A Comparison of Retinoblastoma Cases in the Philippines

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ABSTRACT

Objective: This study compared the demographics, clinical profile, treatment, and outcomes of retinoblastoma patients seen at medical institutions in the Philippines between two time periods: 2010 to 2015 and 2016 to 2020.

Methods: This was a multicenter, analytical, cohort study using review of medical charts and databases of retinoblastoma patients seen in 11 medical institutions from 2010 to 2020.

Results: There were 636 patients (821 eyes) included in this study: 330 patients were seen in 2010 to 2015 while 306 in 2016 to 2020. More cases per annum were seen in the latter timeline. The number of patients with

unilateral disease was not significantly different between the two time periods (p=0.51). Age at onset of symptom, age at initial consultation, and delay in consult were also not significantly different between the two time periods (p>0.05). Patients had significantly different distributions of intraocular grades (p<0.0001) and systemic staging (p<0.0001) between the two time periods. Enucleation was the most common surgical treatment performed in both timelines. There was significant difference in the status of patients based on the need for systemic chemotherapy (p<0.01). There was significant difference in outcome between the two time periods, including the proportions of living and deceased patients.

Conclusion: This study compared the most comprehensive data on retinoblastoma patients in the country. There was no improvement in early health seeking behavior based on similar age at initial consult and delay in consult. Enucleation remained the most common treatment mode as opposed to chemotherapy due to similar percentage of patients with unilateral disease, an indication for enucleation rather than chemotherapy.

Keywords: retinoblastoma, Philippines, epidemiology, clinical profile, treatment, outcomes

Retinoblastoma is a malignancy that affects the retina during childhood.[1] The Philippines was one of the countries that registered the most cases of retinoblastoma globally in 2013 and was projected to be among the leading sources of retinoblastoma cases in 2023.[2] From 1977 to 2001, there was a five-fold increase of cases in the country.[3] Aside from the increasing number of retinoblastoma cases, available literature highlights the high percentages of advanced and extraocular diseases among retinoblastoma patients in the country. Noguera *et al.* found advanced intraocular disease in 69% and extraocular disease in 16% among their cohort in 2011.[4] In 2020, the Global Retinoblastoma Study Group reported a higher percentage of extraocular disease at 37% in their Filipino cohort.[5] These explain the low survival rates from retinoblastoma in the country, from 53% in northern Luzon to 28% in southern Philippines.[6,7]

Programs to improve awareness and survival among retinoblastoma patients in the Philippines have been implemented by the Philippine Academy of Ophthalmology (PAO), the professional society of Filipino ophthalmologists, the Philippine Society of Pediatric Ophthalmology and Strabismus (PSPOS), a subspecialty society of the PAO, and other organizations. The Philippine Health Insurance Corporation (PHIC) has also increased its insurance coverage thru the "No Balance Billing' policy in 2011, including for cancer treatment in its Z benefits package in 2012. But there has been no direct and updated comparison between demographics, clinical presentation, treatment options, and outcomes of retinoblastoma patients in the country to determine how the diagnosis and management of the disease have changed in the past decade.

Similarly, most available data on retinoblastoma are from Luzon. The Philippines is an archipelago of 7,641 islands divided into 3 major island groups: Luzon in the north, Mindanao in the south, and the Visayas in between. These 3 island groups are further grouped into 17 administrative regions. Given the high number of cases in the country and the severity of the cases upon diagnosis, a comprehensive and a more representative data set are needed.[8-10] This study invited several eye care specialists practicing in different institutions all over the Philippines who diagnose and manage retinoblastoma cases to compare their data on retinoblastoma patients seen between two time periods: from 2010 to 2015 and from 2016 to 2020. The objectives of this study were to compare the demographics, clinical presentation, mode of treatment, and the clinical outcomes of retinoblastoma patients seen at the 11 participating Philippine institutions between the 2 time periods.

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METHODS

This was a multicenter, retrospective, cohort study that employed review of medical charts and hospital databases of retinoblastoma patients seen in the Ophthalmology and Pediatrics departments of the participating institutions in the Philippines from 2010 to 2020. This study employed the same data set in a prior publication and analyzed into 2 divided but unequal time periods: from 2010 to 2015 and 2016 to 2020.[10] This study received ethics approval from the Department of Health Single Joint Review Ethics Board and institutional review boards, if present, of each participating institution. The Declaration of Helsinki and the Philippine Data Privacy Act of 2012 were observed in the conduct of this study.

The inclusion and exclusion criteria were described in a prior publication.[10] The following data were collected from the medical charts: institution where the patient was evaluated, age at consult, sex, town and province of origin, ocular involvement (unilateral or bilateral), date of birth, age at initial symptom, date of initial consult, reason for delay of consult (if applicable), presenting symptom, family history, intraocular grading on initial consult, diagnostic imaging and laboratory results (ocular ultrasound, magnetic resonance imaging [MRI], computed tomography [CT] scan, cerebrospinal fluid analysis, bone marrow aspiration), surgical intervention done (enucleation, exenteration, etc), presence of high-risk features on histopatholoic studies, interventions done and number of sessions (chemotherapy, radiotherapy, laser treatment, cryotherapy), latest systemic staging, date at last consult, and status. For geographical origin, the patient's permanent address was used. For standardization, delay of consult was defined as the interval between the age at onset of symptom and the age at initial consult. Intraocular grading was based on the International Intraocular Retinoblastoma Classification (IIRC) or the International Classification for Retinoblastoma (ICRB), depending on which grading was used by the participating institution. Patients with visible extraocular mass or significant proptosis were assigned to have extraocular disease as their IIRC/ICRB grading. Patients without IIRC/ICRB grading but had available ocular ultrasound results or underwent upfront enucleation with available histopathology report were graded based on these data. Patients without International Retinoblastoma Staging System (IRSS) staging but with available cranial and orbital imaging readings (e.g., CT, MRI scan) and histopathology reports were staged based on the available data. For patients evaluated in more than 1 participating institutions and received different IRSS stages, the latest IRSS stage was used. For bilateral disease, the IRSS stage of the worse eye was used for staging the patient.

For systemic chemotherapy, the patients were classified into *not needed* (responsive to local therapy or with surgically resectable and totally resected disease with no high-risk features), *completed* (completed ≥6 cycles of chemotherapy), and *incomplete/abandoned* (as stated or those who received less than 6 or the recommended cycles of chemotherapy for reasons not due to death). Follow-up interval was the duration between the date of initial consult and the date of last consult.

For outcomes, the patients were classified as *alive* (confirmed thru phone call or per chart entry, no recurrence on last follow-up after completion of recommended treatment, or was currently undergoing treatment), *dead* (mortality recorded in the treating institution or confirmed thru phone call or per chart entry) or *others* which consisted of abandonment, refusal, no additional data and referred. *Abandonment* was defined as patient having started diagnostic evaluation or treatment but did not complete recommended modes of treatment, number of cycles, or push through with recommended diagnostics during treatment that are not due to death. *Refusal* was when no consent was provided by the caregivers to undergo any diagnostic or treatment or were lost to follow-up before any diagnostic or treatment was started. Lastly, *referred* occurred when the patient was transferred to a non-participating institution as requested by the patient's caregiver.

Statistical Analyses

Frequencies, measures of central tendency and dispersion were used to summarize the data using Microsoft Excel Ver. 3 2013 (Microsoft Corp. Redmond, Washington USA). Pearson's chi-squared

test of independence was used to analyze gender and involvement (unilateral vs bilateral). Mann-Whitney U test was used to compare intraocular grading distribution, systemic staging distribution, types of surgery done, high risk features, systemic chemotherapy, radiotherapy, and outcomes between the two time periods. Student t-test was used to compare age at onset of symptom, age at initial consultation, delay in consultation, and length of follow-up between the two time periods. Stata 14 (StataCorp LP, College Station, Texas, USA) was used for statistical analysis. Statistical significance was set at $p<0.05$.

RESULTS

A total of 636 patients (821 eyes) were diagnosed with retinoblastoma in the 11 participating institutions from 2010 to 2020. Three-hundred thirty (330) retinoblastoma patients (423 eyes) were seen from 2010 to 2015 and 306 patients (398 eyes) from 2016 to 2020. **Table 1** lists each participating institution and the number of its patients included in the study. Two were tertiary private hospitals while one was a private ambulatory eye center. The rest were tertiary government-run hospitals. Two had available data from 2016 onwards only.

From 2010 to 2015, a mean number of 55±12 new cases were seen annually versus 61±6 new cases annually from 2016 to 2020. Patients from Luzon accounted for 55% of cases seen from 2010 to 2015 and 58% from 2016 to 2020 (**Table 1**).

The regional distribution of retinoblastoma patients is summarized in **Table 2**. In both timelines, Region 4A had the most retinoblastoma cases (18% and 19%, respectively), followed by the National Capital Region (12% and 13%, respectively) and Region 11 at 11% of patients. Region 9 recorded the lowest absolute number of cases in both timelines.

Males accounted for 60% and 51% of patients seen from 2010 to 2015 and 2016 to 2020, respectively. There was a significant change in the gender distribution over time (x^2=4.28, p=0.04). There was no significant change in the number of patients with unilateral or bilateral disease between the two time periods (x^2=0.44, p=0.51). Median age at onset of symptom (12 [interquartile range{IQR}4,24] for 2010-2015 vs. 12 [IQR 4,24] months for 2016-2020, p=0.9), age at initial consultation at the participating institution (24 [IQR 13,36] vs. 27 [IQR 14,38] months, p=0.6), and delay in consult (8 [IQR 2,16] vs. 10 [IQR4,19] months, p=0.1) between the two time periods were all not significantly different. Among patients with data on reason for delay of consultation, financial issue was the most common reason cited by parents of patients at 60% and 69% over the two time periods, respectively. It was followed by lack of access to a medical facility (11% vs. 9%, respectively) and wrong diagnosis (10% vs. 6%, respectively).

Table 1. The 11 participating institutions, their regional location, and number of retinoblastoma patients seen in the 2 time periods.

Institution	Region	Island Group	Number of Patients		Total, n (%)
			2010-2015	2016-2020	
Cagayan Valley Medical Center	Region 2	Luzon	2	2	4 (0.6)
Baguio General Hospital and Medical Center	Cordillera Administrative Region	Luzon	24	16	40 (6.0)
Jose B. Lingad Memorial Regional Hospital	Region 3	Luzon	0	3	3 (0.6)
Philippine General Hospital	National Capital Region	Luzon	162	142	304 (48.0)
East Avenue Medical Center	National Capital Region	Luzon	51	23	74 (11.5)
Manila Doctors Hospital	National Capital Region	Luzon	11	9	20 (3.0)
Rizal Medical Center	National Capital Region	Luzon	0	10	10 (1.5)
Legazpi Eye Center	Region 5	Luzon	2	4	6 (0.8)
Cebu Velez General Hospital	Region 7	Visayas	1	8	9 (1.5)
Northern Mindanao Medical Center	Region 10	Mindanao	5	4	9 (1.5)
Southern Philippines Medical Center	Region 11	Mindanao	72	85	157 (25.0)
Total			330 (52.0%)	306 (48.0%)	636 (100.0)

Table 3 summarizes the distribution of presenting symptoms of patients seen from 2010 to 2015 and 2016 to 2020. Leukocoria was the most common presenting symptom in patients seen in both time periods (43% and 55%, respectively). One hundred ninety-five (195) eyes (25%) had no data on presenting symptoms. Of these, 143 patients with bilateral disease had no documented presenting symptom on their better eye.

Table 2. Regional distribution of retinoblastoma patients seen from 2010-2015 and 2016-2020.

Region	Patients N (%)		Total Patients N (%)
	2010-2015	2016-2020	
National Capital Region	41 (12.5)	39 (13.0)	80 (12.5)
Cordillera Administrative Region	13 (4.0)	5 (2.0)	18 (3.0)
1 – Ilocos Region	13 (4.0)	12 (4.0)	25 (4.0)
2 – Cagayan Valley	13 (4.0)	16 (5.0)	29 (4.5)
3 – Central Luzon	16 (5.0)	21 (7.0)	37 (6.0)
4A - CALABARZON	58 (18.0)	57 (19.0)	113(18.0)
4B - MIMAROPA	10 (2.5)	5 (2.0)	15 (2.5)
5 – Bicol Region	17 (5.5)	23 (7.5)	40 (6.0)
6 – Western Visayas	4 (1.0)	6 (2.0)	10 (1.5)
7 – Central Visayas	4 (1.0)	12 (4.0)	16 (2.5)
8 – Eastern Visayas	8 (2.0)	15 (5.0)	23 (3.5)
9 – Zamboanga Peninsula	2 (0.5)	2 (0.5)	4 (0.5)
10 – Northern Mindanao	6 (1.5)	14 (4.0)	20 (3.0)
11 – Davao Region	37 (11.0)	33 (11.0)	70 (11.0)
12 - SOCCSKSARGEN	15 (4.5)	22 (7.0)	37 (6.0)
13 - Caraga	12 (3.5)	13 (4.0)	25 (4.0)
Bangsamoro Autonomous Region of Muslim Mindanao	6 (1.5)	5 (1.5)	11 (2.0)
No data	56 (18.0)	5 (1.5)	61(9.5)
Total	330 (100.0)	306 (100.0)	636 (100.0)

Table 3. Distribution of the presenting signs and symptoms of the retinoblastoma patients seen in the two time periods

Signs and symptoms	Patients N(%)		Total Patients, N(%)
	2010-2015	2016-2020	
Leukocoria or cat's eye reflex	183	219	402 (48.0)
Proptosis	53	25	78 (10.0)
Swelling	14	37	51 (6.0)
Mass	14	18	32 (4.0)
Strabismus	13	8	21 (2.0)
Redness	9	6	15 (1.5)
Buphthalmos	8	3	11 (1.5)
Incidental finding on screening	4	4	8 (0.8)
Blurring of vision	3	2	5 (0.7)
Pain	0	1	1 (0.1)
Phthisis	1	0	1 (0.1)
Corneal haziness	1	0	1(0.1)
No data	120	75	195 (25.0)
Total	423	398	821 (100.0)

Table 4 shows the distribution of retinoblastoma patients based on IIRC/ICRB grading. Based on the IIRC and ICRB grading systems, retinoblastoma patients seen from 2010 to 2015 had significantly different grade distribution compared to those seen from 2016 to 2020 ($p<0.0001$).

Table 4. Distribution of patients based on the IIRC/ICRB grading.

IIRC/ ICRB Grade	Patients N(%)		P-value
	2010-2015	2016-2020	
A	2 (0.5)	5 (1.0)	0.0001
B	15 (3.5)	17 (4.0)	
C	17 (3.5)	26 (6.0)	
D	18 (4.5)	33 (8.0)	
E	166 (39.0)	178 (45.0)	
Extraocular	115 (27.0)	103 (26.0)	
No data	90 (22.0)	36 (10.0)	
Total	423 (100.0)	398(100.0)	

*****IIRC- International Intraocular Retinoblastoma Classification; IRCB - International Classification for Retinoblastoma

Based on the IRSS , the stages of retinoblastoma patients seen from 2010 to 2015 were also significantly different from those seen from 2016 to 2020 ($p<0.0002$) [**Table 5**].

Table 5. Distribution of patients based on the IRSS staging.

IRSS Stage	Patients N(%)		P-value
	2010-2015	2016-2020	
0	2 (0.5)	3 (1.0)	0.0001
1	104 (31.0)	120 (39.0)	
2	26 (8.0)	19 (6.0)	
3	62 (18.0)	74 (23.0)	
4	65 (20.0)	56 (18.0)	
No data	71 (22.5)	34 (13.0)	
Total	330 (100.0)	306(100.0)	

*IRSS - International Retinoblastoma Staging System

Enucleation was the most common surgery performed for both timelines at 65% and 66%, respectively for 2010 to 2015 and 2016 to 2020. There was no significant difference in the type of surgery done over time ($p=0.54$) [**Table 6**]. **Table 7** shows the distribution of enucleated eyes based on presence of high-risk features. There was a significant difference in presence of high-risk features of enucleated eyes ($p<0.0001$) over time.

There was a significant difference in the retinoblastoma patient distribution based on systemic chemotherapy received between the two timelines (**Table 8**). The Philippine General Hospital (PGH) and the Southern Philippines Medical Center (SPMC), the two institutions with data on radiotherapy on 109 patients, noted significant difference in the status of patients needing radiotherapy ($p<0.04$) (**Table 9**). There were 8 and 16 eyes treated with cryotherapy in 2010 to 2015 and 2016 to 2020, respectively. There were 8 eyes in 2010

to 2015 while 33 eyes in 2016 to 2020 treated with laser therapy.

Table 6. Distribution of eyes based on surgical intervention.

Type of Surgical Intervention	Patients N(%)		P-value
	2010-2015	2016-2020	
None	127 (30.0)	122 (31.0)	0.54
Enucleation	243 (58.0)	230 (57.0)	
Secondary Enucleation	29 (6.8)	32 (9.0)	
Exenteration	7 (1.0)	6 (1.0)	
Incisional Biopsy	1 (0.2)	0 (0.0)	
No data	16 (4.0)	8 (2.0)	
Total	423 (100.0)	398 (100.0)	

Table 7. Distribution of enucleated eyes based on presence of high-risk features.

Number and Type of High-Risk Features (HRF)		Patients N(%)		P-value
		2010-2015	2016-2020	
No HRF		102 (37.5)	70 (27.0)	0.0001
1 HRF	Positive Margin	16 (6.0)	16 (6.0)	
	Choroidal Involvement	18 (7.0)	37 (14.0)	
	PLONI	5 (2.0)	17 (7.0)	
	Anterior Chamber	12 (4.0)	13 (4.45)	
	Scleral Perforation	6 (2.0)	1 (0.05)	
	Subtotal	57 (21.0)	84 (31.5)	
2 to 5 HRF	Positive Margin	32	28	
	Choroidal Involvement	47	75	
	PLONI	30	43	
	Anterior Chamber	40	27	
	Scleral Perforation	39	44	
	Subtotal	68 (25.0)	81 (31.5)	
No data		45 (16.5)	27 (10.0)	
Total		272 (100.0)	262 (100.0)	

*PLONI – Post laminar optic nerve invasion

Table 8. Distribution of patients based on systemic chemotherapy status.

Systemic Chemotherapy	Patients N(%)		P-value
	2010-2015	2016-2020	
No need	36 (11.0)	13 (4.0)	0.01
Completed	113 (34.0)	134 (44.0)	
Ongoing	3 (1.0)	6 (2.0)	
Abandoned/Incomplete due to other reasons	88 (27.0)	72 (24.0)	
Incomplete due to death	27 (8.0)	26 (8.0)	
Refused	14 (4.0)	10 (3.0)	
Referred	3 (1.0)	0 (0.0)	
No data	46 (14.0)	45 (15.0)	
Total	330 (100)	306 (100)	

The median length of follow-up was correspondingly longer in patients seen from 2010 to 2015 than those seen from 2016 to 2020 (17 [IQR 5,54] months vs. 10 [IQR5,24], respectively, $p<0.0001$). There was a significant difference in the distribution of outcomes of patients over time ($p<0.0001$) (**Table 10**). A total of 57 (7%) globes were salvaged, 23 and 34 globes from 2010 to 2015 and 2016 to 2020, respectively.

Table 9. Distribution of retinoblastoma patients based on radiotherapy status.

Radiotherapy	Patients N(%)		P-value
	2010-2015	2016-2020	
Done	25 (56.0)	34 (56.0)	0.04
Not done due to other reasons	4 (14.0)	8 (13.0)	
Not done due to death	6 (3.0)	2 (3.0)	
Refused	3 (6.0)	4 (6.0)	
No data	10 (21.0)	13 (22.0)	
Total	48 (100)	61(100)	

Table 10. Distribution of patients based on outcomes.

Outcome		Patients N(%)		P-value
		2010-2015	2016-2020	
Alive	Confirmed	93 (28)	123 (40)	0.0001
	No recurrence on last visit	21 (6)	3 (1)	
	Ongoing treatment	4 (1)	5 (2)	
	Subtotal	118 (35.0)	131 (43.0)	
Dead		94 (28.0)	98 (31.0)	
Abandonment		58 (17.0)	29 (9.0)	
Refusal		12 (4.0)	5 (2.0)	
Referred to a non-participating institution		5 (2.0)	1 (0.5)	
No data		42 (14.0)	43 (14.5)	
Total		330 (100)	306 (100)	

Discussion

This study compared the largest and most comprehensive data on retinoblastoma patients in the country in terms of the number of patients included, geographical coverage, and the number and type (private and public) of participating institutions. The authors initially aimed to divide the cohort into 2 equal groups with 6 years duration each (from 2010 to 2015 and from 2016 to 2021) to determine if there are changes in the patterns on demographics, clinical presentation, treatment, and clinical outcomes over time. However, due to logistical issues, data collection was only done up to 2020. Aside from the shorter duration of the second timeline (5 versus 6 years), the lower absolute number of cases from 2016 to 2020 could be due to the mobility restrictions

imposed during the COVID-19 pandemic in 2020. However, the annual average of new cases was still higher from 2016 to 2020 and can be attributed to the increasing national population over time.[11] The changes in the number of cases recorded from Regions 6, 7, 8 and 10 between the two timelines can be from better record keeping with less number of patients without data on province of origin in the later timeline. For the same reason, missing data was reduced from 56 in 2010 to 2015 to 5 in 2016 to 2020.

More males (60%) were affected in the earlier time period despite the country's equal sex distribution for the age group based on the Philippine Statistics Authority's National Census in 2015 and 2020.[12] Fabian *et al.* reported a similar finding of high male-to-female ratio in their global retinoblastoma cases and attributed it to gender discrimination in access to healthcare in Asia, particularly India.[13] However, the Philippines is not known to have similar issues like in India.[13,14] The male predominance in the 2010-2015 timeline is less than the 1967 to 1977 and the 1985 to 1995 series of Espiritu and company.[3] It was similar though to their 1996-2001 series.[3] The sex distribution in this cohort eventually equalized over time, similar to the study by Noguera *et al.* covering the years 1998 to 2008, reflecting the general global finding of no sex predilection for retinoblastoma.[4,13] This can then be a recurring pattern as was noted in the previous local series.[3,4]

Eight (8) out of the 11 participating institutions were located in Luzon and this largely accounted for the predominance of retinoblastoma patients from Luzon. Region 4A and the National Capital Region were the regions with the most retinoblastoma cases as they are the most populated in the country, with 15% and 12%, respectively, of the national population living in these 2 regions based on the 2020 Philippine Statistics Authority Population census.[11] However, Region 11 ranked third at 11% despite being only the 8th most populated region in the country, suggesting a higher incidence of retinoblastoma in the region.[11] On the other hand, Region 9 registered the lowest number of cases at 2 for each timeline, despite being 13th of the 17 regions in terms of share in the national population.[11]

The percentages of unilateral disease did not differ between the two timelines and were even similar to Espiritu *et al.*'s 1996-2001 series.[3] However, they were lower than that of the Global Retinoblastoma Study Group (78%).[5] Espiritu *et al.* attributed the increasing percentage of patients with bilateral retinoblastoma to increased survival of retinoblastoma patients from prior generations who eventually passed the disease to their offspring, a common pattern seen among those with bilateral disease.[3] Based on this, more patients with bilateral disease may be expected as there was significant difference in the outcomes of retinoblastoma cases over time.

It is alarming that despite having similar age at onset of symptom over time and continuing efforts from organizations like the PAO and the PSPOS to increase awareness on the disease, there was no improvement in the age at initial consult and delay of consultation over time. Financial concerns remained the major cause in the delay despite improvement in healthcare financing through increased coverage by the PHIC, as cost particularly the non-medical ones (fare, food and accommodation) remained high or are even increasing.[15,16] Majority of the patients were seen in institutions located outside their regions of residence as availability of properly equipped institutions remained limited and are concentrated in the metropolitan areas.[17,18]

Leukocoria remained the most common presenting symptom in both timelines. This should help with the early detection of retinoblastoma as it is easily identifiable with the use of portable phone cameras.[10] There were significant differences in intraocular grading and systemic staging over time despite similar delay in consultation. However, the difference in systemic stages may have resulted from improvement in surgical technique when doing enucleation as a result of increasing attention to train residents to perform the procedure on affected eyes.

The percentages of grade E eyes in both timelines were less than those from India, Indonesia and Pakistan, the first, 3rd and 4th leading countries with the most reported retinoblastoma cases globally.[2,14, 19-25] In the same report, the Philippines ranked 6th.[2] Patients with IRSS Stages 2 to 4 in both timelines were both lower compared to those in Indonesia since their series had a longer delay in consultation.[25] However, the results of this study are still high especially when compared to developed

countries. These data should keep clinical practitioners and policy makers aware of the national situation and guide them in implementing programs and policies to help improve the local situation on retinoblastoma detection and management.

Enucleation remained the most common treatment mode in both timelines as opposed to other countries like India which has shifted to systemic chemotherapy as its most common treatment modality for retinoblastoma.[26] This is secondary to the similar percentages of patients with unilateral advanced disease, for which enucleation is favored over systemic chemotherapy.[27] Changes in the distribution of patients needing systemic chemotherapy between the two timelines reflect the changes in the number of eyes without high-risk features and did not need adjuvant systemic chemotherapy over time. Increased awareness on the benefit and acceptance of systemic chemotherapy over time may have contributed to the change in proportion of patients who completed their cycles, from 34% to 44% in 2010 to 2015 and 2016 to 2020, respectively. Although there was change in patients' status on systemic chemotherapy, a quarter of the 2016 to 2020 cohort was still a high number. Efforts to educate the parents of patients are still needed to address the stigma associated with systemic chemotherapy. Financial issues, especially over non-medical ones, need to be addressed as well since the systemic chemotherapy regimen for retinoblastoma is given for at least 6 cycles spaced almost a month apart.[27] The costs incurred by patients while receiving interval treatments in a facility away from their place of residence remain high.[16] Some transient houses provide free to low-cost accommodations in Manila to patients of PGH and similar programs can be implemented in other cities.[28] The increase in the absolute number of eyes from 8 to 16 and 8 to 33 which underwent cryotherapy and laser therapy, respectively, can be a result of increased availability of the human resources and equipment to deliver them.

Follow-up periods for both timelines were short as a result of the overall high percentages of patients who died (28 and 31%), abandoned (17% and 9%) and who were lost to follow-up (14.0 and 14.5%). The percentage of living patients (35% and 43%) were still lower than the series from Pakistan (64-66%), India (83-94%) and China (81-98%) which highlight the need for improvement in the management of retinoblastoma cases.[20-26,29-35]

This study is limited by its retrospective nature. Incomplete data ranged from 10% to 17% which highlight the need for better recordkeeping by medical staff who evaluate retinoblastoma patients in the country. A prospective study may also better address the high number of incomplete data as the latter can significantly alter the findings of this retrospective study. Four institutions used established digital databases which can serve as an example to follow for other institutions. A national retinoblastoma registry can then be established from these digital databases. There are also regions with limited representations; several institutions from different regions were invited to participate in this study but were unable to do so. Funding can also be explored in the future to be able to incentivize institutional investigators as well as hire research assistants for data collection.

In conclusion, there was no improvement in early health seeking behavior based on similar age at initial consult and delay in consult over time. Enucleation remained the most common treatment mode as opposed to chemotherapy due to similar percentages of patients with unilateral disease, an indication for enucleation rather than chemotherapy.

REFERENCES

1. Mendoza PR, Grossniklaus HE. The Biology of Retinoblastoma. *Prog Mol Biol Transl Sci* 2015;134:503-516.
2. Usmanov RH, Kivelä T. Predicted trends in the incidence of retinoblastoma in the Asia-Pacific region. *Asia-Pac J Ophthalmol* 2014;3:151–7.
3. Espiritu RB, de Jesus AA, Valera EG, Mercado GJ. Epidemiological pattern of retinoblastoma at the Philippine General Hospital. *Philipp J Ophthalmol* 2004;29:136-139.
4. Noguera SI, Mercado GJV, Santiago DE. Clinical Epidemiology of retinoblastoma at the Philippine General Hospital: 1998-2008. *Philipp J Ophthalmol* 2011;36:128-32.
5. Global Retinoblastoma Study Group, Fabian ID, Abdallah E, *et al.* Global Retinoblastoma Presentation and Analysis by National Income Level. *JAMA Oncol* 2020 May 1;6(5):685-695.
6. Tan RJD, Ballesteros KFB. Retinoblastoma Outcomes in a Tertiary Hospital in Northern Luzon, The Philippines: A 15-Year Experience. *South Asian J Cancer* 2022 Mar 22;11(2):160-163.

7. Malabanan-Cabebe CGP, Santos-Gonzales MA, Te AVR, *et al*. Retinoblastoma in the Southern Philippines: Clinical Outcomes of Retinoblastoma Patients in a Davao Tertiary Hospital. *Acta Med Philipp* 2024;58(6):45-51.
8. Mercado GVJ, Tan RJD. Addressing the Need for Complete and Updated Data on Retinoblastoma in the Philippines. *Philipp J Ophthalmol* 2022;47(1):4-8.
9. Tan RJD. Increasing Response to the Call for Complete and Updated Data on Retinoblastoma in the Philippines. *Philipp J Ophthalmol* 2023; 48(2):49-51.
10. Tan RJD, Mercado GVJ, Cabrera PE, *et al*. Philippine Retinoblastoma Initiative Multi-eye center Study 2010-2020. *Int J Ophthalmol* 2024; 17(1):144-156.
11. Philippine Statistics Authority. Highlights of the Philippine Population 2020 Census of Population and Housing (2020 CPH). 2021: https://psa.gov.ph/content/highlights-philippine-population-2020-census-population-and-housing-2020-cph (accessed January 23, 2023).
12. Philippine Statistics Authority. Age and Sex Distribution in the Philippine Population 2020 census and housing. 2021: https://www.google.com/search?q=sex+distribution+of+children+in+the+Philippines&oq=sex+&gs_lcrp=EgZjaHJvbWUqCAgAEEUYJxg7MggIABBFGCcYOzIGCAEQRRg5MgoIAhAuGLEDGIAEMg0IAxAuGIMBGLEDGIAEMgwIBBAAGBQYhwIYgAQyBggFEEUYPDIGCAYQRRg8MgYIBxBFGD3SAQc5NzhqMGo3qAIAsAIA&sourceid=chrome&ie=UTF-8 (accessed May 5, 2024).
13. Fabian ID, Khetan V, Stacey AW, *et al*. Sex, gender, and retinoblastoma: analysis of 4351 patients from 153 countries. *Eye (Lond)* 2022;36(8):1571-1577.
14. Tan, R.J. Clinical Presentation, Treatment and Outcomes of Retinoblastoma in India: A Literature Review. *Philipp J Health Res Dev* 2022;26(2):61-72.
15. Philippine Health Insurance Corporation. PHILHEALTH CIRCULAR No. 2017-0017 Strengthening the Implementation of the No Balance Billing Policy (Revision 2). 2017: https://www.philhealth.gov.ph/circulars/2017/circ2017-0017.pdf (accessed January 23, 2023).
16. Tan RJD, Leon LP. The Cost of Managing Congenital Rubella Syndrome in a Tertiary Government Hospital in Northern Luzon, Philippines. *Acta Med Philipp* 2023;57(1):41-46.
17. Antonio CAT. The Continuing Challenge of Maldistribution of Human Resources for Health. *Acta Med Philipp* 2022;56(8):3-4.
18. Tan RJD, Dacuma MGB. Factors affecting childhood blindness and visual impairment in Baguio General Hospital and Medical Center. *Philipp J Health Res Dev* 2021;25(3):54-63.
19. Sahu S, Banavali S, Pai S, *et al*. Retinoblastoma: Problems and Perspectives from India. *Pediatr Hematol Oncol* 1998;15(6):501-508.
20. Islam F, Zafar SN, Siddiqui SN, Khan A. Clinical course of retinoblastoma. *J College Physicians Surg Pak* 2013;23(8):566-569.
21. Tan RJ, Umerez DC, Alindayu JI, *et al*. Retinoblastoma in South Asia: A scoping review. *Asian J Cancer Care Prev* 2021;6(4).
22. Adhi M, Kashif S, Muhammed K, Siyal N. Clinical pattern of Retinoblastoma in Pakistani population: Review of 403 eyes in 295 patients. *J Pak Med Assoc* 2018;68(3):376-80.
23. Singh U, Katoch D, Kaur S, *et al*. Retinoblastoma: A Sixteen-Year Review of the Presentation, Treatment, and Outcome from a Tertiary Care Institute in Northern India. *Ocul Oncol Pathol* 2017;4(1):23-32.
24. Adhi M, Kashif S, Muhammed K, Siyal N. Clinical pattern of Retinoblastoma in Pakistani population: Review of 403 eyes in 295 patients. *J Pakistan Med Assoc* 2018;68(3):376-80.
25. Soebagjo H, Prastyani R, Sujuti H, *et al*. Profile of Retinoblastoma in East Java, Indonesia. *Int J Epidemiol & Infection* 2013;1(3):51-6.
26. Kaliki S, Patel A, Iram S, *et al*. RETINOBLASTOMA IN INDIA: Clinical Presentation and Outcome in 1,457 Patients (2,074 Eyes). *Retina* 2019;39(2):379-391.
27. Astudillo PPP. Retinoblatoma. In: Santiago APD, Valbuena MN, eds. Pediatric Ophthalmology and Strabismus: A Comprehensive Guideline. Manila, Philippines: Department of Ophthalmology and Visual Sciences, Philippine General Hospital, University of the Philippines Manila, 2022; v.1, chap.16: 239-247.
28. Lalu GP. Temporary houses for cancer patients from provinces considered by Manila LGU. 2020: https://newsinfo.inquirer.net/1229922/temporary-houses-for-cancer-patients-from-provinces-considered-by-manila-lgu (accessed May 5, 2024).
29. Chawla B, Hasan F, Azad R, *et al*. Clinical presentation and survival of retinoblastoma in Indian children. *Br J Ophthalmol* 2015;100(2):172-178.
30. Gao J, Zeng J, Guo B, *et al*. Clinical presentation and treatment outcome of retinoblastoma in children of South Western China. *Medicine (Baltimore)*. 2016;95(42):e5204.
31. Luo X, Ye H, Ding YG, *et al*. Clinical characteristics and prognosis of patients with retinoblastoma: 8-year follow-up. *Turk J Med Sci* 2015;45(6):1256-62.
32. Jin L, Zhang W, Pan H, *et al*. Retrospective investigation of retinoblastoma in Chinese patients. *Oncotarget* 2017;8(65):108492-108497.
33. Tan RJ. Clinical Features, Treatment and Outcomes of Retinoblastoma in China. Asian Journal of Oncology 2022: https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0042-1744449.pdf (accessed January 23, 2023).
34. Shah P, Narendran V, Kalpana N. Outcomes of Intra- and Extraocular Retinoblastomas from a Single Institute in South India. *Ophthalmic Genet* 2013;36(3):248-250.
35. Zia N, Hamid A, Iftikhar S, *et al*. Retinoblastoma Presentation and Survival: A four-year analysis from a tertiary care hospital. *Pak J Med Sci* 2020;36(1):S61-S66.