



AIDS-Related Kaposi's Sarcoma (AKS) and Treatment Outcome at Muhimbili National Hospital and Ocean Road Cancer Institute in Tanzania

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ABSTRACT

Published Online: 03 June 2022

Background: Kaposi's sarcoma (KS) is a systemic multifocal angiomatous tumor presenting with purplish macular/papular, plaques or nodular lesions and four clinicopathological types namely classical/sporadic (CKS), African endemic (EKS), iatrogenic (IKS) and AIDS-associated (AKS). It is the commonest HIV/AIDS-related cancer in Africa. The introduction of highly-active-antiretroviral-therapy (HAART) has drastically reduced the incidence of KS and altered its clinical course but in Tanzania few current reports have been documented on treatment outcome including its use. The aim of this study was to determine the frequency, clinical presentation, treatment and associated factors at Muhimbili National Hospital (MNH) and the Ocean Road Cancer Institute (ORCI).

Methods: A hospital-based cross-sectional study using archival records of patients admitted at MNH from January-December 2015 and treatment information/outcome from ORCI.

Results: Out of 120 patients 71.7% were HIV positive (AKS), the rest were endemic (EKS) and males were older and more frequently affected than females. Majority (61.5%, n=64/104) with KS morbidity and mortality (62.5%, n=10/16) were from younger age-groups probably due to AKS. AKS patients more frequently (23.33%, n=28/120) presented with generalized disease compared to EKS (5.83%, n=7/120) [$p = 0.0263$]. Histopathologically, advanced (plaque+nodular) lesions were more (58.3%, n=72/120) frequent in AKS. Most (95%) of AKS patients received HAART and majority (95.95%, n=71/74) were alive during data collection ($p < 0.0001$). Apparently, more (88.2%) patients with EKS were alive compared to AKS (86.0%). Conversely, majority (81.3%, n=12/16) of those dead had AKS.

Conclusion: KS is still common in Tanzania, mostly in association with HIV/AIDS. AKS contributed to younger age, generalized disease and advanced histopathological stages at presentation. Chemo-radiotherapy and radiotherapy-alone modalities appeared more beneficial and showed less mortality. The use of HAART seems to reduce the negative impact of AKS.

KEYWORDS:

Kaposi's sarcoma, HIV/AIDS, Presentation, Treatment, HAART, Tanzania

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*Cite this Article: Amos Rodger Mwakigonja, Alina Mehboob Murji (2022). AIDS-Related Kaposi's Sarcoma (AKS) and Treatment Outcome at Muhimbili National Hospital and Ocean Road Cancer Institute in Tanzania. International Journal of Clinical Science and Medical Research, 2(6), 28-36

LIST OF ABBREVIATIONS

1. AKS-AIDS-related Kaposi's sarcoma
2. HAART- Highly Active Antiretroviral Therapy
3. CKS- Classical Kaposi's sarcoma
4. EKS- African Endemic Kaposi's sarcoma
5. KS- Kaposi's sarcoma
6. SSA-Sub Saharan Africa
7. ORCI-Ocean Road Cancer Institute

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BACKGROUND

Kaposi's sarcoma is a systemic multifocal angiomatous malignant tumor characterized by multiple red-to-purple macular or papular skin lesions slowly evolving to plaques or nodules. Initially it was described in 1872 by Moritz Kaposi as an *idiopathic multiple pigmented sarcoma of the skin*.(1, 2)

Kaposi's sarcoma (KS) presents in four clinicopathological types namely classical/sporadic (CKS), African endemic (EKS), iatrogenic (IKS) as well as AIDS-associated (AKS) all of which are causally associated with the human herpes virus type 8 (HHV-8), also known as Kaposi's sarcoma herpes virus (KSHV) discovered in 1994 by Chang & Moore (3) and identified in tissue biopsies all KS types (including AKS and EKS from Muhimbili, Tanzania) by an international research collaborative group that included Tanzania. (4) All the four clinical types of KS present in the same way histopathologically as patch, plaque or nodular lesions.(5, 6)

Clinically, AKS varies from its classical form by its rapid clinical course, widespread dissemination as well as mucosal, visceral and lymph node involvement including presenting in younger subjects. The oral mucosa is the initial site of localization in 10–20% of all HIV associated KS and we have previously reported an OKS frequency of 11% from Muhimbili National Hospital.(5)

Antiretroviral therapy

The introduction of highly active antiretroviral therapy (HAART) has drastically reduced the incidence of Kaposi's sarcoma and altered its clinical course. Optimal control of HIV infection using HAART is an integral part of successful Kaposi's sarcoma therapy. It should be the first step in therapy. Response to such therapy can be anywhere from 20-80% based on stage of disease and the amount of pretreatment.(7-10)

HAART may be tried as the only modality used in non-visceral disease but for visceral disease, chemotherapy may be added. For locally symptomatic disease, radiation therapy may be introduced. In patients with widespread skin involvement, extended-field electron beam radiation therapy (EBRT) has been effective in controlling the disease.(11, 12)

Kaposi sarcoma is the most common HIV/AIDS-related cancer in Africa, and it is more common in men than women. Due to improved HIV treatment, Kaposi sarcoma rates have decreased, with about 6 new people diagnosed each year for every million people in the United States.

Better treatments have also improved survival rates for people with Kaposi sarcoma. When HIV and AIDS first became widespread, the five-year survival rate of people with Kaposi sarcoma was less than 10%.(10, 13) Now the most recent data from the National Cancer Institute (NCI) shows five-year survival rates of about 72%, this shows the effectiveness of treatment.(13) More effective treatments for

HIV/AIDS are improving the survival rate both by treating the infections associated with HIV/AIDS and the Kaposi sarcoma.(13)

According to a study about changes in the pattern of Kaposi's sarcoma at Ocean Road Cancer Institute (ORCI) in Tanzania, Kaposi's sarcoma proportions declined from 10.1% in 2003 to 7.4% in 2011.(14) Females were shown to have increased oral and generalized lesions and higher numbers of lesion compared to males. Anti-retroviral therapy duration showed a protective effect with oral, generalized and number of lesion locations. With increasing number of patients receiving prolonged anti-retroviral therapy, studies show investigation needs to be done for long-term effect of anti-retroviral therapy in Tanzania.(14) Although numerous studies on AKS have been done globally and in Africa including Tanzania few current reports have been documented on the treatment outcome including the use of HAART and other options available. Thus the aim of this study is to determine the frequency, clinical presentation, treatment as well as associated factors of Kaposi's sarcoma including HIV association among patients at Muhimbili National Hospital (MNH) and ORCI. It is hoped that data from this current study will add to the bridging of the knowledge gap and help clinicians improve management and follow up of AKS patients including HAART adherence.

METHODOLOGY

Study Design:

This was a hospital-based descriptive cross-sectional study using archival medical records. Patients' records were retrieved at MNH and then treatment information/outcome was traced from ORCI.

Study area:

Muhimbili National Hospital (MNH) and the Ocean Road Cancer Institute (ORCI) in Dar es Salaam Tanzania. At Muhimbili National Hospital the study was done in the then Histopathological Unit at the Central Pathology Laboratory (CPL). Muhimbili National Hospital is a national referral and university teaching hospital with 1,500 bed facility and attending about 1000-1200 outpatient and inpatients per week (www.mnh.or.tz). The histopathology unit is capable of handling about 13000 biopsies per year and capacity of performing immunohistochemistry and special stains for different tissues. ORCI is also the national referral and original cancer treatment center as well as a university teaching hospital as well where chemotherapy, immunotherapy, hormonal therapy, radiotherapy as nuclear medicine are available (www.orci.or.tz).

Study Population:

All Kaposi's sarcoma patients admitted in wards at Muhimbili National Hospital and Ocean Road Cancer Institute from January 2015 to December 2015.

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Inclusion criteria and exclusion criteria:

This study included all Kaposi's sarcoma patients during the study period whose data was available.

It excluded those patients whose non-Kaposi's sarcoma patients, patients outside the study period as well as those whose data was not retrievable.

Sampling method:

Convenient sampling all patients meeting the inclusion criteria.

Data management and analysis:

Data was analyzed using the Statistical Package for Social Sciences (SPSS) Software version 17. Descriptive statistics will be used to present results. Categorical data was presented using proportions while continuous variables will be summarized using means (standard deviation) or medians (range). Comparison of proportions will be done using the chi squared test and displayed by means of 2 by 2 tables. A p-value of less than 0.05 will be considered statistically significant. The Fisher Exact Test will be used for small samples.

Ethical considerations

Ethical clearance and permissions will be obtained from the MUHAS institutional review board (IRB) and permission was sought from the Muhimbili National Hospital and ORCI

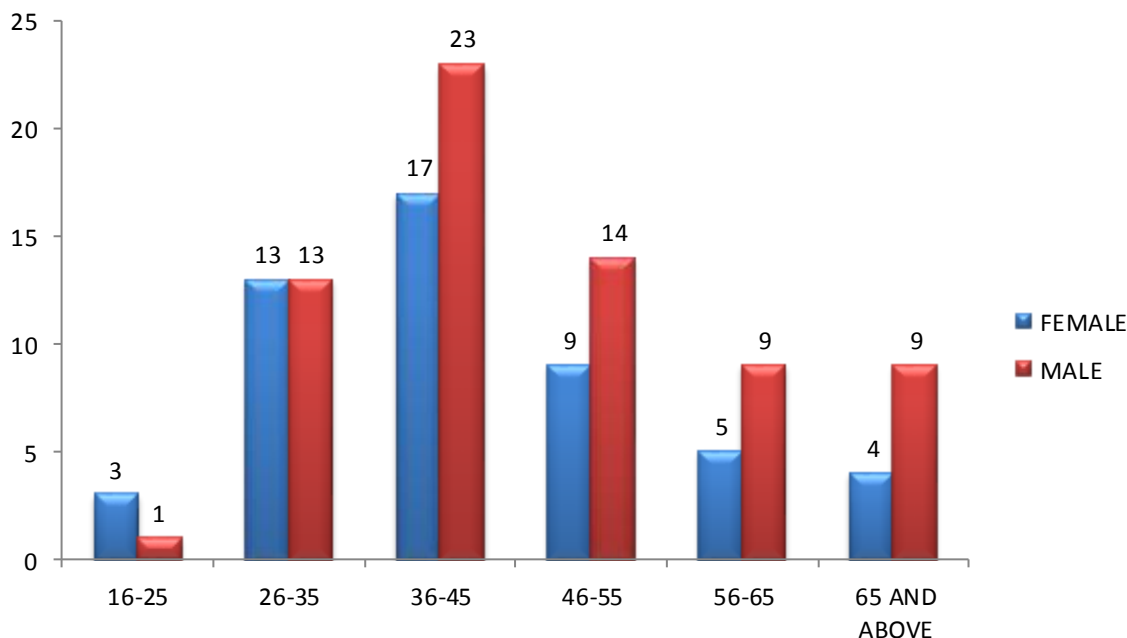
Management for to collect data. HIV status was retrieved from clinical records. Patients' information was not disclosed throughout the study and personal identifying data is not included in the report.

RESULTS

In 2015 during the study period of 12 months, a total of 120 KS cases were collected at MNH and as expected, majority (59.2%, n=71) were males and 40.8% (n=49) females (M:F ratio=1.45:1, P = 0.0483, statistically significant). A great majority of these (71.7%, n=86/120) who were HIV infected (AKS) and the rest endemic KS (EKS) [P = 0.0016, statistically significant] and for AKS the male to female ratio was 1.35:1.

The peak (33.3%) age group for Kaposi's sarcoma was between 36-45 years (n=40 for both males and females (**Figure 1**)). The mean age was 45.2 years with SD of 13. The median age for Females was 42 and the males was 43 years.

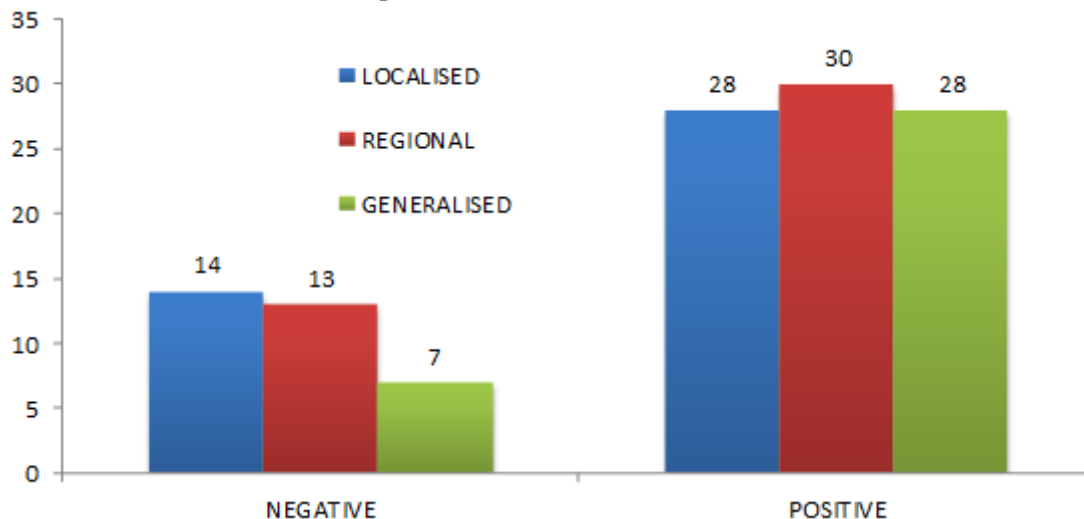
Figure 1: The distribution of KS with age groups



As expected, AKS patients were more likely to present with generalized disease (23.33%, n=28/120) compared to only

5.83% (n=7/120) EKS patients (p = 0.0263, statistically significant) [**Figure 2**].

Figure 2: The distribution of KS with clinical presentation/disease extent



For purposes of this study, histopathological lesions were assigned as either early (patch stage) or late/advanced (plaque or nodular stages) and as expected, majority (58.3%, n=72/120) of patients who presented with advanced

histological disease (plaque+nodular stages) had AKS while only 25.8% (n=31/120) of patients with advanced lesions had EKS ($p = 0.0014$, statistically significant) [Table 1].

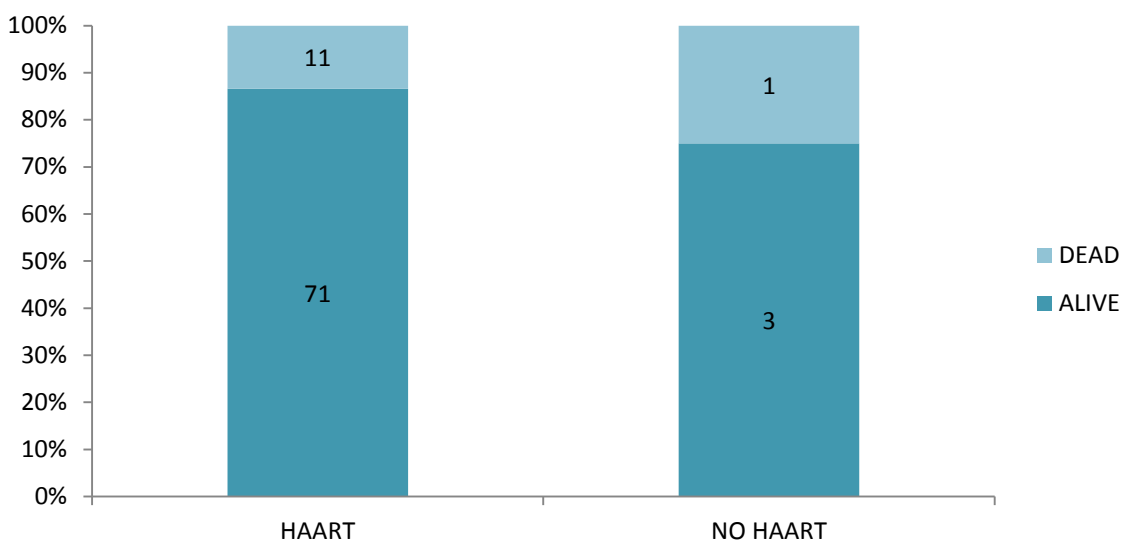
Table 1: Histological presentation of KS lesions according to HIV serostatus of patients

HIV Serostatus	Patch No. (%)	Nodular No. (%)	Plaque No. (%)	Total No. (%)
Positive (AKS)	16 (0.83%)	58 (48.3%)	12 (10%)	86 (71.7)
Negative (EKS)	3 (2.5%)	29 (24.1%)	2 (1.7%)	34 (28.3)
Total	19 (15.8)	87 (72.5)	14 (11.7)	120 (100)

A total of 74 out of 86 (86.0%) AKS patients were alive during data collection and out of these a great majority (95.95%, n=71/74) were using HAART and only 4.05% (n=3/74) of those alive were not using HAART ($p < 0.0001$,

highly statistically significant) [Figure 3]. This indicates that HAART has a role in promoting survival among HIV seropositive patients with KS even among Tanzanian patients.

Figure 3: HAART use and outcome among AKS patients



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Proportionately, it appears that slightly more (88.2%) patients with EKS were alive during data collection compared to 86.0% of those with AKS and conversely

majority (81.3%, n=12/16) of patients who were dead during data collection had AKS (Table 2)

Table 2: The proportion of alive KS patients during data collection against their HIV serostatus

HIV Serostatus	Alive No. (%)	Dead No. (%)	Total No. (%)
Positive (AKS)	74 (86.0)	12 (14.0)	86 (71.7)
Negative (EKS)	30 (88.2)	4 (11.8)	34 (28.3)
Total	104 (86.7)	16 (13.3)	120 (100)

Furthermore, majority (39.2%, n=47/120) were being given Radiotherapy-alone followed by Chemotherapy alone (36.7%, n=44/120) while only a few (9.2%, n=11/120) took the Chemo-Radiotherapy combination (Table 3). Out of these, majority (44.2%, n=45/104) of patients who were alive during data collection were receiving Radiotherapy-alone and similarly, for those in the Radiotherapy-alone arm, most (95.7%, n=45/47) were alive during data collection suggesting superiority of this treatment modality. Apparently, the Chemo-Radiotherapy and the

Chemotherapy-alone arms showed the same proportions of patients who were alive and dead during data collection implying that the former did not show superiority in treatment outcome/benefit over the later, at least in the index ORCI cohort.

Unexpectedly, majority (50.0%, n=8/16) of KS patients who were dead during data collection were receiving Chemotherapy-alone suggesting this treatment modality had the worst outcome in the index cohort and comparatively, that Radiotherapy may be superior in benefit to KS patients.

Table 3: The proportion of alive KS patients during data collection against their treatment modality

ORCI TREATMENT	ALIVE No. (%)	DEAD No. (%)	TOTAL No. (%)
NONE	14 (13.5, 77.8)	4 (25.0, 22.2)	18 (15.0)
CHEMOTHERAPY	36 (34.6, 81.8)	8 (50.0, 18.2)	44 (36.7)
RADIOTHERAPY	45 (44.2, 95.7)	2 (12.5, 4.3)	47 (39.2)
CHEMO-RADIOTHERAPY	9 (8.7, 81.8)	2 (12.5, 18.2)	11 (9.2)
TOTAL	104 (100, 86.7)	16 (100, 13.3)	120 (100.0)

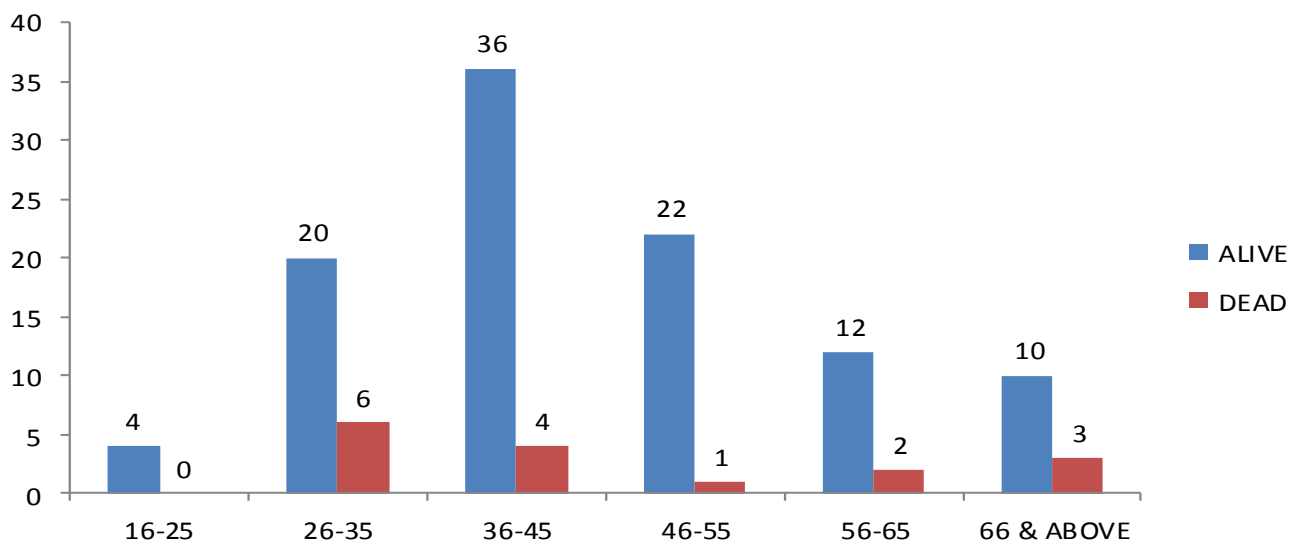
Key: None=includes patients who either had not yet started or consented to any form of treatment for KS during data collection.

As regards the association of outcome with age-groups, the figure (4) below shows that majority of those alive during data collection were from the age-group 36-45 years.

Furthermore, the fact that majority (61.5%, n=64/104) of KS patients who were alive during data collection were from the age-group 0-45 years, and similarly majority (62.5%,

n=10/16) of KS patients who died were from the same age-group (Figure 4), supports the notion that AKS affects more frequently the younger; and economically productive population, probably due to higher HIV and HHV-8 transmission rates in this age groups (p-value=0.000).

Figure 4: Distribution of outcome according to age-groups



DISCUSSION

From this study it has been found that out of all 120 Kaposi's sarcoma patients, 86(71.7%) were HIV positive (that means AIDS-related KS or AKS) and 28.3% HIV- or African Endemic Kaposi's sarcoma (EKS) in the year 2015. This frequency is very similar to a previous report by Mwakigonja *et al.*, in 2008 which showed the frequency of AKS to be 77.5% and 22.5% were HIV- (EKS),(15) but higher than a previous study done at Bugando Medical Center in which the frequency of AKS was 49.2%.(16) This apparent discrepancy in findings from within Tanzania as well as from other sub-Saharan African (SSA) countries might partly be due to geographical, ethnic, social, occupational but also biological factors resulting in late diagnosis and limited access to HAART.

In our current study, the peak age-group was 36-45years corresponds well to the mean age of 35.8 years in our previous report on mostly cutaneous KS together with a few lymphadenopathic KS.(15) This age is also similar the 37 years median age reported by Gervas & Mgaya in 2021.(17) However, this seems to be slightly higher than the 32 years median age in our other previous report which focused on only oral KS [OKS](5) as a sampling bias. Furthermore, in our current study, females were significantly younger compared to males which is similar to our previous report where the median age for males and females was 38 and 31 years respectively(5) and also it is similar to studies done in northern Nigeria(18) and in ORCI in Tanzania.(14) Similar to our previous reports, males were affected more than females with a ratio of 1.35:1, which was almost the same as of 1.4:1 reported from Bugando for the period of 10 years(16) as well as from Muhimbili more recently(17) and also similar to the study done in Nigeria which was 1.3:1 and from South Africa.(5) However, our previous report showed an increased male:female ratio or MFR of 2.75:1

suggesting increased male susceptibility to KS compared to females(15) or conversely that women were more protected to KS development partly theorized to be due to hormonal differences as well as pregnancy.(5) However, in our previous OKS cohort, MFR was 1:2.3 was partly attributed to sampling bias, different site (mucosal) of anatomical presentation as well as sexual practices probably including heterosexual receptive oral sex.(5)

As regards clinical presentation, the most common overall presentation in our current study was regional disease while AKS patients were more likely to present with generalized disease compared to EKS. This finding expected and well in keeping with the setting of AKS.(5, 6, 15)

Histopathologically, advanced KS subtypes were (plaque and nodular patterns) were more (58.3%) frequently seen AKS as compared to the 25.3% in EKS. This is also in keeping with an established notion that HIV drives a more aggressive disease (AKS) as reported previously (5, 6, 15) which could partly be due to a biological cross-talk between HIV and KSHV or HHV-8 which is the causative organism of all forms of KS.(19, 20) Several modalities of treatment have been used for Kaposi's sarcoma including chemotherapy, radiation therapy as well as Highly Active Anti-Retroviral Therapy (HAART) in patients with AIDS-related Kaposi's sarcoma (AKS). (11) The choice of treatment is determined by the stage of Kaposi's sarcoma, its rate of progression, the degree of immune competence and also HIV association. Thus, out of 86 patients who were seroconverted, 82 (95%) received HAART and from these 82.6% were alive during data collection and those who didn't receive HAART 25% of them had died during data collection. Those who died could be due to non-adherence to medication, drugs side effects as well as possible comorbidities. However it's difficult to state with certainty what proportion of patients with AIDS-related Kaposi's

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sarcoma will benefit from HAART alone as it varies with individual patient's characteristics, disease staging as well as drug compliance.

In our current study histological regression of existing KS lesions has been shown in response to HAART alone as implied by the fact that most were alive during data collection and this may be different with a previous study done at Bugando Medical Center where those who received HAART were only 56.4% (16) and most were given chemotherapy alone since by that time radiotherapy was not available in the Lake Zone as well. It is noteworthy that our current findings suggest that radiotherapy alone or together with HAART may be superior to chemotherapy alone or in combination with radiotherapy. However, a previous report from Mbeya, Tanzania has shown a favourable treatment outcome for patients treated with chemotherapy together with HAART which would probably be attributed to the addition of the later.(7, 9) Moreover, the finding that mortality rate in this current study appears lower (13.3%, n=16/120) compared to the 24.2% reported in a previous Bugando study(16) could partly be attributed to availability of radiotherapy facilities besides chemotherapy at ORCI while by that time only chemotherapy besides HAART was available in the Lake Zone. The Oncology Center at Bugando is much newer than the age-old ORCI in Dar es Salaam. However, differences in the disease burden, comorbidities as well as experience in cancer treatment between the two centers could also have contributed to the apparent disparity.

CONCLUSION

Kaposi's sarcoma is still a common malignancy in Tanzania and particularly in association with HIV and AIDS despite the advent of the use of HAART. Most of the patients had regional-generalized presentation and nodular skin lesions similar to most previous reports. In our current study, radiotherapy seems to be more beneficial as more patients lived and less death occurred although chemo-radiotherapy was comparably effective as well. Similar to reports from elsewhere HAART was more frequently associated with those alive and less mortality during data collection implying its benefit among AKS patients. The use of a full dose of chemotherapy together with HAART may also result in desirable outcome. HIV screening, use of HAART and early diagnosis of KS will go a long way in reducing morbidity as well as mortality from this AIDS-defining cancer (ADC).

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