ORIGINAL ARTICLE

Retinoblastoma in the Southern Philippines: Clinical Outcomes of Retinoblastoma Patients in a Davao Tertiary Hospital

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ABSTRACT

Background. Retinoblastoma is the most common intraocular cancer in childhood in the Philippines. Most data though on demographics, clinical profile, treatment options, and outcomes in the country are from the National Capital Region.

Objectives. This study aimed to describe the demographics, clinical profile, treatment done, and outcomes of retinoblastoma patients seen in a public tertiary referral center in Davao from 2011-2020 to make available literature more representative of the status of retinoblastoma in the Philippines.

Methods. An analytical cross-sectional study was conducted using the records of retinoblastoma patients seen in a tertiary government hospital located in Davao Region from January 2011 to December 2020.

Results. There were 157 patients included in the analysis. Seventy-three (46%) were female with 44% coming from the Davao Region. One hundred seven (69%) patients had unilateral disease. Median age at initial consultation for patients with unilateral disease was significantly older than those with bilateral disease ($p<0.003$). Tumors were extraocular in 82 (40%) eyes. In the intraocular group, 36% of the eyes belonged to International Classification of Retinoblastoma (ICRB) Groups D and E. Enucleation was the most commonly performed treatment. Survival rate was 28%.

This is the first report to provide epidemiologic and clinical data on retinoblastoma in the literature, including survival data, from Mindanao. Advanced stages and extraocular cases of retinoblastoma remain high. Delay of consultation contributed to the prognosis and clinical outcome of the disease.

Conclusion. Advanced stages and extraocular cases of retinoblastoma remain significantly high in the country, even in Mindanao.

Keywords: retinoblastoma, clinical profile, treatment, outcomes, survival rate, Mindanao

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INTRODUCTION

Retinoblastoma is a childhood malignancy arising from immature cells in the retina which was first reported by Benedict in 1929.[1] Annually, there are 8,000 to 9,000 new retinoblastoma cases reported worldwide.[2] In large populations with high birth rates such as in Asia and in Africa,

the incidence and consequences of retinoblastoma has been the greatest, resulting in a global burden.[3] Retinoblastoma has an annual incidence of 7.7-8.9 per million Filipino children ages 0 to 14 years, with leukocoria or cat's eye reflex as the most common presenting symptoms.[4] It is the most common malignant intraocular tumor accounting for 91% of all malignant intraocular tumors in the country.[2] Different classification and staging systems exist to describe the extent of intraocular and extraocular disease and prognosticate. Surgery remains the primary treatment option in countries where advanced disease is predominant and often, survival rates are low. However, there has been recent shift to the use of systemic chemotherapy even for advanced cases.

The countries with high incidence were reported to have the highest mortality rate with up to 40 to 70% of these patients dying, compared to 3 to 5% in Europe, Canada and USA.[5-7] In some developing countries, mortality rate is still high with 95% of cases.[8] This is mostly likely because of the delay in treatment due to a late diagnosis. Poverty and lack of knowledge or awareness of the impact of the disease delay access to care.[9] Most available data on retinoblastoma in the Philippines are from Luzon, specifically the Philippine General Hospital in Manila.[2,10-13] However, a quarter of the country's 110 million citizens resides in Mindanao. Reviewing the clinical profile of retinoblastoma in Southern Philippines Medical Center (SPMC) can help identify differences when compared to existing local and international literature which is vital in evaluating, updating, or establishing local management guidelines, policies, and programs in the hospital and in the country. Reviewing the treatment outcomes of the patients can also help evaluate how SPMC fared in the management of patients with retinoblastoma in the past decade. This will further help identify problems and therefore improve on areas where there are deficiencies.

METHODS

This analytical cross-sectional study was conducted with the approval of the institutional Ethics Review Board and adhered to the principles of the Declaration of Helsinki. The Data Privacy Act of 2021 was observed in handling the data collected from this study. A chart review of diagnosed retinoblastoma patients seen by the Department of Ophthalmology and the Oncology Section of the Department of Pediatrics of the Southern Philippines Medical Center (SPMC), the largest Department of Health-run hospital in the Philippines located in Davao City and the largest referral center in Mindanao, from January 2011 to December 2020, was done. The following data were retrieved from the medical records: 1) demographics: age at onset of symptom, age at first consultation with SPMC, sex, and address; 2) clinical profile: laterality of involvement, presenting symptom, family history, grading using the International Classification of Retinoblastoma (ICRB) and staging using the International Retinoblastoma Staging System (IRSS); 3) treatment: underwent surgery, date of surgery, type of surgery, histopathology result, presence of high-risk features, underwent chemotherapy, number of cycles, route of delivery, and underwent radiotherapy and local therapy; and 4) outcomes: treatment refusal, treatment abandonment, survival status and globe salvage.

Frequency, percentage, mean, median, standard deviation, and interquartile range were computed, and tables and graphs were used to summarize findings using Microsoft Excel Ver. 3 2013 (Microsoft Corp.; Redmond, Washington, USA). Mann-Whitney U test was used to compare the median ages at initial onset of symptoms and the median ages at initial consultation in the institutions between groups. A Kaplan-Meier estimate was done for survival analysis. Kaplan-Meier log rank test was done to determine if survival was associated with laterality of disease and sex. A p-value of <0.05 was considered significant.

RESULTS

Demographics

There were 157 patients with 207 eyes included in this study. An average of 16 new cases annually were seen from 2011-2020. Eighty-four (54%) were male. Most patients came from the Davao region (44%). The regional distribution of the patients is summarized in Figure 1.

Clinical Profile

There were 107 (69%) patients with unilateral disease while 50 had bilateral. Two patients with bilateral involvement had trilateral disease. The overall median age at initial onset of symptoms was 18 (7,26) months. The median age (1st interquartile range, 3rd interquartile range) at initial onset of symptoms for patients with unilateral disease was 19 (8,30) months and 12 (4,20) months for bilateral. The age at initial onset of symptoms of patients with unilateral disease was significantly older (p<0.001) than those with bilateral disease.

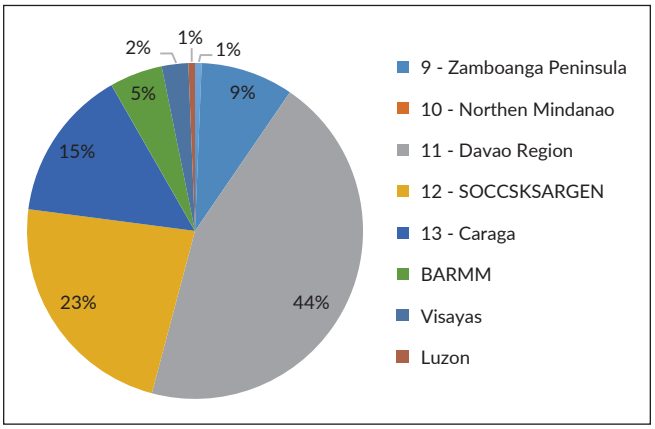

Figure 1. Regional distribution of retinoblastoma patients seen in SPMC from 2011-2020.

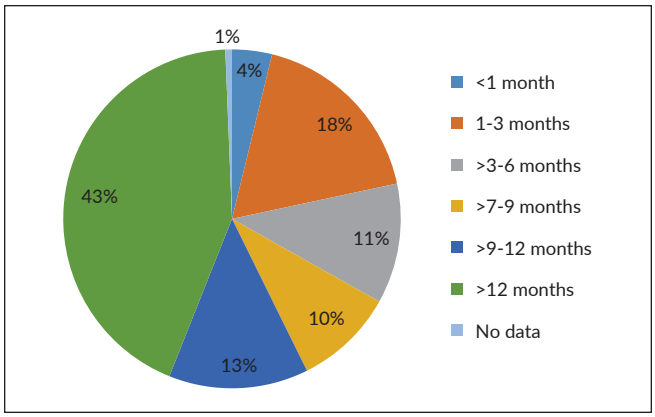

Figure 2. Distribution of length of delay in consultation.

The overall median age at initial consultation was 28 (22,42) months. The median age at initial consultation for patients with unilateral disease was 30 (24,48) months while 28 (17,35) months for bilateral. The age at initial consultation for patients with unilateral disease was significantly older ($p<0.003$) than those with bilateral disease.

The overall median delay of consultation was 11 (4,20) months. Delay of consultation was derived from the difference of the date or age at the onset of initial symptom of retinoblastoma and of the date or age at initial consult with the institution, or the delay of consultation noted in the chart if there was no data on the date or age at the onset of initial symptom. The median delay of consultation was 11 (4,21) months of patients with unilateral disease while 13 (7,19) months for bilateral disease. There was no significant difference in the delay of consultation between patients with unilateral and bilateral disease ($p=0.81$). The distribution of the delay in consultation is summarized in Figure 2.

Leukocoria was the most common presenting symptom in 95 (46%) eyes followed by proptosis at 50 (24%) eyes. Forty-nine (24%) eyes had no data on presenting symptom since only the presenting symptom of the worse eye for those with bilateral disease were noted. Based on the International Classification of Retinoblastoma (ICRB) which was determined clinically on the initial consult with the institution, 1 eye belonged to Group A, 4 eyes to Group B, 16 eyes to Group C, 16 eyes to Group D, and 76 eyes to Group E. Eighty-two (40%) eyes cannot be classified based on ICRB due to the presence of extraocular disease while 12 did not have any data. The distribution of eyes using ICRB grading based on laterality is summarized in Table 1. Aside from the five ICRB Group D eyes from patients with unilateral disease, the rest of the eyes which presented with ICRB Group A-D belonged to patients with bilateral and trilateral diseases.

Based on the International Retinoblastoma Staging System (IRSS) which was determined after imaging and enucleation had been done, 2 patients belonged to Stage 0, 48 to Stage 1, 6 to Stage 2, 44 to Stage 3, and 50 to Stage 4. Seven patients had no data due to treatment refusal or incomplete data. The distribution of patients based on laterality is summarized in Table 2.

Treatment

Enucleation was the most commonly performed treatment option done in 123 (59%) eyes, with 60 undergoing secondary enucleation. Primary or upfront enucleation refers to performing the surgery without any prior intervention (e.g., systemic chemotherapy, local therapy such as laser) while secondary enucleation refers to performing the surgery after another intervention/s was given, often systemic chemotherapy for mass reduction. Three orbits underwent

Table 1. Distribution of Eyes Using ICRB Grading Based on Laterality of Disease[14]

ICRB grading	Description	Unilateral	Bilateral	Trilateral	Total number of eyes
A	Mass/es is/are ≤3 mm (base dimension or thickness)	0	1 (1%)	0	1
B	Mass/es is/are >3 mm (base dimension or thickness), macular location (≤3 mm to foveola), juxtapapillary location (≤1.5 mm to disc) or additional subretinal fluid (≤3 mm from margin)	1 (1%)	3 (3%)	0	4
C	Mass with subretinal seeds ≤3 mm from mass, vitreous seeds ≤3 mm from mass or both subretinal and vitreous seeds ≤3 mm from mass	2 (1%)	13 (14%)	1 (25%)	16
D	Mass with subretinal seeds >3 mm from mass, vitreous seeds >3 mm from mass, or both subretinal and vitreous seeds >3 mm from mass	5 (5%)	11 (12%)	0	16
E	Extensive mass occupying >50% globe or with neovascular glaucoma, opaque media from hemorrhage in anterior chamber, vitreous or subretinal space, invasion of postlaminar optic nerve, choroid (>2 mm), sclera, orbit, or anterior chamber	42 (40%)	34 (35%)	0	76
Extraocular		55 (52%)	25 (26%)	2 (50%)	82
No data		2 (1%)	9 (10%)	1 (25%)	12
Total		107 (100%)	96 (100%)	4 (100%)	

Table 2. Distribution of Patients Using IIRS Based on Laterality of Disease[15]

Staging	Description	Unilateral	Bilateral	Trilateral	Total number of patients
0	Eye with disease but not enucleated	2 (1%)	0	0	2
1	Eye enucleated, completely resected histologically	31 (30%)	17 (35%)	0	48
2	Eye enucleated, microscopic residual tumor	4 (3%)	2 (5%)	0	6
3	Regional extension	29 (28%)	15 (31%)	0	44
4	Metastatic disease	35 (34%)	13 (27%)	2 (100%)	50
No data		6 (4%)	1 (2%)	0	7
Total		107 (100%)	48 (100%)	2 (100%)	157

exenteration and one eye had no data. For patients with unilateral disease, 76 (71%) patients underwent enucleation, with 41% undergoing secondary enucleation. The remaining 31 patients did not undergo enucleation where the 24 were diagnosed with IRSS Stage 3 or 4 and was offered systemic chemotherapy instead and followed-up. One underwent exenteration while the remaining six patients had no data.

For patients with bilateral disease, 48 (48%) eyes underwent enucleation, with 30 undergoing secondary enucleation. Fifty eyes did not undergo any surgery while two underwent exenteration. Thirteen (26%) patients did not undergo any surgeries with all but two with no data, diagnosed with IRSS stage 3 or 4. Twelve (24%) patients underwent bilateral surgery, with two patients undergoing enucleation in one eye and exenteration on the other orbit. Of the 12, all except one had IRSS stage of ≥2.

Of the 123 eyes which underwent enucleation, 45 (36%) eyes had no high-risk feature (HRF), 30 had 1 HRF, 19 had >1 HRF, and 29 with no data. High-risk feature includes positive optic nerve margin, posterior laminar optic nerve involvement (PLONI), massive choroidal involvement, scleral involvement, and anterior chamber involvement. Massive choroidal involvement was the most common HRF present in 29 (59%) eyes. Table 3 summarizes the distribution of the enucleated eye based on the presence of HRF.

One hundred twelve patients underwent systemic chemotherapy with 60 patients undergoing neoadjuvant regimen. For the 45 (29%) patients who did not undergo systemic chemotherapy, 14 did not need it while the remaining were advised treatment but refused. For patients with unilateral disease, 63 (59%) patients underwent systemic chemotherapy, with 26 undergoing neoadjuvant regime. For patients with bilateral disease, all except one, did undergo systemic chemotherapy. Thirty-four (69%) patients underwent neoadjuvant regimen. Fourteen patients received additional external beam radiotherapy. Ten eyes received laser photocoagulation with one from a patient with unilateral disease.

Outcomes

The median follow-up period was 8 (4,19) months. There were 44 (28%) patients confirmed alive, 57 (36%) confirmed dead, and 56 lost to follow-up. Of the 56 patients lost to follow-up, 10 refused any intervention, 6 completed their prescribed treatment, 34 abandoned their prescribed treatment (either did not complete their prescribed number of cycles for systemic chemotherapy or did not push thru with additional treatment regimen such as enucleation, systemic chemotherapy, or radiotherapy), and 6 did not have any additional data. The disposition of the patients is summarized below based on the laterality of the disease (Table 4). Nine globes (4%) of the 13 patients confirmed alive with bilateral disease were salvaged. There was no data on the visual acuity of the 9 salvaged globes in the last follow-up.

Table 3. Distribution of the Enucleated Eye Based on the Presence of High-risk Features

High-risk Feature (HRF)	Number of Enucleated Eyes		
	Unilateral	Bilateral	Total
None	24	21	45 (36%)
1 HRF	18	12	30 (24%)
Positive Margin	9	3	12
Choroidal Involvement	7	6	13
PLONI	1	3	4
Anterior Chamber	0	0	0
Scleral Perforation	1	0	1
>1 HRF	17	2	19 (15%)
Positive Margin	7	1	8
Choroidal Involvement	14	2	16
PLONI	8	0	8
Anterior Chamber involvement	5	2	7
Scleral involvement	9	1	10
No data	17	12	29 (25%)

** PLONI – posterior laminar optic nerve involvement*

Table 4. Disposition of Patients Based on Laterality of Disease

	Unilateral	Bilateral	Trilateral	Total
Confirmed Alive	31	13	0	44
Confirmed Dead	38	17	2	57
Lost to Follow-up				
Treatment Refused	7	3	0	10
Treatment Completed	2	4	0	6
Treatment Abandoned	23	11	0	34
No Data	6	0	0	6

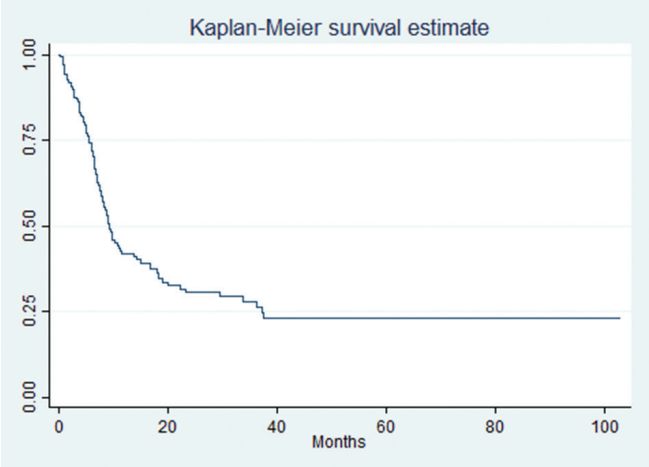

Figure 3. Kaplan-Meier survival estimate.

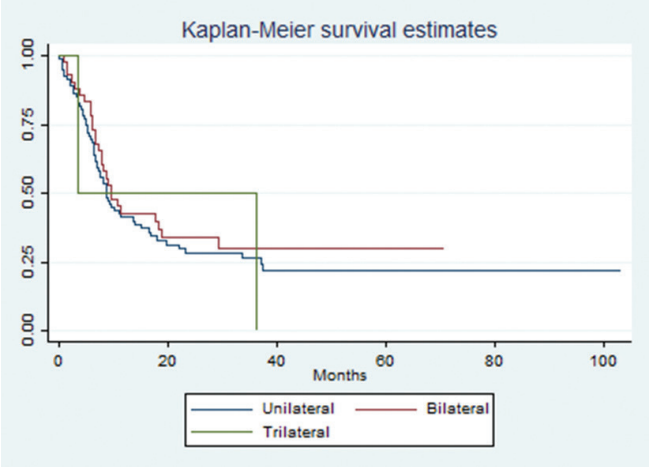

Figure 4. Kaplan-Meier survival based on the laterality of the disease.

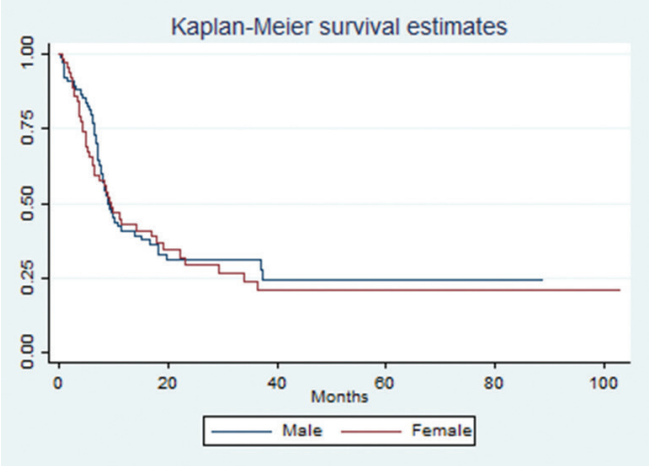

Figure 5. Kaplan-Meier survival based on sex.

With the assumption that all lost to follow-up patients who completed treatment are alive while lost to follow-up patients who refused or abandoned treatment, the Kaplan-Meier survival estimate is shown in Figure 3.

Survival estimate is at around 45% on the 1st year, around 30% on the 2nd year, around 28% on the 3rd year and 25% after. Survival rates did not differ based on the laterality of the disease (p=0.66) (Figure 4) and on sex (p=0.69) (Figure 5).

DISCUSSION

This study is the first to present epidemiologic and clinical data, including survival rates, on retinoblastoma patients in the literature seen in and who were from Mindanao. The study was conducted in the Southern Philippines Medical Center (SPMC), a referral center for retinoblastoma management in Mindanao, and is located in Davao City. Expectedly, almost half of the patients in the study were from the Davao Region (Region 11) where Davao City is located, followed by Soccsksargen (Region 12) and CARAGA (Region 13). Northern Mindanao Region (Region 10) was only 4th in the ranking and this can be due to the presence of another tertiary government hospital which serves as a referral center in that region and its nearby regions. SPMC also receives patients from the Zamboanga Region (Region 9) and BARMM. Fifty-four percent of the patients were male, showing no sex disease predilection even in Mindanao, similar to Suckling et al.'s and Noquera et al.'s findings.[11,16] The slight predominance of males in both unilateral and bilateral cases in this study may be secondary to the predominance of males in the population of the Philippines, with a high male to female ratio.[17] Majority of the patients had unilateral retinoblastoma (69%), similar to local literature.[11] Unilateral disease was likewise more common in India (57-67%), Turkey (74%), and Taiwan (79%).[18-22] This is also the first local literature on retinoblastoma to report trilateral disease. Two (1%) patients presented with trilateral disease, similar to the series of Sahu et al.'s in India but lower than that the series of Zia et al.'s 0.1% in Pakistan.[23-25]

The age at initial onset of symptoms for patients with unilateral disease in this study is significantly older (p<0.001) than those with bilateral disease, similarly observed in a local study and in Turkey.[11,26] However, Noguera et al.'s series had a younger age at initial symptom of 7 months compared to this study's 12 months.[11] The overall age at initial consultation in this study is older than Noguera et al.'s and Tan and Buyucan's 24 months but younger than the Filipino cohort in the Global Study on Retinoblastoma Group's 33 months.[11,13,25] It is also older than Taiwan's and Turkey's 25 months.[20,26] Thus, the overall delay of consultation is also high at 11 months compared to local studies and in Pakistan, although shorter than in Indonesia's 12 months.[25,27]

The most common presenting symptom remained to be leukocoria (46%), similar to previous reports.[11,13,18-20,28] Next was proptosis (24%), a finding comparable with a study in

Pakistan.[29] This reflects the high proportion of extraocular disease in this study. Proptosis is suggestive of extraocular presentation and is common in developing countries.[30] Eyes classified with advanced stages under the ICRB (Grades D and E) were at 44%, lower than Noguera et al.'s 69% and Huang et al.'s 81% in China.[11,31] However, Noguera et al.'s extraocular disease was lower at 16% compared to this study's 40%.[11] Based on IRSS, 63% of the patients were classified with extraocular disease or those with stage ≥2, higher than Tan and Buyucan's and the Filipino cohort in the Global Study on Retinoblastoma Group's 45%.[13,25] Late diagnosis in developing countries highly correlates with progression to advanced disease.[31]

Enucleation was the most commonly performed procedure in this study with 59%. Primary or upfront enucleation is often offered to patients with unilateral involvement with advanced disease (ICRB Grade D and E), which was high in this study. It is also offered for the worse eye with advanced disease of patients with bilateral involvement. This is unless parents wish to explore other treatment options first. Secondary enucleation can be done for this, or if extraocular involvement is present or suspected. Commonly, systemic chemotherapy is given first usually for mass reduction and easier surgical removal.[32] The enucleation rate in this study is lower than in Tan and Buyucan's series in Northern Luzon (79%) and in Cameroon (75%) probably as a result of enucleation as the preferred primary treatment option for retinoblastoma in their institutions due to absence of facility and equipment for the other treatment options.[14,33] However, it is higher than in India (46%) and Pakistan (41%) probably as a result of their institutions' preference for and successful use of systemic chemotherapy.[22,29] Half of the enucleations done both in unilateral and bilateral disease in this study were secondary, highlighting the increased use of systemic chemotherapy as a neoadjuvant in SPMC as well. Due to advanced disease, twelve patients had to undergo bilateral surgeries. This is also the first study to present histopathologic data in a clinicoepidemiologic study locally. The proportion of enucleated eyes with ≥1 high risk features was high at 39% compared to Cabrera et al.'s local histopathologic study of 33%.[12] And this is in the setting where 25% of the enucleated eyes in this study had no histopathologic data, which can further increase the number. Eighty percent of patients which required systemic chemotherapy underwent treatment, similar to a series in Pakistan.[29] This is also the only local literature with comprehensive data on treatment options done for retinoblastoma patients.

The follow-up period was short at 8 months which may be secondary to the low confirmed survival rate at 28%. The survival rate is lower than Tan and Buyucan's in Northern Luzon, in India and in China.[13,34,35] It is higher though than Adhi et al.'s in Pakistan and Handayani et al.'s in Indonesia.[27,29] The generally low survival rate can be explained by the high proportion of patients with extraocular disease. The proportion of patients who were lost to follow-up was also high with 18% refusing any treatment while 61% abandoning their prescribed treatment. Common causes identified for the delay were lack of information on the disease and financial concerns for medical consultation locally, in India and in Africa.[11,28,33,36,37] As oppose to data from the United States where male retinoblastoma patients were found to have lower survival rate than females which was attributed to the male X-linkage and the more severe disease present among males in the series, sex was found to have no effect in the survival rates of our patients.[38] This may be explained by the equal presence of advanced disease in both sexes. Also, despite patients with unilateral disease presenting at a later age compared to those with bilateral disease, the two groups had no significant difference in terms of survival. This can still be a result of the similar length of delay in consultation and the high proportion of advanced and extraocular disease in both groups.

Due to the retrospective nature of the study, completeness of data was a limitation. However, all missing data were labelled as "no data", as can be seen in the results. The use of electronic medical records or dedicated retinoblastoma evaluation sheet in the future may address this for future studies. Similarly, despite provision of data from Mindanao, there remains regions in the country without data. As such, a multicenter study on retinoblastoma is recommended.

CONCLUSION

Seventy-three (46%) patients were female with 44% coming from the Davao Region. One hundred seven (69%) had unilateral disease. Median age at initial consultation for patients with unilateral disease was significantly older than those with bilateral disease ($p<0.003$). Tumors were extraocular in 82 (40%) eyes. In the intraocular group, 36% of the eyes belonged to groups International Classification of Retinoblastoma Groups D and E. Enucleation was the most commonly performed treatment. Survival rate was 28%. Advanced intraocular retinoblastoma and presence of metastasis are common in patients seen in SPMC from 2011 to 2020 leading to low survival rate.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

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