PATTERN OF BLADDER CANCER AT UNIVERSITY TEACHING HOSPITAL, LUSAKA, ZAMBIA IN THE ERA OF HIV EPIDEMIC

By

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DECLARATION

I declare that this dissertation represents my own work and that it has not previously been submitted for a degree, diploma or other qualification at this or another University. I further declare that all sources I have quoted have been indicated and acknowledged by means of complete references. It has been prepared in accordance with the prescribed guidelines for the post graduate studies Dissertations of the University of Zambia.

Researcher's Signature …… Date ……

Supervisor's Signature …… Date ……

ABSTRACT

Background: Human Immunodeficiency Virus (HIV) is endemic to Zambia and is associated with changes in the patterns of both AIDS and non- AIDS defining cancers. Bladder cancer is one malignancy that has been noted to increase in the era of HIV/ AIDS epidemic. This study sought to describe the pattern of cancer of the bladder at UTH in the era of HIV/AIDS epidemic in respect with the epidemiological characteristics, prevalence of HIV infection and the histological types of bladder cancer in patients with cancer of the bladder.

Patients and Methods: A prospective cross sectional, hospital based study was performed at the University Teaching Hospital (UTH), Lusaka, Zambia, between November 2009 and November 2010. Patients with bladder cancer who presented to the hospital during this period were recruited and parameters studied included patients demographics, clinical presentation, HIV status and pathology of cancer. Data collected was analyzed using SPSS 17.

Results: A total of 53 patients with median age of 57.49 years who had histological confirmed bladder cancer were recruited during this one year period. The male to female ratio was 1.3 to 1. Haematuria was a presenting complaint in over 94 % of patients and anemia was found in 82% of patients. Of the 53 patients, HIV infection was found in six patients (11.3 %). Squamous cell carcinoma was the most common histological type (60.4%) followed by Transitional cell carcinoma (30.2%) and adenocarcinoma was least common type (9.4%). Schistosoma infection was found in 14 patients all had SCC. The study found a statistically significant reduction in the mean age of bladder cancer in HIV infected patients.

Conclusions: Squamous cell carcinoma is still the most common histological type of bladder cancer in Zambia and it's strongly associated with schistosomia infection. Haematuria remains to be the most common presenting symptom in bladder cancer patients.

DEDICATION

To my father Aaron Kaipu Mapulanga and my mother Ester Musole Tombi Mapulanga

To all the patients with cancer of the bladder for bringing to light their experiences and patience during their suffering.

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ABBREVIATIONS

AIDS.....Acquired Immunodefiency Syndrome

BCG.....Bacille-Calmette Guerin

DNA.....Deoxyribonucleic Acid

HAART.....Highly Active Anti Retroviral Therapy

HIV.....Human Immunodeficiency Virus

K.S…….. ……..Kaposi's sarcoma

NHL……..Non Hodgkin Lymphoma

SCC.....Squamous cell carcinoma

TCC.....Transitional Cell Carcinoma

TNM.....Tumor, Node, Metastasis

UTH.....University Teaching Hospital.

Chapter One

INTRODUCTION

The United Nations joint programme on AIDS estimated that by the end of 2008, there were 33 million people who were infected with HIV worldwide of which 24.5 million people are in sub-Sahara Africa, making the region the most affected by the epidemic.[1]Despite pioneering efforts to control the epidemic, Zambia in southern Africa has one of the highest HIV/AIDS epidemic with an estimation of 1100000 people living with HIV infection and a prevalence rate of 14.3%. [2] The number will quite likely increase as access to life extending antiretroviral therapies increases.

The HIV epidemic provides an opportunity to study the risk of cancers in immunosupressed populations and thus make conclusions on the association of cancer and HIV. Cancer of the urinary bladder is one such cancer which has been noted to have increased in prevalence in the era of HIV epidemic. According to the audit reports of the department of surgery at the University Teaching Hospital, for the year 2007, cancer of the bladder was the leading cause of death among urology patients [21].Of the 32 mortalities recorded that year, 20 patients died of cancer of the bladder. Other reports from the same audit show that cancer of the bladder is the most common cause of non erective hospital admission in urology units.

In Zambia, relatively few studies have been done on patterns of cancer among HIV infected patients because both the cancer registry and the histopathological records do not capture the HIV status of patients. Therefore it is not possible to determine whether the reported trends of cancer of the bladder are due to HIV infection or other factors. It's against that background that this study sought to describe the pattern of bladder cancer in the era of HIV epidemic and attempt to formulate hypothesis on the association between cancer of the bladder and HIV infection.

In Zambia, bladder cancer represents a national health problem ranked second urological malignancy, second to cancer of the prostate.[3] A retrospective study of

the pattern of urological cancers in Zambia between periods January 1990 and December 2005 showed that cancer of the prostate was the most common urological malignancy (54.6%), followed by cancer of the bladder (21.1%) and cancer of the penis (18.6%).[3]According to the Zambia National Cancer Registry, bladder cancer accounts for 7-8% of diagnosed cancers. This is an underestimation because the registry only relies on voluntary notification of cases of cancer treated in all hospitals in Zambia.

Aetiology

The aetiology of cancer of the bladder is said to be due to the alteration in the cellular DNA of the epithelial cells lining the bladder. Changes in the epithelial behavior governed by DNA results in the disturbance of the cell ability to control its growth. It's the uncontrolled cell growth that leads to tumor development. The entire urothelium from the renal pelvis to the bladder is susceptible to malignant transformation. This malignant transformation occurs at the DNA level so that there is induction of oncogenes and suppression of tumor suppressor genes.

Risk factors

There are several factors that have been found to be linked to the malignant transformation of bladder urothelium. This includes chemicals and biological factors. Among the chemicals linked to the development of cancer of the bladder includes: 2-naphythalimine, 4-aminobiphenyl, benzidine, chlornaphazine. Occupations which use susceptible chemicals such as: textile workers, dye workers, rubber and leather workers, paint workers are recognized to be at high risk of cancer of the bladder. The behaviour risk factor includes cigarette smoking. Cancer of the bladder is very rare before the fourth decade of life and males are more susceptible than females.[4]

Metaplasia in the bladder epithelial cells is a well recognized predisposing factor to cancer of the bladder. Bladder irritation due to bladder stone, indwelling urinary catheter and bladder infections does cause metaplasia. A well studied predisposing infective cause is infection with Schistosoma hematobium causing schistosomiasis. This infection which is common in most African countries has been shown to be responsible for predominance of Squamous cell carcinoma as opposed to transitional cell carcinoma. Schistosomia infection is noted to cause metaplasia of urothelium since the infection is mostly in the

urinary system. Not only do the cells alter the architectural but also the DNA structure so that with time it becomes malignant.

Pathology

The normal urothelium of the bladder is composed of three to eight cell layers of transitional cells. The cells are arranged in a water tight manner to prevent the leak of urine from the urinary system. This urothelium rests on the basement membrane and deeper to it is a muscle layer. The muscle layer is covered by the serosa with the perivesical tissue.

Bladder cancer starts from the epithelium and spreads deeper to the serosa and perivesical tissues. The staging of bladder cancer is thus dependant on how far the tumor has spread.

There are three most recognized types of bladder cancer.

1. Transitional cell carcinoma (TCC)
2. Squamous cell carcinoma (SCC)
3. Adenocarcinoma.

Transitional cell carcinoma arises from the normal urothelium and tends to be superficial at the time of diagnosis. It carries a better prognosis as compared to SCC. It's the most common bladder cancer in America and Europe accounting for 90% of bladder cancer while SCC accounts for less than 10% of cases.[4] However this proportion is opposite in Africa from Egypt down to South Africa with SCC accounting for most of the bladder cancer [12].

Squamous cell carcinoma usually arises from the bladder epithelium that has undergone metaplasia due to chronic cystitis from bladder stones or infection from schistosomiasis. SCC usually presents at an early age and with an advanced stage so that it carries a poor prognosis. The association of bladder cancer and schistosomiasis has been extensively studied.

Adenocarcinoma is the least common type of bladder cancer accounting for less than 2% of the cases. It arises from the glandular tissue and remnants of the urachus.

Grading

Grading of cancer of the bladder is based on how close the tumor cells are to the original bladder epithelial cells. It considers the degree of anaplasia. Several types of grading systems have been proposed by different pathologists. The most commonly accepted one has three grades:

Grade1. Well differentiated

Grade2. Moderately differentiated

Grade3. Poorly differentiated.

The high the grade the worse the prognosis. Higher graded tumors have a higher rate of recurrence after surgical treatment. Therefore a higher grade is strongly associated with poor outcome following cystectomy.

Staging

Staging refers to the extent of the cancer spread. The initial staging system was proposed by Jewett and Strong and was later revised by Marshall .Currently the most commonly used staging system was developed by the American Joint Committee on Cancer in 1997. Its takes into account the primary tumor stage (T stage), the lymph node status (N stage) and metastatic site (M stage). This is commonly referred to as the TNM staging system.

TNM

Definitions

Primary tumor (T) Stage

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Ta: Noninvasive papillary carcinoma
- Tis: Carcinoma *in situ* (i.e., flat tumor)
- T1: Tumor invades sub epithelial connective tissue
- T2: Tumor invades muscle
    - pT2a: Tumor invades superficial muscle (inner half)
    - pT2b: Tumor invades deep muscle (outer half)
- T3: Tumor invades perivesical tissue
    - pT3a: Microscopically
    - pT3b: Macroscopically (extravesical mass)

- T4: Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, or abdominal wall
    - T4a: Tumor invades the prostate, uterus, vagina
    - T4b: Tumor invades the pelvic wall, abdominal wall

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in a single lymph node 2 cm or smaller in largest dimension
- N2: Metastasis in a single lymph node larger than 2 cm but 5 cm or smaller in largest dimension; or multiple lymph nodes 5 cm or smaller in largest dimension
- N3: Metastasis in a lymph node larger than 5 cm in largest dimension

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

Clinical Presentation

The most common symptom of cancer of the bladder is haematuria.[4] This can be microscopic or macroscopic and it's mostly painless. The fact that the cardinal symptom is painless haematuria makes the presentation rather late so patients tend to present with advanced disease. Other symptoms include dysuria, frequency, and necroturia. In patients with less advanced disease, there are no signs on examination. Patients with advanced disease and having severe haematuria may present with signs of anaemia and bladder mass.

Diagnosis of cancer of the bladder can be made with an ultrasound and cystoscopic examination of the bladder. Cystoscopy is very sensitive and can pick superficial lesions as opposed to ultrasound that tends to be useful if bladder mass is big. Urinary cytology has been shown to be very sensitive. Other investigations assist in staging of the tumor and establishing extent of metastasis. These include renal function tests, liver function test and CT scan

Chapter Two

LITERATURE REVIEW

Cancer of the bladder is common in Zambia being the second commonest urological tumor second to prostate. [3] Its very common along the great Rift valley of Africa from Egypt down to South Africa. This has been attributed to high prevalence of Schistosoma hematobia infection .Much of the evidence supports the association between schistosomiasis and bladder cancer: this includes the geographical correlation between the two conditions, the distinctive patterns of gender and age at diagnosis, the clinic pathological identity of Schistosoma-associated bladder cancer, and extensive evidence in experimentally infected animals. [7]

There is a strong relationship between cancer of the bladder and Bilhazia.[8]. Bilharzia is associated with metaplasia of bladder epithelium resulting in Squamous cell carcinoma being the most common type of cancer of the bladder. The proportion of SCC varied from 54 to 81% of all bladder cancer cases in different areas of endemic infection, which contrasts to Western countries, where the frequency of SCC in bladder cancer cases is much lower (3 to 10%) [4] . In Nigeria where bladder cancer makes up 6.4% of national cancer cases, 53% are Squamous cell type and 35% are transitional cell type. The mean age being 48years with a male to female ratio of 5.2: 1.[9] Egypt has shared the same histological pattern with 51% being SCC and 21% being TCC and 11% are Adenocarcinoma. Of the 51% cases of SCC, Schistosoma hematobia ova were isolated in the tissues in 68 %.[10] A recent study in the upper Egypt showed that in the north of the country , SCC constituted 67.6% of bladder cancers while TCC constituted 15.4% and adenocarcinoma accounted for 8.5% of the cases. In Zimbabwe data supports the causal relationship between S.haematobium and SCC. A histological survey shows that 69% were SCC and the rest were TCC with patients of SCC being younger than those with TCC by 50% against 20% and mean age of less than 50years.[11]

According to a hospital based histological survey conducted at the University Teaching Hospital in Lusaka in 1983, Elem showed that of the 784 urological tumors,

12% were bladder cancer. Of these 51% were Squamous cell carcinomas with 32% demonstrating S.haematobium ova in the histological tissues. It was also reported that the stage of presentation was high being mostly stage three and four [8]. A latest retrospective study of the pattern of urological cancers in Zambia for the periods of 1990 to 2005 showed that bladder cancer constituted about 21.1% of urological malignancies an increase from 12% from the previous study [3] . The same study showed that there was a significant increase in adenocarcinoma of the bladder to 22% while SCC constituted 46.2% and TCC of 23.4%. The two studies showed that cancer of the bladder is consistent with the pattern in the Great Rift Valley region. While an increase in cases of the bladder cancer can be attributed to improved urological services and availability of diagnostic methods, the studies in Zambia could not exclude the effect of HIV infection on cancer of the bladder as the data did not capture the HIV status of the patients.

There have been noticeable changes in pattern of cancer of bladder in the HIV era from the predominant SCC to TCC as shown by a study done in Egypt for the period of 1996-2000 which showed that of the 56 patients that were recruited, 39 had TCC while only 17 had SCC a reverse from the traditional distribution [10] .A recent study reviewed the patterns of bladder cancer in Egypt over the past 26 years from 1980 to 2005, showed that the histological profile of bladder cancer has changed were Squamous cell carcinoma has become the predominant type of bladder cancer. The first half of the study period from 1980 to 1990 showed that SCC was predominant type of bladder cancer while in the second half (1990 to 2005), TCC become the predominant type of bladder cancer.[12] Compared to patients diagnosed in 1980, patients diagnosed 26years later had 6 times greater odds of having TCC. Older age was also significantly associated with TCC and males were more likely than females to have bladder cancer. Relatively few studies have been conducted to study the relationship of cancer of the bladder with HIV infection. A retrospective study performed involving HIV positive patients with bladder cancer a review of case series showed that most patients (10/11) had TCC and that patients presented at the younger age.[13]

Biggar examined changes in the risk of cancer among men in high HIV/AIDS risk areas of San Francisco in USA and noted increases in urinary tract tumors including cancer of the bladder. [14] However the study had limitations because the individual's HIV status was not known. Studies of the effect of HIV on cancer incidence rates in USA showed that there was an increase in bladder cancer incidence rate by 2.7. [15] Still the study did not take individuals HIV status to correlate with cancer rates.

The first case of AIDS in Zambia was reported in 1983.[16] By April 1986 the disease had been included in the notifiable diseases and by 1997 the government of Zambia had already implemented large coordinated programme to combat AIDS. Since then Zambia has seen a change in the presentation of cancers in association with the HIV infection. Among the malignances, Kaposi's sarcoma and non-Hodgkin lymphomas have clear epidemiological association with HIV. [17] However HIV can alter the clinical course of other malignances such as cancer of the bladder. According to 2008 WHO report on the global AIDS epidemic, globally there were an estimated 33milllion people living with HIV in 2007.Sixty seven percent are in Sub-Saharan while southern Africa is home to 35% of people living with HIV infection.[1]Zambia which by 2005 was reported to have a prevalence rate of 16%, showed a reduction according to preliminary results of the 2007 Zambia demographic and Health Survey (ZDHS) to 14.3%. [2] Zambia's HIV prevalence is still high in urban areas (19.7%) and lowest in rural areas (10.3%). The results also showed that HIV prevalence was high among persons in age group 35-39 at 23.6%. The above figures show that Zambia has one of the highest HIV prevalence in Southern Africa.

Chapter Three

STATEMENT OF PROBLEM

Cancer of the bladder is a very aggressive urological malignancy carrying a high mortality rate. Its obstructive effect on the urinary tract, loss of blood from bleeding tumor and metastasic spread makes the cancer one of the leading cause of death among urology patients. In UTH urology section, reports showed that for the year 2007, cancer of the bladder accounted for about 60% of mortality cases [21]. The above situation is contrary to what is expected of reduced cases of cancer of the bladder in view of efforts to reduce the known risk factors, Bilharziasis in particular and the fact that Zambia is not very industrialized for people to be exposed to chemical carcinogen. Health authorities have gone to great lengths to treat schistosomiasis infection as early as possible in areas where it is endemic. The pattern of the cancer distribution has been shown from the same audits to involve even urban areas of Zambia where human contact with water bodies infested with Schistosoma is very minimal and therefore not to be a risk of developing cancer of the bladder

Other reports of studies suggest that HIV increases the occurrence of cancers among immunocompromised patients and the age at which cancers presents in HIV patients is much reduced from the traditional old age of most cancers in immunocompetant patients.[4]

A general increase in cases of cancer has been recorded in the HIV era in Zambia in keeping with Burton's Law [5]. In Zambia cancer of the bladder has been reported to be one of the ten most common cancers in the light of HIV pandemic. Among the most common cancers includes: cancer of the cervix, Kaposi's sarcoma, cancer of the eyes, lymphoma, cancer of the prostate and soft tissue sarcoma. [6] Efforts have been made to provide antiretroviral therapy to minimize the effect of HIV infection and there are other measures to reduce the prevalence of HIV from the national prevalence rate of 14.3%, a fairly high rate. [2] The important question is whether the HIV epidemic has affected the pattern of bladder cancer in Zambia.

Chapter Four

STUDY JUSTIFICATION

In view of the worldwide publicity on the association of HIV and certain cancers, there are both programmatic and scientific reasons for conducting epidemiological studies on the pattern of bladder cancer in the era of HIV infection for the ART programme on one hand and clinical care of cancer patients on the other hand. In selecting Zambia and UTH in particular, several factors were considered: the increased cases of bladder cancer seen in the urology section and that only UTH is the tertiary referral hospital and the only specialist hospital were urological cases are referred to for the nation.

Studies of the effect of HIV infection on cancer incidence rates have all shown that the rates of Kaposi's sarcoma and NHL are greatly increased in persons infected with HIV but have conflicting results on cancer of the bladder. Patil et al reviewed histopathological records of cancer at the University Teaching Hospital, Lusaka, Zambia for the period of 1980 to 1989 and showed that bladder cancer accounted for 6.3% of adult malignancies. [5]. Bowa et al later reviewed histopathological reports for the period of 1990 to 2005, and noted that although cancer of the bladder was one of the top ten, it accounted for 3.2% of all malignancies.[6] The Zambia cancer registry on the other hand reports that for the year 2007, cancer of the bladder accounted for 3% of the cancers. This is an underestimation since not all cancers are captured and certain provinces did not report. The above data shows conflicting results on the trends of cancer of the bladder in the light of HIV infection despite the hospital departmental audits reporting an increase in the number of bladder cancers admission and deaths.

Changes have been seen in other parts of Africa that had the same pattern of cancer of the bladder as Zambia. In Egypt one study showed a change in pattern from the traditional SCC to predominant TCC, a reverse from the previous status. Another study in Egypt from the National Cancer Institute of Cairo University , showed a change in pattern over 26years period from 1980 to 2005 where transitional cell carcinoma was more common than Squamous cell carcinoma in the second half of the study period that corresponded to the HIV era.

It’s therefore imperative that a study be conducted to determine the pattern of bladder cancer in the era of HIV in Zambia a country that initially shared the same histopathological distribution of bladder cancer type as Egypt. Such a study will surely establish preliminary data on this cancer and HIV/AIDS for further study on the association of cancer of the bladder and immunosupression caused by HIV infection. Such kind of information will provide a guide in the establishment of protocol on the management of cancer of bladder in HIV infected patients who live in this part of the world where HIV infection is endemic and at its peak. Above all it will help in formulating screening programme for HIV infected people and establish the most efficient way to screen for this cancer early enough when cure can be guaranteed.

Chapter Five

OBJECTIVES

Research Question

What impact has the HIV epidemic has on the pattern of bladder cancer in patients presenting to the University Teaching Hospital.

Objectives

General Objective

To determine the pattern of bladder cancer in patients presenting to the University Teaching Hospital in the era of HIV epidemic.

Specific objectives:

1. To describe the socio-demographic characteristics of patients presenting with cancer of the bladder at the UTH.

2. To determine the prevalence of HIV infection in patients with cancer of the bladder

3. To determine the histological pattern of cancer in patients with cancer of the bladder

Chapter Six

METHODOLOGY

Study design

The study was a cross sectional survey where both the qualitative and quantitative data was collected. Its was a hospital based study

Study site

The study was conducted at the University Teaching Hospital in Lusaka, Zambia. All patients with a diagnosis of cancer of the bladder referred from all the districts of the country during the study period of November 2009 and November 2010 were recruited into the study.

Study population

Cases were defined as those patients with a histological proven primary cancer of the urinary bladder regardless of the stage of presentation. Participants included all patients in and out patients of both urology units at the hospital

Inclusion criteria

Participants were patients with primary bladder cancer with histological results and who agree to undergo an HIV test after counseling. The study only recruited adult patients.

Exclusion criteria

Patients who declined to undergo an HIV test and were less than 15years of age at the time of the study were excluded from the study

Sampling and sample size

Convenient sampling was employed were all patients with cancer of the bladder who presented to the urology units during the study period were recruited. The sample size was determined by how many participants presented during the 12months study duration.

Data collection

The study used personal interview to collect social- demographic data (age, sex, residence) and presenting symptoms of the patients. Physical findings, laboratory results including HIV test results, cystoscopic findings and histopathological report were entered into the data collection sheet.

Data processing and analysis

Data collected was entered into Excel programme and exported to SPSS version 17 where variable were named recoded and measures and values were assigned. Data analysis was done which included descriptive analysis, cross tabulation, independent sample T test and Fishers test. Chi- square could not be computed because the sample size could not produce five and more figures in all the cells.

Ethical considerations

Approval was obtained from the University of Zambia Biomedical and Research Ethics committee (UNZAREC). An informed consent was obtained from all the participants, security and confidentiality of all the information obtained was guaranteed and maintained through out the study duration and after. The study made sure that the participation of participants in the study was purely voluntary and participants were assured that they could withdraw from the study at any time if they felt injured or inconvenienced with no consequence of their treatment.

Chapter Seven

DATA PRESENTATION/ RESULTS

7.1 : Socio-demographic characteristics of patients

A total of 53 patients with cancer of the bladder were recruited over the period of one year from November 2009 to November 2010. The youngest was 25years and the oldest was 80 years. The mean age was found to be 57.49 years. Figure 1 shows the age distributions in categories.

Figure1: Age distribution in categories

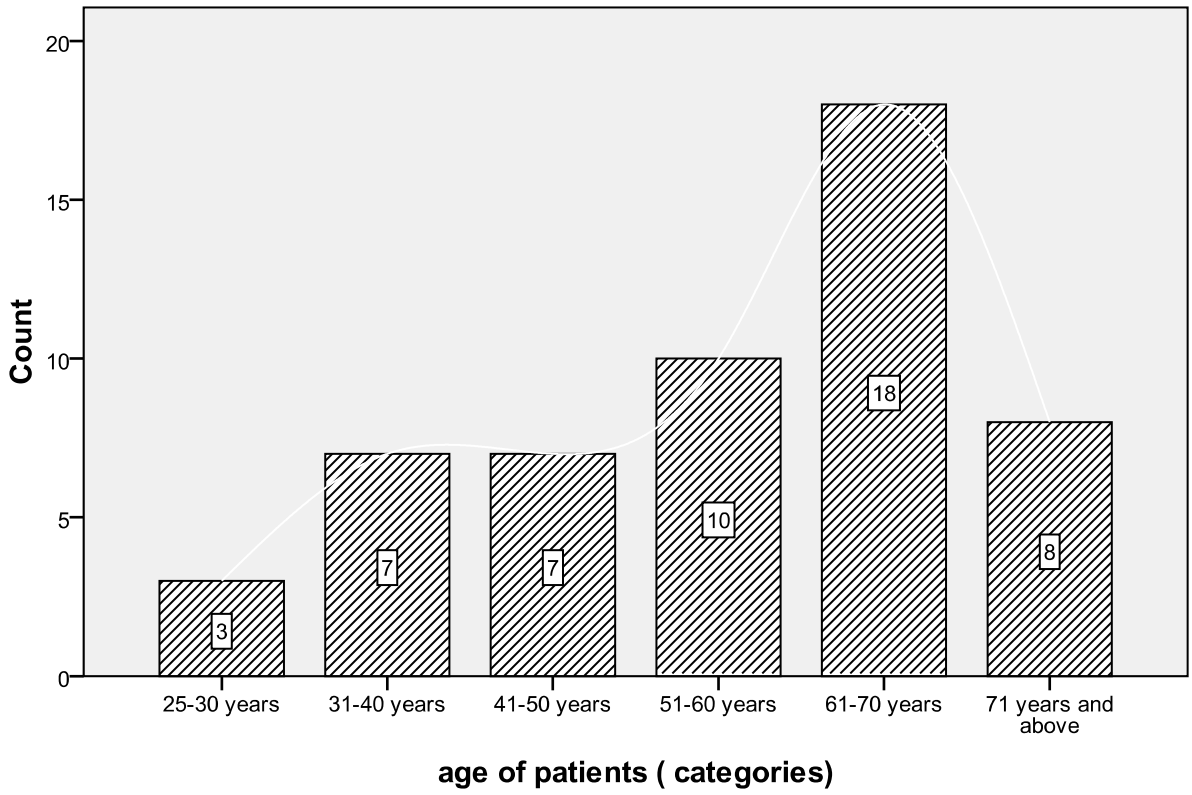

Figure 1 shows that the youngest patient was aged between 25 years and the oldest was 81years. It also shows that the disease reaches the peak at the age of 61- 70years and prevalence drops above the age of 70 years.

The study showed that cancer of the bladder was more in males than in females with the male to female ratio of 1.3: 1. Of the total of 53 patients, 23 were females and 30 were males. This is shown in Figure 2.

Figure 2. Gender distribution of patients

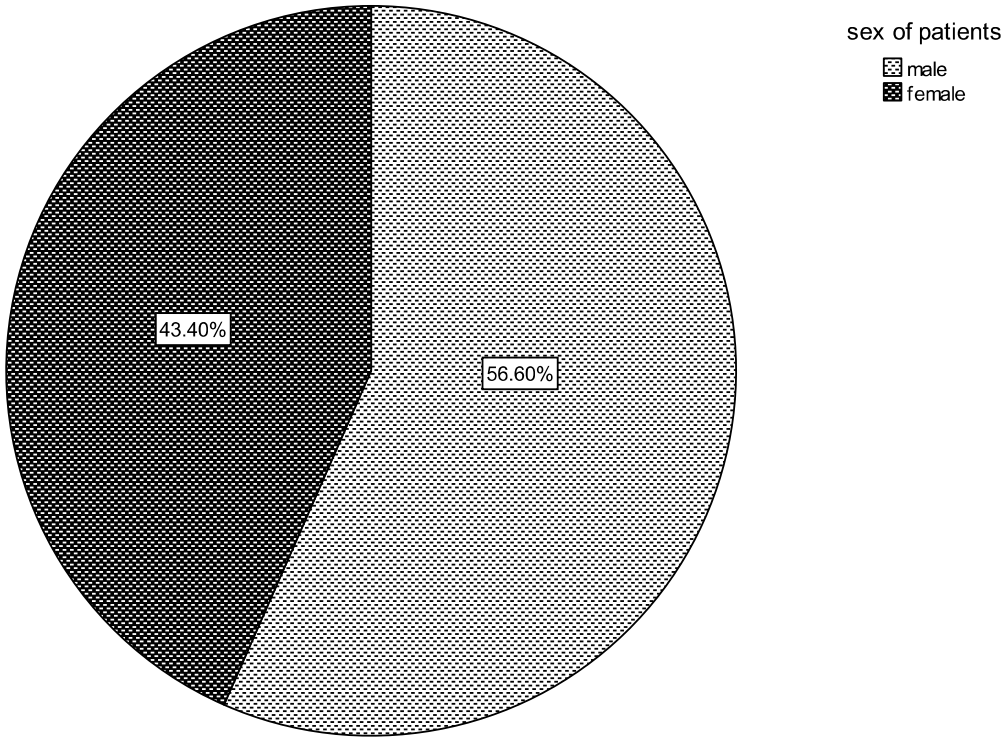

Figure 2 shows that most patients (56.60%) were males and females constituted 23 (43.40%) of patients with bladder cancer giving a male predominance of the disease.

The overall mean age was found to be 57.49 years while the mean age among females was younger than that of males. This is shown in table 1.

Table 1 : Mean age against gender of participants

	sex of patients	N	Mean	Std. Deviation	Std. Error Mean
Age of patients	male	30	58.93	13.380	2.443
	female	23	55.61	16.814	3.506

Table 1 shows that the mean age in males was higher (58.93 years) than in females were it was found to be 55.61 years. The overall mean age was found to be 57.49 years.

Participants residence was collapsed from the districts into provinces for easy of presentation and analysis. Table 2 shows the original provincial residence of patients.

Table 2: provincial residence of patients

Province	Number	Percent	Cumulative Percent
Lusaka	18	34.0	34.0
Central	3	5.7	39.6
Copper belt	3	5.7	45.3
Southern	6	11.3	56.6
Eastern	15	28.3	84.9
Western	1	1.9	86.8
North - Western	1	1.9	88.7
Northern	2	3.8	92.5
Luapula	4	7.5	100.0
Total	53	100.0	

Table 2 shows that most patients (18) came from Lusaka province followed by Eastern province which had 15 patients with bladder cancer. Western and North- Western provinces had the least number of patients.

Figure 3 shows the distribution of patients from their provinces

Figure 3 : Provincial distribution of patients

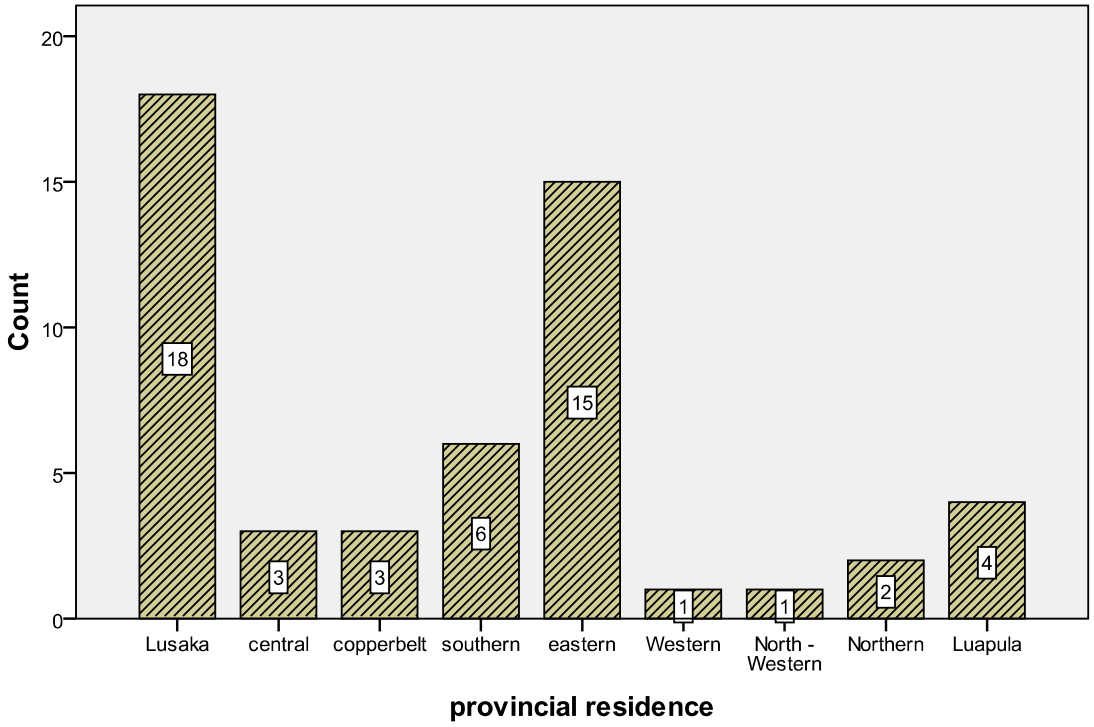

Figure 3 shows that Lusaka province had most patients with bladder cancer and Western and North- Western had the least patients of only one patient.

7.2: Clinical presentation of bladder cancer patients

Among the presenting symptoms in patients were: haematuria, dysuria, necroturia, urinary retention and abdominal mass. This is shown in table 3.

Table 3: Presenting symptoms in patients

	Frequencies		Percent of
	N	Percent	Cases
Haematuria	50	39.1%	94.3%
Dysuria	48	37.5%	90.6%
Necroturia	18	14.1%	34.0%
Urinary retention	5	3.9%	9.4%
Abdominal swelling	7	5.5%	13.2%
Total	128	100.0%	

Table 3 shows that most patients (94.3%) presented with haematuria among other symptoms while urinary retention was the least (9.4%) presenting symptoms in patients.

All the patients in the study did not have jaundice at presentation but most patients had anaemia and few had abdominal mass on examination. This is shown in Table 4.

Table 4: Physical findings in patients

		Responses	
		number	Percent
	patients with anaemia	34	87.2%
	patients with abdominal mass	5	12.8%
Total		39	100.0%

Table 4 shows that 34 patients (87.2%) of the 53 patients were clinically anaemic at presentation and only 5 patients had an abdominal mass on physical examination.

The degree of anaemia in patients is shown in Table 5

Table 5: Severity of anaemia in patients

			Cumulative
	number	Percent	Percent
	No anaemia	18	34.0	34.0
	Mild anaemia	17	32.1	66.0
	Moderate anaemia	14	26.4	92.5
	Severe anaemia	4	7.5	100.0
	Total	53	100.0	

Table 5 shows that of the 34 patients with anaemia, most patients (17) had mild anaemia, while 14 patients had moderate anaemia and only 4 had severe anaemia.

7.3: Prevalence of HIV infection among bladder cancer patients

The prevalence of HIV infection in patients with cancer of the bladder in shown in Table 6 and Figure 3.

Table 6: Prevalence of HIV infection in patients

HIV status	number	Percent	Cumulative Percent
HIV negative	47	88.7	88.7
HIV positive	6	11.3	100.0
Total	53	100.0	

Figure 4: Prevalence of HIV infection among participants

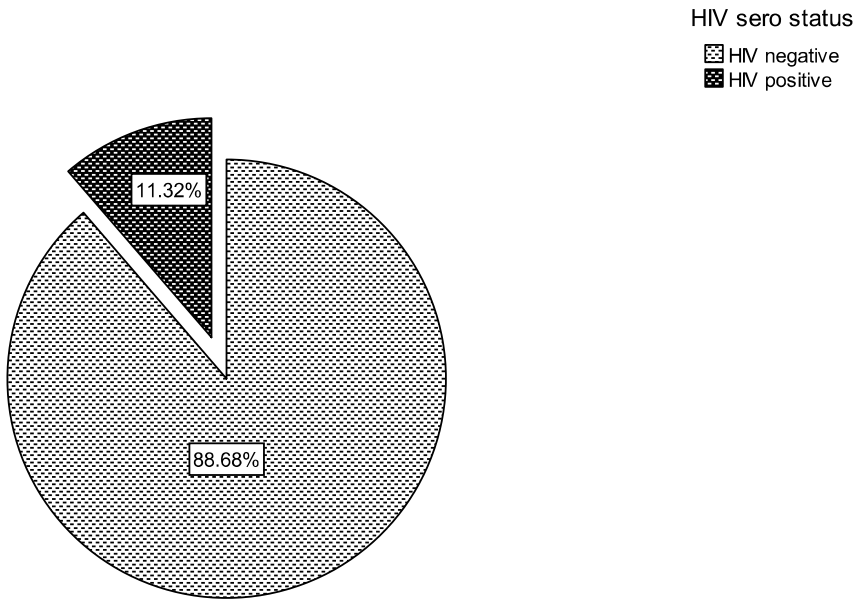

Table 6 and Figure 3 shows that of the total 53 patients, most patients (88.7%) were did not have HIV infection while 6 patients were HIV positive. Of the 6 with HIV infection 4 were known retroviral disease patients on HAART and 2 were diagnosed during the study.

7.4: Histological pattern of bladder cancer in the patients

Table 7 shows the histological types of bladder cancer the patients' studied.

Table 7: Histological types of bladder cancer in patients

	Frequency	Percent	Cumulative Percent
Adenocarcinoma	5	9.4	9.4
Squamous cell carcinoma	32	60.4	69.8
Transional cell carcinoma	16	30.2	100.0
Total	53	100.0	

Figure 4 shows the comparison of histological type of bladder cancer in the patients

Figure 5: Histological type of bladder cancer

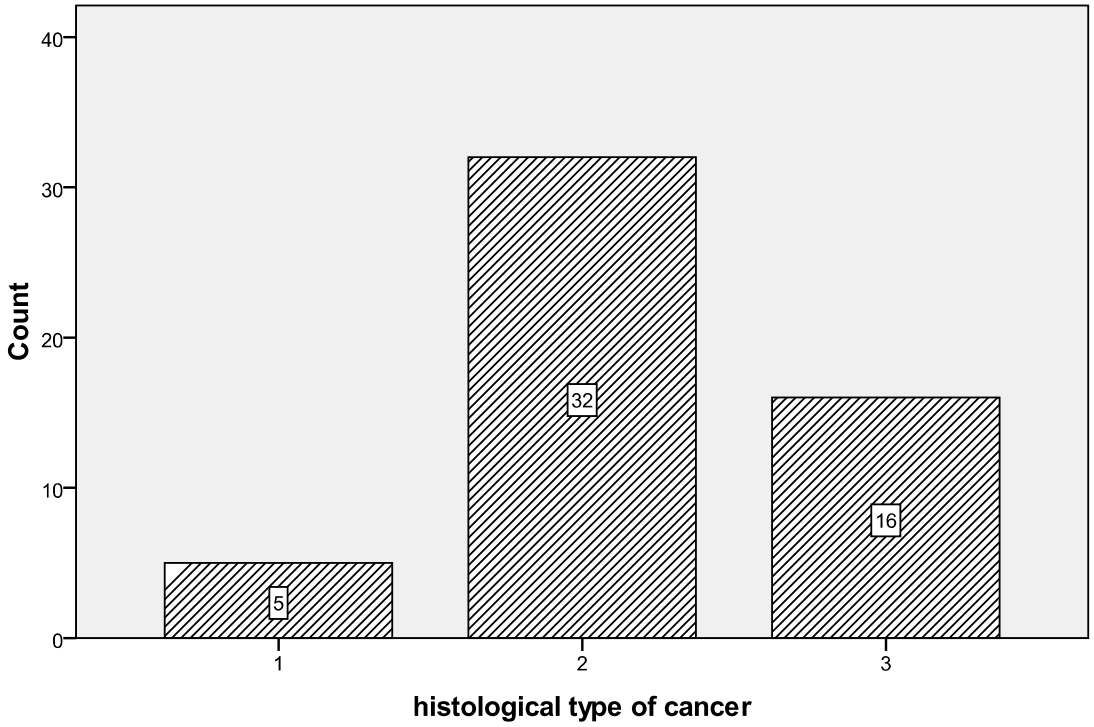

Table 7 and Figure 4 shows that Squamous cell carcinoma was the most common (60.4%) histological type followed by Transional cell carcinoma (30.2%) and adenocarcinoma was the least common type.

Table 8 shows the distribution of types of bladder cancer according to the provincial residence of the patients.

Table 8: histological type vs. residence of patients

	Province	histological type of cancer			
		adenocarcinoma	Squamous cell carcinoma	Transional cell carcinoma	Total
	Lusaka	2	10	6	18
	Central	0	2	1	3
	Copper belt	2	0	1	3
	Southern	0	4	2	6
	Eastern	1	11	3	15
	Western	0	1	0	1
	North -Western	0	1	0	1
	Northern	0	1	1	2
	Luapula	0	2	2	4
Total		5	32	16	53

Table 8 shows that eastern province had the highest (11/32) number of SCC type of bladder followed by Lusaka province (10/32). No patient from Copper belt province had SCC. Transional cell carcinoma was common (6/16) in patients from Lusaka province.

Table 9 shows how schistosomial infection found in histology was distributed.

Table 9 : Distribution of infection according to provincial residence

	Province	evidence of schistosomia infection		
		no	yes	Total
	Lusaka	14	4	18
	Central	3	0	3
	Copper belt	3	0	3
	Southern	5	1	6
	Eastern	8	7	15
	Western	1	0	1
	North - Western	1	0	1
	Northern	1	1	2
	Luapula	3	1	4
Total		39	14	53

Table 9 shows that most of the schistosomial infections came from patients (7/14) from Eastern province. Lusaka province which had highest cases of bladder cancer had only 4 patients with schistosomial infection.

Table 10 shows the comparison of mean age of the three histological type of bladder cancer

Table 10: Comparison of histological type of bladder cancer vs. mean ages

	Number	Minimum age	Maximum age	Mean age
Adenocarcinoma	5	30	80	64.40
Squamous cell carcinoma	32	25	80	54.47
Transitional cell carcinoma	16	40	75	62.63

Table 10 shows that the mean age of SCC was lower (54.47 years) while adenocarcinoma had the highest. Transional cell carcinoma had a mean age of 62.63 years.

Table 11 shows the comparison of mean ages of patients with bladder cancer between bilharzial associated SCC and non bilharzial SCC

Table 11: Comparison of mean ages among two type of SCC

	Number	Minimum age	Maximum age	Mean age
Non-bilharzial SCC	18	27	78	59.39
Bilharzial SCC	14	25	80	48.14

Table 11 shows that the mean age for bilharzia SCC was lower than for non bilharzia SCC

Figure 6 shows the distribution of the three histological types in different gender of patients

Figure 6 : Histological type against gender

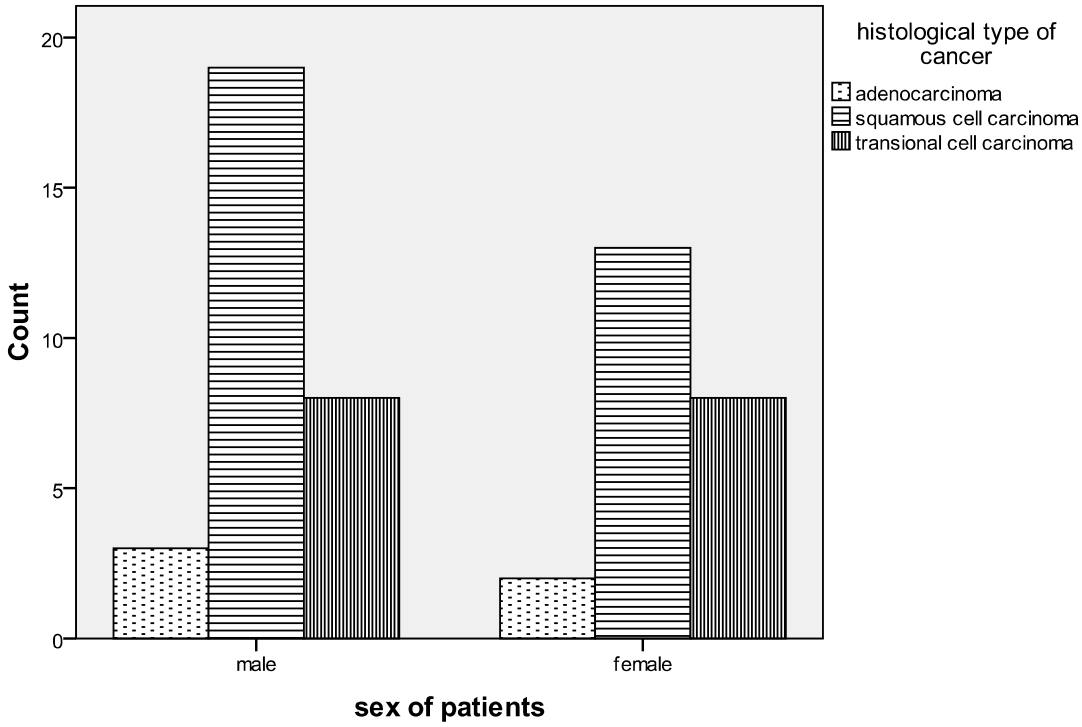

Figure 6 show that SCC was the most common histological type of bladder cancer in both males and females. Of the total 32 male patients 19 had SCC and of the 23 females 13 had SCC.

Table 12 shows histological type of bladder cancer against the HIV sero status.

Table 12: histological type vs. HIV sero status

Count

HIV sero status		histological type of cancer			
		Adenocarcinoma	Squamous cell carcinoma	Transitional cell carcinoma	Total
	negative	5	27	15	47
	positive	0	5	1	6
Total		5	32	16	53

Table 8 shows that all the cases of adenocarcinoma occurred in patients without HIV infection. The majority of patients who were HIV positive (5/6) had SCC type of bladder cancer. Only one patient who had HIV infection had TCC type of bladder cancer.

Figure 6 shows co existence of HIV and Schistosoma infection in bladder cancer patients

Figure 7: Existence of HIV and schistosomial infection

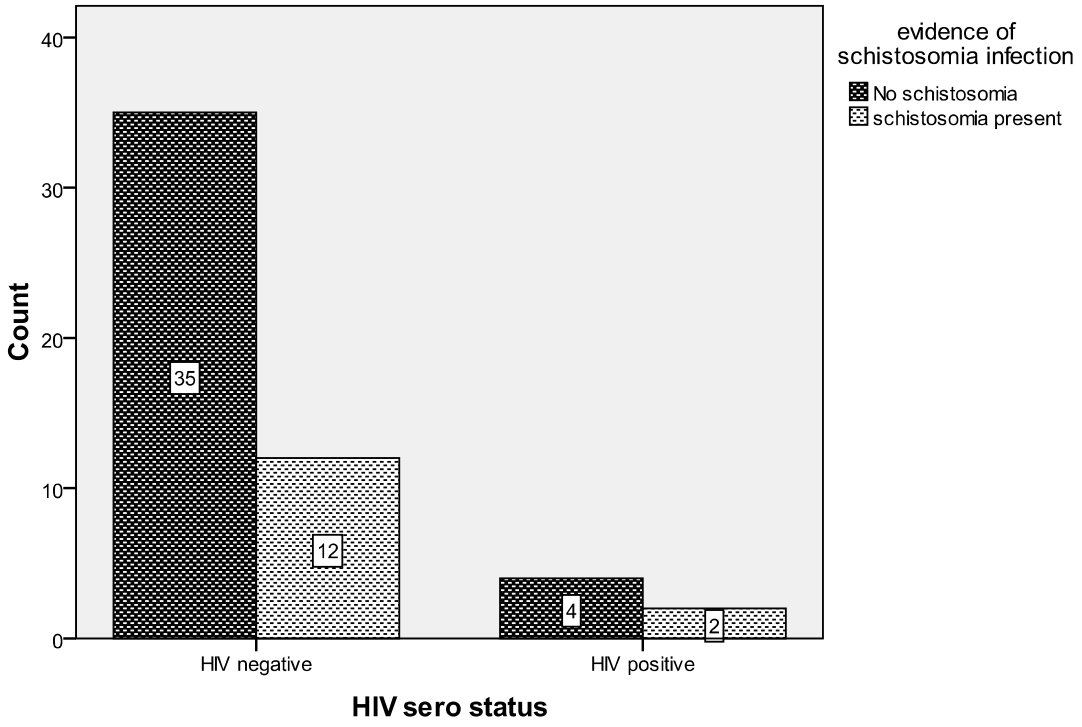

Figure 6 shows that of the total 6 patients that were HIV positive, schistosoma infection was found in 2 patients. Of the total 47 patients that were HIV negative, schistosomia was found in 12 patients.

Chapter Eight

DISCUSSION

8.1: Socio- demographic characteristics

8.1.1: Age distribution of patients

The mean age of patients with bladder cancer in this study was 57.49 years which agrees with a study from Egypt that found that the mean age of bladder cancer cases was 58.34years.[18] This mean age is less than what is reported in the literature for other parts of the world where Lynch and Cohen reported that the mean age of urothelial carcinoma in USA is 67years for males and 71 years for females.[4] In this study the mean age in male patients was 58.93 years and for females was 55.61 years. This shows that there is no statistical difference between males to females ($t = 0.778$, $df = 41.184$, $P = 0.441$) The findings are in contrast to earlier studies in USA where there is a statistical difference in gender for the mean age at the time of diagnosis of bladder cancer.[4] However the study agrees with another study in Zambia which showed that the peak age of bladder cancer was found to be in the age range of 56 and 65 years.[3] In this study the peak age for bladder cancer was found to be age ranges of 61 and 70years.

8.1.2: Gender distribution among patients

The study shows there is a male predominance in bladder cancer with a male to female ratio of 1.3: 1. This agrees with other studies within the country and outside the country that the disease is more common in males. Bowa et al found that the male to female ratio among patients with bladder cancer was 2: 1.[3] Other studies outside the country reports a wide disproportion of 4: 1 ratio.[4,12,18] The narrow ratio in this study can be attributed to the fact that in Zambia males and females are equally exposed to the risk factors like schistosomia where both males and females do participate equally in farming although

boys are slightly more exposed to swimming in schistosoma infected streams and males smoke more than females. This is in contrast to other countries such as Egypt were males engage in farming in dam areas much more than females hence the ratio is as wide as 4: 1 with male predominance.[12,18]

8.1.3: Residential distribution of patients

The patients in this study came from all the nine provinces of Zambia although some provinces such as North- Western and Western had only one patient each. Lusaka province had the most patients followed by Eastern province. The high figure recorded from Lusaka and Eastern provinces can be attributed to the accessibility to the main referral hospital, UTH which is located within Lusaka province, while Eastern province has a strongest referral system where patients are provided with transport to reach their referral destination. The presence of St. Francis mission hospital with specialists who are able to diagnose bladder cancer and refer patients makes may contribute to high figures from that province. However the risk factor for most patients which is schistosoma infection was isolated in most patients from Eastern province. Of the total 15 patients from this province, schistosomial infection was isolated in 7 patients. On the other had Lusaka province which had a total of 18 patients, schistosomial infection was only isolated in 4 patients. This agrees with geographical distribution that Eastern province is largely a rural settlement and people are more likely to be engaged in fishing, swimming and other activities that bring them into contact with schistosoma infected water bodies.

8.2: Clinical presentation among patients

8.2.1: Presenting symptoms

The most common presenting symptom in patients with bladder cancer was found to be haematuria. This was found to be in 94.3% of cases. This agrees with other studies that haematuria is the most common symptom [4, 12, 18] .Messing and Valencourt (1990) found that painless haematuria most common presenting symptoms in up to 90% of patients

with bladder cancer. This strengthens that teaching that in an adult with haematuria, they should be evaluated for cancer of the urinary system since haematuria is a very sensitive symptom in bladder and renal cancer. The fact that the cardinal symptom of bladder cancer is painless haematuria makes presentation of patients very late in the disease progression as most patients may have gotten used to schistosomial infection which has the same symptom of haematuria.

8.2.2: Physical findings among patients

All the patients recruited in this study had no evidence of liver involvement in that none had jaundice. However clinical anaemia was found in 87.2% patients. This correlates with the above finding that haematuria is the most common presenting symptom. Only 5 patients in this study had a palpable abdominal mass. This agrees with other findings that physical examination is most patients are normal of a signs specific to cancer of the bladder.[4] The fact that spread to the liver was rare in this study agrees with other studies that SCC which is common in Zambia which points to extensive mural fibrosis associated with SCC and hence this type of cancer.[18]

8.3: HIV prevalence among bladder cancer patients

The prevalence of HIV infection in the patients studied was 11.3% where only six patients out of the 53 were HIV positive. Of the 6 who were HIV positive, only two were diagnosed during the study while the other four were already on HAART. This prevalence of HIV infection is lower than the national prevalence of HIV in Zambia which currently is reported to be 14.3%. This may suggest that bladder cancer may not be an AIDS defining malignancy. A recent 2008 epidemiologic study using HIV/AIDS Cancer Match Study data reported a lower incidence of bladder cancer in the HIV population as compared to the general population [20] .This low level of HIV prevalence rate agrees with previous studies in the country that bladder cancer was not among the top five cancers at UTH.[6] In a retrospective study of the pattern of malignancies at UTH from January 1997 to December 2005, it was found that the five most common cancers in males were Kaposi's sarcoma, cancer of the eye, soft tissue sarcoma, prostate cancer and non- Hodgkin's lymphoma. In females the most common cancers were cancer of the cervix, cancer of the eye, breast cancer, Kaposi's sarcoma and non- Hodgkin's lymphoma.

8.4: Histological pattern of bladder cancer

8.4.1: Histological types of bladder cancer

Histopathological examination in this study showed that 60.4% of the cases had SCC, 30.2% had TCC and adenocarcinoma constituted 9.4%. (Table 7). This agrees with the previous studies done in Zambia which showed that SCC is most predominant type of bladder cancer. [3] Bowa et al found that the histological type of bladder cancer was mainly SCC (46.2%), TCC constituted 23.4% and adenocarcinoma had 22.2%. However this study showed that 2/3 of the cases was SCC as contrasted with the above study of SCC constituting less than half of the cases. The study agrees with some studies in Africa which shows that SCC is the most predominant in Africa. [18] Zarzour et al in a study of muscle invasive bladder cancer in Upper Egypt showed that 67.6% of cases had SCC, 15.4% had TCC.[18] This agrees with the traditional pattern of bladder cancer in Egypt. However a study on the changing patterns of bladder cancer in Egypt over the past 26 years showed that from period of 1990 to 2005 the most common type of bladder cancer was TCC constituting about 73% while SCC decreased from 78% in 1980 to 27% in 2005.[12] This change in pattern has been attributed to the decline in schistosoma infection in Egypt. This is as a result of control of the parasite in the water bodies and treatment of patients with active schistosomial infection. Zambia is however still paying the toll of the previously high prevalence of schistosomial infection. The bilharzia control programme was just launched less than six years ago and is still far from controlling the infection in the endemic areas.

This study also showed that were no statistical association between gender and histological type of bladder cancer (F= 0.525, P = 0.842). Of the 30 male patients: 19 had SCC and 8 were TCC. The total of 23 female patients, 13 had SCC and 8 had TCC. This agrees with other report that suggests that there is no association between the type of bladder cancer and gender [4] .

8.4.2: Distribution of schistosomial infection

Results of the distribution of schistosomial infection show that most of the cases that had schistoma infection were residents from Eastern province. Although Lusaka province had most cases of bladder cancer, only 4 patients had schistosomia in their biopsies. This is expected because Lusaka is mostly urban settlement and the human contact with bodies of water is less as compared to Eastern province which is largely rural and the population tends to have contact with water streams either as swimming, fishing or farming.

8.4.3: Mean age at first presentation in different histological types

The study showed that among bladder cancer patients that was no statistical significance in mean age between SCC and TCC. From the study the mean age for SCC was 54.47±15.73 years and for TCC the mean age was found to be 62.63 ± 10.83 years. There was no statistical difference between the two (t= -1.861, df = 46, P = 0.069) . This contrast with a study in Egypt which showed there was a statistical difference between SCC and TCC mean age at the time of diagnosis (58.3 vs. 50.3 years , $P < 0.001$) [18]. The small sample size in our study may account for the difference in results.

The study found interesting results regarding the mean age in patient with SCC. Of the total 32 patients with SCC, the mean age in patients with positive schistosoma infection was 48.14 years and in schistosoma negative SCC the mean age was found to be 59.39 years. This shows that there was a statistical difference in mean age at first diagnosis between schistosoma positive and negative ($P < 0.05$). This shows that schistosoma positive patients presented at a younger age than schistosomia negative bladder cancer (48.14 vs. 59.39 years). This finding agrees with other reports that patients with schistosomia associated bladder cancer presents at a younger age than non schistosomia SCC bladder cancer. [19] . Shokeir et al reports that the mean age of patients with bilharzial bladder cancer was 10-20 years lower than in non bilharzial cancer.

8.4.4: Analysis of histological types of bladder cancer type with HIV status

A cross tabulation of histological type against HIV status showed that of the patients who had HIV infection 5/6 had Squamous cell carcinoma and only one had TCC. This may suggest that HIV infection may be associated with SCC which traditionally presents at an earlier age and at more advanced stage than TCC. That would mean that, the most common diagnosis of hemorrhagic cystitis given to HIV infected patients with haematuria needs to have a cystoscopic evaluation to exclude malignancy before they are diagnosed to have hemorrhagic cystitis which is presumed to be benign as opposed to malignant bladder cancer. The findings in this study contrast with a small retrospective study involving HIV positive patients with bladder cancer. The study showed that the mean age was 55years and most patients (10/11) had Transitional cell carcinoma and only one had SCC [13].However this study agrees with the younger mean age of patients with bladder cancer in HIV positive. In our study the six patients had a mean age of 50.3 years still a younger age compared to the overall mean in bladder cancer patients. However in this study there was no statistical association between sero status and histological type of the bladder cancer ($F= 0.971$, $P = 0.812$).

The study found no significant existence of co infection of HIV and schistosoma infection. It was found that of the six patients who were HIV positive only 2 had schistosoma infection. These two had SCC type of bladder cancer

.

Study strengths

This study has several strengths. The study design of a prospective study allowed collection of information of the demographic characteristics of patients with bladder cancer over the period of one year. This computation of gender ratios, age distribution of specific histological type of bladder cancer and residential distribution of bladder cancer in Zambia.

The study to our understanding is the first of such a kind in Zambia to capture the HIV status of patients with bladder cancer and therefore able to describe the prevalence of HIV infection in patients with cancer of the bladder in Zambia. This is in contrast with the previous studies that were either histopathological based or from the cancer registry that did not capture the HIV status of patients and could therefore not describe HIV prevalence.

The quality of data was generally high as data collection, coding, entry of data and analysis was done by one personnel the researcher which limits variability in the results that would otherwise may have occurred with several study personnel recording differently and reporting the history and clinical findings in patients.

Study limitations

The study had a number of limitations. Since the study setting was a hospital based type of study, it relied on patients reaching the referral hospital from their respective district and provincial hospitals. A good number of patients may have not reached the hospital during the study time and hence certain provinces recording lower numbers of cases. Therefore it may not be possible to generalize the results to a national level but only propose some hypothesis for further study.

The study duration of one year is fairly short for such a rare disease and therefore the sample size accrued during this study was not adequate enough to allow the computation of chi- square test as some cells of the tables had values less than five and makes the chi-square test invalid.

Chapter Nine

9. CONCLUSIONS AND RECOMMENDATIONS

9.1: CONCLUSIONS

The Pattern of bladder cancer in Zambia in an era of HIV epidemic has not changed significantly. The disease is still male predominant with a slightly reduced male to female sex ratio and disease peaking in the sixth decade an age younger than the developed countries.

The prevalence of HIV infection is lower than the national prevalence of HIV in the general population and therefore cancer of the bladder may not be an AIDS defining malignancy since its prevalence is lower in the HIV infected patients

Squamous cell carcinoma has continued to be the most predominant histological type in Zambian patients although there is noticeable increase in the cases of adenocarcinoma.

Zambia is still paying the toll of the high prevalence of schistosoma infection especially in the rural areas of the country.

Studies to determine the exact histological features of bladder cancer in HIV infected patients are needed as more people with HIV infection continues to live longer as a result of national wide roll out of anti retroviral treatment in Zambia.

9.2: RECOMMENDATIONS

- There is need to eradicate the schistosoma parasite from the streams of water where there are likely to come into contact with people so that the long term effects of the infection are minimized. Schistosoma associated bladder cancer is one type of cancer that is preventable.
- There is also need to provide anti parasitic treatment to people who are actively secreting the schistosoma ova in urine both to break the infection cycle and to provide treatment for the infected one so that cases of bladder cancer associated with schistosoma are reduced.
- Haematuria should be regarded as serious symptom and patients should be adequately evaluated for cancer of the urinary system and bladder cancer excluded before a patient is considered to have hemorrhagic cystitis especially in HIV infected patients.
- This kind of a study needs to be done over an additional three to four years to exactly determine the effect of HIV infection on bladder cancer and get a sample size adequate enough to allow computation of tests of association such as chi-square.

BUDGET

Item	Unit cost (ZMK)	Quantity	Total
1. Laboratory			
a) Histopathological results	100, 000	55	5,500, 000
b) Blood results	10,000	55	550,000
c) Specimen bottles	20,000	55	1,100,000
d) Syringes and needles	5,000	55	275,000
Subtotal			**7, 425, 000**
2. Stationary			
a) Flash disc	350, 000	2	700,000
b) Bond paper	30,000	5	150,000
c) Printer toner	350,000	3	1,050,000
d) SPSS soft ware	400,000	1	400,000
Subtotal			**2,300,000**
3. Personnel			
a) Researcher training in SPSS	2,000,000	1	2,000,000
b) Research assistants	250,000	2	500,000
c) Patients transport refunds -	50,000	53	2,650,000
d) Ethics committee	500,000	1	500,000
Subtotal			**5,650,000**

4. Secretarial services			
a) Research proposal typing	250,000	1	250,000
b) Proposal photocopying	10,000	5	50,000
c) Proposal binding	10,000	5	50,000
d) Research report typing	300,000	1	300, 000
d) Research report photocopying	15,000	5	75,000
f) Research report binding	10,000	5	50,000
Subtotal			**775,000**
Total			**16,125,000**
Contingency fund 10%			**1,612,500**
Grand total			**17,737,500**

APPENDIX 1: DATA COLLETION SHEET

1. Patient features
    1. Study Number…….
    2. Age……..
    3. Sex : Male □ Female □
    4. Residence ……
2. Presenting complaints
    i. haematuria Yes □
    No □
    ii. Dysuria Yes □
    No □
    iii. Necroturia Yes □
    No □
    iv. Urinary retention Yes □
    No □
    v. Abdominal swelling Yes □
    No □
    vi. Others……
3. Physical Examination findings
    i. Anaemia Yes □
    No □
    ii. Jaundice Yes □
    No □
    iii. Abdominal mass Yes □
    No □
4. Laboratory Findings
    i. HIV Positive □
    Negative □

    ii. Liver function Normal □

Impaired □

iii. Renal Function Normal □

Impaired □

iv. Anemia No anaemia □

Mild anemia □

Moderate anemia □

Severe anemia □

5. Histological type SCC □

TCS □

Adenocarcinoma □

Other……..

6. Presence of schistosomia ova in tissue Yes □

No □

APPENDIX 2 : PARTICIPANT INFORMATION SHEET

My name is Dr. Victor Mapulanga, a resident doctor in urology, department of surgery at the University Teaching Hospital. Am conducting a study on cancer of the bladder and its relation with HIV infection. The purpose of the study is to determine whether there is a relationship between cancer of the bladder and HIV infection.

Am requesting you to participate in the study by giving blood on voluntary basis for an HIV test and will only be collected once. Only 2ml of blood will be drawn for the HIV test from your vein in your arm. Blood will be drawn by a qualified medical practitioner.

During the collection of blood, you may experience some discomfort or bruising at the site of collection. To minimize this, trained personnel will collect blood using the smallest needle which is sterile, not used before and free of germs and aseptic technique will be employed.

Although you may not directly benefit from participating in the study, you will make major contribution to the information known about cancer of the bladder and HIV. In the future others will benefit because doctors and scientist will learn how HIV affects cancer of the bladder.

The study will not delay your treatment nor prolong your stay in the hospital. The researcher will keep the records and results of your blood locked in the cabinet and the keys will be kept by the researcher and the results will not be disclosed to other people neither will other people be told of you participation in the study.

If you feel that you have been injured or inconvenienced as a direct participation in the study, you are at liberty to withdraw from the study at any time without any penalty or loss of benefits.

In any case of any questions or seek clarifications please contact me Dr. Victor Mapulanga on 0977465152, department of surgery, university Teaching Hospital , P/B RW1X, Lusaka.

You may also contact the chairman of the University of Zambia Biomedical and Research Ethics Committee. Ridgeway campus. P.O Box 50110, Lusaka, Zambia telephone 0211-256067.

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Certificate of Consent

Your signing of this form means that you understand the information presented and that you want to participate in the study. You understand that participation is voluntary and you may withdraw from the study at any time. If you agree to participate in the study, kindly sign the consent form that follows.

I ……of address……..
On this day of ……month of ……. Of the year…….. Do understand the importance and the risks of participating in this study have been explained to me
I have read the foregoing information, or it has been read to me. I have had an opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research and agree to the terms of the study as laid by the researcher.

Signature or print of participant …….

Name of the participant ……

Date…… (Day / month / year)

Statement by a witness

I have witnessed the accurate reading of the consent form to the participant, and the individual has had an opportunity to ask questions. I confirm that the participant has given consent freely

Name of witness : …….

Signature of witness: ……
Date : ……. (Day / month / year)

Statement by the researcher

I have accurately read out the information to the participant and to the best of my ability made sure that the participant understands that the following will be done:

1. Standard urological evaluation as prescribed by the hospital protocol
2. Counseling and testing for HIV

I confirm that the participant was given an opportunity to ask questions and all the questions have been answered correctly and to the best of my ability. I confirm that the participant was not coerced into giving consent and consent has been given freely and voluntarily.

Name of researcher: ……

Signature of Researcher:……..

Date:…… (Day / month / year)

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