

## Primary Malignant Orbito-Ocular Tumours in Northern Ghana

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**ABSTRACT**

**Background:** Primary malignant orbito-ocular tumours (OOTs) frequently affect the younger age groups. Though mostly curable, they are a major cause of morbidity and even mortality in developing countries. The aim of this review was to describe the spectrum and clinico-pathological features of primary malignant OOTs in northern Ghana.

**Material and Methods:** This study was a retrospective histopathological review from 1st June, 2013 – 30th June, 2019. Data were analysed using SPSS version 23 (SPSS Inc, Chicago, Ill); associations were determined by Fisher's exact test.

**Results:** There were 32 (72.7%,  $p < 0.0001$ ) primary malignant OOTs; the mean age of patients was  $28.7 \pm 22.3$  years with a slight female predominance (56.3%). The conditions in descending order included: retinoblastoma (50.0%), invasive squamous cell carcinoma (SCC) (43.8%), Non-Hodgkin's lymphoma (NHL) (3.1%) and malignant meibomian gland tumour (3.1%). The mean age of patients with retinoblastoma was  $3.3 \pm 4.5$ , with 62.5% being female ( $P = 0.2890$ ). Approximately, 12.5% had bilateral disease. The mean age of patients with SCC was  $47.0 \pm 19.7$  years, 57.1% being females ( $P = 0.7064$ ). All presented with conjunctiva and/or eyelid involvement well differentiated invasive SCC was the commonest histological subtype. The commonest presentation for intraocular tumours was proptosis (62.5%). All the intraocular tumours were diagnosed clinically and confirmed histopathologically in enucleated specimens. Approximately, 62.5% of the intraocular tumours grossly involved the entire intra-ocular space retina with vitreous seeding (Reese-Ellsworth Classification Group V), with 81.3% and 75.0% significantly involving the optic nerve but not the surgical/ resection margins and over 30% of the choroid, respectively. Half were TNM stage 3 tumours.

**Conclusion:** The spectrum of primary malignant OOTs in Northern Ghana in descending order were: retinoblastoma, SCC, NHL and malignant meibomian gland tumour. All presented late with advanced disease beyond salvage.

**Keywords**

Primary orbito-ocular, Tumours, Malignant, Retinoblastoma, Squamous cell carcinoma, Northern Ghana, Tamale.

**Introduction**

Primary malignant orbito-ocular tumours (OOTs), although not as common as the head and neck tumours, once present cause vision impairment, low productivity, social neglect, increased morbidity and mortality [1-3]. Visual impairment, either at birth (congenital) or during childhood impact negatively in all fields of the affected

individual's development [4]. These lesions are thus of a great public health importance in most developing countries such as Ghana.

The spectrum and frequency of primary malignant OOTs varies among studies globally [1,5-7]. For instance, Mohammed et al., (2006) in their study in Nigeria reported the following frequencies of these conditions: retinoblastoma 40.3%, squamous cell carcinoma 33.1% and Burkitt's lymphoma 9.6%. However, Amusa et al., (2004), over a period of ten years did not see any case of

orbito-ocular Burkitt's lymphoma.

Primary malignant orbito-ocular tumours are classified, based on anatomic locations, into: intraocular, orbital, conjunctival and eyelid tumours [7-9]. Mohammed et al., (2006) in Nigeria found the commonest site of these tumours to be intraocular. Orbito-ocular malignancies are found to be common within the first decade of life with a mean age of 4.5 years [7,10]. Some publications found equal sex distribution, [1, 5,7,11], but Otoh et al., (2004) found a male predominance.

The clinical presentation of primary malignant OOTs may mimic developmental disorders, infectious conditions and benign neoplastic diseases of the eye. Patients may thus resort to several treatment options, including herbal medicines and self-medications, and will only present to a health facility when the disease is clinically advanced. Most of the patients may thus present late with proptosis with vision loss at their first attendance to hospital in developing countries [8,12,13].

There is no prior published report of primary malignant orbito-ocular tumours from the northern part of Ghana. The aim of this review is to describe the spectrum and clinico-pathological features of primary orbito-ocular tumours in the northern part of Ghana.

## Material and Methods

### Study design

This was a retrospective review from 1st June, 2013 to 30th June, 2019.

### Study site

The study was conducted in the Department of Pathology, Tamale Teaching Hospital (TTH). The Department receives specimens from TTH and other health facilities within northern Ghana.

### Data collection and analysis

All histopathological request forms, the histology reports and the corresponding histology slides of all orbito-ocular lesions diagnosed in our institution from 1st June 2013 to 31st June 2019 were reviewed. Primary malignant orbito-ocular tumours were then extracted from the group as the study population. Data were collected on the demographic and the clinico-pathological features of all the primary orbito-ocular tumours diagnosed during the period of review. Data were entered into a statistical data base and analysed using SPSS software version 23.0 (SPSS Inc., Chicago, Ill). The results were presented in bar charts and frequency tables. Fisher's exact test was used to compare common variables where applicable.

### Inclusion Criteria

All histologically confirmed malignant primary orbito-ocular tumours diagnosed during the period of study were included.

### Exclusion Criteria

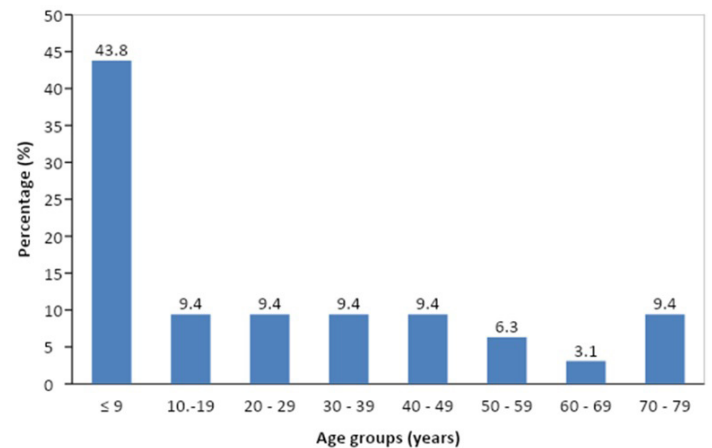
All poorly fixed specimens and those with incomplete records were excluded.

## Results

### Clinico-pathological features of primary malignant orbito-ocular tumours

A total of 54 orbito-ocular cases were reviewed from 1st June 2013 to 30th June 2019. The great majority 44 (81.5%) were neoplastic with, 10 (18.5%) being non-neoplastic lesions ( $p < 0.0001$ ). There were 32 (72.7%) primary malignant orbito-ocular tumours, with 12 (27.3%) benign lesions ( $p < 0.0001$ ).

This manuscript will deal with only the primary malignant OOTs. The ages of the 32 patients diagnosed with primary malignant OOTs ranged from 0.5 – 79 years, with a mean age of  $28.7 \pm 22.3$  years, approximately, 43.8% of the patients were in the age group of 0 to 9 years (Figure 1).



**Figure 1:** Age distribution of patients diagnosed with primary malignant orbito-ocular tumours.

The common primary malignant OOTs were retinoblastoma 16 (50.0%) and invasive squamous cell carcinoma 14 (43.8%). Half of the tumours were intraocular, followed by conjunctival and eyelid tumours. There were 18 (56.3%) females. Many of the patients presented with conjunctiva and/or eyelid involvement (43.8%), followed by those with proptosis with vision loss (31.3%) (Table 1, Figures 2). Only 8 (25.0%) had stated the duration of their symptoms at presentation. A little above half (53.1%) were diagnosed from enucleation specimens (Table 1), (Figure 3,4,5).

		Frequency (n)	Percentage (%)
Primary malignant orbito-ocular tumours	Retinoblastoma	16	50.0
	Invasive squamous cell carcinoma	14	43.8
	Non-Hodgkin's lymphoma	1	3.1
	Malignant meibomian gland tumour	1	3.1
Anatomical location	Intraocular	16	50.0
	Conjunctiva/eyelid	13	40.6
	Orbital	3	9.4
Gender	Female	18	56.2
	Male	14	43.8

Symptoms	Conjunctival/eyelid growth	14	43.8
	Proptosis with vision loss	10	31.3
	Poor vision	4	12.5
	White reflex/ Leukocoria	2	6.3
	Eye masses	2	6.3
Duration of symptoms at presentation (Months)	0 – 12	5	62.5
	>12	3	37.5
Type of surgical procedure / specimens	Enucleation	17	53.1
	Excision	10	31.1
	Exenteration	3	9.4
	Debulking surgery	1	3.1
	Incision biopsy	1	3.1

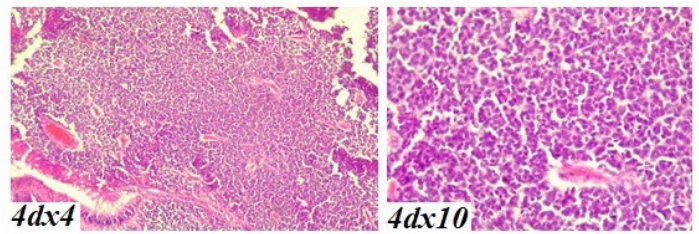
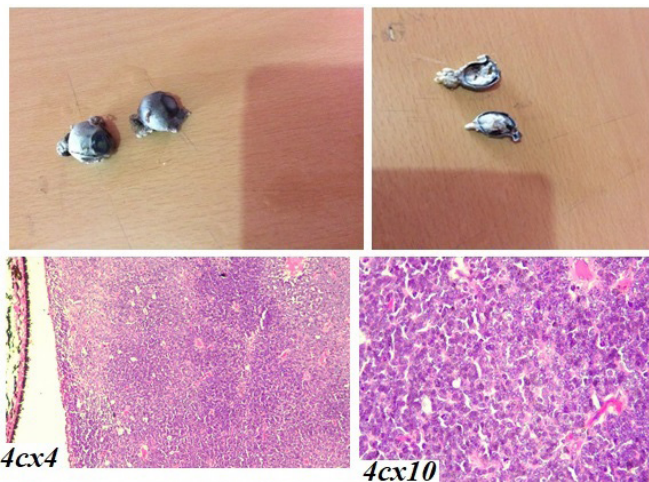
**Table 1:** Clinico-pathological features of primary malignant orbito-ocular tumours.



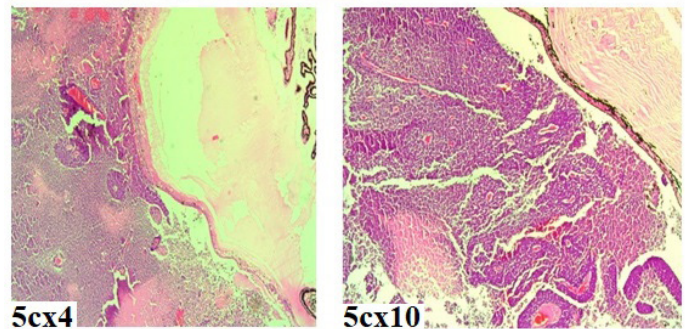
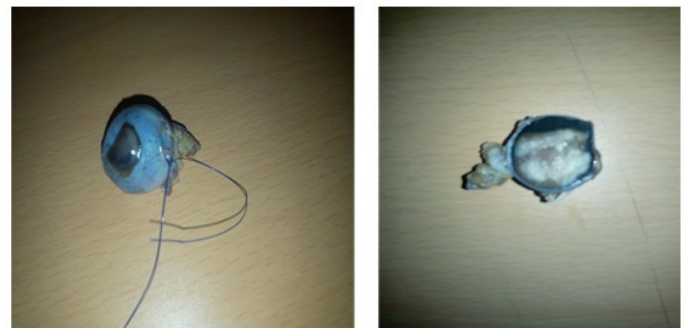
**Figure 2:** Retinoblastoma in an 18-month-old girl with proptosis of the left eye.



**Figure 3:** Squamous cell carcinoma of the conjunctiva growing extensively inside the orbit and compressing the globe.



**Figure 4a:** Bilateral retinoblastoma Reese-Ellsworth Classification Group V (RECGV) in a 12-month-old girl. **4b:** The cut surfaces of a retinoblastoma in a 12-month-old girl with bilateral retinoblastoma showing tumour involving the entire retina, vitreous. **4c:** Histological section from the left eye of the 12-month-old girl with bilateral retinoblastoma showing sheets of primitive cells with rosette formation. **4d:** Histological section from the right eye of the 12-month-old girl with bilateral retinoblastoma showing sheets of primitive cells with rosette formation.



**Figure 5a:** Enucleation specimen of the left eye of a two-year old boy with retinoblastoma showing a whitish patch. **5b:** The cut surface of the left eye in a two-year-old boy showing massive tumour involving the entire retina, vitreous and anterior segment. **5c:** Histological section from the left eye of the two-year-old boy retinoblastoma showing sheets and masses of primitive cells with areas of necrosis.

### Primary malignant conjunctival and/ or eyelid tumours

There were 14 (43.8%) malignant tumours involving the conjunctiva and/or the eyelids. Their ages ranged from 24 – 79 years with a mean age of  $47.0 \pm 19.7$  years. There was no patient aged less than 20-years. There was a slight female predominance, (57.1%;  $P = 0.7064$ ) (Table 2).

A total of 6 (42.9%) had stated the duration of the symptom at the time of presentation (Table 2). Approximately, 35.7% had extensive surgeries such as exenteration (Table 2, Figure 3), because of advanced disease. Invasive well differentiated squamous cell carcinoma was the commonest histological subtype (Table 2; Figure 3).



		Frequency (n)	Percentage (%)
Age groups (years)	20 - 29	3	21.4
	30 - 39	3	21.4
	40 - 49	2	14.3
	50 - 59	2	14.3
	60 - 69	1	7.1
	70 - 79	3	21.4
Gender	Female	8	57.1
	Male	6	42.9
Symptoms	Conjunctiva and eyelid growth	14	100.0
Duration of symptoms at presentation (months)	0 – 12	3	50.0
	>12	3	50.0
Surgical procedure/ specimens	Excision	9	64.3
	Exenteration	3	21.4
	Debulking	1	7.1
	Enucleation	1	7.1
Histological grade	Well differentiation	10	71.4
	Moderately differentiation	2	14.3
	Poorly differentiation	2	14.3

**Table 2:** Clinico-pathological features of patents diagnosed with invasive squamous cell carcinoma of the conjunctiva and/or eyelid.

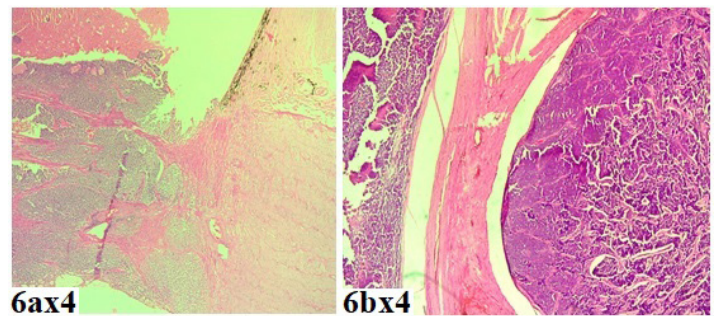
### Primary malignant intraocular tumours

The ages of the 16 retinoblastoma patients ranged from 0.5 – 18 years, with a mean age of  $3.3 \pm 4.5$  years. Two patients (2, 12.5%) had bilateral disease (Figure 4a, b). The majority of patients (10, 62.5%) were in 0 – 9 years age group (Table 3). There were 10 (62.5%) females with 6 (37.5%) males. The commonest symptom of retinoblastoma was proptosis with no perception of light. This occurred in 10 patients (62.5%). All the cases were diagnosed clinically and confirmed in enucleated specimens (Figures 4 and 5). Approximately, 62.5% of the tumours involved the entire retina with vitreous seeding (Reese-Ellsworth Classification Group V) (Table 3, Figures 4 and 5). The great majority (81.3%) had optic nerve involvement but the resection/ surgical margins were free (Figures 5 and 6). The uveal tract (75.0%) and the choroid (37.5%) were also involved respectively (Table 3). Approximately 50.0% of the cases were diagnosed as being TNM stage 3 (Table 3).

		Frequency (n)	Percentage (%)	P-values
Age (years)	≤1	6	37.5	
	2	4	25.0	
	3	4	25.0	
	10	1	6.3	
	18	1	6.3	
Symptoms	Proptosis with no perception of light	10	62.5	
	Severe visual impairment	4	25.0	
	Leukoria	2	12.5	

Gross tumour volume	Entire retina with vitreous seeding	10	62.5	
	Two-thirds of the retina with vitreous seeding	2	12.5	
	Half of the retina with vitreous seeding	4	25.0	
Optic nerve invasion with free surgical/ resection margins	Yes	13	81.3	<0.0001
	No	3	18.7	
Uveal tract invasion	Yes	12	75.0	0.0121
	No	4	25.0	
Necrosis of tumour	Yes	15	93.8	
	No	1	6.2	
TNM staging	pT1NxMx	2	12.5	
	pT2	6	37.5	
	2aNxMx	2	33.3	
	2cNxMx	4	66.7	
	pT3	8	50.0	
	3bNxMx	3	37.5	
	3cNxMx	5	62.5	

**Table 3:** Clinico-pathological features of patients with retinoblastoma.



**Figure 6:** Retinoblastoma with minimal (6a) and extensive optic nerve invasion (6b).

### Discussion

Primary malignant intraocular neoplasms are relatively rare, but they can be fatal if not diagnosed early and treated promptly. This current study found a relative proportion of primary malignant orbito-ocular tumours (OOTs) of 72.7% among all neoplastic orbito-ocular lesions; the spectrum of malignant primary OOTs was: retinoblastoma, invasive squamous cell carcinoma, Non-Hodgkin's lymphoma and malignant meibomian gland tumour. This is the first study in Ghana that looked at primary malignant OOTs as a single disease entity. However, the pattern of conditions presented in this study is similar to what was reported in some previous studies in West Africa [5-7]. For instance, Mohammed et al., (2006) in their study [7] in Nigeria reported the pattern as retinoblastoma, squamous cell carcinoma and Burkitt's lymphoma, quite similar to what we reported here in our study. However, the current study differs from that of Amusa et al., (2004) [1], also from Nigeria, who did not have any orbito-ocular lymphoma recorded in their ten-year study. Again, this study differs from Koopman et al.,

(2011) study from the Netherlands where no case of retinoblastoma was reported as a common primary eye malignancy. Furthermore, this current study did not find melanoma as a primary malignancy, contrary to studies that reported it as the most prevalent intraocular tumour globally particularly in adults [9,15]. The absence of melanoma in the Tamale study may be attributed to the small sample size, short study period and racial differences [1,6,16]. It could also be due to the fact that orbito-ocular melanoma is a rare condition in Africa as reported in previous studies [9,15,16]. The common anatomical site for the tumours in this study was the intraocular region. This is similar to that reported in previous studies [7,8,9].

The patients in this current study were very young. For instance, 43.8% were within the first decade of life. This is in line with previous studies in Africa that found the disease to have predilection for individuals within the first decade of life [7,10]. Females were slightly more than their male counterparts. This differs from studies that found no sex differences [1,5,7,11], and that of Otoh et al., (2004) that found the disease to be common in males.

Patients with orbito-ocular tumours commonly presented with proptosis, similar to reports in other studies [8,12,13,17]. For patients to present in our health institutions with proptosis as a primary sign of orbito-ocular tumours at first attendance is an indication of advanced or a neglected disease. About three decades ago, Volker et al., (1983) [8] in their study reported proptosis as the commonest primary clinical presentation of ocular tumours. Evidence in support of the advanced clinical state at presentation of orbito-ocular tumours in northern Ghana as reported in this current study is that more than half of the patients had enucleation or exenteration because their eyes were not salvageable. The choice of extensive surgery as a management option for advanced orbito-ocular disease may not be peculiar to this current study alone. For instance, Aghogho et al., (2009) [17] in Nigeria similarly reported using enucleation or exenteration as a common surgical method for managing orbito-ocular tumours.

The current study found invasive squamous cell carcinoma to be the commonest tumour involving the conjunctiva and/or the eyelids, commoner among young adults, and absent in the first two decades of life. This is in keeping with studies that found the disease to be the most common malignant lesion in the conjunctiva and similarly in young adults [17-19]. Squamous cell carcinoma was commonly diagnosed in excision biopsy specimens, similar to what was reported by Aghogho et al., (2009) in their study in Nigeria.

Retinoblastoma is the commonest primary malignant orbito-ocular tumour in this study with a modal age of 0.1 years, many being females. The demographic features of retinoblastoma in this current study are not supported by previous publications, but confirm reports that the disease is the most common malignant intraocular tumour in children globally, especially in the 0 - 4 age group [9,17-22]. There are studies that have shown that retinoblastoma is highly prevalent in African countries [18-22].

Also, available data on pediatric malignancies in Ghana have found it to be equally common among Ghanaian children [23-25]. For instance, Painstil et al., (2015) [25] in their study in the Ashanti Region of Ghana reported retinoblastomas as the fourth common pediatric cancer. This study however differs from the studies from Southern Ghana [25-27] that reported the disease to be common among males. Furthermore, studies in Ghana decades ago found this type of pediatric cancer to be a common cause of cancer related mortality [26,27]. Patients diagnosed with retinoblastoma in this study presented late with advanced disease and visual loss. This clinical picture is similar to previous publications in southern Ghana [12,13,28]. This clinical stage at presentation may be due to the fact that the symptoms of retinoblastoma are not evident early in the disease; besides patients and/or their relatives may even have attempted other treatment options until complications such as increasing pain, eye and vision loss set in [28]. All the patients had extensive surgery (enucleation) because the affected eye(s) could not be salvaged. Histologically, in most of the patients, the tumour either involved the entire eye or more than two-thirds of it. Again, there was significant optic nerve, uveal tract and choroid invasion by the tumour. Large tumour size at diagnosis, invasion of the optic nerve, the uveal tract and the meninges have been identified by previous studies as poor prognostic markers of retinoblastoma ([9,30,31] and these were all present in the current study. Again, the clinical stage of diagnosis of any neoplastic lesion have been found to be an important predictor of prognosis and hence treatment outcome. In the current study, 87.5% of the cases confirmed to be retinoblastomas were of high TNM stage (II – III). The combined clinico-pathological features of patients diagnosed with retinoblastoma in our study in Northern Ghana suggest poor treatment outcomes, poor prognosis and hence reduced survival rate.

This study did not group the cases into sporadic and those resulting from germline mutation. However, 2 (12.4%) of patients with intraocular tumours were bilateral and in children aged 1-year. This value is lower than the 30.0% reported in other studies [9]. The argument is that children born with bilateral retinoblastoma have a mutation in the RB1 gene (germline mutation); and this puts them at an increased risk of developing retinoblastoma in both eyes, and also several tumours within the eye, and even extra-ocular tumours such as osteosarcomas [9]. Therefore, the two patients in this current study require long follow up and surveillance.

## Conclusion

Primary malignant orbito-ocular tumours are diagnosed in relatively young patients, with female predominance. Retinoblastoma is the commonest tumour with intraocular region as the site commonly involved. Patients with these tumours commonly present late with advanced disease beyond salvage.

## Recommendations

A prospective study on retinoblastoma that will be aimed at addressing the following:

- The association between patient sociodemographic characteristics and the clinico-pathological features of

retinoblastoma at presentation.

- The association between the socio-economic status of the patients and or their relatives and the clinico-pathological features of the disease, particularly treatment outcome.
- The influence of health providers, primary health care workers on early reporting of orbito-ocular malignancies.

This is very important, because previous studies regarding malignancies involving different anatomical sites of the human body have shown that, patient clinical features including treatment and prognosis to be significantly associated with the demographic parameters and socioeconomic status [32-39].

### Author's Contributions

BGB provided the clinical history and also performed the surgeries. EDM prepared the tissue, reported the slides and drafted the manuscript. EDM and BGB, read through the manuscript, edited and approved the final copy for publication.

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