UNIVERSITY OF NAIROBI

A FIVE-YEAR REVIEW OF THE OUTCOMES ON THE MANAGEMENT OF CANCER OF THE CERVIX AT KENYATTA NATIONAL HOSPITAL.

A RESEARCH DISSERTATION, SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN OBSTETRICS AND GYNAECOLOGY, IN THE SCHOOL OF MEDICINE, COLLEGE OF HEALTH SCIENCES AT THE UNIVERSITY OF NAIROBI.

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DECLARATION:

I declare that this is my original work and has not, to the best of my knowledge, been presented anywhere else.

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To my late parents, Mrs. Gladys Atieno Omollo-Juma and Mr. Clement Juma Mwaya.

ABBREVIATIONS AND DEFINITION OF TERMS:

FIGO:	International Federation on Gynaecology and Obstetrics
HIV:	Human Immunodeficiency Virus
HPV:	Human papilloma virus
KNH-UoN ERC:	Kenyatta National Hospital-University of Nairobi Ethics and Research Committee
MOH:	Ministry of Health
SPSS®	Statistical Package for the Social Sciences
STIs	Sexually Transmitted Infections
WHO:	World Health Organisation
Parity X:	Pregnancy that went up to 28 gestational weeks or more
Parity Y:	Pregnancy that did not attain 28 gestational weeks

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ABSTRACT

Background:

Cervical cancer is the leading cause of cancer-related morbidity and mortality among women in sub-Saharan Africa and other developing countries. Kenyatta National Hospital has over the years been the referral centre of choice for many Kenyans for the treatment of cancer of the cervix where different management modalities are offered depending on the stage of the disease. Late diagnosis has limited treatment options and this affects the survival rates.

Objective:

To determine the outcomes of management of patients with cancer of the cervix at Kenyatta National Hospital: a five-year review.

Methodology:

A retrospective cohort study was carried out over the five - year period of 2007-2012 to determine the outcomes of management at KNH and document the survival rates for future appraisal in service delivery at the Hospital. The exposures were the 4 arms of treatment in which surgery 81, radiotherapy 81, chemotherapy 60 and combined therapy 87 patients records were reviewed for the treatment modalities respectively and the outcomes of interest were the survival rates. The sampling frame included all patients managed for cervical cancer at Kenyatta National Hospital from July 2007-June 2012 and had a clinical staging and histological diagnosis. Data on patients' demographics, stage at diagnosis, specific management given was collected using standardised data retrieval forms. Two and five-year survival rates were generated. Analysis was done using SPSS®. The study proposal was submitted to the KNH-UoN Ethics and Research Committee for review and approval before being carried out.

Results:

The age of the participants varied from 23 years to 91 years (mean of 47.76), while the mode was 46 years. Sixty five percent of the participants were between the age group of 35 years and 54 years. Squamous cell carcinoma was the most common histological diagnosis (89.3 %). Adeno carcinoma accounted for 8.4% of the diagnoses. Thirty seven percent of the participants had early stage disease (up to FIGO stage IIa), while 63% of the participants had advanced stage disease (from stage IIb to IVb). Only 132 (42 .7 %) of the participants had recorded tests for HIV infection of whom about 45 % were positive. The overall survival rates were 47.6% and 14.9% at two and five years respectively. The staging of the disease ($p < 0.001$, $p = 0.001$), the mode of treatment **(<0.001 (χ^2), <0.001 (χ^2))** were shown to have an association with the 2 and 5 year survival rates respectively.

Conclusion:

A total of 309 participants were reviewed for the four treatment arms: Surgery 81, Radiotherapy 81, Chemotherapy 60 and Combined 87. A hundred and fourteen (37%) of the participants had early stage disease (Up to FIGO stage IIa), while 195 (63%) of the participants had advanced stage disease (from stage IIb to IVb). The overall survival rates were 47.6% at two years and 14.9% at 5 years. The study highlights the association of late diagnosis of cervical cancer and survival rate in which the survival was only 31.9 % at 2 years and 3.6% at 5 years for stages IIb to IVb. This

compares with 70.1% at 2 years and 51.9% at 5 years for early stage disease (up to stage IIa). The predictors of survival were age at diagnosis, staging of the disease at diagnosis and the mode of treatment offered. Among other recommendations, radiotherapy services in public institutions should be devolved to the counties to reduce delay in initiating treatment after diagnosis and reduce defaulting and loss to follow-up due to distance and cost.

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1.0 BACKGROUND:

Cervical cancer is a disease in which the cells of the cervix become abnormal and start to grow uncontrollably, forming tumours. Worldwide the prevalence rate of cervical cancer is approximately 1 million annually. Cancer of the cervix is most common in developing countries. In developed countries, the incidence decreased by 80% and death by 70% due to pap smear screening.(1).

About 84 per cent of cervical cancer cases occur in less developed countries. The highest incidence of cervical cancer was in Africa, Latin America and the Caribbean; and the lowest incidence in Northern America and Oceania(2). Risk factors for developing cervical cancer include early age at first coitus, multiple sexual partners, multi-parity, lack of barrier contraception, and history of sexually transmitted infections, low socio – economic status and degree of effective mass screening(3). Determinants of cervical cancer include age variability, reduced incidence in nuns and virgins. Male circumcision is partially protective; HIV –HPV relation is documented as an aggravating factor (4, 5).

Cervical cancer pathology is seen 80% on the ectocervix and 20% on the endocervix. It may grossly appear as exophytic (arising from the cervix), ulcerative (excavates the cervix) or infiltrative (usually endocervical). Histology is mainly squamous cell carcinoma (85-90%), adenocarcinoma and mixed type. Cervical cancer may spread via direct extension, the lymphatic system, haematogenously or rarely by direct implantation of cancer cells.

Staging of cervical cancer is important in determining prognosis; formulating line of treatment and comparing the results of one to another. Staging is principally clinical by pelvic examination and supplementary by use of Chest X-rays, Intra-venous urography and cysto/proctoscopy(3).

In cervical cancer, the patient profile is usually multiparous, pre-menopausal with history of post-coital/inter-menstrual bleeding. The symptoms vary from irregular continued per vaginal bleeding, offensive per vaginal discharge, pelvic pain, leg oedema, bladder symptoms (dysuria, haematuria, incontinence, fistula and increased frequency), ureteral obstruction, and rectal involvement (diarrhoea, rectal pain, bleeding, fistula). Physical examinations reveals a cervical mass which maybe friable, fungating or ulcerative. Bimanual examination reveals the extent of the tumour to the vaginal sidewalls, bladder induration through the anterior fornixes; rectal exam determines parametrial involvement, pelvic wall involvement, nature of induration of the rectal mucosa, whether it is smooth or nodular. (5, 6).

Diagnosis is confirmed by biopsy; for a small mass, a wedge biopsy to include portion of healthy tissue is done. For a big tumour, samples are taken from an involved and a non-involved area. Haemorrhage is contained by plugging.

Complications of cervical cancer include haemorrhage, ureteric pain due to pyelitis, pyelonephritis, hydronephrosis, pyometra, vesico-vaginal and recto-vaginal fistulae and death. Common causes of death include Uraemia (due to ureteric obstruction leading to hydroureter and Hydronephrosis which predispose to infection, compromising kidney function), haemorrhage leading to anaemia, sepsis due to peritonitis, cachexia and metastasis (lungs 36 %, Lymph nodes 30%, bone 16%, abdominal cavity 7%).

Approach to management can be divided into two approaches; Preventive and Curative management. While efforts for Preventive management have increased in the developing countries like Kenya, we still have a significant population that would benefit from the curative approach due to late presentation at the time of diagnosis for the victims(7, 8).

Primary preventive management involves identifying high risk women (high risk to HPV infection, early intercourse, early age of 1st pregnancy, too many/ frequent births, low socioeconomic status and poor maintenance of local hygiene); identifying high risk males (multiple sexual partners, previous wife died of cervical cancer); prophylactic HPV vaccine (the bivalent Cervarix and the quadrivalent Gardasil); use of condoms, increase age of marriage and pregnancy; and removal of the cervix during hysterectomy(5, 9).

Secondary preventive management includes screening (Pap smear, VIA/VILI); and down-staging screening whereby in high incidence and low screening areas, a speculum exam done by a trained personnel may be able to grossly distinguish between a normal (pink, round, smooth, doesn't bleed easily) from an abnormal (reddish, red or white particles, growth or ulcer, friable) cervix.

Curative management of cervical cancer is a team approach involving the Gynaecologist, Radio-oncologist, Urologist, Interventional Radiologist and Internist among others. The patient is reviewed and an individualised care plan is made by considering the general condition of the patient, stage of the disease, facilities available (medical, surgical and radiotherapy) and the wishes of the patients. Anaemia and malnutrition if present are corrected as part of pre-treatment preparations to enable the patient to withstand surgery and promote tissue oxygenation for effective ionising effect of irradiation (9, 10).

The treatment modalities of cervical cancer include primary surgery (radical hysterectomy, pelvic exenteration), primary radiotherapy, and chemotherapy and combination therapy. Palliative treatment is a comprehensive care for relief of symptoms along with treatment of cervical cancer in advanced stage. Palliation is given to relieve pain, stop bleeding and stop purulent/ foul smelling per vaginal discharge.

Prognosis for patients with cervical cancer depends on the staging and is usually expressed in a 5-year survival rate for each stage. Risk factors for recurrence include a large tumour size, lymphovascular space invasion, positive lymph nodes and advanced stage disease. The pelvic sidewalls are the most common sites of recurrence. Features of recurrence are pain in the pelvis, back, unilateral leg oedema, ureteral obstruction, vaginal bleeding, palpable tumour in the pelvis and lymphadenopathy. Most recurrences occur in the first 2 years and follow-up of 3-4 months interval in the first 2 years is paramount, then 6-monthly for the next two, then annually. A thorough physical exam, cervical/vaginal cytology and a chest x-ray annually are done to rule out metastases during the revisits.

2.0 LITERATURE REVIEW

Cervical cancer is the most common gynaecologic malignancy in the world, and the second most frequently diagnosed cancer in women worldwide after breast cancer(2). The majority of cases (85%) occur in developing countries where it accounts for almost 12% of all female cancers. High-risk regions, with estimated Age-Standardised Rates over 30 per 100,000, include Eastern Africa (42.7), Melanesia (33.3), Southern (31.5) and Middle (30.6) Africa. The rates are lowest in Australia/New Zealand (5.5) and Western Asia (4.4). Cervical cancer remains the most common cancer in women in Eastern and Middle Africa(2).

The World Health Organization estimated cervical cancer worldwide incidence for the year 2012 to be 528,000 cases with a mortality rate of 266,000 cases. The 5 -year prevalence rate by 2012 was estimated at 1,547,000 cases(2). About 87% cervical cancer deaths occur in the less developed regions, with an estimated mortality of 230,000 cases for an incidence of 445,000 cases and a comparable 5 - year prevalence of 1,258,000 cases in 2012.

In the developed world the incidence rate is 83,000 with 35,000 mortalities and a 5-year prevalence of 289,000. In the developing world, the incidence is 445,000 with 230,000 mortalities and a 5-year prevalence rate of 1,258,000. The huge difference is due to the high uptake of prevention and early detection measures like vaccines and widespread screening in the developed countries.

In Africa, the incidence is estimated at 92,000 with a mortality of 57,000 and a 5-year prevalence rate of 236,000(2). According to the Ministry of Health, the Government of Kenya places cancer as the third highest cause of morbidity in the country after Infectious diseases and cardiovascular

diseases(11). National data is mainly hospital based. However, the ministry reports cervical cancer as the most common cause of cancer related deaths in Kenya. The incidence of cervical cancer in Kenya is estimated to be 2,454 women per year with annual number of deaths estimated at 1,676 women. Gichangi et al and Rogo et al, found that cervical cancer was the most common gynaecological malignancy diagnosed at Kenyatta national hospital(12, 13).

In the absence of accelerated interventions for screening, detection and early treatment, the incidence of cervical cancer is projected to rise to 4,261 resulting in 2955 deaths in the year 2025. It has been reported that there are 10 to 15 new cases of cervical cancer in Nairobi each week(14, 15). About 70-80% of cancer cases are diagnosed in advanced stages due to lack of awareness, inadequate screening and diagnostics facilities, lack of treatment facilities, high cost of treatment and low socioeconomic status affecting health seeking behaviour(16). The number of radiation centres are also limited with only one public facility i.e. Kenyatta National Hospital with the privately owned being out of reach for the majority of the population in need due to cost.

Although Cancer of the cervix is easily detectable and curable in its early stages only about 5% of women in developing countries undergo screening for cervical cancer as compared to over 40% in developed countries, and 70% or higher in countries that have shown marked reduction in incidence and prevalence of cervical cancer. In Kenya, the government has stepped up its campaign on the relatively affordable Visual Inspection using Acetic Acid and Lugol's Iodine (VIA/VILI) to address the low uptake of screening services countrywide (11, 17).

It is therefore not surprising that in Kenya, where screening rates are still low, and the majority of women present with advanced disease. Kenyatta National Hospital in conjunction with the Medical school of the University of Nairobi have played a critical role in addressing the large number of clients seeking treatment due to advanced stages of the disease. The study will seek to review the efforts of these two institutions in the delivery of cervical cancer management to the patients who presented to them over the years and form a basis of future policy guidance in the management of the same.

Human papilloma Virus (HPV) infection is present in 99.7% of all cervical cancers. High-risk HPV types 16, 18, 31, 33, 35, 45, 52, and 58 are associated with 95% of squamous cell carcinomas of the cervix (4, 5). HPV 16 is most commonly linked with squamous cell cervical cancer; HPV 18 is most commonly present in adenocarcinoma. Most HPV infections are transient, resulting in either no change in the cervical epithelium or low-grade intraepithelial lesions that are often spontaneously cleared. The progression from high-grade lesion to invasive cancer can take up to 10-15 years.

Although cervical cancer is now a preventable disease and occurrence of invasive cancer is viewed as a failure of screening, the incidence is still high in the country necessitating the need for treatment of the cases diagnosed concurrent with the preventive efforts (6, 18). Diagnosis of cervical cancer is based on histology and staging. The International Federation of Gynaecologists and Obstetricians (FIGO) came up with a staging protocol to standardise care and be able to measure outcomes as per the treatment provided(8, 19).

As management of the disease is based on the staging, stage IA is treated by surgery and /or radiotherapy; stage 1B and IIA can be treated with surgery, radiotherapy or chemo-radiation. Advanced disease (from Stage IIB -IVB), treatment would include concomitant chemo-radiation and brachytherapy (3).

Cervical neoplasia in Kenya appears to be a late consequence of venereally transmitted carcinogenic agents(20). In a study to analyse the factors contributing to the low survival of cervical cancer patients undergoing radiotherapy in Kenya, Kaplan Meier survival curves projected two year survival at <20%(18).

MANAGEMENT OUTCOMES IN DIFFERENT REGIONS.

In Brazil current estimates indicate that every year 19,603 women are diagnosed with cervical cancer and 8,286 die from it. The crude mortality rate for Brazil is 9.4 (8.9 for world) for 100,000 women (2) .It is the second most frequent cancer after breast cancer in terms of incidence and mortality. The age - standardised incidence rate is 23.4 (16.2 world average) per 100,000 women with new cases being more common at the age of 15-54 years.

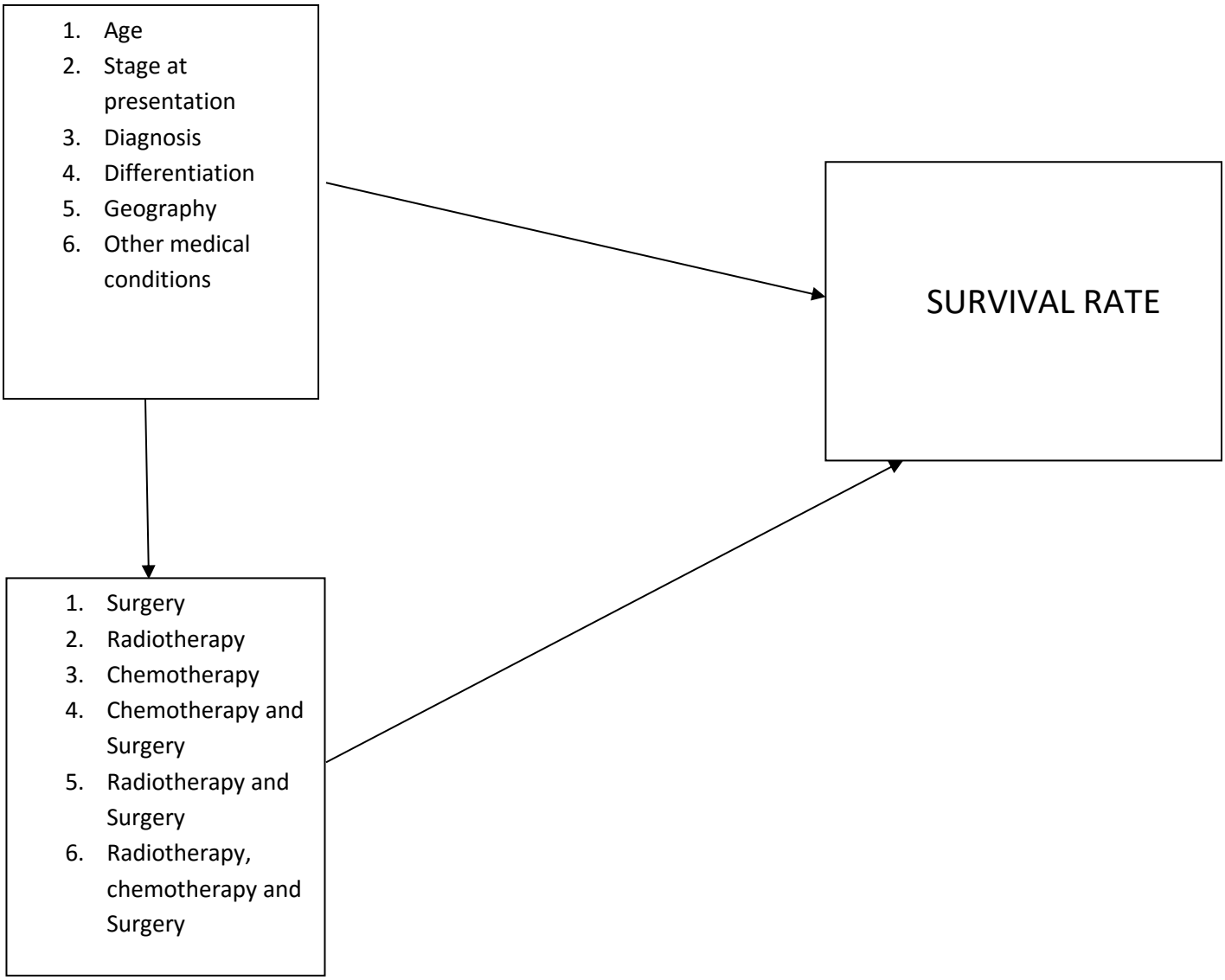
In India, Cervical cancer is ranked as the most frequent cancer in a population of approximately 365.71 million women above 15 years of age. The incidence is estimated at approximately 132,000 and 74,000 deaths annually, accounting to nearly 1/3rd of the global cervical cancer deaths. The high rates are associated with low levels of knowledge and awareness of the disease and prevention measures available (21, 22).

In Egypt late presentation has contributed to increased mortality rate. The fact that the disease does not have any signs makes a large number of women discover their infection very late and when these women visit a specialist they are beyond treatment in most cases. The culture of secrecy among women makes it difficult for medical examinations to be done. Coupled with high costs of vaccines and poverty, the health care system in the country has to grapple with the treatment of advanced disease(23).

In a retrospective study of patients seen at the Gynaecologic oncology unit of Ahmadu Bello University Teaching Hospital, Zaria, Nigeria between November 2005 and November 2009, All the cervical cancers reviewed were confirmed by histological examination; the FIGO clinical staging was used; Social classification was based on patients' educational status and their husbands' occupation. It was noted that surgery combined with adjuvant chemotherapy was usually offered in most centres in Nigeria which lacked radiotherapy. In Zaria there is a radiotherapy machine but it has a high patient load and so the time interval between diagnosis and treatment was considerably long(24).

2.6 CONCEPTUAL FRAMEWORK:

Variables such as age, stage of presentation, diagnosis, differentiation and other co-morbidities were documented and associations with the treatment arms and survival rates analysed. The older a person is the more probable she may have other medical conditions like hypertension, and this may influence the survival rates. Older patients may have co-morbidities that may not allow them to undergo surgery and as such affect the survival rate. The survival rate is also influenced by the staging of the disease as diagnosis at advanced stages of the disease has been shown to have a poor survival rate.



2.4 RATIONALE:

In Kenya it is noticeable that there is an increase in the incidence and prevalence of the disease and also that patients present late with a variety of complications all which affect the survival of the patients. KNH is the largest public referral hospital in Kenya where patients with cancer of the cervix receive treatment. Kenya is resource-limited hence the need to examine the outcomes based on the care given and therefore identify gaps and areas of improvement. The survival rate of patients treated for cancer of the cervix at KNH has not been reviewed despite the large number of patients accessing different treatment modalities.

The choice of treatment depends on the clinical stage of the disease and the availability of treatment facilities. At KNH there is a radiotherapy machine but it has a high patient load and so the time interval between diagnosis and treatment is considerably long. The high incidence of this disease in developing nations needs to be reduced and so better treatment methods are urgently required. The triple approach (surgery, radiotherapy and chemotherapy) for treating cancer of the cervix should be replicated in the County Governments. The motivation for this study is that cervical carcinoma in developing nation's needs to be addressed urgently and managed as such.

2.5 RESEARCH QUESTION:

What are the outcomes of management of patients with cancer of the cervix at Kenyatta National Hospital?

2.5.1. NULL HYPOTHESIS:

Late presentation has no impact on the survival rates of patients with cancer of the cervix receiving different treatment modalities.

2.5.2. ALTERNATIVE HYPOTHESIS:

Late presentation has a direct negative impact on the survival rates of patients with cancer of the cervix receiving different treatment modalities.

3.0 STUDY OBJECTIVES:

3.1 MAIN OBJECTIVE:

To determine the outcomes of management of patients with Cancer of the cervix at Kenyatta National Hospital: a five year review.

3.1.2 SPECIFIC OBJECTIVES:

1) To describe the socio-demographic characteristics of patients presenting with cancer of the cervix at Kenyatta National Hospital.
2) To determine the specific management offered to the patients with cancer of the cervix in terms of histological diagnosis, staging and treatment.
3) To assess the 2 and 5-year survival rates of patients with cancer of the cervix managed at Kenyatta National Hospital.
4) To compare the correlation between the socio-demographic characteristics and the outcomes of management for the patients with cancer of the cervix.

4.0 METHODOLOGY:

4.1 STUDY DESIGN:

A retrospective cohort study design was used in which 309 file records of patients who received different treatment options for cancer of the cervix between 2007 -2012 were sampled. Eighty one records each were for patients who received Surgery and radiotherapy, while sixty and eighty seven records were sampled for patients who received chemotherapy and combined therapy respectively. Data for 2 and 5- year survival rates were obtained from each record.

4.2 STUDY AREA AND POPULATION:

This study was done at Kenyatta National Hospital in Nairobi, Kenya. It is the largest referral and teaching hospital Kenya. It is an 1800 bed – capacity hospital with 50 wards, 22 out-patient clinics and 24 theatres. The University of Nairobi Medical School is located within its premises.

The study population was patients who were treated at Kenyatta National Hospital for cervical cancer in the 5 – year period as stated. Their medical records were available in a well-organized registry at the department of medical records of the hospital.

4.3 INCLUSION CRITERIA:

- All patients managed for cervical cancer at Kenyatta National Hospital from July 2007-June 2012.
- All patients with clinical staging and a histological diagnosis.
- All patients whose vital status is known at two years from the time of histological diagnosis.

4.4 EXCLUSION CRITERIA:

- Patients whose records were incomplete including records of either death or survival.

4.5 SAMPLE SIZE CALCULATION:

The study analysed 316 cases (79 cases for each of four treatment group – 1. Surgery, 2. Radiotherapy, 3. Chemotherapy, 4. Combination therapy). This sample size is powered for comparison of four independent groups at 5% level of significance, 80% power of test, and 5% margin of error. The following proportions for key outcome variables were used: Death = 51% (Ferlay J, GLOBOCAN 2012 v1.0). Cure rate and recurrence was assumed to be 50% of the surviving patients, i.e. 25% of the total population.

The following formula was used (25).

$$n=(\rho 0(1-\rho 0)+\rho 1(1-\rho 1))(\Phi^{-1}(\alpha/(2\tau))+\Phi^{-1}(\beta)\rho 0-\rho 1)^2$$

Where,

- $\rho 1$ is the rate, proportion, or probability to be tested
- $\rho 0$ is the comparison value
- Φ^{-1} is the standard normal quantile function
- α is Type I error
- τ is the number of pairwise comparisons to be made
- β is Type II error, meaning 1- β is power
- n is sample size

The calculation was done using R statistical software giving a sample size of **79** for each group thus a total of **316 (79*4)** for four groups**.**

4.6 SAMPLING METHOD:

All available files for patients managed for cancer of cervix from 2007-2012 were used for sampling. The files that fulfilled the inclusion criteria in terms of complete records, staging and clinical diagnosis were then identified.

A multi- stage sampling was done. Cases were categorized into five clusters (by year of file opening), one cluster for each year of the study. For each year, the file numbers were classified as per the exposure of interest whether surgery, radiotherapy, chemotherapy or combined.

Thereafter, systematic random sampling was done by selecting every second case in a treatment group that fits the inclusion criteria to a minimum of 16 cases per treatment group per year except for patients who received the chemotherapy in which all the records were used for the study.

4.7 DATA COLLECTION AND MANAGEMENT:

4.7.1 PROCEDURES:

All available files that fulfilled the inclusion criteria were reviewed using a retrospective data retrieval form that covered the general patient profiles, time of histological diagnosis, the staging, the treatment modalities received and the outcomes in terms of cure, remission, lost to follow-up and recurrence and those who succumbed. After data cleaning and adjusting for errors, a total of 309 participants were used for the study. 81 participants were treated by surgery, 81 by radiotherapy, 60 by chemotherapy and 87 by combination therapy.

The Principal investigator trained the two research assistants on the study protocol and procedures a week before starting data collection.

4.7.2 DATA COLLECTION INSTRUMENTS:

Data was collected using standardized data retrieval forms for every patient file reviewed. The forms were serialized and anonymous. Filled forms were collected every day, filed and stored safely. Data was stored in a password protected computer and a dedicated USB drive as a back-up under the custodian of the Principal investigator.

4.8 DATA ANALYSIS:

4.8.1 MEASURES:

The study measured the survival rates by cumulative density (for example if a patient survived for 13 months and another for 18 months, they will be evaluated under the 2 - year survival rates in spite of the difference on their survival times.

If a patient survived for 3 years and another for 4 years, they will be evaluated under the 5 - year survival rates in spite of the difference on their survival times):

The status of survival or death was determined through phone calls to the patients and next of kin. Out of the 309, it was possible to determine conclusively the status of survival of 234 of the cases. In 75 of the cases, it was not possible to establish the actual status and thus in the analysis for each treatment modality, the unknown survival status was indicated as such.

Independent variables: Age, Gender, staging of disease.

Collected data was cleaned by checking the questionnaires for errors and frequency distribution. Cleaned data was then coded and entered into SPSS® for analysis by the Principal investigator. Univariate analysis was done by use of frequency distributions and proportions for categorical variable such as gender. Bivariate analysis was done using chi-square and t-test to assess any

observed differences and to test the association of dependent variables and various socio-demographic characteristics.

4.9 ETHICAL CONSIDERATIONS:

Permission to carry out the study was sought and obtained from the Kenyatta National Hospital/University of Nairobi - Ethics and research Committee (KNH/UoN - ERC) Review board. Further, written permissions from the Department of Medical records, Kenyatta National Hospital, were sought and obtained to access the patients' data. This study bore minimal risk on the participants. Respondents' names were not recorded on the data retrieval forms.

4.10 STUDY LIMITATIONS:

A prospective study on the patients with cervical cancer would have been a more appropriate way of doing this study. However, the constraints of resources and time for a five-year prospective study would be very expensive, hence the choice of a retrospective study. In the review, it was taken that all patients were given treatment of the best possible standards and quality for their specific stage of presentation. Out of the 309 study subjects, survival for 234 cases was determined conclusively. The 75 cases lost to follow-up are potential sources of selective bias which could result in underestimation of the survival rates. Kaplan Meier method could not be used to assess the survival rates as it was not possible to get the exact dates of demise for the majority of the participants.

5.0 RESULTS:

A total of 309 records were retrieved from the Hospital Records department. The distribution of the patients according to the treatment modalities is as shown in table 1. It is noteworthy that only 60 records were found for patients who received chemotherapy alone.

5.1 Socio-demographic characteristics of study sample:

Table 1: Socio-demographic characteristics of the participants:

	Surgery	Radiotherapy	Chemotherapy	Combined	Total
Age:					
Mean	42.46	51.21	49.15	48.52	47.76
SD	9.007	13.282	11.021	9.832	11.323
Range (Min-Max)	43 (23-66)	56 (26-82)	58 (33-91)	43 (29-72)	68 (23-91)
Total	81	81	60	87	309
Age groups:					
Below 35 years	13 (16%)	6 (7.4%)	2 (3.3%)	5 (5.7%)	26 (8.4%)
35-44 years	37 (45.7%)	19 (23.5%)	21 (35%)	28 (32.2%)	105 (34.0%)
45-54 years	23 (28.4%)	28 (34.6%)	16 (26.7%)	30 (34.5%)	97 (31.4%)
55-64 years	7 (8.6%)	12 (14.8%)	18 (30 %)	16 (18.4%)	53 (17.2%)
65 years and above	1 (1.2%)	16 (19.8)	3 (5%)	8 (9.2%)	28 (9.1%)
Total	81	81	60	87	309
Parity X:					
Mean	3.56	5.21	4.78	4.79	4.58
SD	2.086	2.635	2.565	2.488	2.515
Range (Min-Max)	9 (1-10)	12 (0-12)	10 (0-10)	12 (0-12)	12 (0-12)
Parity Y:					
Mean	0.31	0.26	0.25	0.16	0.24
SD	0.683	0.755	0.968	0.479	0.718
Range (Min-Max)	3 (0-3)	4 (0-4)	6 (0-6)	3 (0-3)	6 (0-6)
Religion:					
Christian	77 (95.1%)	78(96.3%)	60 (100%)	84 (96.6%)	299 (96.8%)
Muslim	4 (4.9%)	2 (5.5%)	0 (0%)	2 (2.3%)	8 (2.6%)
Other	0 (0%)	1 (1.2%)	0 (0%)	1 (1.1%)	2 (0.6%)
HIV Status:					
Positive	27 (33%)	14(17.3%)	6 (10%)	13 (14.9%)	60 (19.4%)
Negative	15 (18.5%)	24 (29.6%)	15 (25%)	18 (20.7%)	72 (23.3%)
Unknown	39 (48.1%)	43 (53.1%)	39 (65%)	56 (64.4%)	177 (57.3%)

Close to 65% of the participants were between 35 years and 54 years. The median age was 46 years, with most of the participants being between the ages of 40 and 55 years (Table 1). Outliers on the age distribution were 23 years as the lowest known outlier and 91 years as the highest known outlier.

Most of the participants had 3 children with the parity ranging from 0 to 12 children. The mean number of children per participant was 4. About 97% of the participants were Christians, with 2.6% being Muslims.

5.2 Histological diagnosis and specific management:

Squamous cell carcinoma was the most common histological diagnosis, found in 276 (89.3 %) participants. Adenocarcinoma accounted for 26 (8.4%) and Adeno-squamous was found in 7 (2.3%) of the participants (figure 1).

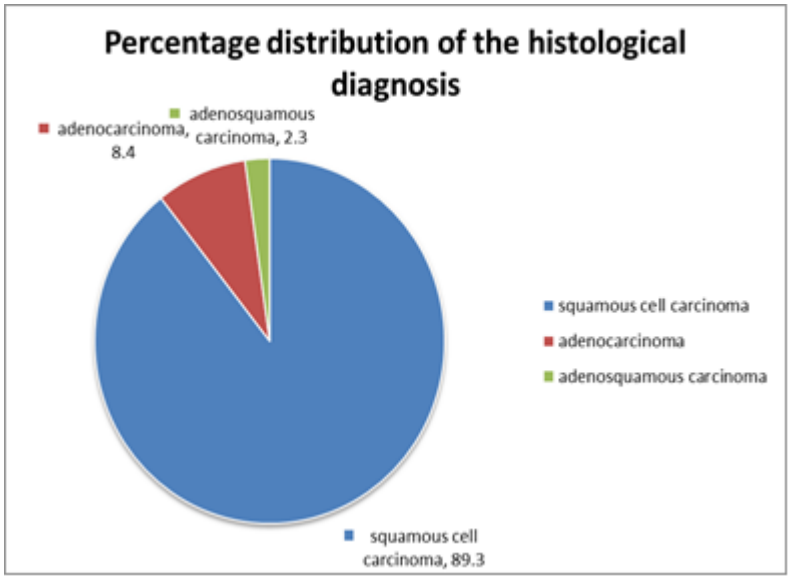


Figure 1: The histological diagnoses of the participants.

The cell differentiation on histology was mostly moderately differentiated (figure 2).

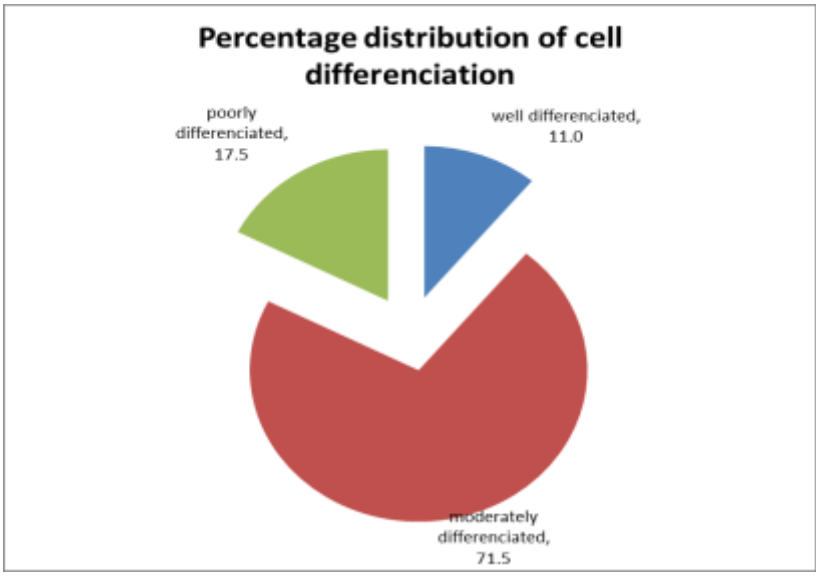


Figure 2: Cell differentiation at histology.

One hundred and fourteen (37%) of the participants had early stage disease (Up to FIGO stage IIa), while 195 (63%) of the participants had advanced stage disease (from stage IIb to IVb). Stage IIIb (22.7%) and stage IIb (22.3%) were the most common clinical stages at diagnosis (Figure 3).

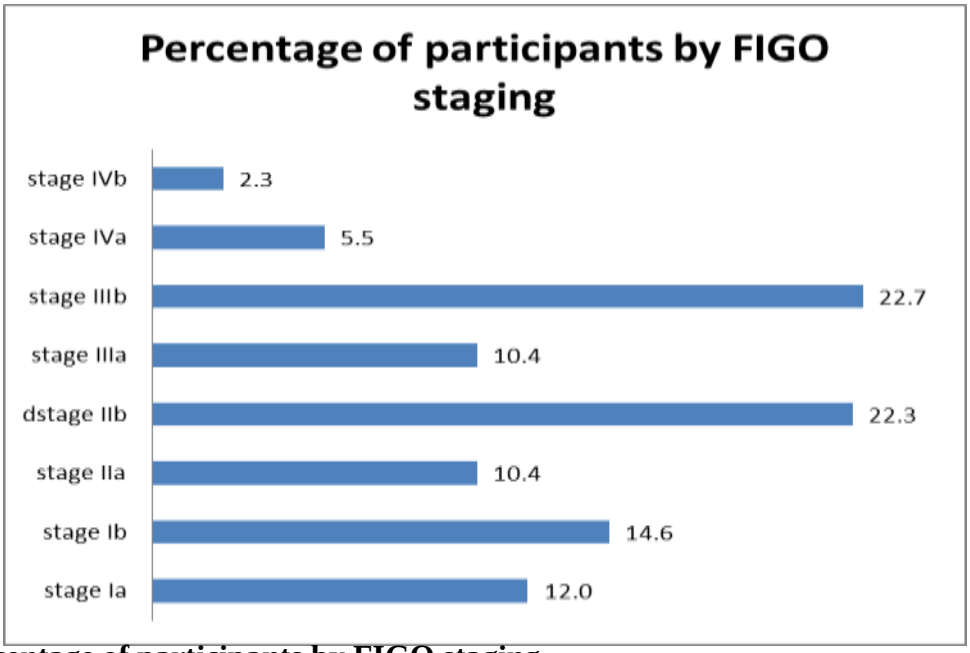


Figure 3: Percentage of participants by FIGO staging.

The duration from onset of symptoms to diagnosis in months had a median of 6 months (range of less than 1 month to 96 months). The duration since diagnosis to treatment in months had a median of 2 months (range of 0.25 to 36 months).

As illustrated in figure 4, only 132 (42 .7 %) out of the 309 participants had recorded tests for HIV infection. Sixty (45 %) of those with known statuses were positive making an overall of 19.4%.

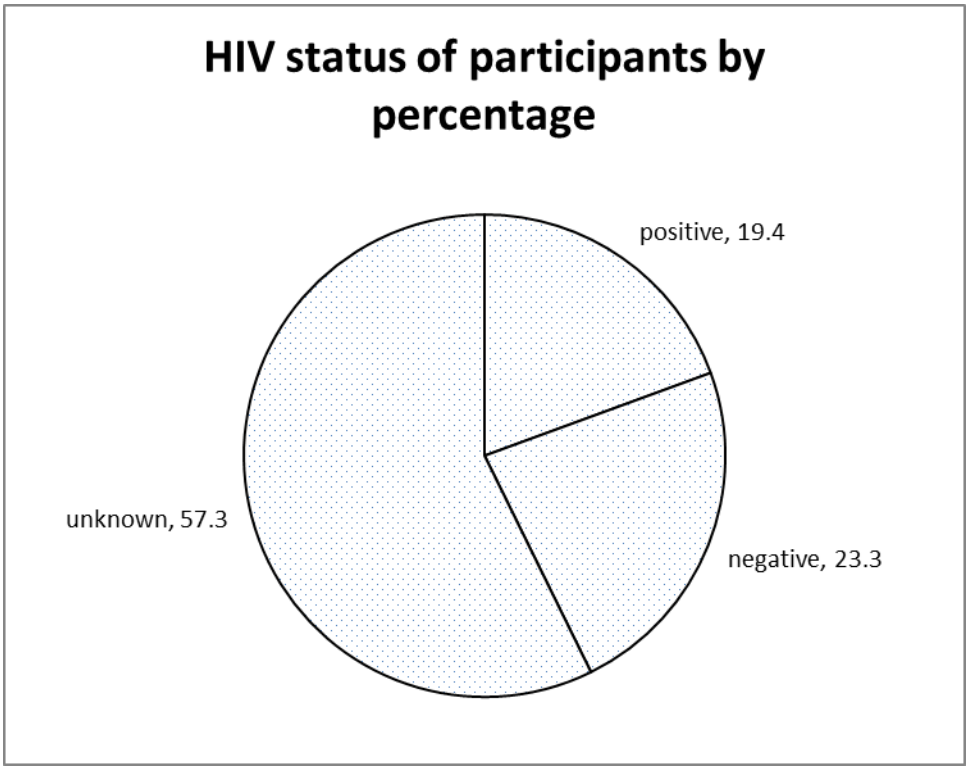


Figure 4: Frequency distribution of the HIV status of the participants.

5.3 Outcomes:

Table 2 and figure 6 present the data on outcomes of treatment according to the treatment options received. From file records and phone calls confirming survival or death status of study participants, the overall survival rate was found to be 47.6 % at 2 years and 14.9% at 5 years. The survival rates as per treatment arms were also analysed and presented below:

	2 year survival rate				**5year survival rate**			
Arms of treatment	**Alive**	**Dead**	**Status unknown**	**Total**	**Alive**	**Dead**	**Status unknown**	**Total**
Surgery	**61 (75.3%)**	3 (3.7%)	17 (21%)	**81 (100%)**	**24 (46.2%)**	11 (21.2%)	17 (32.7%)	**52 (100%)**
Radiotherapy	**19 (23.5%)**	38 (46.9%)	24 (29.6%)	**81 (100%)**	**4 (5.2%)**	51 (66.2%)	22 (28.6%)	**77 (100%)**
Chemotherapy	**29 (48.3%)**	21 (35.0%)	10 (16.7%)	**60 (100%)**	**2 (4.3%)**	36 (76.6%)	9 (19.1%)	**47 (100%)**
Combined	**38 (43.7%)**	25 (28.7%)	24 (27.6%)	**87 (100%)**	**9 (10.5%)**	51 (59.3%)	22 (28.6%)	**86 (100%)**
Total	**147 (47.6%)**	87 (28.2%)	75 (24.3%)	**309 (100%)**	**39 (14.9%)**	149 (56.9%)	74 (28.2%)	**262 (100%)**

Table 2: Survival rates of participants as per the treatment arms

The 2-year survival rate ranged from a low of about 24% for patients who received radiotherapy to a high of 75% for surgery. The lowest survival rate at 5 years was 4.3% among patients who received chemotherapy and highest at 46.2% for those who received Surgery. (Table 2 and figure 5).

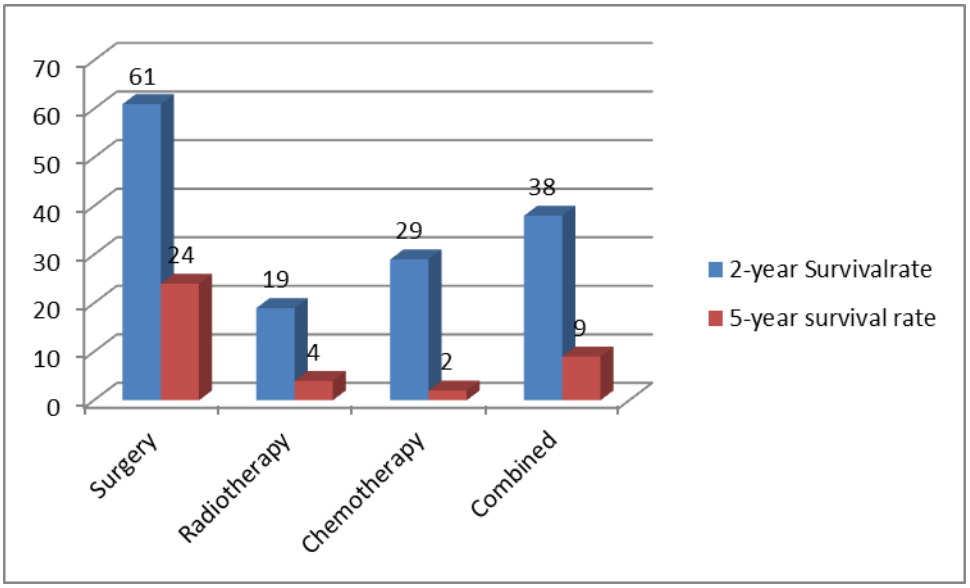


Figure 5: Percentage of survival rates as per the treatment arms.

Analyses of survival according to different exposures (staging, treatment arms, radiotherapy, histology, HIV status) was undertaken and the results are presented in tables 3 and 4.

Compared to the staging of the disease, the 2-year and 5-year survival rates were highest for stage Ia (91.9% and 77.3% respectively) and reduced as the staging advanced (Table 3).

Table 3: Survival rates as per FIGO staging.

	2 year survival rate				5year survival rate			
FIGO staging	**Alive**	**Dead**	**Status unknown**	**Total**	**Alive**	**Dead**	**Status unknown**	**Total**
Ia	**34 (91.9%)**	0 (0.0%)	3 (8.1%)	**37 (100%)**	**17 (77.3%)**	2 (9.1%)	3 (13.6%)	**22 (100%)**
Ib	**28 (62.2%)**	6 (13.3%)	11 (24.4%)	**45 (100%)**	9 (26.5%)	**14 (41.2%)**	11 (32.4%)	**34 (100%)**
IIa	**18 (56.3%)**	6 (18.8%)	8 (25%)	**32 (100%)**	4 (14.8%)	**14 (51.9%)**	9 (33.3%)	**27 (100%)**
IIb	**27 (39.1%)**	15 (21.7%)	**27 (39.1%)**	**69 (100%)**	7 (11.1%)	**29 (46.0%)**	27 (42.9%)	**63 (100%)**
IIIa	9 (28.1%)	**14 (43.8%)**	9 (28.1%)	**32 (100%)**	2 (6.7%)	**19 (63.3%)**	9 (30.0%)	**30 (100%)**
IIIb	24 (34.3%)	**31 (44.3%)**	15 (21.4%)	**70 (100%)**	0 (0%)	**50 (79.4%)**	13 (20.6%)	**63 (100%)**
Iva	5 (29.4%)	**10 (58.8%)**	2 (11.8%)	**17 (100%)**	0 (0%)	**14 (87.5%)**	2 (12.5%)	**16 (100%)**
IVb	2 (28.6%)	**5 (71.4%)**	0 (0%)	**7 (100%)**	0 (0%)	**7 (100%)**	0 (0%)	**7 (100%)**
Total	**147 (47.6%)**	87 (28.2%)	75 (24.3%)	**309 (100%)**	39 (14.9%)	**149 (56.9%)**	74 (28.2%)	**262 (100%)**

As shown in table 3, 37% (114) of the participants had early stage disease (Up to FIGO stage IIa), while 63% (195) of the participants had advanced stage disease (from stage IIb to IVb). Early stage disease (up to stage IIa) had a survival rate of 70.1% at 2 years and 51.9% at 5 years. This compares to only 31.9 % at 2 years and 3.56% at 5 years for stages (IIb to IVb).

Survival rates correlated with the exposure variables revealed significant associations with staging, treatment arms, radiotherapy, and age at admission (Table 4).

There were no significant associations between survival rates and histological diagnosis, duration from onset of symptoms to diagnosis, duration from diagnosis to treatment and the HIV status (Table 4).

Parameter	**2 year survival rate**	**5 year survival rate**
FIGO staging of disease	**<0.001**	**0.001**
Treatment Arms	**<0.001 (χ^2)**	**<0.001 (χ^2)**
Radiotherapy	**<0.001(χ^2)**	**<0.001 (χ^2)**
Age at admission	0.558 (t-test)	**0.046 (t-test)**
Histological diagnosis	2.57	0.82
Duration from onset of symptoms to diagnosis (month)	0.305	0.152
Duration from diagnosis to treatment(month)	0.312	0.530
HIV Status	0.702	0.303

Table 4: Correlation of Survival rates with other variables.

6.0 DISCUSSION:

The aim of the study was to review the outcomes of management for patients with cancer of the cervix at Kenyatta National hospital. Survival rates were higher in the early stage disease (up to stage IIa) than in the advanced stages of the disease. It was also established that most patients were seen for the first time at KNH already in the advanced stages of the disease.

The findings on the demographics of the participants revealed a mean age of 47 years with a mode of 46. The population appears to be slightly older than that reported in a study in Nigeria where a total of 209 participants of cancer of the cervix were found to have a mean age of 39.6 ± 10.4 years (26).

The mean number of children per participant was 4 (range of 0-12) which is consistent with a developing country like Kenya where low socioeconomic status is associated with early sexual debut and related high parity. the Kenya National Bureau of Statistics had a parity of 3.9 for their 2014 findings (27).

Most of the participants were of the age group 35-54 years which is from the mid reproductive age to menopause. Only 8.4 % of participants were below the age of 35. In a study to determine the level of intervention for cervical abnormalities in the age group (20-25yrs) of the Northern Ireland population, Al-Kalbani et al found that Screening women under the age of 25 years cause unnecessary referral for further management and may also result in considerable anxiety and

psychosexual morbidity with a potential of negative impact on the future pregnancy outcomes(28). However, the study shows a need for being vigilant even in the age groups of 20-25 years.

The study showed that histological diagnosis was mostly squamous cell carcinoma (89.3%), with only 8.4% being adenocarcinoma and 2.3 % the mixed type. The findings are consistent with India where Squamous cell carcinoma accounted for 85-90% of all diagnoses, adenocarcinoma accounted for 10-15%. The cell differentiation was reported as moderately differentiated in 71.5% of the results. Poorly differentiated cells have been shown to have a poor prognosis.

The staging of the disease was mainly done clinically by examination under anaesthesia and also by use of lab investigations and radiology. The purpose of staging was to formulate the line of treatment, determine prognosis and compare the results of one to another, It was noted that most of the participants were in FIGO stage IIb (22.7%) and IIIb (22.3%) at the time of diagnosis. Thirty seven percent (114) of the participants had early stage disease (Up to FIGO stage IIa), while 63% (195) of the participants had advanced stage disease (from stage IIb to IVb). This scenario of late diagnosis is replicated in other african countries like South Africa (29). Of concern and in concurrence with the study hypothesis, is that most participants were diagnosed with advanced stage disease. Late diagnosis was shown to have an association with the treatment offered and the survival rates.

It was found that the time taken from the onset of symptoms to the diagnosis varied from less than 1 month to 96 months (mode of 6 months) showing that our mechanisms for screening and early diagnosis were not readily available to the larger population of women in our country. At the

moment screening services are not offered to all women visiting hospitals as a routine. The duration since diagnosis to treatment in months had a range of two weeks to 36 months. Some clients unfortunately succumbed while awaiting their bookings for radiotherapy due to the large numbers in need of the service. It was noted that clients with early staged disease were treated much faster as the hospital has a policy of giving priority to such clients especially those with a staging that is amenable to surgery. This helps in preventing the upstaging of the disease in case of a long waiting period. This group had the best survival rates.

HIV status was known or tested in only 42.7% of the participants. Of these, 45% were positive. The survival rates for those participants who tested positive were 55 % at 2 years and 18.3% at 5 years. With more than 50% of the participants having their status unknown, it was not statistically possible to draw any associations between HIV and cervical cancer from the study population. However Salters et al observed elevated rates of cancer among HIV-positive women compared to a general population sample with increased risk for cancers of viral-related pathogenesis(30).

The overall survival rates were 47.6% at two years and 14.9% at 5 years. For the specific treatment arms studied, surgery was found to have the largest survival rates of 75.3% and 46.2% at 2 and 5 years respectively, while radiotherapy had the least survival rate at 23.5% (2-years). This is due to the fact that surgery was mainly offered to early-stage disease with high possibility of total cure whereas Radiotherapy was the main mode of treatment for advanced-stage disease.

The survival rates were also correlated with the staging where stage 1 disease had a 91.9% survival rate at 2 years and 77.3% at 5 years. It was noted that the survival rates decreased with increase in the staging of the disease. Worldwide, survival rates have shown a similar pattern where stage 1 disease has a survival rate of over 90%, stage II (60-80%), stage III (50%) and less than 30% for stage IV(31).

With respect to Early versus Advanced stage disease; early stage disease (up to stage IIa) had a survival rate of 70.1% at 2 years and 51.9% at 5 years. This compares to only 31.9 % at 2 years and 3.56% at 5 years for stages (IIb to IVb). The findings were consistent as surgery is usually the preferred mode of treatment for early stage disease and as such has better prognosis.

The staging of the disease ($p < 0.001$, $p = 0.001$), the mode of treatment (<0.001 (χ^2), <0.001 (χ^2)) and specifically radiotherapy, were shown to have an association with the 2 and 5 year survival rates. The age of the participants was also noted to be of significance to the 5- year survival rates. No association of statistical significance was noted between the survival rates and duration of symptoms, diagnosis and onset of treatment. The staging of the disease, describing the extent of spreads of the cancer determined the treatment and indirectly the outcomes. It was noted that early stage disease (up to stage IIa) had better survival rates than Advanced-stage disease. The mode of

treatment showed significant association with the survival rates; Radiotherapy was mainly used as palliative due to late presentation of the patients and as such its use and benefit was limited to mostly palliation.

7.0 CONCLUSION:

A hundred and fourteen (37%) of the participants had early stage disease (Up to FIGO stage IIa), while 195 (63%) of the participants had advanced stage disease (from stage IIb to IVb).

The overall survival rates were 47.6% at two years and 14.9% at 5 years. The study highlights the association of late diagnosis of cervical cancer and survival rate in which the survival was only 31.9 % at 2 years and 3.6% at 5 years for stages IIb to IVb. This compares with 70.1% at 2 years and 51.9% at 5 years for early stage disease (up to stage IIa).

The predictors of survival were age at diagnosis, staging of the disease at diagnosis and the mode of treatment offered.

8.0 RECOMMENDATIONS:

1. To avoid late diagnosis, Gynaecology Out-patient clinic and Comprehensive Care Clinic at Kenyatta National Hospital should routinely do pap smears on all clients regardless of symptomatology.
2. Training in Obstetrics and Gynaecology should consider inclusion of acquisition of skills for Wertheim's hysterectomy to increase access of early initiation of surgical interventions in cancer of the cervix away from the training institutions.
3. Deliberate effort to reduce the delay from diagnosis to treatment.
4. Radiotherapy services in public institutions should be devolved to the counties to reduce delay in initiating treatment after diagnosis and reduce defaulting and loss to follow-up due to distance and cost.

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10.0 TIMEFRAME:

2014									2015					
	May	Jun	July	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun
Proposal Development	X	X	X	X										
Review by Supervisors				X	X	X								
Ethics						X	X	X						
Data collection									X					
Data Entry										X				
Data Analysis											X			
Report Writing												X		
Project Defense													X	
Manuscript for publishing														X

11.0 BUDGET:

Item	**Unit/ Particulars**	**Unit Cost**	**Quantity**	**Totals (KShs.)**
Internet Access	Month	1000	8	8000
Proposal	50 pages	500	6	3000
Questionnaires	6 pages	100	50	5000
Consent forms	4 pages	50	50	2500
Thesis: Printing Binding	 50 pages 50 pages	 3000 1000	 6 6	 18000 6000
Flash disk	4 GB	3	2000	6000
Voice Recorder		17,000	1	17,000
Statistician professional fees	Hour	4000	15	60000
Research Assistants (2)	Day	1000	20	40000
Airtime	Week	1000	4	4000
Sub-total				**117,500**
Contigency	15% of all costs			17,625
TOTAL				**KSh. 135,125**

12.0 APPENDICES:

Code – 0369462

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Ref: KNH-ERC/ MOD/94

3rd March, 2015

Dr. Juma Sylvan
Dept. of Obs/Gynae
School of Medicine
University of Nairobi

Dear Juma

Re: Approval of modifications: A ten-year review of the outcomes on the management of cancer of the cervix at Kenyatta National Hospital (1999-2009) (P679/11/2014)

Refer to your communication of 18th February, 2015.

The KNH/UoN-ERC has reviewed and approved modification of the following:

1. Title to read: A five year review on the outcomes of management of cancer of the cervix at Kenyatta National Hospital (2007-2012)

Thanks for the update

Yours sincerely

PROF. M. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College f Health Sciences, UoN
The Deputy Director CS
The Chairperson, KNH/UoN-ERC
The Dean, School of Medicine, UoN
The Chairman, Dept of Obs/Gynae, UoN
Supervisors: Prof. Oyieke James Bill Onjua, Dr. Lubano Kizito

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KENYATTA NATIONAL HOSPITAL APPROVED 02 FEB 2015 KNH/UoN-ERC P.O. Box 20723-00202 NRB.

Ref: KNH-ERC/A/38

2nd February, 2015

Dr. Juma Sylvan
Dept. of Obs/Gynae
School of Medicine
University of Nairobi

Dear Dr. Juma,

Research Proposal: A ten-year review of the Outcomes on the Management of Cancer of the Cervix at Kenyatta National Hospital (1999-2009) (P679/11/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 2nd February 2015 to 2nd February 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study
This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.erc.uonbi.ac.ke**

Dr. Juma Sylvan,

P.O. Box 102768,

Jamia 00101,

NAIROBI.

30TH September 2014

TO:

The Assistant Director,

Division of Health Records,

Kenyatta National Hospital,

Nairobi.

Dear Sir/madam,

RE: REQUEST FOR PERMISSION TO UNDERTAKE A STUDY ON THE MANAGEMENT OUTCOMES OF CERVICAL CANCER AT YOUR INSTITUTION

I am a Post graduate student at the Department of Obstetrics and Gynaecology, University of Nairobi.

I would like to request for permission to carry out a study entitled "**A FIVE-YEAR REVIEW OF THE OUTCOMES ON THE MANAGEMENT OF CANCER OF THE CERVIX AT KENYATTA NATIONAL HOSPITAL (2007-2012).**"

I pledge to fully adhere by the principles of Research as clearly spelt out by the KNH-UON Ethics and Research committee.

Yours faithfully,

Dr. Juma Sylvan

H58/79381/2012

Dr. Juma Sylvan,

P.O. Box 102768,

Jamia 00101,

NAIROBI.

30TH September 2014

TO:

The Assistant Director,

Division of Reproductive Health,

Kenyatta National Hospital,

Nairobi.

Dear Sir/madam,

RE: REQUEST FOR PERMISSION TO UNDERTAKE A STUDY ON THE MANAGEMENT OUTCOMES OF CERVICAL CANCER AT YOUR INSTITUTION.

I am a Post graduate student at the Department of Obstetrics and Gynaecology, University of Nairobi.

I would like to request for permission to carry out a study entitled "**A FIVE-YEAR REVIEW OF THE OUTCOMES ON THE MANAGEMENT OF CANCER OF THE CERVIX AT KENYATTA NATIONAL HOSPITAL (2007-2012).**"

I pledge to fully adhere by the principles of Research as clearly spelt out by the KNH-UON Ethics and Research committee.

Yours faithfully,

Dr. Juma Sylvan

H58/79381/2012

DATA EXTRACTION SHEET ON OUTCOMES OF MANAGEMENT OF CERVICAL CANCER AT KENYATTA NATIONAL HOSPITAL (2007-2012).

Admission Number---------- **Admission Date** ----------

Age---------- **Parity**__----------

Study Number---------- **Religion**----------

1. a. Histological diagnosis (tick where appropriate).

a. Squamous Cell carcinomas ☐

b. Adenocarcinomas ☐

c. Adenosquamous carcinoma ☐

d. Others ☐

1b. Differentiation

a. Well-differentiated ☐

b. Moderately differentiated ☐

c. Poorly differentiated ☐

2. Staging of the disease (tick where appropriate).

a. stage Ia ☐
b. Stage Ib ☐
c. Stage IIa ☐
d. Stage IIb ☐
e. Stage IIIa ☐
f. Stage IIIb ☐
g. Stage IVa ☐
h. Stage IVb ☐

3a. Duration since onset of symptoms to diagnosis (tick where applicable)

a. Weeks ☐ Specify……
b. Months ☐ Specify……
c. Years ☐ Specify----------

3b. Duration since onset of diagnosis to onset of treatment (tick where applicable)

a. Weeks ☐ Specify……
b. Months ☐ Specify……
c. Years ☐ Specify----------

4. Other medical conditions:

HIV Status:
positive……negative……unknown…….

Others (specify)……..

5. Treatment process offered (tick appropriately)

a. Surgery ☐
b. Radiotherapy ☐
c. Chemotherapy ☐
d. Surgery and Radiotherapy ☐
e. Surgery and Chemotherapy ☐
f. Radiotherapy and Chemotherapy ☐
g. Surgery, Radiotherapy and Chemotherapy ☐

6. Outcomes of treatment offered after 2 years

a. Cure ☐
b. Remission ☐
c. Recurrence ☐
d. Loss to follow-up ☐
e. Death ☐

7. Outcomes of treatment offered after 5 years

a. Cure ☐
b. Remission ☐
c. Recurrence ☐
d. Loss to follow-up ☐
e. Death ☐