SURVIVAL OF PATIENTS WITH KAPOSI SARCOMA AT OCEAN ROAD CANCER INSTITUTE; A RETROSPECTIVE STUDY

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MMed (Clinical Oncology) Dissertation
Muhimbili University of Health and Allied Sciences
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By

Halfani Chakou, MD

A Dissertation Submitted in partial Fulfillment of the Requirement for the Degree of Master of Medicine (Clinical Oncology) of the Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that he has read and hereby recommend for acceptance of dissertation entitled "**Survival of patients with Kaposi sarcoma at ocean road cancer institute; a retrospective study"**, in fulfillment of the Requirement for the Master Degree of Medicine in Clinical Oncology of Muhimbili University of Health and Allied Sciences.

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Dr. Khamza Maunda

(Supervisor)

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Date

DECLARATION AND COPYRIGHT

I, Chakou Halfani, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

Signature……. Date……..

DEDICATION

This dissertation is dedicated to

My beloved wife Beatrice Chao,

My daughter Brenda Chakou

My Son Baingana Chakou

And my dear sisters Sumbuo Halfani and Chuki Halfani

Without them life means nothing to me.

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Head Cancer Prevention & Coordinator of Training-ORCI & MUHAS
My Teacher and Supervisor

Beatrice Chao
My Dear Wife

ABSTRACT

Background

Kaposi sarcoma (KS) is a vascular endothelia tumor caused by HH8 facilitated by immune suppression either by organ transplant treatment or AIDS. KS is the most common type of all cancers in HIV-AIDS patients and second most prevalent of all cancer at ORCI. ORCI receives patients with endemic and epidemic KS; however most patients with KS are HIV positive, but the difference in characteristics between these diseases in terms of disease profile, patients' characteristics, their prognosis and response to treatment modalities is not known leading to hindrance in provision of quality care and improving survival of the KS patients attending ORCI.

Objective and Methodology

The purpose of this study was to determine the overall survival and interaction of its determinants for patients with KS attending ORCI. Retrospective descriptive study, using structured questionnaire, data extracted from KS patients treated at ORCI in 2006. Descriptive, Bi-variate Analysis, Ordinal Regression, Life Tables and Kaplan Meier survival analysis as well as SPSS 16.0 and Log rants validity test were used during data analysis.

Results

Mean age at KS diagnosis was found to be 40 ± 12.012 years, male diagnosed with KS older than female with mean age at diagnosis being 42.60 ± 12.6 and 35.1 ± 9.7years respectively. Average duration patients wait after diagnosis before the start of treatment was found to be 30 ± 120 days. Dar es Salaam, 49.7% contributed the largest proportion of patients seen at ORCI. Male are more affected by KS with a ratio of 1.6:1 than female while radiotherapy found to be most preferred modality of treatment, 82% of all patients compared with 38.6% treated by chemotherapy. Skin was the most common mode of presentation seen on 87.3% of all patients. Median and average survival of KS patients

were found to be 8 ± 0.613 months and 15.863 ± 1.407 months respectively. Primary organ of presentation and patient residence has shown significantly to influence survival while age, sex, treatment modality, hemoglobin level, time taken waiting for treatments found to be survival predictors, serum white cell counts, and modality of treatment or treatment compliance has not proved to influence survival. HIV still found to be major cofactor with about 90% of tested KS patients had infected with HIV.

Conclusion

Overall and median survival of patients with KS treated at ORCI was significantly low compared to other parts of the world; this has been contributed by factors stipulated in this study and possible differences in disease profile of patients seen at ORCI compared with other settings. Prospective studies are advised to sharpen our knowledge on this interaction as well as exerting more effort in treating KS patient early after diagnosis and joining CTC and cancer care for better outcome.

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LIST OF ABBREVIATIONS

ACTG	AIDS Clinical Trial Group
AIDS	Acquired Immunodeficiency Syndrome
DNA	Deoxyribo Nucleic Acid
EKS	Epidemic Kaposi Sarcoma
HAART	Highly Active Anti Retroviral Drugs
HHV8	Human Herpes Virus 8
HIV	Human Immunodefiency Virus
KPS	Kanofsky Performance Status
KS	Kaposi Sarcoma
LTF	Loss of Follow-up
MUHAS	Muhimbili University of Health and Allied Sciences
ORCI	Ocean Road Cancer Institute
RT	Radiotherapy
TNM	Tumor, Nodal status, Metastasis
WHO	World Health Organization
CTC	Clinic for treatment and care for AIDS
KSHV	Kaposi Sarcoma Herpes Virus
SD	Standard Deviation
PITC	Provider Initiated Testing and Counseling

CHAPTER ONE

1. INTRODUCTION

1.1 Background

Kaposi sarcoma was described initially in 1872 by a Hungarian dermatologist, Moritz Kaposi(1). Kaposi sarcoma is a spindle-cell tumor thought to be derived from excessive proliferation of spindle cells thought to have an endothelial cell origin(2),(3). Despite their heterogeneity, the tumors are predominantly composed of KSHV genomic material with immunohistochemical markers of both lymphoid, spindle, and endothelial cells. Although the cell of origin is still unknown, increased endothelial factor VIIIa antigen, spindle cell markers such as smooth muscle alpha-actin, and macrophage markers such as PAM-1, CD68, and CD14 expressed by these spindle cells have been observed. This suggests a pluripotent mesenchymal progenitor. The spindle cells proliferate in a background of reticular fibers, collagen and mononuclear cells including macrophages, lymphocytes and plasma cells. They tend to be vascular involving in either the reticular dermis (patch stage) or the entire thickness of the dermis (plaque or nodular stage).

Human herpes virus 8 (HHV-8) genomic sequences have been identified by polymerase chain reaction in more than 90% of all types of Kaposi sarcoma lesions (including epidemic and endemic forms), suggesting a causative role for this DNA virus(4). The current working hypothesis is that HHV-8 must be present for the disease to develop. It is transmitted in saliva. Blood-borne transmission has yet to be proved. HIV significantly increases the risk of immune suppression.

KS can be primarily categorized into four types(5):

Epidemic AIDS-related KS,

This entity occurs in patients with advanced HIV infection and is the most common presentation of KS. It is the most common malignancy seen in HIV-infected patients, especially where access to highly active antiretroviral therapy (HAART) is limited. The presence of decreased CD4 counts and increased HIV-1 viral loads are independent prognostic factors in the development of epidemic KS.

Immunocompromised KS,

Is an entity usually occurs following solid-organ transplantation or in patients receiving immunosuppressive therapy. The incidence of Kaposi sarcoma is increased 100-fold in transplant patients (6), compared to general population.However, individuals with congenital immunodeficient states are not at increased risk for developing KS.

Classic (sporadic) KS

Is an entity typically occurs primarily in elderly men of Mediterranean and Eastern European background. It has a male predominance with a male-to-female ratio of 10-15:1. The age of onset is between 50 and 70 years.Classic Kaposi sarcoma usually carries a protracted and indolent course. Common complications include venous stasis and lymphedema. As many as 30% of patients with classic KS subsequently may develop a second malignancy, typically a non-Hodgkin lymphoma(7).

Endemic African KS

Is an entity usually occurs primarily in men but also in women and children who are HIV seronegative in Africa andmay an indolent or aggressive course. It was relatively uncommon before the AIDS epidemic. Since the advent of AIDS, it has increased about 20-fold in the African countries of Malawi, Swaziland, Uganda, Zambia, and Zimbabwe(8).

Clinical presentation of KS varies widely. AIDS-related KS carries a variable clinical course ranging from minimal mucocutaneous disease to widespread organ involvement. The lesions may involve the skin, oral mucosa, lymph nodes, and visceral organs. Most patients present with cutaneous disease while visceral disease may occasionally precede cutaneous manifestations. Classic Kaposi sarcoma has a more indolent course of 10-15 years or more with very gradual enlargement of cutaneous lesions and development over years of new ones. These lesions result in venous stasis and lymphedema of the lower extremities. Visceral lesions occur in the GI tract, lymph nodes, and other organs but are usually incidental findings at autopsy. The brain is usually spared.

Diagnosis of KS is done by histological examination of the tissue biopsy from suspected lesion of a patient with typical findings that includes proliferation of spindle cells, prominent slitlike vascular spaces, and extravasated red blood cells. Other investigation are done to evaluate disease profile, fitness for the treatment, and to provide hallmark for further disease monitoring. For HIV patients' viral load and CD4 counts are important investigations.

The staging of KS does not fall under normal TNM classification. There is no clearly accepted mode of classification. However, ACTG classify KS into poor or good risk category depending on immune status, KPS performance, presence of systemic illness and burden of disease.

Treatment of KS usually depends on presentation and stage of the disease; it can be surgery, RT, chemotherapy, cryotherapy, HAART for HIV positive patients or combination therapy.

1.2 Literature Review

KS was initially described as an uncommon tumor among elderly Mediterranean men, and subsequently reported among African children in the 1960s(6).The association with immunodeficiency was first reported in patients undergoing solid organ transplantation(9), but in 1981, an epidemic of KS among young men that have sex with men in the United States served as the harbinger of a new immunodeficiency syndrome, subsequently identified as being caused by HIV(10). As the HIV epidemic progressed, KS was found almost exclusively among men that have sex with men (10).

Nowadays, Kaposi sarcoma is a multidisciplinary condition, not only observed by dermatologists. Since the HIV epidemic in the 80s and 90s of the last century, more insight into the etiology of Kaposi sarcoma has been acquired. With the onset of the HIV/AIDS epidemic, KS can occur at any age group from infancy to elderly. Case report of a more aggressive, disseminated type of KS was diagnosed in a 6-month-old infant in Tanzania(11).Characteristics of KS have shown some differences prior and after the HIV/AIDS (12). AIDS infected children younger than 5 years are at high risk for developing KS, possibly reflecting low resistance to human herpesvirus (HHV) 8 infection (13). It is also likely that an increased susceptibility to HHV8 infection and morbidity is related to progressive immunodeficiency. Recognition of the high KS risk in small children warrants considerations of possible prevention measures including HIV/HHV8 vaccination and therapeutic options. The mean age in males decreased from 44.9 to 37.2 years for the periods of 1980-82 and 1990-92 respectively with no significant change in mean age that was observed in females. Gender distribution has altered significantly: the post-AIDS era studies recorded a male-female ratio of 2.6:1 compared with that of the pre-AIDS era 1980-82 studies which was 4:1. Phypps et al & Wambura et al studies have shown that gender differences influences clinical presentation and response of KS between men and women, thus suggesting that gender affects the pathophysiology of KS, which may have implications for the prevention, diagnosis, and treatment of KS in both men and women(15)(16).

HIV-1 infection is a potential cofactor of KS(14), this highlight the possibilities of change of patient demographic characteristics and disease profile and therefore ongoing studies are critical to ensure good provisions of care to patients and control of the disease in general.

Huang KM et al (2006) in Taiwan demonstrated that treatment of endemic KS with radiotherapy alone was safe and effective(17), Treatment for immunosuppressive associated KS is based on withdraw of immunosuppressive agent, radiotherapy for cutenously localized disease but the benefit of chemotherapy has not been demonstrated (18). In AIDS related KS, HAART is significant in improving survival and controlling progression of the diseases(19).

Urassa et al in Dar es Salaam (1998) found that 50% of EKS lesions were of nodular type. Patients with EKS had significantly lower levels of CD4+ T- lymphocytes and CD4:CD8 ratio but significantly higher CD8+ T-lymphocytes compared to controls. Patients with AKS had significantly lower levels of CD4+ T-lymphocytes and also CD4:CD8 ratios but significantly higher percentage of CD8+ T-lymphocytes when compared with EKS patients. These findings indicate that in both forms of KS there is a certain degree of immunological disturbance which is more conspicuous in AKS because of HIV infection and suggests that HIV-1 acts synergistically with the aetiological agent (HHV-8) to cause a more aggressive type of KS(20).

Agaba PA et al (2009)in Jos Nigeria and his colleague studied presentation and survival of AIDS related KS and found that, they were similar with pre-mentioned studies in age and body mass index profile but patients with AIDS-KS had more tuberculosis co-infection, lower median CD4 count and higher mortality. Surprisingly, patients with AIDS-KS had lower levels of median viral load (29,347 copies/mL) compared with controls (80,533 copies/mL)(21).

Stebbing J et al. (2006) studied factors that affect survival of patients with AIDS associated KS and concluded that;patients having Kaposi's sarcoma as the AIDS-defining illness, CD4 counts lower than 200 cells per microlitre of blood, age above 50 and having another AIDS-associated illness at the same time have poorer prognosis compared to opposite group(22).

Rutherford et al (1990) studied survival following diagnosis of Kaposi's sarcoma for AIDS patients in San Francisco and found that, the median survival time was 17 months for patients diagnosed with KS alone, with a five-year survival rate of 8.7 percent. Predictors of survival were age and year of diagnosis. Decreased survival rates were seen with increasing age at time of diagnosis. Survival was longer for patients diagnosed in the earlier years of the study (1981 to 1983) compared with those diagnosed in 1984 or later. Race or ethnicity and risk group were not found to be predictors of survival rate in KS patients(23).

S. Franceschil et al (1996) studied survival of classic Kaposi's sarcoma and found that, 1, 5 and 10 year survival rates were 0.92, 0.69 and 0.46 respectively. Median survival was 9.4 years (i.e. not different from the study areas general population of the same sex and age), and also survival did not vary according to sex and tumour site (i.e. lower limbs only or other)(24).

After reviewing studies that have been conducted locally and internationally it’s became clear that; studies to identify correlation/interplay between disease profile, patient demographic features, treatment modalities and overall survival were lacking in our settings; as well as these factors and their interaction are continually changing with time worldwide that we could no longer rely on conclusions from previous studies. This study therefore contributed vital information so as to improve our knowledge, compare our situation with findings of other parts of the world and help us improve the survival of KS patients.

1.3 Problem statement

KS is the most common type of cancer in HIV-AIDS patients attending ORCI. It is the second most prevalent of all cancer at ORCI. KS worsens the prognosis of HIV patients and its presence mark advanced HIV diseases, WHO stage four. Currently there is no valuable information regarding disease profile, social demographic features of KS patients or determinant factors for their survival. However the situation is very critical to the extent that there is no agreeable modality of treatment which has been shown to be successful in improving the survival of KS patients in our setting. Therefore patients are allocated to chemotherapy, RT, or surgery in absence of evidence based protocols.

ORCI receives patients with endemic and epidemic KS; however most of patients with KS are HIV positive, but the different in characteristics between these diseases in term of disease profile, patients' characteristics, their prognosis and response to treatment modalities is not known leading to hindrance in provision of quality care and improving survival of patients with KS attending ORCI.

Number of patients with KS attending ORCI increases annually, among other factors this may be due to increased knowledge of the population about the disease, improve in infrastructure that allows patients from the remote areas to reach ORCI, improvement of the referral system, rise of KS incidence and aging of the population due to increased life expectancy. The rise of KS incidence in absence of crucial information is a set-back to our fight against KS.

Commonest site of KS involvement are lower limbs, often complicated by severe lymphoedema that can be unilateral or bilateral. This interferes with quality of life and performance which eventually contribute to economic retardation of individual patient, his/her family, country and world at large. Other forms of visceral presentation usually are associated with poorer prognosis.

Limited resources are allocated to care and treatment of cancer in our third world countries. The effective and appropriate use of these resources in provision of care to KS patients depends solely on evidence based treatments. The lack of these studies as pointed out in literature review clearly elaborated the problem we were facing and needs immediate solution.

1.4 Rationale

Tanzania is a third world country that is experiencing tremendous increases in incidence of KS especially EKS due to high prevalence of HIV/AIDS which impair immunity and finally leading to development of KS. This highlighted the need of further studies to characterize the disease and find best treatment options

Knowing survival of patients with KS and their determinants is critical to the success of the fight against KS and its associated morbidity. This study was expected to provide characteristics of patients with KS attending our setting in term of disease profile, social demographic characteristics and immune status and therefore aid to create targets in term of health education, treatment and capacity building. By understanding KS survival determinants it was expected that more efforts will be allocated proportional to the degree of detrimental contribution of determinants to overall survival.

Absence of scientific studies in relation to interaction between the survivals of KS, with modality of treatment, immune status, disease profile and patient demographic characteristics in our setting clearly underlined the need of this study so as to increase our knowledge about KS and improve the prognosis and quality of life.

1.4. Objectives, Expected Outcomes & Hypothesis

1.4.1. General Objective

To determine overall survival of patients with Kaposi Sarcoma at ORCI for the period of 2006-2011

1.4.2. Specific Objectives

1. To determine social demographic characteristics and disease profile of patients with KS attending ORCI
2. To determine immune status at diagnosis of patients with KS attending ORCI
3. To determine modality of treatment of patients with KS attending ORCI
4. To determine overall survival of patients with KS attending ORCI.
5. To determine the relationship between social demographic characteristics, disease profile, immune status, modality of treatment and overall survival of patients with KS attending ORCI.

1.4.3. Outcome

Five years survival and factors affecting overall survival is known. For fixed factors such as age and sex clinicians shall use appropriate aggressiveness in their treatment and monitoring, while for modifiable factors such treatment modalities can be manipulated efficiently. Areas that need further studies are highlighted so as to improve quality of a care and overall survival of patient with KS in our settings.

CHAPTER TWO

2. METHODOLOGY

2.1 Study Design

Retrospective descriptive study, using KS patient files treated at ORCI in 2006.

2.2 Study setting

The study was conducted at ORCI, the only cancer treatment centre in Tanzania. All patients with cancer countrywide are referred to ORCI for evaluation and treatment. Tanzania has no national cancer registry, therefore ORCI cancer registry is expected to provide a reflection of KS cases of Tanzania in 2006; however some patients may be LTF due to go overseas or poor treatment/follow-up clinics compliance or have left the country.

Most of patients attended ORCI must have printed and signed histology results confirming the histological type of cancer. The patient was then registered in new case register book, where patient details such as serial number, name of patient, date of birth, type of cancer and residence are documented. After registration, a file opened for the patient where all information about consultation, treatment and follow-up documented.

2.3 Study population

Included all age groups; male and female patients that attended ORCI with KS in 2006.

2.3.1. Inclusion criteria

All KS patients with attached histology results or clinically diagnosed that attended ORCI and first diagnosed with KS in 2006

2.3.2. Exclusion criteria

KS Patients without adequate information in the file to provide the needed endpoints or hasn’t attended/diagnosed with ORCI in 2006.

2.4 Endpoints

Each patient followed for five years. The end points of these study was death, **LFP** or **alive**. All deaths certified by medical doctor in the patient file or reported by next of kin via mobile phone communication with principle investigator using information provided in the file. LFP if the patient did not attend arranged follow-up and his live/death status could not be retrieved by any means. Alive if the patient was alive at last time when was seen by doctor at follow-up clinic or after contacts to his/her next of kin.

2.5 Sample size

Patients with KS attended at ORCI in 2006 and meets inclusion criteria included in the study. Sample size calculated based on statistical method suggested by J. H. Abramson (25). The following information is used to determine the sample size required for this study.

Level of Significance 5%

Power 80%

Median survival time for classic KS patients' is9.4 years (24)

Median survival time for epidemic KS is 17 months (23)

Time to start entry of the last subject is 60 months

Follow-up period of the last subject is 12 months

Allow non inclusion criteria of 10% of subjects

N = Sample size = 166.

Therefore a sample size of 166 needed for this study. 189 people included in the study to compensate for LTF.

2.6 Sampling method

KS patients registered at ORCI in 2006 used in preference to other years due to the fact that this is the most recent year for study that needs five years of patient follow-up. Bearing in mind the difficulties in data recording, compiling and storage in our settings, 2006 patient information was more likely to be retrievable and of reasonable quality for coming with true scientific conclusions than any other year that may be taken.

2.7 Data collection

Data collected using preformed questionnaires attached in appendix-1 and patient information extracted from 2006 ORCI patient registration book and patient files. Data were checked for completeness and accuracy using epidata software.

2.8 Informed consent

Informed consent from the patient was impractical and unnecessary based on nature of study and patient availability, however consent from data handlers was taken as their cooperation in this study was vital.

2.9 Legal permission

Permission to conduct the study at the ORCI and the use of patient files obtained from the authority of ORCI.

Using new case register, KS patient was selected, their files retrieved and their information necessary to accomplish this study such as their disease profile, social demographic features, immune status and modality of treatment filled on patient data sheets/questionnaire. The patient's next of kin was contacted as necessary through mobile phones for missing information using contacts provided in the files. However very few numbers were reachable and next of kin provided required cooperation.

2.10 Ethical clearance

Ethical clearance was obtained from the Ethics Committee of MUHAS. Permission from Executive Director ORCI also Head of Clinical Oncology Departments MUHAS to look into the files obtained. Consent from ORCI data handling staffs to provide files and appropriate assistance during data collections also obtained.

2.11 Data analysis

Descriptive, multivariate analysis and ordinal regression methods were used for data analysis. Data entered and analyzed using the SPSS 16.0 software. Log rants test and Kaplan Meyer methods used to test the null hypothesis and analyzing how different factors affecting KS survival respectively. Confidence interval of 95% and p-value as

the index for the null hypothesis was applied, $p < 0.05$ of the observed outcome regarded as statistically significant.

2.12 Study limitations

Incomplete data due to poor record keeping is among important drawback in this study as most other retrospective studies in developing countries were enough resources are not in place for collection, handling and storage of clinical data. Important data such as marital status, information on B symptoms, cancer stage, CD4 levels, Viral Load and etc were missing in most of the patient's files. However it's my hope that information retrieved is adequate to meet study objectives.

CHAPTER THREE

3. RESULTS

In 2006 a total of about 256 KS patients attended ORCI. Among them 67 patients has significantly incomplete data in their files, therefore only 189 patients whose data met the objectives of this study were available has been included into the study, these patients are adequate bearing in mind that the calculated sample size needed to provide reliable results were 166 patients.

3.1 Social Demographic Characteristics

Males (60.8%) were more affected than females. The mean patient age at diagnosis found to be 40 years old, SD 10.012, while the youngest and oldest ages diagnosed with KS is 5 years old and 76 years old respectively. Male KS patient's population is older than female population with mean age at diagnosis with their respective SD being 42.60 SD 12.6 and 35.1 SD 9.7 years respectively.

Table 1: Shows socio-demographic characteristics of patients diagnosed with KS at ORCI (N-189)

Variable	*Category*	*Frequency*	*Percentage (%)*
Age in Years	0-5	1	0.5
	6-18	1	0.5
	19-45	141	74.6
	>45	46	24.3
Sex	Male	115	60.8
	Female	74	39.2
Residence	Dar es Salaam	94	49.7
	Zanzibar	1	0.5
	Mainland Regions	89	47.1
	Outside Tanzania	5	2.6

3.2 Disease Profile

Patients attended ORCI in 2006 showed extensive diversity in term of their disease characteristics. Cancer diagnosis always needs confirmation by histolopathological investigation. However it has been seen that only 63% of patients were diagnosed via histology while significant proportion of them, 37% started either chemotherapy or radiotherapy just by clinical diagnosis.

Start of treatment after KS diagnosis was significantly delayed with mean duration of 30 ± 120.313 days between KS diagnosis to start of treatment

Average hemoglobin among patients was 10.04g/dl, SD 2.3. 3.7% of the patients had moderate to severe anemia requiring blood transfusion before start of their treatment. Male patients were averagely less anemic than female patients with mean serum hemoglobin level being, 10.35 g/dl, SD 2.28 and 9.57 g/dl, SD 2.24 respectively.

Table 2: Shows disease profile of patients with KS attended ORCI (N=189)

Variable	*Category*	*Frequency*	*Percentage (%)*
Duration from Diagnosis to Start of Treatment in Days	0-7	107	56.6
	8-30	53	28
	31-90	19	10.1
	>90	10	5.3
Presenting Location	Skin	165	87.3
	Oral Cavity	23	12.2
	Visceral	1	0.5
Serum WBC Level	0-3.4	39	20.6
	3.5-11	142	75.1
	>11	8	4.2
Serum Neutrophils Level	0-1.9	74	39.2
	2-7.5	110	58.2
	>7.5	5	2.6
Serum Lymphocytes Level	0-0.9	33	17.5
	1-3.5	146	77.2
	>3.5	10	5.3
Serum Platelet Level	0-149	29	15.3
	150-400	133	70.4
	>400	27	14.3
Serum Hemoglobin Level	0-11.5	142	75.1
	11.6-16.7	47	24.9

3.3 Treatment Modalities

All 189 patients included into this study either received one of the treatment options at ORCI or both. Treatments options available at ORCI for KS patients are chemotherapy, radiotherapy or both. Chemotherapy was used either as a single agent such as Vincristine or Epirubicin; or combination chemotherapy such as ABV (Adriamycin, Bleomycin and Vincristine). For radiotherapy, only EBR was given as a single fraction dose in most circumstances. Treatment intent was palliative and radiotherapy was repeated up to five (5) times in symptomatic palliations to patients.

About 18% of patients treated by chemotherapy as a sole modality of treatment, 60.8% treated by radiotherapy alone while 21.2% treated by both radiotherapy and chemotherapy in a combined approach.

The frequency distribution of chemotherapy treatments is shown in the table 2. It is important to note that chemotherapy compliance was very poor among KS patients treated ORCI 2006.

Table 3: Shows treatment modalities among patients with KS treated ORCI (N=189)

Variable Category	*Frequency*	*Percentage (%)*
Chemotherapy Use Yes	74	38.6
No	116	61.4
Radiation Use Yes	155	82.0
No	34	18.0
ART Use Yes	117	61.9
No	72	38.1
Type of Chemotherapy Used Epirubicin	10	5.3
Vincristine	30	15.9
ABV/AEV	32	16.9
Others	2	1.1
No	115	60.8
Number of Chemotherapy Cycles Received 0	115	60.8
1	13	6.9
2	7	3.7
3	4	2.1
4	4	2.1
5	8	4.2
≥6	38	20.1
Number of Radiotherapy Session 0	34	18.0
1	87	46.0
2	50	26.5
3	13	6.9
4	3	1.6
5	2	1.1

3.4 Immune Status

Unfortunately no CD4 data could be retrieved in the file as patients were not routinely tested for CD4 at that time. Significant proportions of patients were also not tested for HIV as table 4 stipulates.

Table 4: Showing distribution of HIV/AIDS status among patients with KS treated ORCI. (N=189)

Variable	*Category*	*Frequency*	*Percentage (%)*
HIV Status	Positive	151	79.9
	Negative	15	7.9
	Unknown	23	12.2

Among HIV positive patients, 77.5% were already on ART before the diagnosis of KS.

Less HIV positive patients (80.1%) received radiotherapy, compared to HIV negative patients (86.7%). However most of HIV positive patients (86.5%) received chemotherapy compared to HIV negative patients (4.1%).

3.5 Overall Survival

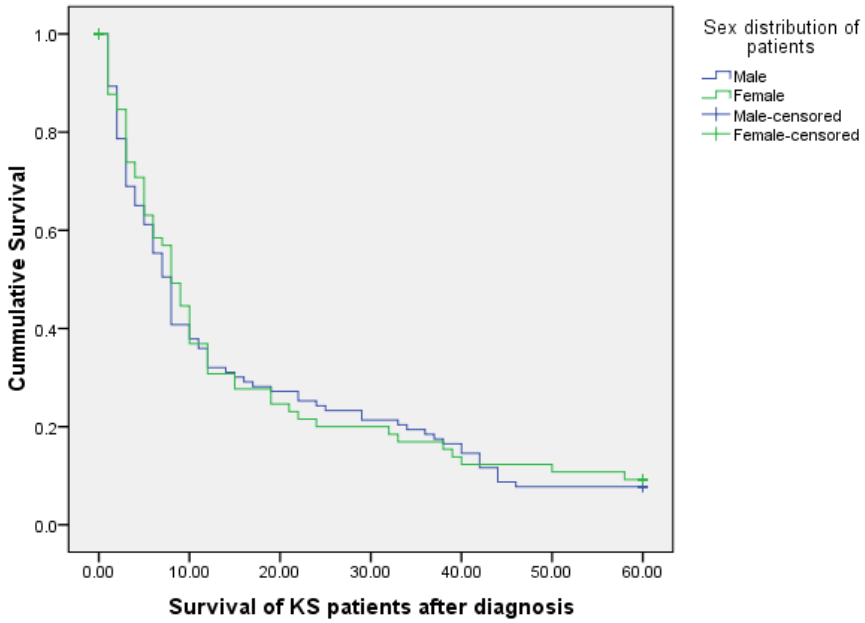
Overall median survival of KS found to be 8 ± 0.613 months while mean survival of 15.863 ± 1.407 months after diagnosis. Patients that were either lost to follow-up or died within the first three (3) months after diagnosis were 37%. 22% of patients either died between the periods of six month to one year while only 38% of the KS patients lived beyond one year after diagnosis. Despite these figures there are still a minority of patients, 8.5%, were alive after four (4) years following diagnosis and five years survival rate was 7.4%.

3.6 Factors influencing Survival of KS patients treated ORCI.

3.6.1 Sex

Male has median and mean survival of 8 ± 0.665 months and 16.015 ± 1.782 months, compared to 8 ± 1.008 months and 15.767 ± 2.291 months of females' respectively. Male one year and two years survival was 28.6% and 21.7% compared to 27% and 17.6% of female, while overall five years survival of female was 8.1% and male 7%. However the elaborated insignificant overall survival differences in short and long term is shown in detail by figure 1 (p-0.795).

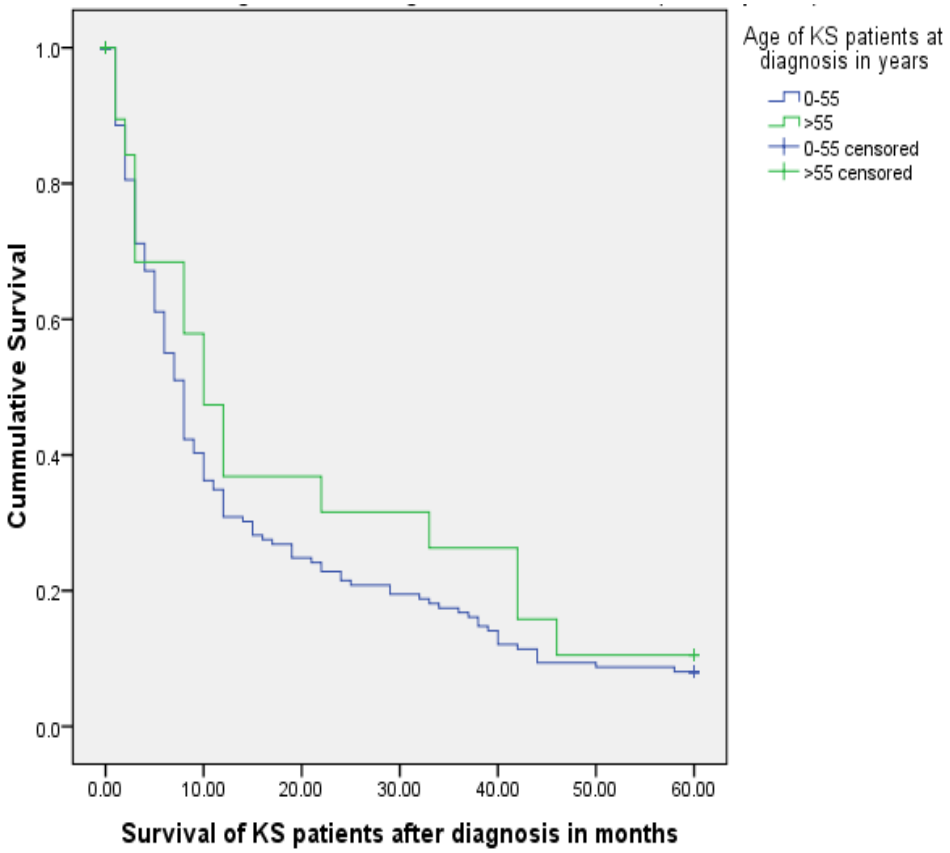
Figure 1: Effects of sex on survival of KS patients (95% CI, p-0.795)



3.6.2 Age

Patients between 0-55 years old has less mean and median survivals of 15.349 ± 1.470 months and 8 ± 0.635 months, compared to patients above 55 years old with mean and median survivals of 19.895 ± 4.572 and 10.00 ± 2.176 months respectively. Elderly patients seems to have favorable survival compared to young patients, however the results are not statistically significant (p-0.330).

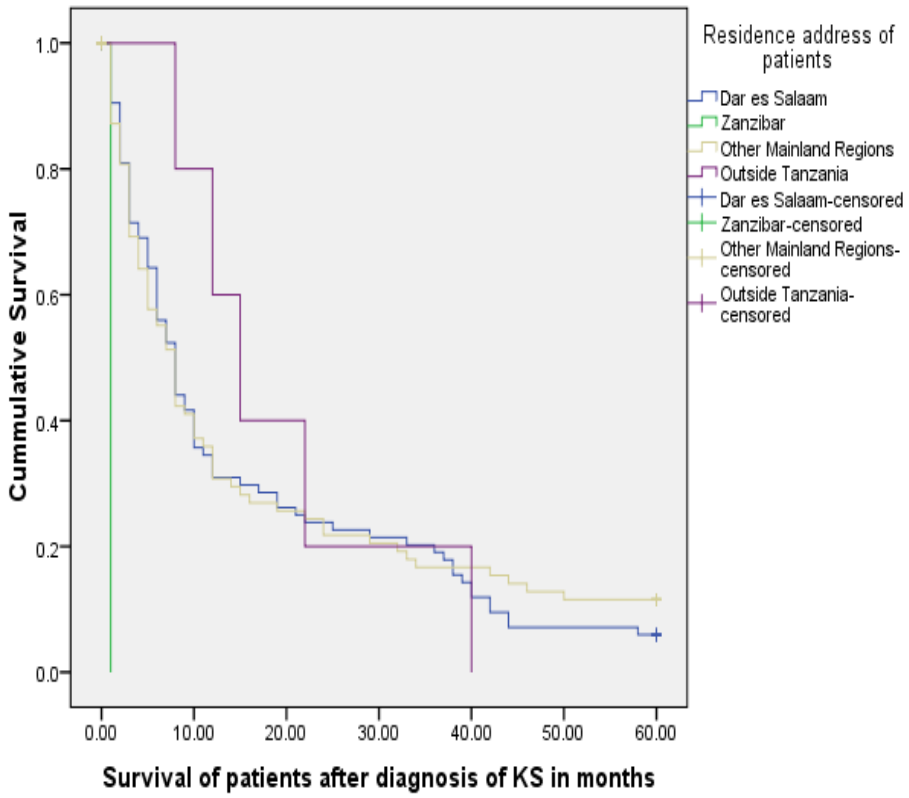
Figure 2: Effects of age at time of diagnosis of KS on survival (95% CI, p-0.330)



3.6.3 Residence

Mean survival of patients from Dar Es Salaam, Tanzania Mainland and Outside Tanzania are 15.571 ± 1.908, 16.141 ± 2.192, 19.400 ± 5.636 months respectively. Surprisingly median survival of patients from Dar Es Salaam and Tanzania Mainland were the same about 8.00 ± 0.910 months and quit significantly less compared to median survival of KS patients (15.00 ± 3.286 months) from outside Tanzania. Generally there are little differences in term of survival of KS patients from Tanzania, while those outside the country have significantly better short term survival (p-0.040).

Figure 3: Effects of residence on survival of KS patients (95% CI, p-0.040)

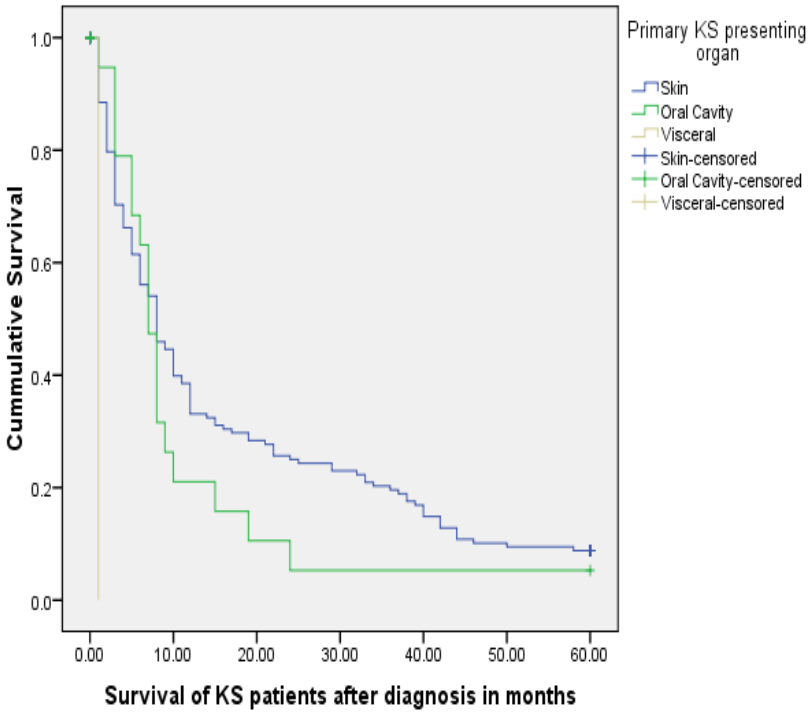


3.6.4 Primary Presenting Organ

Primary presenting organ found to affect survival of the patients dramatically (p-0.012). Visceral had worst prognosis with mean and median survival of 1 ± 0 months. Skin has good prognosis with mean survival of 16.595 ± 2.939 months compared to 10.947 ± 1.540 months of oral cavity.

Patients with skin presentation at diagnosis had better two years survival of 22.4% compared with patients that presented with mucous membrane lesions who had 4.4% two years survival as figure 4 stipulates in detail.

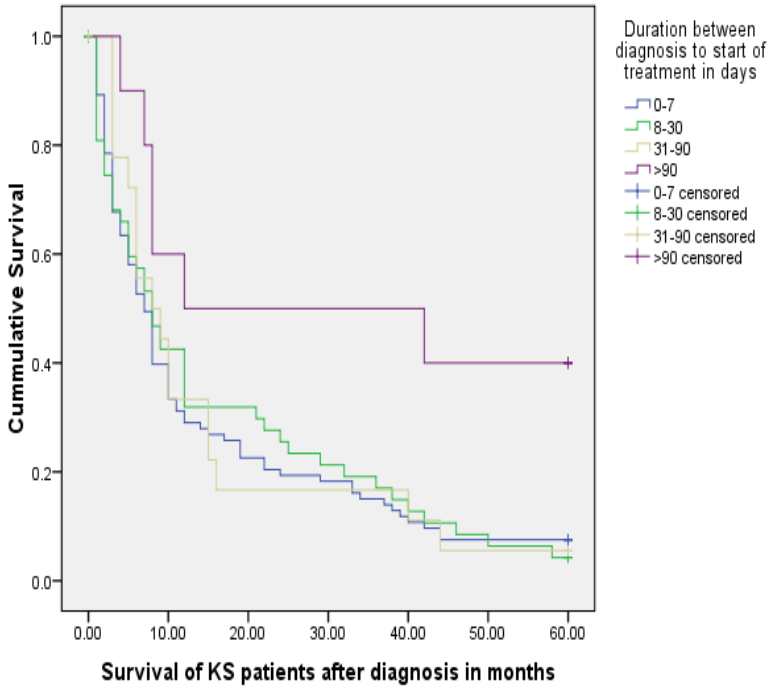
Figure 4: Effects of primary presenting organ to survival of KS (95% CI, p-0.012)



3.6.5 Duration between diagnosis and start of treatment

Surprisingly delay of starting treatment has shown to have insignificant survival advantage (p-0.077). Those who treated within 90 days after diagnosis has average survival of 15.912 ± 2.581months, while those treated more than 90 days after diagnosis has average survival of 32.100 ± 7.872 months.

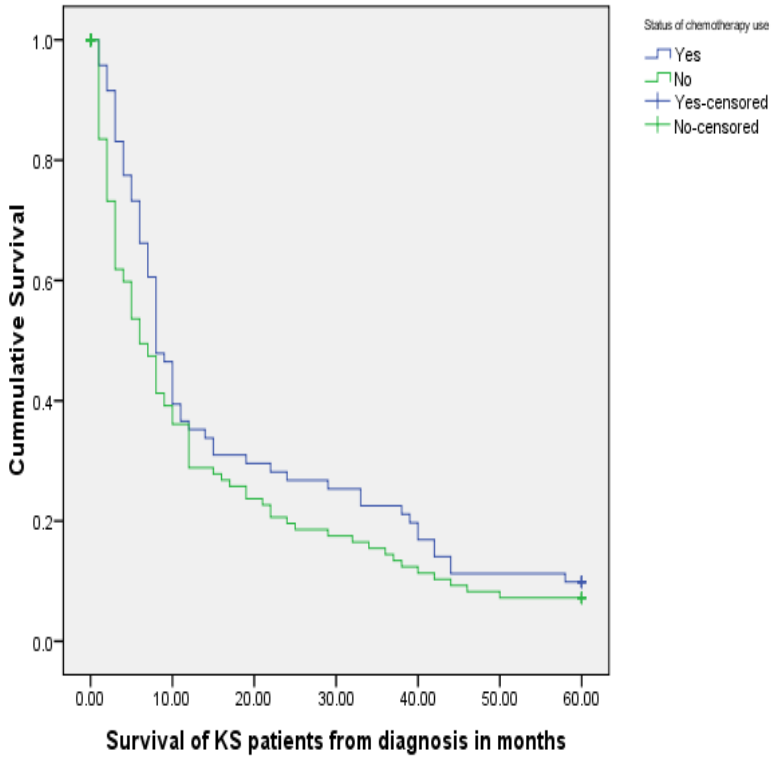
Figure 5: Effects of delaying treatment on survival of KS patients (95% CI, p-0.077)



3.6.6 Chemotherapy Usage

Chemotherapy was seen insignificantly (p-0.122) to improve both short and long-term survival of KS patients; with those that used chemotherapy having one, two and five year's survival of 34.3%, 26.1%, 9.6% compared with those who were not given chemotherapy, 24.2%, 16.4%, 6% respectively. Median survival of patients received chemotherapy were 8 ± 0.842 months, compared to 6 ± 1.094 months of those who didn't received chemotherapy. More details displayed in the figure 6.

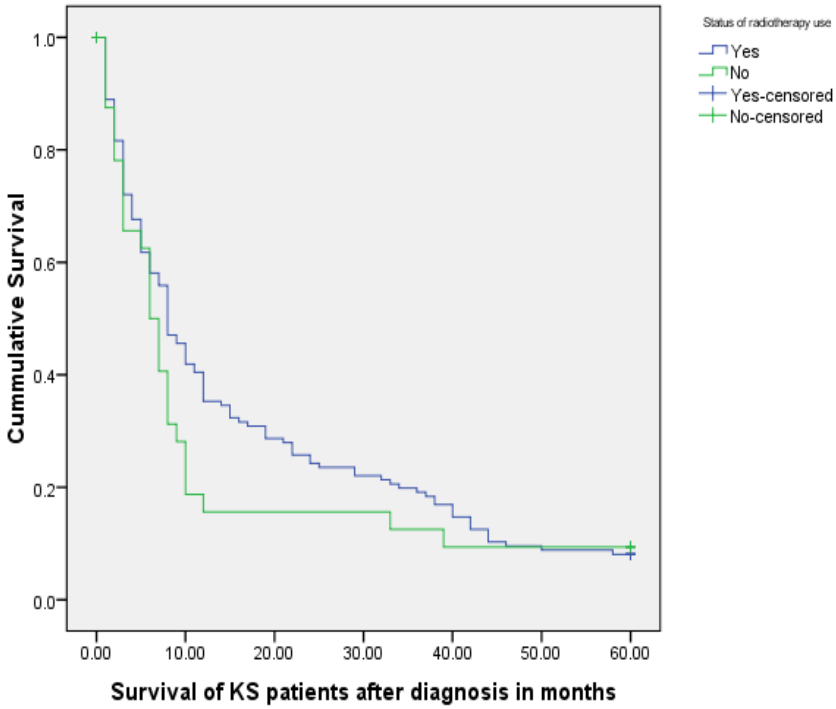
Figure 6: Effects of chemotherapy use on survival of KS patients (95% CI, p-0.112)



3.6.7 Radiotherapy Usage

Those treated by radiotherapy has average survival of 16.662 ± 1.575 months compared to 12.469 ± 3.049 months of those who did not recessive radiotherapy. Despite patients treated by radiotherapy having one and five years survival of 30.9% and 7.1% compared to those that did not received radiotherapy having 14.7% and 8.8% respectively, radiotherapy has not shown to influence survival of KS (p-0.272).

Figure 7: Effects of radiotherapy use on survival of KS patients (95% CI, p-0.272)



3.6.8 HIV Status

KS HIV infected patients has very low average and median survivals of 15.044 ± 1.547 months and 8.000 ± 0.714 months compared to uninfected KS patients who had 29.462 ± 6.094 months and 33.000 ±10.785 months respectively. HIV infections seem insignificantly (p-0.057) to impair both short and long term survivals of KS patients as stipulated by figure 8.

Figure 8: Effects of HIV infection on the survival of KS patients (95% CI, p-0.057)

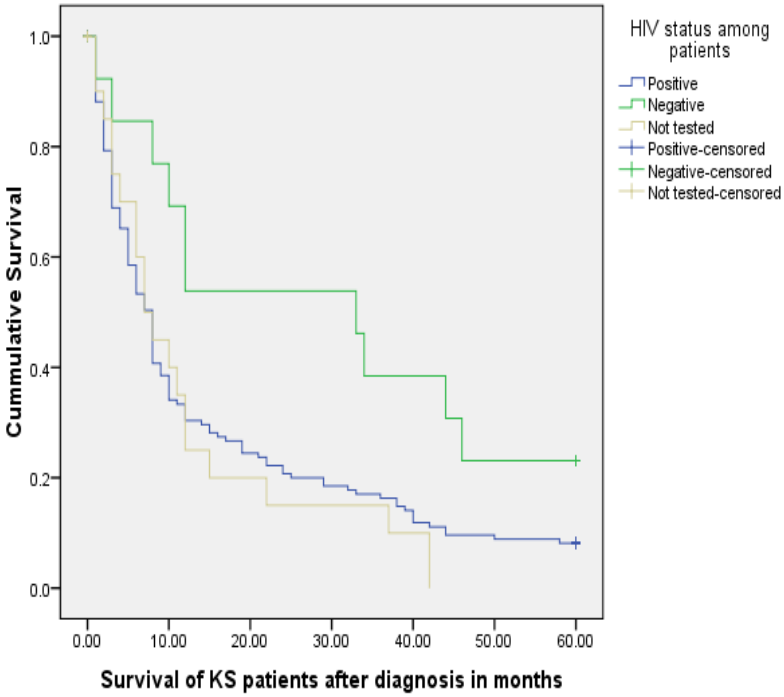


Table 5: Summarizing factors affecting survival of KS patients treated ORCI (N=189)

		Overall Survival in years			*P-Value*
Variable	***Category***	1	2	5	
Sex					
	Male	33 (28.7%)	25 (21.7%)	8 (7%)	0.795
	Female	20 (27%)	13 (17.6%)	6 (8.1%)	
Age in years	0-55	46 (27.5%)	32 (19.2%)	12 (7.2%)	
	>55	7 (32%)	6 (27.3%)	2 (9.1%)	0.330
Mode of Presentation					
	Skin	49 (29.7%)	37 (22.4%)	13 (7.9%)	0.012
	Oral cavity	4 (17.4%)	1 (4.3%)	1 (4.3%)	
	visceral	0	0	0	
Chemotherapy Use					
	Yes	26 (35.1%)	20 (27%)	7 (9.6%)	0.112
	No	27 (23.5%)	18 (15.7%)	7 (6%)	
Radiotherapy Use					
	Yes	48 (30.1%)	33 (21.3%)	11 (7.1%)	0.272
	No	5 (14.7%)	5 (14.7%)	3 (8.8%)	
HIV Status					
	Positive	41 (27.2%)	28 (18.5%)	11 (7.3%)	0.057
	Negative	7 (46.7%)	7 (46.7%)	3 (20%)	
	unknown	5 (21.7%)	3 (13%)	0	
ART Use					
	Yes	39 (33.3%)	27 (23%)	10 (8.5%)	0.752
	No	13 (19.5%)	10 (14.9)	4 (6%)	

Other factors such as type of chemotherapy, number of radiotherapy sessions, total white blood cells, leucocytes and lymphocytes serum levels had no statistically significant correlation with survival of the patients. Hemoglobin level seems to impair short term survival with no impact on long term survival such as patients with hemoglobin below 4mg/dl had 100% mortality within three months after diagnosis.

CHAPTER FOUR

4. DISCUSSION

KS is heavily linked with HIV as previous studies (10) (14) where up to 91% of tested patients were HIV positive. AIDS were seen to affect survival of KS patients as found by previous studies (21) (22), 46.7% and 18.5% were found to be 2 years survival of epidemic KS and classic KS respectively.1 and 5 years survival for classic KS was found to be 46.7% and 20% respectively, which is significantly lower compared to some previous studies such as S. Franceschil et al (1996) who found 1 and 5 years survival rates were 92% and 69% respectively. This might be attributed by late presentation of KS at ORCI settings or differences in disease profile of classic KS seen in Tanzania compared to the other parts of the world.

As found in some studies (15) conducted during this AIDS era, KS has shown to affect all age groups, however younger HIV positive patient of 5 years old, was diagnosed to have KS compared to previously reported in 6 years old (11). KS has also been seen in elderly male of 76 years old. Mean age at diagnosis was 40 ± 10.012 years for both sexes while for male raised from 37.2 years of 1990-92 to 42.60 ± 12.6 years and female has mean age of 35.1 ± 9.7 years. This improvement of age at diagnosis can be attributed by ART treatment as 77.5% of HIV positive patients were on ART. Male to female ratio were 1.6:1, compared to some post AIDS era studies which showed male to female ratio of 2.6:1 (15)(16).

This study showed significant proportional, 37% of patients diagnosed clinically despite guidelines that necessitates histopathological confirmation. This may results into patients without KS being unnecessarily treated.

The mean time from diagnosis to treatment at ORCI was 30 ± 120 days. This is very long duration bearing in mind that KS can progress so rapidly and change stage prior to

start of the treatment. Machine breakdown and long waiting time for investigation results are among the reasons for delay in starting the treatment.

KS patients attended ORCI shows extensive diversity in term of disease characteristics as seen in some other studies (21). Skin presentation especially lower limbs is most common mode of presentation, visceral caries the least frequent presentation however this also might be attributed by lack of facilities and pro-activeness in diagnosis of visceral KS in our settings as most of patients might be mislabeled to have PTB or other chronic illness. Mode of presentations influence survival with visceral caries the worst prognosis consistently with other studies (26).

Majority of patients had leucopenia, lymphopenia and neutropenia, however this has not shown to have any impact on survival, but profound low serum white blood cell level can make patients colonized by pathogens including normal flora that may have profound effect on quality of life of patients. Bearing in mind those KS treatments especially chemotherapy is myelosuppressive this high proportion of patients having impaired white cell counts prior to treatments pose significant possibility of exaggerating toxicity of treatment.

As in some previous studies (17), radiotherapy was mainstay of treatment modality with 82% of patients received radiotherapy. Radiotherapy was not seem to influence survival of KS compared to findings of C Huang K-M, Hsu C-H, Cheng JC-H, Lai M-K, Jeng S-C, Ting L-L, et al. In contrary to Maloba, Were Edward et al 2008, chemotherapy was seen insignificantly to improve both long term and short term survival. This insignificant correlation may be attributed to pronounced poor chemotherapy compliance shown by the study subjects. Bleomycin and Vincristine combination was not found to be superior over vincristine alone on influencing survival of KS, against previous studies (26).

Patient place of residence significantly affects survival, with those patients from other country has higher short term survival, with low long term survival compared to Tanzanians. This may be attributed by improved care at their home countries or confounded by good social economic status of these patients which make them afford to

move across borders to search for medical care and eventually has improved general health care and knowledge compared to other KS patients in the study.

Overall median and 5 years survival were significantly lower about 8 months and 7.4% compared to 17 months and 8.7% respectively found by Rutherford et al (2006). Predictors of survival were found to be patient place of residence and primary presenting organ as (26), while modality of treatment, age, sex, serum blood counts, HIV status and delay of starting treatment after diagnosis does not shown to affect survival.

CHAPTER FIVE

5.1. CONCLUSION

This study showed some similarities with other previous studies in term of social demographic features and disease profile. Males were still more affected by KS than females however the ratio has decreased to 1.6:1, compared to 2.6:1 found by Wambura et al and Phypps et al (15) (16). Large proportions of these patients have impaired blood cell levels with thrombocytopenia (15.3%), leucopenia (20.6%), neutropenia (39.2%), lymphopenia (17.5%) and anemia (74.1%). These deficiencies and especially that of hemoglobin can interfere with either effectiveness or toxicity of the treatment; and therefore blood products and antibiotics should be part and parcel in management of KS patients if better treatment outcomes are required.

Delay to start treatment after diagnosis with average duration of 30 ± 120.012 days, coupled by significant failure to complete treatment, especially chemotherapy where non compliance reaches up to 48.6% are among major setback factors that attributed great part to poor survival of patients seen in this study. Bearing in mind that these factors can be modified extensively, therefore the proper use of this study results will pave the way towards improving survival of our patients cost effectively.

HIV status is still a major cofactor, however significant numbers of patients, 12.2%, were not tested for HIV, and 22.5% of those HIV positive were not on ART, all these are against national guideline where all KS patients suppose to receive PITC and KS is AIDS defining illness that necessitate ART regardless of patient CD4 level. Bearing in mind that 1, 2 and 5 years survivals of HIV positive KS patients who were on ART was 33.3%, 23% and 8.5% compared to 19.5%, 14.9% and 6% of those HIV positive patients who were not on ART respectively, untested patients and those HIV positive who were not on ART could significantly lower overall survival of patients seen in this study.

Primary organ affected significantly influencing survival of KS, therefore extensive investigation to rule out visceral involvement before the start of treatment is required so as determine prognosis appropriately and start proper treatment option.

This study also found incomplete patient history taking, examination, investigation such absence CD4 counts, status of B symptoms, Performance status and etc; therefore highlight the need of continuous efforts for their implementation.

5.2. RECOMMENDATIONS

This study give way to the following recommendations in order to improve treatment and care of KS patients as well as facilitating future studies.

- Frequent internal CME should be conducted to doctors and nurses emphasizing to inclusion of HIV/AIDS counseling and testing as well as ART for all KS patients attending ORCI.
- All patients must be treated promptly after a histopathological diagnosis has been made; and using clinical diagnosis for cancer should be discouraged.
- ORCI should improve data storage practice so as to facilitate upcoming retrospective studies for betterment of patients, institution and scientific society in general.
- More prospective studies should be conducted to prove the interaction of survival and its predictors such as treatment modality and disease profile as well as to evaluate the courses of high rates of chemotherapy abscondement among patients
- Well structured health education should be given to every KS patient attending ORCI prior to treatment so as to improve treatment compliance and overall patient’s follow-up.
- Well structured consultation forms should be implemented so that important basic information about patient, disease and treatment modalities can be filled in so as to avoid missing information.

REFERENCES

1. van Kessel A, Quint KD. [Moritz Kaposi and his sarcoma]. Ned Tijdschr Geneeskd. 2011;155(45):A3879.

2. Gasperini P, Espigol-Frigole G, McCormick PJ, Salvucci O, Maric D, Uldrick TS, et al. Kaposi sarcoma herpesvirus promotes endothelial-to-mesenchymal transition through Notch-dependent signaling. Cancer Research [Internet]. 2012 Jan 11 [cited 2012 Feb 29]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/22237624

3. Clinical aspects and management of AIDS-related Kaposi's sarcoma. [Internet]. [cited 2012 Mar 1]. Available from: http://reference.medscape.com/medline/abstract/11423260

4. Dupuy S, Lambert M, Zucman D, Choukem S-P, Tognarelli S, Pages C, et al. Human Herpesvirus 8 (HHV8) sequentially shapes the NK cell repertoire during the course of asymptomatic infection and Kaposi sarcoma. PLoS Pathog. 2012 Jan;8(1):e1002486.

5. Kaposi Sarcoma [Internet]. [cited 2012 Mar 1]. Available from: http://emedicine.medscape.com/article/279734-overview#showall

6. Kaposi Sarcoma - Dana-Farber Cancer Institute [Internet]. [cited 2012 Feb 29]. Available from: http://www.dana-farber.org/Adult-Care/Treatment-and-Support/Kaposi-Sarcoma.aspx#Before_Treatment:Cancer_Summary

7. Kaposi's Sarcoma — NEJM [Internet]. [cited 2012 Mar 1]. Available from: http://www.nejm.org/doi/full/10.1056/NEJM200004063421407

8. Prevalence of human herpesvirus 8 infection before the acquired immunodeficiency disease syndrome-related epidemic of Kaposi's sarcoma in East Africa. [Internet]. [cited 2012 Mar 1]. Available from: http://reference.medscape.com/medline/abstract/10547397

9. Chen Y, Zhao L, Qiu S-P, He X. Kaposi sarcoma of the ureter after liver transplant: case report and literature review. Exp Clin Transplant. 2012 Feb;10(1):70–2.

10. Sullivan RJ, Pantanowitz L, Casper C, Stebbing J, Dezube BJ. Epidemiology, pathophysiology and treatment of Kaposi sarcoma-associated herpesvirus disease: Kaposi sarcoma, primary effusion lymphoma, and multicentric Castleman disease. Clin Infect Dis. 2008 Nov 1;47(9):1209–15.

11. Manji KP, Amir H, Maduhu IZ. Aggressive Kaposi's sarcoma in a 6-month-old African infant: case report and review of the literature. Trop. Med. Int. Health. 2000 Feb;5(2):85–7.

12. Epidemiology of Kaposi's sarcoma in Sweden prior to the acquired immunodeficiency syndrome - Dictor - 2006 - International Journal of Cancer - Wiley Online Library [Internet]. [cited 2012 Feb 29]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/ijc.2910420307/abstract?systemMessage=Wiley+Online+Library+will+be+disrupted+3+Mar+from+10-13+GMT+for+monthly+maintenance

13. Amir H, Kaaya EE, Manji KP, Kwesigabo G, Biberfeld P. Kaposi's sarcoma before and during a human immunodeficiency virus epidemic in Tanzanian children. Pediatr. Infect. Dis. J. 2001 May;20(5):518–21.

14. Amir H, Shibata HR, Kitinya JN, Kwesigabo G. HIV-1 associated Kaposi's sarcoma in an African population. Can J Oncol. 1994 Nov;4(4):302–6.

15. Phipps W, Ssewankambo F, Nguyen H, Saracino M, Wald A, Corey L, et al. Gender differences in clinical presentation and outcomes of epidemic Kaposi sarcoma in Uganda. PLoS ONE. 2010;5(11):e13936.

16. Wamburu G, Masenga EJ, Moshi EZ, Schmid-Grendelmeier P, Kempf W, Orfanos CE. HIV - associated and non - HIV associated types of Kaposi's sarcoma in an African population in Tanzania. Status of immune suppression and HHV-8 seroprevalence. Eur J Dermatol. 2006 Dec;16(6):677–82.

17. Huang K-M, Hsu C-H, Cheng JC-H, Lai M-K, Jeng S-C, Ting L-L, et al. Radiotherapy of classic Kaposi's sarcoma in Taiwan, an area where classic Kaposi's sarcoma is not prevalent. Anticancer Res. 2006 Dec;26(6C):4659–63.

18. Kaposi Sarcoma Treatment (PDQ®) - National Cancer Institute [Internet]. [cited 2012 Mar 7]. Available from: http://www.cancer.gov/cancertopics/pdq/treatment/kaposis/HealthProfessional/page4

19. Mwanda OW, Fu P, Collea R, Whalen C, Remick SC. Kaposi's sarcoma in patients with and without human immunodeficiency virus infection, in a tertiary referral centre in Kenya. Ann Trop Med Parasitol. 2005 Jan;99(1):81–91.

20. Urassa WK, Kaaya EE, Kitinya JN, Lema LL, Amir H, Luande J, et al. Immunological profile of endemic and epidemic Kaposi's sarcoma patients in Dar-es-Salaam, Tanzania. Int. J. Mol. Med. 1998 Jun;1(6):979–82.

21. Agaba PA, Sule HM, Ojoh RO, Hassan Z, Apena L, Mu'azu MA, et al. Presentation and survival of patients with AIDS-related Kaposi's sarcoma in Jos, Nigeria. Int J STD AIDS. 2009 Jun;20(6):410–3.

22. Predicting survival in patients with Kaposi's sarcoma. Nature Reviews Clinical Oncology. 2006 Aug 1;3(8):408–408.

23. Survival following diagnosis of Kaposi's sarcoma for AIDS patients in San Francisco. Survival trends for patients with AIDS [Internet]. [cited 2012 Mar 16]. Available from: http://www.readabstracts.com

24. Franceschi S, Arniani S, Balzi D, Geddes M. Survival of classic Kaposi's sarcoma and risk of second cancer. Br J Cancer. 1996 Dec;74(11):1812–4.

25. J. H. Abrahamson, Soft ware WinPep. PORTAL, calculation of sample size for a retrospective survival studies, 2006.

26. Maloba, Were Edward. Factors influencing Kaposi's Sarcoma treatment outcome at Uganda Cancer Institute, 2008-07.

APPENDIX

Appendix i: QUESTIONNAIRE

Survival of patient with KS attended ORCI in 2006.

***PART I: General Info* &Demorgraphic Data**

1. Registration no: _____
2. Date of starting treatment____/____/_____
3. Date of histological diagnosis: ____/____/_____
4. Year of birth_____
5. Sex _____
6. District _____
7. Region _____
8. Religion_____
9. Duration of treatment_____
10. Modality of treatment:

1.Chemotherapy	Radiotherapy	HAART	Combination	Others

11. Marital status:_____

PART 2: Disease Profile& Outcome

1. HIV Status

Positive	Negative

2. Hematologyresults prior to treatments

   Viral load _____ CD4 count _____

   Total WBC Count_____ Total Netrophils Count_____

   Total Lymphocyte Count_____

   Hemoglobin_____ Platelet Count_____

3. Presence of B Symptoms
   a. Fever _____
   b. Weight loss > 10% in one month period_____
   c. Significant night sweats_____
1. Location of presenting lesion _____
2. Date of Death_____
3. Date of LFP_____
4. Date of Successful 5years follow-up_____

THE END