PREDICTORS OF FIVE-YEAR OVERALL SURVIVAL IN WOMEN TREATED FOR CERVICAL CANCER AT THE KENYATTA NATIONAL HOSPITAL IN 2008

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Predictors of Five-Year Overall Survival in Women Treated for Cervical Cancer at the Kenyatta National Hospital in 2008

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DECLARATION

This thesis is my original work and has not been presented to any other university for the award of a degree.

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DEDICATION

This thesis is dedicated to my father Mr. John Osok and Professor James Todd, Department of Population Health, London School of Hygiene and Tropical Medicine. I have accomplished so much because of your support and encouragement. Thank you for motivating me to complete my project in spite of the numerous challenges that arose along the way.

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ABBREVIATIONS AND ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
AJCC	American Joint Committee on Cancer
BRM	Biological Response Modifiers
CGA	Comprehensive Geriatric Assessment
CIS	Carcinoma in situ (also referred to as Stage 0)
CT Scan	Computed tomography (also referred to as a CAT scan)
DFS	Disease Free Survival
DNA	Deoxyribonucleic Acid
EBRT	External Beam Radiotherapy
EFS	Event Free Survival
ERC	Ethical Review Committee
FDA	Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics
GAVI	Global Alliance for Vaccines and Immunization

GLM	Generalized Linear Model
HICs	High Income Countries
HIV	Human Immunodeficiency Virus
HPSR	Health Policy and Systems Research
HPV	Human papilloma virus
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
ICC	Invasive Cervical Cancer
JHPIEGO	Johns Hopkins Program for International Education in Gynecology and Obstetrics
KDHS	Kenya Demographic and Health Survey
KEMRI	Kenya Medical Research Institute
KNH	Kenyatta National Hospital
LEEP	Loop electro-surgical excision procedure
LMICs	Low and Middle Income Countries

MRI	Magnetic Resonance Imaging
NCDs	Non-Communicable Diseases
OS	Overall Survival
PFS	Progression Free Survival
RCT	Randomized Controlled Trial
SCC	Squamous Cell Carcinoma
SSA	Sub-Saharan Africa
SSC	Scientific Steering Committee
TTF	Time to Treatment Failure
UoN	University of Nairobi
VIA	Visual Inspection with Acetic Acid
VILI	Visual Inspection with Lugol's Iodine
VIAM	VIA using Magnification Devices
WHO	World Health Organization

DEFINITIONS OF OPERATIONAL TERMS

Adjuvant cancer care refers to any treatment that is given following the primary, initial or main treatment.

Biological response modifiers (BRMs) - these are substances the human body naturally produces and can also be synthesized in laboratories as drugs for treatment.

Biopsy involves testing of samples of tissue by a pathologist to confirm the presence or absence of cancer cells.

Cancer collectively refers to more than one hundred diseases that are characterized by abnormal cell growth and the ability of these cells to spread throughout the body via the blood and/or lymphatic system.

Chemotherapy refers to the use of chemical agents for the control or treatment of disease.

Colposcope is a diagnostic tool that combines a bright light with a magnifying lens to make it easier to examine cervical tissue.

Cryotherapy also known as cryosurgery, it involves the sequential freezing and thawing of cells to cause necrosis.

Cytology refers to the study of cells in terms of their origin, structure, function and pathology.

Data mining refers to analysis of data to establish relationships that have not previously been defined or characterized.

FIGO Staging the International Federation of Gynaecology and Obstetrics (FIGO) developed a staging system for cancers of the vulva, cervix, endometrium and sarcomas. The staging system is designed to provide uniform terminology for better communication among health professionals, enable determination of prognosis and treatment planning.

Hormone therapy refers to the use of hormones for treatment and control of disease.

Hydronephrosis swelling of the kidney(s) due to a buildup of urine as a result of a blockage or obstruction that prevents urine from draining out of the kidney and into the bladder.

ICD-10 refers to the International Classification of Diseases, tenth revision is a system used by healthcare providers to classify and code all diagnoses, symptoms and procedures recorded in conjunction with hospital care.

Immunotherapy refers to treatment or prevention of disease by enhancing the body's immune system functions. This is achieved by use of biological response modifiers.

LEEP loop electro-surgical excision procedure is a treatment for abnormal cells on the cervix.

Pap Smear this refers to the Papanicolaou test which is also known as Pap test, cervical smear or smear test. It is a method of cervical screening used to detect potentially pre-cancerous and cancerous processes in the uterine cervix.

Radiotherapy refers to treatment of disease using radiation and is also referred to as radiation therapy.

Speculum- is a medical tool that is designed for investigating body orifices/openings. Its form is based on the orifice to be examined.

Stata a statistical software package used by researchers for data analysis.

STEPS Survey refers to STEPwise approach to surveillance (STEPS). It is a simple standardized method for collecting, analyzing and disseminating data in WHO member countries. It represents two types of surveillance systems; adult risk factor surveillance and stroke surveillance.

Systemic therapy refers to chemotherapy and/or immunotherapy

TAH Total abdominal hysterectomy which is a surgical procedure where the uterus and cervix are removed.

Wertheim's Hysterectomy Also called radical hysterectomy and is a surgical procedure where the uterus, cervix and part of the vagina, along with the parametrium (the connective tissue that surrounds the cervix).

ABSTRACT

Cervical cancer is the fourth most commonly diagnosed and the fourth leading cause of cancer death among women worldwide. In many low- and middle-income countries (LMICs) including Kenya cervical cancer remains the leading cause of cancer death among women. This situation is due to the fact that despite the existence of effective preventive and early detection programs, lack of implementation in LMICs leads many women suffering from the disease to premature death. This study was aimed at estimating the five-year overall survival rates for women with cervical cancer in Kenya. To achieve this, the study employed a retrospective cohort design where medical records of all patients who commenced treatment for cervical cancer in 2008 were reviewed retrospectively over a period of five years from 2008- 2013. Data analysis involved the use of Stata v14.2 to generate descriptive statistics and conduct survival analysis. The five-year overall survival estimate for women with cervical cancer at Kenyatta National Hospital (KNH) in 2008 was found to be 59%. Stage of disease at diagnosis, type of treatment received and whether or not treatment was initiated and completed are the three factors revealed to have the strongest influence on patient survival. Occupation which was used as a proxy for socio-economic status (SES) did not reflect the financial burden imposed on patients seeking treatment. However, the loss to follow up was significantly high at a rate of 82.3%; with no deaths observed after the first year, the overall survival estimate is only accurate over the first year. The results of this study provided insight on the relationship between various socio-demographic and clinical factors and patient outcomes of cervical cancer treatments at KNH. Moreover, it highlighted the ongoing health system challenges surrounding provision of and access to cancer treatment. The results will inform policy makers and health service providers on the quality and accessibility of available cervical cancer treatments as delivered within our healthcare setting.

CHAPTER ONE

INTRODUCTION

1.1 Background

The term cancer collectively refers to more than one hundred diseases that are characterized by abnormal cell growth and the ability of these cells to spread throughout the body via the vascular and/or lymphatic system (ACS, 2011a). According to the American Cancer Society, cancer is caused by both extrinsic factors (e.g. tobacco, chemicals, radiation, and infectious organisms) and intrinsic factors (e.g. inherited mutations, hormones, immune conditions, and mutations that occur from metabolism). These causal factors may act together or in sequence to initiate or promote carcinogenesis. The development of most cancers requires multiple steps that occur over many years (ACS, 2011a).

The International Agency for Research on Cancer (IARC) estimates that in 2018 there were 18.1 million new cancer cases and an estimated 9.6 million cancer deaths worldwide (Bray *et al.*, 2018). Of these, 1,055,172 (5.8%) of new cases and 693,487 (7.2%) deaths are estimated to have occurred in Africa in 2018. Cervical cancer was the second most commonly diagnosed cancer in Africa among women and for both sexes accounting for 19.6% (119,284) of new cancer cases. It was also the leading cause of cancer related deaths among women and for both sexes with an estimated 81,687 (11.8%) deaths in Africa (Ferlay *et al.*, 2018). In Kenya specifically, there were an estimated 5,250 new cervical cancer cases in 2018 making the disease the second most commonly diagnosed cancer among women after breast cancer (Ferlay *et al.*, 2018). With regards to cancer-related deaths, cervical cancer remains the leading cause of cancer-related deaths among women in Kenya and was responsible for 3,286 deaths (Ferlay *et al.*, 2018).

Cancer is not a rare disease in Africa. However, due to the overwhelming burden of communicable diseases, several studies suggest that there are minimal facilities for cancer management in Africa (Stefan, 2015). This may explain why despite the growing concerns over cancer, there remains low levels of awareness among the populations and health professionals, lack of skilled human resources for cancer prevention and control, inadequate oncological health-services infrastructure and few effective preventive and screening programs (Sankaranarayanan *et al.*, 2011; Boyle *et al.*, 2019; Vanderpuye *et al.*, 2019). These factors have resulted in late-stage presentation and diagnosis of cancer with poor outcomes (ACS, 2011b; Boyle *et al.*, 2019). For example, an analysis of population-based cancer survival data found that five-year age-standardized relative survival did not exceed 22% for any cancer site in The Gambia, or 13% for any cancer site except breast (46%) in Uganda (Sankaranarayanan et al., 2011).

The limited literature available on cancer survival rates in sub-Saharan Africa (SSA) reflects the scarcity of data available on the incidence and trends of common cancers across SSA. Only 10.5% of the African population is covered by population-based cancer registries (Gakunga, Parkin, and On behalf of the African Cancer Registry Network, 2015). Unfortunately, most of these registries do not meet the International Agency for Research on Cancer's (IARC) criteria for high-quality incidence data with regards to completeness, validity and timeliness (Curado *et al.*, 2007). This is evidenced by the fact that only five cancer registries (covering approximately 1% of Africa's population) met the criteria for inclusion in Cancer Incidence in Five Continents Volume IX (Curado *et al.*, 2007; Stefan, 2015; ACS, 2018). Jointly, the lack of quality data and limited healthcare financing continues to severely impede the implementation of effective and evidence-based cancer prevention and control programs (ACS, 2011b; Stefan, 2015).

1.2 Statement of the Problem

Cervical cancer is the fourth most common cancer among women globally (Ferlay *et al.*, 2018). If no action is taken, the annual number of new cases of cervical cancer is

expected to increase globally from 570,000 to 700,000 between 2018 and 2030, while the annual number of deaths is projected to rise from 311,000 to 400,000 (Ferlay *et al.*, 2018, 2020). Notably, in low-and-middle-income countries (LMICs), the incidence of cervical cancer is twice as high and the death rates three times as high as those observed in high-income countries (HICs) (Arbyn *et al.*, 2011). Kenya alone is expected to see an increase in new cases from 5,240 to 7,870 between 2020 and 2030 and a similar increase in deaths from 3,210 to 4,930 in the same period (Ferlay *et al.*, 2020). This large geographic variation in cervical cancer rates is primarily a reflection of the differences in availability of screening, which can detect and allow for the removal of precancerous lesions, and to a lesser extent human papillomavirus (HPV) infection prevalence (Vaccarella *et al.*, 2013, 2017). For these reasons, cervical cancer is regarded as a preventable disease.

Women with abnormal cervical tissue require treatment whether the diagnosis is for precancerous lesions or invasive cervical cancer (ICC) (Finocchario-Kessler *et al.*, 2016). Unfortunately, many women (56-80.6%) are identified once their cervical cancer is at an advanced stage as evidenced by studies in Kenya (Maranga *et al.*, 2013), Tanzania (Mosha *et al.*, 2009) and Nigeria (Abdullahi *et al.*, 2012). Moreover, the proper staging of ICC requires an assessment of the vagina, parametrium, urinary bladder and rectum using a combination of clinical and endoscopic procedures to determine the stage of disease (I – IVB) (Bhatla *et al.*, 2019). Instances of inadequate laboratory facilities, personnel shortages and lack of financial capability among patients may result in treatment decisions being made without proper diagnoses or adequate information.

Treatments for ICC include a range and combination of strategies including hysterectomy (requires surgical facilities), radiotherapy (external and intracavitary radiotherapy infrastructure), and chemotherapy (WHO, 2014). In most African countries, these treatments are either limited to capital cities or are not available at all. Consequently, palliative care with symptom control and support becomes the most likely

option for severely late stage cervical cancer and for women with less advanced disease, but who cannot afford or access treatment (Finocchario-Kessler *et al.*, 2016).

Even though survival data for cervical cancer is limited, the estimated 5-year survival for women diagnosed with cervical cancer in 7 African countries between 2005-2009 was 56.3 % (range 19.5–96 %) (Allemani *et al.*, 2015). As such, treatment of cervical cancer and quality of life of cervical cancer survivors remain two under researched areas in African countries (Finocchario-Kessler *et al.*, 2016). Owing to the high morbidity and mortality experienced by women with cervical cancer in the African setting, targeted research is urgently needed to inform feasible and sustainable strategies to maximize the number of women reached with services.

1.3 Justification

Africa accounts for less than 1% of worldwide research publications but is home to nearly 15% of the world's population (ACS, UICC and IARC, 2019). Of the generally limited research conducted on the continent, it is fair to assume that an extremely small proportion of these publications are dedicated to cancer research based on several published reports citing limited cancer data (Stefan, 2015; Finocchario-Kessler *et al.*, 2016; Boyle *et al.*, 2019). As a result, many African countries including Kenya are likely developing and implementing cancer control and management policies, strategies and guidelines largely based on foreign populations whose dynamics and experiences are significantly different.

Each country and locality needs cancer research tailored towards understanding local disease burdens and identifying knowledge gaps with an intention of improving population health (ACS, UICC and IARC, 2019). It is against this backdrop that this retrospective cohort study aims to examine the relationship between social and clinical factors among cervical cancer patients in Kenya relative to patient outcomes.

The study will accomplish its objective using survival analysis to estimate five-year overall survival. The time period of the study is 2008-2013 and the start year of 2008 is purposely selected because it coincides with an era when Kenya had only one fully fledged cancer treatment centre based at the Kenyatta National Hospital in the capital city, Nairobi. The study findings will a) identify locally available cervical cancer treatment options, b) elucidate predictive factors of survival among cervical cancer patients in Kenya and c) identify methodological considerations to enhance the quality of future cancer survival studies in low resource settings. In this way, the findings may offer guidance for the development of responsive and locally relevant policies regarding clinical management of cervical cancer and promote a higher quality design and implementation of cancer survival studies in low resource settings.

1.4 Research Questions

1) What are the treatment options available for cervical cancer at Kenyatta National Hospital (KNH)?
2) What are the socio-demographic and clinic predictors influencing patient outcomes of women treated for cervical cancer in KNH?
3) What are the five-year overall survival rates for women treated for cervical cancer at the KNH?

1.5 General Objective

To determine the five-year overall survival rates and associated predictors among women treated for cervical cancer at KNH between January and December 2008.

1.5.1 Specific Objectives

The specific objectives of this research are;

1) To determine the treatment options available for cervical cancer at KNH.

2) To determine the socio-demographic and clinical predictors patient outcomes among women treated for cervical cancer in KNH.
3) To determine the five-year overall survival rates among women treated for cervical cancer at KNH.

CHAPTER TWO

LITERATURE REVIEW

2.1 Epidemiology of Cancer

There are more than one hundred diseases characterized by abnormal cell growth and the ability of these cells to spread throughout the body via the blood and/or lymphatic system. These are collectively referred to as cancer and when they occur they are treated using surgery, radiation, chemotherapy, hormones and immunotherapy (ACS, 2011b).

In 2015 the World Health Organization (WHO) estimated that cancer was the first or second leading cause of premature death in 91 out of 172 countries, and ranked third or fourth in 22 additional countries (Bray *et al.*, 2018). Between the years 2000 and 2002, the most common cancers in the developing world were lung, breast, cervical, stomach, colorectal and liver cancers (Kanavos, 2006). In 2018 this trend remained the same in Africa as seen in Appendix 1 (Bray *et al.*, 2018).

Globally cervical cancer was estimated to be responsible for 570,000 new cancer cases and 311,000 deaths making it the fourth most commonly diagnosed cancer and the fourth leading cause of cancer related deaths (Bray *et al.*, 2018). In 2001, cervical cancer was the second most common cancer to affect women, and was the main cause of cancer mortality in many LMICs, where the disease generally presents as a large tumour of advanced stage (Green *et al.*, 2001). In Appendix 1, it is evident that the incidence and mortality trends observed in 2001 persist in Africa. In 2018 cervical cancer remained the second most commonly diagnosed cancer affecting women and the leading cause of cancer related deaths among women in Africa (Bray *et al.*, 2018). Appendix 2, which is specific to Kenya, shows that similarly in Kenya cervical cancer was the second most commonly diagnosed cancer affecting women and was responsible for the largest proportion of cancer mortality among women in 2018.

2.2 Cervical Cancer Control in Africa

A national cancer control programme (NCCP) is a public health program designed to reduce the number of cancer cases and deaths and improve quality of life of cancer patients, through the systematic and equitable implementation of evidence-based strategies for prevention, early detection, diagnosis, treatment, and palliation, making the best use of available resources (WHO, 2002). Unfortunately, only 11 African countries have a current NCCP (Duncan *et al.*, 2019).

The risk of cervical cancer is associated with early initiation of sexual activity, increased number of sexual partners of females and/or their partners, HIV infection, high parity, use of oral steroid contraceptives, smoking and alcohol consumption (WHO, 2014). Genital hygiene and male circumcision have also been found to be important factors in the development of cervical cancer (Kashyap *et al.*, 2019; Morris *et al.*, 2019). Of particular importance is sexual behaviour of females since it determines risk of exposure to sexually transmitted oncogenic human papilloma viruses (mainly subtypes 16, 18 &31) (Haile *et al.*, 2018). Also, sexually transmitted infections that cause chronic cervico- vaginal inflammation may increase the risks of cervical cancer (Kawata and Koga, 2020).

Strategies for reducing cervical cancer morbidity and mortality primarily include the following;

a) **National Screening programmes:** Before the introduction of screening programmes in the 1960s and 70s, the incidence of cervical cancer in Europe, North America, Australia and New Zealand was similar to what is seen in Africa today (Johnson *et al.*, 2018). Most screening programmes in HICs utilize the Papanicolaou test which is often abbreviated as Pap test or Pap smear.

A Pap smear involves opening of the vaginal canal with a speculum followed by collection of cells at the outer opening of the cervix called the transformation zone

(where the squamous cervical cells meet the inner glandular endocervical cells). The collected cells are then examined under a microscope for early detection of cellular abnormalities which may either be pre-cancerous or cervical cancer (Fontham *et al.*, 2020).

Cervical cancer screening should not start before 30 years of age. Pap smear screening with coverage of 80% of the total female population above the age of 35 would be most effective in reducing the incidence of cervical cancer Screening women between the ages of 30 and 49 years, even just once, will reduce deaths from cervical cancer (WHO, 2014).

Few if any organized national cancer screening programmes exist in Africa for many reasons including few if any good quality cytology services, difficulties of long- term follow up in some communities, lack of education and limited infrastructure (Duncan *et al.*, 2019). These reasons have encouraged the development of alternative methods to the Pap smear for screening and treatment for cancerous lesions. One such alternative method is screening by visual inspection after acetic acid impregnation of the cervix (University of Zimbabwe and JHPIEGO, 1999). This approach has a high negative predictive value (93%) and if combined safely with an affordable and effective means of treatment like cryotherapy then both screening and treatment could be given to patients during the same visit removing the need for follow ups (Chirenje *et al.*, 2001). Sankaranarayanan et al (2005) reviewed the performance of these alternatives compared to conventional cytology as shown in table 2.1 below (Sankaranarayanan *et al.*, 2005; Denny, Quinn and Sankaranarayanan, 2006).

Table 2.1: Performance and characteristics of different cervical cancer screening methods

SCREENING TEST	SENSITIVITY	SPECIFICITY	CHARACTERISTICS
Conventional cytology	Moderate (44–78%)	High (91–96%)	Requires adequate healthcare infrastructure; laboratory based; stringent training and quality control
HPV-DNA testing	High (66–100%)	Moderate (61–96%)	Laboratory based; high throughput; objective, reproducible and robust; currently expensive
Visual inspection methods*			Low technology; low cost
VIA	Moderate (67–79%)	Low (49–86%)	Linkage to immediate treatment possible; suitable for low-resource settings
VIAM	Moderate (62–73%)	Low (86–87%)	
VILI	Moderate to high (78-98%)	Low (73–93%)	
Colposcopy	Low (44–77%)	Low (85–90%)	Expensive; inappropriate for low-resource settings
Polar Probe	Moderate (67–74%)	Low (65–72%)	High technology but gives immediate result and could be linked to immediate treatment

**VIA- visual inspection with acetic acid; VIAM- VIA using magnification devices; VILI- visual inspection with Lugol's iodine.*

a) HPV vaccination: Primary prevention for cervical cancer is now possible through vaccination with one of four licensed vaccines: a) The two bivalent HPV (2vHPV) vaccines, i) CervarixTM (GlaxoSmithKline [GSK] Biologicals, Belgium) and ii) Cecolin® (Xiamen Innovax Biotech Co. Limited, China), contain L1 antigens from HPV 16 and 18; b) The quadrivalent HPV (4vHPV) vaccine, Gardasil®, contains L1 antigens from HPV 6, 11, 16, and 18; and c) the nonavalent HPV (9vHPV) vaccine, Gardasil-9®, contains L1 antigens from HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58 (both Merck Sharp & Dohme Corp., United States). Provision of this vaccine to young girls and women not infected with HPV could offer significant protection against these serotypes that cause cervical cancer. Recent studies confirm that protection lasts for more than 12 years after

vaccination (Lehtinen et al., 2017; Murillo and Ordóñez- Reyes, 2019; Spinner et al., 2019; Kjaer et al., 2020).

From the above, the biggest challenge in initiating national cancer control programmes in Africa is a lack of resources in terms of finances and trained professionals to design, manage and implement these programmes. Very little is known about the structure, processes and outcomes of cancer control activities in LMICs. The development of high-quality health data sources and improved capacity for health services research would promote better understanding of the current situation and identify areas of improvement of oncology health services across LMICs (Hanna and Kangolle, 2010).

2.3 Cervical Cancer Knowledge, Screening Coverage and HPV Infection in Kenya

2.3.1 Cervical Cancer Knowledge and screening coverage

The 2014 Kenya Demographic and Health survey estimates that 75% of women age 15-49 have heard of cervical cancer however only 14% have had a cervical cancer screening test. Of those women who reported ever having a cervical cancer test done, 62% had a Pap smear while 32% had visual inspection (KNBS and ICF Macro, 2015).

On the other hand, the 2015 STEPS survey estimated that 11% of women age 18-69 years had ever had a cervical cancer screening test. Also, approximately one quarter (23.6%) of these women had both heard about cervical cancer screening methods and been screened. Only 16% of women age 30-49 years had ever been screened for cervical cancer. Likelihood of screening was higher among women residing in urban areas (23%) compared to those in rural areas (14%). Prevalence of screening was noted to increase with advances in education level and socio-economic status (SES) (MoH, KNBS and WHO, 2015).

2.3.2 Prevalence of HPV Infection in Kenya

HPV infection plays a key role in cervical carcinogenesis and is a major risk factor for the development of cervical cancer (Walboomers *et al.*, 1999; Bosch *et al.*, 2002; Bosch and De Sanjosé, 2003; Böhmer *et al.*, 2003; Schiffman and Kjaer, 2003; zur Hausen, 2006; Woodman, Collins and Young, 2007). The oncogenic HPV-types commonly associated with cervical cancer development are 16, 18 and 31. Bruni et al (2016) conducted a systematic review of the literature on HPV prevalence in Kenya (Bruni *et al.*, 2016). Their findings show a higher prevalence of HPV-type 16 infection among females with low-grade lesions, high-grade lesions and cervical cancer compared to females with normal cytology (Figure 2.1).

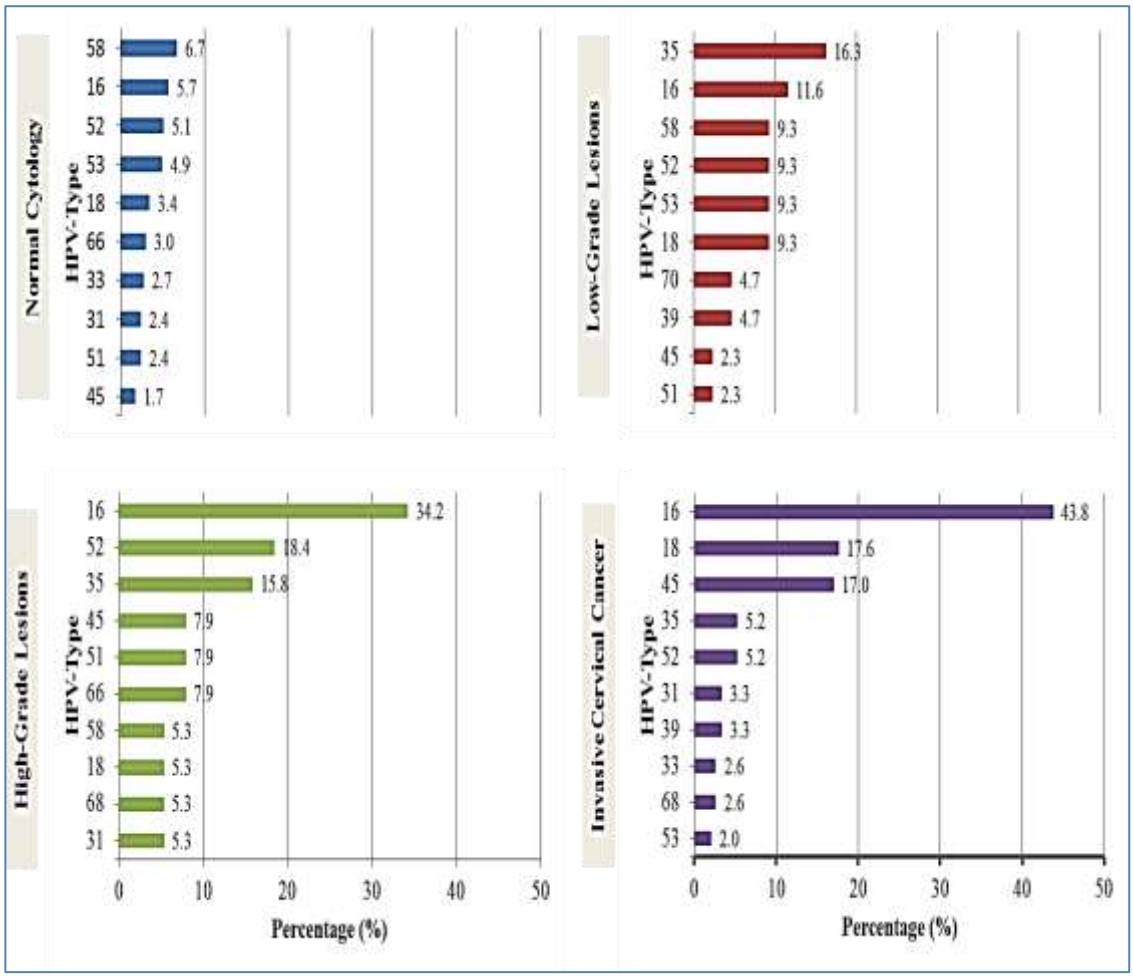


Figure 2.1: Ten most frequent HPV oncogenic types among women with and without cervical lesions in Kenya (Adapted from Bruni et. al. 2016)

2.4 Diagnosis and Management of Cervical Cancer

2.4.1 Cervical Cancer Diagnosis

Cervical cancer is defined as a cancer that forms in tissues of the cervix which is an organ connecting the uterus to the vagina. It is a slow- growing cancer that usually has no symptoms until the disease is in advanced stages (NCI, 2012). There are three major ways in which cervical cancer may be screened for (NCI, 2012);

i) Lab tests specifically the Pap test

ii) Cervical exam using a colposcope which can be done at the doctor's office or clinic.

iii) Biopsy

The biopsy is the only sure way to confirm the presence of cancer cells for the majority of cancers (NCI, 2012).

2.4.2 Cervical Cancer Staging

Following diagnostic confirmation, it is important to determine the extent of the disease. This is referred to as staging. The stage of cancer is based on whether the cancer has invaded nearby tissues or spread to other parts of the body (NCI, 2012). Once the cancer spreads it is referred to as metastatic cervical cancer. The commonly used tests to determine staging of the disease are a pelvic exam, Chest X- ray, CT scan or MRI.

Cervical cancer has four stages like other cancers. While there are several staging systems that can be used for cervical cancer, the most commonly used is the International Federation of Gynaecology and Obstetrics' (FIGO) staging system which was established in 1988 (Kim and Song, 2009). The current classification system is provided in table 2.2 below (Pecorelli, 2009).

Table 2.2: Revised 2009 FIGO classification system for cervical carcinoma

FIGO STAGE	FINDINGS
Stage 0	**Carcinoma in situ (pre-invasive carcinoma)**
Stage I	**Cervical carcinoma confined to uterus (extension to corpus should be disregarded)**
IA	**Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥7 mm**
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	**Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA***
IB1	Clinically visible lesion ≤4.0 cm in greatest dimension
IB2	Clinically visible lesion <4.0 cm in greatest dimension
Stage II	**Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina**
IIA	**Without parametrial invasion**
IIA1	Clinically visible tumour <4 cm in greatest dimension
IIA2	Clinically visible tumour >4 cm in greatest dimension
IIB	**With obvious parametrial invasion**
Stage III	**The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney****
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	**The carcinoma has extended beyond the true pelvis or has involved (biopsyproven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV**
IVA	Spread of the growth to adjacent organs e.g. bladder and rectum
IVB	Spread to distant organs e.g. liver, lungs and brain

* All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not N7.00 mm. Depth of invasion should not be N5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with "early (minimal) stromal invasion" (~1 mm). The involvement of vascular/lymphatic spaces should not change the stage allotment.

** On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

Prior to the revised 2009 FIGO classification system for cervical carcinoma provided above, the pre-2009 FIGO classification system was in place (Maranga *et al.*, 2013). It is availed here (Table 2.3) for comparison with the current criteria. It is also the focus of this research project as it was the staging criteria in use during the study's time period of interest (January-December 2008).

Table 2.3: The pre-2009 FIGO staging system for cervical carcinoma

FIGO STAGE	FINDINGS
IA	Micro-invasive Carcinoma
IB	Macroscopic Invasive cancer confined to the cervix
IIA	Tumour extending to the upper third of vagina but not to the parametrium
IIB	Tumour extending to the parametrium
IIIA	Tumour involving the lower third vagina with no extension to the pelvic side wall
IIIB	Tumour extending to the pelvic side wall and/or hydronephrosis or non-functioning kidney
IVA	Tumour involving adjacent pelvic organs i.e. bladder or rectum
IVB	Extra pelvic spread, e.g. metastasis to the liver, lungs etc

2.4.3 Treatment Options for Cervical Cancer

The treatment options for women with cervical cancer are radiation, surgery, chemotherapy or a combination of these methods. The choice of treatment is determined by the size of the tumor and whether it has spread to other organs and tissues. The intention to have children in future also influences the choice of treatment. The 2013 National Guidelines for Cancer Treatment advise that 5-Flourouracil, Cisplatin, Paclitaxel, Navelbine, Topotecan, Carboplatin, Docetaxel, Gemcitabine, Ifosfamide, Hydroxyurea and Mitomycin C. However, where resources are limited, it is recommended to use 5-Flourouracil with or without Cisplatin (MoH, 2013).

In 1999 five randomized controlled trials (RCT) studies were published which demonstrated the superiority of concurrent chemo-radiation over radiotherapy alone in the management of cervical cancer (Keys *et al.*, 1999; Morris *et al.*, 1999; Rose *et al.*,

1999; Whitney *et al.*, 1999; Peters *et al.*, 2000). These studies led to the adoption of chemo-radiation with cisplatin as the standard treatment for locally advanced disease (Mangioni *et al.*, 1999; Thomas, 2000; Green *et al.*, 2005). Other studies and reviews continue to support the use of chemo-radiation to treat locally advanced cervical cancer (Kesic, 2006; Pearcey *et al.*, 2007; Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration, 2008; Shanta *et al.*, 2010; Vale *et al.*, 2010). Two studies in particular propose best practice for the treatment of locally advanced cervical cancer as chemo-radiation which includes brachytherapy (Yalman *et al.*, 2003; Shanta *et al.*, 2010) (Shanta et al., 2010, Yalman et al., 2003). However, the final choice of treatment is ultimately based on an oncologist's judgement on individual cases.

2.5 Cancer Treatment Outcomes

An outcomes working group defined outcomes as the products, both positive and negative, of cancer treatment (Fetting *et al.*, 1996). There are two types of outcomes namely cancer outcomes and patient outcomes. Cancer outcomes are defined as measures of the effect of treatment on the cancer itself i.e. complete and partial response, response duration, time to progression and tumor markers. Patient outcomes are defined as the measures of the effect of treatment on the patient i.e. survival, toxicity and quality of life (Fetting *et al.*, 1996).

The outcomes of cancer treatment can be generalized as follows (Fetting *et al.*, 1996);

- Survival
- Quality of Life
- Treatment toxicity which is measured in three dimensions: frequency, severity and duration.
- Measures of cancer toxicity including measures of tumor response (i.e. complete response, partial response, response duration, and time to progression), biomarkers (e.g. CA-125), and cancer- induced abnormalities in common blood tests (e.g. Alkaline Phosphatase).

- Cost- effectiveness analysis: though not a treatment outcome it can provide important perspective when treatment costs are high and benefits are small or when treatment benefits are modest.

The most important outcome of cancer treatment is survival (Fetting *et al.*, 1996). Survival can be measured as;

a) **Overall survival (OS):** refers to the percentage of people in a study or treatment group who are alive after a certain period of time following diagnosis with or treatment for a disease such as cancer. It is often stated as a five-year survival rate.
b) **Disease- free survival (DFS):** is particularly important where adjuvant care is given (O'Shaughnessy *et al.*, 1991).
c) **Progression- free survival (PFS):** is especially important in metastatic disease (O'Shaughnessy *et al.*, 1991).
d) **Time to treatment failure (TTF):** similar to PFS except that in this analysis deaths are censored either at the time of death or at an earlier visit representing informative censoring i.e. non- random pattern of loss from the study (FDA, 2007).
e) **Event- free survival (EFS):** refers to survival free of any bad outcome including failure to attain a complete remission, relapse or even death due to toxicity (Gaynon *et al.*, 1993).

Appendix 3 highlights the advantages and disadvantages of overall, disease- free, progression- free and time to treatment survival outcomes. Survival outcomes can be represented in several ways including percent surviving at a particular time, median survival and percentage reduction in the odds of death over a time interval or at a particular point in time (Fetting *et al.*, 1996).

The choice between alternative treatment approaches often involves a trade- off between length and quality of life; survival alone does not answer the question of whether the

gains in survival justify the toxicity (Fetting *et al.,* 1996). Quality- adjusted survival provides an alternative framework within which trade- offs that influence treatment choices can be explicitly defined, as in decision and cost- effectiveness analyses, to assess the effectiveness of alternative therapies (Detsky and Naglie, 1990). In order to calculate the quality- adjusted survival one would have to determine the patients' health related quality of life (HRQL) (Angus *et al.*, 2001).

Since this research project will focus on the desk review of medical records, the patient outcome of interest will be five-year overall survival (OS).

2.6 Global Estimates for five-year Overall Survival for Cervical Cancer

The five-year overall survival rate for cervical cancer in the U.S. is 67.5% (Howlader *et al.*, 2015). This is significantly higher than 61.4% in England (ONS, 2019) but significantly lower than the 72% rate observed in Australia (AIHW, 2014). In China, Singapore, the Republic of Korea and Turkey the five-year overall survival rates range from 63-79% (Sankaranarayanan *et al.*, 2011). However, in Africa rates of less than 25% have been observed in the Gambia and Uganda (Sankaranarayanan *et al.*, 2011). There are currently no available estimates for five-year overall survival rates for cervical cancer patients in Kenya. However, the mortality rate is likely to be similar to that observed in Gambia and Uganda owing to shared health system and population challenges.

2.7 Cancer Care Continuum

The cancer care continuum is not restricted to cancer treatment. It consists of every cancer-related health service spanning from prevention to end of life care. Failure at any level of this continuum can have a negative impact on cancer patient outcomes and overall population health. It is just as important for individuals at increased risk of developing cancer to have access to high quality preventive and screening services as it is for patients with terminal illness to access end of life care that assures them of a

dignified death. The conceptual framework below (Figure 2.2) by Zapka et. al. (2003) summarizes the cancer care continuum for breast and cervical cancer (Zapka *et al.*, 2003).

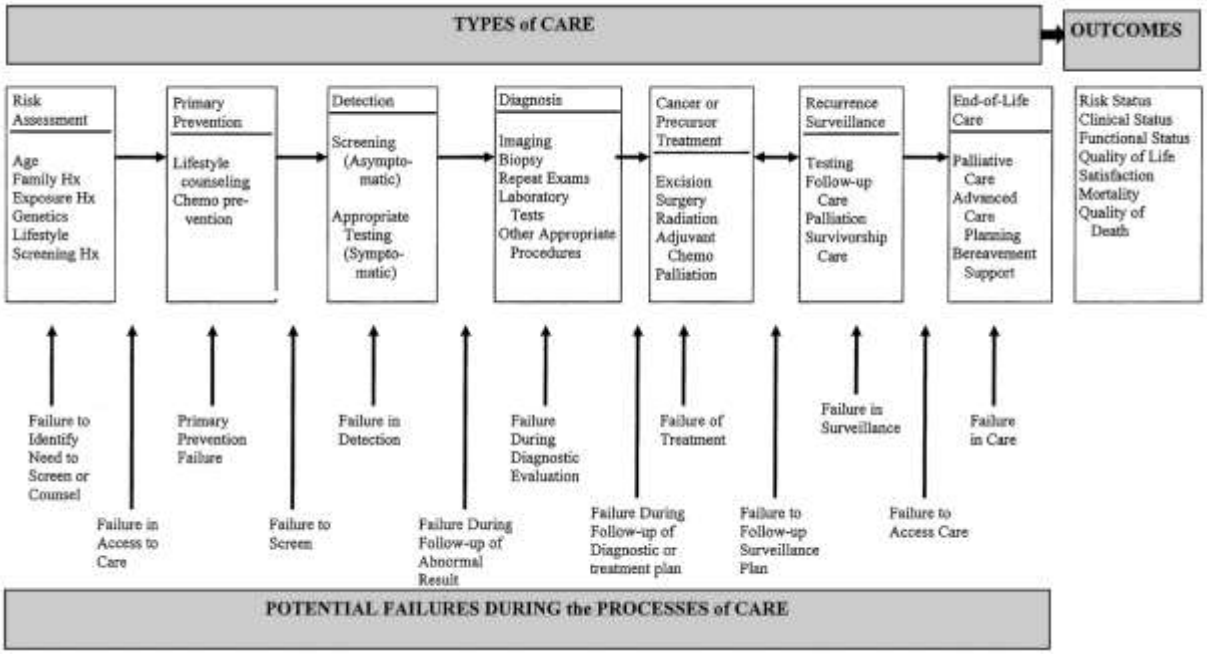


Figure 2.2: Cancer Care Continuum for Breast and Cervical Cancer Screening.

(Adopted from Zapka et. al. 2003.)

In order to continuously improve the quality of the cancer care continuum, it is necessary to identify all failures within the continuum. Addressing the failures would require an in-depth examination of all factors at individual, community, health system and policy levels that may be contributing to observed failures.

2.7.1 Prognostic vs Predictive Factors of Cancer Survival

A prognostic factor is defined as a factor, generally measured before treatment, that has an impact on a patient′s outcome "independently" of received treatment. On the other hand, predictive factors are expected to be able to identify patients who will benefit from

a specific treatment (Paesmans, 2012). Based on the fact that the term ‘Cancer’ represents a group of over 100 diseases, it follows that prognostic and predictive factors vary from one cancer to the next. For example, the best predictors for breast cancer survival are cancer stage classification, tumour size (TS), total axillary lymph nodes removed (TLN), and positive lymph nodes (PLN) (Ganggayah *et al.*, 2019) while lung cancer they are cancer stage classification (Alghamdi, Alshehri and Farhat, 2017) and histology (Paesmans, 2012).

While clinical factors appear to have the strongest potential for predicting cancer patient survival as demonstrated above, prognostic factors such as patient sociodemographic and cultural characteristics are often associated with barriers to the receipt of high-quality and timely cancer care (Halpern and Brawley, 2016). These barriers, in turn, may significantly affect an individual patient's long-term functional status, quality of life, and survival (O’Keefe, Meltzer and Bethea, 2015).

The best strategy to conclusively identify and differentiate between prognostic and predictive factors for cancer survival is to actually draw out the cancer care continuum for a specific group of cancer patients. From the continuum, a list of variables corresponding socio-demographic and clinical factors can be generated. These variables will then be subjected to statistical analyses to accurately ascertain their impact on cancer survival. Below is a theoretical framework (Figure 2.3) called Model of Pathways to Treatment (Walter, Webster and Scott, 2011). In this model, the cancer journey from symptom recognition through help seeking, diagnosis and treatment, is considered an iterative process composed of events and processes with distinguishable intervals (Mwaka *et al.*, 2016). These events and associated intervals are influenced by factors such as patient demographics, healthcare access and disease factors, including rate of progressions and histological subtypes. In using the MPT, researchers and policymakers can gain insight into actual points along the journey where delay may occur and hence provide opportunities for design of targeted interventions (Scott *et al.*, 2013).

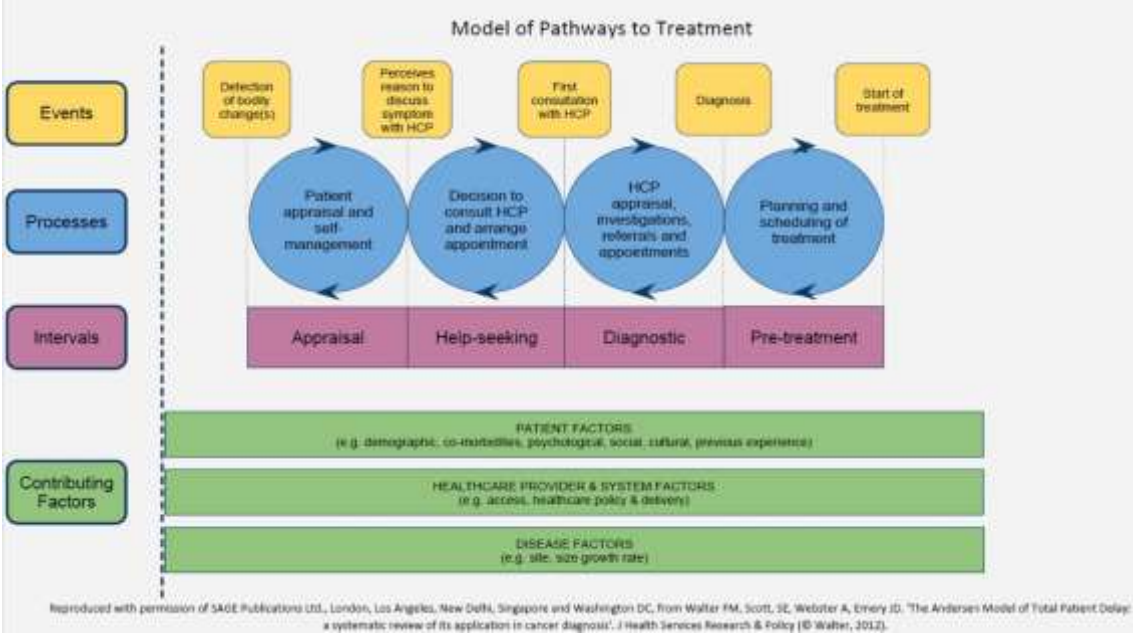


Figure 2.3: Model of Pathways to Treatment

2.7.2 Survival Analysis

Survival analysis is also referred to as time to event analysis. In cancer research, survival is an interval beginning from the time of an illness diagnosis until death (Somi *et al.*, 2012). Time-to-event models, like Cox regression, can utilize all subjects in the study and model their survival probabilities for a range of times with a single model (Mobadersany *et al.*, 2018). Statistical analyses are traditionally conducted using a mathematical formula based on a hypothesis. This is why predictive models using statistical analyses have high explanatory power but low predictive power (Lee *et al.*, 2018). It is also the reason why many researchers are increasingly turning to machine learning to more accurately predict cancer patient outcomes. Machine learning is algorithm-based using data without rule-based programming hence ignoring noise and outliers by extracting only important features from the data for the predictive model (Lee *et al.*, 2018).

2.8 Knowledge Gaps

National health systems are distinct and unique in terms of their processes, organization and human resources and infrastructural investments. As such, national cancer care continuums will often reflect the unique qualities of the overall health system. For this reason, each country and locality needs cancer research tailored towards understanding local disease burdens and identifying knowledge gaps with an intention of improving population health (ACS, UICC and IARC, 2019). Across the cancer care continuum, treatment of cervical cancer and quality of life of cervical cancer survivors have already been identified as two under researched areas in African countries (Finocchario-Kessler *et al.*, 2016). This study will focus on treatment of cervical cancer with a special emphasis on individual patient and health system characteristics (i.e., socio-demographic and clinical factors). This is because understanding the factors that create cancer health care disparities can help researchers, clinicians, and policymakers develop strategies and interventions to reduce them thereby improving cancer patient outcomes (Halpern and Brawley, 2016).

CHAPTER THREE

MATERIALS AND METHODS

3.1 Study Site

The Kenyatta National Hospital (KNH) was the study site. It is the largest public hospital in Kenya with a primary mandate to provide specialized health-care services to patients on referral from lower level hospitals across the country (Auditor General, 2012). The Hospital has a 1500 bed capacity and also facilitates medical training and research, and participates in national health-care planning. Radiotherapy, heart surgery, neurosurgery, renal dialysis and kidney transplant operations, plastic and reconstructive surgery, orthopedic surgery and burns management are among some of the specialized healthcare services provided at KNH (Auditor General, 2012). With specific regards to cervical cancer, the departments of Obstetrics and Gynecology and Radiotherapy make up the largest invasive cervical cancer (ICC) treatment centre in Kenya receiving patients from all over the country (Maranga *et al.*, 2013). The Cancer Treatment Centre at KNH receives between 2,000-3,000 new patients annually and averages between 50-60 new patients per week (Auditor General, 2012).

3.2 Study Design

This was a retrospective cohort study employing a review of medical files of patients treated for cervical cancer over a period of five years from 2008- 2013 depending on the start date of treatment. Medical records belonging to cervical cancer patients who presented with illness for the first time at KNH between January and December 2008 were reviewed to facilitate the extraction of patient related data e.g. socio-demographic characteristics, staging of disease, treatment given and patient outcomes over the five year follow-up period. The extracted data was then analysed to determine the five-year overall survival rates for women treated for cervical cancer.

3.3 Study Population

The study population was cancer patients who presented with cervical cancer for the first time at KNH between January and December 2008.

3.4 Sampling Procedures

All medical records belonging to cervical cancer patients who underwent treatment at KNH between in 2008 were identified, retrieved and reviewed. Patient information was collected from records located at the health information department (HID) and radiotherapy clinic (RC) at KNH.

At the HID, medical records pertaining to hospital admissions for cervical cancer treatment were retrieved by HID staff from the registry based on the international classification of diseases (ICD)-10 topographic code C53.9 which denotes malignant neoplasm of cervix uteri, unspecified. From the HID medical records registry, records of both patients who were discharged following treatment and those who died while admitted were retrieved (i.e. the HID runs two registries, one for patients discharged and considered active/open, and the other for deceased patients).

In the RC which is also referred to as the cancer treatment centre, outpatient records are available for all cancer patients who had visited the clinic. Unlike the HID, the RC operates only one registry which contains open or active files. Once a patient dies within the hospital or they receive notification their file is stored away unfiled in office cupboards. Also, the RC outpatient records are not coded per cancer type instead they are filed based on patient numbers. As a result, the RC staff gave advice on the physical location of records for patients whose first visit to the clinic was between January and December 2008. For 2008, we skimmed through approximately 2,367 records to identify those belonging to cervical cancer patients.

3.4.1 Inclusion Criteria

1) Only patients who presented with illness for the first time at KNH between January and December 2008 were considered for inclusion in the study based on review of their medical record.
2) Cervical cancer diagnosis was confirmed through tissue biopsy.

3.4.2. Exclusion Criteria

1) Cervical cancer patients whose records indicated that they first presented with illness at KNH prior to January 2008 and after December 2008 were excluded from study.
2) Patients who had a clinical diagnosis [i.e. diagnostic imaging (abdominal ultrasound), digital vaginal examination and/or examination under anesthesia] were also excluded from the study. This is because the gold standard for cancer diagnosis is a biopsy.

3.5 Data Collection

Data mining through reviewing medical records of cervical cancer patients was undertaken between February and August 2014 to establish the following;

1) Socio-demographic characteristics of women seeking cervical cancer treatment at KNH.
2) Clinical characteristics of the women who presented with illness at KNH.
3) Available treatment options based on variations in the care that cervical cancer patients received at KNH.
4) Patient outcome stratification which were broadly categorized as death, loss to follow up and alive at 5 years.

A sample of the study questionnaire is provided in Appendix 3. The variables selected for inclusion in the questionnaire were informed through literature review. These were also restricted to those variables most likely to be reported in medical records.

3.6 Data Management and Analysis

All relevant patient information was extracted from the medical records using a specially designed electronic data entry form in Epi Info 7. The data entry form allowed for common terminologies to be ascertained and facilitated consistency in data extraction. The data collected was regularly backed up on an external hard drive. Statistical analysis was done using Stata v14.2 with data for analysis manually exported from the Epi Info database as required.

3.6.1 Quantitative Data Analysis

3.6.1.1 Descriptive Statistics

Summary statistics including frequency distributions were generated for;

a) Socio-demographic factors including age, marital status and education level.
b) ***Important Note:*** Being that the medical records reviewed for this study belonged to women who initiated treatment at the Kenyatta National Hospital between January and December 2008, the variable region of residence was defined based on the former provincial administrative boundaries that existed prior to 2013 (Figure 3.1).
c) Factors associated with clinical presentation e.g. stage of disease, histological sub-types and co-morbidity with other NCDs

3.6.1.2 Bivariate Analysis

This section of the data analysis plan tested statistical associations between patient outcomes (i.e. death, loss to follow up and alive at 5 years) and both socio-demographic

and clinical factors using Pearson's Chi-Square test of association. A p-value of 0.05 was used to interpret all analysis results.

Figure 3.1: A map of the eight former administrative provinces of Kenya. Adapted from the Economist: Middle East and Africa Section- 1st November 2007 (print edition).

3.6.1.3 Survival Analysis

This was restricted to factors demonstrating statistically significant associations with patient outcomes as determined by the analysis in section 3.6.1.2.

a) Kaplan-Meier survival analysis was conducted to estimate mean survival time until death and median survival time i.e. time at which 50% of subjects have

reached the event- death. This analysis was also be used to generate Kaplan-Meier survival curves.

Kaplan-Meier survival curves allow for the comparison of the proportions of individuals surviving at any specific time but they do not provide a comparison of the total survival experience of the groups under consideration. To overcome this weakness, the log rank test, was additionally conducted. It is the most popular method for comparing survival of groups and takes the whole follow up period into account. The log rank test tests the null hypothesis that there is no difference between the populations in the probability of an event (death in this instance) at any time point (Bland and Altman, 2004). It is most likely to detect a difference between groups when the risk of an event is consistently greater for one group than another. However, it is unlikely to detect a difference when survival curves cross for example when comparing a medical with a surgical intervention (Bland and Altman, 2004).

a) Conduct mortality hazard ratio analyses using Cox proportional hazards regression. Cox regression was used because most deaths occurred in the first year hence mortality was observed to be constant.

The univariate and multivariate hazard ratios were then compared to establish which factors determine the five-year overall survival rates of cervical cancer patients treated at KNH. Using regression analyses, the statistically significant associations detected using the Chi-square and log rank tests were quantified.

3.7 Ethical Considerations

In addition to a review by KEMRI's Scientific Steering Committee (SSC) and the Scientific and Ethics Review Unit (SERU), the UoN/KNH ethical review committee also reviewed the proposal. Two ethical approvals were obtained for this study.

3.7.1 Anticipated Benefits of the Study

This study assisted in the determination of factors influencing five-year overall survival rates among cervical cancer patients treated at KNH. This information is useful in informing health policies focused on enhancing access to preventive and curative health services for cervical cancer. Additionally, it presents a case for more advanced clinical and epidemiological studies to confirm the study findings.

3.7.2 Potential Risks and Harms of the Study

There were no physical, psychological or emotional risks and harms associated with this study because no direct contact with patients was required. However, to protect patient privacy and confidentiality access to the full data set containing patient identifiable information was restricted to myself (as the MSc. student and principal investigator). An anonymized data set was generated for data analysis following the completion of data collection.

3.7.3 Informed Consent

Consent to review medical records was provided at institutional level through an ethical approval letter from the UoN/KNH Ethics Review Committee. Clearance for data collection was provided in the form of a signed approval on an official hospital form by the Heads of Department at the Hospitals' Health Information and Radiotherapy Departments which was then submitted to KNH's Research Office for record purposes.

3.7.4 Measures for ensuring confidentiality

i) **Access to data:** This was limited to the principal investigator, a consultant data analyst and the academic supervisors.
ii) **Storage of data:** All data was stored in soft copy format in the principal investigator's laptop with backup copies of the files in an external hard disk in folders that are password protected.

iii) **Duration and location of storage of the data:** aside from the principal investigator's laptop which is mobile, the external hard disk is located in the principal investigator's office. This data will be stored for an infinite period.

3.7.6 Assumptions and Limitations of the study

This study made the following assumptions;

i) Assumes patient records are well documented and complete.
ii) Assumed patients started and completed all their treatment in the same health facility.

This study had the following limitations;

i) Some records may have been missed out for various reasons including no review was done of the deceased patient files at the RC as these are not organized into a record registry, death on arrival to the hospital before diagnostic confirmation and misplaced files.

   Mitigation: The hospital staff responsible for management of medical records personally retrieved medical records to ensure that all relevant records were identified and few were lost.
ii) Lack of a centralized national database for vital registration prevented the determination of how many other patients may have died outside of KNH.
iii) Lack of a centralized national health system database prevented the effective follow up of patients who may be continuing to receive care in alternative health facilities across the country.

   Mitigation for ii) and iii): Most appropriate mitigation would have been to retrieve telephone contacts of patients and their kin. However, the project lacked resources to facilitate telephone follow-ups.

CHAPTER FOUR

RESULTS

A total of 617 medical records of women treated for cervical cancer at the Kenyatta National Hospital (KNH) were retrieved and screened for inclusion in this study. The number of records that qualified for inclusion in the study was 481 while 136 cases were excluded. Of the 136 records that were excluded from the study, 97 were excluded on the basis that the women had begun cervical cancer treatment prior to January 2008 and hence were continuing patients. Among the remaining 39 cases, 17 were excluded as the patients were ailing from non- cancerous illnesses. A further 18 cases were excluded because patients were treated for clinically diagnosed cervical cancer (i.e. no tissue biopsy was done). One case was excluded because the patient had a benign tumour of the cervix (Adenofibroma of the Cervix). The last three cases were excluded owing to wrongly coded files such that the records were marked as those of cervical cancer patients though the patients were suffering from other cancers i.e. bladder, breast and ovarian cancers.

4.1 Treatment Options Offered at KNH

The results in this section correspond to the first specific objective which was *'to determine the treatment options available for cervical cancer in KNH'*. A review of the patients' medical records confirmed the following treatment options;

i) **Surgery**- Hysterectomies were offered to patients found to have early-stage disease. Two types of hysterectomies were noted: a) Total abdominal hysterectomy (TAH) and Wertheim's Hysterectomy (also referred to as radical hysterectomy).
ii) **Radiation therapy**- two types were offered i.e. external beam radiation therapy (EBRT) and brachytherapy. It was however noted that throughout the study

period the brachytherapy machine was broken down and where patients could afford it, referral were given to Mulago hospital in Uganda.

iii) **Chemotherapy**- the main chemotherapeutic agents used were Cisplatin and Flourouracil.

Overall, there were 31 women (6.4%) in the study who either did not receive any treatment at KNH or it could not be established from their hospital records whether recommended treatment was initiated. The most common treatment options for cervical cancer patients at KNH is radiotherapy (62.2%; 299/481) and chemo-radiation (13%; 67/481). The least common treatment options were surgery only and surgery plus chemotherapy. In further analyses least common treatment options are designated 'other' which accounted for 4.4% (21/481) of the study population.

The records further demonstrated a pattern in which treatment was determined by the stage of disease at diagnosis and adjusted based on patient progress. This coupled with the fact that brachytherapy was not available, prompted statistical testing for associations between recommended treatment and stage of disease and treatment completion.

4.1.1 Testing for a Statistical Association between Recommended Treatment and Stage of Disease

Using Pearson's Chi-Square test of association, the p-value obtained of <0.001 is highly significant relative to the significance level of 0.05. It indicates that for patients treated at KNH there is a very strong association between the treatment recommended by the treating physician and the stage at which the disease is diagnosed.

4.1.2 Testing for a Statistical Association between Recommended Treatment and Treatment Completion

Majority of patients (50.9%; 245/481) completed their treatment while 29.1% (140/481) did not complete their treatment. The proportion of women who never started treatment was 20% (96/481).

The Pearson's Chi-Square test was conducted to test for an association between recommended treatment and treatment completion. The p-value of the Chi-Square statistic was <0.001 in relation to the 0.05 significance level. This is highly statistically significant and strongly suggests that the type of treatment recommended may determine whether or not a patient completes treatment at KNH.

4.2 Preliminary Identification of Socio-Demographic and Clinical Predictors of Patient Outcomes

This section is related to specific objective two, *'to determine the socio-demographic and clinical predictors patient outcomes among women treated for cervical cancer in KNH'*. The entire section is divided into two major parts: Descriptive statistics (sub-sections 4.2.1-4.2.3) and bivariate analysis (sub-section 4.2.4).

4.2.1 Descriptive Statistics for Socio-Demographic Characteristics

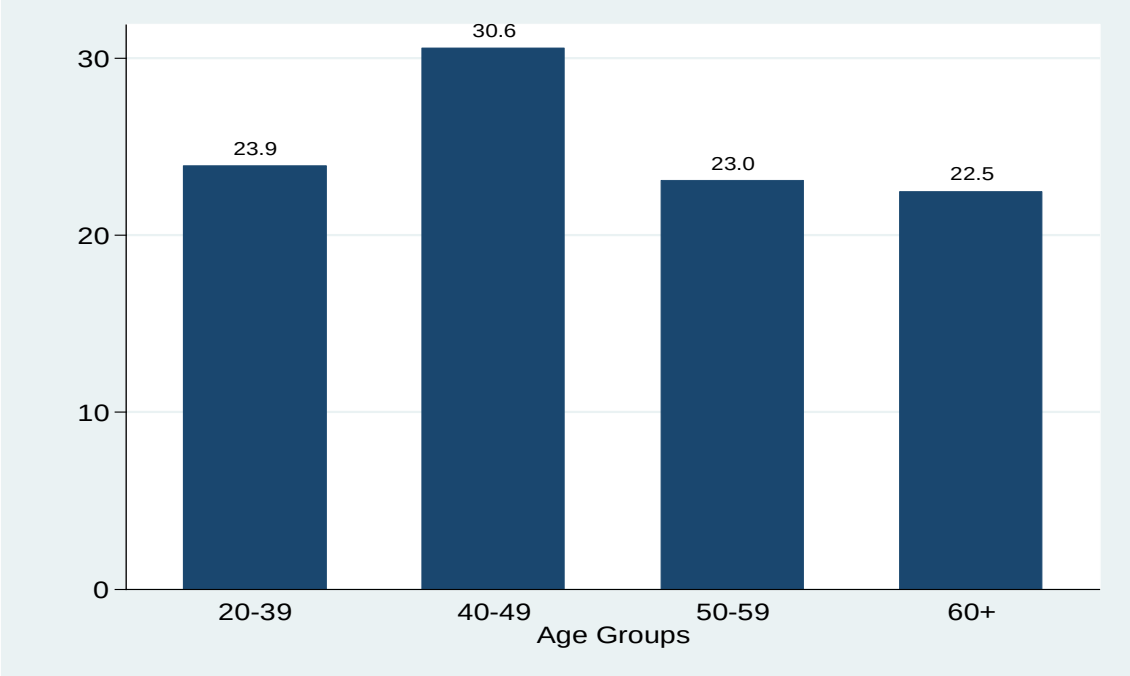
4.2.1.1 Age of the Study Population

There were no missing values for this variable. The mean age for the women in this study was 49 years (95% CI; 48.3, 50.6) while the median age was 48 years. The age range for the study participants was 20-86.

By dividing the women into four age groups (i.e. 20-39, 40-49, 50-59 and 60+), it was observed that the 40-49 age group was the largest representing 30.6% (147/481) of the women in the study. The 60+ age group was the smallest and represented 22.5%

(108/481). Of all the four age groups only the 40-49 age group was significantly larger than the rest. The remaining age groups had strikingly similar proportions (Figure 4.1).

Also, the reproductive age range was 20-49. Hence women of reproductive age accounted for 54.5% (262/481) of the sample group. This is a significantly larger than the proportion of women who were aged 50 and above i.e. 45.5% (Figure 4.1).



Figures 4.1: The proportions of the women participants across the four age groups

4.2.1.2 Marital Status within the Study Group

The marital status of 176 (36.6%) women could not be established from reviewing their medical records. The majority of women for whom their marital status was recorded were married (40.3%; 194/481) while never married/single women made up the smallest category accounting for 7.3% (35/48) (Table 4.1).

4.2.1.3 Education Levels of the Women Participants

Education level was not documented for 67.6% (325/481) of the women. For the women whose education levels were recorded, the majority (17.0%; 82/481) had a primary school education. Those with at least secondary school education made up 7.7% (37/481) of the study population. Overall, women with tertiary education (i.e. college and university) formed a minority and accounted for 1.7% of the study population (Table 4.1).

4.2.1.4 Region of Residence of the Study Population

None of the patients reported residing in the North Eastern region of Kenya. Despite the hospital being located in Nairobi Province, the highest number of patients identified as residents of Central region (32.0%; 154/481). Nairobi had the third highest (14.4%; 69/481) while Coast and Western regions had the least representations at 4.8% and 3.5% respectively.

Region of residence was also used to generate a new variable 'Access to Care' which estimates distance travelled by road to reach Nairobi (Table 4.1).

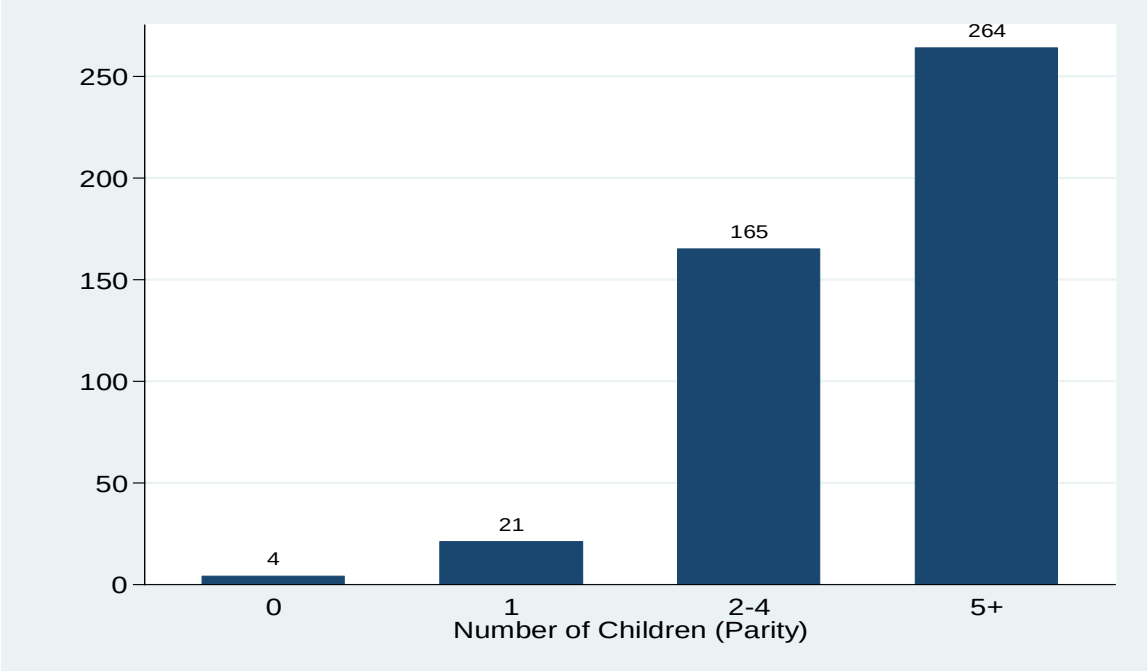
4.2.1.5 Occupation of the Women Participants

The occupations or source of livelihood of 175 women (36.4%), could either not be determined from the record or no information was recorded. For the women whose occupations were documented, the self-employed and housewife categories were the largest accounting for 24.7.9% (119/481) and 24.3% (117/481) of the study sample respectively.

4.2.1.6 Parity among the Women Participants

No information on parity was recorded for 27 (5.6%) of the women in the study. Among the women whose parity was recorded, the number of children reported ranged from 0-

13. The mean number of children was 5.3 (95% CI; 5.1, 5.6) while the median number of children was 5. The majority of women (54.9%; 264/481) had 5 or more children (Figure 4.2).



Figures 4.2: The frequency distribution of parity among the women participants

4.2.1.7 HIV Status

More than half the study group did not have their HIV status recorded. The unknown/missing category therefore became the largest representing 53.6% (258/481) of the women participants. A closer look at the frequency distributions reveals that despite the large number of women whose status was unknown, a larger proportion of women with a known status (34.1%; 164/481) were HIV negative.

4.2.1.8 Pap Smear Screening

In 88.6% (426/481) of the records reviewed no details of the women's history of cervical cancer screening was provided. Only 8.9% (43/481) of the study women reported a

history of Pap smear testing and for many their smears initiated their individual journey to a formal diagnosis.

The frequency distributions for all the socio-demographic characteristics evaluated during analysis are provided in Table 4.1 below.

Table 4.1: Distribution frequencies for the socio-demographic characteristics of the women participants

Socio-demographic Characteristics		Frequency (N=481)*	Percent (%)
Variable	**Categories**		
Age	20-39	115	23.9
	40-49	147	30.6
	50-59	111	23.0
	60+	108	22.5
Marital Status	Never Married/Single	35	7.3
	Married	194	40.3
	Divorced/Widowed	76	15.8
Educational Level	None	29	6.0
	Primary	82	17.0
	Secondary	37	7.7
	Tertiary	8	1.7
Regions of Residence	Central	154	32.0
	Coast	23	4.8
	Eastern	102	21.2
	Nairobi	69	14.2
	Nyanza	43	8.9
	Rift-Valley	67	13.9
	Western	17	13.5
Access to Care	Nairobi	71	14.8
	≤3 hours from Nairobi by road	263	54.7
	>3 hours from Nairobi by road	141	29.3
Occupation	Casual/Retired/Unemployed	52	10.8
	Housewife	117	24.3
	Professional	18	3.7
	Self- employed	119	24.7
Parity	0	4	0.8
	1	21	4.4
	2-4	165	34.3
	5+	264	54.9
HIV Status	Positive	59	12.3
	Negative	164	34.1
Pap Smear Screening	Yes	43	8.9
	No	12	2.5

*The number of cases for each characteristic is variable across different categories as data recording in medical records varied.

4.2.2 Descriptive Statistics for Clinical Presentation

4.2.2.1 Diagnostic Methods

It was noted that every patient underwent a digital vaginal examination. Also, for the analysis Pap smear test and colposcopy were considered screening tests. On this basis 94.4% (454/481) of the women had only a biopsy done and 5.6% (27/481) underwent screening prior to the recommendation for a biopsy.

4.2.2.2 Histological Types of Cervical Cancer Reported among Women Participants

There was no histology information from cervical tissue biopsies collected for 5.2% (25/481) of the women participants. The largest proportion of histological types reported were squamous cell carcinoma representing 84.4% (406/481) of all the tumours while Adenocarcinomas represented 6.2% (30/481). Other histology types accounted for 4.2% (20/481) of the tumours with further details given in Table 4.2 below.

Table 4.2: Histology types of cervical cancer reported among women participants who had biopsies

Histological Sub-Group	Histological Type	Frequency (N=481)
Epithelial Tumours	Squamous cell carcinoma, not otherwise specified	319
	Squamous cell carcinoma keratinizing	50
	Squamous cell carcinoma non-keratinizing	29
	Squamous cell carcinoma papillary	1
	Early invasive (micro-invasive) squamous cell carcinoma	4
	Cervical squamous cell carcinoma in situ	3
	Adenocarcinoma of the cervix	17
	Mucinous adenocarcinoma of the cervix	3
	Villoglandular adenocarcinoma	7
	Endometrioid adenocarcinoma of the cervix	2
	Clear cell adenocarcinoma of cervix	1
	Adenosquamous carcinoma of the cervix	1
	Adenoid cystic carcinoma of the cervix	1
	Undifferentiated carcinoma of cervix	11
	Small cell carcinoma of cervix	1
Mesenchymal tumours	Leiomyosarcoma of cervix	1
Mixed epithelial & mesenchymal tumours	Carcinosarcoma of the cervix	1
Precursor lesions of cervical SCC	Carcinoma In Situ	2
	Moderate Dysplasia	2
Missing		25

4.2.2.3 Cervical Cancer Staging at Diagnosis among the Women Participants

The International Federation of Gynecology and Obstetrics (FIGO) staging system (Section 2.3.2.) is used at the Kenyatta National Hospital. Carcinoma in Situ (CIS) or Stage 0 cervical cancer is the earliest form of the disease that may also be referred to as pre-cancer. Only 2 women in this study population were diagnosed at this early stage. The majority of women were diagnosed at the more advanced stages of disease predominantly stage 2 (33.1%; 159/481) and 3 (40.5%; 195/481). Out of 481 women no information on staging was recorded for 20 women who accounted for 4.2% of the study population. Figure 4.3 provides complete frequency distributions for each stage.

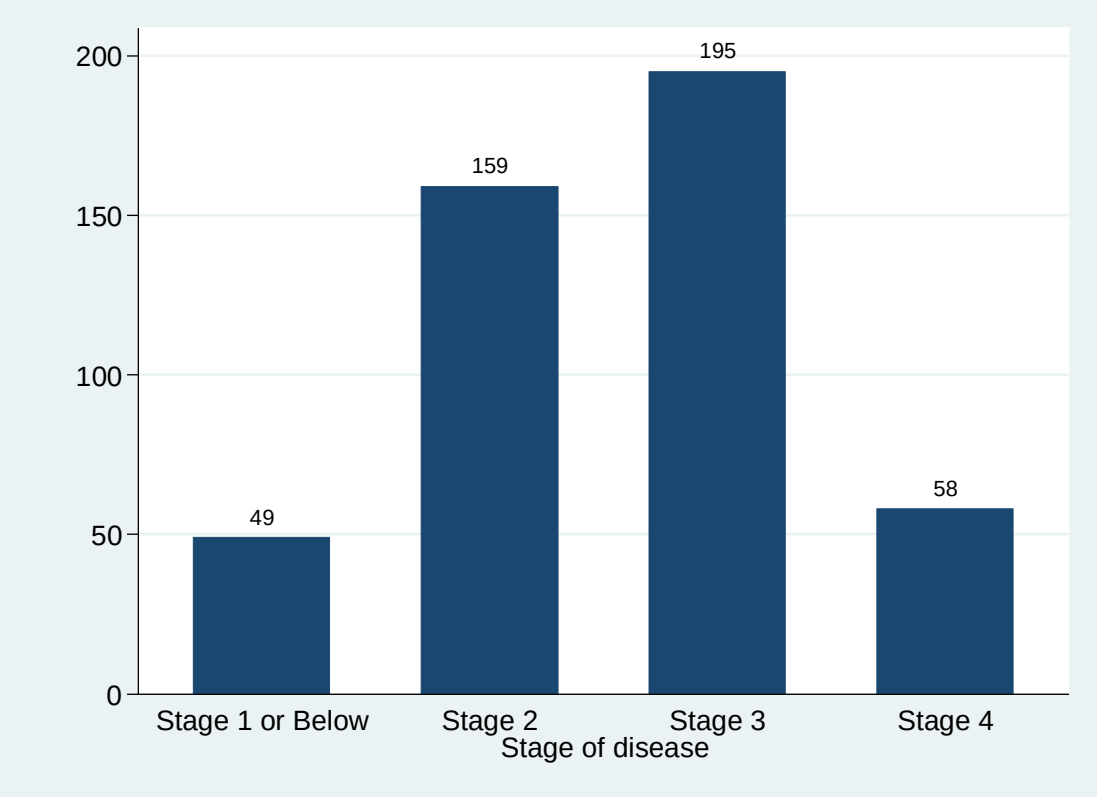


Figure 4.3: The frequency distributions for stage of disease

4.2.2.4 Prevalence of Comorbidity with other NCDs in the Study Population

Three NCDs were considered namely diabetes, hypertension and heart disease. Only 2women (0.4%) were reported to have diabetes while 3 (0.6%) others had diabetes and hypertension. Twenty-three (4.8%) others were noted to have hypertension while none suffered from heart disease.

The majority of women (94.2%; 453/481) did not suffer from any of the three NCDs considered during this study. Overall the prevalence of NCD comorbidity was low in this sample population.

4.2.3 Referral Status of the Study Participants

Referral status was not a focus area of the study. It presented an area of interest owing to its suspected relationship with region of residence.

No information on referral status was recorded for 2.3% (11/481) of the study women whereas a strikingly large proportion (74.6%) was referred to KNH from other health facilities. Notably no patients in this study population were referred from North Eastern region. Figure 4.4 shows that the highest numbers of referrals came from Central, Eastern and Rift-Valley regions.

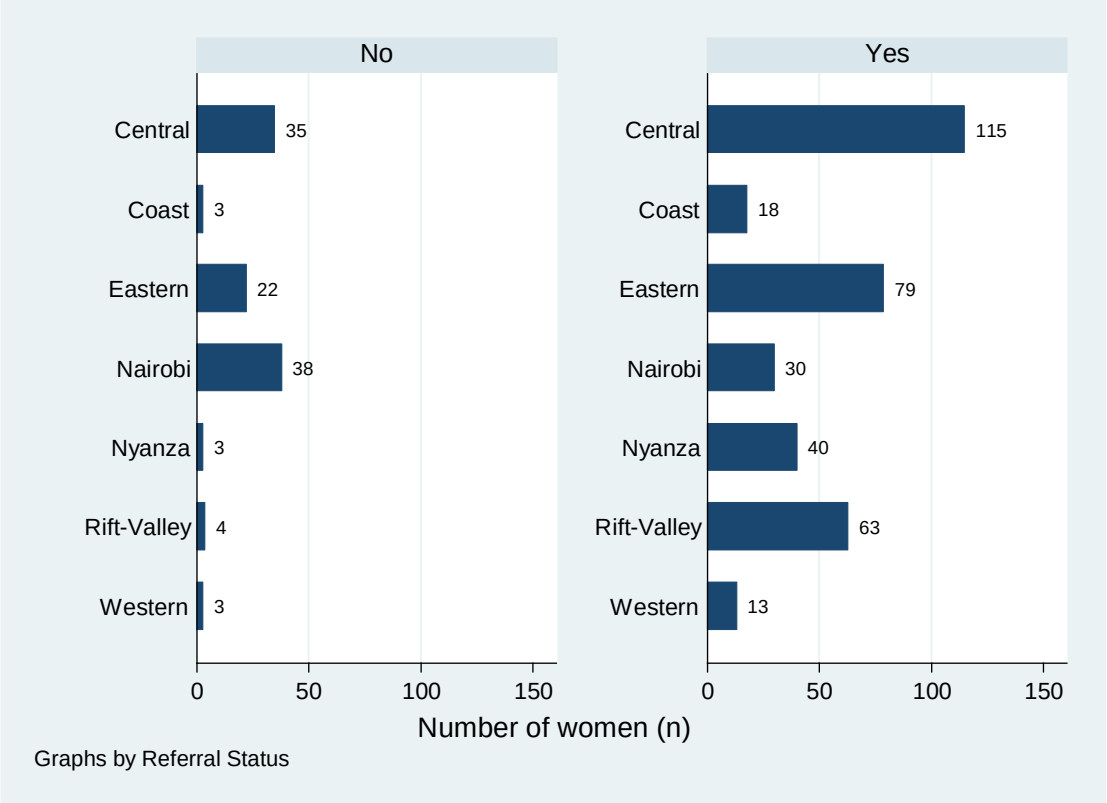


Figure 4.4: Number of referrals from each of the eight former administrative regions

4.2.3.1 Testing for a Statistical Association between Patient Referral and Regions of Residence

The Pearson's Chi-Square test was conducted to test for an association between patient referrals and regions of residence. Using a significance level of 0.05, the p-value associated with the Chi-Square statistic is <0.001 which is highly statistically significant and suggestive of a strong relationship between referrals and regions of residence for patients treated at KNH.

4.2.4 Results of the Bivariate Analysis Using Pearson's Chi-Square

This section of the results reports on the three main patient outcomes (i.e. death, loss to follow up and alive at 5 years) relative to both socio-demographic and clinical variables.

4.2.4.1 Patient Outcomes, Socio-demographic and Selected Characteristics

Overall, the majority (82.3%; 396/481) of women were lost to follow up. The Chi-Square test results indicate that none of the socio-demographic variables considered during this analysis directly influenced patient outcomes particularly survival after 5 years. All the p-values were greater than the 0.05 significance level.

A complete summary of the proportions representing each patient outcome and socio-demographic variable and the Chi-Square test results is found in table 4.12 below.

Table 4.3: Cross-tabulation of patient outcomes vs socio-demographic and selected characteristics

Variables		No. of Cases[a]	No. of Deaths n (%)	LTFU n (%)	Alive at 5 Years n (%)	χ^2 *P* Value
Overall		481	50 (10.4)	396(82.3)	35 (7.3)	
Age, years	20–39	115	14 (12.2)	96 (83.5)	5 (4.4)	.83
	40–49	147	13 (8.8)	123(83.7)	11 (7.5)	
	50–59	111	12 (10.8)	89 (80.2)	10 (9.0)	
	60+	108	11 (10.2)	88 (81.5)	9 (8.3)	
Marital status	Never married/Single	35	6 (17.1)	29 (82.9)	0 (0.0)	.36
	Married	194	27 (13.9)	155(79.9)	12 (6.2)	
	Divorced/Widowed	76	15 (19.7)	55 (72.4)	6 (7.9)	
Education	None	29	12 (41.4)	17 (58.6)	0 (0.0)	.16
	Primary	82	26 (31.7)	55 (67.1)	1 (1.2)	
	Secondary	37	6 (16.2)	29 (78.4)	2 (5.4)	
	Tertiary	8	1 (12.5)	7 (87.5)	0 (0.0)	
Region of residence	Central	154	15 (9.7)	16 (10.4)	123(79.9)	.10
	Coast	23	0 (0.0)	2 (8.7)	21 (91.3)	
	Eastern	102	8 (7.8)	7 (6.9)	87 (85.3)	
	Nairobi	69	13 (18.8)	6 (8.7)	50 (72.5)	
	Nyanza	43	5 (11.6)	1 (2.3)	37 (86.1)	
	Rift- Valley	67	8 (11.9)	1 (1.5)	58 (86.6)	
	Western	17	0 (0.0)	2 (11.8)	15 (88.2)	
Access to care	Residing in Nairobi	71	13 (18.3)	52 (73.2)	6 (8.5)	.05[b]
	≤3 hours from Nairobi by road	263	27 (10.3)	214(81.4)	22 (8.4)	
	>3 hours from Nairobi by road	141	9 (6.4)	125(88.7)	7 (5.0)	
Occupation	Casual/Retired/Unemployed	52	10 (19.2)	42 (80.8)	0 (0.0)	.20
	Housewife	117	16 (13.7)	94 (80.3)	7 (6.0)	
	Professional	18	0 (0.0)	17 (94.4)	1 (5.6)	
	Self-employed	119	21 (17.7)	89 (74.8)	9 (7.6)	
Parity	0	4	1 (25.0)	2 (50.0)	1 (25.0)	.39
	1	21	2 (9.5)	19 (90.5)	0 (0.0)	
	2–4	165	15 (9.1)	141(85.4)	9 (5.5)	
	5+	264	28 (10.6)	215(81.4)	21 (8.0)	
HIV status	Positive	61	10 (16.4)	49 (80.3)	2 (3.3)	.22
	Negative	164	20(12.2)	131(78.9)	13 (7.9)	
Pap smear screening	Yes	43	3 (7.0)	36 (83.7)	4 (9.3)	.14
	No	12	3 (25.0)	9 (75.0)	0 (0.0)	

[a]The number of cases for each characteristic is variable across different categories as data recording in medical records varied and analysis was confined to data available.

[b]Borderline statistical significance relative to a P=.05 significance level.

Abbreviations: χ^2, chi-squared test; LTFU, loss to follow-up

4.2.4.2 Patient Outcomes and Clinical Factors

4.2.4.2.1 Patient Outcomes and Diagnostic Methods

Across all the diagnostic methods categories most women were lost to follow up (LTFU) similar to the overall trend. The p-value associated with the Chi-Square statistic (p= 0.87) is greater than the 0.05 significant level showing no statistical association between patient outcomes and the method of diagnosis for women treated at KNH (Table 4.4).

Table 4.4: Cross-tabulation of patient outcomes vs diagnostic methods

Factor		No. of Cases	No. of Deaths (%)	LTFU (%)	ALIVE AT 5 YRS (%)	□² P-Value
Overall		481	50 (10.4)	394 (81.9)	35 (7.3)	
Diagnostic Method	Biopsy Only	454	48 (10.4)	373 (82.2)	33 (7.3)	0.87
	Screening and Biopsy	25	2 (7.4)	21 (85.2)	2 (7.4)	

4.2.4.2.2. Patient Outcomes and Histological Types

The Chi- Square test results showed no statistical association between tumor histology and patient outcome for this population of women (Table 4.5).

Table 4.5: Cross-tabulation of patient outcomes vs main histology types

Factor		No. of Cases	No. of Deaths (%)	LTFU (%)	ALIVE AT 5 YRS (%)	χ^2 P-Value
Overall		481	50 (10.4)	394 (81.9)	35 (7.3)	
Histology Groups	Squamous cell carcinoma	406	39 (9.6)	336 (82.8)	31 (7.6)	0.90
	Adenocarcinoma	30	4 (13.3)	24 (80.0)	2 (6.7)	
	Other	20	1 (5.0)	17 (85.0)	2 (10.0)	

4.2.4.2.3 Patient Outcome and Staging of Disease

The p-value associated with the Chi-Square statistic is less than 0.001 and significantly less than the 0.05 significant level. This is highly suggestive that for women treated for cervical cancer at KNH the staging of cervical cancer strongly influences patient outcomes (Table 4.6).

Table 4.6: Cross-tabulation of patient outcomes vs cervical cancer staging

Factor		No. of Cases	No. of Deaths (%)	LTFU (%)	ALIVE AT 5 YRS (%)	χ^2 P-Value
Overall		481	50 (10.4)	394 (81.9)	35 (7.3)	
Staging	Stage 1 and below	49	0 (0.0)	46 (87.8)	3 (12.2)	<0.001
	Stage 2	159	9 (5.7)	132 (83.0)	18 (11.3)	
	Stage 3	195	26 (13.3)	160 (82.1)	9 (4.6)	
	Stage 4	58	13 (22.4)	45 (77.6)	0 (0.0)	

4.2.4.2.4 Patient Outcomes and NCD Comorbidity

The Chi-Square test suggests that there was no statistically significant association between NCD comorbidity and patient outcomes (Table 4.7).

Table 4.7: Cross-tabulation of patient outcomes vs NCD comorbidity

Factor		No. of Cases	No. of Deaths (%)	LTFU (%)	ALIVE AT 5 YRS (%)	χ^2 P-Value
Overall		481	50 (10.4)	394 (81.9)	35 (7.3)	
NCD Comorbidity	Diabetes	2	1 (50.0)	1 (50.0)	0 (0.0)	0.26
	Hypertension	23	5 (21.7)	16 (69.6)	2 (8.7)	
	Diabetes + Hypertension	3	0 (0.0)	3 (100.0)	0 (0.0)	
	None	453	44 (9.7)	376 (82.3)	33 (7.3)	

4.2.4.2.5 Patient Outcomes and Clinical Management

Here the myriad of treatment combinations was condensed into three major groups for ease of analysis. These are;

i) **Radiotherapy:** whereby only radiotherapy was administered or radiotherapy plus another treatment with the exception of chemotherapy.
ii) **Chemo-radiation:** those patients whose treatment combinations incorporated both radiotherapy and chemotherapy.
iii) **Other:** Those who had neither chemo-radiation nor radiotherapy as part of their treatment.
iv) **None:** Patients received no treatment at all.

The p-value of less than 0.001 provides very strong statistical evidence that in KNH the treatment option received by cervical cancer patients is strongly associated with the observed patient outcomes (Table 4.8).

Table 4.8: Cross-tabulation of patient outcomes vs treatment options

Factor		No. of Cases	No. of Deaths (%)	LTFU (%)	ALIVE AT 5 YRS (%)	χ^2 P-Value
Overall		481	50 (10.4)	394(81.9)	35 (7.3)	
Treatment Option	Radiotherapy	299	22 (7.4)	257 86.0)	20 (6.7)	<0.001
	Chemo-radiation	67	2 (3.0)	51 76.1)	14 (20.9)	
	Other	21	2 (9.5)	18 (85.7)	1 (4.8)	
	None	94	24 (25.5)	70 (74.5)	0 (0.0)	

4.2.4.2.6 Patient Outcomes and Treatment Status

The Chi-Square test is suggestive of a strong statistically significant association between patients' treatment status and patient outcomes (Table 4.9). The highest number of deaths were recorded among who never started treatment.

Table 4.9: Cross-tabulation of patient outcomes vs treatment status

Factor		No. of Cases	No. of Deaths (%)	LTFU (%)	ALIVE AT 5 YRS (%)	χ^2 P-Value
Overall		481	50 (10.4)	394 (81.9)	35 (7.3)	
Treatment Status	Completed	245	7 (2.9)	210 (85.7)	28 (11.4)	<0.001
	Incomplete	140	18 (12.9)	115 (82.1)	7 (5.0)	
	Never Started	96	25(26.0)	71 (74.0)	0 (0.0)	

4.3 Survival Analysis and Five-Year Overall Survival

The results in this section are linked to specific objective three, *'to determine the five-year overall survival rates among women treated for cervical cancer at KNH'*. The analysis in this section was restricted to the four factors shown previously to have a

strong association with patient outcomes (i.e., access to care, stage of disease, type of treatment received and treatment status). Age was included because it is a well-known confounder.

4.3.1 Kaplan-Meier Survival Analysis

Overall, there were an estimated 10 deaths per 100 person-years and an overall five-year survival rate of 59% (Table 4.10).

4.3.1.1 Age

The Kaplan-Meier analysis shows that the survival probability of age group 20-29 was the lowest at most time points when compared to other age groups (Figure 4.5). The age group 20-29 also had the highest death rate with an estimated 15 deaths per 100 person years which was significantly higher than other age groups (Table 4.10). However, the p-value of 0.70 associated with the log rank test statistic is much greater than the 0.05 significance level indicating that the observed differences in survival across the age groups studied at all time points in the study are not statistically significant. This supports the Chi-Square test results presented in Table 4.3 where no statistically significant association was found between age and patient outcomes.

No median survival time estimates (the time at which 50% of the subjects have reached the event) could be generated by age group.

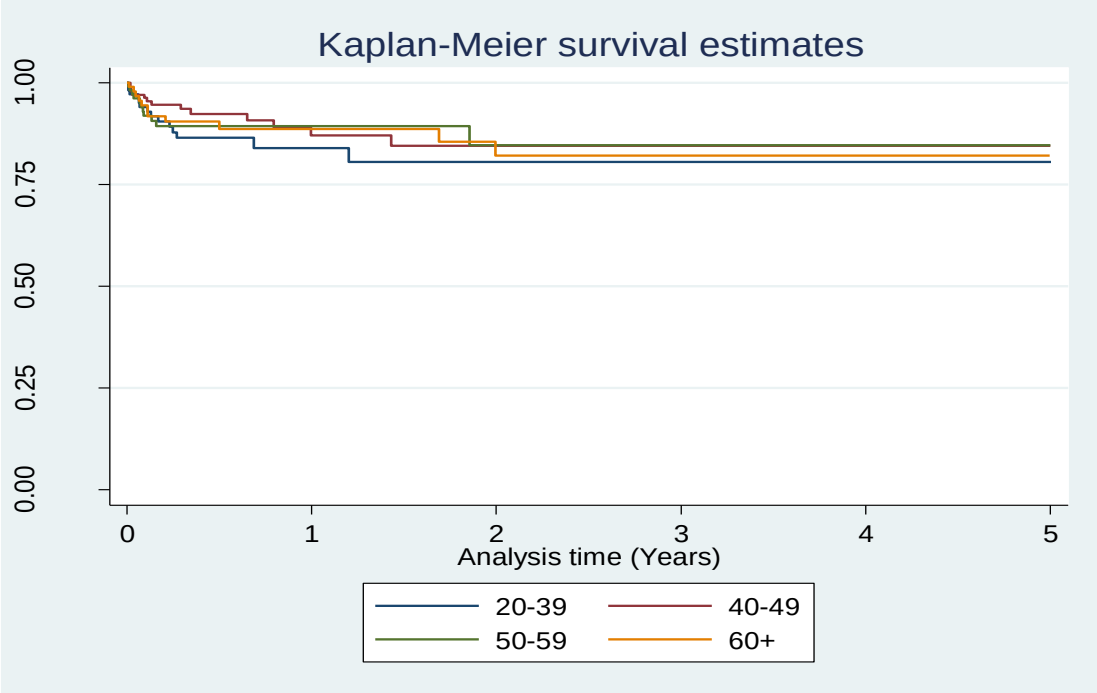


Figure 4.5: Kaplan-Meier survival curves for age groups

4.3.1.2 Access to care

The highest rate of death was observed among patients who resided 3 hours or less away from Nairobi by road which is a category representing the largest proportion of women (Table 4.10). Beyond survival and because all reported deaths occurred within KNH, the rates also suggest that deaths occurring among women living furthest away from Nairobi were least likely to be reported. No median survival times could be estimated for the variable 'Access to Care'.

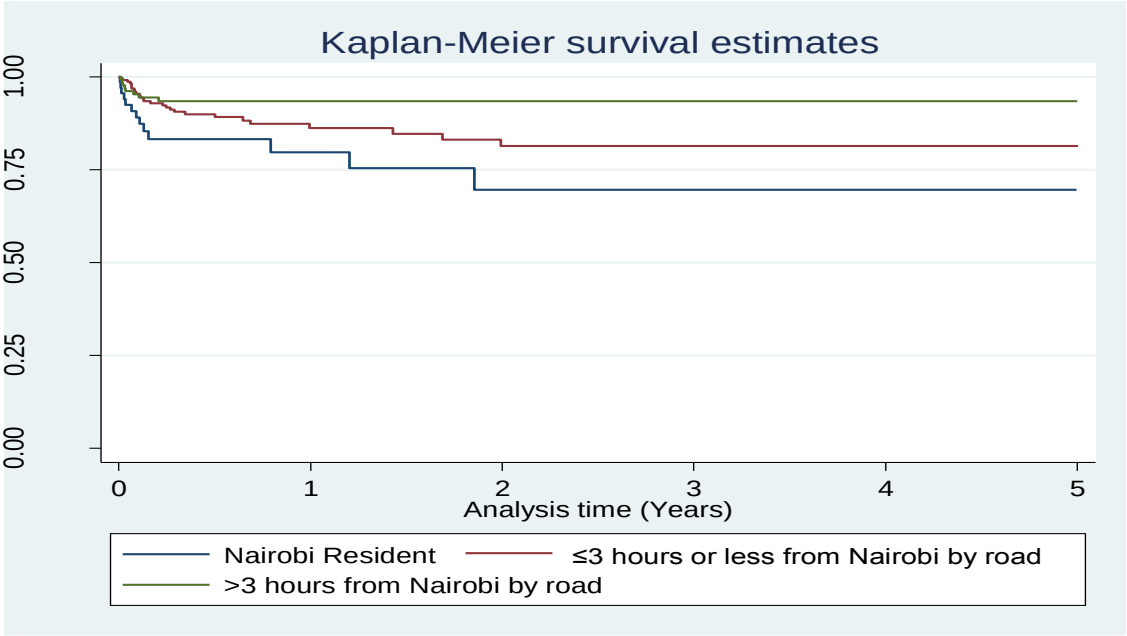


Figure 4.6: Kaplan-Meier survival curves for access to care

A p-value of 0.01 obtained from the log rank test indicates that the differences in survival between the three groups (Figure 4.6) are not statistically significant contrary to the Chi- Square results in Table 4.3.

4.3.1.3 Stage of Disease

Females with Stage 4 cervical cancer had a median survival of approximately fourteen and a half months and the highest rate of death estimated at 68 deaths per 100 person years. The lowest rate of death was observed among women diagnosed with stage 2 and below cervical cancer (Table 4.10).

In the Kaplan-Meier analysis, the survival probability for Stage 4 cancer was significantly lower compared to other stages (Figure 4.7). The p-value associated with the log rank test statistic was <0.001 which relative to a significance level of 0.05 is highly statistically significant and indicative that there is significant difference in survival times between the four stages of disease studied at all time points in the study.

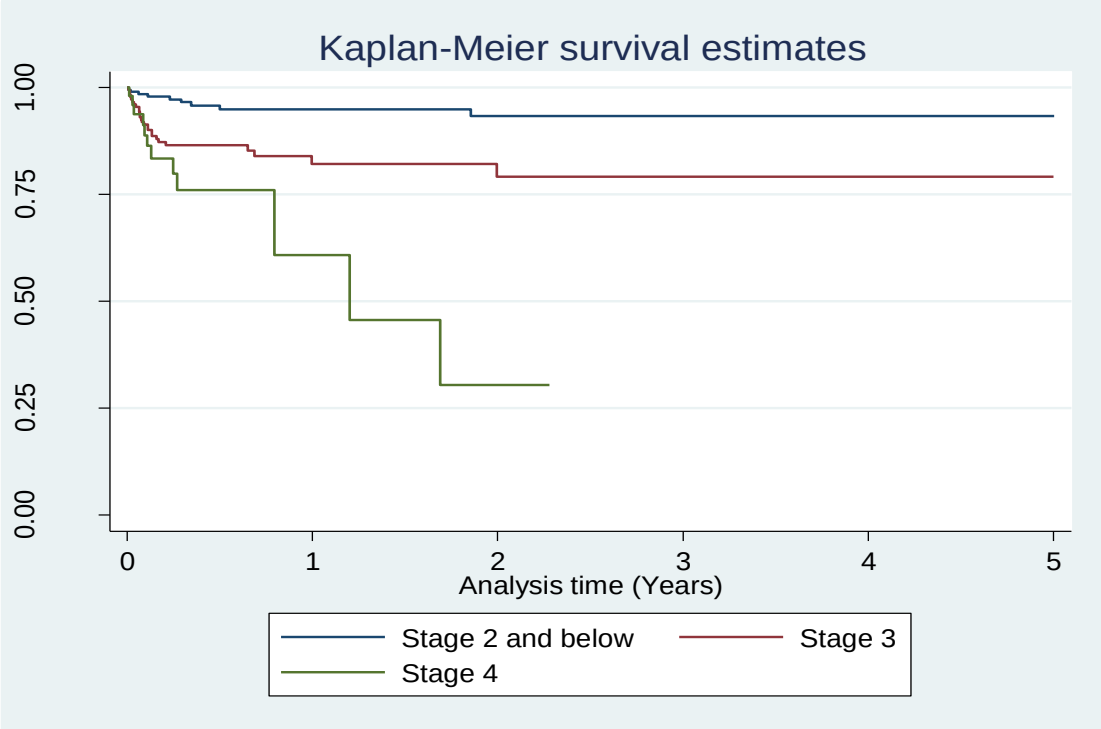


Figure 4.7: Kaplan-Meier survival curves for stage of disease

4.3.1.4 Type of Treatment

For women who did not receive any treatment their median survival was estimated at approximately two and a half months. The lowest rate of death was observed among women who received chemo-radiation i.e. 1 death per 100 person years (Table 4.10).

A p-value of <0.001 was obtained from the log rank test showing that there is a significant difference in survival times between the different treatment groups studied at all time points in the study. This supports the findings of a strong association between clinical management and KNH patient outcomes as presented in Table 4.3.

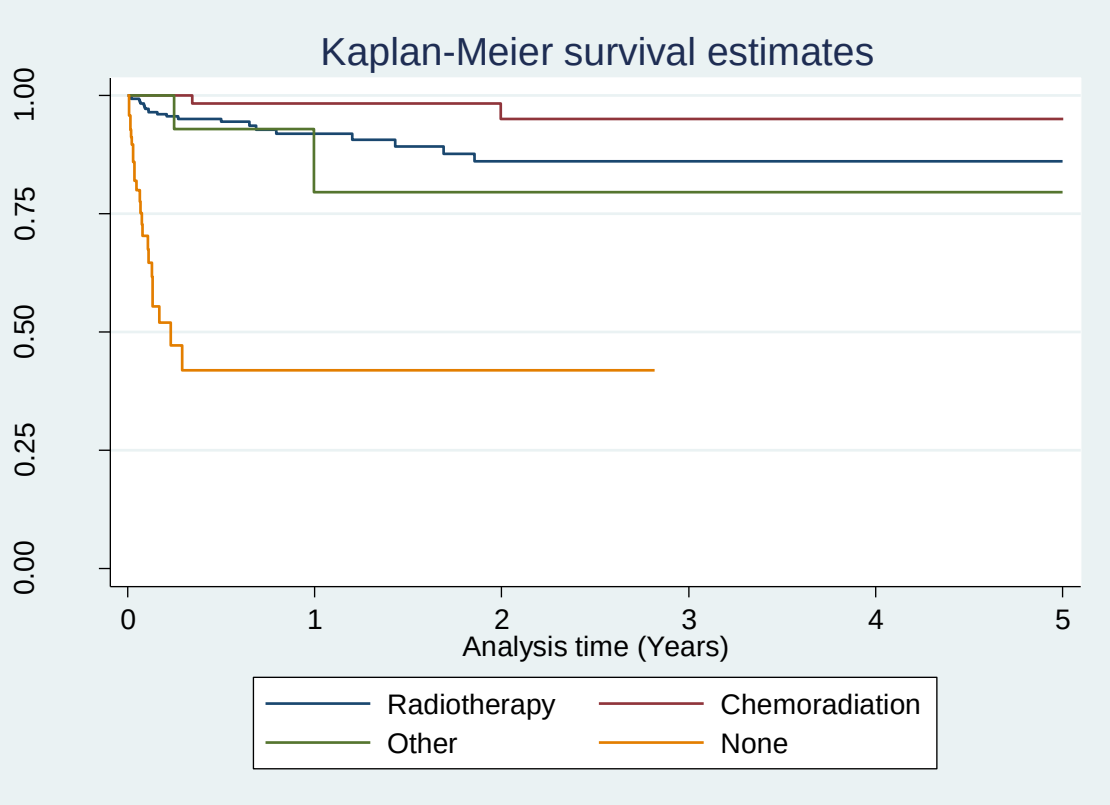


Figure 4.8: Kaplan-Meier survival plot for treatment groups

4.3.1.5 Treatment Status

Similar to women who received no treatment in section 4.6.1.4. above, women who never started treatment had a median survival time of approximately 3 months while women who completed treatment had the lowest rate of death estimated at 2 deaths per 100 person years (Table 4.10). The log rank test suggests that the differences in survival among women whose treatments were completed, incomplete or never started are

statistically significant. This implies that treatment status influences survival.

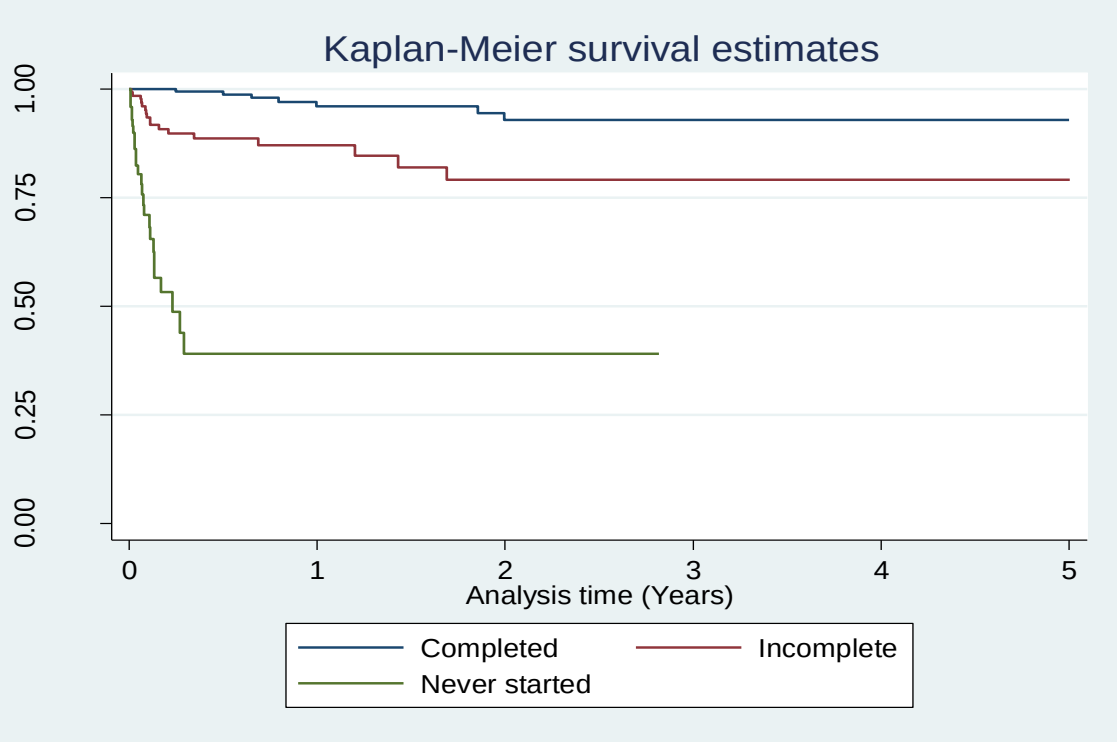


Figure 4.9: Kaplan-Meier survival plot for treatment status

Table 4.10 below presents the rate of failure and median survival as estimated from Kaplan-Meier survival analysis.

Table 4.10: Kaplan-Meier estimates for median survival and rate of failure

	Factors	Median Survival (Yrs)	Person Time	Failure	Rate	95% CI		Log Rank Test
						Lower Limit	Upper Limit	P-Value
Overall	460	-	494.06	49	0.10	0.07	0.13	
Age Groups	20-39	-	94.97	14	0.15	0.08	0.24	0.70
	40-49	-	167.50	13	0.08	0.05	0.13	
	50-59	-	114.62	11	0.10	0.05	0.17	
	60+	-	116.98	11	0.09	0.05	0.16	
Access to Care	Residing in Nairobi	-	73.77	13	0.17	0.10	0.30	0.01
	≤3 hours from Nairobi by road	-	274.12	27	0.10	0.07	0.14	
	>3 hours from Nairobi by road	-	141.83	8	0.06	0.03	0.11	
Stage of Disease	Stage 2 or below	-	291.96	9	0.03	0.01	0.06	<0.001
	Stage 3	-	160.92	26	0.16	0.11	0.24	
	Stage 4	1.20	17.59	12	0.68	0.38	1.20	
Type of Treatment	Radiotherapy	-	312.18	21	0.07	0.04	0.10	<0.001
	Chemo-radiation	-	147.27	2	0.01	0.00	0.05	
	Other	-	22.03	2	0.09	0.02	0.36	
	None	0.21	12.58	24	1.91	1.28	2.85	
Treatment Status	Completed	-	337.86	7	0.02	0.01	0.04	<0.001
	Incomplete	-	143.33	17	0.12	0.07	0.19	
	Never Started	0.23	12.87	25	1.94	1.31	2.87	

4.3.2 Mortality Rate Ratio Analyses

4.3.2.1 Univariate Analysis of Survival

4.3.2.1.1 Age

Women in the age groups of 40-49, 50-59 and 60+ had lower mortality hazard ratios (HRs) when compared to the 20-39 age group (Table 4.11). The lowest mortality HR was observed with the 40-49 age group. These were consistent with the findings of the Kaplan-Meier survival analysis which showed that women aged 20-39 had the highest rate of death.

4.3.2.1.2 Access to Care

Those patients residing more than 3 hours away from Nairobi by road had the lowest HR (Table 4.11). This is unlikely to correspond with an actual reduced risk of dying but rather it is suggestive of their reduced likelihood to die within KNH or even have the death reported to KNH. This is because in 2008 KNH was the only hospital in Kenya offering comprehensive care for cervical cancer patients.

4.3.2.1.3 Stage of Disease

Women in stages 3 (HR= 3.74) and 4 (HR= 8.22) were all shown to be more likely to die compared to women diagnosed with stage 2 or below cervical cancer (Table 4.11).

4.3.2.1.4 Type of Treatment

Women who received chemo-radiation were 71% less likely to die compared to women who received radiotherapy. Those who received no treatment were 13.1 times more likely to die compared to those who received radiotherapy (Table 4.11).

4.3.2.1.5 Treatment Status

The least risk of dying was observed among women who completed their treatment. Women who never received any treated were at the greatest risk of dying and 42.1 times more likely to die compared to women who completed treatment.

4.3.2.2 Multivariate Analysis of Survival

4.3.2.2.1 Age

The p-values associated with the multivariate HRs were all greater than 0.05 and hence not statistically significant (Table 4.11). After controlling for access to care, stage of disease, type of treatment and treatment status, the results demonstrated that the hazard

of dying is greatest within the 60+ age group and not the 20-29 age group as suggested by the Kaplan-Meier and univariate analyses.

4.3.2.2.2 Access to Care

The results are consistent with Kaplan-Meier and univariate analyses where residing outside Nairobi corresponded with a reduced risk of dying. Of particular interest is the observation that the risk of dying is not only least but statistically significant among women residing more than 3 hours away from Nairobi by road (Table 4.11). Once more taking into consideration that in 2008 KNH was the only hospital in Kenya offering comprehensive cancer care, it is unlikely that the reduced risk corresponds to actual risk of death but rather indicates reduced probability of dying at KNH or having their death reported to KNH.

4.3.2.2.3 Stage of Disease

The results of the multivariate analysis are consistent with both Kaplan-Meier and univariate analyses which indicate that the risk of dying significantly increases the higher the stage of disease (Table 4.11). This suggests that the stage of disease at diagnosis impacts significantly on patient outcomes and may partially determine the patients' risk of dying.

4.3.2.2.3 Type of Treatment

In contrast with the Kaplan-Meier and univariate analyses, the multivariate HRs indicate that women who receive treatment options without either radiotherapy or chemo-radiation were at the greatest risk of dying. Not only is the p-value associated with their multivariate HR statistically significant it supersedes the risk of dying among women who did not receive treatment (Table 4.2).

4.3.2.2.3 Treatment Status

Women who never started treatment had the greatest risk of dying and were 28.3 times more likely to die compared to those who completed treatment (Table 4.11). This was consistent with both Kaplan-Meier and univariate analyses.

Table 4.11: Univariate and Multivariate Estimates Using Cox Regression of Mortality Hazard Ratios and 95% Confidence Intervals

		Univariate				Multivariate		
			95% CI				95% CI	
Factors		Hazard Ratio	Lower Limit	Lower Limit	Sig.	Hazard Ratio[a]	Lower Limit	Upper Limit
Age, years	20–39	1.00	-	-	-	-	-	-
	40–49	0.64	0.30	1.36	0.36	0.68	0.29	1.55
	50–59	0.76	0.34	1.67	0.61	1.25	0.53	2.93
	60+	0.78	0.35	1.72	0.40	1.46	0.61	3.50
Access to care	Residing in Nairobi	1.00	-	-	-	-	-	-
	≤3 hours from Nairobi by road	0.53	0.27	1.03	0.15	0.58	0.27	1.22
	>3 hours from Nairobi by road	0.28	0.12	0.68	0.04	0.39	0.15	0.97
Stage of disease	Stage 2 or below	1.00	-	-	-	-	-	-
	Stage 3	3.74	1.75	8.00	0.01	3.12	1.37	7.07
	Stage 4	8.22	3.42	19.76	0.00	5.50	2.18	13.89
Treatment received	Radiotherapy	1.00	-	-	-	-	-	-
	Chemoradiation	0.29	0.07	1.24	0.21	0.39	0.09	1.72
	Other	1.50	0.35	6.38	0.01	8.89	0.61	49.04
	None	13.09	7.07	24.25	0.70	1.44	0.22	9.52
Treatment status	Completed	1.00	-	-	-	-	-	-
	Incomplete	5.11	2.12	12.31	0.00	7.60	2.79	20.66
	Never Started	42.26	17.71	100.81	0.00	28.25	3.75	212.94

[a] Hazard ratio adjusted for age, access to care, stage of disease, treatment status, and treatment received.

Abbreviations: CI, confidence interval; sig, significance.

CHAPTER FIVE

DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 Discussion

5.1.1 Treatment Options

The treatment options offered to cervical cancer patients at KNH during the 2008-2013 period was consistent with international practice (Rose, 2002; Nwachukwu, Mayadev and Viswanathan, 2018). It is important to note that international cervical cancer treatment guidelines and recommendations have remained relatively unchanged since 1999 (Gupta *et al.*, 2017). The treatment regimens offered during the study period are also consistent with the National Guidelines for Cancer Management which were released in August 2013 (MoH, 2013).

The strong association between recommended treatment and stage of disease is indicative that in KNH the choice of treatment or treatment combination was based on the stage of disease and tumour response. Women with early-stage disease were treated using radical hysterectomy and/or radiotherapy while all patients with advanced stage 2B disease and above received either radiotherapy or chemo-radiation. Disease progression also influenced the patients' treatment plans. For example, patients who received radiotherapy only but on follow-up had advanced disease were likely to undergo additional radiotherapy before receiving chemotherapy if necessary.

The equally strong association observed between recommended treatment and treatment completion. A significant proportion of the women either did not complete treatment or never started treatment. The most commonly cited reason for this was the prohibitive cost of treatment. The cost mentioned here should not be restricted to the cost of medical care but include the indirect cost of medical care associated with travelling and residing in Nairobi for the duration of treatment. This is because several patients were admitted

to hospital for radiotherapy (typically outpatient service) due to distance from their area of residence.

Furthermore, all the women who required brachytherapy following external beam radiotherapy (EBRT) had to be referred to Mulago hospital in Uganda to access the service. This finding has also been reported in a cohort study conducted on cervical cancer patients from March 2008- February 2010 (Maranga *et al.*, 2013). The reason being the equipment at KNH was broken down during that period.

5.1.2 Predictive Factors

This study found 1) stage of cancer at diagnosis, 2) type of treatment received and 3) treatment status (i.e., whether or not treatment was initiated and completed) to be the strongest predictive factors of overall survival among women treated for cervical cancer in KNH in 2008.

1) Stage of Cancer at Diagnosis

The multivariate Cox regression model showed that chances of survival were reduced with an increase in the stage of cervical cancer at diagnosis. This is similar to the findings of a recent study in rural India whereby the 5-year overall survival of stage IA cervical cancer patients was 95.1% and 5.3% for stage IV patients (Jayant *et al.*, 2016). Another study in Ethiopia also concluded that chances of survival decreased with an increase in stage of cancer at diagnosis (Wassie *et al.*, 2019). Generally, stage of disease at diagnosis is a well-known predictor of survival not just for cervical cancer but for all cancers. This is because a higher stage of disease corresponds to advanced disease which is more difficult to treat and cure (Brierley, Gospodarowicz and O'Sullivan, 2016).

A high proportion of women in this study presented with late-stage disease (i.e., Stages III and IV). This observation is to not unique to Kenya and has been reported in several low- and middle-income countries (LMICs) (Sankaranarayanan *et al.*, 2011; Jayant *et al.*, 2016; Wassie *et al.*, 2019; Balasubramaniam *et al.*, 2020). In all instances, the high

proportion of women with late-stage disease was associated with low survival rates in the study countries.

Maranga et al (2013) additionally raise concerns over the possibility of 'under-staging' (i.e. where women had more advanced disease than was diagnosed) impacting negatively on patient outcomes (Maranga *et al.*, 2013). Similar to their study at KNH, it was noted during this study that initial staging and tumour response were primarily assessed using digital vaginal examination because few patients could afford additional tests such as ultrasound, X-Ray, CT Scan or MRI.

2) Type of Treatment Received

In this study, the majority of women received radiotherapy alone or following surgery. It is internationally accepted that the best treatment for women with locally advanced cervical cancer is chemoradiation (Gupta *et al.*, 2017). The multivariate Cox regression model concurred with this best practice recommendation even though the differences in survival between those who received chemoradiation vs radiotherapy were not statistically significant. This is consistent with a recent study that showed patients to have better outcomes when they receive radiotherapy either alone or in combination with other treatments (Balasubramaniam *et al.*, 2020). However, many other recent studies suggest that radiotherapy in the absence of chemotherapy is not as effective in treating locally advanced cervical cancer (Wang *et al.*, 2017; Wassie *et al.*, 2019; Yang *et al.*, 2019; Tian *et al.*, 2020).

What was striking in this study is that women who received 'other' treatments that did not incorporate radiotherapy or chemoradiation had the worst outcomes. This is an observation that might be indicative of those patients receiving sub-optimal treatment and follow-up for several reasons including not being able to attend clinic or afford treatment.

3) Treatment Status

Slightly over half of the women completed treatment. The multivariate Cox regression model indicates that women who did not complete treatment were at a greater risk of dying compared to women who completed treatment while those who never started treatment had the greatest risk of dying.

In addition to the prohibitive cost of treatment, many women were rendered ineligible for chemo-radiation in cases where hydronephrosis had resulted in impaired kidney function; a condition often associated with advanced cervical cancer. A prospective study in Uganda similarly reported this condition as a major drawback in offering patients chemo-radiation which is the cornerstone of best practice for locally advanced cervical cancer (McArdle and Kigula-Mugambe, 2007). Elderly women (i.e., 60 and above) in this study were also not offered chemotherapy as age is a known risk factor for increased toxicity and decreased tolerance (Wedding *et al.*, 2007; Owusu and Berger, 2014). However, there is increasing evidence that comprehensive geriatric assessments can accurately identify elderly patients who would benefit from chemo-radiation (Wedding *et al.*, 2007; Wang *et al.*, 2017).

It was also noted that for most patients it took on average 2-3 months from diagnosis to commencement of treatment. This situation was reported by Maranga et al (2013) with the main reasons for delay cited as financial constraints, difficulties with travelling, inability to gain admission to crowded hospital oncology wards and queues of patients awaiting treatment with the single radiotherapy machine at KNH (Maranga *et al.*, 2013). In addition, a 2012 KNH audit of specialized healthcare delivery revealed that it took an average of two months for new patients to see a clinical specialist for the first time; approximately four months for booked patients to attend their first radiotherapy session and one and a half months for those for chemotherapy; a waiting period of five months for patients who need brachytherapy; and twenty two days for the release of histological laboratory reports (Auditor General, 2012). Inadequate treatment ultimately results in

poor patient outcomes for cervical cancer patients (Kanavos, 2006; UICC, 2008; Maranga *et al.*, 2013).

5.1.3 Socio-Demographic Factors

The best recorded socio-demographic variables were age, region of residence and parity. However, an interesting finding in this study was that none of the socio-demographic factors were found to influence survival with the exception of 'Access to Care' which was a modified variation of the 'Region of Residence' variable. The most plausible explanation for this is low power of the bivariate analyses which was as a result of poor and inconsistent documentation of socio-demographic variables within medical records and the fact that the high loss to follow up was unlikely to be evenly distributed across the socio-demographic factor categories.

In the multivariate Cox regression model, lowest risk of dying was consistently demonstrated among women who resided more than 3 hours away from Nairobi by road (one of three categories for the 'Access to Care' variable). Taking into consideration that in 2008 KNH was the only hospital offering comprehensive cancer care in Kenya it is unlikely that risk of dying would reduce the further away a patient resided from Nairobi. It is therefore proposed that the risk calculated here refers to the probability of a cervical cancer patient treated at KNH dying in KNH or at the very least their death being reported to KNH. Subsequently, patients residing further away from KNH were likely to die in alternative locations with no notifications given to KNH. This is supported by the fact that all deaths reported in this study not only occurred in the first year but they also occurred within KNH.

While the model did not adequately depict the relationship between region of residence (i.e., time taken to travel to KNH) and overall five-year survival, existing evidence consistently suggests that a patient's region of residence can contribute to late-stage diagnosis which ultimately leads to poor patient outcomes especially if the patients

reside in medically underserved regions or regions of low socio-economic status (Barry and Breen, 2005; McLeod *et al.*, 2011; Maranga *et al.*, 2013; Wassie *et al.*, 2019).

5.1.4 Referral Status and Region of Residence

Referral status was not a focus of the study. However, a very strong association was found between referral status and region of residence. The finding is consistent with the fact that KNH was the only specialist cancer treatment centre in Kenya in 2008 and is located within the capital city Nairobi. Therefore, many cancer patients had to travel to Nairobi in order to access services or consult oncologists. This raises questions with regards to which alternative care pathways are available for patients not able to reach Nairobi or any other major city or town where oncology services are located.

Studies in the US found that a woman's place of residence was an important predictor of late-stage diagnosis of breast or cervical cancer (Barry and Breen, 2005; Benard *et al.*, 2017; Abdalla *et al.*, 2020). This is because an area that is economically and socially distressed is most likely to be medically underserved impacting negatively on health knowledge as well as health seeking behaviour among residents. In India, New Zealand and Kenya, studies have shown that transportation (including the financial cost of travelling long distances to cancer centres), the required time to travel, and the levels of tiredness experienced by patients, are barriers to accessing treatment, resulting in some women with cervical cancer not attending scheduled appointments or refusing treatment altogether (McLeod *et al.*, 2011; Dutta, Biswas and Muhkherjee, 2013; Maranga *et al.*, 2013).

The GLOBOCAN 2008 database provides an estimate of 2,454 new cases of cervical cancer in Kenya in 2008 (Ferlay *et al.*, 2008); however, this study only accounts for 481 women who sought treatment at KNH. In order to improve the referral system and health service delivery, there is need to determine of all the patients referred, how many access services at referral facilities and what happens to those not able to honour their referrals.

5.1.5 Five-Year Overall Survival

The overall mortality rate ratio was estimated to be 10 deaths per 100 person years. Because a high proportion of women (82.3%) were lost to follow up, the overall five-year survival of 59% is unreliable. It is also likely that the overall survival estimate is only accurate over the first year since all deaths in the study were reported within the first year.

The following four reasons could explain why 82.3% of the women were lost to follow up rendering the overall five-year survival rate unreliable;

i) Some women only came to KNH for radiotherapy services and upon completion resumed care under their primary physician in a different facility.
ii) Others completed initial treatment and opted not to return.
iii) There were those who did not receive any treatment i.e. never started treatment.
iv) And those who dropped out of treatment.

Also, this study being restricted to the review of medical records, no effort was made to contact patients or their next of kin to conclusively determine patient progress. However, the above results are consistent with the findings of a previous study at the same health facility which placed the loss to follow up of cervical cancer patients at 41.1% during the study's 2-year follow- up period (Maranga *et al.*, 2013).

Despite the above limitation the estimate is still significantly lower than observed rates in most parts of the world; 61.4% in England (ONS, 2019), 67.5% in the US (Howlader *et al.*, 2015), 72% in Australia (AIHW, 2014) and between 63-79% in China, Singapore, the Republic of Korea and Turkey (Sankaranarayanan *et al.*, 2011). It is therefore likely that the estimated overall five-year survival rate for women with cervical cancer in Kenya is between the rates of less than 25% in the Gambia and Uganda (Sankaranarayanan *et al.*, 2011) and 38.63% as observed in a recent study in Ethiopia (Wassie *et al.*, 2019).

5.2 Conclusions

The treatment options provided at the Kenyatta National Hospital (KNH) are in line with international best practices for the management of locally advanced cervical cancer. The strongest predictive factors of five-year overall survival among women treated for cervical cancer in KNH in 2008 were stage of disease at diagnosis, type of treatment received and treatment status i.e., whether or not treatment was initiated or completed. Distance from KNH is another factor that demonstrated predictive potential but which was not well characterized in this study. Furthermore, it is likely that the predictive value of socio-demographic factors was not accurately assessed in this study owing to poor and inconsistent reporting within the medical records. This resulted in the associated bivariate analyses having much lower power than was necessary to detect an association if any between socio-demographic factors and patient outcomes. The significantly high loss to follow up among cervical cancer patients additionally resulted in the overall five-year survival estimate being unreliable.

5.3 Recommendations

The study recommendations are divided into two categories i.e., recommendations of policy and practice, and recommendations for future research.

5.3.1 Recommendations for Policy and Practice

1. **Primary Prevention**

There is strong and overwhelming evidence, both experimental and epidemiological, that the human papillomavirus (HPV) plays a key role in cervical carcinogenesis (Walboomers *et al.*, 1999; Bosch *et al.*, 2002; Bosch and De Sanjosé, 2003; Böhmer *et al.*, 2003; Schiffman and Kjaer, 2003; zur Hausen, 2006; Woodman, Collins and Young, 2007). Therefore, there is value in implementing HPV vaccination for young girls aged 9-13 as this could potentially build a cohort of women at very low risk of cervical

cancer. Prophylactic HPV vaccines as a primary intervention against ICC may be implemented as part of the WHO's widespread Expanded Program of Immunization for children in LMICs through partnership with the Global Alliance for Vaccines and Immunization (GAVI) (Maranga *et al.*, 2013). The key challenges anticipated in launching HPV vaccination in LMICs include competing disease burdens, sustainability of an immunization program for adolescents, affordability, cost effectiveness, cultural acceptability, lack of political will, and mobilizing public support (Agosti and Goldie, 2007).

2. Cervical Cancer Screening

With approximately 80% of cancers in Kenya being diagnosed in the late stages, stage appropriate treatments are often aggressive and costly (MoH, 2011). Though chemo-radiation is recommended for locally advanced cervical cancer, few patients would benefit due to the high cost of treatment, limited access to health services and/or cancer related complications particularly anemia and hydronephrosis which rules out administration of chemotherapy (Green *et al.*, 2005; Kanavos, 2006; McArdle and Kigula-Mugambe, 2007). Therefore, the introduction of national screening programmes and the provision of accessible radiotherapy facilities should be the major priorities in the LMICs such as Kenya (McArdle and Kigula-Mugambe, 2007).

Investing in setting up a proven effective LMIC relevant national screening programme and increasing the treatment options would allow for more pre-invasive and early-stage cancers to be detected and treated (Obi and Ozumba, 2008; WHO, 2014). It would also allow for the use of simple outpatient procedures to destroy or remove precancerous tissue instead of aggressive approaches such as cone biopsy or hysterectomy which are expensive and often result in overtreatment of women (WHO, 2014).

4. Enhancing Public-Private partnerships for improved service delivery

Delays in treatment were often due to patients' lack of funds for treatment and also due to a high demand for services based on the fact that KNH is the only public health facility in Kenya offering comprehensive and relatively cheap cancer care. With an increase in the number of private for-profit cancer treatment centres, it would be beneficial for government to look into partnerships for health service delivery that would ultimately subsidize care for patients and allow for treatment to be provided in a timely and efficient way. It would also reduce the need for patients to travel outside the country to access affordable care and the need for fundraising for medical care as is currently happening.

Increasingly, governments around the world are turning to the private sector for partnerships to develop, finance and provide health infrastructure and services (Roehrich, Lewis and George, 2014). In this way governments aim to avoid up-front capital expenditure and to harness private-sector efficiencies, while private-sector partners aim for a return on their investment. These partnerships are not always successful at achieving their goals however they remain attractive owing to their high potential for improvement (Barlow, Roehrich and Wright, 2013; Roehrich, Lewis and George, 2014; Whyle and Olivier, 2016).

5) **Adopting Comprehensive Geriatric Assessments (CGAs) for elderly cancer patients**

During this study, it was noted that women who were aged 60 and above were not offered chemotherapy due to valid but 'unconfirmed' concerns they would not tolerate treatment very well. There is increasing evidence in support for administration of chemotherapy in elderly patients with few or no limitations based on comprehensive geriatric assessment (CGA) (Wedding *et al.*, 2007; Wang *et al.*, 2017).

Age is often perceived as progressive loss of stress tolerance owing to progressive decline in functional reserve of multiple organ systems, a high prevalence of comorbid conditions, limited socioeconomic support, reduced cognition, and a higher prevalence

of depression (Balducci and Extermann, 2000; Repetto and Balducci, 2002). However, aging is also a highly individualized process and many times chronologic age will not reflect the functional reserve and life expectancy of an individual (Cline, 2014). Owusu and Berger (2014) note that CGAs are able to account for these diversities in ageing by;

1. Recognizing potentially treatable conditions such as depression or malnutrition, which may lessen the tolerance of cancer treatment but can be reversed with proper intervention;
2. Assessing an individual's functional reserve;
3. Providing a gross estimate of individual life expectancy
4. Adopting a common language to classify older cancer patients.

The CGA allows the practitioner to recognize at least three stages of aging (Owusu and Berger, 2014):

1. People who are functionally independent and without comorbidity- these are candidates for any form of standard cancer treatment except bone marrow transplant.
2. People who are frail (dependence in one or more activities of daily living, three or more comorbid conditions, one or more geriatric syndromes) - candidates for palliative treatment.
3. People in between- candidates who may benefit from some special pharmacological approach, for example reduction in the initial dose of chemotherapy with subsequent dose escalations.

Several studies show that the CGA can predict morbidity and mortality in older patients with cancer, and identify problems relevant to cancer care that would otherwise go unrecognized (Mohile and Magnuson, 2013; Sourdet *et al.*, 2020). Their adoption in the Kenyan healthcare setting would be most beneficial to older patients with cancer.

1. Universal Health Coverage (UHC)

While it was not the focus of the study, one of the main reasons for not receiving care and treatment on time was owing to a lack of finances as documented in some patient records. This implies health inequalities which not surprisingly disproportionately affect women of a lower socio-economic status. A 2018 study showed that while the Kenya has ensured the inclusion of cancer patients in National Hospital Insurance Fund (NHIF) and private insurance schemes, limits imposed on the number of treatments, based on the type of cancer, modality and costs of drugs, often result in incomplete treatments for patients and contribute to poor outcomes (Atieno *et al.*, 2018). UHC has an important role to play in ensuring that all citizens have access to timely and quality health services. In Kenya, it may be beneficial to focus on the following four areas;

a) ***Human Resources:*** The number of health workers specializing in oncology still remains low with approximately only 35 oncologists for a population of 47 million (BBC Africa, 2019). There needs to be a strategic plan in place dedicated to training more health workers in oncology including identifying existing cadres of health workers, such as physicians and surgeons, who can be equipped with additional skills in oncology.
b) ***Infrastructure:*** More public/government cancer treatment centres are required to meet the increasing demand for services and reduce the distance travelled to access care and treatment. Studies in Kenya confirm that public health sector offers more affordable oncology health services while keeping the same quality as private sector (Atieno *et al.*, 2018; Wambalaba *et al.*, 2019; Makau-Barasa *et al.*, 2020).
c) ***Revolving Cancer Drug Fund:*** This may provide a sustainable solution to availing cancer drugs to all Kenyans at the best price.
d) ***Centralized health system database:*** This would link health facilities and enable both clinicians and researchers review the full medical history of a patient including determining if a patient is continuing care in an alternative health

facility. This type of system could help reduce loss to follow-up in cohort studies.

1. **Vital Registration**

This is also referred to as civil registration and is a system by which a government records the vital events of its citizens and residents including births, deaths, marriages, divorces and adoptions. Presently, Kenya's vital registration system is devolved, fragmented and largely manual making it difficult for researchers of chronic illnesses including cancer to use the system to establish whether a patient lost to follow-up may have died. Investments in a centralized automated vital registration system would go a long way in improving the quality and quantity of cancer survival studies.

2. **Cancer Registration Coverage**

The current National Cancer Control Strategy 2017-2022 prioritizes the expansion of cancer registration coverage in the country (MoH, 2017). The strategy recognizes that in order to improve cancer health services in the country, there is need for an accurate determination of the cancer burden in the country. Through the guidance of the strategy national government should put in place policies and budget allocation to support existing cancer registries and for the establishment of additional population-based registries. The cancer registries would not only capture the cancer burden in the country but also provide a platform to support clinical and epidemiological cancer research.

5.3.2 Recommendations for Future Research

The sole reliance on reviewing medical records in this study not only resulted in a high level of loss to follow up but also raised many unanswered questions. The following four recommendations for future research will not only ensure a comprehensive understanding of cancer care in Kenya but will also improve the quality of cancer survival studies.

1. **Qualitative Research**

Qualitative research methods specifically focus group discussions (FGDs) and key informant interviews (KIIs) would have provided the perceptions and sentiments of cervical cancer patients. This would have provided a greater context within which the predictive factors of survival could be interpreted. It is therefore advisable for future studies to adopt a mixed methods design.

2. **Prospective Cohorts**

Within the current setup, there are no timelines by which the national government is likely to invest in centralized health systems and vital registration databases. This means that cancer survival studies are likely to continue facing high losses to follow up. One way to mitigate this is by focusing more on short-term (1-3 years) prospective cohort studies. This has multiple advantages which include;

a) A reasonable cost for conducting the studies compared to longer term follow-ups.
b) Access to current and up to date contact information to facilitate prospective follow-ups.
c) These studies would focus strongly on the period immediately after diagnosis and highlight any challenges and gaps in the timely initiation of care and treatment.

1. **Patient Follow-Ups**

For both retrospective and prospective cohort studies, it would be important to incorporate telephone follow-ups. Prospective cohort studies with adequate financing may also have an opportunity to utilize community health unit structures to follow up patients not available on phone but whose residences were well documented and mapped using GIS.

2. **Cancer Research Networks**

Owing to the difficulties in conducting cancer research specifically cancer survival and quality of life studies in low resource settings, cancer researchers should be encouraged to form research networks with other researchers as well as key stakeholders. This would ensure efficient use of limited resources for cancer research through avoidance of study replications within the same consortium, facilitate multidisciplinary cancer research, allow for secondary data analysis using pooled data from past studies and drafting of mutual research priorities.

REFERENCES

Abdalla, E. *et al.* (2020) 'Racial differences in 5-year relative survival rates of cervical cancer by stage at diagnosis, between African American (black) and white women, living in the state of Alabama, USA', *BMC Cancer*, 20(1), p. 830.

Abdullahi, S. *et al.* (2012) 'Cancer of the cervix in unscreened West African women', *Journal of Basic and Clinical Reproductive Sciences*, 1, p. 44.

ACS (2011a) *Cancer in Africa*. Atlanta: American Cancer Society.

ACS (2011b) *Global Cancer Facts & Figures 2nd Edition. Atlanta: American Cancer Society*. Atlanta: American Cancer Society.

ACS (2018) 'Global cancer facts & figures 4th edition', *Am Cancer Soc*.

ACS, UICC and IARC (2019) *The Cancer Atlas: Third Edition*. Atlanta: American Cancer Society.

Agosti, J. M. and Goldie, S. J. (2007) 'Introducing HPV vaccine in developing countries—key challenges and issues', *New England Journal of Medicine*, 356(19), pp. 1908–1910.

AIHW (2014) *Cancer in Australia: An Overview*. Canberra: Australian Institute of Health and Welfare.

Alghamdi, H. I., Alshehri, A. F. and Farhat, G. N. (2017) 'An overview of mortality & predictors of small-cell and non-small cell lung cancer among Saudi patients', *Journal of Epidemiology and Global Health*, 7(Supplement 1), pp. S1–S6.

Allemani, C. *et al.* (2015) 'Global surveillance of cancer survival 1995–2009: analysis of individual data for 25 676 887 patients from 279 population-based registries in 67 countries (CONCORD-2)', *The Lancet*, 385(9972), pp. 977–1010.

Angus, D. C. *et al.* (2001) 'Quality-adjusted survival in the first year after the acute respiratory distress syndrome', *American journal of respiratory and critical care medicine*, 163(6), pp. 1389–1394.

Arbyn, M. *et al.* (2011) 'Worldwide burden of cervical cancer in 2008', *Annals of Oncology*, 22(12), pp. 2675–2686.

Atieno, O. M. *et al.* (2018) 'Pilot study assessing the direct medical cost of treating patients with cancer in Kenya; findings and implications for the future', *Journal of Medical Economics*, 21(9), pp. 878–887.

Auditor General (2012) *Performance Audit Report of the Auditor-General. Specialized Healthcare Delivery at Kenyatta National Hospital; Waiting-time for Cancer, Renal and Heart Patients*. Nairobi, Kenya: Office of the Auditor General.

Balasubramaniam, G. *et al.* (2020) 'Survival rate of cervical cancer from a study conducted in India', *Indian Journal of Medical Sciences*, 0.

Balducci, L. and Extermann, M. (2000) 'Management of cancer in the older person: a practical approach', *The oncologist*, 5(3), pp. 224–237.

Barlow, J., Roehrich, J. and Wright, S. (2013) 'Europe sees mixed results from public-private partnerships for building and managing health care facilities and services', *Health Affairs*, 32(1), pp. 146–154.

Barry, J. and Breen, N. (2005) 'The importance of place of residence in predicting late-stage diagnosis of breast or cervical cancer', *Health & place*, 11(1), pp. 15–29.

BBC Africa (2019) 'Kenyan survivors: Cancer is "national disaster"', *BBC News*, 1 August. Available at: https://www.bbc.com/news/world-africa-49191685#:~:text=Three%20recent%20high%2Dprofile%20deaths,the%20Journal%20of%20Global%20Oncology.

Benard, V. B. *et al.* (2017) 'Cervical cancer survival in the United States by race and stage (2001- 2009): Findings from the CONCORD- 2 study', *Cancer*, 123, pp. 5119–5137.

Bhatla, N. *et al.* (2019) 'Revised FIGO staging for carcinoma of the cervix uteri', *International Journal of Gynecology & Obstetrics*, 145(1), pp. 129–135.

Bland, J. M. and Altman, D. G. (2004) 'The logrank test', *Bmj*, 328(7447), p. 1073.

Böhmer, G. *et al.* (2003) 'No confirmed case of human papillomavirus DNA-negative cervical intraepithelial neoplasia grade 3 or invasive primary cancer of the uterine cervix among 511 patients', *American journal of obstetrics and gynecology*, 189(1), pp. 118–120.

Bosch, F. X. *et al.* (2002) 'The causal relation between human papillomavirus and cervical cancer', *Journal of clinical pathology*, 55(4), pp. 244–265.

Bosch, F. X. and De Sanjosé, S. (2003) 'Chapter 1: Human papillomavirus and cervical cancer—burden and assessment of causality', *JNCI monographs*, 2003(31), pp. 3–13.

Boyle, P. *et al.* (2019) 'Cancer in Africa: the way forward', *ecancermedicalscience*, 13.

Bray, F. *et al.* (2018) 'Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries', *CA: a cancer journal for clinicians*, 68(6), pp. 394–424.

Brierley, J., Gospodarowicz, M. and O'Sullivan, B. (2016) 'The principles of cancer staging', *ecancermedicalscience*, 10.

Bruni, L. *et al.* (2016) 'Human papillomavirus and related diseases in Kenya', *Summary report*.

Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration (2008) 'Reducing Uncertainties About the Effects of Chemoradiotherapy for Cervical Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 18 Randomized Trials', *Journal of Clinical Oncology*, 26(35), pp. 5802–5812.

Chirenje, M. *et al.* (2001) 'A randomised clinical trial of loop electrosurgical excision procedure (LEEP) versus cryotherapy in the treatment of cervical intraepithelial neoplasia', *Journal of Obstetrics and Gynaecology*, 21(6), pp. 617–621.

Cline, D. D. (2014) 'A Concept Analysis of Individualized Aging', *Nursing Education Perspectives*, 35(3). Retrieved from https://journals.lww.com/neponline/Fulltext/2014/05000/A_Concept_Analysis_of_Individualized_Aging.9.aspx.

Curado, M.-P. *et al.* (2007) *Cancer incidence in five continents, Volume IX*. IARC Press, International Agency for Research on Cancer.

Denny, L., Quinn, M. and Sankaranarayanan, R. (2006) *Chapter 8: Screening for Cervical Cancer in Developing Countries. Vaccine, 24*. S3/71-7.

Detsky, A. S. and Naglie, I. G. (1990) 'A clinician's guide to cost-effectiveness analysis', *Annals of Internal Medicine*, 113(2), pp. 147–154.

Duncan, K. *et al.* (2019) 'Challenges and opportunities in the creation and implementation of cancer control plans in Africa', *ecancermedicalscience*, 13. doi: 10.3332/ecancer.2019.938.

Dutta, S., Biswas, N. and Muhkherjee, G. (2013) 'Evaluation of socio-demographic factors for non-compliance to treatment in locally advanced cases of cancer cervix in a rural medical college hospital in India', *Indian journal of palliative care*, 19(3), p. 158.

FDA (2007) ‘Guidance for the industry: clinical trial endpoints for the approval of cancer drugs and biologics’. Food and Drug Administration. Retrieved from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.

Ferlay, J. *et al.* (2008) *GLOBOCAN 2008 V1.2, Cancer incidence and mortality worldwide: IARC CancerBase No.10*.

Ferlay, J. *et al.* (2018) *Global Cancer Observatory: Cancer Today*. Retrieved from https://gco.iarc.fr/today (Accessed: 20 September 2018).

Ferlay, J. *et al.* (2020) ‘Global Cancer Observatory: Cancer Tomorrow’. Retrieved from https://gco.iarc.fr/tomorrow (Accessed: 4 February 2021).

Fetting, J. *et al.* (1996) ‘Outcomes of cancer treatment for technology assessment and cancer treatment guidelines’, *Journal of Clinical Oncology*, 14(2), pp. 671–679.

Finocchario-Kessler, S. *et al.* (2016) ‘Cervical cancer prevention and treatment research in Africa: a systematic review from a public health perspective’, *BMC Women’s Health*, 16(1), p. 29.

Fontham, E. T. H. *et al.* (2020) ‘Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society’, *CA: A Cancer Journal for Clinicians*, 70(5), pp. 321–346.

Gakunga, R., Parkin, D. M., and On behalf of the African Cancer Registry Network (2015) ‘Cancer registries in Africa 2014: A survey of operational features and uses in cancer control planning’, *International Journal of Cancer*, 137(9), pp. 2045–2052.

Ganggayah, M. D. *et al.* (2019) 'Predicting factors for survival of breast cancer patients using machine learning techniques', *BMC Medical Informatics and Decision Making*, 19(1), p. 48.

Gaynon, P. S. *et al.* (1993) 'Improved therapy for children with acute lymphoblastic leukemia and unfavorable presenting features: a follow-up report of the Childrens Cancer Group Study CCG-106.', *Journal of Clinical Oncology*, 11(11), pp. 2234–2242.

Green, J. *et al.* (2005) 'Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix', *Cochrane Database of Systematic Reviews*, (3).

Green, J. A. *et al.* (2001) 'Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis', *The Lancet*, 358(9284), pp. 781–786.

Gupta, S. *et al.* (2017) '928O_PR - Neoadjuvant chemotherapy followed by surgery (NACT-surgery) versus concurrent cisplatin and radiation therapy (CTRT) in patients with stage IB2 to IIB squamous carcinoma of cervix: A randomized controlled trial (RCT)', *Abstract Book of the 42nd ESMO Congress (ESMO 2017) 8-12 September 2017, Madrid, Spain*, 28, p. v627.

Haile, Z. T. *et al.* (2018) 'Association Between Risky Sexual Behavior and Cervical Cancer Screening Among Women in Kenya: A Population-Based Study', *Journal of Community Health*, 43(2), pp. 238–247.

Halpern, M. T. and Brawley, O. W. (2016) 'Insurance status, health equity, and the cancer care continuum', *Cancer*, 122(20), pp. 3106–3109.

Hanna, T. P. and Kangolle, A. C. T. (2010) 'Cancer control in developing countries: using health data and health services research to measure and improve access,

quality and efficiency', *BMC international health and human rights*, 10, pp. 24–24.

zur Hausen, H. (2006) 'Perspectives of contemporary papillomavirus research', *HPV Vaccines and Screening in the Prevention of Cervical Cancer*, 24, pp. iii–iv.

Howlader, N. *et al.* (2015) 'SEER cancer statistics review, 1975-2013'. National Cancer Institute. Bethesda, MD. Available at: https://seer.cancer.gov/archive/csr/1975_2013/.

Jayant, K. *et al.* (2016) 'Improved survival of cervical Cancer patients in a screened population in rural India', *Asian Pacific journal of cancer prevention: APJCP*, 17(11), p. 4837.

Johnson, L. G. *et al.* (2018) 'Implementation strategies to improve cervical cancer prevention in sub-Saharan Africa: a systematic review', *Implementation Science*, 13(1), p. 28.

Kanavos, P. (2006) 'The rising burden of cancer in the developing world', *Cancer Initiatives in Developing Countries., 30 October 2005: Paris, France*, 17, pp. viii15–viii23.

Kashyap, N. *et al.* (2019) 'Risk Factors of Cervical Cancer: A Case-Control Study', *Asia-Pacific journal of oncology nursing*, 6(3), pp. 308–314.

Kawata, K. and Koga, H. (2020) 'Sexually transmitted infections and cervical cancer: Knowledge and prevention awareness among female university students in Japan', *Nursing Open*, 7(4), pp. 1139–1145.

Kesic, V. (2006) 'Management of cervical cancer', *Gynaecological Cancers*, 32(8), pp. 832–837.

Keys, H. M. *et al.* (1999) ‘Cisplatin, Radiation, and Adjuvant Hysterectomy Compared with Radiation and Adjuvant Hysterectomy for Bulky Stage IB Cervical Carcinoma’, *New England Journal of Medicine*, 340(15), pp. 1154–1161.

Kim, H. S. and Song, Y. S. (2009) ‘International Federation of Gynecology and Obstetrics (FIGO) staging system revised: what should be considered critically for gynecologic cancer?’, *Journal of gynecologic oncology*. 2009/09/30 edn, 20(3), pp. 135–136.

Kjaer, S. K. *et al.* (2020) ‘Final analysis of a 14-year long-term follow-up study of the effectiveness and immunogenicity of the quadrivalent human papillomavirus vaccine in women from four nordic countries’, *EClinicalMedicine*, 23.

KNBS and ICF Macro (2015) *2014 KDHS Key Findings*. Rockville, Maryland: Kenya National Bureau of Statistics and ICF Macro.

Lee, S. *et al.* (2018) ‘Prediction of Cancer Patient Outcomes Based on Artificial Intelligence’, in *Artificial Intelligence-Scope and Limitations*. IntechOpen.

Lehtinen, M. *et al.* (2017) ‘Ten-year follow-up of human papillomavirus vaccine efficacy against the most stringent cervical neoplasia end-point—registry-based follow-up of three cohorts from randomized trials’, *BMJ Open*, 7(8), p. e015867.

Makau-Barasa, L. K. *et al.* (2020) ‘A review of Kenya’s cancer policies to improve access to cancer testing and treatment in the country’, *Health Research Policy and Systems*, 18(1), p. 2.

Mangioni, C. *et al.* (1999) ‘Concurrent platinum-based chemo- and radiotherapy for locally advanced cervical cancer: a new gold-standard treatment?’, *Annals of oncology : official journal of the European Society for Medical Oncology*, 10(6), pp. 647–648.

Maranga, I. O. *et al.* (2013) 'Analysis of factors contributing to the low survival of cervical cancer patients undergoing radiotherapy in Kenya', *PloS one*, 8(10), pp. e78411–e78411. doi: 10.1371/journal.pone.0078411.

McArdle, O. and Kigula-Mugambe, J. B. (2007) 'Contraindications to cisplatin based chemoradiotherapy in the treatment of cervical cancer in Sub-Saharan Africa', *Radiotherapy and Oncology*, 83(1), pp. 94–96.

McLeod, M. *et al.* (2011) 'Achieving equitable outcomes for Māori women with cervical cancer in New Zealand: health provider views', *The New Zealand medical journal*, 124(1334), pp. 52–62.

Mobadersany, P. *et al.* (2018) 'Predicting cancer outcomes from histology and genomics using convolutional networks', *Proceedings of the National Academy of Sciences*, 115(13), p. E2970.

MoH (2011) 'National Cancer Control Strategy 2011-2016'. Department of Non-Communicable Diseases, Ministry of Health, Kenya.

MoH (2013) 'National Guidelines for Cancer Management'. Nairobi, Kenya. Ministry of Health. Available at: https://knh.or.ke/wp-content/uploads/2017/08/National-Cancer-Treatment-Guidelines2.pdf

MoH (2017) 'National Cancer Control Strategy 2017-2022'. Department of Non-Communicable Diseases, Ministry of Health, Kenya.

MoH, KNBS and WHO (2015) 'Kenya STEPwise Survey for Non Communicable Diseases Risk Factors 2015 Report.' Ministry of Health, Division of Non-Communicable Diseases, KNBS and WHO.

Mohile, S. G. and Magnuson, A. (2013) 'Comprehensive geriatric assessment in oncology', *Cancer and Aging*, 38, pp. 85–103.

Morris, B. J. *et al.* (2019) 'Does Male Circumcision Reduce Women's Risk of Sexually Transmitted Infections, Cervical Cancer, and Associated Conditions?', *Frontiers in public health*, 7, pp. 4–4.

Morris, M. *et al.* (1999) 'Pelvic Radiation with Concurrent Chemotherapy Compared with Pelvic and Para-Aortic Radiation for High-Risk Cervical Cancer', *New England Journal of Medicine*, 340(15), pp. 1137–1143.

Mosha, D. *et al.* (2009) 'Factors associated with management of cervical cancer patients at KCMC Hospital, Tanzania: a retrospective cross-sectional study', *Tanzania Journal of Health Research*, 11(2), pp. 70–74.

Murillo, R. and Ordóñez- Reyes, C. (2019) 'Human papillomavirus (HPV) vaccination: from clinical studies to immunization programs', *International Journal of Gynecologic Cancer*, 29(8), p. 1317.

Mwaka, A. D. *et al.* (2016) 'Social, demographic and healthcare factors associated with stage at diagnosis of cervical cancer: cross-sectional study in a tertiary hospital in Northern Uganda', *BMJ Open*, 6(1), p. e007690.

NCI (2012) 'What you need to know about cervical cancer'. Rockville, Maryland, National Cancer Institute.

Nwachukwu, C. R., Mayadev, J. and Viswanathan, A. N. (2018) 'Concurrent Chemoradiotherapy for Stage IIIB Cervical Cancer—Global Impact Through Power', *JAMA Oncology*, 4(4), pp. 514–515.

Obi, S. and Ozumba, B. (2008) 'Cervical cancer: Socioeconomic implications of management in a developing nation', *Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology*, 28, pp. 526–8.

O'Keefe, E. B., Meltzer, J. P. and Bethea, T. N. (2015) 'Health disparities and cancer: racial disparities in cancer mortality in the United States, 2000–2010', *Frontiers in public health*, 3, p. 51.

ONS (2019) 'Cancer survival in England - adults diagnosed'. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed

O'Shaughnessy, J. *et al.* (1991) 'Commentary concerning demonstration of safety and efficacy of investigational anticancer agents in clinical trials', *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, 9(12), pp. 2225–2232.

Owusu, C. and Berger, N. A. (2014) 'Comprehensive geriatric assessment in the older cancer patient: coming of age in clinical cancer care', *Clinical Practice (London, England)*, 11(6), p. 749.

Paesmans, M. (2012) 'Prognostic and predictive factors for lung cancer', *Breathe*, 9(2), p. 112.

Pearcey, R. *et al.* (2007) 'Impact of Adoption of Chemoradiotherapy on the Outcome of Cervical Cancer in Ontario: Results of a Population-Based Cohort Study', *Journal of Clinical Oncology*, 25(17), pp. 2383–2388.

Pecorelli, S. (2009) 'Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium', *International Journal of Gynecology & Obstetrics*, 105(2), pp. 103–104.

Peters, W. A. *et al.* (2000) 'Concurrent Chemotherapy and Pelvic Radiation Therapy Compared With Pelvic Radiation Therapy Alone as Adjuvant Therapy After

Radical Surgery in High-Risk Early-Stage Cancer of the Cervix', *Journal of Clinical Oncology*, 18(8), pp. 1606–1613.

Repetto, L. and Balducci, L. (2002) 'A case for geriatric oncology', *The Lancet Oncology*, 3(5), pp. 289–297.

Roehrich, J. K., Lewis, M. A. and George, G. (2014) 'Are public–private partnerships a healthy option? A systematic literature review', *Social Science & Medicine*, 113, pp. 110–119.

Rose, P. G. *et al.* (1999) 'Concurrent Cisplatin-Based Radiotherapy and Chemotherapy for Locally Advanced Cervical Cancer', *New England Journal of Medicine*, 340(15), pp. 1144–1153.

Rose, P. G. (2002) 'Chemoradiotherapy for cervical cancer', *European Journal of Cancer*, 38(2), pp. 270–278.

Sankaranarayanan, R. *et al.* (2005) 'A critical assessment of screening methods for cervical neoplasia', *Alliance for Cervical Cancer Prevention: Shifting the Paradigm*, 89, pp. S4–S12.

Sankaranarayanan, R. *et al.* (2011) 'An overview of cancer survival in Africa, Asia, the Caribbean and Central America: The case for investment in cancer health services', *IARC scientific publications*, 162, pp. 257–91.

Schiffman, M. and Kjaer, S. K. (2003) 'Chapter 2: Natural History of Anogenital Human Papillomavirus Infection and Neoplasia', *JNCI Monographs*, 2003(31), pp. 14–19.

Scott, S. *et al.* (2013) 'The model of pathways to treatment: conceptualization and integration with existing theory', *British journal of health psychology*, 18(1), pp. 45–65.

Shanta, V. *et al.* (2010) 'Evolution in the Management of Locally Advanced Cervical Cancer: The Experience of Cancer Institute (WIA), Chennai, India', *Asian Pacific journal of cancer prevention : APJCP*, 11, pp. 1091–8.

Somi, M. *et al.* (2012) 'Evaluation of Treatment and Survival Rates in Patients with Esophageal Cancer Referred to Imam Khomeini Hospital, Tabriz, Iran', *Govaresh*, 17(1), pp. 33–38.

Sourdet, S. *et al.* (2020) 'Impact of the comprehensive geriatric assessment on treatment decision in geriatric oncology', *BMC Cancer*, 20(1), p. 384.

Spinner, C. *et al.* (2019) 'Human Papillomavirus Vaccine Effectiveness and Herd Protection in Young Women', *Pediatrics*, 143(2), p. e20181902.

Stefan, D. C. (2015) 'Cancer Care in Africa: An Overview of Resources', *Journal of Global Oncology*, 1(1), pp. 30–36.

Thomas, G. M. (2000) 'Concurrent chemotherapy and radiation for locally advanced cervical cancer: The new standard of care', *Gynecologic Cancer: Evolving Management Issues*, 10(1), pp. 44–50.

Tian, T. *et al.* (2020) 'Comparison of survival outcomes of locally advanced cervical cancer by histopathological types in the surveillance, epidemiology, and end results (SEER) database: a propensity score matching study', *Infectious Agents and Cancer*, 15(1), p. 33.

UICC (2008) 'Access to cancer drugs. A UICC position paper, revision 2008/2009'. International Union Against Cancer. Retrieved from http://www.uicc.org/templates/uicc/pdf/special20reports/access_to_cancer_drugs_uicc.pdf

University of Zimbabwe and JHPIEGO (1999) ‘Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting. University of Zimbabwe/JHPIEGO Cervical Cancer Project’, *Lancet (London, England)*, 353(9156), pp. 869–873.

Vaccarella, S. *et al.* (2013) ‘Worldwide trends in cervical cancer incidence: Impact of screening against changes in disease risk factors’, *European Journal of Cancer*, 49(15), pp. 3262–3273.

Vaccarella, S. *et al.* (2017) ‘Cervical cancer in Africa, Latin America and the Caribbean and Asia: Regional inequalities and changing trends’, *International journal of cancer*, 141(10), pp. 1997–2001.

Vale, C. *et al.* (2010) ‘Substantial Improvement in UK Cervical Cancer Survival with Chemoradiotherapy: Results of a Royal College of Radiologists’ Audit’, *Clinical oncology (Royal College of Radiologists (Great Britain))*, 22, pp. 590–601. doi: 10.1016/j.clon.2010.06.002.

Vanderpuye, V. *et al.* (2019) ‘Cancer care workforce in Africa: perspectives from a global survey’, *Infectious Agents and Cancer*, 14(1), p. 11.

Walboomers, J. M. M. *et al.* (1999) ‘Human papillomavirus is a necessary cause of invasive cervical cancer worldwide’, *The Journal of Pathology*, 189(1), pp. 12–19.

Walter, F., Webster, A. and Scott, S. (2011) ‘The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis’, *J Health Ser Res Policy*, 10.

Wambalaba, F. W. *et al.* (2019) ‘Prevalence and capacity of cancer diagnostics and treatment: a demand and supply survey of health-care facilities in Kenya’, *Cancer Control*, 26(1), p. 1073274819886930.

Wang, W. *et al.* (2017) 'Outcome and toxicity of radical radiotherapy or concurrent Chemoradiotherapy for elderly cervical cancer women', *BMC Cancer*, 17(1), p. 510.

Wassie, M. *et al.* (2019) 'Survival status and associated factors of death among cervical cancer patients attending at Tikur Anbesa Specialized Hospital, Addis Ababa, Ethiopia: a retrospective cohort study', *BMC Cancer*, 19(1), p. 1221.

Wedding, U. *et al.* (2007) 'Tolerance to Chemotherapy in Elderly Patients with Cancer', *Cancer control : journal of the Moffitt Cancer Center*, 14, pp. 44–56.

Whitney, C. W. *et al.* (1999) 'Randomized Comparison of Fluorouracil Plus Cisplatin Versus Hydroxyurea as an Adjunct to Radiation Therapy in Stage IIB-IVA Carcinoma of the Cervix With Negative Para-Aortic Lymph Nodes: A Gynecologic Oncology Group and Southwest Oncology Group Study', *Journal of Clinical Oncology*, 17(5), pp. 1339–1339.

WHO (2002) 'National cancer control programmes : policies and managerial guidelines'. Retrieved from: https://apps.who.int/iris/handle/10665/42494.

WHO (2014) 'Comprehensive cervical cancer control: A guide to essential practice. Second Edition'. World Health Organization. Retrieved from https://apps.who.int/iris/bitstream/handle/10665/144785/9789241548953_eng.pdf;jsessionid=3842300CBFD70D064569683E12A5CE97?sequence=1

Whyle, E. and Olivier, J. (2016) 'Models of public-private engagement for health services delivery and financing in Southern Africa: A systematic review', *Health Policy and Planning*, 13, pp. 1515–1529. doi: 10.1093/heapol/czw075.

Woodman, C. B. J., Collins, S. I. and Young, L. S. (2007) 'The natural history of cervical HPV infection: unresolved issues', *Nature Reviews Cancer*, 7(1), pp. 11–22..

Yalman, D. *et al.* (2003) ‘Prognostic factors in definitive radiotherapy of uterine cervical cancer’, *European journal of gynaecological oncology*, 24(3–4), pp. 309–314.

Yang, J. *et al.* (2019) ‘Effect of radiotherapy on the survival of cervical cancer patients: an analysis based on SEER database’, *Medicine*, 98(30).

Zapka, J. G. *et al.* (2003) ‘A Framework for Improving the Quality of Cancer Care’, *Cancer Epidemiology Biomarkers & Prevention*, 12(1), p. 4.

APPENDICES

Appendix I: Top 10 Estimated Global and Africa Cancer Statistics for 2018

	Estimated New Cases		Estimated Deaths	
	Male	**Female**	**Male**	**Female**
WORLDWIDE	Lung	Breast	Lung	Breast
	1,377,500	2,081,200	1,188,000	630,000
	Prostate	Colorectum	Liver	Lung
	1,282,500	817,000	550,800	579,600
	Colorectum	Lung	Stomach	Colorectum
	1,035,500	722,400	513,000	399,000
	Stomach	Cervix Uteri	Colorectum	Cervix Uteri
	684,000	567,600	486,000	315,000
	Liver	Thyroid	Prostate	Stomach
	598,500	438,600	361,800	273,000
	Bladder	Corpus Uteri	Oesophagus	Liver
	427,500	378,400	356,400	235,200
	Oesophagus	Stomach	Pancreas	Pancreas
	399,500	352,600	226,800	205,800
	Non- Hodgkin lymphoma	Ovary	Leukemia	Ovary
	285,000	292,400	178,200	184,800
	Kidney	Liver	Bladder	Oesophagus
	256,500	240,800	151,200	151,200
	Leukemia	Non- Hodgkin lymphoma	Non-Hodgkin lymphoma	Leukemia
	247,000	223,600	145,800	130,200
	Others	Others	Others	Others
	2,907,000	2,485,400	1,242,000	970,200
	Estimated New Cases		**Estimated Deaths**	
	Male	**Female**	**Male**	**Female**
AFRICA	Prostate	Breast	Liver	Cervix Uteri
	80,971	168,690	42,786	81,687
	Liver	Cervix Uteri	Prostate	Breast
	43,530	119,284	42,298	74,072

	Colorectum	Colorectum	Lung	Liver
	30,650	31,196	27,531	20,776
	Lung	Ovary	Colorectum	Colorectum
	28,310	21,925	20,254	19,780
	Non-Hodgkin Lymphoma	Non-Hodgkin Lymphoma	Non-Hodgkin Lymphoma	Ovary
	27,032	21,555	18,879	16,702
	Kaposi Sarcoma	Liver	Stomach	Non-Hodgkin Lymphoma
	20,714	21,249	15,645	13,516
	Bladder	Leukemia	Oesophagus	Stomach
	20,368	14,304	15,444	13,062
	Stomach	Stomach	Leukemia	Oesophagus
	17,025	14,123	13,813	12,259
	Leukemia	Thyroid	Kaposi Sarcoma	Leukemia
	16,410	14,033	11,486	12,021
	Oesophagus	Corpus Uteri	Bladder	Lung
	15,828	12,919	10,982	10,217
	Others	Others	Others	Others
	145,718	169,338	97,413	102,864

Source: GLOBOCAN 2018

Appendix II: Top 5 Estimated New Cancer Cases and Deaths in Kenya for the Year 2018

Estimated New Cases			Estimated Deaths		
Male	**Female**	**Total**	**Male**	**Female**	**Total**
Prostate 2864	Breast 5985	Breast 5985	Oesophagus 2390	Cervix uteri 3286	Oesophagus 4351
Oesophagus 2384	Cervix Uteri 5250	Cervix Uteri 5250	Prostate 1663	Breast 2553	Cervix uteri 3286
Colorectum 1134	Oesophagus 1996	Oesophagus 4380	Stomach 995	Oesophagus 1961	Breast 2553
Kaposi Sarcoma 1070	Colorectum 1182	Prostate 2864	Liver 752	Stomach 1073	Stomach 2048
Non-Hodgkins Lymphoma 1064	Stomach 1099	Colorectum 2316	Colorectum 735	Ovary 765	Prostate 1663

Source: GLOBOCAN 2018

Appendix III: A Comparison of the Important Survival Outcomes

OUTCOME	ADVANTAGES	DISADVANTAGES
Overall survival (OS)	• Universally accepted direct measure of benefit • Easily measured • Precisely measured	• May involve larger studies • May be affected by crossover therapy and sequential therapy • Includes non- cancer deaths
Disease- Free Survival (DFS)	• Smaller sample size and shorter follow-up necessary compared with survival studies	• Not statistically validated as surrogate for survival in all settings • Not precisely measured; subject to assessment bias, particularly in open-label studies • Definitions vary among studies
Progression- Free Survival (includes all deaths) or **Time to Treatment Failure** (deaths before progression censored)	• Smaller sample size and shorter follow-up necessary compared with survival studies • Measurement of stable disease included • Not affected by crossover or subsequent therapies • Generally based on objective and quantitative assessment	• Not statistically validated as surrogate for survival in all settings Not precisely measured; subject to assessment bias particularly in open-label studies • Definitions vary among studies Frequent radiological or other assessments • Involves balanced timing of assessments among treatment arms

Adapted from FDA, 2007

Appendix IV: Epi Info Questionnaire

Patient Study ID
1234567

PATIENT DEMOGRAPHICS

Patient Specific Data

Identifiable patient data included for purposes of triangulating data within and across hospital departments.

q1	Patient Name ***(Full names as provided within the medical record)***	
q2	Hospital Name	
q3	Medical Record ID ***(Provide hospital number for the first source record)***	
q4	Date of birth ***(write 99 if day or month not known, 9999 if year not known)***	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ dd mm yyyy
q5	Age or approximate age ***(As reported within the medical record)***	⌊_⌋⌊_⌋ years

q7	Highest level of education completed?	**Circle only one response** 1 None 2 Primary

Marital Status

q6	Which is the patient's marital status?	**Circle only one response** 1 Never Married/Single 2 Married 3 Divorced 4 Widowed 9 Unknown

Education & literacy

		3 Post- primary/Vocational 4 Secondary/A- Level 5 College (Middle Level) 6 University 9 Unknown

Occupation

q8	What does the patient do for a living? ***(Write down the patient's occupation as documented in the social history)***	……

Residence

q9	In which former administrative province does the patient reside?	**Circle only one response** 1 Central 2 Coast 3 Eastern 4 Nairobi 5 North Eastern 6 Nyanza 7 Rift- Valley 8 Western 9 Unknown
q10	Specify the patient's area of residence as documented in their medical record? ***(this can include country of origin, city, district, town and/or village)***	…….

Parity

q11	Does the patient have any children?	Yes 1 No 2 Unknown 9 **No/Unknown→ 0**
q11a	If yes, how many children does the patient have?	⌊__⌋⌊__⌋

ACCESS TO PREVENTIVE HEALTH SERVICES FOR CERVICAL CANCER

Pap Smear History

q12	Has the patient ever had a Pap Smear?	Yes 1 No 2 Unknown 9 **No/Unknown→ 0**
q12a	If yes, please provide details of the patient's last Pap Smear? (i.e. date and place)	**…….**

HIV Status

q13	What is the patient's HIV status?	Yes 1 No 2 Unknown 9

PATIENT DIAGNOSTICS

Diagnosis

q1	Date of diagnostic testing ***(write 99 if day or month not known, 9999 if year not known)***	⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋ ⌊__⌋⌊__⌋⌊__⌋⌊__⌋ dd mm yyyy	
q1	Method of diagnosis ****Biopsy refers to punch biopsy, LEEP, endocervical curettage or cone biopsy***	**Select all applicable options** Lab test (Pap Smear) Cervical exam (Colposcopy) Tissue sample (Biopsy) Digital vaginal examination	1 → **q16a** 2 → **q16b** 3 → **q16c** 4 → **016d**
q1	**Diagnostic test results:**	**Write complete details of each diagnostic test result**	
q16a	Results of lab test (Pap Smear)	…….	
q16 b	Results of cervical exam (Colposcopy)	…….	
q16c	Results of tissue sample (Biopsy)	…….	
q16 d	Results of digital vaginal examination (DVE)	…….	

Staging of Disease

q17	Method of Staging	**Select all applicable options** Chest X-Ray CT Scan MRI Examination under anesthesia	1 → **0** 2 → **q18b** 3 → **q18c** 4 → **q18d**
q18	**Reports of clinical staging reports**	**Write complete details of each staging test result**	
q18a	Chest X-Ray	……	
q18b	CT Scan	……	
q18c	MRI	……	
q18d	Examination under anesthesia (EUA)	……	
q19	Stage of disease at diagnosis ***Based on the pre-2009 FIGO classification system for cervical cancer***	**Circle only one response** Carcinoma In Situ IA1 IA2 IB1 IB2 IIA1 IIA2 IIB	 1 2 3 4 5 6 7 8

		IIIA	9
		IIIB	10
		IVA	11
		IVB	12

Referral Details

q20	Was the patient referred for treatment at the current facility?	Yes 1 No 2 **no → q22**
q21	If yes, from which facility were they referred?	**…….**

Co-morbidity

q22	List any pre-existing conditions the patient may have?	**…….**

q2	Provide the date when treatment commenced ***(write 99 if day or month not known, 9999 if year not known)***	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ dd mm yyyy
q2	Provide the stage of disease at the start of treatment	**Circle only one response** Carcinoma In Situ 2 IA1 3 IA2 4 IB1 5 IB2 6 IIA1 7 IIA2 8 IIB 9 IIIA 10 IIIB 11 IVA 12 IVB
q2	Is the stage of disease at the start of treatment different from the stage of disease at diagnosis?	Yes 1 No 2 **no → q27**

q2	If yes, please provide details of the stage at treatment.	**…….**	
q2	Calculated 5-year mark (date) since treatment was initiated ***(write 99 if day or month not known)***	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ dd mm yyyy	
q2	Patient status at the 5-year mark (date)	**Circle only one response** Alive at 5 years Dead Loss to follow-up (LTFU)	1 2 → **q29** 3 → **00**

q2	If the patient's status is dead, provide the date of death ***(write 99 if day or month not known)***	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ dd mm yyyy
q3	If patient's status is LTFU, provide the date the patient was last seen ***(write 99 if day or month not known)***	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ dd mm yyyy

PATIENT TREATMENT

Treatment Details

This section of the Epi Info database is designed as a form within the larger data entry form, and allows for multiple and unlimited entries to facilitate detailed documentation of each patient's treatment and care.

Visit number ***Refers to both one-day clinic***	⌊_⌋⌊_⌋

appointments and each week of a hospital admission.	
Date of hospital visit/Date of Admission ***In the case of multiple week admissions, additionally serves as the first day of the week being summarized into a visit.***	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ dd mm yyyy
Date of discharge (Admissions Only) ***For patients admitted for multiple weeks, this date also marks the end of each week's summarized entry into single visit.***	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ dd mm yyyy
Visit details ***For patients admitted for multiple weeks, each week is summarized into a single visit.***	…….
Patient progress ***Any comments about treatment received or missed and the patient's health are documented in this section.***	…….
Date of next visit ***This date indicates the next scheduled one-day clinic appointment.*** ***For multiple week admissions, this date also represents the first day in the next week to be summarized into a single visit.***	⌊_⌋⌊_⌋ ⌊_⌋⌊_⌋⌊_⌋⌊_⌋ dd mm yyyy