ESTIMATING THE SURVIVAL OF PATIENTS WITH CANCER OF THE CERVIX AT KENYATTA NATIONAL HOSPITAL IN NAIROBI, KENYA

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MASTER OF SCIENCE

(RESEARCH METHODS)

JOMO KENYATTA UNIVERSITY OF AGRICULTURE AND TECHNOLOGY

2013

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Dissertation submitted in partial fulfillment for the degree of Master of Science in Research Methods to Jomo Kenyatta University of Agriculture and Technology

2013

DECLARATION

I hereby declare that this dissertation submitted to the Jomo Kenyatta University of Agriculture and Technology is original work and has not been submitted in any form for the examination for a degree or diploma to any other university.

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DEDICATION

This dissertation is dedicated to my dear parents; Mr. Khaemba Murumba Wanjala and Mrs. Hellen Nafula Khaemba for giving me the first lessons in life and for the great sacrifices they have made to enable me achieve my academic dreams.

ACKNOWLEDGEMENT

For the successful completion of this work, I am thankful to God.

I would like to convey my sincere appreciation to the secretariat, Regional Universities Forum for Capacity Building in Agriculture (RUFORUM) for facilitating my studies through financial sponsorship.

To Jomo Kenyatta University of Agriculture and Technology (JKUAT) for providing facilities and a conducive environment ideal for studies I am so grateful. Special thanks to the management of the Faculty of Agriculture under the leadership of the Dean, Prof. Kamau Ngamau for successfully facilitating the MSc. Research Methods program, Cohort II.

To my supervisors Prof. Charles Mutai and Ms. Caroline Mugo for their invaluable input and support, I am eternally grateful.

My appreciation goes to the Kenya Medical Research Institute (KEMRI), Centre for Clinical Research, Pathology and Oncology Research Unit for giving me the insight to carry out this study and to the Nairobi Cancer Registry staff for their invaluable support during the development of this research idea.

To the Kenyatta National Hospital / University of Nairobi Ethics and Research Committee under the headship of Prof. Guantai for speedily reviewing my proposal and granting me ethical clearance, I am eternally grateful.

Special thanks to the management of Kenyatta National Hospital, Medical Records section for allowing me access to patientsô information. It surely proved to be the most ideal study site. To the patients and the next of kin to deceased patients who agreed to participate in this study I am very grateful because it is through your voluntary participation that I have been able to come up with this dissertation.

To the Nairobi Hospice staff for their support specifically during the follow up phase of this study especially Dr. Langõ I am thankful.

To my classmates from the Common Market of Eastern and Southern Africa region for their support and cooperation during this course, I am so grateful.

Lastly, I wish to convey my heartfelt appreciation to my family; my dear parents, my lovely siblings Winnie, Arwin and Noel for prayers and support during the preparation of this dissertation.

TABLE OF CONTENTS

DECLARATION ii
DEDICATION iii
ACKNOWLEDGEMENT iv
TABLE OF CONTENTS v
LIST OF TABLES vii
LIST OF FIGURES viii
LIST OF APPENDICES ix
LIST OF ABBREVIATIONS x
ABSTRACT xi
CHAPTER ONE 1
1.0 INTRODUCTION 1
1.1 Statement of the problem 4
1.2 Justification 5
1.3 Research questions 5
1.4 Objectives 5
1.4.1 General objective 5
1.4.2 Specific Objectives 5
CHAPTER TWO 6
2.0 LITERATURE REVIEW 6
2.1 Cervical Cancer 7
2.1.1 Cervical Cancer Risk Factors 7
2.1.2 Symptoms 10
2.1.3 Diagnosis 10
2.1.4 Treatment 11
2.1.5 Prevention 12
2.2 Statistical Methods 13
2.2.1 Survival analysis 13
2.2.2 Relative survival 13
2.2.3 Cure fraction 15
2.2.4 Kaplan-Meier analysis 15

2.2.5 Cox regression model....16
CHAPTER THREE....17
3.0 RESEARCH METHODOLOGY....17
3.1 Study design....17
3.2 Study site....17
3.3 Study population....17
3.3.1 Inclusion criteria....17
3.3.2 Exclusion criteria....18
3.4 Sampling....18
3.4.1 Sample size determination....18
3.4.2 Sampling procedure....18
3.5 Data collection methods....19
3.6 Data management and analysis....19
3.7 Ethical consideration....20
CHAPTER FOUR....21
4.0 RESULTS....21
4.1 Demographic characteristics....21
4.2 Cure fraction....25
4.3 Survival time....255
4.4 Cox Proportional Hazards Regression models....31
4.4.1 Cox PH regression....31
4.4.2 Testing for proportional hazards assumption....34
CHAPTER FIVE....36
5.0 DISCUSSION, CONCLUSION AND RECOMMENDATIONS....36
5.1 Discussion....36
5.2 Conclusion....38
5.3 Recommendations....38
References....40
APPENDICES....45

LIST OF TABLES

Table 1: Patientsô diagnostic details 23
Table 2: Treatment options given to patients 24
Table 3: Median Survival Times 25
Table 4: Pairwise comparison at different stages of diagnosis 26
Table 5: Survival difference 29
Table 6: Estimation using Breslow method 32
Table 7: Stepwise regression 33
Table 8: Final Cox PH regression model 34
Table 9: An assessment of the Cox PH assumption 35

LIST OF FIGURES

Figure 1: Marital Status of patients..... 21
Figure 2: Level of education of patients 22
Figure 3: Survival curve..... 28
Figure 4: Survival difference curves with Stage as Strata 30

LIST OF APPENDICES

Appendix 1: Case follow up checklist 45
Appendix 2: Introduction and consent for patient 47
Appendix 3: Introduction and consent for the next of kin 50
Appendix 4: Ethics approval letter 53
Appendix 5: Life Table 55
Appendix 6: Survival Table 59
Appendix 7: Analysis Codes in R 61

LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
AIDS	Acquired Immunodeficiency Syndrome
ARR	Adjusted Relative Risk
CI	Confidence interval
Df	Degrees of freedom
DNA	Deoxyribonucleic Acid
ERC	Ethics and Research Committee
FIGO	International Federation of Gynecology and Obstetrics
HIV	Human Immunodeficiency Virus
HPV	Human Papillomavirus
HR	Hazard ratio
IVP	Intravenous pyelogram
JKUAT	Jomo Kenyatta University of Agriculture & Technology
KEMRI	Kenya Medical Research Institute
KNH	Kenyatta National Hospital
LEEP	Loop electrosurgical excision procedure
MRI	Magnetic Resonance Imaging
NCR	Nairobi Cancer Registry
PH	Proportional Hazard
UON	University of Nairobi
WHO	World Health Organization

ABSTRACT

Cervical cancer ranks as the second most frequent cancer among women globally. The majority of patients present in advanced disease stages, leading to high mortality rates. Information on the survival of cervical cancer patients in Kenya which is necessary in estimating the burden of the disease and informing policy shifts in management of the disease is lacking. The objective of this study was to estimate the cure fraction, the survival time and rate and, identify covariates that significantly affect the survival of patients with cervical cancer in Nairobi, Kenya. A retrospective, descriptive non-intervention study of selected patients with cancer of the cervix was carried out in Nairobi at Kenyatta National Hospital. A total of 211 patients with an initial diagnosis of cancer of the cervix between January 2005 and June 2007 were followed up for five years respectively. Of the 211 patients, 108 (51.18%) of them were confirmed dead within that period, 15 (7.11%) were still alive and 88 (41.70%) were lost to follow up. Most of the patients were from low income areas (60.19%) within Nairobi, followed by those from middle income areas (37.91%) with the smallest proportion coming from high income areas (1.90%). The patientsô ages ranged from 14 to 76 years; the median age was 46 years while the mean 46.45 years. The probability of surviving beyond the maximum amount of time (60 months) was estimated at 0.198. The cumulative proportion surviving at the end of the study interval was 0.67 at stage I, 0.36 at stage II, 0.15 at stage III and 0 at stage IV. The median survival time at stage I was 60 months, 23.02 months at stage II, 10.14 months at stage III and 9.73 months at stage IV. Patients with an initial diagnosis at stage II, stage III and stage IV had an increased risk of death 6.29, 13.71 and 15.47 times respectively those diagnosed at stage I. The age of patients, stage at diagnosis and level of education significantly affected the survival. Early detection of cervical cancer and, prompt and comprehensive treatment should be taken up to improve the overall survival of the patients.

CHAPTER ONE

1.0 INTRODUCTION

Cancer of the cervix is a serious public health problem globally, especially in developing countries where it is the second most common cancer in women. Developing countries bear a disproportionate burden of the disease, experiencing age-standardized mortality rate that are twice those experienced in developed countries. Every year, approximately half a million new cases of cancer of the cervix are reported globally, 80% of which occur in developing countries, where the disease is also the leading cause of cancer-related death among women (Sankaranarayanan *et al*., 2001). Globally there are about 500,000 cervical cancer new cases and 250,000 deaths each year. The huge disparities in morbidity and mortality between developed and developing countries exist largely because over the last few decades, developed countries have implemented effective programmes for its prevention, in some countries reducing incidence and mortality by up to 80% (Sankaranarayanan *et al*., 1998; 2001).

In Africa, Southern Africa has one of the highest reported age-standardized incidence rates of cancer of the cervix (higher than 40 per 100,000 women) and existing data indicate that the incidence of disease is actually increasing in some parts of sub-Saharan Africa. In South Africa, cancer of the cervix causes significant cancer-related morbidity and mortality among women (Fonn *et al*., 1993). It has been estimated that 5000 new cases of the disease are reported annually, accounting for 16.7% of all cancers reported annually in the country (Sitas *et al*., 1997). Though these data were reported in the late 1980ôs it is unlikely that these patterns have changed much over the last 20 years. This is in connection to the current increase of cancer cases in Kenya.

Cervical cancer is the term used for a malignant neoplasm arising from cells originating in the cervix uteri. The most common symptom of cervical cancer is abnormal vaginal bleeding but in some cases there may be no obvious symptoms until the cancer has progressed to an advanced stage. Treatment usually consists of surgery in early stages,

and chemotherapy and/or radiotherapy in more advanced stages of the disease. There are two types of cervical cancer: squamous cell carcinoma and adenocarcinoma.

Most cervical cancer cases (99%) are linked to genital infection with human papillomavirus (HPV) especially Type 16 or 18, which is the most common viral infection of the reproductive tract (WHO report, 2008). HPV is a common sexually-transmitted virus that does not always cause symptomatic disease in infected individuals. Existing evidence indicates that more than 97% of all cancers of the cervix are associated with persistent infection of HPV. Cancer of the cervix is a disease with a long latent period, which means it develops over a long period of time. The natural history of the disease is such that the disease is induced by HPV and persistent HPV infection progresses into a pre-invasive (pre-cancer) stage, characterized by the presence of pre-cancerous cells in the cervix (broadly called dysplasia). Women are most commonly infected with HPV in their teens, 20s or early 30s, but it may take as long as 15-20 years for the disease to progress from HPV infection through low-grade to high-grade dysplasia and finally to cancer of the cervix. High grade dysplasia is a precursor for cancer of the cervix (Kjaer, 2002; Koutsky *et al*., 2002).

In sub-Saharan Africa, the causes of high mortality rates are associated with poor access to medical facilities, poor nutrition, late presentation with the disease, poor quality care, low rate of follow-up, and women not completing treatment due to rural barriers. Cultural factors also play a role in the rates of cervical cancer including: early marriage, polygamous marriage, and high gender parity. These factors afflict women and girls living in rural areas at much greater rates (Pisani, 1999). Cervical cancer generally affects multiparous women in the early post-menopausal years. In high-fertility developing countries these women are the primary source of moral and educational values for their school-age children. The premature loss of these mothers has important social consequences for the community. An average 26 years of life are lost per female patient dying of cervical cancer (Pisani, 1999).

In Kenya, current estimates indicate that every year, 2454 women are diagnosed with cervical cancer and 1676 die of the disease. Cervical cancer ranks as the second most frequent cancer among women in Kenya, and the second most frequent cancer among

women between 15 and 44 years of age. About 38.8% of women in the general population are estimated to harbour cervical HPV infection at a given time, and 60.9% of invasive cervical cancers are attributed to HPVs Type 16 or 18 (HPV and Related Cancers WHO, 2010). Data from the Nairobi Cancer Registry (NCR) indicate that cancer incidence is increasing in Kenya. It now numbers among the top 10 causes of mortality. The three most common cancers in men are those of the oesophagus, prostate and Kaposiôs sarcoma. In women, breast cancer is the most commonly diagnosed form of the disease, followed by cervical and esophageal cancers, respectively. Breast and cervical cancer account for more than 40 % of female cancer cases. The majority of patients present at advanced disease stages, leading to high morbidity and mortality rates. This occurs despite the known facts of reduced morbidity and mortality from primary prevention and early detection.

1.1 Statement of the problem

Cancer of the cervix uteri is the second most common cancer among women globally, with an estimated 529,409 new cases and 274,883 deaths in 2008. About 86% of the cases occur in developing countries (WHO, 2010). The highest incidence rates were in Central and South America, the Caribbean, sub-Saharan Africa, and Southern Asia. Rates were lowest in the Middle East, North America, Australia, China, and parts of Western Europe (ACS, 2011). In several Western countries, where screening programs have long been established, cervical cancer rates have decreased by as much as 65% over the past four decades (ACS, 2011).

Cancer of the cervix is the leading cause of cancer deaths in women in Kenya. It affects approximately 2,500 women and causes about 1,700 deaths every year. If preventive measures are not taken up by 2025 it is projected that the number of new cases will rise to 4300 and deaths to 3000 annually (Ministry of Public Health and Sanitation, 2013).

High prevalence of cervical cancer is shifting from developed nations to poorer, less medically equipped countries and is spreading fast among the poor who have little capacity and low financial muscle to manage it. Age of acquisition is decreasing as many young people are being diagnosed with this disease and this unfavorable trend is thought to reflect increases in HPV prevalence from changing sexual behaviors (WHO, 2007; ACS, 2011).

The survival of cancer patients is an important indicator of the treatment response. The consequences of attempts to manage cancer of the cervix on the survival duration of patients in Kenya are not known while cases are increasing. Currently, there are no survival studies that have been conducted on cervical cancer in Kenya, unlike in other parts of the world. This study therefore comes up with findings on the five year survival rates and survival duration of patients with cervical cancer considering the initial stage of diagnosis and other covariates such as education level, age, smoking behaviour, alcohol intake, grade of cervical cancer, treatment given, residence and HIV status of patient. This information is necessary in informing policy shifts in management of the disease.

1.2 Justification

Survival analysis of data on cancer of the cervix patients provides information on prognosis of affected patients, the beneficial effects of different treatment options, emerging causes of mortality that form the basis for planning and improving health services. Currently, there is lack of empirical evidence on the survival rates and survival duration of cervical cancer patients and factors that influence patientsô survival in Kenya. This study is vital because it will provide information which shall be used in combating cervical cancer through improvements in the disease management and inform policy formulation.

1.3 Research questions

- What is the fraction of patients that survive past five years?
- What is the survival duration of patients with cervical cancer at different stages of initial diagnosis?
- Which covariates affect survival?

1.4 Objectives

1.4.1 General objective

To estimate the survival time and rate of patients with cervical cancer in Nairobi, Kenya

1.4.2 Specific Objectives

(1) To estimate the cure fraction of patients with cervical cancer in Nairobi between January 2005 and June 2012

(2) To estimate the survival time of patients with cervical cancer in Nairobi between January 2005 and June 2012

(3) To identify covariates that significantly affect the length of survival of patients with cervical cancer in Nairobi between January 2005 and June 2012

CHAPTER TWO

2.0 LITERATURE REVIEW

Cancer is a generic term for a large group of diseases that can affect any part of the body. One defining feature of cancer is the rapid creation of abnormal cells that grow beyond their usual boundaries, and which can then invade adjoining parts of the body and spread to other organs. This process is referred to as metastasis. Metastases are the major cause of death from cancer. Cells become cancerous because of damage to Deoxyribonucleic Acid (DNA). DNA is ubiquitous in cells and directs all its actions in a normal cell. When DNA gets damaged the cell either repairs the damage or the cell dies. In cancer cells, the damaged DNA is not repaired, but the cell doesnôt die like it should. Instead, this cell goes on making new cells that the body does not need which will all have the same damaged DNA as the first cell does (WHO, 2008).

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries (WHO, 2007). Cancer killed 7.6 million people in 2005, three quarters of whom were in low and middle income countries and by 2015 the number is expected to rise to 9 million and increase further to 11.5 million in 2030. Every year at least 7 million people die of cancer, more than HIV/AIDS, malaria and tuberculosis combined (WHO, 2007). The burden of cancer will increase rapidly in the near future largely due to increase in the numbers of elderly people and adoption of western lifestyles especially by developing countries. Poor cancer survival in developing countries is attributed to late diagnosis; usually at an advanced stage and limited access to timely and standard treatment.

2.1 Cervical Cancer

Cervical cancer is cancer that starts in the cervix, the lower part of the uterus (womb). Invasive cervical cancer is one of the most successfully treatable cancers when detected early through regular screening. The most common cause of cervical cancer is infection of human papillomavirus (HPV) (ACS, 2005). Women have an increased risk of being infected by HPV if sexual debut is at an early age or have had many sexual partners. Although an HPV infection is the major cause of cervical cancer, few women with an HPV infection actually progress to a cancer diagnosis. There are some risk factors that may influence the progression of cervical cancer such as leaving the HPV infection untreated and allowing it to persist for a long period of time, smoking cigarettes, immunosuppression, and nutritional status. Low socioeconomic status has also been identified to be a risk factor for cervical cancer (ACS, 2005).

The survival rate for women with pre-invasive cervical cancer lesions is almost 100%. Screening practices can help detect cervical cancer in its pre-invasive stage. About 90% of women diagnosed with cervical cancer survive after the first year of diagnosis (ACS, 2005).

2.1.1 Cervical Cancer Risk Factors

One study examined sexual behaviours and cigarette smoking as risk factors for cervical cancer among women in the United States and Venezuela. The study showed that cervical cancer cases with more than two lifetime sexual partners had a 1.7 times increased risk for cervical cancer when compared to women with two or less sexual partners (Sierra-Torres *et al*., 2003).. The mean number of sexual partners was significantly higher in the cases with cervical cancer when compared to the healthy control group. It was also identified that the overall mean age at first sexual intercourse was significantly different in the cases group than for the control group. The mean age of first sexual intercourse for the cases was 16.45 years and 18.32 years for the control groups. Of the cases, 83% of the women were 18 years old or younger at the time of first intercourse compared to 58% of women in the control groups. Beginning sexual

intercourse at age 18 or younger accounted for a 3.9 times increased risk for cervical cancer and was a significant finding (Sierra-Torres *et al*., 2003).

In the same study smoking behaviour and the risk for cervical cancer was examined. Participants were asked whether they were currently smoking cigarettes, had smoked in the past, or had never smoked. For those that had smoked in the past or currently, the amount of cigarettes calculated in pack years were used to indicate amount of cigarette exposure. Overall, 60% of the participants in the cervical cancer cases group reported a history of smoking while only 46% of the healthy control groups indicated a history of tobacco use. A significant increase in risk for cervical cancer was found among current cigarette smokers. The increase in risk is related to heavy smoking since women smoking over 15 pack-years had a significantly higher risk for cervical cancer. The risk for cervical cancer was increased 7.7 times among the U.S. women that smoked cigarettes (Sierra-Torres *et al*., 2003). A similar study examined active and passive cigarette smoking as a risk factor for cervical cancer. The study recognized that active cigarette smoking has been identified being causally associated with cervical cancer. The analysis was conducted as a large community based prospective cohort study among Washington County, Maryland residents. The study was based on two cohorts who were created from data collection from two private censuses in 1963 and 1975. Approximately 98% of the households participated in the 1963 census, and 90% of households participated in the 1975 census (Trimble *et al*., 2005). The study included 26,381 women from the two cohorts and all participants were over 25 years of age, had no prior diagnoses of cancer, and were not missing any information on age, gender, and smoking status. The 2 cohorts were then followed over time for first-time cervical cancer occurrences by linking personal identification information collected during the two censuses with the Washington County cancer registry. A major shift in tobacco exposure identified between the two cohorts was that the percentage of women who had never smoked but lived with a smoker decreased from 25% in 1963 to 15% in 1975. However, the percentage of women who were former smokers increased from 9% in 1963 to 15% in 1975 (Trimble *et al*., 2005). The study revealed that the risk for cervical cancer development was significantly increased among women who were active smokers in

both of the cohorts with an adjusted relative risk (aRR) of 2.6 in the 1963 group and 1.7 in the 1975 group. It was also shown in both of the cohorts that passive smoking was in fact associated with an increased risk of cervical cancer. The association of passive smoking and development of cervical cancer was stronger in the 1963 cohort with an aRR of 2.1, and an aRR of 1.4 in the 1975 cohort. The association between passive smoking and development of cervical cancer was statistically significant in only the 1963 group (Trimble *et al*., 2005).

The study also revealed other risk factors to cervical cancer including education and marital status. The relative risk of cervical cancer in women with 12 or more years of education compared to women with less than 12 years of schooling was 0.6 in the 1963 as well as 1975 cohorts. The study also found that women who were divorced or separated were at a significantly higher risk for developing cervical cancer compared to women who were married (relative risk of 1.6 in 1963 and 2.0 in 1975) (Trimble *et al*., 2005). Alcohol consumption may also act as an indirect risk factor for cervical cancer. One study found that as the number of alcohol related behaviours and consumption increased the proportion of participants in the study who had recently had multiple partners increased from 8% to 48% in females and from 23% to 61% in males (Santelli *et al*., 2001). Another study also found that alcohol use, especially during the time of previous sexual intercourse, was strongly associated with an increased likelihood of multiple sexual partners (Santelli *et al*., 2001). As discussed earlier, an increase in sexual partners leads to an increased risk for cervical cancer.

Studies have also shown that Women whose mothers took the drug DES (diethylstilbestrol) during pregnancy in the early 1960s to prevent miscarriage have been associated with high risk of cervical cancer (Noller, 2007).

2.1.2 Symptoms

The most common symptoms are abnormal vaginal bleeding between periods, after intercourse, or after menopause and continuous vaginal discharge, which may be pale, watery, pink, brown, bloody, or foul-smelling (Noller, 2007). Cervical cancer may spread to the bladder, intestines, lungs, and liver. Patients with cervical cancer do not usually have problems until the cancer is advanced and has spread. Symptoms of advanced cervical cancer may include: back pain, bone pain or fractures, fatigue, leaking of urine or faeces from the vagina, leg pain, loss of appetite, pelvic pain, single swollen leg and weight loss.

2.1.3 Diagnosis

Pap smears screen for pre-cancers and cancer, but do not make a final diagnosis. If abnormal changes are found, the cervix is usually examined under magnification, called colposcopy. Pieces of tissue are surgically removed (biopsied) during this procedure and sent to a laboratory for examination (Noller, 2007).

If the woman is diagnosed with cervical cancer, the health care provider will order more tests to determine how far the cancer has spread. This is called staging. Tests may include: Chest x-ray, CT scan of the pelvis, cystoscopy, Intravenous pyelogram (IVP) or (Magnetic Resonance Imaging) MRI of the pelvis.

2.1.4 Treatment

Treatment of cervical cancer depends on, the stage of the cancer, the size and shape of the tumor, the woman's age and general health and her desire to have children in the future.

Early stage cervical cancer can be cured by removing or destroying the precancerous or cancerous tissue. There are various surgical ways to do this without removing the uterus or damaging the cervix, so that a woman can still have children in the future. Types of surgery for early cervical cancer include:

- Loop electrosurgical excision procedure (LEEP) which uses electricity to remove abnormal tissue
- Cryotherapy which freezes abnormal cells
- Laser therapy which uses light to burn abnormal tissue

A hysterectomy (removal of the uterus but not the ovaries) is not often performed for cervical cancer that has not spread. It may be done in women who have had repeated LEEP procedures.

Treatment for more advanced cervical cancer may include radical hysterectomy, which removes the uterus and much of the surrounding tissues, including lymph nodes and the upper part of the vagina. Pelvic exenteration can also be used; it is an extreme type of surgery in which all of the organs of the pelvis, including the bladder and rectum, are removed.

Radiation may be used to treat cancer that has spread beyond the pelvis, or cancer that is recurrent. It is used to kill cancer cells and shrink tumors. Radiation therapy is either external or internal. Internal radiation therapy also referred to as brachytherapy uses a device filled with radioactive material, which is placed inside the woman's vagina next to the cervical cancer. External radiation therapy beams radiation from a large machine onto the body where the cancer is located. Brachytherapy allows use of a higher total dose of radiation to treat a smaller area and in a shorter time than is possible with external beam radiation treatment (NCCN, 2011; Smith, 2010).

Chemotherapy uses drugs to kill cancer. Some of the drugs used for cervical cancer chemotherapy include 5-FU, cisplatin, carboplatin, ifosfamide, paclitaxel, and cyclophosphamide. Sometimes radiation and chemotherapy are used before or after surgery (NCCN, 2011).

However some types of cervical cancer do not respond well to treatment. There are chances that the cancer may recur after treatment especially women who have treatment to save the uterus have a high risk of recurrence. Surgery and radiation can cause problems with sexual, bowel, and bladder function (NCCN, 2011).

2.1.5 Prevention

A vaccine called cervarix to prevent against infection of HPV types 16 and 18 that are most responsible for causing cervical cancer is now available even in Kenya. In June 2006, the U.S. Food and Drug Administration approved the vaccine called Gardasil, which prevents infection against the two types of HPV responsible for most cervical cancer cases as well. Studies have shown that the vaccines prevent early-stage cervical cancer and precancerous lesions (NCCN, 2011).

Practicing safe sex and avoid partners who participate in high-risk sexual activities reduces risk of HPV and other sexually transmitted diseases. Getting regular Pap smears can help detect precancerous changes, which can be treated before they turn into cervical cancer (NCCN, 2011). Women should avoid active and passive cigarette smoking because research has shown that it is associated with an increased risk of cervical cancer (Trimble *et al*., 2005).

2.2 Statistical Methods

2.2.1 Survival analysis

Survival analysis involves modeling time to event data. The response is often referred to as a failure time, survival time or event time. The survival time response is usually continuous. The cure fraction is the proportion of patients who survived the disease and no longer experience the excess mortality rate (Lambert *et al*., 2007). Therefore, it assumes that a proportion of the cancer patients, P will be statistically cured and the other proportion, 1- P, will experience excess mortality rate. The cure fraction model is used to estimate both the cure fraction and the relative survival of patients.

The survival function $S(t) = \Pr(T > t) = 1 - F(t)$ gives the probability that a subject will survive past time t. As t ranges from 0 to 1, the survival function has the following properties:

- It is non-increasing
- At time $t = 0$, $S(t) = 1$; the probability of surviving past time 0 is 1
- At time $t \longrightarrow \infty$, $S(t) \longrightarrow 0$; as time goes to infinity, the survival curve tends towards 0 (Lee *et al*, 2003).

2.2.2 Relative survival

Relative survival is estimated from life tables as the ratio of the observed survival of the patients (where all deaths are considered events) to the expected survival.

Relative survival as used here is the observed survival among cancer patients divided by the expected survival in the general population. Five-year relative survival rates are commonly used as a way to evaluate and compare different treatment options. Although someone who has survived five years after a cancer diagnosis is not necessarily ñcured,ò the five-year relative survival analysis is considered a good indication that the cancer is responding to treatment and that the treatment is successfully extending the life of the individual with cancer (Lambert *et al*, 2007).

There are different stages of cervical cancer, ranging from stage I through stage IV. The staging system measures how far the disease has advanced. Cervical Cancer 5 year survival rates by stage are estimated to be as follows (Fayed, 2006):

Stage IA: This is micro invasive which is the very early cervical cancer. The five-year survival rate ranges from 96 to 99 percent. Treatment options at this stage include surgery.

Stage IB: In this stage, the cancer is visible without the use of a microscope. Five-year survival rates for this stage of cervical cancer are 80 to 90 percent. Common treatments include surgery, chemotherapy and radiation.

Stage II: In this stage, cancer has spread outside the uterus to adjacent tissue, but has not reached the lower third of the vagina or all the way to the lateral wall of the pelvis. Five-year survival is 65 to 69 percent. Common treatments are surgery, radiation and chemotherapy.

Stage III: In this stage the cancer has advanced beyond the parameters for stage II or has caused changes in the kidney. Five-year survival is 40 to 43 percent. Common treatments include chemotherapy and radiation.

Stage IV: This is the last stage of cervical cancer. In this stage the cancer has left the pelvis and affected more distant organs. The five-year survival rate for this stage of cancer is 15 to 20 percent. Treatments include chemotherapy and radiation.

2.2.3 Cure fraction

This is the proportion of patients that survive the disease and no longer experience excess mortality rate. The cure fraction estimates the proportion of cancer patients who are statistically cured and not necessarily medically cured that is they experience the same rate of mortality as the general population. Therefore, it assumes that a proportion of the cancer patients, □ will be statistically cured and the other proportion, 1 − □ will experience excess mortality rate. In this approach there is no need to know the actual cause of death because it includes all causes of death whether or not it is directly or indirectly associated with the diagnosis of cancer (Lambert, 2007). Excess mortality is mortality that is attributable to the crisis conditions. It can be expressed as a rate (the difference between observed in cancer patients and non-crisis mortality rates), or as a total number of excess deaths.

2.2.4 Kaplan-Meier analysis

Kaplan-Meier estimator is used in estimating the survival curve. Its goal is to estimate a population survival curve from a sample. If every patient is followed until death, the curve may be estimated simply by computing the fraction surviving at each time. However, in most studies patients tend to become lost to follow up or move away therefore a Kaplan-Meier analysis allows estimation of survival over time, even when patients drop out or are studied for different lengths of time (Varaj, 2007).

2.2.5 Cox regression model

Suppose one wants to find out the relation between the survival probability S(t) and some covariate X, let $S_0(t)$ denote the survival function in case $X = 0$ and $S_X(t)$ is the survival function in case $X = x$ for a specific value of x. The Cox regression model assumes that:

$$S_X(t) = \{S_0(t)^{\exp(\beta x)}\}$$

Where β is the log hazard such that when $\beta > 0$, higher x values are associated with increased risk of event and when $\beta < 0$, higher x values are associated with reduced risk of the event.

For instance**,** Stage is an important determinant of survival: cases with distant metastasis had a risk of death some three times that of patients with localized disease, therefore detection and prompt treatment should improve overall survival from cancer of the cervix (Wabinga *et al*., 2003).

CHAPTER THREE

3.0 RESEARCH METHODOLOGY

3.1 Study design

A retrospective, descriptive non-intervention study was carried out in which cervical cancer cases diagnosed between January 2005 and June 2007 were followed up to January 2010 and June 2012 for five years respectively to determine an individualôs survival duration. It involved the use of available information from medical records on cervical cancer patients and follow up of patients by contacting and interviewing the patients or their next of kin to determine the vital status of patients in case of missing or unclear details from available records. Follow up was also done using medical records at the Nairobi Hospice for patients who had been referred there.

3.2 Study site

This study was conducted at Kenyatta National Hospital in Nairobi, Kenya. This facility is ideal for this study because it provides high quality and specialized cancer treatment and it has the capacity to handle all referrals in Kenya. It also handles a large number of patients. This makes it a hospital of choice for a large proportion of cancer patients.

3.3 Study population

3.3.1 Inclusion criteria

Women were included if they:

- Were residents of Nairobi for at least 6 months
- Had a new diagnosis of cervical cancer between January 2005 and June 2007
- Were between 14-79 years

Follow up of these patients was conducted to establish their status by the end of five years from their individual initial dates of diagnosis.

3.3.2 Exclusion criteria

Women were excluded if they:

- Were 80+ years because the cure fraction is less reliable for this age group (Lambert *et al*., 2007)
- Were diagnosed based on death certificate or autopsy

3.4 Sampling

3.4.1 Sample size determination

Using the WHO manual ósSample size determination in Health studiesô (Lwanga *et al*., 1991) the sample size was estimated as follows:

Test survival rate	50%
Anticipated survival rate	40%
Level of significance (□)	5%
Power of the test (□)	90%
Confidence level (□)	95%

Using the formula

$$□ = □□_{□□□□} □ \sqrt{□□_{□}□1 - □_{□}□□} + □_{□□□□} □ \sqrt{□□_{□}□1 - □_{□}□□□}^{□} / (□_{□□} □_{□})^{□}$$

For $□_{□} = 0.50$ and $□_{□} = 0.40$ the sample size is 211.

3.4.2 Sampling procedure

Purposive sampling method was used. Criteria used were according to the explained inclusion and exclusion criteria.

3.5 Data collection methods

Data collection techniques involved the use of primary and secondary data collection methods. The main source of data in this study was medical records. Personal information of the patients, their diagnosis and treatment given was established by searching of hospital records. Interview of cervical cancer patients or their next of kin was also done in case of missing or unclear information from medical records. The next of kin were contacted to establish if the patients were alive or dead and incase they were deceased their dates of death. These Interviews were only carried out on patients and their next of kin in cases where they were reachable through contacts provided for in medical records and they consented to it. The next of kin were also interviewed for patients who were minors. Follow up was also done using medical records at the Nairobi Hospice for patients who had been referred there. The data collection tool was the checklist otherwise referred to as data compilation form (Appendix 1).

The covariates that were considered in this study are: education level, age, residence, smoking behaviour, alcohol intake, grade of cervical cancer, stage of cervical cancer, treatment given and the HIV status of the patient.

3.6 Data management and analysis

Excel was used to capture data and produce some descriptive graphics. R version 2.15.1(R Core Team, 2012) and SPSS version 18 statistical software were used for statistical analysis. Survival analysis was performed using the Kaplan-Meier estimator. The Life Table was used to estimate both the cure fraction and the relative survival of patients. The log-rank test was performed to compare the expected number of events at each stage of diagnosis against the observed values. The Cox Regression model was used to study the association between the survival with potential risk factors and other covariates.

3.7 Ethical consideration

Patientsô confidentiality was considered. Serial numbers were used during data entry, analysis, reporting and will be upheld even in publishing to ensure the patientsô identification is anonymous. Personal consent was sought before conducting interviews. Ethical approval was granted by the Kenyatta National Hospital / University of Nairobi Ethics and Research Committee.

CHAPTER FOUR

4.0 RESULTS

4.1 Demographic characteristics

A total of 211 patients with an initial diagnosis of cancer of the cervix between January, 2005 and June 2007 were followed up for five years respectively. All patients were alive at the time the diagnosis was made. A total of 108 (51.18%) of them were confirmed dead within that period, 15 (7.11%) were still alive and 88 (41.70%) were lost to follow up. The patientsô ages range from 14 to 76 years; the median age is 46 years while the mean is 46.45 years. As shown in Figure 1 53.08% of these patients were married. The marital status of some patients was unknown because it was not captured in the medical records and attempts to contact them or their next of kin for interviews were futile while some of them who were reachable especially through telephone declined to participate in interviews.

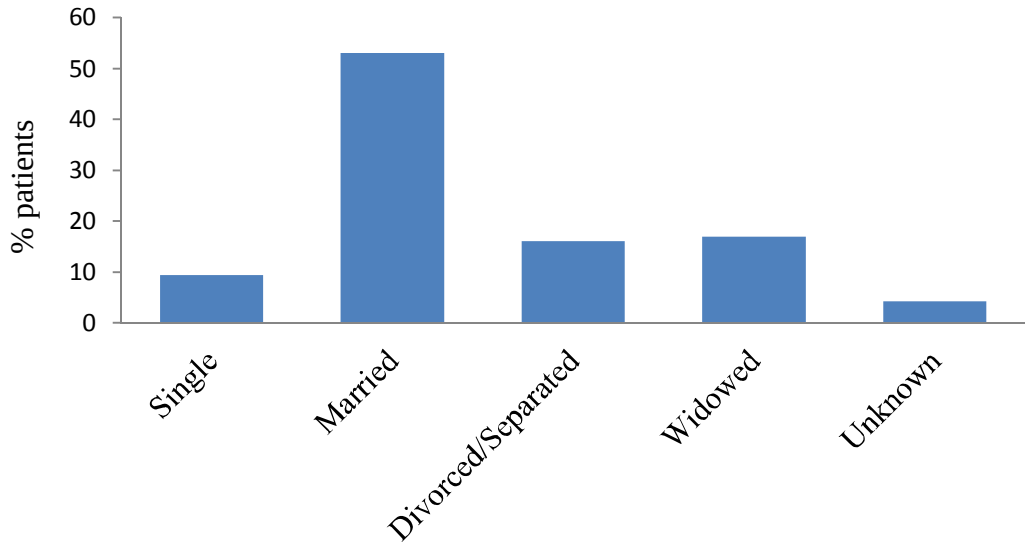

Figure 1: Marital Status of patients

The results further indicated that 49.76% and 47.39% of the patients had never engaged in cigarette smoking and alcohol intake respectively. Only 1.42% and 3.32% had a history of smoking and drinking alcohol, respectively, while the rest their drinking and alcohol intake behaviour could not be ascertained.

The residential areas in Nairobi are classified as high, middle and low income areas (NCC, 2007). The largest proportion of patients were from low income areas (60.19%), 37.91% from middle income areas with the least proportion coming from high income areas (1.90%).

As shown in Figure 2, the largest proportion of patients had highest level of education attained at primary (47.87%) and the least having attained university education (0.47%).

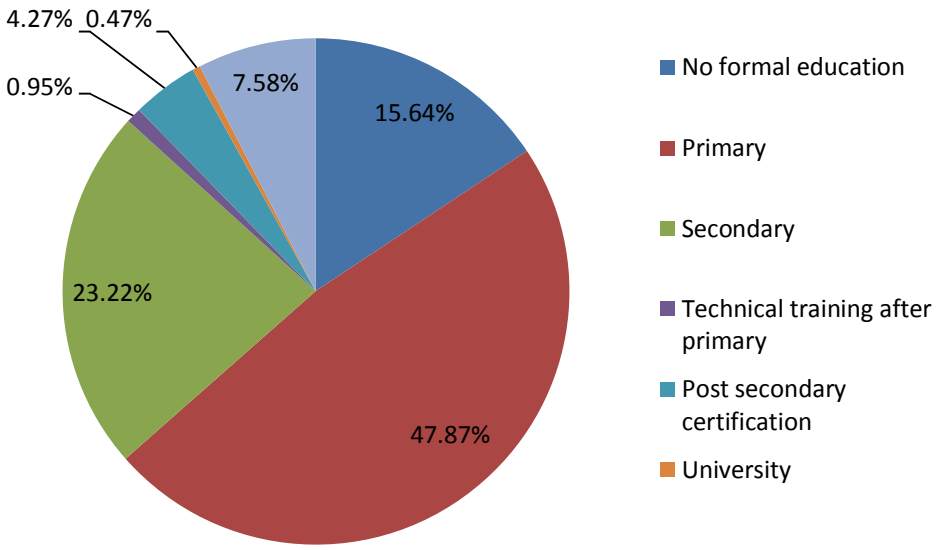

Figure 2: Level of education of patients

Diagnosis

There is evidence that most of the participants did not engage in regular screening for cervical cancer. As shown in Table 1, most patients were diagnosed histologically (57.3%) and at the same time at late stages of the tumor that is as from stage II. Most of the tumors were poorly differentiated (19.43%). The HIV status of most patients could not be ascertained from medical records which were heavily relied on to provide accurate information because the information was not captured.

Table 1: Patients' diagnostic details

	Number of patients	% patients
Method of diagnosis		
Histology	121	57.35
Cytology	48	22.74
Others	42	19.91
Stage at diagnosis		
Stage I	15	7.11
Stage II	50	23.70
Stage III	63	29.86
Stage IV	30	14.22
Unknown	50	25.12
Grade		
Well differentiated	14	6.64
Moderately differentiated	38	18.01
Poorly differentiated	41	19.43
Undifferentiated/Anaplastic	10	14.22
Unknown	108	25.12
HIV Status		
Negative	48	22.75
Positive	25	11.85
Unknown	138	65.40

Treatment

The treatment given to individual patients indicate that 46.45% of the patients were surgically treated, 60.19% received external radiotherapy while only 4.74% received Brachytherapy and 14.22% were given chemotherapy (Table 2).

Table 2: Treatment options given to patients

Treatment	Frequency	Percent
None / Unknown	45	21.33
S	36	17.06
S+ EBR	46	21.80
S + EBR + B	2	0.95
S + EBR + B + C	3	1.42
S + EBR + C	11	5.21
EBR	50	23.70
EBR + C	10	4.74
EBR + B + C	3	1.42
EBR + B	2	0.95
C	3	1.42

Key
S ï Surgery
EBR - External Beam Radiation
B - Brachytherapy (Internal Beam Radiation)
C ï Chemotherapy

4.2 Cure fraction

An interval of 3 month was used in this analysis as shown in the Life Table (Appendix 5).

The cumulative proportion of patients surviving at the end of the study interval (5 years) is 0.67 for those diagnosed at stage I, 0.36 at stage II, 0.15 at stage III and 0 at stage IV (Appendix 5). The greatest number and proportion of terminal events (death) occurred as from stage II. A patient who has survived for five years after a cancer diagnosis is not necessarily medically cured but is considered statistically cured because the five-year relative survival analysis is considered a good indication that the cancer is responding to treatment and that the treatment is successfully extending the life of the cancer patient.

4.3 Survival time

In an overall test of the equality of survival times (Table 3) across patients diagnosed at different stages, based upon the differences in group mean was significant (Wilcoxon statistic=15.88, df=4, $p<0.05$). This means therefore that survival curves of at least two stages are significantly different.

Table 3: Median Survival Times

Stage at diagnosis	Median Time (Months)
Stage I	60.00
Stage II	23.02
Stage III	10.14
Stage IV	9.73
Unknown	8.06

The pairwise comparison tests for stages at diagnosis (Table 4) showed that the survival of patients diagnosed at stages I and II, I and III, and I and IV were statistically significantly different ($p<0.05$) while there were no significant differences between stages, II and III, and III and IV ($p>0.05$).

.

Table 4: Pairwise comparison at different stages of diagnosis

Stage	**Stage**	**Wilcoxon (Gehan) Statistic**	**Df**	***p-value***
I	II	5.578	1	0.018
	III	9.594	1	0.002
	IV	10.874	1	0.001
	Unknown	11.476	1	0.001
II	I	5.578	1	0.018
	III	2.105	1	0.147
	IV	2.722	1	0.099
	Unknown	5.296	1	0.021
III	I	9.594	1	0.002
	II	2.105	1	0.147
	IV	0.173	1	0.677
	Unknown	0.729	1	0.393
IV	I	10.874	1	0.001
	II	2.722	1	0.099
	III	0.173	1	0.677
	Unknown	0.06	1	0.806
Unknown	I	11.476	1	0.001
	II	5.296	1	0.021
	III	0.729	1	0.393
	IV	0.06	1	0.806

Right censoring was done on observations that were either alive or lost to follow up. The survival table (Appendix 6) is a descriptive table that details the time until the terminal event. The Kaplan-Meier estimator was used because it incorporates information from all of the observations available, both censored and uncensored, by considering any point in time as a series of steps defined by the observed survival and censored times. The number at risk is the number surviving, while the survival is the proportion of cases surviving from the start of the table until the corresponding time like in this case of the probability of surviving beyond the maximum time (60 months) is estimated at 0.198. The survival curve, Figure 3 gives a visual representation of the survival trend. Drops in the survival curve occur whenever the terminal event occurs to a patient. The survival curve describes the relationship between the probability of survival and time as inverse. The red dotted line shows that at 10 months about 50% of patients were still alive (Figure 3). The Figure shows a sharp drop in the survival of patients within the first few (approximately 15) months, indicating that most of the patients experienced the event early.

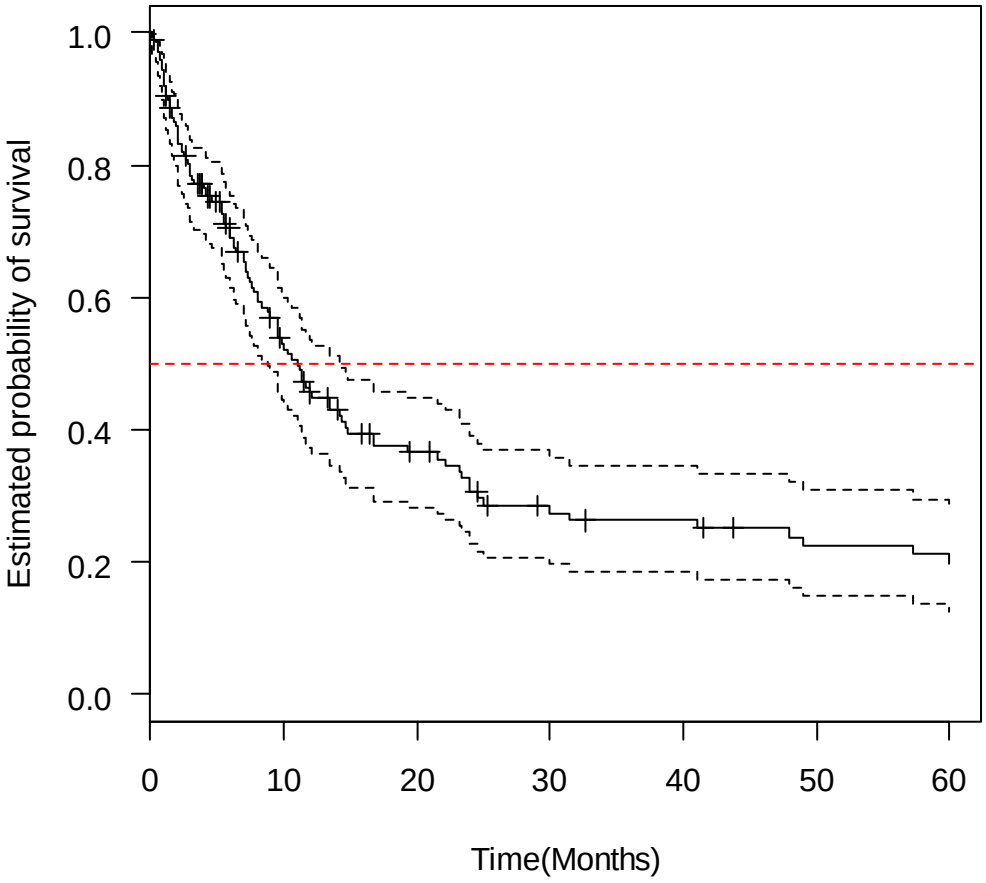

Figure 3: Survival curve

Comparing Survival functions with Stage as Strata

The median survival time at stage I was 60 months, 23.02 months at stage II, 10.14 months at stage III and 9.73 at stage IV (Table 3). Using the log-rank test, the survival at different stages of diagnosis were significantly different ($G^2 = 20$, $df = 4$, $p<0.05$), indicating that the survival at different stages of diagnosis is significantly different as shown in Table 5. This is also graphically depicted in Figure 4 which also shows that the risk of death was higher at advanced stages.

Table 5: Survival difference

Stage at Diagnosis	No. of Patients	Observed	Expected	χ^2	Log-rank
Stage I	15	2	12.5	8.81	10.19
Stage II	50	21	30.8	3.10	4.43
Stage III	63	32	26.8	1.02	1.39
Stage IV	30	19	12.6	3.25	3.76
Unknown	53	34	25.4	2.94	3.88

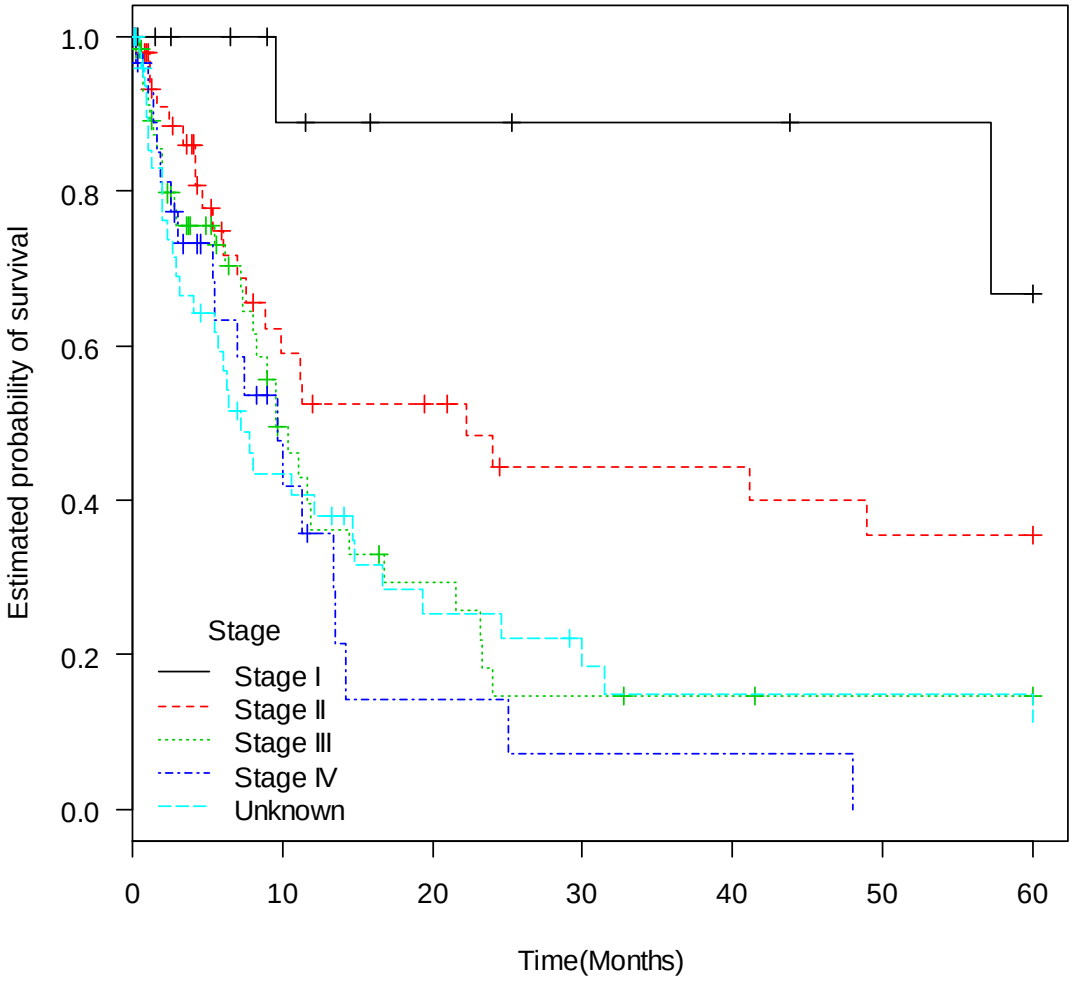

Figure 4: Survival difference curves with Stage as Strata

4.4 Cox Proportional Hazards Regression models

4.4.1 Cox PH regression

Cox PH regression models the effect of covariates on the hazard rate. Cox regression is performed using the Breslow method. Since we donôt have extensive tied death times, the Breslow method is efficient computationally. Results in Table 6 show that the stage at diagnosis and level of education significantly affect the survival while some treatment options significantly affect the survival as well.

Table 6: Estimation using Breslow method

Covariate	HR	95 % CI LL	95 % CI UL	p-value
Age	9.841e-01	0.96210	1.0067	0.166592
Drinking Behaviour				
No History of drinking	1			
History of drinking	3.939e-01	0.10812	1.4351	0.157857
Unknown drinking behaviour	1.107e+01	0.74042	165.3672	0.081482
Level of Education				
No formal education/Primary	1			
Post primary education	2.653e-01	0.25933	0.7337	0.001766
Unknown education level	6.798e-01	0.29287	1.5778	0.368909
Grade				
Well differentiated	1			
Moderately differentiated	4.669e-01	0.16851	1.2935	0.142912
Poorly differentiated	-6.633e-01	0.22904	1.9207	0.449160
Undifferentiated/Anaplastic	3.843e-01	0.07680	1.9236	0.244516
Unknown grade	7.122e-01	0.27112	1.8709	0.490973
HIV Status				
HIV Negative	1			
HIV Positive	1.025e+00	0.50370	2.0869	0.945158
HIV status unknown	6.914e-01	0.41998	1.1382	0.146764
Income Zone				
High Income zone	1			
Medium income zone	6.156e+07	0.00000	Inf	0.995492
Low income zone	3.629e+07	0.00000	Inf	0.995625
Smoking behaviour				
No history of smoking	1			
History of Smoking	1.501e-01	0.01000	2.2525	0.169955
Unknown smoking behaviour	1.079e-01	0.00719	1.6183	0.107052
Stage at diagnosis				
Stage I	1			
Stage II	7.123e+00	1.58961	31.9218	0.010299
Stage III	1.377e+01	3.03171	62.5414	0.000683
Stage IV	1.391e+01	2.89369	66.8776	0.001015
Unknown stage	1.071e+01	2.33490	49.1550	0.002282
Treatment				
None / Unknown	1			
S	6.414e-01	0.29700	1.3853	0.258355
S+ EBR	8.662e-01	0.45367	1.6537	0.663258
S + EBR + B	2.012e-01	0.01898	2.1335	0.183204
S + EBR + B + C	1.084e-01	0.01377	0.8530	0.034767
S + EBR + C	2.039e-01	0.07896	0.5266	0.001020
EBR	5.295e-01	0.28651	0.9787	0.042507
EBR + C	3.264e-01	0.11889	0.8964	0.029835
EBR + B + C	1.635e-08	0.00000	Inf	0.995161
EBR + B	6.721e-01	0.07978	5.6626	0.714833
C	3.841e-01	0.04760	3.0994	0.369105

Stepwise regression

To check whether all the nine variables deserve to be included in the model, stepwise regression was used. The AIC was lowest when four covariates were removed that is grade, HIV status Drinking behaviour and Smoking behaviour as shown in Table 7 below. They were therefore excluded in subsequent analysis.

Table 7: Stepwise regression

Covariate	Df	AIC
none		922.04
Age	1	925.26
Education	2	926.12
Income zone	2	927.85
Treatment	10	932.43
Stage at diagnosis	4	939.79

After removing the variables that did not deserve to be in the model, Table 8 shows that the age of a patient, stage at initial diagnosis and level of education significantly affects the survival, and some treatment options also significantly affect the survival as well. Three treatment options which are S + EBR + B + C, S + EBR + C and EBR significantly affected the survival of patients($\square < 0.05$). There was evidence of a steady increase in the risk of death with advancements in stage at initial diagnosis. Patients with an initial diagnosis at stage II, stage III and stage IV had an increased risk of death 6.29, 13.71 and 15.47 times respectively those diagnosed at stage I($\square < 0.05$). Patients who had attended school beyond primary school were at a reduced risk of 0.493 compared to those who attended no formal education/primary education($\square < 0.05$).

Table 8: Final Cox PH regression model

	HR	95 % CI LL	95 % CI UL	p
Age	9.782e-01	0.95977	0.9971	0.02400
Level of education				
No formal education/Primary	1			
Post primary education	4.953e-01	0.30030	0.8170	0.00590
Unknown education level	8.400e-01	0.38277	1.8434	0.66000
Income zone				
High income zone	1			
Medium income zone	5.414e+07	0.00000	Inf	1.00000
Low income zone	4.109e+07	0.00000	Inf	1.00000
Stage at diagnosis				
Stage I	1			
Stage II	6.294e+00	1.42400	27.8220	0.01500
Stage III	1.371e+01	3.08593	60.9422	0.00058
Stage IV	1.547e+01	3.28162	72.8937	0.00054
Unknown stage	1.122e+01	2.51520	50.0218	0.00150
Treatment				
None/Unknown	1			
S	7.306e-01	0.36332	1.4691	0.38000
S+ EBR	9.154e-01	0.51936	1.6134	0.76000
S + EBR + B	2.251e-01	0.02905	1.7436	0.15000
S + EBR + B + C	1.086e-01	0.01413	0.8353	0.03300
S + EBR + C	2.553e-01	0.10209	0.6382	0.00350
EBR	4.799e-01	0.27368	0.8415	0.01000
EBR + C	3.838e-01	0.14550	1.0123	0.05300
EBR + B + C	1.919e-08	0.00000	Inf	1.00000
EBR + B	7.799e-01	0.09626	6.3197	0.82000
C	4.119e-01	0.05238	3.2397	0.40000

4.4.2 Testing for proportional hazards assumption

Proportional hazards assumption assumes that the hazard for any individual is a fixed proportion of the hazard for any other individual. In Cox PH regression, survival curves must have hazard functions that are proportional over time (i.e. constant relative hazard). Table 9 shows that the global test gives a *p* value that is not significant suggesting that the assumption has not been violated (p = 0.0946).

Table 9: An assessment of the Cox PH assumption

	Rho	Chi square	p-value
Age	-0.132059	2.89e+00	0.0889
History of drinking	-0.123335	1.71e+00	0.1916
Unknown drinking behaviour	-0.122538	3.74e+00	0.0531
Post primary education	-0.038901	1.97e-01	0.6569
Unknown education level	0.015033	3.18e-02	0.8585
Moderately differentiated	-0.026518	8.59e-02	0.7694
Poorly differentiated	0.010626	1.39e-02	0.9061
Undifferentiated/Anaplastic	-0.064498	5.75e-01	0.4484
Unknown grade	0.057829	4.39e-01	0.5076
HIV Positive	-0.015431	3.58e-02	0.8500
HIV status unknown	0.035595	1.66e-01	0.6838
Medium income zone	0.234953	8.88e-08	0.9998
Low income zone	0.204265	6.18e-08	0.9998
History of smoking	0.156355	6.07e+00	0.0138
Unknown smoking behaviour	0.107057	2.87e+00	0.0904
Stage II	-0.098226	1.11e+00	0.2918
Stage III	-0.037330	1.61e-01	0.6878
Stage IV	-0.009740	1.10e-02	0.9165
Unknown stage	-0.092710	9.90e-01	0.3197
S	-0.032036	1.47e-01	0.7019
S+ EBR	-0.104431	1.44e+00	0.2307
S + EBR + B	0.114554	1.45e+00	0.2278
S + EBR + B + C	0.074574	5.92e-01	0.4416
S + EBR + C	0.097685	8.88e-01	0.3459
EBR	0.000815	9.28e-05	0.9923
EBR + C	0.077729	6.36e-01	0.4251
EBR + B + C	-0.184500	1.10e-07	0.9997
EBR + B	0.090271	9.06e-01	0.3412
C	0.012615	1.66e-02	0.8974
GLOBAL	NA	3.94e+01	0.0946

CHAPTER FIVE

5.0 DISCUSSION, CONCLUSION AND RECOMMENDATIONS.

5.1 Discussion

This study has demonstrated that the probability of surviving beyond five years when a patient is diagnosed with cancer of the cervix is estimated at 0.198 using the Kaplan-Meier estimator and the cumulative proportion surviving at the end of the study interval is 0.67 at stage I, 0.36 at stage II, 0.15 at stage III and 0 at stage IV. The median survival time at stage I is 60 months, 23.02 months at stage II, 10.14 months at stage III and 9.73 at stage IV. A similar study of 261 patients with cancer of the cervix registered by the Kampala population-based cancer registry, Uganda, between 1995 and 1997 had overall observed and relative survival for 3 years was 52.4 and 59.9% respectively (Wabinga *et al*, 2003). This indicates that more than 50% of patients in Kampala survived beyond three years while in this study only 26.3% of patients survived beyond three years.

According to the Cox regression model that was used to identify covariates that significantly affect the survival of patients with cancer of the cervix; the age of patients, stage at diagnosis and level of education proved to be significant. Some treatment options also proved to significantly affect the survival of patients. Only 7.11% of patients were ascertained to have had a diagnosis at stage I which shows that most of the patients were diagnosed at advanced stages. Also among cases that were treated by radiotherapy in Nairobi between 1974 and 1979 patients with an initial presentation at stage I was only 7% (Rogo *et al*, 1990). Similar studies conducted in Africa show that the stage at diagnosis is mostly advanced. The case of Kampala, Uganda where they recorded 27.9% of patients with an initial diagnosis at stage I is more than three times the proportion in this study. This difference is attributed to high levels of health awareness and easy access to medical facilities in Kampala (Wabinga *et al*, 2003). This explains why the survival is low in this study. In another study stage at diagnosis proved to be the only covariate that influences the survival significantly (Sankaranarayanan *et al*, 1998).

Stage of disease is important in determining the nature of treatment. At KNH patients between stage I and III are given radiotherapy treatment while those at stage IV are given chemotherapy treatment. Brachytherapy otherwise called internal beam radiation allows use of a higher total dose of radiation to treat a smaller area and in a shorter time than is possible with external beam radiation treatment. About 60.67% of patients had an initial diagnosis between stage I and III and 60.19% were given external radiotherapy treatment. The amount of radiation therapy for curative purposes for patients diagnosed at advanced stages should be about 80 gray (Gy) (Portence *et al* (2001) but most patients received about 50Gy. This is because most of the patients in this study were being referred to Mulago Hospital in Kampala, Uganda for brachytherapy but because most of them were from low income zones they could not afford the treatment. Only 4.74% of the patients in this study received Brachytherapy while 60.19% of received external radiotherapy. In the Kampala study only one in four patients (16 out of 63) had received both external beam and internal radiation, almost half of the patients (30 out of 63) received radiotherapy treatment by external beam alone and nine cases by internal radiation alone (Wabinga *et al*, 2003).

In another study in Brazil the following variables were analyzed: age; tumor staging; histopathological type of tumor and level of education among other factors in association with the survival using Cox proportional hazards regression model. As for level of education, those with 11 years of schooling or more showed a significantly better survival (Carmo *et al*. 2007). On the other hand this study has also demonstrated that patients who had attended school beyond primary school were at a reduced risk compared to those who attended no formal education/primary education. This could be attributed to the fact that more educated women usually seek health care regularly and promptly, and have more knowledge on prevention and thus their disease is detected at an earlier phase with more successful treatment as opposed to those who attained only elementary education and those who never attended formal education.

5.2 Conclusion

The outcome of this study provides important information for public health decision making and estimates patientsô chance of survival. The findings of this research show that the survival of patients is poor compared to similar studies carried out in Africa.

Patients with distant metastasis had an increased risk of death compared to those with localized cancer of the cervix. The cumulative proportion surviving at the end of the study interval is 0.67 at stage I, 0.36 at stage II, 0.15 at stage III and 0 at stage IV. The greatest proportion of terminal events (death) occurred as from stage II. The probability of surviving beyond five years is estimated at 0.198. The median survival time at stage I was 60 months, 23.02 months at stage II, 10.14 months at stage III and 9.73 at stage IV. The age of patients, the stage at diagnosis and the level of education attained significantly affected the survival of patients.

5.3 Recommendations

Early detection of cervical cancer through regular screening programs of women and prompt and comprehensive treatment should be taken up to improve the overall survival of the patients.

Improved awareness is an integral part of controlling cervical cancer. This can be done by having health education on cervical cancer incorporated in the teaching curriculums by the Ministry of education just like it has been done for HIV / AIDS. Carrying out regular screening programs and community mobilization activities among other channels can be used also used to create awareness. This will encourage women to attend regular screening therefore increasing chances of diagnosis at the precancerous stage which is 100% curable. As discovered in this study there have been cases of uptake of herbal therapy and seeking religious intervention and in turn ignoring prescribed medication; this has posed a great danger to the health of such patients who eventually go back to the hospitals when the situation is much worse. Information on the availability of the HPV vaccine is some health facilities is unknown to many Kenyans. Therefore extensive and

expansive awareness will reduce the high mortality of patients with cancer of the cervix among women associated with ignorance.

Government intervention to reduce the burden of the cost of cancer treatment on the patients is very necessary. This is because cancer treatment is very expensive for an average Kenyan and the poor cannot afford it. In most cases they are undertreated because they cannot meet the high costs of treatment. Decentralizing cancer treatment by the national government is an important intervention. This will reduce the number of patients who have to wait before they undergo especially curative treatment for those diagnosed at advanced stages because as a result of long queues, their conditions are worsened. There is also need for improved and more efficient equipment required in cancer treatment as the existing ones are greatly strained and some of them are archaic. These interventions will greatly improve the survival of patients diagnosed with the disease.

Further research on the time to remission and time to relapse, and the effect of treatment on the disease should be carried out to give more insight into the burden of the disease and disease management.

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APPENDICES

Appendix 1: Case follow up checklist

CASE FOLLOW UP CHECKLIST

CONFIDENTIAL **CODE _____**

A. PERSONAL DETAILS

1. Patientôs name: _____

2. Identification No._____ 3. Marital Status_____4.Tel.no._____

5. Date of Birth / / 6. Place of birth _____

7. Estate of residence _____8. Religion

9. Education level _____ 1 – Christian 2 – Muslim 3 – Hindu 4 – Other _____

11. Smoking ☐ [1.Never 2.Smoker 3. Ex-smoker 4. Unknown]

12. Alcohol intake ☐ [1.Never 2.Moderate 3. Addict 4. Unknown]

B. DIAGNOSIS

13. Date of diagnosis / / 14. Method of Diagnosis ☐

1 – Clinical only
2 – Clinic. Invest. / Ultra sound
4 – Biochem. Immuno test
5 – Cytology/Haematology
6 - Histology

15. Primary Site _____

16. Histology _____

17. Grade ☐ 18. Stage ☐

1 – Well differentiated
2 – Moderately differentiated
3 – Poorly differentiated
4 – Undifferentiated/Anaplastic
5 – Unknown

19. TREATMENT: [1-YES; 2-NO; 0=UNKNOWN]

Surgery ☐	Date / /	EBR ☐	Date / /
Chemotherapy ☐	Date / /	Brachytherapy ☐	Date / /

20. Other treatment received _____

21. Hospital No. _____

D. FOLLOW UP

22. Hospice No. _____

SURVIVAL

25. Current Status ☐ 1=Dead 0=Alive 26. Date Last Contact/Date of death: _____ / _____/ _____

27. If Dead Cause of Death _____

HIV STATUS:(-ve) ☐ (+ve) ☐

28. Other Concurrent illness_____

29. Remarks_____

_____

Name: _____Sign: _____

(Must be the principal investigator or cancer registrar assigned to collect data)

Date _____

Appendix 2: Introduction and consent for patient

INFORMED CONSENT FORM

ESTIMATING THE SURVIVAL OF PATIENTS WITH CERVICAL CANCER IN NAIROBI, KENYA

PRINCIPAL INVESTIGATOR: KHAEMBA EMMA NELIMA

INTRODUCTION:

I am a second year student of Jomo Kenyatta University of Agriculture and Technology (JKUAT) pursuing MSc. in Research Methods. I am undertaking a research project titled ñEstimating the survival of patients with cervical cancer in Nairobi, Kenyaò that will enable me to come up with an MSc thesis that will be submitted to my institution for award of degree. I would like to seek your permission to participate in this study. Please read the consent form below. I will be very glad if you accept my request to volunteer as a participant in my study.

THE PURPOSE OF STUDY

(1) To estimate the cure fraction of patients with cervical cancer in Nairobi between 2005 and 2011
(2) To estimate the survival time of patients with cervical cancer in Nairobi between 2005 and 2011
(3) To identify covariates that significantly affect the length of survival of patients with cervical cancer in Nairobi between 2005 and 2011

The information you provide will aid in planning strategic policy interventions which will assist in effective health care delivery.

PROCEDURE

The purpose of this form is to obtain your consent to participate in this study. If you choose to participate, you will be asked questions. Participation is voluntary and you can choose not to answer any individual question or all of the questions. However, we hope you will participate in this interview.

BENEFITS

There are no direct benefits to you by choosing to participate in this study. However, the results of this study will be communicated back to the health facility for necessary action by the health authority and to KEMRI who will also take action depending on the outcome. The results will also be issued in writing by thesis and publication as part of requirements by the university. The information you provide will aid in planning strategic interventions which can assist in effective health care delivery in Kenya.

WHAT ARE THE RISKS OF THE STUDY

Apart from the inconveniences caused by taking part of your time, the process is safe and there are no risks involved. However, we will try as much as we can to make sure that we save on your time.

WHAT ABOUT CONFIDENTIALITY?

All the information obtained will be strictly confidential and data password protected, only accessed by the individual investigator. Participants in the study will be kept anonymous, being identified only by the Principal investigator.

CONTACT INFORMATION

For any inquiries in the event of any research related questions, comments or complains the following persons will be available for contact:

Principal Investigator: Khaemba Emma Nelima

Telephone: +254 713 521 672

Email: emmank2@yahoo.com

OR

KNH/UON Ethics and Research Committee

P.O Box 20723-00202,

Nairobi, Kenya

Email: uonknh_erc@ounbi.ac.ke

Telephone: +254 272 6300-19 Ext 44102

At this point, do you want to ask me anything about the study?

Subject Submission:

I, the undersigned have understood the above information which has been fully explained to me by the investigator. I have agreed to voluntarily consent to participate. I was given the chance to ask questions and I received satisfactory responses.

Name of Participanté .

Signature of the person obtaining consenté é é é é é é é é Dateé é é é é é

(Must be the principal investigator or cancer registrar assigned to obtain consent)

Appendix 3: Introduction and consent for the next of kin

INFORMED CONSENT FORM

ESTIMATING THE SURVIVAL OF PATIENTS WITH CERVICAL CANCER IN NAIROBI, KENYA

PRINCIPAL INVESTIGATOR: KHAEMBA EMMA NELIMA

INTRODUCTION:

I am a second year student of Jomo Kenyatta University of Agriculture and Technology (JKUAT) pursuing MSc. in Research Methods. I am undertaking a research project titled ñEstimating the survival of patients with cervical cancer in Nairobi, Kenyaò that will enable me to come up with an MSc thesis that will be submitted to my institution for award of degree. I would like to seek your permission to participate in this study. Please read the consent form below. I will be very glad if you accept my request to volunteer as a participant in my study.

THE PURPOSE OF STUDY

(1) To estimate the cure fraction of patients with cervical cancer in Nairobi between 2005 and 2011

(2) To estimate the survival time of patients with cervical cancer in Nairobi between 2005 and 2011

(3) To identify covariates that significantly affect the length of survival of patients with cervical cancer in Nairobi between 2005 and 2011

The information you provide will aid in planning strategic policy interventions which will assist in effective health care delivery.

PROCEDURE

The purpose of this form is to obtain your consent to participate in this study. If you choose to participate, you will be asked questions. Participation is voluntary and you can choose not to answer any individual question or all of the questions. However, we hope you will participate in this interview.

BENEFITS

There are no direct benefits to you by choosing to participate in this study. However, the results of this study will be communicated back to the health facility for necessary action by the health authority and to KEMRI who will also take action depending on the outcome. The results will also be issued in writing by thesis and publication as part of requirements by the university. The information you provide will aid in planning strategic interventions which can assist in effective health care delivery in Kenya.

WHAT ARE THE RISKS OF THE STUDY

Apart from the inconveniences caused by taking part of your time, the process is safe and there are no risks involved. However, we will try as much as we can to make sure that we save on your time.

WHAT ABOUT CONFIDENTIALITY?

All the information obtained will be strictly confidential and data password protected, only accessed by the Principal investigator. Participants in the study will be kept anonymous, being identified only by the Principal investigator.

CONTACT INFORMATION

For any inquiries in the event of any research related questions, comments or complains, the following persons will be available for contact:

Principal Investigator: Khaemba Emma Nelima

Telephone: +254 713 521 672

Email: emmank2@yahoo.com

OR

KNH/UON Ethics and Research Committee

P.O Box 20723-00202,

Nairobi, Kenya

Email: uonknh_erc@ounbi.ac.ke

Telephone: +254 272 6300-19 Ext 44102

At this point, do you want to ask me anything about the study?

Subject Submission:

I, the undersigned have understood the above information which has been fully explained to me by the investigator. I have agreed to voluntarily consent to participate. I was given the chance to ask questions and I received satisfactory responses.

Name of Participanté .....

Next of kin to.....Relationship.....

Signature of the person obtaining consenté é é é é é é é .Dateé é é é é é

(Must be the principal investigator or cancer registrar assigned to obtain consent)

Appendix 4: Ethics approval letter

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
(254-020) 2726300 Ext 44355

KNH/UON-ERC
Email: uonknh_erc@uonbi.ac.ke
Website: www.uonbi.ac.ke
Link:www.uonbi.ac.ke/activities/KNHUoN

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/101

8th May 2012

Khaemba Emma Nelima
AG332/1827-2010
Jomo Kenyatta University of Agriculture and Technology
NAIROBI

Dear Emma

Research proposal: "Estimating the Survival of patients with Cervical cancer in Nairobi, Kenya" (P147/03/2012)

This is to inform you that the KNH/UoN-Ethics & Research Committee (ERC) has reviewed and **approved** your above cited research proposal. The approval periods are 8th May 2012 to 7th May 2013.

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.uonbi.ac.ke/activities/KNHUoN**

Yours sincerely

PROF A.N. GUANTAI
SECRETARY, KNH/UON-ERC

c.c. The Deputy Director CS, KNH
The Principal, College of Health Sciences, UON
Supervisors: Miss Caroline Wanja Mugo, JKUAT
Dr. Charles Mutai, KEMRI

Appendix 5: Life Table

First-order Controls	Interval Start Time	Number Entering Interval	Number Withdrawing during Interval	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Hazard Rate	Std. Error of Hazard Rate
Stage 1	0	15	4	0	0	1	1	0	0	0
	3	11	0	0	0	1	1	0	0	0
	6	11	1	0	0	1	1	0	0	0
	9	10	2	1	0.11	0.89	0.89	0.1	0.04	0.04
	12	7	0	0	0	1	0.89	0.1	0	0
	15	7	1	0	0	1	0.89	0.1	0	0
	18	6	0	0	0	1	0.89	0.1	0	0
	21	6	0	0	0	1	0.89	0.1	0	0
	24	6	1	0	0	1	0.89	0.1	0	0
	27	5	0	0	0	1	0.89	0.1	0	0
	30	5	0	0	0	1	0.89	0.1	0	0
	33	5	0	0	0	1	0.89	0.1	0	0
	36	5	0	0	0	1	0.89	0.1	0	0
	39	5	0	0	0	1	0.89	0.1	0	0
	42	5	1	0	0	1	0.89	0.1	0	0
	45	4	0	0	0	1	0.89	0.1	0	0
	48	4	0	0	0	1	0.89	0.1	0	0
	51	4	0	0	0	1	0.89	0.1	0	0
	54	4	0	0	0	1	0.89	0.1	0	0
	57	4	0	1	0.25	0.75	0.67	0.21	0.1	0.09
	60	3	3	0	0	1	0.67	0.21	0	0
Stage 2	0	50	9	5	0.11	0.89	0.89	0.05	0.04	0.02
	3	36	7	5	0.15	0.85	0.75	0.07	0.06	0.02
	6	24	1	4	0.17	0.83	0.62	0.08	0.06	0.03
	9	19	0	3	0.16	0.84	0.53	0.09	0.06	0.03

Appendix 5 continued

First-order Controls	Interval Start Time	Number Entering Interval	Number Withdrawing during Interval	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Hazard Rate	Std. Error of Hazard Rate
Stage 2	12	16	1	0	0	1	0.53	0.09	0	0
	15	15	0	0	0	1	0.53	0.09	0	0
	18	15	1	0	0	1	0.53	0.09	0	0
	21	14	1	1	0.07	0.93	0.49	0.09	0.03	0.03
	24	12	1	1	0.09	0.91	0.44	0.09	0.03	0.03
	27	10	0	0	0	1	0.44	0.09	0	0
	30	10	0	0	0	1	0.44	0.09	0	0
	33	10	0	0	0	1	0.44	0.09	0	0
	36	10	0	0	0	1	0.44	0.09	0	0
	39	10	0	1	0.1	0.9	0.4	0.09	0.04	0.04
	42	9	0	0	0	1	0.4	0.09	0	0
	45	9	0	0	0	1	0.4	0.09	0	0
	48	9	0	1	0.11	0.89	0.36	0.09	0.04	0.04
	51	8	0	0	0	1	0.36	0.09	0	0
	54	8	0	0	0	1	0.36	0.09	0	0
	57	8	0	0	0	1	0.36	0.09	0	0
	60	8	8	0	0	1	0.36	0.09	0	0
Stage 3	0	63	14	13	0.23	0.77	0.77	0.06	0.09	0.02
	3	36	8	1	0.03	0.97	0.74	0.06	0.01	0.01
	6	27	2	6	0.23	0.77	0.57	0.08	0.09	0.04
	9	19	2	6	0.33	0.67	0.38	0.08	0.13	0.05
	12	11	0	1	0.09	0.91	0.35	0.08	0.03	0.03
	15	10	1	1	0.11	0.89	0.31	0.08	0.04	0.04
	18	8	0	0	0	1	0.31	0.08	0	0
	21	8	0	3	0.38	0.63	0.19	0.07	0.15	0.09
	24	5	1	1	0.22	0.78	0.15	0.07	0.08	0.08
	27	3	0	0	0	1	0.15	0.07	0	0
	30	3	1	0	0	1	0.15	0.07	0	0
	33	2	0	0	0	1	0.15	0.07	0	0

Appendix 5 continued

First-order Controls	Interval Start Time	Number Entering Interval	Number Withdrawing during Interval	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Hazard Rate	Std. Error of Hazard Rate
Stage 3	36	2	0	0	0	1	0.15	0.07	0	0
	39	2	1	0	0	1	0.15	0.07	0	0
	42	1	0	0	0	1	0.15	0.07	0	0
	45	1	0	0	0	1	0.15	0.07	0	0
	48	1	0	0	0	1	0.15	0.07	0	0
	51	1	0	0	0	1	0.15	0.07	0	0
	54	1	0	0	0	1	0.15	0.07	0	0
	57	1	0	0	0	1	0.15	0.07	0	0
	60	1	1	0	0	1	0.15	0.07	0	0
Stage 4	0	30	5	6	0.22	0.78	0.78	0.08	0.08	0.03
	3	19	3	3	0.17	0.83	0.65	0.1	0.06	0.04
	6	13	1	2	0.16	0.84	0.54	0.1	0.06	0.04
	9	10	2	3	0.33	0.67	0.36	0.11	0.13	0.08
	12	5	0	3	0.6	0.4	0.15	0.09	0.29	0.15
	15	2	0	0	0	1	0.15	0.09	0	0
	18	2	0	0	0	1	0.15	0.09	0	0
	21	2	0	0	0	1	0.15	0.09	0	0
	24	2	0	1	0.5	0.5	0.07	0.07	0.22	0.21
	27	1	0	0	0	1	0.07	0.07	0	0
	30	1	0	0	0	1	0.07	0.07	0	0
	33	1	0	0	0	1	0.07	0.07	0	0
	36	1	0	0	0	1	0.07	0.07	0	0
	39	1	0	0	0	1	0.07	0.07	0	0
	42	1	0	0	0	1	0.07	0.07	0	0
	45	1	0	0	0	1	0.07	0.07	0	0
	48	1	0	1	1	0	0	0	0.67	0
Unknown	0	53	10	14	0.29	0.71	0.71	0.07	0.11	0.03
	3	29	1	4	0.14	0.86	0.61	0.07	0.05	0.03
	6	24	2	6	0.26	0.74	0.45	0.08	0.1	0.04

Appendix 5 continued

First-order Controls	Interval Start Time	Number Entering Interval	Number Withdrawing during Interval	Number of Terminal Events	Proportion Terminating	Proportion Surviving	Cumulative Proportion Surviving at End of Interval	Std. Error of Cumulative Proportion Surviving at End of Interval	Hazard Rate	Std. Error of Hazard Rate
	9	16	0	1	0.06	0.94	0.42	0.08	0.02	0.02
	12	15	2	3	0.21	0.79	0.33	0.08	0.08	0.05
	15	10	0	1	0.1	0.9	0.3	0.08	0.04	0.04
	18	9	0	1	0.11	0.89	0.27	0.07	0.04	0.04
	21	8	0	0	0	1	0.27	0.07	0	0
	24	8	0	1	0.13	0.88	0.23	0.07	0.04	0.04
	27	7	1	0	0	1	0.23	0.07	0	0
	30	6	0	2	0.33	0.67	0.15	0.07	0.13	0.09
	33	4	0	0	0	1	0.15	0.07	0	0
	36	4	0	0	0	1	0.15	0.07	0	0
	39	4	0	0	0	1	0.15	0.07	0	0
	42	4	0	0	0	1	0.15	0.07	0	0
	45	4	0	0	0	1	0.15	0.07	0	0
	48	4	0	0	0	1	0.15	0.07	0	0
	51	4	0	0	0	1	0.15	0.07	0	0
	54	4	0	0	0	1	0.15	0.07	0	0
	57	4	0	0	0	1	0.15	0.07	0	0
	60	4	3	1	0.4	0.6	0.09	0.06	0	0

Appendix 6: Survival Table

Time (Months)	Number at risk	Number of event	Survival	95 % CI LL	UL
0.1	211	1	0.995	0.967	0.999
0.2	205	1	0.990	0.962	0.998
0.4	195	1	0.985	0.955	0.995
0.5	192	1	0.980	0.948	0.993
0.6	187	2	0.970	0.934	0.986
0.7	185	2	0.959	0.920	0.979
0.8	180	1	0.954	0.913	0.976
0.9	176	2	0.943	0.899	0.968
1.0	173	4	0.921	0.873	0.952
1.1	167	3	0.905	0.853	0.939
1.3	163	1	0.899	0.846	0.935
1.4	159	2	0.888	0.833	0.925
1.6	156	3	0.871	0.813	0.912
1.8	153	1	0.865	0.807	0.907
1.9	152	1	0.859	0.800	0.902
2.0	151	5	0.831	0.768	0.878
2.3	143	1	0.825	0.762	0.873
2.4	141	1	0.819	0.755	0.868
2.5	140	1	0.813	0.749	0.863
2.7	136	1	0.807	0.742	0.858
2.8	135	1	0.801	0.735	0.853
2.9	133	2	0.789	0.722	0.842
3.0	131	1	0.783	0.715	0.837
3.1	130	1	0.777	0.709	0.832
3.3	129	1	0.771	0.702	0.826
4.0	122	1	0.765	0.695	0.821
4.2	120	2	0.752	0.681	0.810
4.6	114	1	0.746	0.674	0.804
5.3	108	2	0.732	0.659	0.792
5.4	106	1	0.725	0.651	0.786
5.5	105	2	0.711	0.636	0.773
5.7	101	1	0.704	0.629	0.767
6.0	99	2	0.690	0.613	0.754
6.2	96	1	0.683	0.606	0.748
6.3	94	1	0.675	0.598	0.741
6.4	93	1	0.668	0.590	0.735
7.0	90	2	0.653	0.574	0.721
7.2	87	2	0.638	0.558	0.708
7.3	85	1	0.631	0.550	0.701
7.4	84	1	0.623	0.542	0.694
7.6	83	1	0.616	0.535	0.687

Appendix 6 continued

Time (Months)	Number at risk	Number of event	Survival	95 % CI LL	UL
7.8	82	1	0.608	0.527	0.680
8.0	81	2	0.593	0.511	0.666
8.3	78	1	0.586	0.503	0.659
8.8	76	1	0.578	0.495	0.652
8.9	75	1	0.570	0.487	0.645
9.5	71	3	0.546	0.462	0.622
9.6	68	1	0.538	0.454	0.615
9.9	66	1	0.530	0.446	0.607
10.0	65	1	0.522	0.438	0.599
10.3	64	1	0.514	0.429	0.592
10.6	63	1	0.505	0.421	0.584
11.0	62	1	0.497	0.413	0.576
11.2	61	1	0.489	0.405	0.568
11.3	60	2	0.473	0.389	0.553
11.6	57	1	0.465	0.380	0.545
11.9	55	1	0.456	0.372	0.536
12.1	53	1	0.448	0.363	0.528
13.4	51	1	0.439	0.355	0.520
13.5	50	1	0.430	0.346	0.511
14.2	48	1	0.421	0.337	0.502
14.4	47	1	0.412	0.328	0.494
14.7	46	1	0.403	0.320	0.485
14.8	45	1	0.394	0.311	0.476
16.7	42	1	0.385	0.302	0.467
16.8	41	1	0.375	0.293	0.458
19.3	40	1	0.366	0.284	0.449
21.5	37	1	0.356	0.274	0.439
22.2	36	1	0.346	0.264	0.429
23.2	35	1	0.336	0.255	0.419
23.3	34	1	0.326	0.246	0.410
24.0	33	2	0.307	0.227	0.390
24.6	29	1	0.296	0.217	0.379
25.0	28	1	0.285	0.207	0.369
30.0	25	1	0.274	0.196	0.357
31.5	24	1	0.263	0.186	0.346
41.1	22	1	0.251	0.175	0.334
48.0	19	1	0.238	0.162	0.321
49.0	18	1	0.224	0.150	0.308
57.2	17	1	0.211	0.138	0.295
60.0	16	1	0.198	0.126	0.281

Appendix 7: Analysis Codes in R

```
#to install packages
install.packages(?survival?)
install.packages(?KMsurv?)
install.packages(?epicalc?)
install.splines('splines')

#To load the libraries
library(survival)
library(KMsurv)
library(splines)
library(epicalc)

#read data into R
cacx <- read.table("C:/Users/Nelima/Desktop/CaCx.txt",header=TRUE, sep="\t",
na.strings="NA", dec=".", strip.white=TRUE)
cacx

#To make columns available for use as variables
attach(cacx)

#create variables
cacx$Drinking<- as.factor(cacx$Drinking)
cacx$Grade<- as.factor(cacx$Grade)
cacx$Residence<- as.factor(cacx$Residence)
cacx$Smoking<- as.factor(cacx$Smoking)
cacx$Stage<- as.factor(cacx$Stage)
cacx$Treatment<- as.factor(cacx$Treatment)
cacx$Maritalstatus<- as.factor(cacx$Maritalstatus)
cacx$Education<- as.factor(cacx$Education)
cacx$Dx<- as.factor(cacx$Dx)

#describe data
codebook(cacx)
summary(cacx)

#create survival object
my.surv.object <- Surv(Time,Censoring)
my.surv.object

#find the KM estimate of the survival function
my.surv<- survfit(Surv(Time, Censoring, type="right") ~ 1, conf.type="log-log",
conf.int=0.95, type="kaplan-meier", error="greenwood", data=cacx)
summary(my.surv)
```

```
plot(my.surv,xlab="Time(Months)",ylab="Estimated probability of
survival",mark.time=TRUE, las=1)
abline(h=0.5,lty="dashed",col="red")
survdiff(Surv(Time,Censoring) ~ Stage, rho=0, data=cacx)
.Survfit <- survfit(Surv(Time, Censoring, type="right") ~ Stage, conf.type="log-log",
conf.int=0.95, type="kaplan-meier", error="greenwood", data=cacx)
summary(.Survfit)
plot(.Survfit,xlab="Time(Months)",ylab="Estimated probability of survival", col=1:5,
lty=1:5, mark.time=TRUE,las=1)

# Comparing functions with age as strata
plot(.Survfit,col=1:5,lty=1:5,xlab="Time(Months)",ylab="Estimated probability of
survival",mark.time=TRUE)
legend("bottomleft", legend=c("Stage I","Stage II","Stage III","Stage IV","Unknown"),
title="Stage", col=1:5, lty=1:5, bty="n")

#cox ph models
CoxModel.1 <- coxph(Surv(Time,Censoring) ~ Age + Drinking  + Education  + Grade
+ HIV  + Residence  + Smoking  + Stage  + Treatment , method="breslow", data=cacx)
summary(CoxModel.1)

#Stepwise regresssion
step(CoxModel.1)

#Testing for proportional hazards
cox.zph(CoxModel.1) -> diag1;diag1
CoxModel.2 <- coxph(Surv(Time,Censoring) ~ Age + Drinking  + Education  + Grade
+ HIV  + Residence  + Smoking  + strata(Stage)  + Treatment , method="breslow",
data=cacx)
summary(CoxModel.2)
cox.zph(CoxModel.2) -> diag1;diag1
```