PATTERN OF ORBITO-OCULO-ADNEXAL TUMOURS AND THEIR ASSOCIATION WITH HIV STATUS AS SEEN AT TWO MAJOR HOSPITALS IN KENYA.

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A DISSERTATION SUBMITTED AS PART FULFILMENT FOR THE DEGREE OF MASTER OF MEDICINE IN OPHTHALMOLOGY OF THE UNIVERSITY OF NAIROBI (KENYA).

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DECLARATION

This dissertation is my original work and has not been presented for a degree in any other University.

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APPROVAL

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To

My husband and closest friend, Shaffique and my loving daughter, Tazyeen who were of great encouragement through out this study.

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SUMMARY

A cross sectional study was carried out from April 2000 to February 2001 at Kenyatta National Hospital and Kikuyu Eye Unit, Nairobi, Kenya to study the pattern of Orbito-Oculo-Adnexal tumours and their association with HIV status.

One hundred and five patients were examined. There were 51 males and 54 females. The mean age was 29.9 years (range 1.08 to 75 years). Thirty-eight (36.2%)patients had Benign tumours. Sixty-seven (63.8%) had premalignant and malignant tumours. Thirty-four (32.4%) patients were HIV seropositive detected by Elisa. Seventy-one (67.6%) patients were HIV seronegative. Out of thirty-four seropositives, seventeen patients (50%) had Squamous cell carcinoma of the conjunctiva, fourteen (41.2%) patients had Pterygium with Squamous cell dysplasia, Two (5.91%) were Kaposis sarcoma and one (2.91%) was case of Pterygium.

Patients with squamous cell carcinoma and pterygium with squamous cell dysplasia were in younger age group (range:20-75years), with peak frequency between 31-40 years. Duration of symptoms varied approximately from 2 weeks to 5 years. However from the duration of signs and symptoms it was noted that tumour growth was rapid and more aggressive in HIV seropositive patients.

Only three (8.8%) patients had systemic manifestations of AIDS. There was 51% association of pterygium (elastosis) in squamous cell carcinoma lesions. There is statistically significant association between squamous cell carcinoma, pterygium with squamous dysplasia and HIV (66%) i.e. p-value <0.001%.

Association between HIV status and the rest of the tumours studied could not be calculated since their figures were not adequate.

2. LIST OF ABBREVIATIONS

KNH	-	Kenyatta National Hospital
KEU	-	Kikuyu Eye Unit
HIV	-	Human Immunodeficiency Virus
AIDS	-	Acquired Immuno-deficiency Syndrome.
LAV	-	Lymphadenopathy Associated Virus
ELISA	-	Enzyme Linked Immunosorbent Assay
CDC	-	Centres for Disease Control
et al	-	and others
CMV	-	Cytomegalovirus
HPV	-	Human papilloma virus

3. INTRODUCTION/LITERATURE REVIEW

3.1 Definition

AIDS is defined for surveillance purposes by the centres for disease control (CDC) in Atlanta and includes patients with evidence of exposure to the AIDS virus who have diseases indicative of an underlying cellular immunodeficiency.

3.2 Epidemiology

The first cases of AIDS in the United States probably had their onset during the latter half of the 1970's[1]. However the first cases were reported in 1981, studies on ocular manifestations started more or less the same time with the first publication being in 1983[2,3,4,5].

The HIV prevalence estimate in general population in Kenya is at 13.5%. The total population of Nairobi is 2,238,105 as per June 2000. Total HIV infected population in Nairobi is 174,747. The HIV prevalence in Nairobi population is estimated at 15.9%[7].

3.3. Background

The acquired immunodeficiency syndrome (AIDS) is a transmissible disease in which the T-cell is infected and damaged, leading to profound immunodeficiency with resultant opportunistic infections and neoplasms[1,2].

AIDS can be considered as bubonic plaque of the 20th century [1,8]. Eye lesions caused by AIDS could present in 54-94% of AIDS patients. Ocular manifestations can be classified as follows[8].

i) HIV related retinopathy.

ii) Non opportunistic infections of the Eye

iii) Opportunistic infection of the eye.

a) C.M.V. retinitis.

b) Cryptococcal infection

iv) Cutaneous hypersensitivity reactions.

v) Neuro Ophthalmological manifestations.

vi) Tumour involvement in HIV seropositive patients.

TUMOUR INVOLVEMENT IN HIV SEROPOSITIVE PATIENTS.

1. Kaposis Sarcoma

Kaposis Sarcoma was the first most common malignancy reported in association with HIV infection. There is substantial evidence linking cytomegalovirus and Kaposis Sarcoma[36]. Kaposis Sarcoma is a highly vascularized, painless mesenchymal tumour affecting the skin and mucous membranes in up to 25% of HIV positive patients. Apparently 20% of such patients have a symptomatic Kaposis Sarcoma of the eyelids or conjunctiva[18, 20]. It has been suggested that HIV infection may play a permissive role in the development, aggressive biologic behaviour and atypical anatomic distribution of these opportunistic neoplasms[36].

The possibility of occult HIV disease should be entertained in a young person with atypical hordeolum or sub-conjunctival haemorrhage, as Kaposis Sarcoma sometimes mimics these common lesions and represents the initial presenting sign of AIDS [18,21]. The lower fornix is affected more often affected than upper[9]. Current concepts regarding the pathogenesis of Kaposis Sarcoma center on a model in which an initial event, possibly infection by human herpes virus 8, transforms normal mesenchymal cells such that they become abnormally sensitive to the high levels of cytokines present during HIV infection. Subsequent proliferation and additional mutational events result in clinically apparent disease[9, 21].

Three stages of ocular adnexal kaposis sarcoma have been described. Clinically stage I and stage II tumours are patchy, flat (less than 3mm in height) and of less than four months duration. Stage III tumours are nodular, elevated (greater than 3 mm in height) and of greater than four months duration[18].

In a study done on ocular Kaposis Sarcoma in Zaire it was found that Kaposis Sarcoma was not common and its presence is related in most cases to HIV infection and could be the first manifestation of HIV infections[22].

A study done in Munich, Germany by Baumanns et al, have reported a significant association between conjunctival microvasculopathy and Kaposis Sarcoma with HIV –1 disease[38].

Present treatment includes systemic chemotherapy for wide spread disease and local methods such as excision, cryotherapy, radiotherapy and intralesional injection. However, the majority of ocular lesions may be followed up with observation only. The appropriate strategy to pursue depends on the overall clinical scenario, including the patient's general health, the extent of disease, the degree of morbidity secondary to local ocular tumours, and the size of the lesions to be treated[21].

2. Lymphomas

a) Non Hodgkins B-Cell Lymphoma.

B-cell lymphoma was the second most common malignancy reported in association with HIV infection[36]. Significant linking between Epstein Barr virus and B-cell lymphoma has been reported[36]. A case report by Matzkin Dc, had shown simultaneous intra ocular and orbital involvement of non-hodgkins lymphoma in the acquired immuno deficiency patient[39].

b) Burkits Lymphoma

Burkits Lymhoma is the most common malignant tumour among children in tropical Africa. The tumour has a predilection for the face and jaws and may be induced by an insect vectored agent[40]. Considerable evidence has been accumulated associating a herpes virus, the Epstein Barr virus with Burkitts Lymphoma, probably by its playing a role in the development of the point mutations in the *c-myc* area[40].

Burkits Lymphoma has been reported to occur in patients at risk of AIDS[9]. Burkits Lymphoma may arise in three clinical forms: African, American and AIDS related. The histopathology of all three forms is identical and consists of tightly packed, small cleared lymphocyte with coarse chromatin, scattered tangible body macrophages giving a "Starry sky" appearance and numerous mitotic figures[28].

Treatment of lymphomas is with systemic chemotherapy and local orbital radiation shielding the globe.

3. Squamous cell carcinoma of the conjunctiva.

Squamous cell carcinoma is the third most frequently described malignancy in association with HIV infection[23,36]. Squamous cell carcinoma of the conjunctiva is an extreme form of a spectrum of conditions, collectively known as ocular surface epithelial dysplasia which range in severity from dysplasia to carcinoma-in-situ and ultimately, to invasive carcinoma[23].

Symptoms can range from none to severe pain and visual loss. Lesions generally arise in the nasal side of the eye and treatment involves local excision, or in more severe cases, enucleation of the eye but the prognosis is usually favourable.

Various aetiological factors are known:

There is significant geographical distribution of Squamous cell carcinoma of the conjunctiva. It may be associated with solar ultraviolet radiation. The incidence of conjunctival squamous cell carcinoma increases by 50% for every 10° closer to the equator. Further more individuals with xeroderma pigmentosum are at higher risk compared to the general population, as are those with a past history of excessive sun exposure.

A study done in Uganda by Templeton (1961-66) estimated the incidence as 1.3 per million per year; by the late 1980s, the incidence had risen ten-fold, to 12 per million per year[23, 24].

A study done in Uganda and Malawi by Atenyi - Agaba et al. showed 83% to 86% of all carcinomas were associated with elastosis as evidence of damage from sunlight[24]. Study done in USA showed 92% prevalence of elastosis in squamous cell carcinoma lesions of conjunctiva[24].

b) Secondly there is an increased association between squamous cell carcinoma and HIV infections. Unusual features of squamous cell carcinoma in HIV infected person are young age group, rapid tumour growth, highly malignant histologic appearance[36]. Squamous cell carcinoma found in atypical fashion should alert the physician to the possibility of HIV infections[23,36].

A study done in Uganda and Malawi showed 78% to 84% of carcinoma patients were HIV positive and the population aetiological fraction was 66%. Two thirds of patients had carcinoma because of HIV infection, and HIV has thus augmented the incidence of conjunctival carcinoma approximately three fold[24].

A retrospective study done in Moshi, Tanzania found a similar epidemic of squamous cell carcinoma of conjunctiva in HIV positive patients. They found tumours were aggressive and in younger age group. The epidemic appeared to be related to HIV infection, on a background of ultraviolet light exposure[40].

A study done by Kesterlyn et al from Rwanda showed the relative risk for conjunctival tumours associated with HIV infection was 13.0[23]. They also found that subjects were young and the tumours were aggressive.

A study done by Kiambo et al, in Congo, Kinshasa showed similar clinical characteristics of squamous cell carcinoma in HIV positive and immuno-competent persons, but occurred in a younger age group and were more aggressive[25].

A study done in Florida, USA had 50% of patients younger than 50 years of age group were HIV positive. They suggested that HIV testing and counseling should be considered in patients younger than 50 years in whom conjunctival intra epithelial neoplasia is diagnosed[41].

The aetiological role of HIV infection is unclear. There is no evidence that HIV is directly carcinogenic. One possibility is a failure of immune surveillance of malignant cells, which could follow from HIV mediated cellular immunosuppresion[24]. The identification of additional HIV associated cancers, has important public health implications, because tumours caused by infections are at least theoretically preventable by early treatment of the infection, or vaccination[23].

c) Human papilloma viruses have been implicated in the aetiology of squamous cell carcinoma of the conjunctiva. With insitu hybridization, Human Papilloma Virus-6 and Human Papilloma Virus-11 have been identified in tissues of benign conjunctival and lacrimal sac papillomas[42,43].

A study done in Uganda and Malawi showed that seven out of twenty (35%) patients with squamous cell carcinoma had Human Papilloma Virus-16 in the conjunctival epithelium and two out of fifteen (13%) of non-cancer patients. They reported that their prevalence in African carcinoma patients was smaller[24]. There is no population data on the prevalence of conjunctival Human Papilloma Virus infection in Africa[24].

d) Recently DNA sequence of a novel Herpes virus have been detected in Kaposis Sarcoma and in skin epidermal proliferation and carcinomas in patients with non HIV associated immunodefieciency[24,37]. It is possible that such agents may also play a role in conjunctival carcinogenesis.

Stages in the formation of Squamous Cell Carcinoma.

i) Features of elastosis (Pterygium) with focal dysplastic changes, which may be graded as mild, moderate and severe, according to the degree of cellular atypia and the disturbance of epithelial architecture[46].

ii) Carcinoma-in-situ: Histologically there is mild to moderate thickening of the epithelium, occurring anywhere in the conjunctiva. It is characterized by large, elongated, hyperchromatic, basaloid cells showing little or no tendency towards maturation. Mitotic activity is usually pronounced[46].

iii) Squamous Cell Carcinoma

This is typically a well differentiated keratinizing tumour arising in the exposed interpalpebral areas of the conjunctiva. It tends to grow in an exophytic fashion and is more often only superficially invasive but may infiltrate into the eye or extend into the orbit. It rarely metastasizes[46].

The treatment of squamous cell carcinoma in early stages is excision of the mass with local radiation therapy and in advanced cases enucleation/exenteration.

4. RATIONALE

Anecdotal information and literature indicate that there is a high incidence of orbito-oculo-adnexal tumours like squamous cell carcinoma of the conjunctiva, Kaposis sarcoma, lymphomas etc. with HIV seropositivity. However, there are orbito-oculo-adnexal tumours like retinoblastomas, lymphangiomas, neurofibromas, gliomas etc whose association with HIV status is not known. Literature is scarce on this information, particularly from Africa.

This study will help in augmenting the knowledge on the pattern of different types of orbito-oculo-adnexal tumours and identify their association with HIV status.

5. OBJECTIVES

1. To determine the pattern of orbito-oculo-adnexal tumours.

2. To determine the association between HIV Seropositivity and orbito-oculo-adnexal tumours.

3. To determine the clinico-pathological characteristics of orbito-oculo-adnexal tumours in relation to the HIV status of patients.

6. METHODOLOGY

6.1 Study design

Cross sectional study.

6.2 Study period

Nine months - from April 2000 to February 2001.

6.3 Case Definition

Patients with orbito-oculo-adnexal tumours seen at KNH eye clinic and KEU.

6.4 Study Location

KNH and KEU

6.5 Study population

Consecutive patients with orbit-oculo-adnexal tumours as seen at KNH Eye Clinic and KEU.

6.6 Resource persons

Ophthalmologist, microbiologist, histopathologist, laboratory technician and HIV counsellors.

6.7 *Sample size determination*

The prevalence of HIV sero-positivity in patients with orbito-oculo-adnexal tumours is assumed to be 20%. To be able to estimate the prevalence to within 10% points of the true value, a minimum sample size of **44** was required.

$$n = \frac{Z^2_{1-\alpha}\, p(1-p)}{d^2}$$

$$n = \frac{1.645^2 \times 0.8 \times 0.2}{0.1 \times 0.1}$$

n = 44

n= sample size.

p= prevalence of HIV sero-positivity in patients with orbito-oculo-adnexal tumours.

p is 20%.

Z = 1.645: standard errors from the mean corresponding to 95% confidence interval

α = 5%: significance level

d = 10 %: absolute precision

6.8 *Inclusion criteria*

Patients with orbito-oculo-adnexal tumours diagnosed histopathologically.

6.9 Exclusion Criteria

1. Refusal of consent for study.
2. Lack of histopathological diagnosis.

6.10 Procedure

All patients with history of growth/mass had counselling for HIV testing. Only those who agreed for HIV testing were included in the study.

Name, Age and Sex were recorded. (See Appendix A). Ophthalmological examination consisted of recording presenting complaint, duration and progression of mass.

Visual acuity, exophthalmometry, extra-ocular muscle function assessment, orbital palpation (for masses), slit lamp examination and fundoscopy were done.

In some cases, X - ray of the orbits and paranasal sinuses, orbital/ocular ultrasonography and computerised axial tomographic examination were done. Counsellors did Pre counselling for HIV serology. When counsellors were not available a doctor did it. Blood was withdrawn for HIV testing. Elisa testing for HIV I/II was done on all study patients. Relevant post counselling was also done.

Histopathological study was done on all the biopsy specimens obtained. Patients with histopathological diagnosis were treated as follows:

a) complete excision of the tumours/enucleation/exenteration

b) referred to radiology for radiation therapy

c) referred to oncologist

d) were admitted in the ward for chemotherapy.

e) patients with systemic problems related to the tumour were referred to the physicians for further management.

6.11 Ethical consideration

a) Details and the purpose of the study were explained to each patient and only those who accepted to participate were recruited (Appendix C).

b) Patients were counselled before taking blood sample for HIV test and the appropriate post counselling was done.

c) All data was kept confidential.

d) Consent was also obtained before illustrative photography of some cases.

e) Equipment used was sterilised before and after use to prevent the spread of infection.

f) The study was approved by the Department of Ophthalmology and the Ethics Committee of KNH.

6.12. Limitations

a) HIV status of individuals were determined by Elisa only and were not confirmed by Western Blot. However the enzyme immunoassay which was used in this study is based on recombinant antigens containing immuno-dominant regions of the *env* and *gag gene* products and was designed to be extremely sensitive and is highly predictive of the presence of the antibody.

b) Patients who did not consent for HIV testing and who did not have histopathological diagnosis were not recruited into the study.

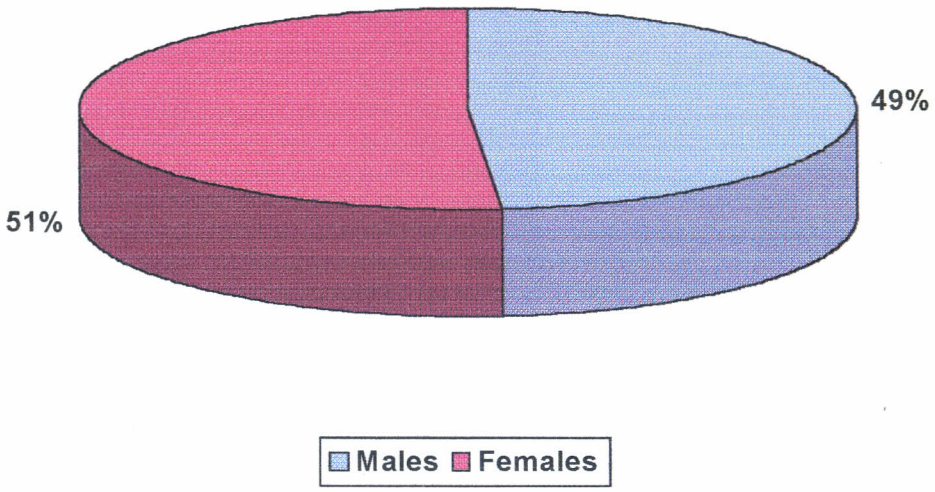
7. RESULTS

Table 1: **Sex ratio of study population:**

Sex	No. of Cases	Percentage
Males	51	48.6
Females	54	51.4
Total	**105**	**100**

M:F 1:1.1

Figure 1.: Distribution by Sex

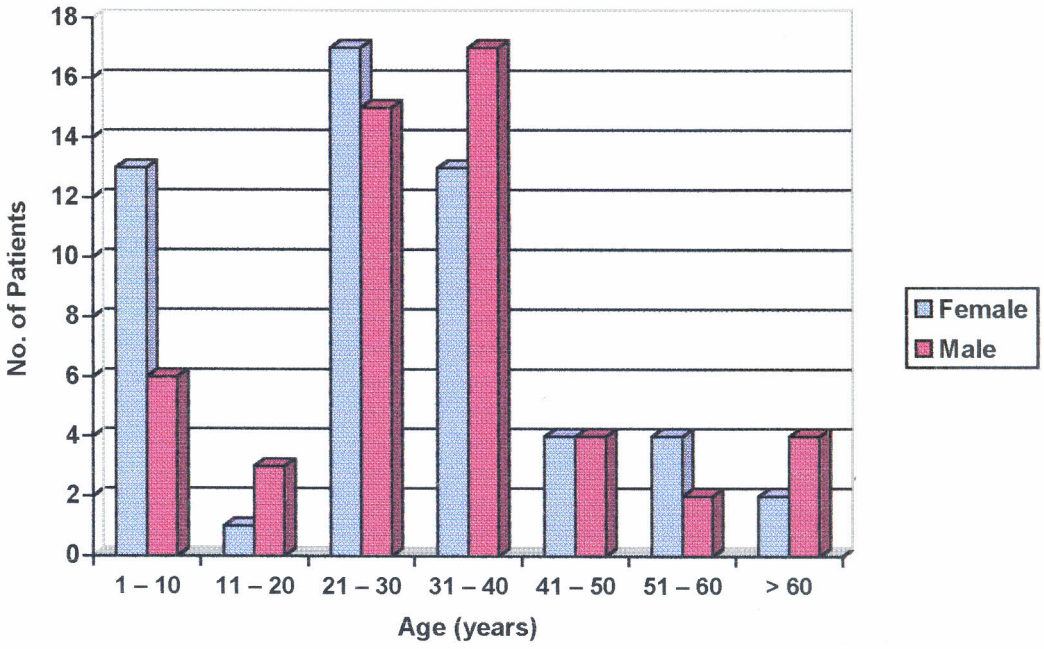


M : F ratio was approximately equal.

Table 2: Distribution by age and sex :

Age group Years	No. of patients		Total
	Female	Male	
1 - 10	13	6	19
11 - 20	1	3	4
21 - 30	17	15	32
31 - 40	13	17	30
41 - 50	4	4	8
51 - 60	4	2	6
>60	2	4	6
Total	**54**	**51**	**105**

Figure 2: Distribution by Age and sex:

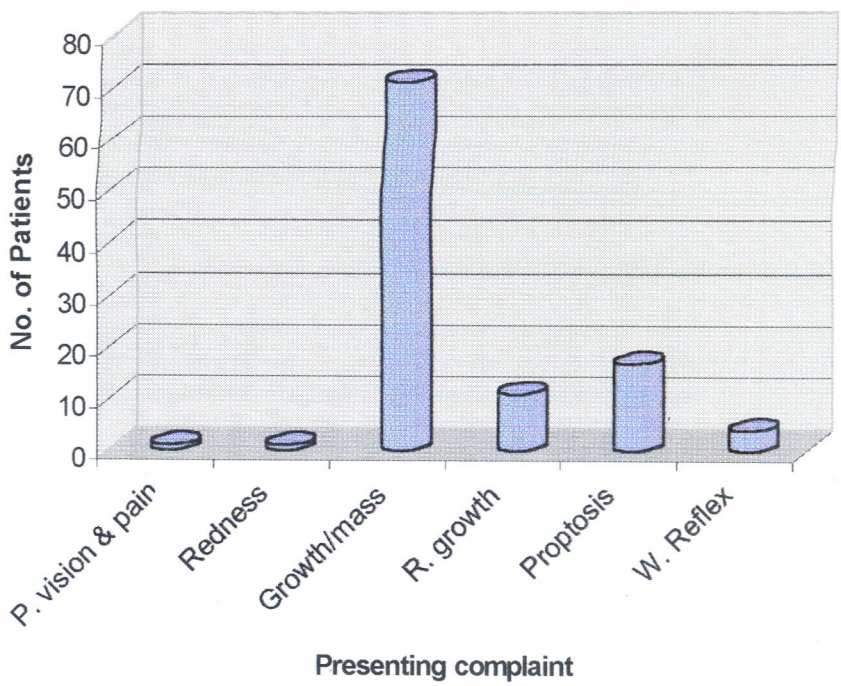


Patients age ranged from 1.08 to 75 years, with a mean of 29.9 years, a median of 30 years and a mode of 35 years. Peak age group was 21-40 years (42.9%)

Table 3: Presenting ocular complaints in the study population:

Ocular Complaints/History	No. of patients n. = 105	Percentage
Poor vision & pain	1	1.0
Redness	1	1.0
Growth/mass	71	67.6
Recurrent growth	11	10.5
Proptosis	17	16.2
White Reflex	4	3.8
Total	**105**	**100**

Figure 3: Distribution of presenting complaints in the study population:

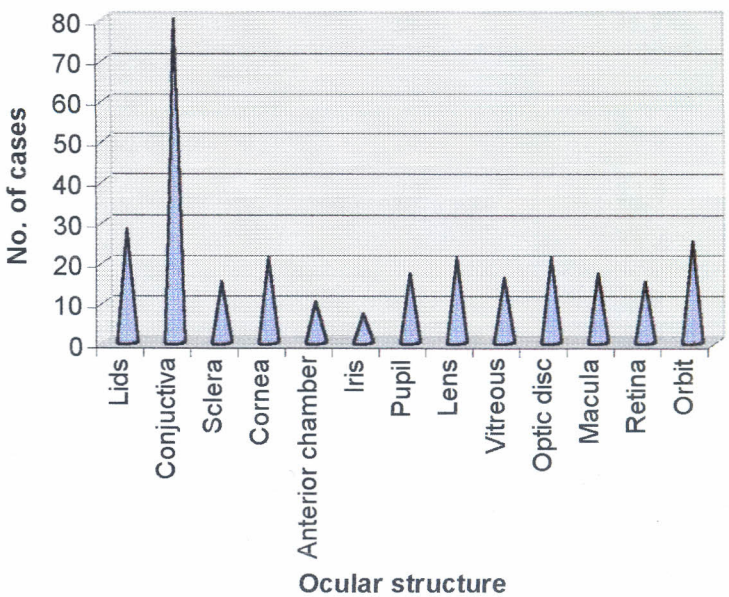


67.6% of the patients' complaint of growth/mass with 10.5% complaint of recurrent growth

Table 4: Ocular involvement in patients with orbito-oculo-adnexal tumours
n = 293

Ocular structure	No. of cases	Percentage
Lids	28	9.6
Conjunctiva	80	27.3
Sclera	15	5.2
Cornea	21	7.2
Anterior chamber	10	3.4
Iris	7	2.4
Pupil	17	5.8
Lens	21	7.2
Vitreous	16	5.5
Optic disc	21	7.2
Macula	17	5.8
Retina	15	5.1
Orbit	25	8.5
Total	**293**	**100**

Fig. 4 **Ocular involvement in patients with orbito-oculo-adnexal tumours**



27.3% of the patients had tumours involving the conjunctiva.

Table 5: **Pattern of Orbito-Oculo-Adnexal Tumours**

	Type of Tumour	No. of Cases n = 105	%
	Benign Tumours		
1	Squamous Papiloma	5	4.8
2	Dermoid Cyst	3	2.9
3	Neurofibrona	2	1.9
4	Fibromatosis	1	1
5	Verrucea Vulgaris	2	1.9
6	Pterygium	13	12.4
7	Granulation Tissue	6	5.7
8	Haemangioma	1	1
9	Lymphangioma	1	1
10	Adenoma	1	1
11	Fibrous Dysplasia	2	1.9
12	Pilocystic Glioma	1	1
	Sub-total	**38**	**36.2**
	Premalignant & Malignant Tumours		
1	Pterygium with Sq dysplasia	24	22.9
2	Squamous Cell Carcinoma	23	21.9
3	Retinoblastoma	12	11.4
4	Burkits Lymphoma	2	1.9
5	Adenocarcinoma	1	1
6	Non-Hodgkins Lymphoma	1	1
7	Rhabbomyosarcoma	1	1
8	Kaposis Sarcoma	3	2.9
	Sub-total	**67**	**63.8**
	Total	**105**	**100**

Out of 105 cases, 38 cases (36.2%) were Benign tumours and 67 cases (63.8%) were premalignant and malignant tumors.

Figure 5: Distribution of histopathological findings in patients with orbito-oculo-adnexal tumours. **n = 105**

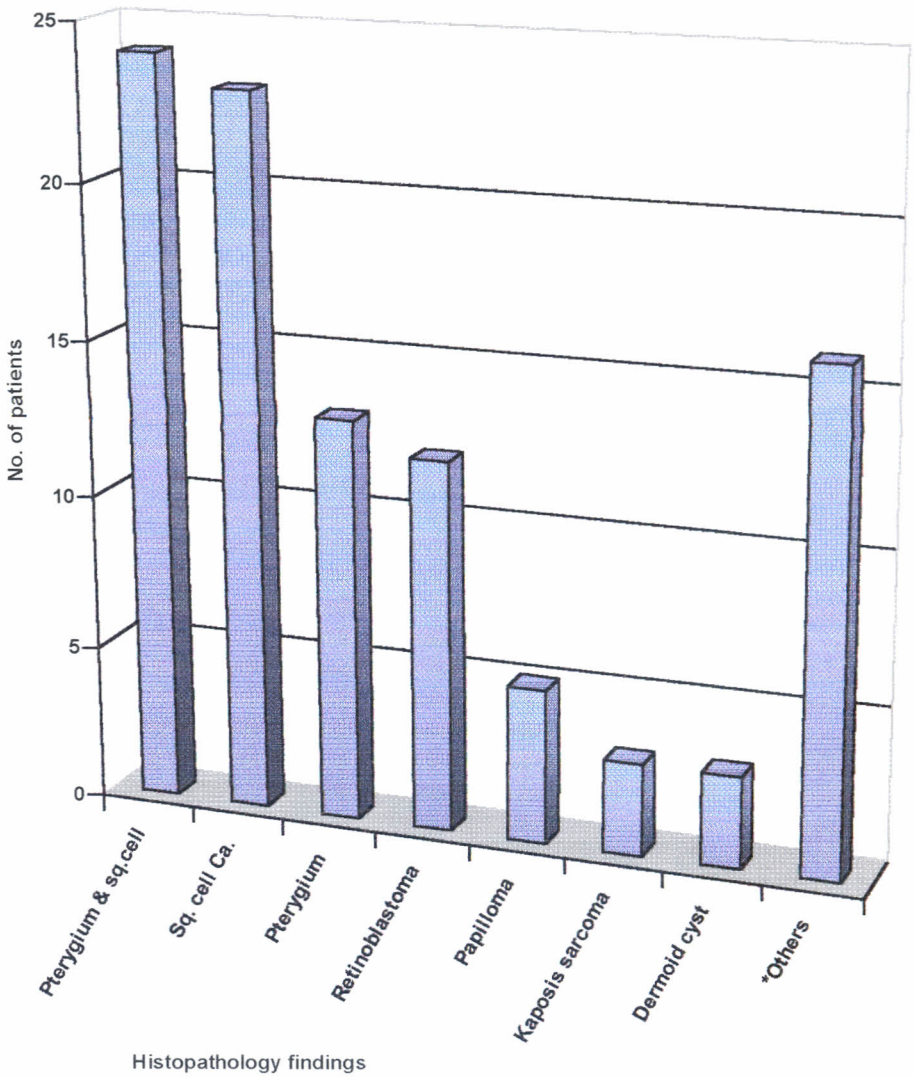


Table 6: Histopathological findings of lid growth:

Growth	No. of cases: 16 n(%)
Papilloma	5 (31.25)
Dermoid cyst	3 (18.75)
Verruca vulgaris	2 (12.5)
Kaposis sarcoma	2 (12.5)
Neurofibroma	2 (12.5)
Fibromatosis	1 (6.25)
Benign adenoma	1 (6.25)
Total	**16(100)**

Figure 6: Distribution of Histopathological findings of lid growth

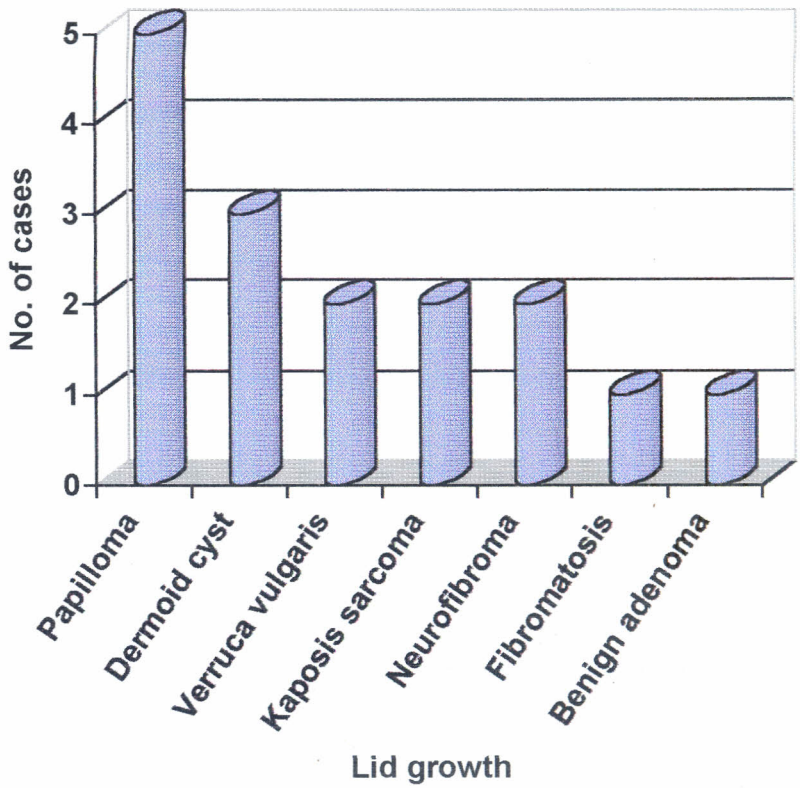
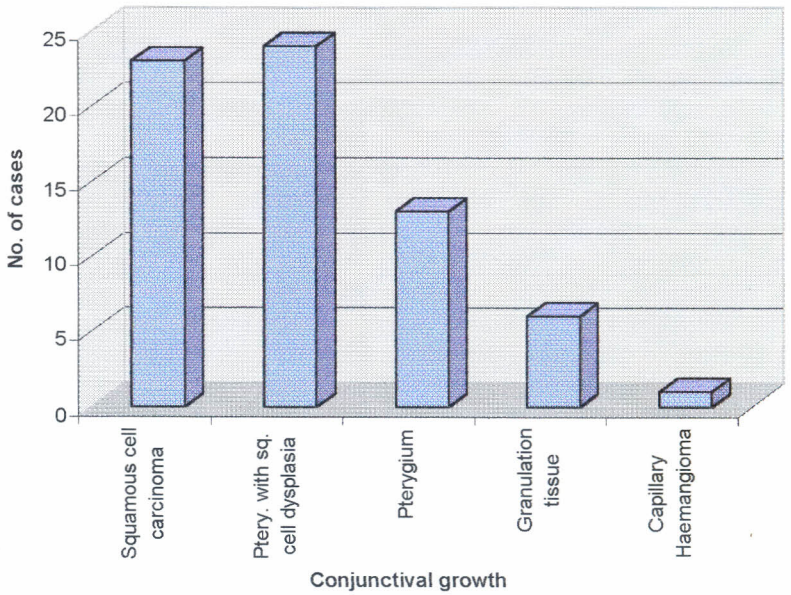


Table 7: Histopathological findings of conjunctival growth

Conjunctival growth	No. of cases: n. = 67 (%)
Squamous cell carcinoma	23 (34.3)
Pterygium with squamous cell dysplasia.	24 (35.8)
Pterygium	13 (19.4)
Granulation tissue	6 (9.0)
Capillary Haemangioma	1 (1.5)
Total	**67 (100)**

Figure 7: Distribution of Histopathological findings of conjunctival growth

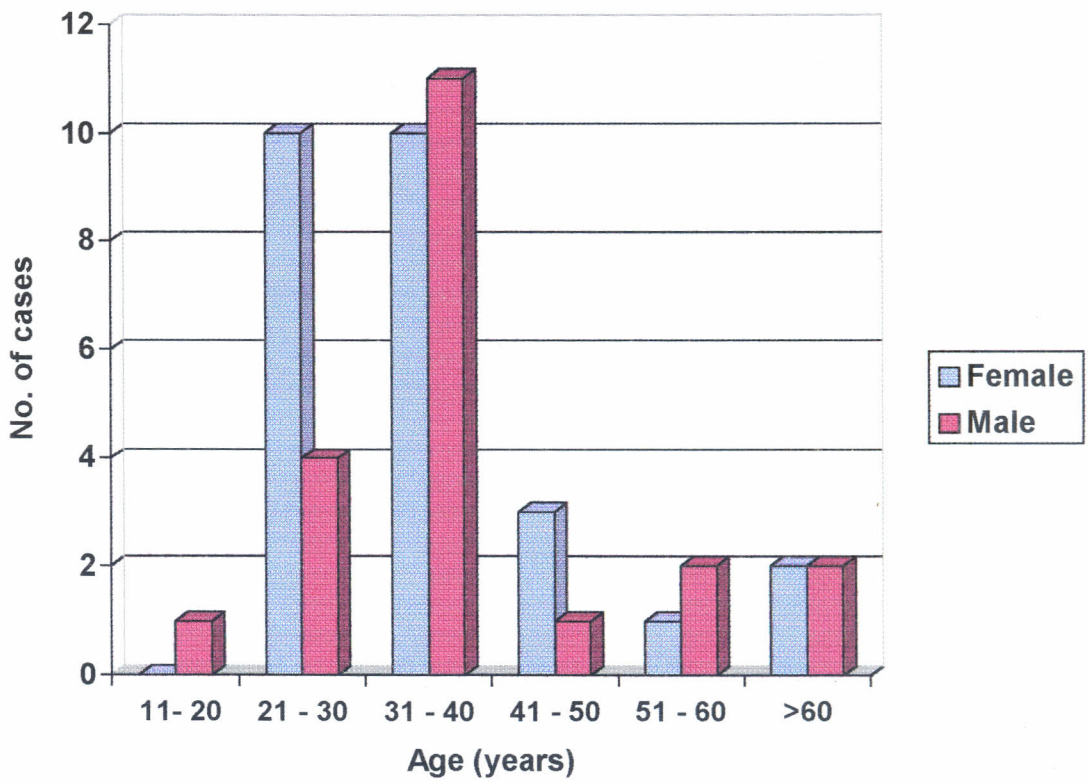


70.1% of the patients with conjunctival growth had squamous cell carcinoma and pterygium with squamous cell dysplasia.

Table 8: Distribution by age and sex of patients with squamous cell carcinoma and pterygium with squamous cell dysplasia of the conjunctiva.

Age group	Patients		Total
	Female	Male	n. = 47
11 - 20	-	1	1 (2.1)
21 - 30	10	4	14 (29.8)
31 - 40	10	11	21 (44.7)
41 - 50	3	1	4 (8.5)
51 - 60	1	2	3 (6.4)
>60	2	2	4.0 (8.5)
Total	**26**	**21**	**47 (100)**

Figure 8: Age and sex distribution of patients with squamous cell carcinoma and pterygium with squamous cell dysplasia of the conjunctiva.

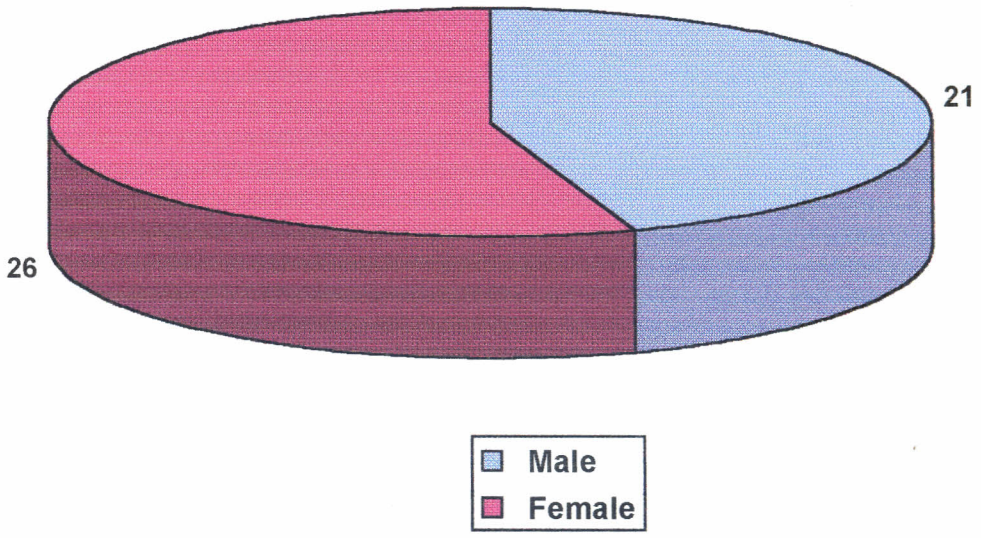


Patients age ranged from 20 to 75 years, with a mean of 37.4 years, a median of 32 and a mode of 35 years. Peak age group was between 21 to 40 years.

Table 9: Sex distribution of patients with squamous cell carcinoma of the conjunctiva and pterygium with squamous dysplasia

	MALE	FEMALE	M:F	TOTAL n. = 47
Squamous cell carcinoma	13	10	1.3:1	23
Pterygium with squamous cell dysplasia	8	16	1:1.2	24
Total	**21**	**26**	**1:1.2**	**47**

Figure 9: Sex distribution of patients with squamous cell carcinoma of the conjunctiva and pterygium with squamous cell dysplasia

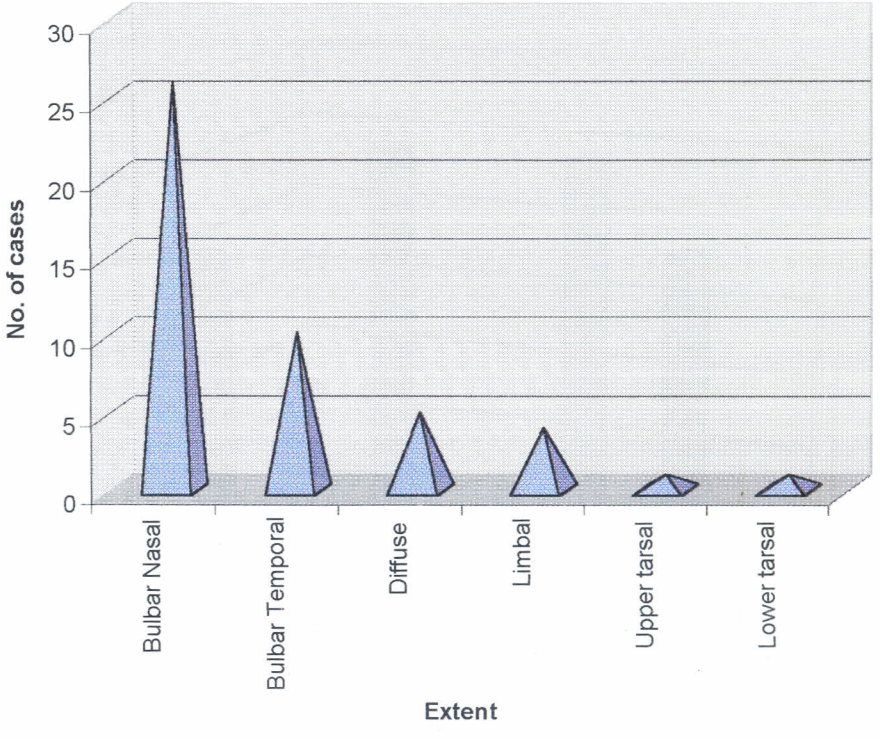


M:F ratio was approximately equal.

Table 10: Extent of conjunctival involvement in the patients with squamous cell carcinoma and pterygium with squamous dysplasia

	Frequency n. = 47	Percent
Bulbar Nasal	26	55.3
Bulbar Temporal	10	21.3
Diffuse	5	10.6
Limbal	4	8.5
Upper tarsal	1	2.1
Lower tarsal	1	2.1
Total	**47**	**100**

Figure 10: Extent of conjunctival involvement in the patients with squamous cell carcinoma and pterygium with squamous dysplasia



55.3% of the patients had growth on the nasal side of bulbar conjunctiva.

Table 11: Histopathological findings in patients with squamous cell carcinoma and pterygium with squamous cell dysplasia

Histopathology	No. of cases n. = 47	*Percent*
Focal dysplasia	8	17.0
Severe dysplasia	5	10.6
In situ	11	23.4
Well Diff.	3	6.4
Moderately Diff.	11	23.4
Poorly Diff.	9	19.1
Total	**47**	**100**

Figure 11: Histopathological findings in patients with squamous cell carcinoma and pterygium with squamous cell dysplasia

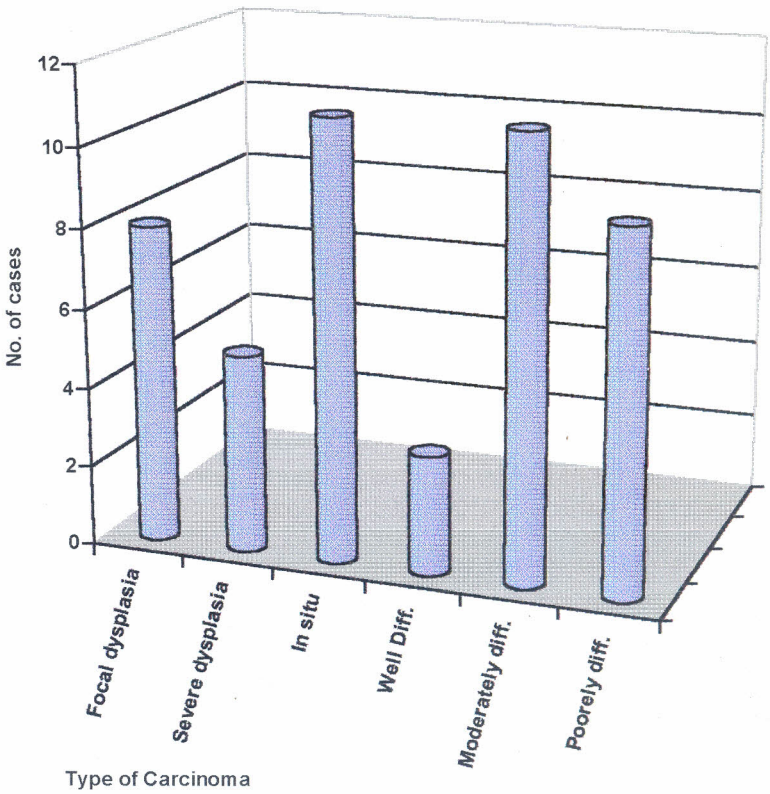
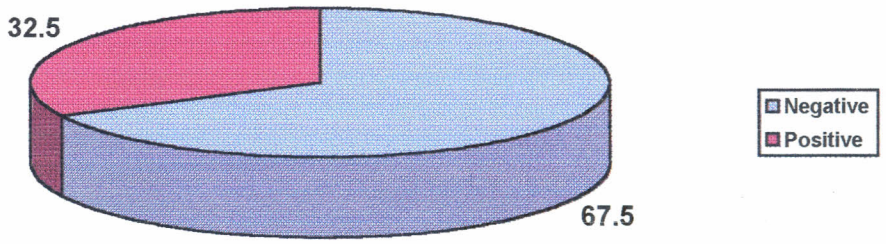


Table 12: HIV serology in patients with orbito-oculo-adnexal tumours

HIV Serology	No.of patients	Percent
Negative	71	67.5
Positive	34	32.5
Total	**105**	**100**

Figure 12: Distribution of HIV serology in patients with orbito-oculo-adnexal tumours



32.5% HIV seropositivity was seen in patients with orbito-oculo-adnexal tumours.

Table 13: Distribution of HIV seropositivity in patients with orbito-oculo-adnexal tumours

Tumour	HIV Seropositive n. = 34	%
Squamous cell carcinoma	17	50.0
Pterygium with squamous cell dysplasia	14	41.2
Kaposi's Sacroma	2	5.90
Pterygium	1	2.90
Total	**34**	**100**

Figure 13: HIV seropositivity in patients with orbito-oculo-adnexal tumours

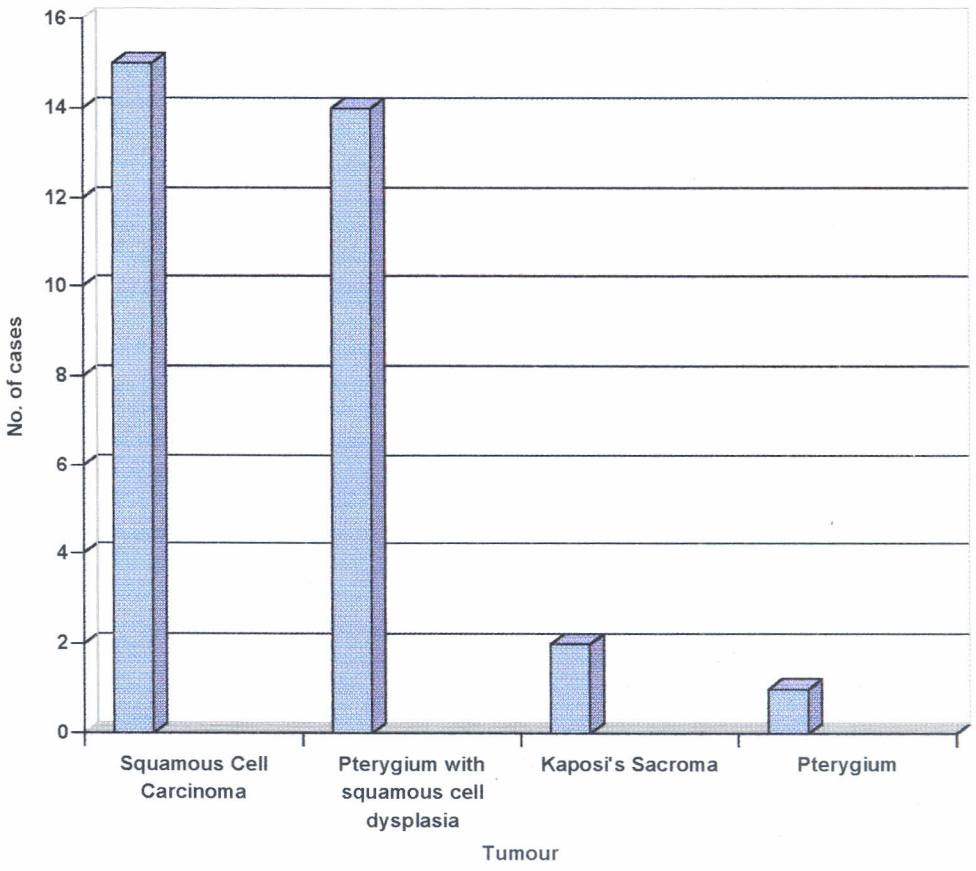
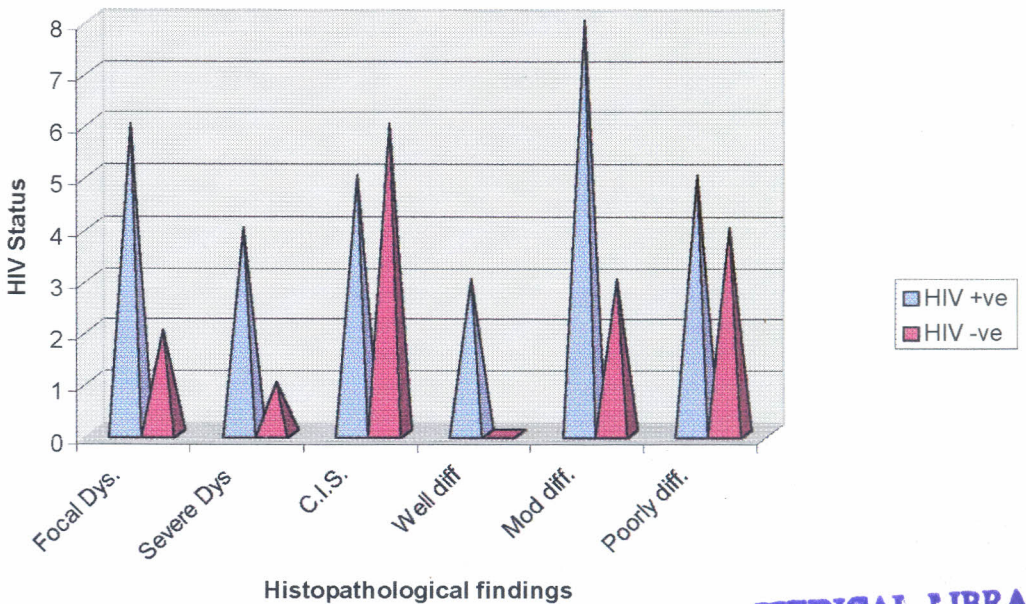


Table 14: Association between histopathological findings of squamous cell Carcinoma and pterygium with squamous cell dysplasia and HIV Seropositivity: n=47

	Focal Dys.	Severe Dys	C.I.S.	Well diff	Mod diff.	Poorly diff.
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
HIV +ve	6(75)	4(80)	5(45.5)	3(100)	8(72.7)	5(55.6)
HIV -ve	2(25)	1(20)	6(54.5)	0	3(27.3)	4(44.4)
Total	**8(100)**	**5(100)**	**11(100)**	**3(100)**	**11(100)**	**9(100)**

Figure 14: **Association between histopathological findings of Squamous cell carcinoma, Pterygium with Sq. cell dysplasia and HIV seropositivity**



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HIV seropositive patients had high malignant potential for squamous cell carcinoma.

Table 15: Association of HIV seropositivity, squamous cell carcinoma and pterygium with squamous cell dysplasia in Uganda, Kenya and Malawi.

	Uganda n=38			Kenya n=47			Malawi n=29		
	+	-	Total	+	-	Total	+	-	Total
Sq. cell. ca	19	8	27	17	6	23	16	3	19
Dsyplasia	8	3	11	14	10	24	9	1	10
	27	11	38	31	16	47	25	4	29

Key: + = Seropositive
- = Seronegative

Table 16: Percentage of HIVseropositivity in patients with squamous cell carcinoma and dysplasia in Uganda, Kenya and Malawi

	Uganda n=38 Sero+ve %	Kenya n=47 Sero+ve %	Malawi n=29 Sero+ve %
Sq. cell.ca & Dysplasia	71%	66%	86%

Table 17: Distribution of age, sex and extent of conjunctival involvement in patients with squamous cell carcinoma and dysplasia in Uganda, Kenya and Malawi

a) Age distribution

	Age in years	
Country	**Range**	**Mean**
Uganda	15-75	35
Kenya	20-75	39
Malawi	22-50	31

b) Sex distribution

Country	**No. of patients**		**Total**	**M:F**
	Male	**Female**		
Uganda	14	24	38	1:1.7
Kenya	21	26	47	1:1.2
Malawi	15	17	36	1:1

c) Extent of Conjunctival involvement:

	No. of patients			
Country	**Nasal(%)**	**Temporal**	***Others**	**Total**
Uganda	30 (83)	6	2	38
Kenya	26(56)	10	11	47
Malawi	24 (86)	4	4	32

*others include:- Uncertain, upper tarsal, lower tarsal and diffuse.

TABLE 18: Comparison of pattern of orbito-oculo-adnexal tumours with previous studies done at KNH.

Diagnosis	Chana H.S.[40] 1982 n=470 no.(%)	Asiyo M.[44] 1987 n=126 no(%)	Ingosi W.[48] 1987 n=123 no(%)	Malakwen C.[45] 1989 n=38 no(%)	Awan H.[1] 1990 n=106 no.(%)	Present series 2001 n=105 (%)
1. Sq. cell Ca	19(4)	9(7)	2(7.7)	1(2.6)	1(1)	23(21.9)
2. Pterygium with Sq. cell Dysplasia						24(22.9)
3. Pterygium			19(73)			13(12.4)
4. Retinoblastoma	68(14.5)			2(5.3)	1(1)	12(11.4)
5. Kaposis Sarcoma	1(0.2)				2(2)	3(2.9)
6. Burkitt's Lymphoma	43(9.2)	1(0.8)		3(7.9)		2(1.9)
7. Papilloma		3(2.4)	1(3.9)			5(4.8)
8. Dermoid cyst	4(0.9)	16(12.6)				3(2.9)
9. Verruca Vulgaris		5(4)				2(1.9)
10. Fibromatosis						1(1.0)
11. Neurofibroma	3(0.6)	1(0.8)				2(1.9)
12. Adenoma						1(1.0)
13. Adenocarcinoma						1(1.0)
14. Fibrous Dysplasia						2(1.9)
15. Rhabdomoyosarcoma	5(1.1)	2(1.6)				1(1.0)
16. Glioma	2(0.4)					1(1.0)
17. Haemangioma	3(0.6)	3(2.4)				1(1.0)
18. Nonhodgkins Lymphoma	1(0.2)	3(2.4)		1(2.6)		1(1.0)
19. Lymphangioma	2(0.4)					1(1.0)
20. Granulation Tissue						6(5.7)

8. DISCUSSION

One hundred and five (105) patients with orbito-oculo-adnexal tumors were studied between April 2000 and February 2001 at KNH eye clinic and KEU. There were 51 males and 54 females. M:F ratio was 1:1.1. There was no significant difference in the number of males recruited compared to females in this study. Awan A. (1980)[49] reported a M:F ratio of 2:1 in his study on orbito-oculo tumours. However, the cause of these discrepancy is not clear.

Ages of the patients ranged from 1.08 to 75 years. Most of the patients were in the younger age groups between 21 and 40 years of age (42.9%). Previous studies done at KNH indicated that most of the patients with orbito-oculo-adnexal tumours were above 40 years of age[44, 45]. A number of tumours included in this study, like squamous cell carcinoma of the conjunctiva may now be presenting at an earlier age due to their association with HIV/AIDS, which is common before the age of 40 years.

All patients in the study presented with history of growth or mass. As shown in table 5, out of 105 cases, 38 cases (36.2%) were benign tumours and 67 cases (63.8%) were premalignant and malignant tumours. A study done by Asiyo (1987)[44], reported 84.8% benign lid tumours and 15.2% malignant lid tumours (n=126). Malakwen (1989)[45], reported 10.5% benign orbital tumours, 26.4% malignant orbital tumours, and 31.6% inflammatory tumours. The majority of malignant lesions in this study were squamous cell carcinoma. Again this preponderance could be due to its association with HIV/AIDS as shown below.

In the present study out of one hundred and five cases, seventy one (67.5%) cases were HIV negative and thirty four (32.5%) cases were HIV positive. Out of thirty four seropositives, seventeen (50%) patients had squamous cell carcinoma of the conjuctiva, fourteen (41.2%) had Pterygium with squamous cell dysplasia and two (5.91%) had Kaposis sarcoma. One patient (2.91%) had Pterygium.

Further histopathological analysis was made of patients who presented with pterygium and conjunctival lesions. The majority of cases were found to be pterygium with squamous cell dysplasia (22.9%) and squamous cell carcinoma (21.9%). In the present study, there is a statistically significant association between squamous cell carcinoma, pterygium with squamous cell dysplasia and HIV (66%) i.e. p-value $< 0.001\%$.

The recently reported higher prevalence of conjunctival tumours in Kenya (and in the neighbouring countries) appears to be largely associated with HIV/AIDS epidemic[24,25,41,42]. The aetiological role of HIV infection in squamous cell carcinoma of the conjunctiva is unclear. Although there is no evidence that HIV is directly carcinogenic, one possibility by which this lesions can arise is a failure of immune surveillance of malignant cells, which could follow from HIV mediated cellular immunosuppresion[24]. However, there are other factors, which may contribute to the high incidence of these tumours in Equatorial Africa, including exposure to ultraviolet light and conjunctival papilloma virus infection.

The association of these factors with suppressed immunity will need to be studied further in relation to pathogenesis of squamous cell carcinoma of the conjunctiva.

Present study showed 66% (n=47) seropositivity in patients with squamous cell carcinoma and dysplasia. This is comparable to a similar study done in Uganda (n = 38) which showed 71% seropositivity. Study done in Malawi (n=29) showed a higher seropositivity of 86% in patients with squamous cell carcinoma. The slight variation in prevalence could be due to the number of patients recruited which range from 29 in Malawi to 47 in Nairobi. Similar increase in squamous cell carcinoma cases had been found in studies done in Congo, Tanzania and Rwanda[23,24,40].

There was one (7.5%) case of Pterygium (n=13), found to be HIV positive. Our study showed 51% association of pterygium (elastosis) with squamous cell carcinoma/dysplasia patients. A study done in Uganda and Malawi found 83-86% association with elastosis[24]. A study done in USA reported 92% association of elastosis with squamous cell carcinoma of conjunctiva[24]. However, with a prevalence of 16% of seropositivity in Nairobi it is possible that there is no association between pterygium and HIV seropositivity[7].

Out of the 105 cases studied, only three cases of kaposis sarcoma were reported. Two out of three cases of Kaposis Sarcoma were HIV seropositive. Previous studies report that Kaposis Sarcoma was the first common malignancy associated with HIV infection[36].

The number of cases of Kaposis sarcoma in this study is too small to determine any association between HIV and Kaposis sarcoma. A study with larger series to determine association between HIV seroposivity and kaposis sarcoma is recommended.

The rest of the tumours reported in this study were in small numbers, represented as follows:

- 12 (11.4%) cases of retinoblastoma were found and all of them were HIV negative.
- 3 cases (2.9%) were of dermoid cyst and were HIV negative.
- 2 cases (4.8%) were of lid papillomas and were HIV negative.
- 2 cases (1.9%) were of neurofibroma and were HIV negative.
- 2 cases (1.9%) of fibrous dysplasia were noted and both were HIV negative.
- 6 cases (5.7%) were of conjunctival granulation tissue which looked suspicious of squamous cell carcinoma were HIV negative.
- The rest of the tumours included one case each of Adenoma, adenocarcinoma, rhabdomyosarcoma, glioma, haemangioma, non hodgkins lymphoma and lymphangioma and were all HIV negative.

Association between HIV and these tumours was not determined as the number was too small to stand any statistical test for useful interpretation.

Clinico-pathological characteristics of orbito-oculo-adnexal tumours in relation to HIV status of patients was determined only in conjunctival pterygium with squamous cell dysplasia and squamous cell carcinoma cases since they were significant in number as compared to other tumours found in the study.

Only three or 8.8% (n=34) cases of conjunctival squamous cell carcinoma had systemic manifestation of AIDS that means most of our patients presented in the initial stage of HIV disease. Ugandan study showed only two or 5.2% (n=38) HIV positive cases with AIDS. While in Malawian study, nearly half of the patients, twelve or 31.6% (n=30) had clinical AIDS[24]. No immunological markers such as blood CD_4 and T cell counts were available for patients with conjunctival carcinoma. The wide difference seen in this study and the Malawian study is unexplained, however, it is known that the tumour can appear before and after the development of AIDS[24].

The majority of patients were in younger age group (21-40 years) compared to previous studies done before HIV epidemic when most of the patients with squmaous cell carcinoma presented after the age of 50 years[44,45]. These results are comparable to other studies done in other African countries like Uganda, Malawi, Tanzania and Congo where the squamous cell carcinoma was also reported in the younger age group[24, 25, 41]. Previous study done by Asiyo (1987) reported highest frequency of Squmaous cell Carcinoma in patients above the age of 50 years[44].

There was no significant difference noted in Male: Female ratio (1:1.2) in patients with squmaous cell carcinoma and dysplasia of the conjunctiva. This was similar to Ugandan study M:F 1:1.7 and Malawian study M:F 1:1[24]. Asiyo (1987) however reported M:F as 2:1 in her patients with squamous cell carcinoma[44].

Patients with conjunctival lesions diagnosed as dysplasias and squamous cell carcinoma, presented in early stages with small lesions. Complete excision was possible in all these cases. Five patients presented with infiltrating tumours and had enucleation. However, advanced fungating squamous cell carcinoma lesions were not seen in this study. The early presentation noted in this study could be due to improving referral system.

Duration of symptoms varied approximately from two weeks to five years. This study did not include follow up. However, empirically it was noted from the analysis of duration of signs and symptoms that, the tumour growth was rapid and more aggressive in HIV seropositive patients.

Morphological distribution of the conjunctival growth indicated that 56% cases were on nasal side of the bulbar conjunctiva. Ugandan study showed a prevalence of 83% cases of squamous cell carcinoma occurring on the nasal side of bulbar conjunctiva. Malawian study showed 86% cases of squamous cell carcinoma as occurring on the nasal side of bulbar conjunctiva. Pterygium are also more commonly seen on the nasal side of the bulbar conjunctiva.

Ultraviolet radiation has been predicted as one of the aetiological factors in the development of squamous cell carcinoma. Pterygium has also been aetiologically associated with ultra violet radiations. Pterygium can be considered as one of the preceding stage especially in the presence of HIV infection.

HIV seropositive patients had high malignant potential for squamous cell carcinoma (Table 12).

- ❖ Seventy five percent or six cases (n=8) of focal dysplasia were HIV positive.
- ❖ Eighty percent or four cases (n=5) of severe dysplasia were HIV positive.
- ❖ Forty five percent or five cases (n=11) of carcinoma-in-situ were HIV positive.
- ❖ A hundred percent or three cases (n=3) of well diff. squamous cell carcinoma were HIV positive.
- ❖ Seventy three percent or eight cases (n=11) of moderately differentiated squamous cell carcinoma were HIV positive.
- ❖ Fifty six percent or five cases (n=9) of poorly differentiated squamous cell carcinoma were HIV positive.

However, these percentages expressed for seropositivity should be cautiously interpreted as number of cases was too small in each category.

9. CONCLUSION

1. A total of 105 patients with orbito-oculo-adnexal tumours were seen in one year. 36.2% had benign tumour and 63.8% had premalignant and malignant tumours. The majority of the premalignant and malignant tumours 44.8% were in the category of squamous cell dysplasia/carcinoma of the conjunctiva.

2. HIV seropositivity is associated with 32.4% of orbito-oculo-adnexal tumours, of which, 66% were noted to be cases of squamous cell carcinoma and squamous cell dysplasia with or without pterygium.

3. The association between the other orbito-oculo-adnexal tumours with clinical AIDS was noted in only 5.2%.

10. RECOMMENDATIONS

1. Long-term study with larger series to determine seropositivity in orbito-oculo-adnexal tumours other than squamous cell carcinoma of conjunctiva.

2. A study of other factors associated with pathogenesis of pterygium, squamous cell dysplasia and squamous cell carcinoma like HPV-16.

11.1 APPENDIX A

QUESTIONNAIRE

1. NAME _____ INDEX NO._____
2. AGE _____
3. SEX _____ MALE _____ FEMALE _____
4. RESIDENCE _____
5. OCCUPATION _____
6. DATE OF EXAMINATION _____
7. BLOOD TEST _____

a) ELISA (FOR HIV ANTIBODY): POSITIVE_____ NEGATIVE_____

b) WESTERN BLOT POSITIVE_____ NEGATIVE_____

8. OCULAR COMPLAINS/HISTORY RE _____ LE_____
9. VISUAL ACUITY RE_____ LE_____
10. EXOPHTHALMOMETRY RE_____ LE_____
11. LIDS RE_____ LE_____
12. CONJUCTIVA RE_____ LE_____
13. SCLERA RE_____ LE_____
14. CORNEA RE_____ LE_____
15. ANTERIOR CHAMBER RE_____ LE_____
16. IRIS RE_____ LE_____
17. PUPIL RE_____ LE_____
18. LENS RE_____ LE_____

19.	VITREOUS	RE_____	LE_____
20.	OPTIC DISC	RE_____	LE_____
21.	MACULA	RE_____	LE_____
22.	RETINA	RE_____	LE_____
23.	CRANIAL N. PALSY	YES_____	NO_____
24.	ORBIT	RE_____	LE_____
25.	X/CT SCAN/US	RE_____	LE_____
26.	HISTOPATHOLOGY	YES_____	NO_____
	NUMBER	RE_____	LE_____
27.	EXTERNAL PHOTOGRAPH	YES_____	NO_____
	NUMBER	RE_____	LE_____

11.2 Appendix B: Clinical Photographs

Figure 1: A study patient with clinical diagnosis of squamous cell carcinoma of the conjunctiva

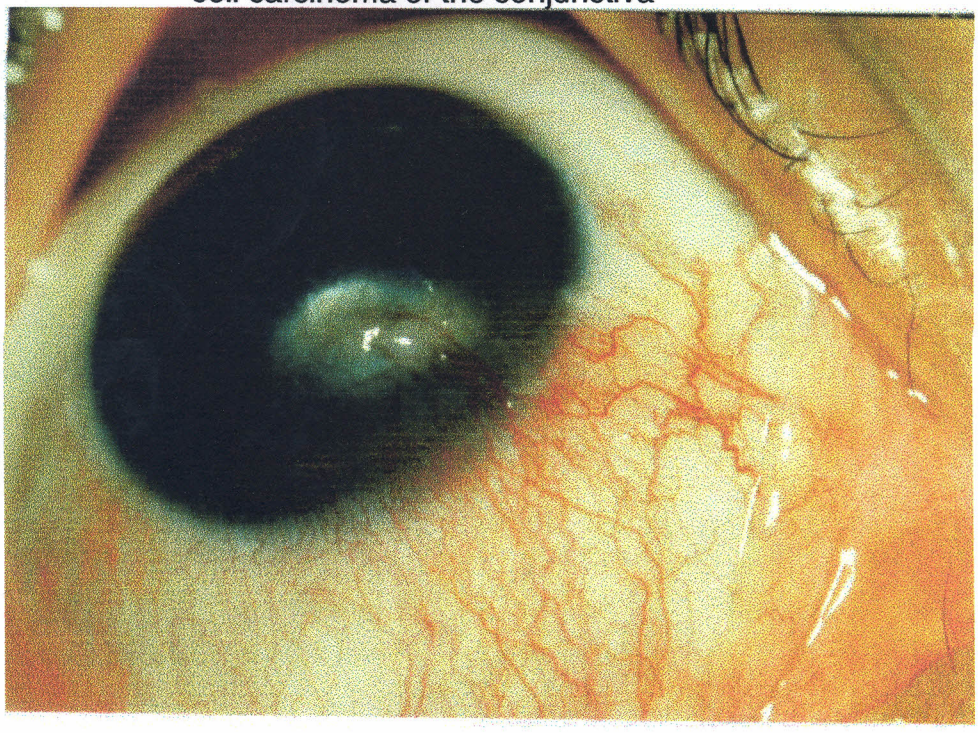


Figure 2: A study patient with diagnosis of pterygium with severe dysplasia of the conjunctiva(arrows)

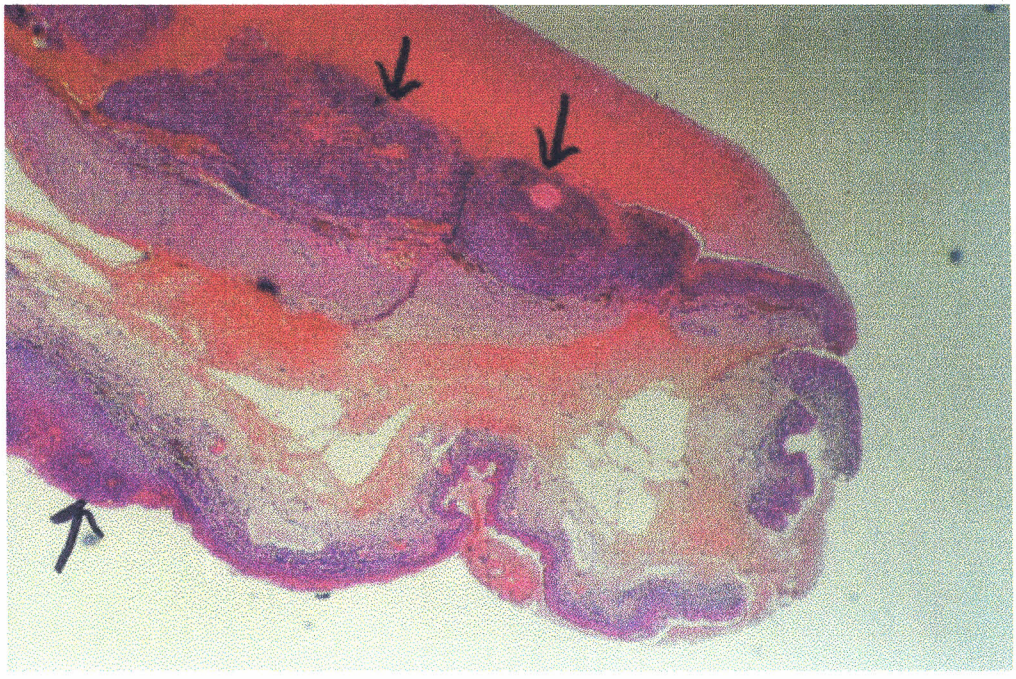


Figure 5: A study patient with diagnosis of squamous cell carcinoma of the conjunctiva

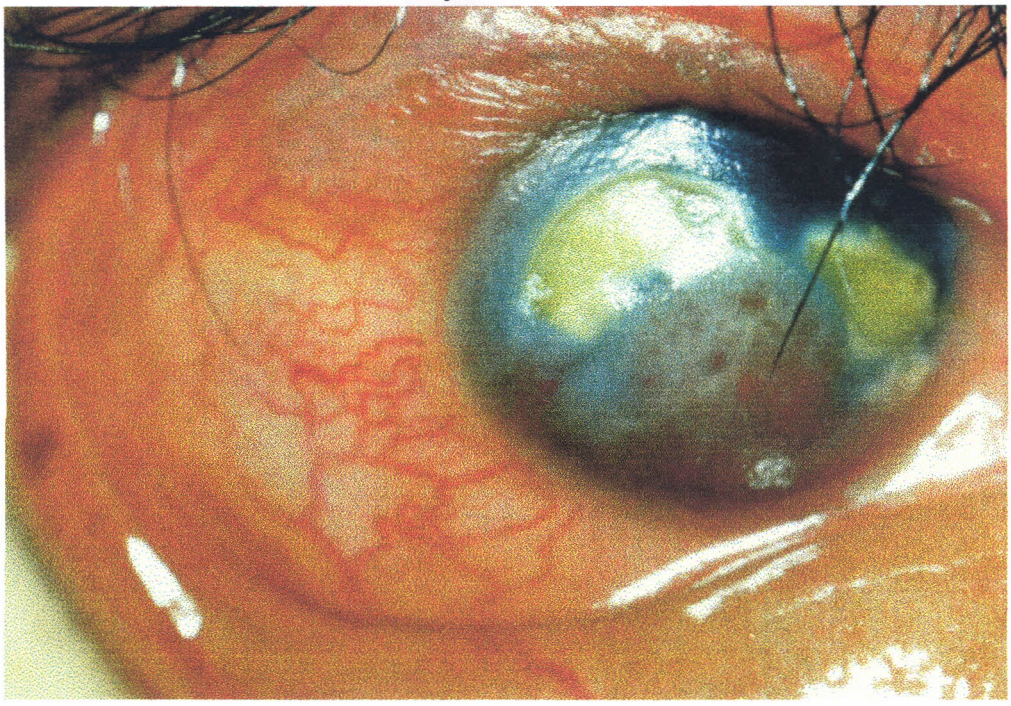


Figure 6: *A study patient with diagnosis of squamous cell* carcinoma - poorly differentiated

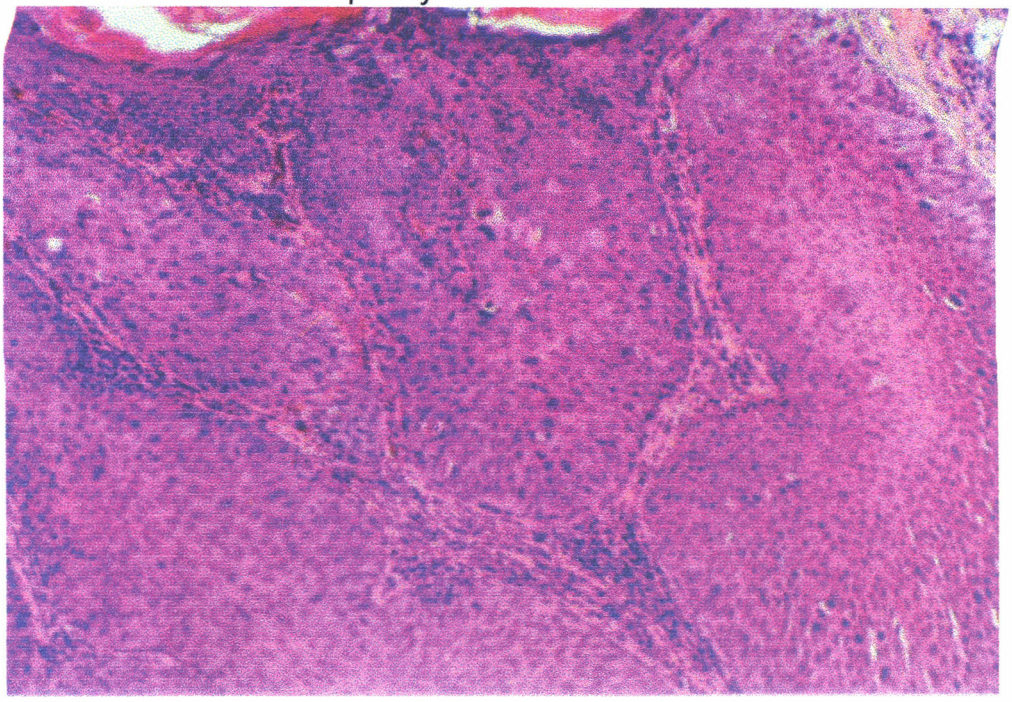


Figure 7: A study patient with optic nevre glioma

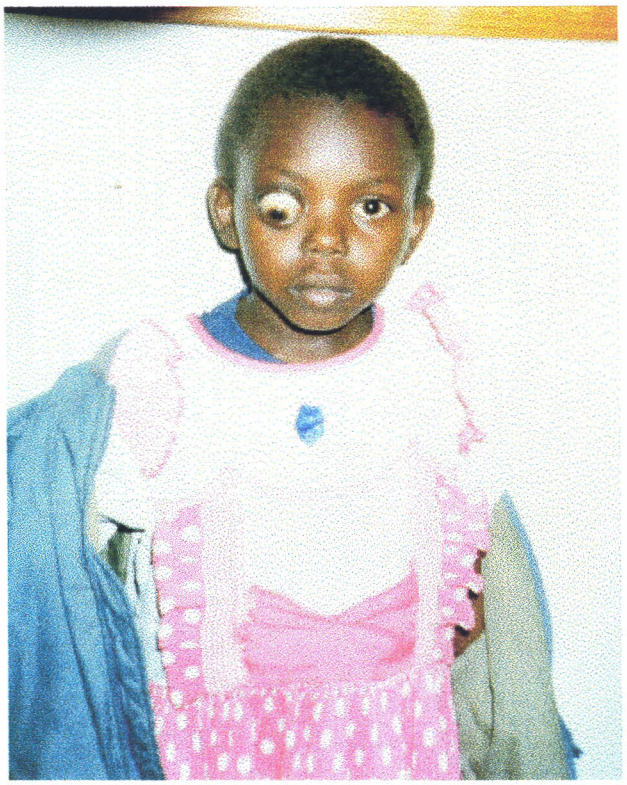


Figure 8: Macroscopic appearance of the orbital mass from the patient above

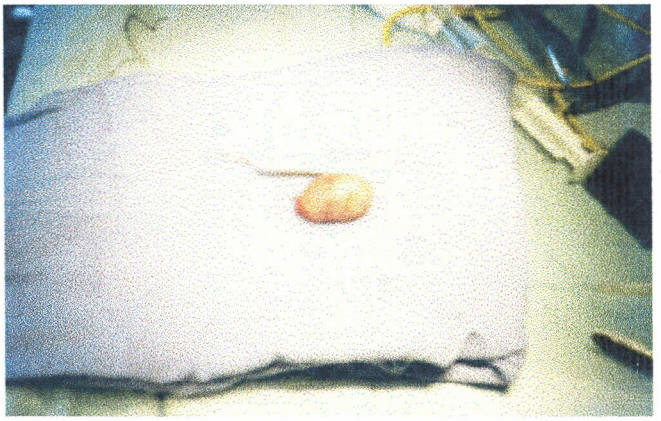


Figure 9: Histopathology of the optic nevre glioma - pilocytic

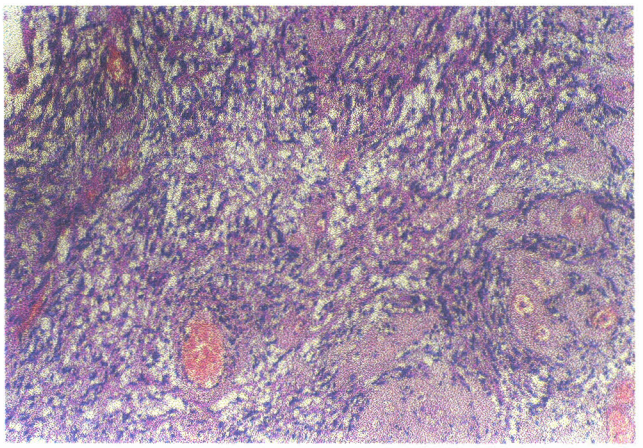


Figure 10: A study patient with a diagnosis of Burkitts Lymphoma

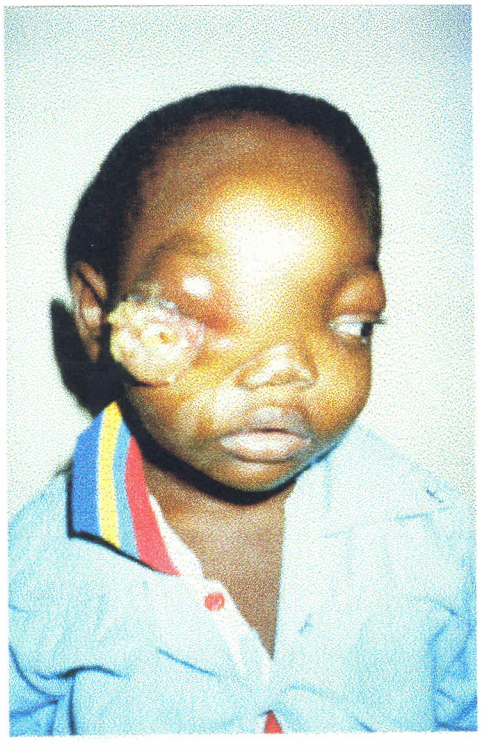


Figure 11: A study patient with a diagnosis of Rhabdomyosarcoma

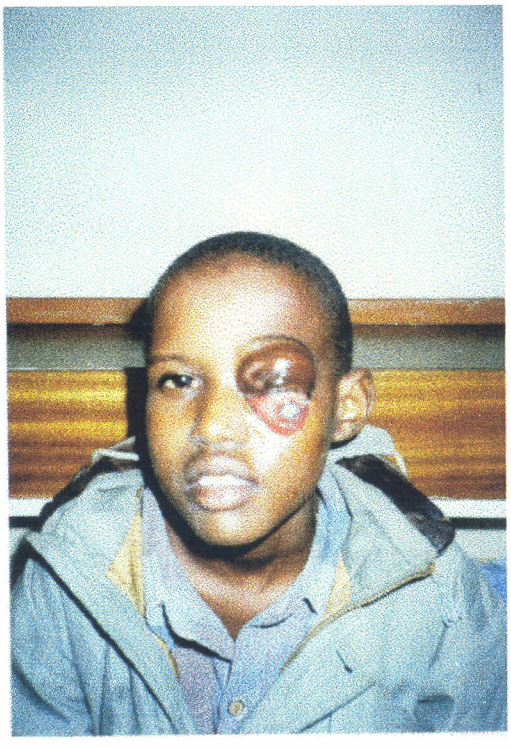
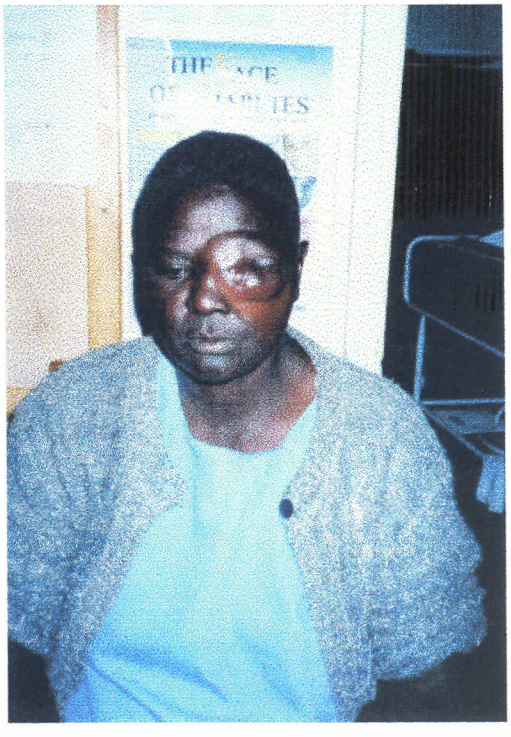


Figure 12: A study patient with a diagnosis of Adenocarcinoma



11.3 APPENDIX C

CONSENT FORM

STUDY: PATTERN OF ORBITO-OCULO-ADNEXAL TUMOURS AS SEEN AT TWO MAJOR HOSPITALS IN KENYA (KNH AND KEU):

I _____FATHER/MOTHER/GUARDIAN

OF_____

P.O. BOX_____

HEREBY GIVE CONSENT FOR INCLUSION IN THIS STUDY: IAM INFORMED THAT THE INFORMATION OBTAINED WILL BE HANDLED IN STRICT CONFIDENCE AND I DO FURTHER CONSENT TO ANY OTHER PROCEDURES WHICH ARE NECESSARY IN THE STUDY AS HAS BEEN EXPLAINED TO ME BY:

DR._____

DATE_____

PATIENT/PARENTS/GUARDIAN'S SIGNATURE _____

DATE_____

DOCTOR'S SIGNATURE _____

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