REVIEW ARTICLE

Clinical presentation, treatment, and outcomes of retinoblastoma in India: A literature review

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ABSTRACT

Background: India has the highest incidence of retinoblastoma globally and is one of the six Asian countries identified to contribute 43% to the global retinoblastoma cases. Data on clinical presentation, treatment, and outcomes were reviewed which can serve as basis in the creation of clinical guidelines, policies and programs, and resource allocation in the diagnosis and management of retinoblastoma in India.

Methodology: Articles on retinoblastoma in India gathered from different databases were reviewed for clinical features, treatment, and outcomes.

Result: Fourteen articles with 3,666 patients involving around 4,945 eyes seen from 1983-2017 were reviewed. The median age at consult ranged from 14-48 months. The median delay of consult ranged from 2-9 months. Majority of the patients were males (59%) and unilateral disease was present in 63%. Family history was reported in 4%. Retinoblastoma was intraocular in at least 75% of eyes. Systemic chemotherapy was the most used treatment option given to >2,042 eyes. Enucleation was done in >1,695 eyes. The mean follow-up period ranged from 4-50 months. Three hundred fifty six (356) patients were lost to follow-up. The functional vision was retained in 134 eyes. The globe salvage rate for Group A was 100%, 94-100% for Group B, and 50-100% in Group C. The highest globe salvage rate for Group D eyes was 85% and 58% for group E. The overall survival rate was 75% (2,233 patients).

Conclusion: Common among the articles was the relatively high proportion of extraocular disease attributed to delay in consult attributed to financial factors and lack of knowledge on the disease.

Keywords: *retinoblastoma, clinical features, treatment, outcomes, India, Asia*

Introduction

India, China, Pakistan, Bangladesh, Indonesia, and the Philippines were listed to be the projected sources of 43% of the world's retinoblastoma cases in 2023 [1,2]. India leads the list projected to contribute 1,435 cases in 2023 to the global cases of retinoblastoma [3]. With such a large number, consolidated data on the clinical presentation, treatment options, and survival outcomes of retinoblastoma are vital in the creation of guidelines, policies and programs, and resource allocation in its management [4-7]. There are many articles on clinical presentation, treatment options, and survival outcomes from India with differing findings considering the geographical area of the country, the awareness of their general population about retinoblastoma, and the availability of treatment options, among others. In an effort to describe the retinoblastoma situation in Asia, especially from the six countries listed by Usmanov and Kivali, Jain *et al*. conducted a review involving articles from said countries. However, only four articles were from India, all from leading eye care facilities. Similarly, the other countries included were Singapore and Thailand, which are Asian countries that offer the latest treatment retinoblastoma options.

As such, this review aimed to better describe the retinoblastoma situation in the said six countries. This article is part of a bigger review made to determine the availability of management options and survival outcomes of retinoblastoma patients in the said countries considering the number of cases

they will contribute to the global burden of retinoblastoma next year. However, for brevity, this article was reduced to clinical presentation, treatment options, and survival outcomes of retinoblastoma patients from India.

Methodology

A review of articles published from 2010-2020 using Pubmed, EMBASE, Scopus, Science Direct, Google Scholar, and Web of Science databases on retinoblastoma in India was done. The terms "retinoblastoma", "India", "clinical", "presentation", "treatment", and "outcome" were used. Time was limited to those published from 2010-2020 and written in English. The initial search yielded 3,240 hits. Abstracts were further reviewed for data on clinical presentation, treatment, and outcomes. Included were case series, original articles, and review articles.Excluded were case reports, case series with less than 10 patients, letters to the editor, commentaries, and perspectives. Articles from other countries or those with study populations from other countries except India were also excluded. Same articles and those with no data on clinical presentation and those which used assumed similar databases based on similarity of authors and institutions involved and of the duration of the study were also excluded to minimize patient redundancy [8]. As such, only articles with the most complete data or the longest follow-up period were included.

Data collected, if present, were age at consult, age at onset of symptom, delay of consult, sex, presenting symptoms, laterality, family history, intraocular involvement, retinoblastoma international grading, and staging system, treatment procedures done, and outcomes. Percentage, mean, median, standard deviation, and interquartile range were computed.

Results

Fourteen articles were included in the analysis. Eleven were observational studies while three were interventional. All were retrospective studies that included 3,666 patients involving around 4,945 eyes seen in India from 1983 to 2017.

Demographics

No significant differences were found in the clinical presentation [except for the International Classification of Intraocular Retinoblastoma Group A ($p<0.007$) and Group C ($p<0.04$)] and deaths ($p=0.48$) of retinoblastoma patients who came from the north, south, east, and west of India [6].

Clinical presentation

The median age at consult ranged from 14-48 months (Table 1). There were large proportions of patients aged >60 months ranging from 8-15% (5,8,9). Sahu *et al*. saw 38 children aged 5-9 years and 6 children aged 10-15 years with retinoblastoma (8). There was even a 32-year old diagnosed with unilateral disease who underwent enucleation and 6 cycles of secondary systemic chemotherapy for high-risk features (4). The median age at consult for bilateral disease was younger (3-25 months) than those with unilateral (13-42 months) [10]. The median age at onset of symptoms was also younger in bilateral disease ($p<0.001$) [4]. However, Padma *et al*. had patients with bilateral disease presenting later than those with unilateral disease (25 months vs. 18). The median duration in the delay of consultation ranged from 2-9 months [10]. Despite the younger median age at presentation in bilateral disease, the median delay of consultation was the same with unilateral (3 months; $p=0.06$) [9].

More males were affected at 59%. The unilateral disease was present in 2,294 (63%) patients of whom five (0.1%) had the trilateral disease. Unilateral disease ranged from 40-83% in the study populations. Three interventional articles had a high percentage of bilateral disease due to patient selection factors [9-13]. Family history was reported in 136 (4%) patients and found to be higher in bilateral disease [6]. Despite consanguinity being common in India, family history was low [10]. Congenital anomalies including cryptorchidism, preauricular buds, microcephaly, and mental retardation were associated in 10% of the cases [8]. Leukocoria was the most common clinical presentation ranging from 36-98% of cases. However, strabismus increased ($p<0.02$) while eyelid swelling decreased ($p<0.001$) as clinical presentations of retinoblastoma from 2000-2015 [6].

Of the four articles that used the International Classification of Retinoblastoma (ICRB), one reported the worse affected eye of each child [11-14]. Other articles used different classification systems or did not classify the patients. Only two articles used the International Retinoblastoma Staging System (IRSS) [4,6]. Retinoblastoma was reported to be intraocular in >3,688(75%) eyes while extraocular in >854 eyes. The median age at presentation was younger in intraocular disease (27 months vs 44). Patients with extraocular disease had a significantly older median age at symptom onset ($p<0.001$), older median age at presentation ($p<0.001$), and a longer delay of consultation ($p<0.001$) [9]. Extraocular disease was also higher in unilateral disease ($p<0.03$) (9).

Table 1. *Clinical Presentation of Retinoblastoma Patients in India.*

Clinical Features	Kabre *et al.*, 2019	Sahu *et al.*, 2016	Subha *et al.*, 2015	Singh *et al.*, 2018	Manjandavida *et al.*, 2014	Kaliki *et al.*, 2019	Bakshi *et al.*, 2010	Shah *et al.*, 2015
Duration	1983-2013	1988-1996	1997-2000	1998-2014	2000-2010	2000-2015	2003-2007	2006-2011
Location	GMCH, Nagpur	TMH, Mumbai	GOH, Egmore	PGIMER, Chandigarh	LVPEI*, Hyderabad	LVPEI**, Hyderabad	AIIMS, New Delhi	AEHPIO, Combahore, Tamilandu
Child/Eye	141/162 ****	296/409	26/32	467/618	101/184	1457/2074	177/231	106/144
Median Age at consult in months (range)	-	42 (2-126)	-	30(0-144)	25 (3-193)	24(1-370)	30 (1-192)	21 mean (0-120)
Unilateral	-	42 (8-126)	-	13 (2-144)	-	30 (1-370)	36 (1-192)	-
Bilateral	-	12 (2-108)	-	3 (0-120)	-	14 (1-276)	24 (1-84)	-
Median Delay of consult (months)	-	8 (1-20)	-	3 (0-84)	2 (0-24)	-	7 (0-60)	-
Sex								
Male	81 (58%)	170 (57%)	14 (54%)	288 (62%)	60 (59%)	812 (56%)	111 (62%)	62 (58%)
Female	60 (42%)	123 (43%)	12 (46%)	179 (38%)	41 (41%)	645 (44%)	66 (38%)	43 (41%)
No data	0	0	0	0	0	0	0	1 (1%)
Laterality								
Unilateral	114 (81%)	183 (62%)	19 (73%)	316 (68%)	18 (18%)	835 (57%)	123 (70%)	68 (64%)
Bilateral	24 (17%)	110 (37%)	7 (27%)	151 (32%)	83 (82%)	622 (43%)	54 (30%)	38 (36%)
Trilateral	2 (0.9%)	3 (1%)	-	0	0	0	-	0
No data	1 (0.1%)	0	-	0	0	0	-	0
Family History	-	5 (2%)	-	19 (4%)	15 (15%)	55 (4%)	-	4 (4%)
Leukocoria (eye)	36 (26%)	290 (98%)	22 children (85%)	375(61%)	70 (70%)	1100 child (75%)	111 child (63%)	81 (77%)
Involvement (eye)		children					children	
Intraocular	NS		7†	451 (73%)	101 (100%)	1889 (91%)	107 (60%)	130
Extraocular	≥44***	≥75****	25†	167 (27%)	0	185 (9%)	60 (34%%)	9
Unclassified	118	96	1†	0	0	0	10 (6%)	5
ICRB (eye)	(child)	RECS (child)		IIRC		ICIoR		IRC
A	3 (2%)	1- 9	-	22 (5%)	16	107 (6%)	-	11 (8%)
B	13 (9%)	2- 17	-	58 (13%)	5	278 (15%)	-	16 (11%)
C	14 (10%)	3- 25	-	20 (4%)	21	127 (7%)	-	2 (1%)
D	24 (17%)	4- 69	-	47 (10%)	40	414 (22%)	-	34 (24%)
E	85 (61%)	5- 80	-	304 (68%)	66	963 (51%)	-	72 (50%)
Unclassified	2	96	-	0	36	-	-	9 (6%)
IRSS (child)						eyes		eyes
0	NS	NS	-	↑	134 (73%)†	933 (45%)	↑	≥39†
1	NS	≥128†	7†	301†	50 (27%)†	925 (45%)	107 (60%)†	≥55†
2	NS	≥20†	21†	↓	0	31 (2%)	↓	9†
3	NS	≥30†	4†	158 (32%)†	0	131 (6%)	42 (24%)†	9†
4	≥44†	≥17†	-	8 (2%)†	0	54 (3%)	18 (10%)†	≥1
Not classified	97	≤101	-	-	0	0	10 (6%)†	

AEHPIO- Aravind Eye Hospital and Postgraduate Institute of Ophthalmology
AIIMS- All India Institute of Medical Sciences
GMCH- Government Medical College and Hospital
GOH – Government Ophthalmic Hospital
IIRC- International Intraocular Retinoblastoma Classification
ICIoR- International Classification of Intraocular Retinoblastoma
IRC- International Retinoblastoma Classification
LVPEI – LV Prasad Eye Institute
NS- Not specified
PGIMER – Postgraduate Institute of Medical Education and Research
RECS - Reese Ellsworth Classification System
TMH- Tata Memorial Hospital
* Center for Sight
** Operation Eyesight Universal Institute for Eye Cancer
***derived
****assumed
†Assumed IRSS classification

Table 1. *Clinical Presentation of Retinoblastoma Patients in India. (continuation)*

Clinical Features	Kumar *et al.*, 2013	Chawla *et al.*, 2016		Padma *et al.*, 2020	Gupta *et al.*, 2020	Sthapit *et al.*, 2018	Rishi *et al.*, 2019
Duration	2008-2011	2009-2013		2009-2014	2009-2018	2013-2017	2013-2017
Location	KGMU, Uttar Pradesh	AIIMS, New Delhi		KMIO, Bengaluru, Kamataka	PGIMER, Chandigarh	LVPEI*, Hyderabad, Telangana	SNMRF, Chennai
Child/Eye	101/131	600/794	67***/87 (assumed)	53/73	24/28	35/38	15/24
Median Age at consult in months (range)	48 (4-144)	29 (1-150)	23	18	36	22 (3-77)	20 (11-94)
Unilateral	-	36	-	18	-	-	-
Bilateral	-	18	-	25	-	-	-
Median Delay of consult (months)	-	3 (1-120)	9	3 (1-5)	-	-	3 (0-12)
Sex							
Male	66 (65%)	367 (61%)	41 (61%)	29 (55%)	14 (58%)	22 (63%)	10 (67%)
Female	45 (35%)	233 (39%)	26 (39%)	24 45%)	10 (42%)	13 (37%)	5 (33%)
No data	0	0	0	0	-	0	
Laterality							
Unilateral	71 (70%)	406 (68%)	47 (70%)	32 (60%)	20 (83%)	16 (46%)	6 (40%)
Bilateral	30 (30%)	194 (32%)	20 (30%)	21 (40%)	4 (17%)	19 (54%)	9 (60%)
Trilateral	0	0	0	0	0	0	0
No data	0	0	0	0	0	0	0
Family History	-	38 (6%)	-	0	0	2 (6%)	0
Leukocoria (eye)	-	498 children (63%)	-	43 (59%)	21 children (88%)	-	-
Involvement (eye)	children				children		
Intraocular	52 (52%)	585 (74%)	46 (69%)	- (42%)	14 (58%)	38	24 (100%)
Extraocular	49 (48%)	209 (26%)	21 (31%)	- (58%)	10 (42%	0	0
Unclassified	0	0	0	-	0	0	0
ICRB (eye)		ICSIR	ICSIR		ICIR/IIRS?		
A	-	-	NS	-	0	0	1 (4%)
B	-	88 (15%)	NS	-	1 (7%)	0	1 (4%)
C	-	-	NS	-	2 (14%)	5 (13%)	4 (17%)
D	-	82 (14%)	8 (17%)	-	6 (43%)	23 (61%)	10 (42%)
E	-	374 (64%)	38 (83%)	-	5 (36%)	10 (25%)	8 (33%)
Unclassified	-	41 (7%)	-	-	0	0	0
IRSS (child)	SJTSS				child		child
0	-	NS	NS	-	1 (4%)	32 (84%)†	9†
1	52	NS	NS	-	13 (54%)	6 (16%)†	6†
2	↓	NS	NS	-	8 (34%)	0	-
3	49	140 (23%)†	21 (31%)† -	-	1 (4%)	0	-
4	↓	26 (4%)†	Stage NS	≥ 12†	1 (4%)	0	-

AIIMS- All India Institute of Medical Sciences
GMCH- Government Medical College and Hospital
ICSIR- International Classification System for Intraocular Retinoblastoma
ICIR- International Classification of Intraocular Retinoblastoma
KGMU- King George's Medical University
KMIO- Kidwai Memorial Institute of Oncology
LVPEI- LV Prasad Eye Institute
SJTSS- St. Jude Tumor Staging System
SNMRF- Sankara Nethralaya/Medical Research Foundation
* Center for Sight

** Assumed IRSS Stage 1 since patient did not need secondary treatment for high risk features
***Chawla et al.'s lost to follow-up
†Assumed IRSS classification
NS- Not specified

The predominance of advanced disease indicated a significant delay in consultation which was attributed to socioeconomic factors and lack of awareness on retinoblastoma [4,10]. The predominance of advanced disease had also shifted the primary goal in some centers of sight-saving to life-saving [4,10]. However, Kaliki *et al.* noted a significant decrease ($p<0.01$) in patients with IRSS Stage 3 at presentation and a significant increase in IRSS Stage 0 from 2000-2015 [6].

Treatment

Twelve articles with 3,233 patients involving >4,274 eyes had data on treatment (Table 2). Treatment was refused for >326 (8%) eyes. Focal therapies were done in >549 (13%) eyes. Systemic chemotherapy was the most used treatment given to >2,042 (48%) eyes with >88 (2%) eyes given as secondary treatment. Enucleation was done on >1,695 (40%) eyes with >330 eyes done as secondary procedure. Nine orbits were exenterated. At least 270 (6%) eyes/orbits received External Beam Radiotherapy (EBRT) with >155 done as secondary procedure. Intraarterial chemotherapy (IAC) was done in 15 eyes while intravitreal chemotherapy (IVC) was done in >31 eyes. Periocular carboplatin or topotecan was given to 112 eyes. Of the 1,685 eyes enucleated, 171 were reported to have high-risk features (HRF).

Kaliki *et al.* used systemic primary chemotherapy more than primary enucleation as management goal has shifted from life- to sight-saving and globe salvage [6]. Singh *et al.* reported 10% of those who received primary systemic chemotherapy had HRF after enucleation [5]. However, they found no difference with metastasis (1 patient vs 7, $p=0.56$), recurrences (10 patients vs 12, $p=0.42$), and death (1 patient vs 12, $p=0.24$) in patients who underwent primary enucleation and those who underwent primary systemic chemotherapy [5].

Different systemic chemotherapy protocols were followed. Two systemic chemotherapy regimens were used (5). Before 2008, the regimen consisted of 1.5 milligram/meter² (mg/m²) vincristine and 600 mg/m² cyclophosphamide, then 80 mg/m² cisplatin and 600 mg/m² etoposide given in a span of 55 hours [5]. The regimen was later changed to 1.5 mg/m² vincristine, 600 mg/m² etoposide, and 300 mg/m² carboplatin (VEC) given in one day. There was no significant difference between the two regimens in terms of HRF (25 eyes vs 7, $p<0.06$), globe salvage (32 eyes vs 36, $p<0.42$), and death (5 patients vs 6) except for recurrence (13 vs 2, $p<0.001$) [5].

Focal therapy was offered for unilateral Group A-C eyes. Primary systemic chemotherapy was added in bilateral disease [5]. For bilateral disease with a Grade D or E eye, secondary enucleation was done to the worse eye. Focal therapy or EBRT was done to the better eye but was enucleated if non-responsive. For unilateral Grade D and E eyes, primary enucleation was offered. In case of refusal, primary systemic chemotherapy was done initially. Then, focal therapy, EBRT, or secondary enucleation was done as deemed fit. Secondary systemic chemotherapy was given for post-enucleation patients with HRF. HRF include presence of retinoblastoma in the optic nerve posterior to the lamina, resection margin, >3 millimeters choroid, anterior chamber, sclera, and extrascleral [5].

Chawla *et al.* offered focal therapy and systemic and periocular chemotherapy for International Classification System for Intraocular Retinoblastoma (ICSIR) Group A to C eyes of patients with unilateral and bilateral disease [9]. Shah *et al.* used 3-6 cycles of primary systemic chemotherapy with focal therapy to Group B eyes [15]. Periocular carboplatin was added on days 2-4 of the cycle for Groups C and D eyes. For recurrent vitreous seeding, EBRT using 36 Gray (Gy) was added. Implantation of Iodine-125 was done in recurrent disease [15]. Gupta *et al.* gave systemic primary chemotherapy to all patients with Grade D eyes and worse using the same dosing for vincristine, higher for carboplatin at 560 mg/m² and lower for etoposide at 150 mg/m² given in 2 days which was repeated monthly [4].

Chemotherapy was also delivered intraarterially (IAC) which was used as a primary treatment in unilateral, non-familial Grade B to E eyes, and secondary treatment for recurrent tumors and vitreous and subretinal seedings [13]. Complete tumor regression was achieved in 7 (47%) eyes and partial regression in 3 (20%) [13]. Intravitreal chemotherapy (IVC) was used for recurrent or recalcitrant seeding in the vitreous. At least 3 cycles of melphalan (5 or 7.5 mg) and/or topotecan (1 mg) were used at a monthly interval, followed up monthly, and repeated as needed. Spread in the needle tract was prevented by doing triple freeze-thaw cryotherapy [12]. Most bilateral cases received prior systemic VEC of differing numbers of cycles.

Manjandavida *et al.* added 15 mg periocular carboplatin on the 3rd cycle of primary systemic chemotherapy for diffuse vitreous seeding [11]. They used at least six cycles of "high dose" vincristine at 0.025 mg/kg weight, etoposide at 12 mg/kg weight for 2 days, and carboplatin at 28 mg/kg weight for focal vitreous seeding after performing cryotherapy to break the blood-retinal barrier and increase intravitreous concentration of agents. They extended to a maximum of 12 cycles if with residual seeding, good visual prognosis, and if enucleation was not preferred [11]. If still not responsive, fractionated EBRT was given at a dose of 39 to 50 Gy.

Table 2. *Treatment of Retinoblastoma Patients in India.*

Treatment	Kabre *et al.*, 2019	Subha *et al.* 2015 [33]	Singh *et al.*, 2018 1998-2014	Kaliki *et al.*, 2019 2000-2015	Manjandavida *et al.*, 2014	Bakhshi *et al.*, 2010 2003-2007
Duration	1983-2013	1997-2000	1998-2014	2000-2015	2000-2010	2003-2007
Location	GMCH, Nagpur	GOH, Egmore	PGIMER, Chandigarh	LVPEI**, Hyderabad	LVPEI*, Hyderabad	AIIMS, New Delhi
Child/Eye	141/162 *****	26/32	467/618	1457/2074	101/101	141/186
Treatment refusal/ No treatment received (child)	NS	-	120 (26%)	122 eyes	-	7
Focal therapy (cryotherapy, transpupillary thermotherapy, laser photocoagulation) (eye)	NS	2	35 children	107***	97	0
Primary Enucleation (eye)	65	18	117 children	674	-	86
Secondary Enucleation (eye)	type NS	-	161 children	-	24	14
Exenteration (eye)	9	-	0	-	-	
Systemic Primary Chemotherapy (eye)	46	2	228 children	1171****	101	56 + 14
Systemic Secondary Chemotherapy (eye)	type NS	1	23 children	-	-	58
Intraarterial Primary Chemotherapy	-	-	-	-	-	-
Intraarterial Secondary Chemotherapy	-	-	-	-	-	-
Intravitreal Primary Chemotherapy	-	-	7 children type	-		-
Intravitreal Secondary Chemotherapy	-	-	NS	-		-
Secondary periocular carboplatin injection	-	-	1	-	73	-
Primary EBRT(eye)	57	10	1	-	-	-
Secondary EBRT(eye)	46	13	61		33	14
High-Risk Histologic Characteristic requiring added treatment (eye)	-	10	31 (18%)	31	-	64*****

AIIMS- All India Institute of Medical Sciences
EBRT- External Beam Radiotherapy
GMCH- Government Medical College and Hospital
GOH – Government Ophthalmic Hospital
PGIMER – Postgraduate Institute of Medical Education and Research
LVPEI- LV Prasad Eye Institute
NS- Not specified
* Center for Sight
** Operation Eyesight Universal Institute for Eye Cancer
***Does not include systemic chemotherapy for intraocular retinoblastoma
****Systemic chemotherapy was also used for globe salvage
*****assumed

Enucleation was done for a non-responsive and blind eye. Sthapit *et al.* used periocular topotecan (POT) for focal and diffuse vitreous seeds in Group D and E eyes delivered concurrently to the primary systemic chemotherapy. Two milligrams of topotecan using a gauge 27 needle in the sub-Tenon's space inferonasally served as the secondary treatment [12]. They used periocular chemotherapy as an alternative for IVC in addressing vitreous seeds during the active phase. Although periocular carboplatin achieved high intraocular concentration after half an hour, topotecan was found to have better scleral penetration, stability, and safety profile. An average of 3 POT was injected for focal vitreous seeding while 4 for diffuse seeding. Systemic chemotherapy with POT achieved a high globe salvage rate of even up to 58% in Group E [13].

Table 2. *Treatment of Retinoblastoma Patients in India. (continuation)*

Treatment	Shah *et al.*, 2015	Padma *et al.*, 2020	Chawla *et al.*, 2016		Gupta *et al.*, 2020	Rishi *et al.*, 2019	Honavar *et al.*, 2018
Duration	2006-2011	2009-2014	2009-2013		2009-2018	2013-2017	2013-2017
Location	AEHPIO, Combahore, Tamilandu	KMIO, Bengaluru, Kamataka	AIIMS, New Delhi		GMCH, Chandigarh	SNMRF, Chennai	LVPEI*, Hyderabad, Telangana
Child/Eye	106/144	53/73	600/794	67***/NS	24/28	15/24	35/38
Treatment refusal/ No treatment received (child)	-	24 (45%)	-	53	0	0	0
Focal therapy (cryotherapy, transpupillary thermotherapy, laser photocoagulation) (eye)	39	-	214 (37%)	-	2 children	15	38
Primary Enucleation (eye) Secondary Enucleation (eye) Exenteration (eye)	64 (60%) 0 0	28 Type NS	289 (49%) 131 (22%) 0	4 3 -	21 children Type NS -	6 5 0	0 6 0
Systemic Primary Chemotherapy (eye)	0	11 +	203 (35%)	10	21 children	9	38
Systemic Secondary Chemotherapy (eye)	6	29 type NS	Type NS	-	3 children	8	4
Intraarterial Primary Chemotherapy	-	-	-	-	-	6	0
Intraarterial Secondary Chemotherapy	-	-	-	-	-	9	0
Intravitreal Primary Chemotherapy	-	-	-	-	-	1	0
Intravitreal Secondary Chemotherapy	9	-	-	-	-	7	16
Secondary periocular carboplatin injection	-	-	-	-	-	-	38
Primary EBRT(eye) Secondary EBRT(eye)	- -	- -	31 (5%) -	- -	1 child 1 child	1 0	0 1
High-Risk Histologic Characteristic requiring added treatment (eye)	9	18	-	-	8	-	-

AEHPIO- Aravind Eye Hospital and Postgraduate Institute of Ophthalmology
AIIMS- All India Institute of Medical Sciences
EBRT- External Beam Radiotherapy
GMCH- Government Medical College and Hospital
KMIO- Kidwai Memorial Institute of Oncology
LVPEI- LV Prasad Eye Institute
NS- Not specified
SNMRF- Sankara Nethralaya/Medical Research Foundation
* Center for Sight

Nausea, vomiting, anorexia, anemia, seizure, blood parameter changes, and fever were reported as complications of systemic chemotherapy while keratopathy, retinopathy, and cataract were reported from EBRT [5,11]. The use of EBRT decreased due to the risk of developing secondary tumors such as sphenoid bone meningioma, optic neuropathy, retinal pathology, and growth malformation [4,5]. Two patients who received systemic chemotherapy and radiotherapy developed osteosarcoma of the tibia and rhabdomyosarcoma at the temporal bone [8]. For IAC, complications included cataract, iris atrophy, posterior synechia, temporary angle narrowing, vitreous hemorrhage, retinal vein occlusion, and sclerosis, optic neuropathy, skin allergy and pigmentation, and temporary blood parameter changes [13]. Manjandavida *et al*. did not have complications from periocular carboplatin in contrast to literatures that reported optic neuropathy and severe fibrosis in the orbit, making secondary enucleation difficult [11]. They believed that this was from the technique used during the injection. Honavar *et al.* only reported transient chemosis of conjunctiva and eyelid edema from POT [12].

Table 3. *Outcomes of Retinoblastoma Patients in India.*

Treatment	Kabre *et al.*, 2019	Singh *et al.*, 2018	Kaliki *et al.*, 2019	Manjandavida *et al.*, 2014	Shah *et al.*, 2015	Chawla *et al.*, 2016		Rishi *et al.*, 2019	Sthapi *et al.*, 2018
Duration	1983-2013	1998-2014	2000-2015	2000-2010	2006-2011	2009-2013		2013-2017	2013-2017
Location	GMCH, Nagpur	PGIMER, Chandigarh	LVPEI**, Hyderabad	LVPEI*, Hyderabad	AEHPIO, Tamilandu	AIIMS, New Delhi		SNMRF, Chennai	LVPEI, Hyderabad
Child/Eye	141/162	467/618	1457/2074	101/101	106/144	600/794	67***/NS	15/24	35/38
Mean Follow-up period (in months)	4	28±44	44	50 ± 21	35±20	21±15	NS	29 ± 14	8
Median (range)	(0-26)	64 (2-190)	30 (3-234)	48 (13-129)	33 (1-75)	(1-60)		(10-51)	7(1-15)
Retained Vision of 20/200 or better (eye)	-	50 (functional VA)	-	74 (96%)	-	-	-	10	
Globe salvage (eye)				77 (76%)					31 (82%)
A	-	22 (100%)	45%	-	11 (100%)	NS (100%)	-	0	-
B	-	58 (100%)	-	-	16 (100%)	83 (94%)	-	1 (100%)	-
C	-	20 (95%)	-	18 + 2† (95%)	2 (100%)	NS (83%)	-	2 (50%)	-
D	-	47 (17%)	-	28 + 6† (85%)	10 (30%)	44 (54%)	-	6 (60%)	-
E	-	0	-	7 + 16† (58%)	-	0	-	1 (12%)	-
Unknown/ Lost to follow-up	16 (11%)	130 (28%)	143 (10%)	-	-	-	67	-	0
Alive	13 (9%)	314 (68%)	1206 (82%)	101 (100%)	95 (90%)	454 (76%)	-	15 (100%)	35 (100%)
Expired	112 (80%)	13 (4%)	108 (7%)	-	11 (10%)	146 (24%)	-	-	0
Kaplan-Meier survival probability									
1	-	-	94%***	-	93%	83%	-	-	-
3	-	-	91%	-	90%	68%	-	-	-
5	-	-	90%	-	89%	65%	-	-	-

AIIMS- All India Institute of Medical Sciences
AEHPIO- Aravind Eye Hospital and Postgraduate Institute of Ophthalmology
EBRT- External Beam Radiotherapy
GMCH- Government Medical College and Hospital
PGIMER – Postgraduate Institute of Medical Education and Research
LVPEI- LV Prasad Eye Institute
SNMRF- Sankara Nethralaya/Medical Research Foundation
* Center for Sight
** Operation Eyesight Universal Institute for Eye Cancer
***Patients with unknown status were not included in the analysis
****Systemic chemotherapy was also used for globe salvage
†needed secondary EBRT

The extraocular disease was treated with 3-6 cycles of primary systemic chemotherapy, secondary enucleation (or exenteration), EBRT of 46 Gy, and then 6-9 more cycles of systemic chemotherapy [6,9,15]. Patients with Group E eyes and worse were worked up for metastasis using complete blood count, computed tomography, magnetic resonance imaging alone starting 2013, abdominal ultrasound, cerebrospinal analysis, and bone marrow aspiration [5]. Chawla *et al.* added chest X-ray and liver and kidney function tests [9].

Padma *et al.* had the highest rate of treatment refusal (45%) and cited treatment complications, visual prognostication, and removal of the eye as reasons [5,10]. Refusal was higher ($p<0.03$) in unilateral disease [6]. Singh *et al*. had a refusal rate for enucleation of 20% [5]. Kumar *et al*. had a high treatment abandonment of 50% mainly due to financial concerns [16]. Patients from rural areas were found to have higher chances of abandonment due to accessibility, financial concerns, lengthy treatment duration, pressure from other members of the family, not wanting enucleation especially for girls, and belief in faith healing/alternative medicine [5]. Financial concerns were mainly from indirect costs (e.g. lost income) since medical services and fares were free and government-subsidized [16] Age, sex, religion, educational level of parents, and laterality were found to be non-contributory to compliance to treatment [17]. However, patients with extraocular disease had a higher chance of abandonment due to the obvious effect of primary systemic chemotherapy and believing that the disease had been cured [16].

Outcomes

Eight articles had data on outcomes (Table 3) with 2,989 patients involving at least 3,955 eyes included in the analysis. The mean follow-up period ranged from 4-50 months. There were 356 (12%) patients lost to follow-up. Functional vision was retained in 134 (3%) eyes. The globe salvage rate for Group A eyes was 100%, 94-100% for Group B, and 50-100%

for Group C. The highest globe salvage rate for Group D was 85% and 58% for Group E. The overall survival rate was 2,233 (75%) ranging from 9% to 90%. Three interventional articles had a 100% survival rate as a result of patient selection factors. The overall mortality was 13%. Kaplan-Meier's 5-year survival probability ranged from 83-94% in the first year, 68-91% in third year, and 65-90% in the fifth year.

A delay in diagnosis, especially of more than six months ($p<0.005$), resulted in advanced disease as the primary cause of death [6,9]. Patients whose initial consultation was at age 2 to 4 years old were associated with a poorer survival rate (HR 1.4, $p<0.001$) [9]. To facilitate earlier diagnosis, it was suggested to enable primary and secondary health care to screen retinoblastoma and for screening to be integrated during vaccination visits [9].

Chawla *et al.*'s survival rate for patients with extraocular disease was 39% with a mean follow-up of 21±15 months while Shah and colleagues was 56% 34 months follow-up [9,15]. Singh *et al.*'s mean interval between presentation and death for patients with metastasis was 5 months (range: 0-34) [5]. However, Chawla *et al.* had 60 (14%) patients with intraocular disease who died and was attributed to 23 having HRF, poor compliance with additional treatments, treatment complications, and other factors (*e.g.* malnutrition, viral infections, comorbidities) [9]. Chawla *et al.* did not find any significant association on sex and laterality to survival rate [9].

In addition to saving sight and life, improving the quality of life should also be part of retinoblastoma management [4]. Disability such as visual and mental from treatment shall be addressed. Similarly, appropriate placement of implants to promote orbital growth and placement of artificial eyes shall be done for cosmesis. Patients need to be followed-up long term for possible secondary cancer and receive genetic counseling when they start a family.

Discussion

This review summarized the clinical presentation, treatment, and outcomes of retinoblastoma patients in India in literature published from 2010-2020. India had the most published articles among the six countries listed to be the source of 43% of global cases in 2023 and even has the largest single-study cohort [3,6]. India accounts for almost a third of global cases annually and has the most projected retinoblastoma cases in 2023 at 1,486 [3].

Asian Indians were found to have a higher risk for optic nerve invasion and massive choroidal invasion compared to North Americans. However, this was attributed to a possible delay in consultation [18]. Although there were no significant differences between the clinical presentation and outcomes of retinoblastoma patients from the four parts of India seen in a facility, there were differences especially in survival rates between articles [6]. The survival rate was lowest in Central India at 9% and highest in South India at 90% [14,15].

The median age range at consult in India was similar to Pakistan but older than China, Indonesia, Philippines, and Western countries [19,20]. The median ages at consult in India were generally similar with the finding that 90 to 96% of retinoblastoma cases were diagnosed at less than five years of age [21]. However, retinoblastoma still needs to be considered even for patients aged >5 years due to India's greater than usual number of patients presenting with the disease even after 5 years old [5,8,9]. India's range of the medians in the delay of consultation was similar to China and the Philippines but shorter than Pakistan and Indonesia [19,20]. The equal median delay of consultation at 3 months can suggest that patients were being seen earlier despite the difference in the median age of symptom onset between unilateral and bilateral disease. Males were more affected at 59% similar to China (58%), Bangladesh (57%), the Philippines (56%), and Indonesia (54%) [19,20]. This is similar to some reports from Central America, Africa, and the Middle East despite no reported global sex preponderance [22-24]. This finding was attributed to treatment preference to males and raised concerns that the health of females in general in India was being overlooked [5,9]. However, a significant decrease was noted in the median age of presentation of females ($p<0.04$) from 2000-2015 [6].

The unilateral disease in India was more common (63%) than bilateral disease, similar to Bangladesh (63%) and Pakistan (61%) [20]. India had a lower proportion of unilateral disease compared to the Philippines (69%), China and Indonesia (79%) [19,20]. Kaliki *et al.* had the highest proportion of bilateral disease in this literature review (43%), excluding the three interventional studies due to patient selection factors. It was even higher than a large study by Abramson *et al.* in the US [25]. Family history was found in 4% despite consanguinity being common in India [26,27]. This is higher than Indonesia (0.6%) and China (1%), similar to Bangladesh (4%), but lower than Pakistan (6%) and the Philippines (8%) [19,20]. Leukocoria remained the most common presenting symptom, even up to 98% [8]. However, retinoblastoma needs to be continuously ruled out in patients presenting with new onset-squint [6].

Since the favored treatment shifted from EBRT to chemotherapy in the 1990s, several classification systems were developed in addition to Reese-Ellsworth Classification System (RECS) such as International Intraocular Retinoblastoma Classification (IIRC) and International Classification of Retinoblastoma (ICRB) [28,29]. However, three articles did not classify patients with intraocular disease while seven used a classification system different from ICRB. Sixty to 90% of patients in Low to Medium Income Countries present with extraocular disease [30]. As such, other systems for extraocular retinoblastoma were proposed including the International Retinoblastoma Staging System (IRSS) and TNM classification system [31-33]. However, only two articles used the IRSS, one even used the St. Jude Tumor Staging System, while none used the TNM classification system. Reporting of classification and staging were not standardized. Although the classification used by a center may depend on their available treatment options, standardized reporting can better describe patient's clinical presentation needed for creating and standardizing treatment protocols. Around 56% [>2762 eyes: 266 (ICRB), 502 (International Classification System for Intraocular Retinoblastoma/ICSIR), 11 (International Classification of Intraocular Retinoblastoma/ICIR), 351 (IIRC), 1,377 (International Classification of Intraocular Retinoblastoma/ ICIoR), 106 (International Retinoblastoma Classification/ IRC), and 149 (RECS)] had advanced intraocular disease (Grade D and E eyes). At least 766 (21%) patients had extraocular disease, higher than those reported by Jubran *et al*. in Los Angeles, California at 5% (34). However, this is below the reported rates in Mexico (29%) and Malaysia (55%) [35,36].

Most common treatment used was systemic chemotherapy, both as primary and secondary option. Its use as primary treatment did not increase metastasis, recurrences, and death compared to enucleation [5]. However, there were centers where enucleation and radiotherapy remained the commonly used treatment [14,37]. A decreasing trend in the use of radiotherapy, both as primary or secondary option, was noted from 2003 onwards as a result of changing guidelines and increased availability of chemotherapeutic agents [14]. The past decade introduced new chemotherapeutic agents such as melphalan and topotecan and different delivery routes. These agents were delivered intraarterially, intravitreally, and periocular. Together with EBRT, they were indicated mostly for vitreous seeding [11-13]. In 2012, IVC was introduced and proven to be effective for vitreous seeding [38]. However, there are only limited centers with the chemotherapeutic agent, expertise, and equipment to perform said procedures.

Treatment protocols depended on laterality, extent, availability of different treatment procedures and patients' preferences. Although Singh *et al*. presented two systemic chemotherapy regimens, the VEC regimen was found to give less recurrence and was more widely used [5]. Cryotherapy was used first prior to systemic chemotherapy to increase the intravitreal concentration of the drugs [11]. For intraocular involvement in unilateral disease belonging to Groups A to C, eyes were treated with focal therapy [5]. Chawla *et al*. added systemic and periocular chemotherapy [9]. Singh *et al*. only used systemic chemotherapy for bilateral cases [5]. Shah *et al*. added periocular chemotherapy for bilateral cases [15]. IAC was used as a primary treatment in unilateral Grade B to C eyes and secondary treatment for recurrent tumors and vitreous and subretinal seedings [13].

For unilateral Groups D and E eyes, primary enucleation was offered [5]. In case of refusal, 2-3 cycles of primary systemic chemotherapy, focal therapy, and secondary EBRT were done with close follow-up [5,9]. Shah *et al.* added periocular carboplatin [15]. IAC was used as a primary treatment in unilateral Grade D to E eyes (13). Implantation of Iodine-125 was done in some recurrent diseases [13]. Secondary enucleation was offered if non-responsive, recurrent, or non-seeing eye. For patients with bilateral disease with Grade D or E eyes, systemic chemotherapy was initially given for chemoreduction. Secondary enucleation was done to the worse eye while focal therapy or EBRT was given to the better eye. If the better eye does not respond to these treatment options, enucleation may be needed [5].

Refusal for treatment including enucleation in India was lower than Malaysia's 31% [36]. However, it is still high compared to the data from developed countries [34]. To be effective, intensive pre-treatment counseling should emphasize that reduction from primary systemic chemotherapy is not equivalent to cure and that acceptable cosmesis post-enucleation is achievable. This was found more effective than post-abandonment counseling [16]. Retinoblastoma support groups and dedicated human resources to call the family of the patients when a follow-up was missed were also found to be effective in lowering treatment refusal and abandonment [15,16]. A significant decrease ($p<0.001$) in treatment refusal was noted from 2000 to 2015 which was attributed to a probable increase in awareness of the disease [6].

The availability of the different treatment options and protocols for retinoblastoma in India has led to better visual and globe salvage as well as survival rates. However, there remain areas with high extraocular disease and low survival

rates. Although financial factors had been the default reason to explain the survival rates in low- to medium-income countries, other factors shall be addressed [39]. Delay in consult and diagnosis and denial of treatment have always been highlighted as the main causes of advanced diseases [9]. These causes are often attributed to the patient's socioeconomic status, lack of proper knowledge of the disease, and limited access to eye care facilities and personnel [39]. Integration of retinoblastoma into pediatric screening programs can also increase awareness especially disease among parents to make regular visits to eye doctors as opposed to waiting for signs of retinoblastoma such as leukocoria and resorting to alternative medicine first [5]. Social services may be allowed to intervene in cases where parents do not consent to any form of treatment or if a patient misses a follow-up as is the case in western countries. However, it is also proper to understand and address the underlying reasons prior to resorting to social service interventions [16]. Distance and difficulty in transport to eye care facilities are also factors as proven by the higher number of defaulters in rural than urban communities [16].

Conclusion

India had the most published articles among the 6 Asian countries with high incidence of retinoblastoma which described differences in the clinical features, treatment, and outcomes of retinoblastoma patients within eyecare facilities in India. However, common was the notable proportion of extraocular disease mainly attributed to delay in consult. This in turn was attributed to financial factors and lack of knowledge of the disease. This has led also to more data on the treatment options for advanced diseases. Standardization of reporting on the classification and staging can help in better understanding the clinical presentation of the patients. Improving patterns had been noted in the large centers. Although newer treatment options were being used already, they were still not widely available. Although functional vision rate was notable in some facilities, there were others still with low survival rates.

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