CLINICO-HISTOPATHOLOGIC STUDY OF MAXILLOFACIAL SARCOMAS SEEN AT THE UNIVERSITY OF NAIROBI DENTAL HOSPITAL: A 10-YEAR REVIEW

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V60/7544/2006

A THESIS SUBMITTED IN F*ART FULFILLMENT FOR THE AWARD OF A MASTER OF DENTAL SURGERY DEGREE IN ORAL AND MAXILLOFACIAL SURGERY

2010

DECLARATION

I hereby declare that this thesis is my original work and has not been submitted in any other university.

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DEDICATION

This thesis is dedicated to my mother, sister, brother-in-law and their family for the tremendous amount of moral support during the period of my postgraduate study.

ACKNOWLEDGEMENTS

I would like to acknowledge my supervisors Professor Chindia, Dr Dimba, Dr Awange and Dr Gathece for their constant guidance and advise on the project. I am greatly indebted to the Ministry of Health for provision of a scholarship to further my studies. Finally, I am most grateful to A. K. Limo and J. Gichana for assisting me locate clinical records and process histopathology specimens in the Oral Pathology Laboratory.

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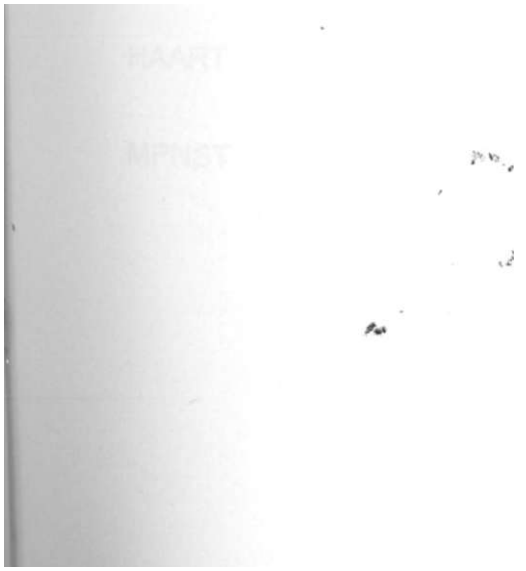

ABBREVIATIONS

ES	Ewing's sarcoma
FBS	Fibrosarcoma
HIV/AIDS	Human Immuno-deficiency Virus/ Acquired immune deficiency syndrome
HNOS	Head and neck osteosarcoma
IF	Intermediate filaments
IHC	Immunohistochemistry
KNH	Kenyatta National Hospital
MFH	Malignant fibrous histiocytoma
RMS	Rhabdomysarcoma
SPSS	Statistical package of social sciences
STS	Soft tissue sarcoma
UNDH	University of Nairobi dental hospital
AJCC	American joint committee on cancer
VS	Versus
HAART	Highly active anti-retroviral treatment
MPNST	Malignant Peripheral Nerve Sheath tumour

ABSTRACT

Background: Sarcomas are malignant neoplasms of mesenchymal origin with no site predilection. Though their occurrence in the head and neck region is rare vis-a-vis other malignancies, their presence is of tremendous concern due to the often grave prognosis.

Objective: To determine the pattern of occurrence, histopathologic types of maxillofacial sarcomas and their proportion in relation to other malignant neoplasms of this region based on archival material accumulated over 10 years (Jan 2000-Dec 2009).

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Study methodology: A retrospective cross-sectional study executed using histopathology records of patients at the University of Nairobi Dental Hospital (UNDH). All cases with a diagnosis of sarcoma, registered between 2000-2009 were evaluated. The data were collected using a special chart.

Results : Of the 527 malignancies recorded over the 10-year period, 427 (81.02%) were of epithelial origin while 100 (18.98%) were sarcomas. Patients with epithelial malignancies were older (54.16 ± 15.94 years) than patients with sarcomas (31.73 ± 16.78) with the differenced having been statistically significant {P<0.01 (0.000)}. Osteosarcoma and Kaposi's sarcoma (KS) were the two most commonly occurring sarcomas (59%) followed by fibrosarcoma (FBS) (19%), and rhabdomyosarcoma (RMS) (10%). Sarcomas peaked in the 3rd decade with 70% occurring below the age of 40

years. The maxilla and the mandible were the most afflicted sites in the maxillofacial region accounting for 52%. The patients, on average, presented to medical personnel about 9 months after noticing the lesion with the most frequent complaint having been swelling.

Conclusion : The present study confirms the relative rarity of maxillofacial sarcomas compared with epithelial malignancies. It also provides data on the histopathologic types and demographic characteristics of maxillofacial sarcomas in a select Kenyan population. The information contributes to the comprehensive documentation of sarcomas that occur globally and is useful in the provision of baseline data upon which future prospective analytical protocols may arise.

Recommendations: ' /.

1: Development of a central data bank to provide for efficient storage as well as retrieval of critical medical information that provides the essential baseline information upon which prospective analyses can be based on.

2: Further studies are required to capture the disease pattern in the Kenyan National population as a whole.

CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW

Sarcomas in general are relatively rare. In the United States, sarcomas account for approximately 1% of all malignancies with 5 to 15% of these lesions occurring in the head and neck region.[1] In Nigeria, a retrospective study by Arotiba et al. (2006) reported 58 sarcomas (12.37%) out of 469 orofacial malignancies.[2] Although head and neck sarcomas occur infrequently in adults, in the paediatric population one in three sarcomas will occur in the head and neck region.[1] Most head and neck sarcomas are of the soft-tissue type with only 20% being of bony or cartilaginous origin.[3] Sarcomas display a diverse array of histology and a wide spectrum of clinical behaviour, ranging from relatively slow growing lesions to aggressive locally and regionally destructive tumours with the potential for systemic metastases. Survival rates for head and neck sarcomas suggest worse outcomes than for their extremity counterparts.[3]

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There exists a limited number ,of reports on individual sarcomas occurring in the maxillofacial region. Most reports are centered on the head and neck region rather than the more limited maxillofacial area. In general, studies on head and neck sarcomas are rare from the literature review. Further, the small number of patients with head and neck sarcomas makes it difficult for prospective studies to be undertaken. Most of the data acquired result predominantly from retrospective reviews of small series of patients with head and neck sarcomas supplemented by an analysis of larger studies from sites outside the anatomic region. Chindia et al. (2000) revealed that, of the 10,897 whole

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body neoplasms reported between 1982-1991 at the Kenyatta National Hospital in Kenya, 985 were sarcomas among which 16% were found in the head and neck region. Also of note was that those sarcomas of the head and neck occurred more in males than in females with an overall ratio of 2:1. In terms of the age and site of occurrence, it was noted that over 70% of the sarcomas occurred earlier than the 4th decade and that approximately 50% of the tumours occurred in the maxillary, mandibular and neck regions.[4] A clinicopathologic study by Adebayo et al. (2005) in Nigeria reported that 20% of maxillofacial malignancies were sarcomas with a slight female to male predilection of 1.3:1.[5] Wanebo et al. (1992) reviewed the head and neck sarcoma registry at Brown University and analysed the treatment results of two hundred and fourteen patients. There were 194 adult tumoUrs and 20 paediatric tumours. The major sites included the parotid, neck, face, forehead and maxilla with only 5% of the tumours occurring in the oral cavity.[6]

Bone sarcomas

Osteosarcoma is the most common primary malignancy of bone, with a reported incidence of 1:100,000.[7] These tumours typically originate in the extremities and the pelvis, with only 6-10% of patients presenting with head and neck primary tumours.[8,9] August et al. (1997) estimated that less than 4% of all recorded osteogenic sarcomas occur in the jaw. The mandible and maxilla are the predominate locations of head and neck osteosarcoma (HNOS), although extragnathic as well as soft tissues sites may be affected.[10] Adebayo et al. (2005), Chidzonga et al. (2007) and Chindia et al. (2001) found the mandible to have been the most common site affected.[5,11,12] There are

differences in disease characteristics between HNOS and osteosarcoma outside the head and neck. The peak age of incidence for osteosarcoma outside the head and neck is in the adolescent years. In contrast, HNOS most commonly affects patients in their 30s.[7,13,14] Distant metastases have been reported in 10-20% of patients with HNOS, compared with 53-75% of patients with disease arising outside the head and neck.[7,15,16,17] The 5-year disease-specific survival rate for patients with HNOS has been poor, with most studies reporting survival rates of 23-37%.[7,8,9]

Ewing's sarcoma (ES) is a malignant primary bone tumour of primitive neuroectodermal derivation which represents 4-7% of all primary bone tumours and is the second most common malignant bone tumour in children.[18,19] Only 3% of cases of osseous ES arise in the head and neck where the calvaria and mandible are most frequently affected. Most ES occur in those aged 20 years or-younger; more than 80% occur in patients aged 30 years or younger. A retrospective analysis of 24 cases by Allam et al. (1993) revealed a median age of diagnosis of 16.5 years.[20] Overall, a slight male predominance exists, but in head and neck sites the sex distribution is equal. Diagnosis of ES remains a challenge and it must be differentiated from other tumours, in particular rhabdomyosarcomas (RMS) which stain positive with muscle-specific actin, desmin, and myogen unlike ES.[18]

Soft tissue sarcomas

Soft-tissue sarcomas (STS) are an uncommon but an important problem in head and

neck oncology. STS constitute less than 1% of all head and neck malignancies and include many histologic subtypes of varied biological behaviour.[1] Fibrosarcomas (FBS) are relatively uncommon tumours and account for 12-19% of STS. More than half of all the tumours arise in the lower extremities; approximately 10% occur in the head and neck, most commonly in the sinonasal tract and neck. FBS may arise in patients of any age and a slight male predominance exists. Most cases occur in those aged 30-60 years. In the African series, no gender bias has been noted with the mandible having been the most common site. Age ranges are similar to those in the western series.[5,11] An infantile variant that occurs in patients younger than 5 years appears to represent a distinct subtype and is associated with a better prognosis.[1]

Since the outbreak of AIDS, Kaposi's sarcoma (KS) has become the most common type of intra-oral sarcoma. Before the outbreak of HIV infection, KS was a rare form of sarcoma and literature from New South Wales showed an overall incidence of 0.0047%. With the advent of HIV infection, the occurrence of KS has rapidly increased and has even reached epidemic proportions in some regions where HIV infection is high. There are some studies which have shown that up to 24% of HIV infected patients have KS.[4] Butt et al. (2001) in an evaluation of oral manifestations of HIV infection at a Kenyan provincial hospital documented 13% of oral KS among 61 patients aged 16 years and above.[22]

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Rhabdomyosarcoma (RMS), a tumour of skeletal muscle origin, is the most common

STS in children and adolescents affecting the head and neck.[23] RMS has three distinct histopathologic types: alveolar, embryonal and pleomorphic. The embryonal type accounts for 70% of all cases and is particularly common in the oral and perioral region.[24] In a review of 88 cases in Zimbabwe, Chidzonga et al. (2007) reported that RMS was the second most common sarcoma predominantly in boys and afflicting mainly the maxilla.[11] Adebayo et al. (2005) reported RMS to have been the third most common sarcoma behind osteosarcoma and chondrosarcoma. Most lesions were noted to occur in the cheek with 50% of the cases in the first decade.[5]

Other sarcomas

The western literature indicates that chondrosarcomas of the head and neck region are relatively rare accounting for 5-10%. However, ih the African series, reviews by Adebayo et al. (2005) and Chidzonga et all: <2007) revealed chondrosarcomas to have been among the most common second only to osteosarcoma in occurrence.[5,11] Several other sarcomas exist but from the literature they occur rarely in the maxillofacial region. These include, leiomyosarcoma, liposarcoma, alveolar soft part sarcoma, haemangiopericytoma, neurogenic sarcoma, malignant fibrous histiocytoma and angiosarcoma.

From the foregoing literature, it is noted that sarcomas are relatively uncommon in the maxillofacial region but their occurrence results in considerable morbidity and mortality. Sarcomas contribute disproportionately to those cases regarded as difficult by surgical Pathologists hence the evolution of auxiliary diagnostic techniques as IHC. However, in

resource poor settings the prohibitive costs involved mean such auxiliary techniques remain beyond reach. Histologic type and grade are known to be reliable predictors of prognosis and are a designated component of the American Joint Committee on Cancer (AJCC) staging system for sarcomas. The multiple staging systems used to classify sarcomas share a common focus on the two most important negative prognostic variables: high histologic grade and the presence of metastatic disease. Size of the primary tumor is an additional prognostic variable of lesser importance[25]. A study undertaken at the Memorial Sloan Kettering cancer centre evaluated the effect of histotype as an independent prognostic factor of soft tissue sarcomas of the extremities. Of note was that after Kaplan-Meier analysis, the prognostic implications of tumour histotype were found to have been significant and persistent over ten years. A review by Wanebo et al. (1992) revealed that the five-year survival differed according to tumour cell type (tumour grade was not available). Patients with chondrosarcoma and dermatofibrosarcoma had survival approaching 100%. Patients with malignant fibrous histiocytoma (MFH) and FS had an intermediate survival of 60% to 70%. The worst survival, less than 50% at 5 years, occurred in patients with osteosarcoma, angiosarcoma, and RMS in decreasing order.[6]

Hibshoosh and Lattes (1997) concluded that the clinical relevance of molecular analysis 'n characterizing sarcoma subtypes has not yet surpassed the accumulated experience °f standard clinical and pathologic criteria.[27] This amplifies the importance of accurate histological diagnosis. Therefore, there is need for basic research to better understand these tumours with regard to prompt intervention. The aim of this study, therefore, was

to determine the demographic pattern of occurrence and histopathologic types of maxillofacial sarcomas as well as their proportion to other malignancies at the UNDH in Kenya.

PROBLEM STATEMENT AND JUSTIFICATION

PROBLEM STATEMENT

Sarcomas are relatively uncommon in the oral and maxillofacial region. However, due to the considerable morbidity associated with their occurrence, effective diagnosis and management is essential. Both bone and STS may not be easily distinguished from other mesenchymal benign tumours and reactive conditions making their clinical diagnosis difficult. Further, sarcomas present a significant challenge in pathologic diagnosis principally due to the considerable morphologic overlap among entities. In addition to this, public awareness is low and some patients wait a considerable time before seeking medical advice. It is probable that patients present late because the tumour is often painless and slow growing-, causing little concern in the early stages. This impacts on the overall prognosis of the patient. Histologic type and grade are known to be reliable predictors of prognosis and are a designated component of the American Joint Committee on Cancer (AJCC) staging system for sarcomas. Thus awareness of the pattern of occurrence and description of the histopathologic types encountered in our setting will help improve the overall care of these patients.

JUSTIFICATION

On a worldwide basis, reports on the pattern of occurrence of sarcomas of the Maxillofacial region are few and often limited to presentation of specific case studies and reviews. As a result data on the patterns of occurrence may be incomplete.

Furthermore, conflicting findings noted between the literature from developing and developed countries on relative frequencies of sarcomas necessitates further research. Due to the grave prognosis associated with sarcomas, generally, there is need for comprehensive documentation of the spectrum of sarcoma entities both locally and globally (Chindia et al, 2000). The evolution of a diverse number of diagnostic techniques for sarcomas illustrates the challenges encountered by pathologists in their diagnosis. Thus the aim of this study is to evaluate the pattern of occurrence, the histopathologic types of maxillofacial sarcomas and their ratio to other malignant tumours in this region. The findings of this study could be used by clinicians and oral pathologists to improve diagnosis. This will in turn lead to better prognosis and quality of life.

OBJECTIVES

BROAD OBJECTIVE

To determine the pattern of occurrence, histopathologic types of sarcomas and their proportion to other malignant tumours of the maxillofacial region over a 10-year period (2000-2009).

SPECIFIC OBJECTIVES

1. To determine the proportion of sarcomas to other malignant tumours of the maxillofacial region.
2. To describe the demographic pattern of occurrence of maxillofacial sarcomas.
3. To determine the histopathologic?,types and grade of sarcomas from the archival records.

CHAPTER 2

2: MATERIAL AND METHOD

2.1: Study area

The study was carried out at the histopathology laboratory of the University of Nairobi Dental Hospital (UNDH) which is located off Argwings Kodhek road opposite the Nairobi Hospital. The hospital serves as a teaching and referral centre providing both undergraduate and postgraduate training. It also houses an oral and maxillofacial pathology laboratory which is the only one of its kind in the country. Concise clinical and histopathological records are kept at the hospital.

2.2: Study population

The study was based on records of patients and tissue specimens (histopathology slides) obtained from the oral pathology laboratory of the UNDH.

2.3: Study design

A retrospective descriptive hospital based study.

2.3.1: Sample size

Due to the small number of sarcomas that present, all sarcomas were included in the study.

2.3.2: Variables

VARIABLE

Sociodemographic variables

Age

Gender

Clinical presentation:

Site

Duration

Histopathologic diagnosis:

Bone: Osteogenic sarcoma

Ewing's sarcoma

Cartilagenous: Chondrosarcoma

Fibrous : Malignant fibrous histiocytoma

Fibrosarcoma

Muscular: Rhabdomyosarcoma

Leiomyosarcoma

Vascular: Angiosarcoma .

Kaposi's sarcoma

Hemangiopericytoma

Neurogenic: MPNST

Fatty: Liposarcoma

Histogenesis unclear: Synovial sarcoma

Alveolar soft part sarcoma

Other malignant tumours (epithelial): SCC and variants

Malignant glandular neoplasms

Malignant melanoma

Odontogenic carcinomas

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2.3.3: Inclusion criteria

1: All cases recorded in the histopathology files in the period between January 2000-December 2009.

2: All sarcomas falling within the orofacial/maxillofacial region.

The orofacial/maxillofacial region was defined by the following landm

Superiorly: imaginary line running along the inferior orbital margin across the nasal base to the opposite side.

Inferiorly: Inferior border of the mandible extending along the stylo-mandibular ligament to the external auditory meatus.

Laterally: Imaginary line extending from the external auditory meatus to the lateral canthus.

**lesions within the oral cavity and the submental, submandibular and sublingual spaces were included.

**The parameningeal areas were not Included in this study.

2.3.4: Exclusion criteria

1: Sarcomas not located within the defined maxillofacial region.

2.3.3: Inclusion criteria

1: All cases recorded in the histopathology files in the period between January 2000-December 2009.

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2.3.4: Exclusion criteria

1: Sarcomas not located within the defined maxillofacial region.

2.3.5: Data collection

2.3.5.1: Method and technique

Data were recorded using a specially designed chart (appendix 1). The data collected included demographic patterns, clinical presentation and the histopathologic variants as previously reported. Only the histopathology reports from the UNDH laboratory were used. Recording of individual sarcomas was done utilizing the simplified clinical classification of the University of Texas M. D. Anderson cancer centre. Permission was sought from the relevant authorities where patients' records were located/stored in other institutions other than the UNDH. The demographic patterns and clinical presentation information were accessioned from the patients' hospital files obtained from the UNDH AND KNH.

Case definition for the study was any sarcoma diagnosed for the first time at the Oral Pathology Laboratory at the UNDH. Recurrent diseases were excluded. Cancer cases were coded according to the International Classification of Diseases.

The histopathology slides of patients diagnosed with maxillofacial sarcomas were located and manually retrieved by the investigator. The slides were re-evaluated with the assistance of two oral/maxillofacial pathologists to confirm the original diagnosis and Provide information of the histopathologic grade of the tumour. Any case(s) noted to have had a discrepancy in the histopathologic diagnosis were re-evaluated to attain a

definitive diagnosis by consensus decision.

Examination of the histopathology slides was done using the Leitz Wetzlar binocular microscope.

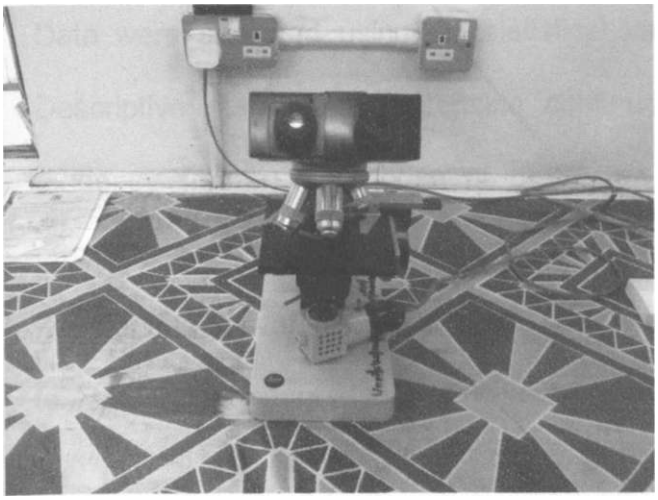

Fig 1: Leitz Wetzlar binocular microscope

The histopathologic criteria that were used for analysis of sarcomas are listed below:

-Degree of differentiation/anaplasia.

-Pleomorphism.

-Nuclear cytoplasmic ratios.

-Mitoses and necrosis.

-Invasive front and desmosomal contact.

-Vascularity.

-Cell typing.

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2.3.6: Data analysis

Data were analyzed using the statistical package for social sciences version 11.5. Descriptive statistics to determine continuous data included measures of central tendency (mean) and those of dispersion (standard deviation). Frequencies and proportions were used to analyze categorical variables. Significant differences between key dependent variables and independent variables were done using the Chi square test and independent t-test. A P value of < 0.05 will be considered significant.

2.3.7: Main outcome measures

1. Demographic pattern of occurrence of maxillofacial sarcomas.

2. Histopathologic variants and histologic grade

2.3.8: Data presentation

Results were presented in the form of bar charts, tables and pie charts.

2.3.9: Minimising errors and biases

1: Pretesting of the data collection form was done.

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2: Data cleaning was done to enhance their validity.

3: In cases where there was discordance in the pathologic diagnosis, the new diagnosis attained under consultative diagnosis was utilized in the statistical analysis.

2.4: Ethical considerations

Approval was obtained from the Ethics, Research and Standards committee of the Kenyatta National Hospital and the University of Nairobi (appendix 3-P170/6/2009). Permission to conduct the study was sought frqm,the UNDH, the Department of Oral and Maxillofacial Surgery, Oral Pathology and Oral Medicine. Information regarding patients' identity was treated with confidentiality

2.5: Data limitations

1: Missing of patients' clinical files, histopathologic reports and microscopic slides.

2: Poorly or unreadable recorded data.

3: Extrapolation of data from previous time to derive statistical conclusions at the present time.

4: There was no calibration of those maintaining clinical/ pathological records.

5: Degeneration of original slides, necessitating preparation of new slides for archival blocks.

CHAPTER 3

RESULTS

Demographic distribution of sarcomas as compared to other malignancies of the maxillofacial region

Over the 10-year study period, 527 cases of malignant neoplasms were recorded among whom 427 (81.02%) were of epithelial origin while 100 (18.98%) were sarcomas. There were more males 273 (52.1%) than females 251 (47.9%). The age range was between 3-90 years with a mean of 49.64 years (SD±18.45 years). Patients with epithelial malignancies were older, 54.16 years ±15.94 (95%CI 52.52 - 55.75), than those with sarcomas who had an average age of occurrence at 31.73 years±16.785 (95%CI 28.37-35.10). The difference was statistically significant (Mann Z= -10. 266, < ¡ >

P<0.01 (0.000). More males had epithelial malignancies than females while there were more females with sarcomas. However, the difference was not statistically significant (X^2=2.09, p=0.15). Fig. 2 shows the histopathologic distribution according to gender.

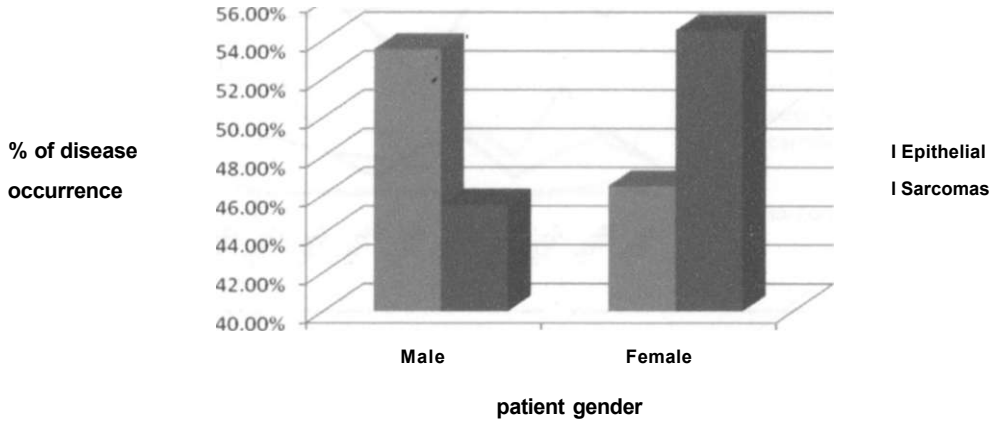

Fig 2: Distribution of histopathologic types according to the gender of the respondents

Among epithelial malignancies, 342 cases (80.79%) were squamous cell carcinoma and its variants, 71 (16.63%) were malignant glandular neoplasms while malignant melanoma and odontogenic carcinomas contributed 11 (2.58%).

More males were afflicted with squamous cell carcinoma 188 (54.97%) than females 154 (45.03%). Malignant glandular neoplasms had an almost equal distribution among males 36 (50.70%) and females 35 (49.30%). All cases recorded for malignant melanoma were seen in females (n=4). More females (57.14%) were afflicted by odontogenic carcinomas than males (42.86%).

The distribution of maxillofacial malignancies by year is illustrated in Fig. 3. Squamous cell carcinoma showed peak incidences in the years 2001 (n=53) and 2009 (n=53) with the lowest incidence noted in 2004 (n=18). Peak incidence of sarcomas was in year 2000 (n=19) with a gradual decrease seen progressively to 2004 (n=4) with another peak in 2007 (n=17). The overall trend seen for malignant glandular neoplasms, malignant melanoma and odontogenic carcinomas was stable over the 10-year period.

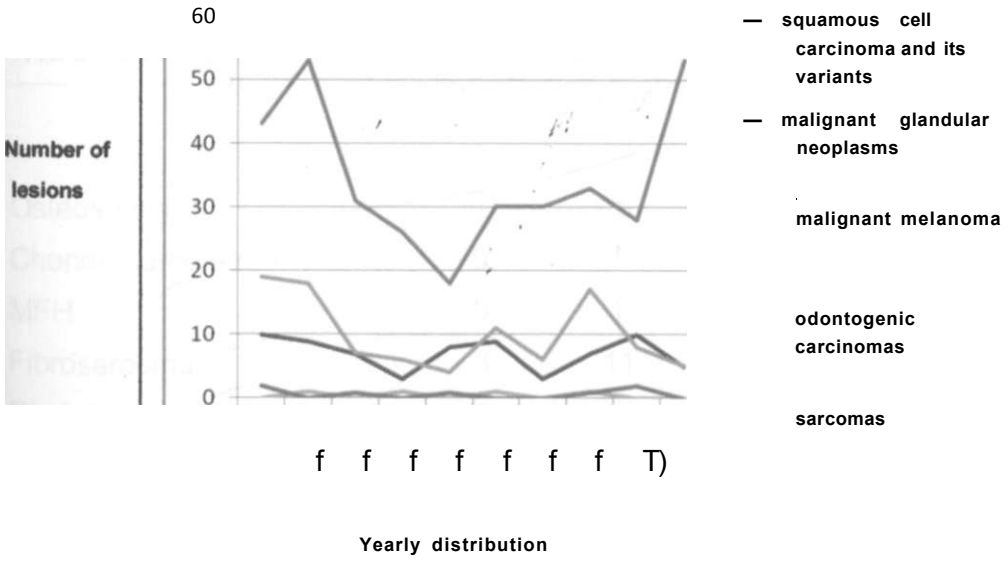

Fig 3: Yearly distribution of maxillofacial malignancies.

Age distribution of sarcomas

Among the 100 cases of sarcoma, 46 (46%) occurred in males while 54 (54%) were found in females with an overall age range of 3 to 90 years. The 20-29-year-old age group was the most commonly affected with 28 cases and a significant proportion of sarcomas (73.19%) occurred in patients less than 40 years of age. There was no statistically significant difference in the ages of male (31.19±17.99 years) and female (32.20±15.84 years) patients at first presentation (p=0.770). Table 1 illustrates the distribution of the sarcoma subtypes among the various age groups. Osteosarcomas were the most common with 30 (30%) cases followed by KS with 29 (29%). FBS and RMS also made up a significant proportion with 19 (19%) and 10 (10%) cases respectively.

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Table 1: Distribution of sarcoma subtypes according to the age groups.

NEOPLASM	AGE OF PATIENT IN YEARS				
	0-19	20-39	40-59	60+	**Total**
Osteosarcoma	10	15	2	3	**30**
Chondrosarcoma	Q	1	1	0	**2**
MFH	0	1	0	0	**1**
Fibrosarcoma	3	11	3	2	**19**
Rhabdomyosarcoma	5	3	1	0	**9**
Angiosarcoma	1	0	0	0	**1**
Kaposi's sarcoma	2	15	10	2	**29**
Haemangiopericytoma (HPf) '	0	1	0	0	**1**
Haemangioendothelioma (HED)	0	2	0	1	**3**
Liposarcoma	0	1	0	1	**2**
Total	**21**	**50**	**17**	**9**	**97**

Site distribution with the various sarcomas

Of the 100 sarcomas recorded, 97 had the site of tumour occurrence indicated. The maxilla was the most commonly affected site with 26 (26.8%) sarcomas while 25 (25.7%) were found in the mandible and 17 (17.5%) occurred in the palate. Eleven cases were found in the tongue so that cumulatively, these 4 sites contributed to 80.5% of the sarcomas.

Fifteen cases of osteosarcoma were found in the maxilla while 12 occurred in the mandible. One was found in the extra-osseous compartment (parotid gland). Five cases of RMS were found in the osseous/bony compartment (maxilla/mandible). Of the 18 FBS recorded, 13 were found within the osseous/bony compartment. Regarding KS, 17 of the 29 cases were typically found in the palate. Table 2 shows the distribution of the various sarcoma subtypes according to site.

Table 2: Distribution of sarcoma types by site.

NEOPLASM	SITE										
	Max	mand	cheek	tongue	FOM	lip	palate	ging/alv	MSG	1° site unclear	**Total**
Osteosarcoma	15	12	–		–	—	·	–	–	1	**28**
Chondrsarcoma	1	1	.	.	.					.	**2**
RMS	3	2	2	1						2	**10**
FBS	5	8	3	.		1	.			1	**18**
MFH	.	.	.	1	.					.	**1**
Angiosarcoma	.	.	1	.		T	•			.	**1**
KS	1		1	6	-	-	17	3		1	**29**
HPT	.	.	.	1		1				.	**2**
HED	.	.	.	2	1					.	3
MPNST	1	.	.	.	.					.	**1**
Liposarcoma	.	2	.	.	.					.	**2**
Total	**26**	**25**	**7**	**11**	**1**	**2**	**17**	**3**		**5**	

Clinical presentation

Of the 100 cases analyzed, 73 cases had information regarding the duration between when the patient first noticed the condition to when they first presented to medical personnel. The average duration was 9.9 months (SD=14.91). One case was diagnosed incidentally on routine medical examination while one patient presented after 9 years.

For patients who presented with sarcomas, 51 clinical records were located. All but one presented with swelling of the affected site. Other prominent features were pain (37%), bleeding (19%), mobility of teeth (12%), limited mouth opening (10%) and paraesthesia (10%). A case of osteosarcoma was diagnosed incidentally during routine dental examination. * » -

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Tissue of origin

Concerning the tissue of origin, 32 sarcomas (32%) were of bony or cartilaginous origin while 68 (68%) were of soft tissue origin. More females (54%) were affected than males (46%). However, the differences were not statistically significant. {X^2=1.222; 1df; p>0.05 (p=0.269)}. Figure 4 displays the distribution of sarcoma tissue types according to gender.

	hard tissue	soft tissue
male	12	34
female	20	34

Fig 4: Distribution of sarcoma tissue types according to gender.

Hard tissue sarcomas

Osteosarcoma

Of the osteosarcomas reviewed, the most commonly affected age group was the 10-19 years with most (83.33%) occurring below 40 years of age. The overall mean age at diagnosis was 28.40 years and a statistically significant difference (p=0.019) was observed between the mean age at first presentation in men (21.18±6.91 years) and females (32.58±17.24 years). Table 3 illustrates the distribution of the subtypes by age. Among the subtypes of osteosarcoma, 14 (46.7%) were of the osteoblastic subtype, 9 (30%) were fibroblastic while *7* (23.3%) were chondroblastic.

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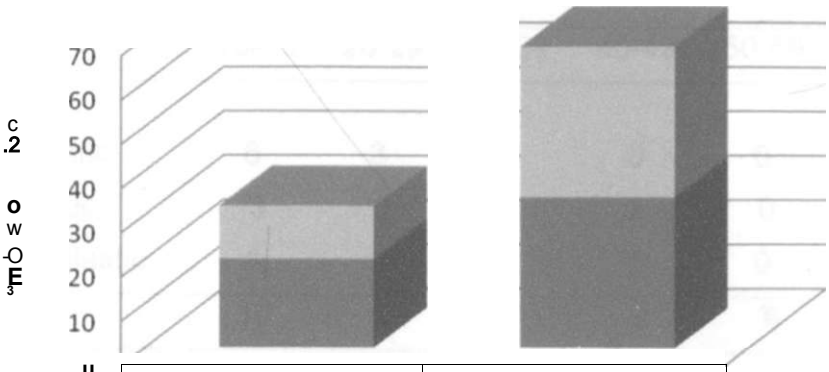

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3e	Age in years						
	10-19	20-29	30-39	40-49	50-59	60-69	Total
joblastic	6	3	4	0	0	1	14
•blastic	3	3	1	1	0	1	9
ndroblastic	1	2	2	1	0	1	7
	10	8	7	2	0	3	30

b **females were affected (63.33%) than males (36.67%) with the same trend having i seen among the subtypes. However, the difference was not statistically significant 0.532; p>0.05 (p=0.892).**

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tological description of hard tissue sarcomas

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5 1; A highly vascular connective tissue matrix containing highly pleomorphic cells and areas of osteoid in varying stages of ition. The nuclei are hyperchromatic, cells exhibit moderate levels of mitosis and there is loss of desmosomal contact.

Table 3: Distribution of osteosarcoma subtypes according to the age group.

Subtype	Age in years						
	10-19	20-29	30-39	40-49	50-59	60-69	Total
Osteoblastic	6	3	4	0	0	1	14
Fibroblastic	3	3	1	1	0	1	9
Chondroblastic	1	2	2	1	0	1	7
Total	10	8	7	2	0	3	30

More females were affected (63.33%) than males (36.67%) with the same trend having been seen among the subtypes. However, the difference was not statistically significant (X^2=0.532; p>0.05 (p=0.892).

Histological description of hard tissue sarcomas

Osteoblastic osteosarcoma

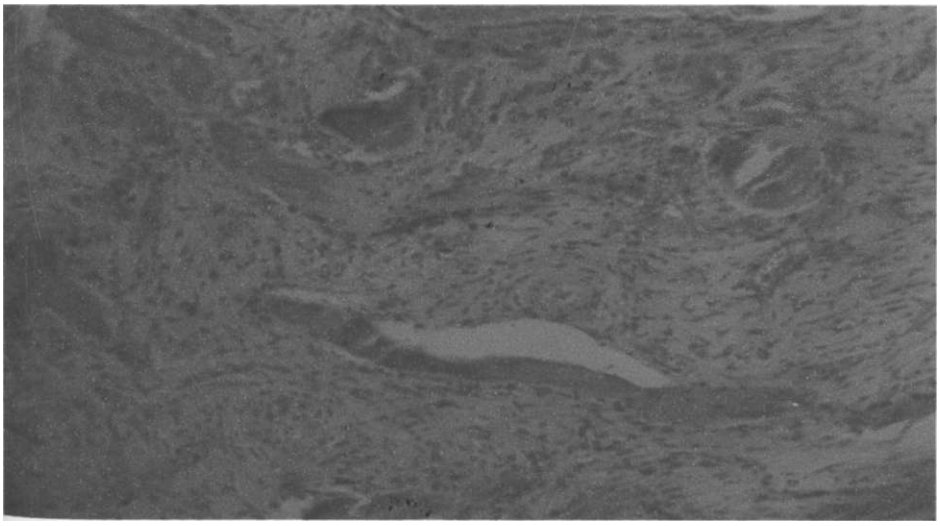

Plate 1: A highly vascular connective tissue matrix containing highly pleomorphic cells and areas of osteoid in varying stages of Saturation. The nuclei are hyperchromatic, cells exhibit moderate levels of mitosis and there is loss of desmosomal contact.

Soft tissue sarcomas

Rhabdomysarcoma

Ten cases of RMS were reviewed. The overall mean age at diagnosis was 17.77 years with no statistically significant difference observed in the ages of males (17.50±20.46 years) and females (17.88±9.40 years) at first presentation (p=0.291). Five of these were of the pleomorphic subtype, 3 were embryonal and 1 was of the alveolar subtype. One case did not have the subtype indicated. An equal number of males and females were affected. More males were affected by the embryonal subtype while more females were affected by the alveolar and pleomorphic RMS. However, the differences were not statistically significant {X^2=1.481\ p>0.05 (p=1.000)}. Of the 8 cases that had the age indicated 4 were found in the 0-9-year-old age bracket. One case of pleomorphic RMS occurred in the 50-59-year-old age bracket. 62.5% of the cases were seen below 20 years of age. Table 4 shows the distribution of the subtypes by age.

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Table 4: Distribution of RMS subtypes according to age.

Subtype	Age in years						
	0-9	10-19	20-29	30-39	40-49	50-59	**Total**
Embryonal	2	1	0	0	0	0	**3**
Alveolar	0	0	1	0	0	0	**1**
Pleomorphic	2	0	1	0	0	1	**4**
Total	**4**	**1**	**2**	**0**	**0**	**1**	**8**

Fibrosarcoma

Over the 10-year period 19 cases of FBS were recorded among which 10 (52.63%) occurred in females while 9 (47.37%) were in males. The mean age at first diagnosis was 32.16 years with no statistical difference noted in the ages of men (39.56±23.85) and women (25.50±10.80) at first diagnosis (p=0.115). The 20-29-year-old age group was the most commonly affected (n=9) with 73.68% of the cases occurring below the age of 40 years. Fig. 5 illustrates the distribution of FBS according to age groups.

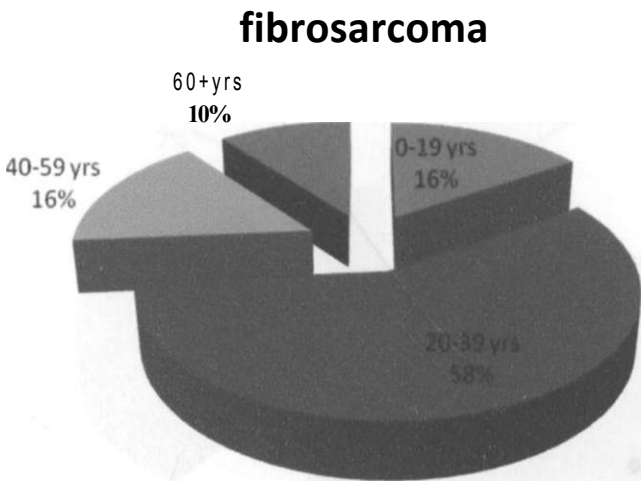


Figure 5: Distribution of FBS according to age groups.

Kaposi's sarcoma

These were the second most frequently occurring maxillofacial sarcomas recorded over the 10-year period (n=29). Majority (72.41%) were found between the ages of 20-50 years. The overall mean age was 36.68 years with no statistical difference (p=0.087) in the age at first presentation of men (33.75±10.80 years) and women (38.29±15.89 years). There was an almost equal distribution between the genders with 15 (51.72%) in males and 14 (48.28%) seen in females. Fig. 6 shows the distribution of KS cases according to age groups.

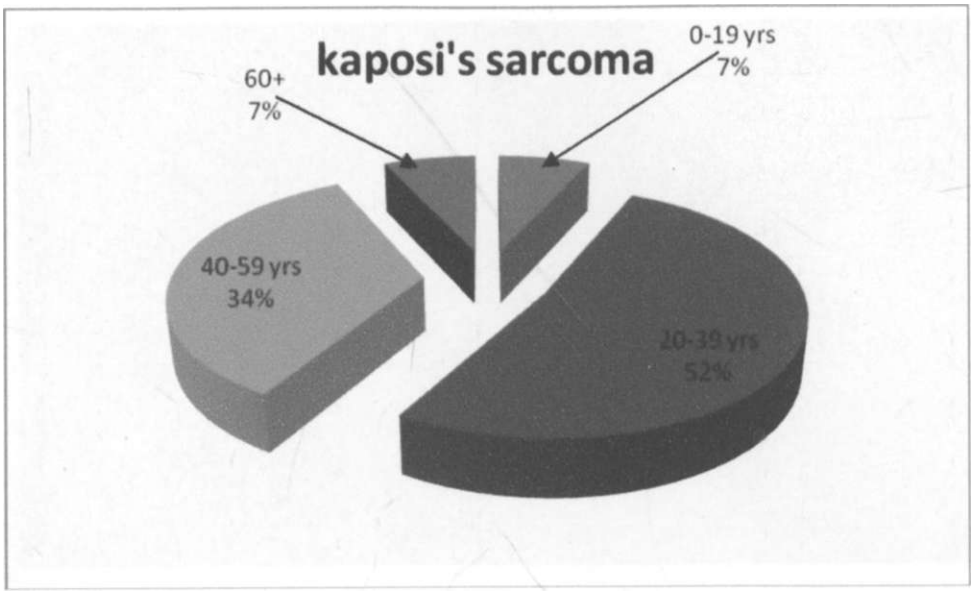


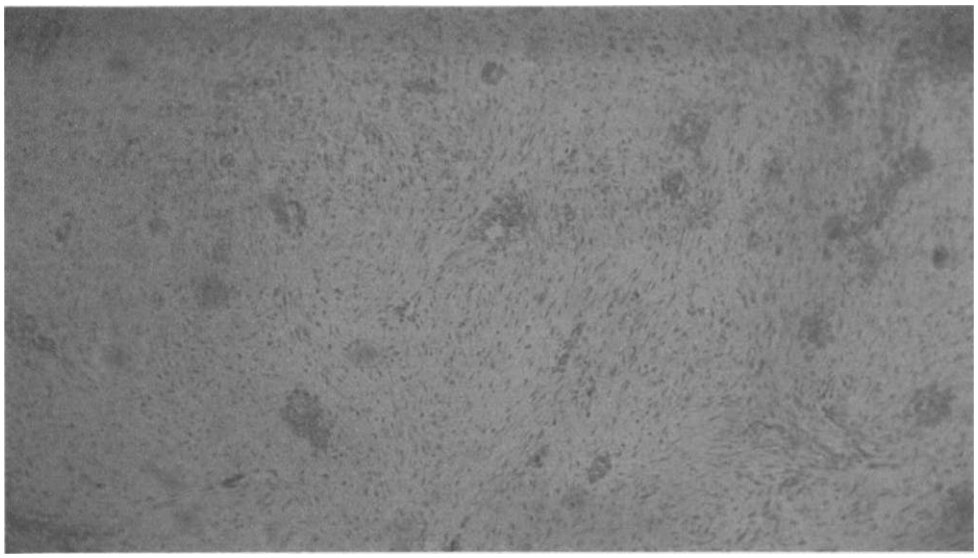
Figure 6: Distribution of Kaposi's sarcoma cases according to the age groups.

Histological description of soft tissue sarcomas

Rhabdomyosarcoma

Plate 2" A highly vascular tissue with pockets of inflammation and necrosis; consisting of highly pleomorphic cells with remnants of striations in the cytoplasm presenting in btiarre patterns such as strap cells. Mitotic index is high and the tumour is diffusely invasive to the surrounding.

FBS



Plat© 3! Masses of immature spindle shaped cells in a loosely packed matrix of collagenous tissue with some packets of inflammation. Tumour is moderately vascular and cells maintain desmosomal contact and original morphology in most cases

MFH

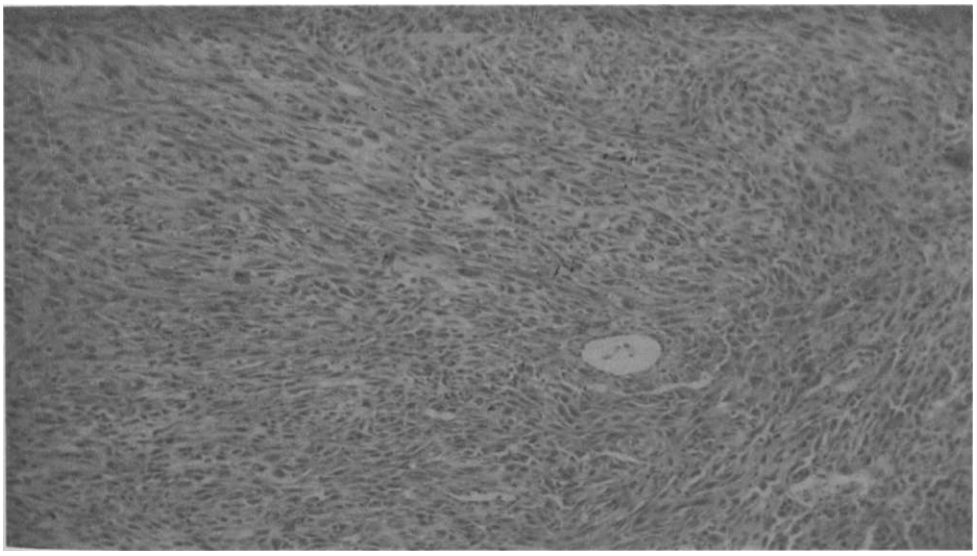


Plate 4: Sections show interlacing pleomorphic spindle shaped fibroblasts interspersed with large round or oval histiocyte-like cells with hyperchromatic nuclei and several abnormal mitoses. In some instances the fibroblasts are arranged in storiform or cartwhhel patterns, necrotic ares are quite'common

*f**

KS

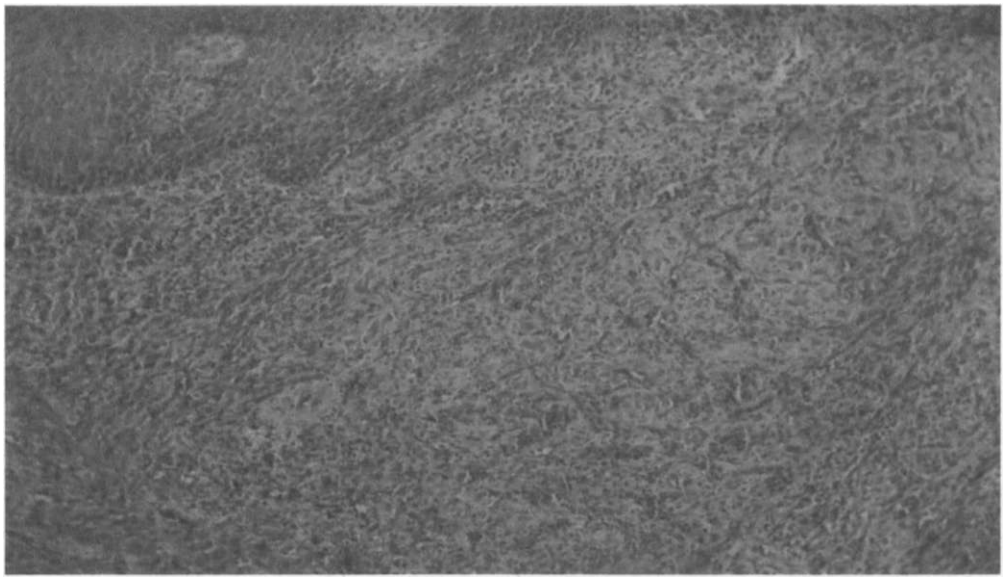


Plate 5: Connective tissue stroma that is grossly invaded by streaming patterns of spindle shaped malignant endothelial cells. The tumour is vascular in terms of capillary supply but also extravasted RBC's in the bulk of its substance

Haemangioendothelioma

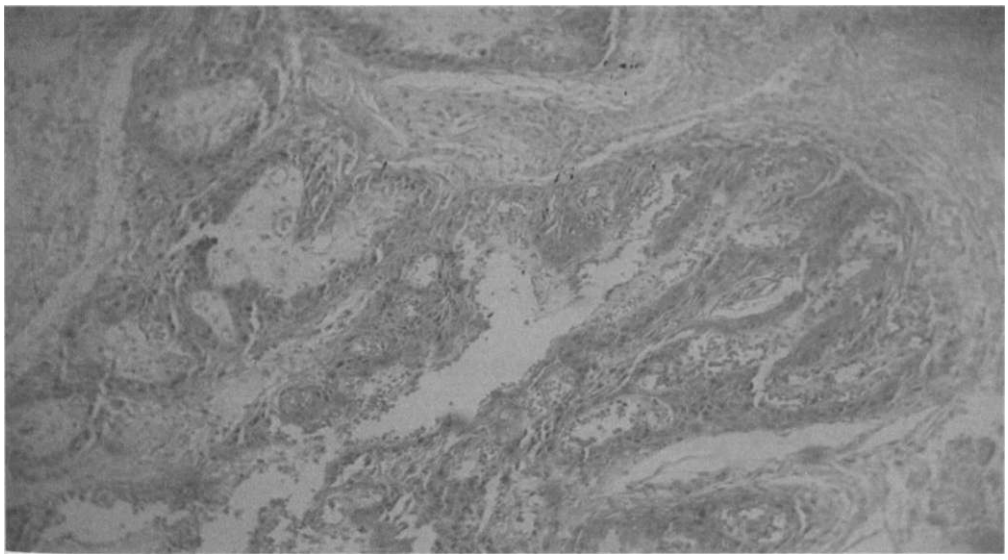


Plate 6: An ulcerated epithelium with otherwise normal morphology overlying masses of highly vascularized tissue with areas of capillary disruption. Invasive neoplastic cells are ovoid to spindle shaped with high levels of pleomorphism, moderate mitotic index but abnormal mitoses. Nuclear cytoplasmic ratios is inverse with prominent nucleoli. Architecture varies from anarchic to perivascular/streaming distribution of cells

Liposarcoma

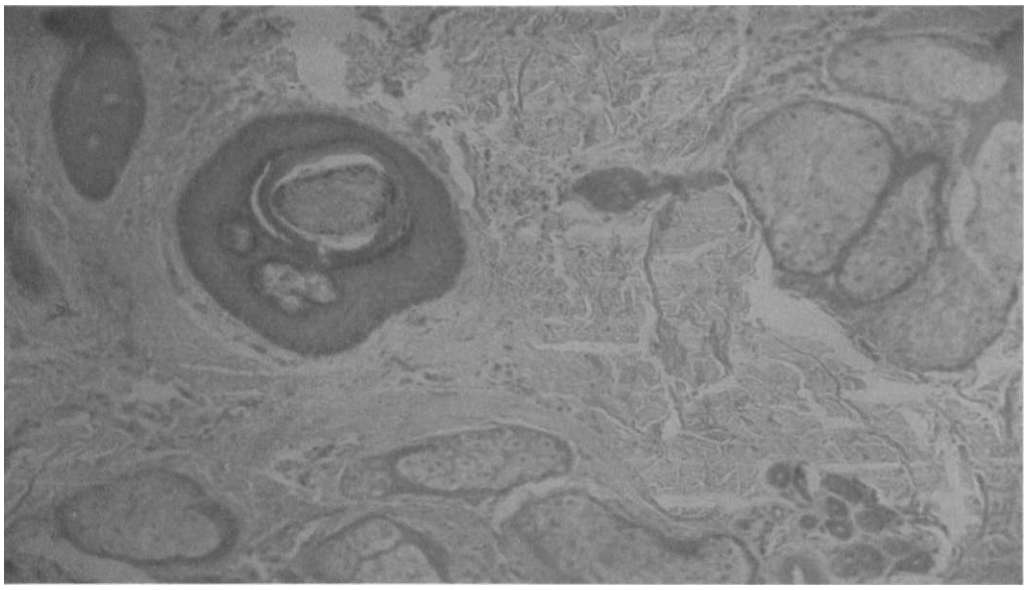


Plate 7: Dermis and underlying connective tissue inclusive of hair roots and sebaceous glands diffusely infiltrated with pleomorphic adipocytes having features of enlarged nuclei and high mitotic index. Invasion is diffuse but the neoplastic mass is largely cohesive - t » ,

Grading of sarcomas:

Ninety sarcomas were graded revealing 72,2% of them as having been high grade in nature (n=65). This trend vyas reflected among the various histotypes except for FBS, MPNST and liposarcoma where low grade variants predominated. Among the low grade variants more males (n=16; 64%) were affected than females (n=9; 36%), while among the high grade variants, more females (n=41; 63.08%) were affected than males (n=24; 36.92%). The difference was statistically significant (x^2=5.361; 1df; P<0.05 (p=0.021).

CHAPTER 4

4.1 DISCUSSION

Distribution of maxillofacial malignancies

Generally, maxillofacial mesenchymal malignancies are rare. In the present study, these neoplasms comprise 19% of all malignant tumours affecting the maxillofacial region. The results show similarity in the occurrence of sarcomas in the maxillofacial region with those seen in Kaduna, Nigeria,[5] though these are higher than those seen in European and Asian populations.[6,28] This may reflect a racial/ethnic bias with higher incidences of maxillofacial sarcomas seen in, African/Black population than in Caucasians speculating a genetic influence in the population

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In the present study, epithelial malignancies (carcinomas) tended to affect patients in older age groups while the maxillofacial sarcomas afflicted younger patients. Similar patterns have been described in the literature from developed countries.[2,4] This implies that genetic factors may have a more significant role to play than environmental influences in the development of maxillofacial sarcomas unlike carcinomas where environmental factors such as tobacco and alcohol usage have been implicated.

Clinical presentation

Sarcomas can be detected during routine examination for other conditions or due to non-specific signs and symptoms. The presenting features of sarcomas are non-specific and depend on tumour location, size, rate of growth, duration and level of cancer awareness in the individual.[1] All but one case seen in this study presented with swelling while a few had pain, mobility of teeth, bleeding from the tumour and trismus. One case was found incidentally on routine dental examination. The average duration of these lesions was short (mean 9.9 months), as has been reported in other studies, reflecting the rapidity of growth of these lesions.

Histopathologic subtypes

Osteosarcoma was the most frequently , diagnosed malignant maxillofacial mesenchymal neoplasm in the present study and this is consistent with previous data from this country[4] as well as from reports from other parts of Africa.[11,35] From the literature, the most common sarcoma is controversial depending on the age group, site and possibly racial factors. RMS has been documented as the most common oral and maxillofacial sarcoma in childhood[29,30,31] while in adults, osteosarcoma predominates.[32,33,34]

Hard tissue sarcomas

Analysis of age and gender distribution of maxillofacial osteosarcomas in this study noted some trends. The mean ages at first presentation of maxillofacial osteosarcoma are consistent with data from other African studies.[5,36] but lower than data from European studies.[7,13,14] From the literature, the average age of onset of osteosarcomas of the jaws and craniofacial bones has been reported to present 10 to 20 years later than for skeletal lesions; and the histopathological variables are more favourable, distant metastases occur less frequently and survival rates are higher.[37,38,39] This study also showed that there was no clear gender predilection. The marginal differences in gender predilection seen in the Kenyan studies ipfer that osteosarcoma has no real preference for any sex in that population. This is in agreement with what has been observed in European or American studies.

There is inconsistency as to the commonest site of occurrence of osteosarcoma in the craniofacial region from data gathered in the African setting. Some authors site the mandible as the most afflicted[5,11,36] while others the maxilla.[35] Nonetheless, the mandible and maxilla contribute disproportionately to the sites affected within the region[1] as was corroborated in our study. In our series the osteoblastic subtype of osteosarcoma was the most common similar to a report by Bertoni et al. (1991) followed by the fibroblastic and chondroblastic subtypes.[40] However, other reports have stated that the chondroblastic subtypes are the most common.[41] The chondroblastic variant has been proposed to be an adverse prognostic factor while the fibroblastic variant to have had the best prognosis[42] although the largest series to date failed to show any

impact of histological subtype on survival.[43]

As would be expected, based on evidence elsewhere[49], CHS were found to have been particularly rare in this series. Only two lesions had been diagnosed over the ten-year period. In general, CHS occurs more often in males, in a ratio of about 2:1; and there are no pathognomonic signs or symptoms presented.[50]

Soft tissue sarcomas

Kaposi's sarcoma has been described as one of the commonest malignant tumours in Africa. It is the commonest cancer associated with HIV infection, occurring in up to one in four AIDS patients.[4] Indeed KS is most prevalent in countries where HIV infection is prevalent. In our report, KS was the second most common maxillofacial malignancy making up 29% with no clear gender predilection as has been noted in more recent publications.[45] It was the most common sarcoma of the head and neck in a report by Chindia et al. (2000) with a male to female ratio of 3:1 [4] The site predilection was in accordance with the findings of other' authors with the palate having been the commonest site [44,45] With the advent of Active Anti-Retroviral Therapy (AART), the development of KS in AIDS patients has decreased and this may explain the lower prevalence of KS in our study[45]

Among the soft tissue sarcomas, aside from KS, FBS was diagnosed most frequently accounting for 19% of the cases. This is slightly higher than those reported by Chindia

et al. (2000) and Adebayo et al. (2005).[4,5] In this series, no clear gender predilection was noted in conformity with literature from other parts of Africa.[5] However, this contrasts with a Dutch report by Slootweg and Muller et al.(1984) which showed a slight female predominance.[46] The mean ages at first diagnosis in this study are consistent with data from both African and the western literature[5,46]. FBS occur in both the soft and hard tissues of the maxillofacial region. Slootweg and Muller (1984) assessed the lesion in the jaws of a Dutch population and found more in the mandible than the maxilla. Our findings concurred with most lesions having been found in the mandible (44%) and maxilla (27%) with few lesions in other sites.

RMS was the fourth most common sarcoma accounting for 10% of all tumours reviewed. This is similar to other African series.[5,11] RMS can occur at any age but the lesion is commonest in the 1st decade of life making it the commonest maxillofacial sarcoma in childhood. In our series, 50% of the neoplasms occurred in the 1st decade thereby corroborating other published series[47,48] RMS may be defined as a malignant tumour of the rhabdomyoblasts and it is estimated to comprise 12% to 56% of all solid malignant tumours in the paediatric age group.[47] A review by William et al. (2004) found that among the subtypes, the embryonal RMS was the most predominant type in the head and neck accounting for over half the cases with most afflicting younger children.[48] The pleomorphic subtype was 'the least common and was mostly found in older patients. In our series the pleomorphic subtype was the most common (n=5) followed by the embryonal subtype (n=3), with one case seen of the alveolar subtype. Lack of a centralized sarcoma team may have influenced the results seen in this study with some

of the paediatric RMS cases having been seen by medical oncologists. Almost all cases were found below 30 years of age with one case of pleomorphic RMS occurring in the 50-59-year-old age group. From the literature, the occurrence of other sarcomas in the maxillofacial region is rare[1,5] and this can explain the relatively few cases seen in this study.

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4.2 CONCLUSIONS

The present study confirms the relative rarity of maxillofacial sarcomas as compared with epithelial malignancies. It also provides data on the relative occurrences of the histopathologic types and demographic characteristics of maxillofacial sarcomas in a select Kenyan population. The information contributes to the comprehensive documentation of sarcomas that occur globally and is useful in the provision of baseline data upon which future prospective analytical protocols may arise.

4.3 RECOMMENDATIONS

1. Development of a central data bank to provide for efficient storage as well as retrieval of critical medical information that- provides the essential baseline information upon which prospective analyses can be based on.
2. Further studies are required to capture the disease pattern in the Kenyan population as a whole and to facilitate comparison with different racial/ethnic populations.

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APPENDIX 1:

DATA COLLECTION FORM: SARCOMAS OF THE MAXILLOFACIAL REGION.

1: PATIENT NUMBER

2: DATE OF DIAGNOSIS.

3: AGE OF PATIENT (YEARS)

4: GENDER OF PATIENT MALE FEMALE

5: RESIDENCE

6: HISTOPATHOLOGIC TYPE: (Simplified clinical classification of Texas M.D cancer centre[1])

BONE SARCOMA:

-OSTEOSARCOMA
-EWINGS SARCOMA
-CHONDROSARCOMA

SOFT TISSUE SARCOMA:

oFIBROSARCOMA
oMALIGNANT FIBROUS HISTIOCYTOMA
oANGIOSARCOMA
oKAPOSI'S SARCOMA
oHAEMANGIOPERICYTOMA
oLIPOSARCOMA
oNEUROGENIC SARCOMA
oRHABDOMYSARCOMA

©LEIOMYOSARCOMA

oSYNOVIAL SARCOMA

oALVEOLAR SOFT PART SARCOMA

oUNSPECIFIED SARCOMA

OTHER MALIGNANT HISTOLOGICAL TYPE OF TUMOUR

Specify

ANY OTHER RELEVANT INFORMATION

7: DURATION IN * ,
DAYS

8: SITE OF TUMOUR (circle the location)

> MAXILLA

>MANDIBLE

>CHEEK

>TONGUE

>FLOOR OF MOUTH

>GINGIVA/ALVEOLUS

>LIP

> PALATE

>RETROMOLAR REGION

>MAJOR SALIVARY GLANDS

>ILL DEFINED ORAL SITES

APPENDIX 2

SARCOMA HISTOPATHOLOGY REPORT

Name

Age

Sex: M

F

Microscopic details:

Histopathologic diagnosis.

TUMOUR GRADING:

Sarcomas:

Mitosis: (1) 0-9/1 Ohpf (2) 10,-19/1 Ohpf (3) 20plus/1 Ohpf

Necrosis: (0) no necrosis (1) 1-50% necrosis (2) >50% necrosis

Degree of differentiation (1) like adult tissue (2) certain histological type
(3) embryonal/undifferentiated

Grade: grade 1: 2 or 3
grade 2: 4 or 5
grade 3: 6,7,8

CSCT
m] ^

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September 3, 2009

Dr. Kamaii Martin
Dept.of Oral & Maxillofacial Surgery
School of Dental Sciences
University of Nairobi

Dear Dr. Kamau

RESEARCH PROPOSAL: "CLINICO-HISTOPATHOLOGIC TYPES OF MAXILLOFACIAL SARCOMAS: A_10 YEAR REVIEW" (P170/6/2009)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and approved your above revised research proposal for the period 3ld September 2009-2nd September 2010.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form pari of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF. C.S. KIGONDU
AG. SECRETARY, KNH/UON-ERC

c.c. The Chairperson, KNH/UON-ERC
The Deputy Director CS, KNH
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