional protocols which are at par to the international guidelines, analysis shows much poorer survival in this study compared to those of developed countries. The cause might be such late presentation of the cases in already advanced stages of the disease.

Introduction

As per Globocan[10] 2018 [Annual Global Cancer related epidemiological data published by Union for International Cancer Control (UICC) affiliated by WHO] and ICMR data[1] (data based on a study affiliated by Indian Council of Medical Research published in 2014 in Indian Journal of Pediatrics, more recent data could not be found during the study), with an incidence rate of up to 12.3 per million children (0-14years), retinoblastoma is the most common intraocular malignancy of childhood. Even though there are enough data about the epidemiology of retinoblastoma in western population, there are only few reports from developing countries like India.

The mortality rate has been much reduced in developed countries over the past several, decades, and eye- or vision-preserving management has improved progressively. However, the mortality rate varies in many developing countries. To improve the survival rate in developing countries, the prognostic factors must be identified. Data from India, more from Eastern India is relatively scarce, hence the study.

Methods

We retrospectively analyzed the medical records of 68 children diagnosed histologically(post enucleation biopsy in cases where there is no potential of restoration of normal vision or painful glaucoma or completely disrupted retina at

the time of diagnosis, decision being Ophthalmologist's call) or radiologically(radiological diagnosis by bilateral orbital ultra-sonogram was preferred in cases where vision sparing intent of treatment was considered and staging/extent of extraocular invasion/presence of bilateral disease/pinealoblastoma was confirmed by MRI of brain and bilateral orbits) at or referred to the Regional Institute of Ophthalmology, Kolkata and treated in conjunction with Department of Radiation Oncology, Medical College & Hospital, Kolkata between January 2013 and December 2017 as retinoblastoma. Workup for distant extraocular spread were done for advanced cases by CSF study (for malignant cells) or radionuclide scans for bony/visceral metastasis (as per physician's suspicion from symptoms).
Information collected included sex, laterality, age at diagnosis, presenting signs, duration of symptoms before diagnosis, lag time before treatment, time from onset to treatment, staging , presence of poor prognostic factors, treatment modality, survival time, and family history, all obtained from medical records and phone calls. This study is based on follow-up data collected till 30th November, 2018.
The patients were followed for a median period of 23.5 ±17.9 months (range 6–71 months).
The International Classification System for Retinoblastoma[2] (Table 1- ICRB) was used to stage the disease on presentation and grossly divided into unilateral and bilateral cases on presentation. Neo-adjuvant chemotherapy/ chemoreduction (Vincristine0.05mg/kg on D1, Etoposide 5mg/kg on D1 & D2, Carboplatin 18.6mg/kg on D1), enucleation, vision sparing procedures, adjuvant chemotherapy (regimen same as chemoreduction) and external beam radiotherapy (EBRT using Thetatron780c Cobalt60: 45Gy/20# in adjuvant setting and 50Gy/25# in radical setting) were given as per grouping and staging.
Descriptive statistical tests were used for analysis of baseline/demographic characteristics. The Kaplan-Meier method was used to calculate the cumulative survival rate, with censoring at the time of last contact. The following factors were analyzed using the Kaplan-Meier method: diagnostic delay (≤5 months or >5 months), age of onset (<36 months or ≥36 months) and time lag in between diagnosis and treatment initiation ((≤2months or >2 months). The cut-off values for grouping time between onset of symptoms and treatment, and lag time before treatment were based on their mean values. Cox multivariate regression analysis was used as a final method for analyzing the significance of the risk factors. P value of less than 0.05 was considered statistically significant.
All analysis were done by IBM SPSS software v.23.

Results

Demography

Among the 68 patients, 36(52.9%) were male and 32(47. 1%) were female.
Of the patients, the majority comprised of the Muslim community (38.24%) but followed by a 25% of the patients comprising exclusively of Kols & Santhals of the 18 tribal communities that reside in Eastern India. Though the 2nd majorities (33.82%) were from Hinduism background, Hindus comprise of the majority population in this part of the country (Figure 2).

Patient characteristics

55 (80.9%) were unilateral cases and 13 (19.1%) were bilateral. With respect to family history, 64 (94.1%) were sporadic cases, 4 (5.9%) were familial (Table 2). The familial nature of the disease could not be confirmed by genetic analysis of Rb1 mutation due to financial constraints. The 4 cases were stamped familial on basis of history of retinoblastoma incidence among 1st degree relatives and siblings.
The median age of onset was 22 ± 19.73 months (range 2-92 months).The median patient age of onset of the unilateral cases was 23 ± 20.6 months, and that of the bilateral cases was 21 ±16.2 months.
Out of the bilateral cases there were 3 cases of which presented with a pinealoblastoma at presentation.

Presenting Signs

The most common presenting signs were leukocoria (30 cases, 44.1%), proptosis (18 cases, 26.5%) and blurred or poor vision (9 cases, 13.2%). The other presenting signs, including congestion (8 cases, 11.8%) and pain (3 cases, 4.4%), were less common. Decrease in visual acuity or poor/blurred vision was complained by parents on basis of their meticulous observation that their children were getting injuries from repeatedly getting hit or obstructed by objects on their path of walking or not responding well to games like peek-a-boo, when bright colored objects were shown to them from one side or both sides of their field of vision. These children were mostly old enough to identify colors or walk without help of their parents. Visual acuity was tested in preschoolers by color tests and picture based visual acuity tests. For infants, pupillary response and "ability to follow target" were recorded.

Diagnostic delay, Lag Time before Treatment after diagnosis and Interval between Onset of Symptoms and Treatment

The delays occurs majorly in the diagnostic pathway. Retinoblastoma being a silent tumor, it takes longer to manifest obvious symptoms to hinder the child's activity, delaying the entire diagnostic process.[6] Therefore, very often, depending on the symptoms, it takes the patient longer to seek medical care.
Delay may also be due to factors related to professional care and health care. The diagnostic workup is often a lengthy process, involving a complex algorithm and serial procedures (described under methods).
Delay also occurred between diagnosis and treatment initiation due to certain waiting period for vacancy of surgery/radiotherapy timing slots as a result of lack of proper infrastructure to handle a greater number of patients.
If the time period between the initial consultation and treatment is prolonged, patients may experience tumor and clinical stage progression, which affects the therapeutic schedule with possible negative influence on prognosis. This is a relevant clinical problem.
The median diagnostic delay was 5 months (range 1-36 months); the median lag time for treatment initiation was 1 month (range, few days to 12 months) and median time interval between onset of symptoms and treatment initiation was 6 months (range 1-39 months).
Causes of such delay enumerated in Figure 5.

Mode of Treatment

For unilateral diseases at diagnosis, treatment was given according to ICRB grouping. Group A was treated with upfront laser photocoagulation. Group B&C was given 2-3 cycles of neo-adjuvant chemoreduction (NACT) followed by photocoagulation for well responsive tumors (assessed by MRI scans). For non-responsive/minimally responsive tumors, if vision can be potentially preserved, EBRT is given, if not/extra-ocular disease is suspected, enucleation was considered. Group D&E were treated in lines of Group B&C if there was possibility of vision preservation, if not, upfront enucleation was considered. Need for adjuvant therapy (radiation/chemotherapy) after surgery was decided by a multimodality tumor board on basis of presence of poor prognostic factors (vide infra).
For bilateral disease, each eye was treated individually in line of treatment of unilateral disease of the respective eye. NACT was considered in almost all cases of bilateral disease.
Table 3 shows the different treatment modalities used in the study cases.

Known poor prognostic factors

From literature, certain established pathological[11] and clinical[12] factors predicting poor prognosis is already known to us. They can be enumerated as: optic nerve transection involvement, choroidal invasion, orbital involvement, extraocular muscle involvement, regional/distal lymph node involvement, CNS dissemination, scleral involvement, anterior chamber seedings, iris infiltration, ciliary body infiltration and distant visceral metastasis.

The most common known poor prognostic factor in patients was post-enucleation biopsy showing optic nerve transection involvement (29.41%). Ciliary body infiltration was the least common (1.47%). 26.47% patients did not show any known poor prognostic marker (Figure 6).
For the sake of ease of understanding, we categorized the cases into advanced and no advanced cases (on presentation). The cases which presented with bilateral disease with at least one sided Group E disease or unilateral Group E disease were put into advanced category, rest in the not advanced category. It was found each year, majority of registered cases presented at an advanced stage (2013- 78.6%, 2014-77.8%, 2015- 83.33%, 2016- 75%, 2017- 91.67%) (Figure 7).

Survival Analysis

Out of the 68 patients studied, 37 patients were still alive till 30th November 2018. 19 out of these 37 patients are living without progression or relapse and 18 patients are living with disease progression or relapse, who are either on palliative or second line treatment.
The median survival was 28.1±2.2 months. For unilateral cases, it was 30.1±2.5 months and for bilateral cases it was 19.7±2.9 months. The overall progression free survival (PFS) was 22.2±2.3 months. For unilateral cases, it was 24.18±2.7 months and for bilateral cases it was 13.9±2.9 months.
On Cox regression analysis, age of onset below 36 months, diagnostic delay of less than 5 months and delay of treatment initiation(after diagnosis) less than 2 months were found to have significant effect on OS ($p<0.05$ and $HR>1$) (Table 4). The former two were found to have significant effect on PFS ($p<0.05$ and $HR>1$) but post diagnosis delay of treatment initiation was not (Table 5).

Discussion

In spite of following the institutional protocols which are at par to the international guidelines, analysis shows much poorer survival in this study compared to those of western countries(Table 6), though their incidence rates are comparable with us(Table 7). The cause might be late presentation of the cases in already advanced stages of the disease.
We can also draw a rough correlation between overall socioeconomic development of a country and pattern of care being received by the patients of that country. It ranges from 100% and 96.3% 5 years survival in first world countries like UK(MacCarthy *et al.*) and USA(Fernandes *et al.*) respectively and reduces to 83% in a third world country like Iran(Naseripour *et al.*) for unilateral cases. For bilateral cases, similar trends are seen.
In the current study, though 5 years follow-up was not possible due to time constraints, it's not very difficult to predict a poorer outcome from median OS of
30.1±2.5 months and median PFS of 19.7±2.9 for unilateral cases and median OS of 19.7±2.9 months and median PFS of 13.9±2.9 for bilateral cases.
Almost 81% of patients presented at an advanced stage of the disease, the reason being accounted by diagnostic and therapeutic delay by virtue of a number of causes, the major one being eluded by apparently nonviolent yet ineffective alternative medicine practices. The causes of refusal of treatment or delay in treatment are multifactorial and include cultural factors, refusal of enucleation, and desire to use alternative medicine or to seek a second opinion, all driven by a strong fear of the loss of an eye. For parents, enucleation is not acceptable as it means the loss of a vital organ and results in major cosmetic destruction and great injury to the child's image. Moreover, a small tumor in this anatomic site does not seem life-threatening to parents. Infants and young children do not complain of the symptoms, so the family ignores the urgent need for treatment.
To sum up, infrastructural insufficiency at remote areas, a long chain of referral centers, silent nature of the disease onset, repulsion from the idea of loss of an eye or adverse effects of conventional management and endorsements of ineffective alternate medical practices results in delay in diagnosis and treatment initiation and also upstaging of the disease.

Limitations: Due to obvious time limitations adequate follow-up and calculation of 5 years or 10 years survival was not possible. LINAC based conformal therapy was not practiced in our institution during the time of treatment of these cases, hence dosimetry related difference in tumor control and its effect on prognosis are unaccounted for. Due to financial constraints, genetic assessment and counselling could not offered. This study being done retrospectively based on medical records and follow-up data recorded by a number of attending consultants and residents of a tertiary care teaching hospital, observer bias can be a significant factor affecting accurate data gathering.

Conclusion

To conclude, a lower age of onset (<36 months) and lesser diagnostic delay (<5 months) were found to significantly affect both OS & PFS positively. Reduced delay in treatment initiation after diagnosis (<2 months) was found to significantly increase OS only.
Hence, programs need to be initiated for educating parents about signs to look for and importance of early diagnosis and treatment initiation. Screening programs can also help in reducing the mortality and morbidity to reach a better outcome. Proper steps should be taken to control inappropriate alternative medicine practices.

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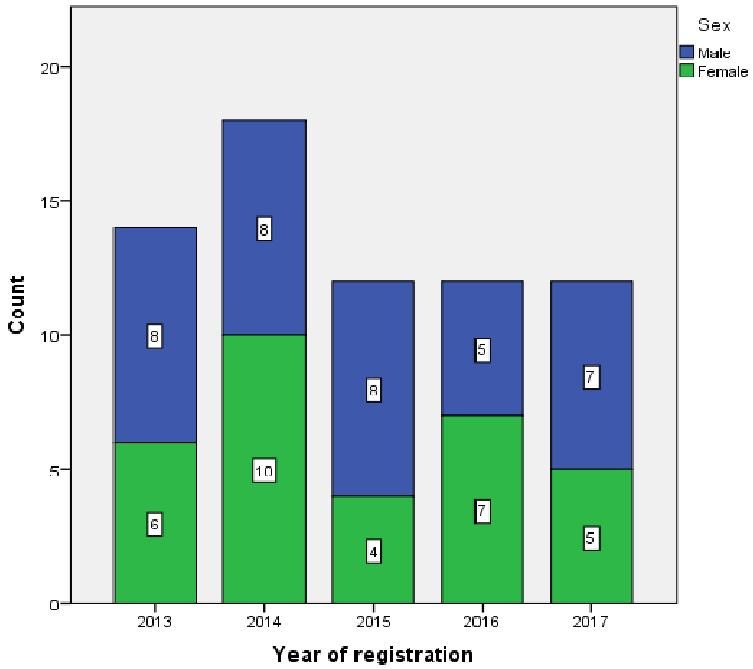

Figure 1: Bar chart showing sex distribution of registered cases from 2013-2017 year wise.

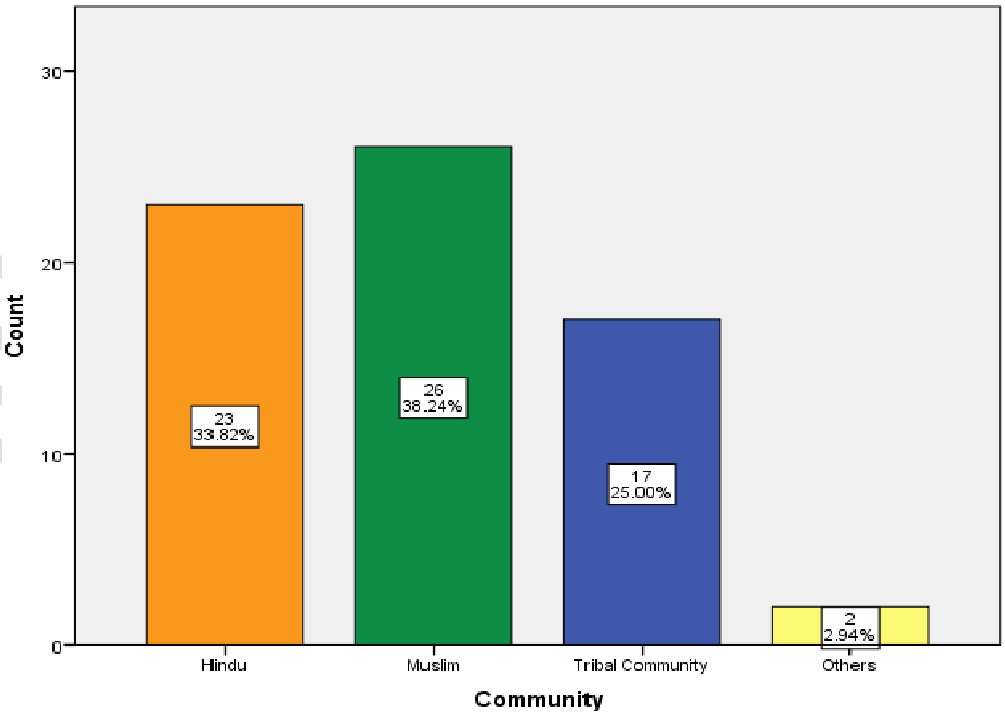

Figure 2: Bar chart showing distribution of registered cases by cultural background.

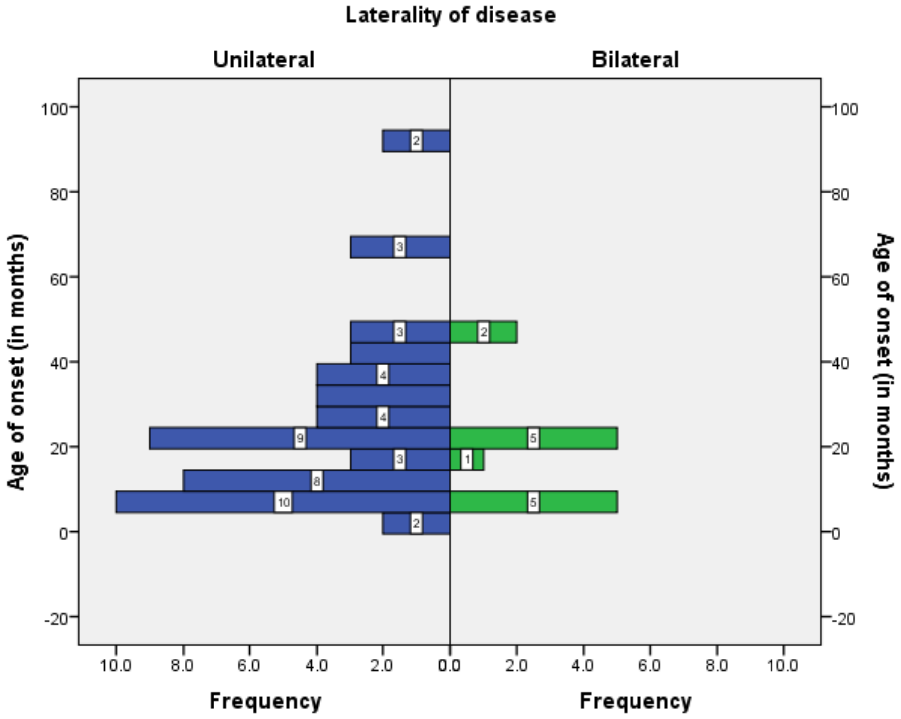

Figure 3: An age-of-onset pyramid with respect to laterality.

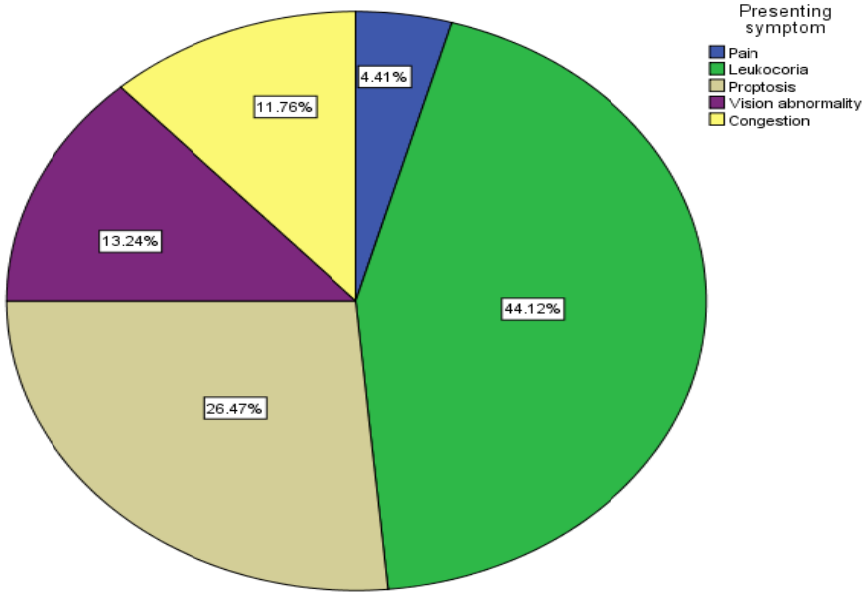

Figure 4: Pie chart showing different presenting symptoms and their frequencies.

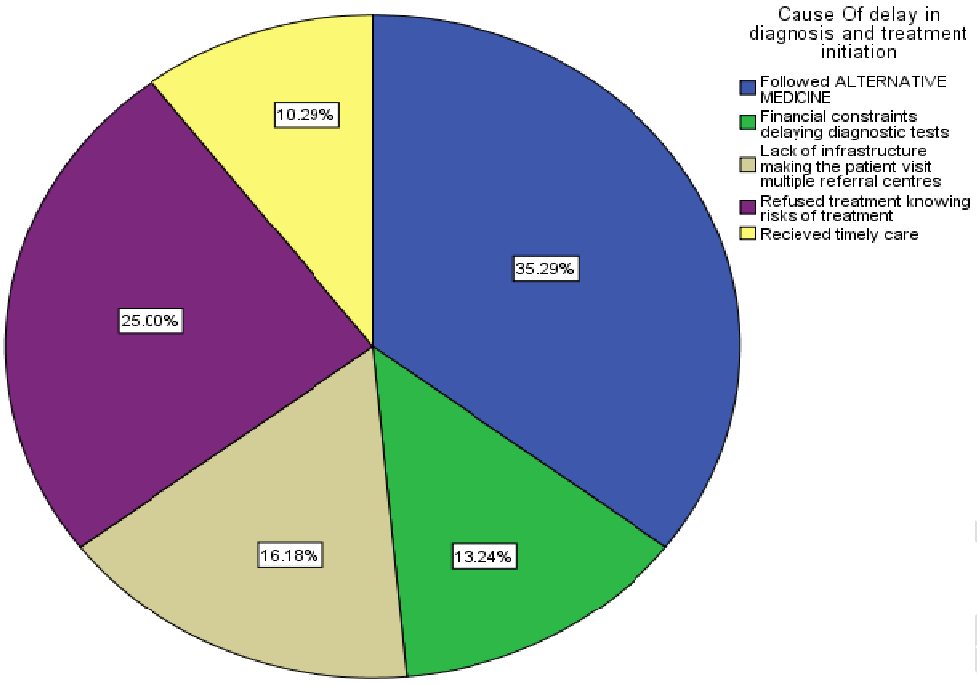

Figure 5: Pie chart showing different reasons for delay in diagnosis and treatment and their frequencies.

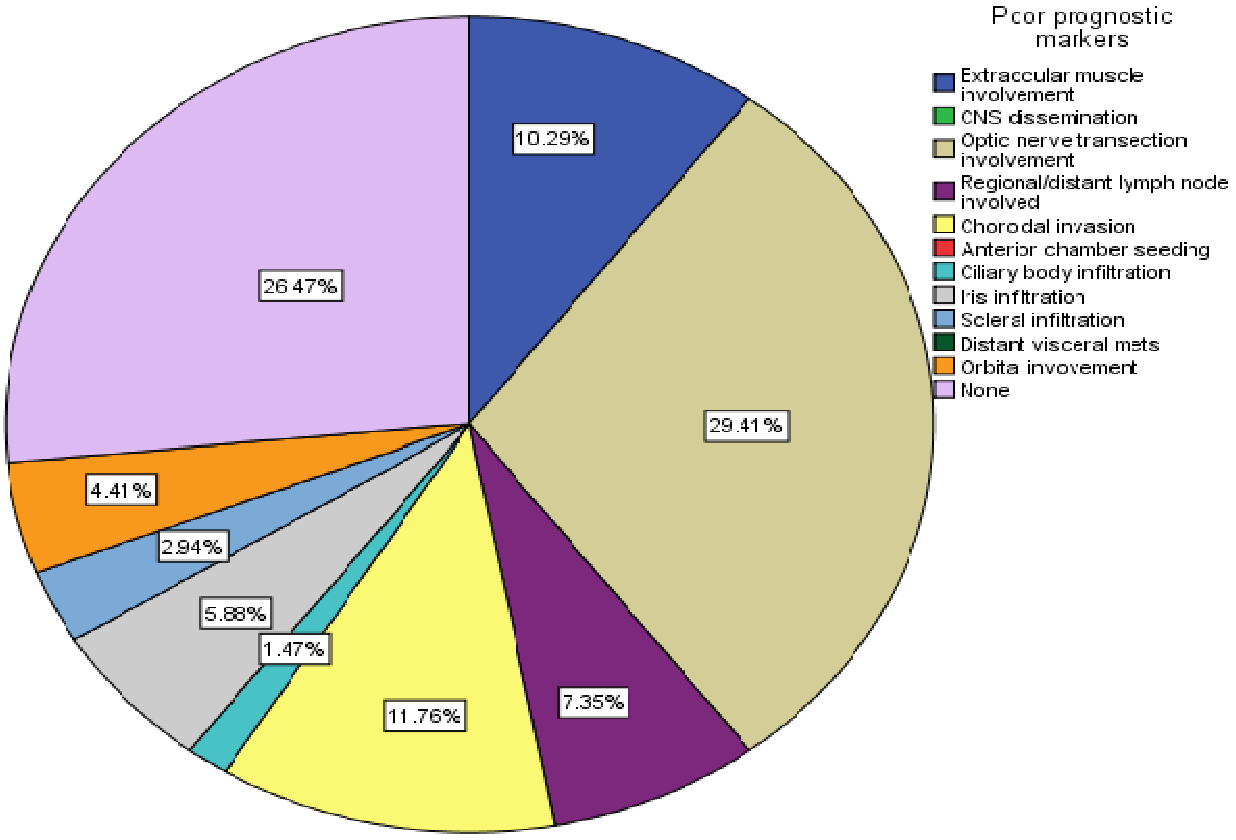

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Figure 6: Pie chart showing frequency of presence of different known poor prognostic factors.

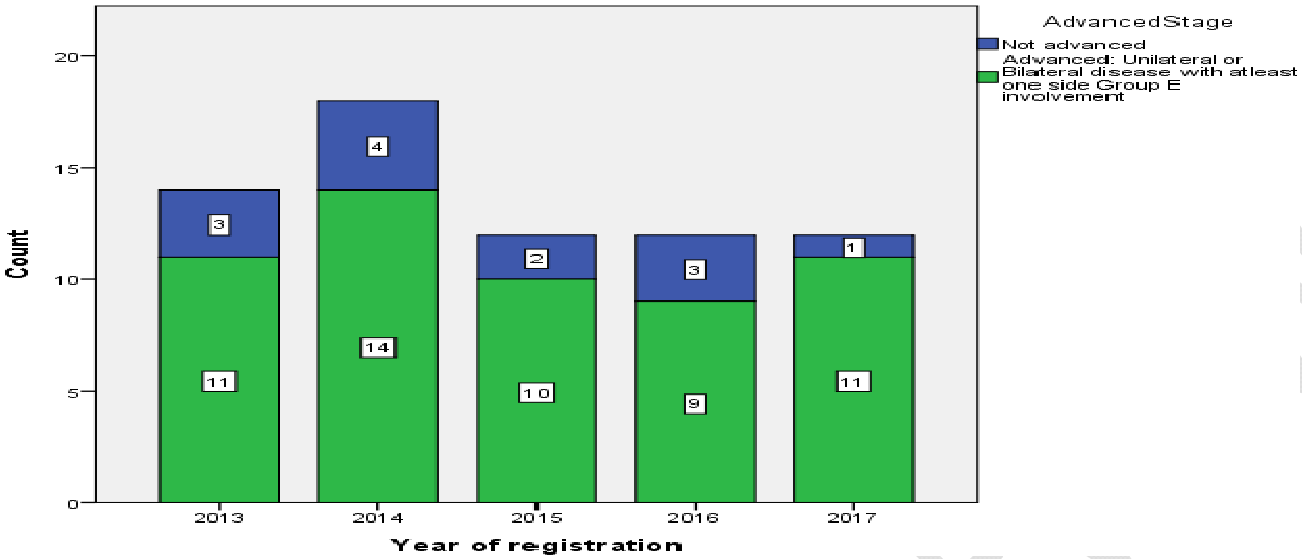

Figure 7: Bar chart showing frequency of cases presenting at an advanced stage from 2013-2017 year wise.

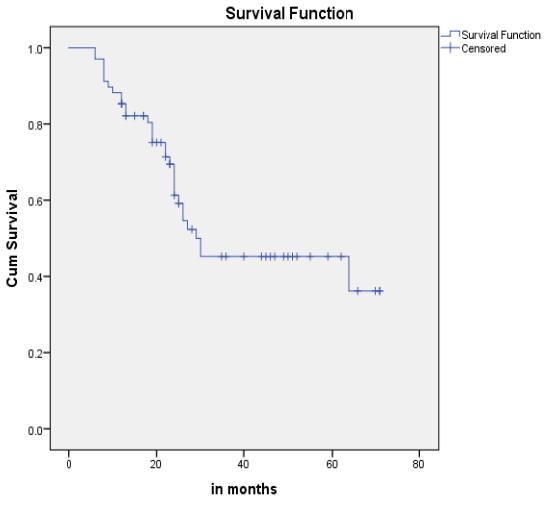

Fig. 8: Kaplan-Meier survival plot showing overall survival.

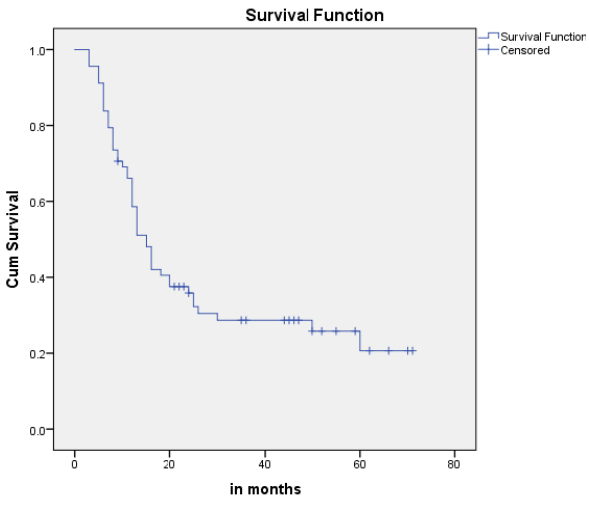

Fig. 9: Kaplan-Meier survival plot showing progression free survival.

Table 1: International Classification of Retinoblastoma (ICRB)

Group A	Small intraretinal tumors (< 3mm) away from foveola and disc.
Group B	Tumors > 3mm, macular or juxtapapillary location, or with 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	Extensive retinoblastoma occupying >50% of the globe with or without neovascular glaucoma, hemorrhage, extension of tumor to optic nerve or anterior chamber.

Table 2: Characteristics of cases with respect to familial nature and laterality.

		Laterality		
		Unilateral	Bilateral	Total
Family history	Familial	1	3	4
	Sporadic	54	10	64
Total		55	13	68

Table 3: Table showing different treatment modalities used percentage of the cases treated by different modalities

Treatment given	Unilateral disease	Bilateral disease	Frequency	%
Photocoagulation	5	--	5	7.4
Enucleation of affected eye only	10	--	10	14.7
Enucleation of both eyes only	--	2	2	2.9

	NACT followed by enucleation followed by Adjuvant RT and photocoagulation of other eye for asymmetric bilateral disease	--	3	3	4.4
	NACT followed by surgery followed by adjuvant RT for unilateral disease	1	--	1	1.5
	Enucleation followed by adjuvant RT	5	--	5	7.4
	NACT followed by enucleation of the affected eye followed by EBRT for both eyes for bilateral disease	--	7	7	10.3
	NACT followed by Radical RT due to lack of feasibility/consent for surgery	3	1	4	5.9
	Enucleation followed by Adjuvant CT	6	--	6	8.8
	Enucleation followed by Adjuvant RT followed by Adjuvant CT	21	--	21	30.9
	NACT followed by focal consolidation therapy followed by Adjuvant chemotherapy	4	--	4	5.9
	Total	55	13	68	100.0

Table 4: Multivariate analysis of prognostic factors (statistically significant ones with HR>1) affecting overall survival, hazard ratios, 95% CI

Variables	Adjusted HR	95% confidence interval	P value
Age of onset<36 months	9.815	0.318 - 30.217	0.000084
Diagnostic delay<5 months	11.213	0.251 - 50.166	0.003
Delay of treatment initiation after diagnosis< 2 months	1.291	0.104 - 16.059	0.048

Table 5: Multivariate analysis of prognostic factors (statistically significant ones with HR>1) affecting progression free survival, hazard ratios, 95% CI

Variables	Adjusted HR	95% confidence interval	P value
Age of onset<36 months	4.844	0.358 - 65.627	0.004
Diagnostic delay<5 months	7.734	0.129 - 46.137	0.037

Table 6: Literature review comparing survival in different countries to current study

Study	Survival in unilateral cases	Survival in bilateral cases
[3]Retinoblastoma in the **United States**: Fernandes *et al.*	5-year OS 96.3%	5-year OS 92.5%
[4]Retinoblastoma in **Taiwan**: Survival Rate and Prognostic Factors: Chang *et al.*	5-year OS 88.1%	5-year OS 64.3%
[5]Retinoblastoma Survival in **Iran**:10 Years' Experience of a Referral Center Naseripour *et al.*	5-year OS 83.0%	5-year OS 63.7%
[6]Retinoblastoma: treatment and survival in **Great Britain** 1963 to 2002.MacCarthy *et al.*	5-year OS 100%	5-year OS 97%
Current study	*Median OS* *30.1±2.5 months* Median PFS 19.7±2.9 months	*Median OS* *19.7±2.9 months* Median PFS 13.9±2.9 months

Table 7: Table comparing incidence rates of retinoblastoma in different countries with India

Country	**Incidence in boys** (AAR per million)	**Incidence in girls** (AAR per million)
USA[6]	**13.2**	**11.2**
UK[7]	**4.5**	**4.1**
Taiwan[8]	**65.8/million live births**	**48.5/million live births**
Iran[9]	**66.7/million live births**	**55.6/million live births**
India[1]	**12.3**	**6.7**