A REVIEW OF RADICAL HYSTERECTOMY AS PRIMARY TREATMENT FOR EARLY STAGE CERVICAL CANCER AT KNH 2013-2018

INVESTIGATOR

DR WYCLIFFE AKIKUVI MUSALIA

H117/27888/2019

A PROJECT DISSERTATION SUBMITTED TO THE UNIVERSITY OF NAIROBI,

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY IN PARTIAL

FULFILMENT FOR FELLOWSHIP IN GYNECOLOGIC ONCOLOGY

2021

DECLARATION

This research is original work and has not been presented for academic award in any other University References I hande to other work has been indicated.

Signature:..... **Date:** 10.11.21

DR. WYCLIFFE Akikuvi **MUSALIA, MBChB, MMed (Obs/Gyn)**

APPROVAL OF SUPERVISORS

This thesis has been submitted with the approval of my supervisors.

Signature:..... **Date:** 29/11/21

PROF S.B. OJWANG (MD, M.Med, MPH, Fell Gyn Onc)

Professor of Obstetrics and Gynecology

Department of Obstetrics and Gynecology, University of Nairobi, Kenya

Signature ..... Date 15.11.2021

DR. ALFRED OSOTI (MBCHB, M.Med , MPH, PhD)

Senior Lecturer,

Department of Obstetrics and Gynaecology, University of Nairobi, Kenya

Affiliate Associate Professor,

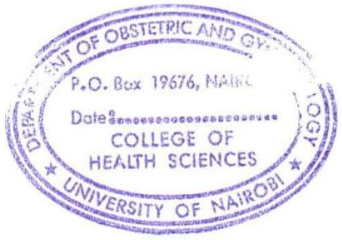
Department of Global Health, University of Washington

II

CERTIFICATE OF AUTHENTICITY

This is to certify that this thesis is the original work of Dr Wycliffe Akikuvi Musalia, Fellow in Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Nairobi, registration number H117/27888/2019. The research thesis was carried out in the Department of Obstetrics and Gynecology, School of Medicine, College of Health Sciences. It has not been presented in any other university for award of a degree/ fellowship.

Signature  Date 15/4/21



PROF EUNICE CHESEREM

MBChB, M.Med, PGDRM

Associate Professor of Obstetrics and Gynecology

Consultant Obstetrician and Gynecologist

Chair, Department of Obstetrics and Gynecology, University of Nairobi

ACKNOWLEGMENTS

Foremost, I wish to acknowledge Professor SBO Ojwang our teacher and mentor for his dedication and guidance throughout the fellowship training. Professor Ojwang taught us with a passion. He shared with us knowledge not only from his vast clinical experience, but also life lessons, painstakingly moulding us into gynecologic-oncologists and better members of society. We are very grateful.

I also wish to thank the Chair, Department of Obstetrics and Gynaecology, Professor Omondi Ogutu under whose leadership this fellowship program was started. Being the Chair, he has stood by our side as the pioneer class and addressed the challenges we faced and thus enabling us to complete the training program successfully.

I do acknowledge my sponsor, Kenyatta National Hospital, for granting me the opportunity to pursue this course enabling me actualize my career aspiration for sub-speciality training in gynecological oncology.

The completion of this research thesis would not have been possible without the input of my supervisors. I therefore thank Professor Alfred Osoti who worked tirelessly together with Professor Ojwang at all stages to ensure that the proposal and thesis write up was completed in time. I also thank Dr. Gamba, Dr Busra, Mr Opiyo and Dr Wambua my research assistants and statistician for the study.

I thank my colleagues in the fellowship program for sharing their knowledge and skills with me. Your support and team-work made adult learning a lot of fun.

Lastly, I give thanks to God and my family. To my dear wife Caroline and our lovely children Humphrey, Shanelle, Sheryl, Shelmith and Christine; the love and encouragement you gave me meant a lot. Your prayers, magical smiles and laughter, gave me the hope I needed to complete the course and to continue striving on.

DEDICATION

I dedicate this thesis study to the late Dr Amin and the women of Kenya with invasive cervical cancer. Dr Amin, we started the journey of this fellowship together but the hand of death separated us. Your memory and legacy will be with us forever.

TABLE OF CONTENTS

APPROVAL BY SUPERVISORS ..... *Error! Bookmark not defined.*

CERTIFICATE OF AUTHENTICITY ..... *II*

ACKNOWLEGMENTS ..... *IV*

Table of Contents ..... *VI*

LIST OF ABBREVIATIONS ..... *VIII*

LIST OF FIGURES AND TABLES ..... *IX*

ABSTRACT ..... *XI*

CHAPTER 1. INTRODUCTION *1*

1.1 Global incidence **1**

1.2 Local data on disease burden and mortality **1**

1.3 Diagnosis and Staging of Cervical Cancer **2**

1.4 Treatment of cervical cancer **2**

1.5 Surgery for cervical cancer **2**

1.6 Radical hysterectomy **3**

1.7 Types hysterectomy **3**

CHAPTER 2. LITERATURE REVIEW *5*

2.1 History of radical hysterectomy **5**

2.2 Safety of Radical Hysterectomy and associated Complications **6**

2.3 Preoperative Assessment and Case Selection **6**

2.4 Neo-adjuvant chemotherapy (NACT) followed by surgery in bulky early stage cervical cancer 7

2.5 Adjuvant (Complementary) Chemoradiation after Radical Hysterectomy **7**

2.6 Survival after radical hysterectomy for invasive cervical cancer **8**

2.7 Radical hysterectomy in Kenya **8**

2.8 CONCEPTUAL FRAMEWORK **9**

2.8.1 Conceptual Framework: Narrative 9

2.8.2 Conceptual Framework: Diagramatic Presentation 10

2.9 STUDY JUSTIFICATION **11**

2.10 STUDY QUESTION **11**

2.11 STUDY OBJECTIVES **11**

2.11.1 Broad Objective 11

2.11.2 Specific objectives 12

CHAPTER 3. METHODOLOGY *12*

3.1 STUDY DESIGN **12**

3.2 STUDY SITE AND SETTING 12
3.3 STUDY POPULATION 14
3.3.1 Inclusion Criteria 14
3.3.2 Exclusion Criteria 14
3.4 SAMPLE SIZE JUSTIFICATION 15
3.5 SAMPLING PROCEDURE 16
3.6 DATA COLLECTION AND MANAGEMENT 16
3.7 DATA ANALYSIS 17
De-identified data was analyzed and summarized as per objective. 17
3.8 ETHICAL CONSIDERATIONS 17
3.9 STUDY LIMITATIONS AND DELIMITATIONS 18
CHAPTER 4. STUDY RESULTS 19
4.1 Social Demographic Characteristics 20
4.2 Preoperative Assessment 22
4.2.1 Clinical Characteristics 22
4.2.2 Preoperative Imaging 24
4.3 SURGICAL OUTCOMES 25
4.3.1 Surgical Approach & Complications 25
4.3.2 Histopathologic findings after radical hysterectomy 26
4.3.3 Complimentary treatment after radical hysterectomy 28
4.4 SURVIVAL ANALYSIS 29
4.4.1 TWO-YEAR SURVIVAL ANALYSIS 30
4.4.2 Survival by FIGO clinical stage 31
4.4.3 FIVE YEAR SURVIVAL ANALYSIS 33
4.4.4 SURVIVAL BY HIV STATUS 34
CHAPTER 5. DISCUSSION 35
5.1 CONCLUSIONS 38
5.2 RECOMMENDATIONS 38
TIMELINES AND WORKPLAN 41
CHAPTER 6. References 42
CHAPTER 7. APPENDICES 47
APPENDIX I: DATA ABSTRACTION FORM 47
APPENDIX II: DUMMY TABLES 52
APPENDIX VII 62
VERBAL CONSENT FORM: CERVICAL CANCER RESEARCH 62

LIST OF ABBREVIATIONS

ASCO: American Society of Clinical Oncology

ASGO: Asian Society of Gynecologic Oncology

CT SCAN: Computerized Tomography scanning

ESGO: European Society of Gynecologic Oncology

EORTC-GCG: European Organization for Research and Treatment of Cancer-Gynecological Cancer Group

ECOG: Eastern Cooperative Oncology Group

FIGO: International Federation of Gynecology and Obstetrics

GLOBOCAN: Global Cancer Incidence, Mortality and Prevalence

GLOBOCAN Kenya: Global Cancer Incidence, Mortality and Prevalence for Kenya

GOK: Government of Kenya

JGOG: Japanese Gynecologic Oncology Group

ICC: Invasive Cervical Cancer

KNH: Kenyatta National Hospital

MOH: Ministry of Health

MRI: Magnetic Resonance Imaging

NACT: Neoadjuvant Chemotherapy

NCCN: National Comprehensive Cancer Network

UON: University of Nairobi

PET SCAN: Positron Emission Tomography scanning

PLND: Pelvic Lymph Node Dissection

WHO: World Health Organization

LIST OF FIGURES AND TABLES

Figure 1: Diagrammatic Presentation of conceptual framework…..Page 09
Figure 2: Study flow chart…….....Page 18
Figure 3: Histogram on age distribution……..Page 20
Figure 4: Histogram on hemoglobin distribution……Page 22
Figure 5: Histogram on disease distribution by FIGO clinical stage distribution……...Page 22
Figure 6: Pie chart on preoperative imaging……...Page 23
Figure 7: Pie chart on surgical approach…….Page 24
Figure 8: Pie chart on acute complications ……Page 25
Figure 9: Pie chart on reasons for non-uptake of complimentary chemoradiation…….Page 28
Figure 10: Kaplan-Meyer overall survival curve……Page 30
Figure 11: Kaplan-Meyer survival curve by HIV status…….……Page 36
Table 1: Classification of Radical Hysterctomy……..Page 04
Table 2: Social demographic characteristics……...Page 19
Table 3: Age distribution and HIV status…..……..Page 20
Table 4: Preoperative clinical characteristics……Page 21
Table 5: Preoperative imaging and disease stage……...Page 23
Table 6: Complications after radical hysterectomy……Page 24
Table 7: Histologic types of cervical cancer after radical hysterectomy……Page 25
Table 8: Proportion of women with risk factors for disease recurrence……Page 26
Table 9: Proportion of women with high risk factors for recurrence by stage…….….Page 26
Table 10: Proportion of women with intermediate risk factors for recurrence…..…...Page 27
Table 11: Proportion of women with indication for complimentary treatment……Page 27
Table 12: Overall survival in months……Page 29
Table 13: Two-year survival by FIGO clinical stage of disease…… ……..…Page 31
Table 14: Five-year survival by FIGO clinical stage of disease……...……Page 34
Table 15: Study budget……..Page 41
Table 16: Workplan and Timelines……Page 42

OPERATIONAL DEFINITIONS

Preoperative assessment: Refers to the clinical, laboratory and radiological evaluation of a patient to determine suitability for surgery

Complementary treatment: Additional treatment after surgery or before surgery for cancer to reduce incidence of disease recurrence

Sedli's Criteria: A scoring tool based on histopathologic findings after radical hysterectomy for invasive cervical cancer to determine women who may benefit from complementary chemoradiation

Early stage cervical cancer: Invasive cervical cancer stage IA to IIA

Bulky early stage cervical cancer: Invasive cervical cancer whose greatest gross diameter in size is > 4 centimeters (revised FIGO stage IB3, IIA2)

Primary treatment: The preferred first option of definitive treatment offered to a patient with invasive cervical cancer.

Concurrent chemoradiation: The administration of chemotherapy together with radiotherapy in the treatment of invasive cervical cancer.

Neoadjuvant Chemotherapy: The initiation of chemotherapy before radical surgery in bulky early stage cervical cancer.

Survival outcome: Duration of life measured from the date of radical hysterectomy as primary treatment for invasive cervical cancer

ABSTRACT

Background

Invasive cervical cancer (ICC) is the leading cause of cancer death among women in Africa and other developing countries of the world. In Kenya, cancer of the cervix is now the leading cause of cancer death and the second most prevalent cancer among females after breast cancer.

Primary surgery or primary chemoradiation alone; or in combination with chemotherapy are utilized for definitive management of invasive cervical cancer. Primary surgical treatment is indicated for early-stage cervical cancer stage IA to IIA. Studies in the developed countries have shown that radical hysterectomy for early-stage ICC is relatively safe and is associated with very good outcomes. Overall five-year survival exceeds 90% for squamous and adenocarcinoma histologic types. Survival is however poor for the non-squamous/adenocarcinoma histologic types at 65%.

The surgical outcomes and survival of women treated surgically for cervical cancer in our setting is however unknown. In this study, we reviewed the medical records of women who had radical hysterectomy as primary treatment for early-stage cervical cancer at KNH between January 2013 to December 2018; and describe the preoperative assessment, surgical outcomes and survival of the cases.

Study Objectives: To determine the preoperative assessment, complications, complementary therapies and survival of women treated primarily by radical hysterectomy for invasive early stage cervical cancer at KNH between 2013-2018.

Methodology

This was a descriptive retrospective cohort study of women who had radical hysterectomy as primary treatment for early-stage cervical cancer at KNH between January 2013 to December 2018. Data from eligible cases was obtained by a questionnaire guided review of files retrieved from the archives of the health records department, KNH. De-identified data was entered on the data abstraction form, stored in an excel database, cleaned and exported to Stata v13 (Stata Corp, College Station, TC, USA) for analysis. Descriptive statistics on social-demographics, preoperative assessment and surgical outcomes were summarized. Means (SD) for continuous data were determined, while categorical data is described in proportions. Kaplan Meier curves

were used to evaluate the survival of study participants. A p-value of <0.05 was considered statistically significant along with the associated 95% confidence interval.

Study Results

A total of 72 files of women who had radical hysterectomy between 2013-2018 were retrieved, 69 were found to be eligible for study.

The mean age of study participants was 44.0 years. Forty three percent were HIV positive of whom 92% were on HAART.

Histologically, most were of squamous cell carcinoma (63.8%) and were clinically staged as FIGO stage IB1 and IB2 (54 %).

Ultrasound (33%) was the commonest preoperative imaging assessment of disease status.

Radical hysterectomy was safe, with 59.4% and 88.4% of cases having no acute or chronic complication respectively. Peri-operative mortality rate was 1.4%.

Almost half of the women (52.2%) were found to have intermediate and high-risk factors for disease recurrence as per Sedli's criteria. More than half (55.6%) of these cases did not receive adjuvant complimentary chemoradiation.

The mean overall survival after radical hysterectomy as primary treatment for ICC was 82.5 months. The 2-year survival rate was 93.3% while 5-year survival was 86.8%.

Conclusions

Radical hysterectomy at KNH as primary treatment for early-stage ICC during the period 2013-2018 was safe with comparable and acceptable outcomes. Efforts need to be made to improve rational preoperative imaging as well as uptake of complimentary chemoradiation after surgery when indicated.

CHAPTER 1. INTRODUCTION

1.1 Global incidence

Globally, cervical cancer is fourth leading cause of cancer death in females (1). The incidence of the disease however varies with level of development. It is less common in the developed countries (Western Europe, Canada, United States, Australia and China) due to Human Papilloma Virus (HPV) vaccination and robust screening programs combining cytology with HPV testing (1, 2). Higher prevalence and mortality are noted in less developed countries (Africa, Central America and India) due to lack of effective screening programs, limited vaccination and other social economic factors. In 2020, the World Health Organization (WHO) estimates that 570000 new cases of cervical cancer were reported while 311000 women died of the disease (2). Eastern Africa has the highest global incidence of the disease and associated mortality.

1.2 Local data on disease burden and mortality

Invasive Cervical Cancer (ICC) is the most common cause of cancer death and also the second most prevalent cancer among females after breast cancer in Kenya. It is the most common genital tract malignancy and it is estimated that 5336 new cases were diagnosed locally in 2020 while 3211 died of the disease (3,4). Most women in Kenya and Africa (60-90%) are usually diagnosed with advanced disease (stage III and IV) due to late presentation, ignorance and delay in diagnosis (5,6,7). High risk human papilloma viruses 16(45%), 18 (15%), 45(15.9%) are commonly found to be positive in women with invasive cervical cancer (8).

Screening for preinvasive disease and management of premalignant lesions remains poor across the African continent and the rest of the developing world (6,9). In Kenya, only 3.5% of women in the reproductive age report having regular cervical screening (9). The low uptake of screening services has been attributed to multiple factors including lack of an effective national screening program, poverty, ignorance and other social cultural factors (5).

Although there is no statistically significant difference in prevalence of cervical cancer among HIV positive women compared to HIV negative women in Kenya; HIV positive women with cervical cancer have been reported to be significantly younger, presenting with more advanced disease and to experience more treatment related toxicities (5, 10).

1.3 Diagnosis and Staging of Cervical Cancer

Women with invasive cervical cancer commonly present with abnormal vaginal bleeding or abnormal vaginal discharge. Patients with advanced disease may present with urinary symptoms, low back pain, renal failure and edema of lower limbs. Diagnosis is confirmed by histopathology from biopsy specimen of cervical lesion followed by staging and triaging to most optimal treatment.

Although previously FIGO 2009 recommended a clinical staging approach for cervical cancer without consideration of radiological findings to allow for comparison of outcomes of treatment between different centers irrespective of setting limitations on diagnostic imaging, this was not without fault.

Clinical staging alone is not very accurate in detecting parametrial, pelvic and para-aortic lymph node involvement. The revised FIGO staging of cervical cancer 2018 recommends the use of imaging by CT SCAN, MRI and even PET CT SCAN where feasible, to determine local and distant extent of the disease (11). The inclusion of findings on imaging in staging of the disease and planning treatment has now been adopted by many gynecologic oncology societies (12,13,14).

1.4 Treatment of cervical cancer

The treatment of cervical cancer is a multi-modal approach determined by stage of disease, institutional guidelines and context. Primary surgery or primary chemoradiation alone; or in combination with chemotherapy are utilized for definitive disease management (12,13,14) Primary chemoradiation is the mainstay treatment for locally advanced cervical cancer stage IIB to IV (12,13,14,15)

1.5 Surgery for cervical cancer

Primary surgical treatment is indicated for early stage cervical cancer stage IA1 to IIA (5,13,14). Surgery may also be used to manage isolated central recurrence confined to the cervix after primary chemoradiation. Vault recurrences after primary surgery may be treated by adjuvant chemoradiation or upper vaginectomy.

Access to safe radical surgery for cancer of the cervix in Kenya and Africa is limited by number of gynecologic-oncologists. Capacity building by establishment of gynecologic oncology treatment centers is now a priority for many African countries (39).

Many surgical procedures have been used in the treatment invasive cervical cancer. Local excisional procedures like large loop excisional biopsy, cone biopsy and trachelectomy may be used in management of early stage, non-bulky invasive cervical cancer when fertility conservation is a key consideration.

1.6 Radical hysterectomy

Radical hysterectomy has been the mainstay primary surgical treatment of early stage cervical cancer. It involves a variable degree of pelvic dissection that includes hysterectomy with a margin of vaginal cuff, parametrial resection plus pelvic and para-aortic lymph node dissection.

1.7 Types of hysterectomy

Better understanding of the spread of early stage cervical cancer has led to modifications in local dissection of parametrial tissues, vaginal cuff excision and ureteric/bladder dissection. The variations in the extent of this dissection has been classified into five classes of hysterectomy as described by Piver-Rutlegde-Smith (Table 1, page 4). Variations to this classification have been proposed by EORTC-GCG and Querlow-Morrow et al (20)

Class I to III hysterectomy are used in primary treatment of cervical cancer while class IV and V are generally indicated for patients with recurrent disease.
Class I is simple extra fascial hysterectomy with no pelvic node dissection. It is indicated for stage IA1 disease. All the other four classes (II to V) involve complete pelvic and para-aortic lymph node dissection

Modifications to the radical hysterectomy have also included dissection of the hypogastric nerve plexus to spare the sympathetic and parasympathetic supply to the bladder in order to limit the neurogenic bladder and sexual dysfunction associated with radical hysterectomy (21,22)

Table 1: Classifications of Radical Hysterectomy

Piver-Rutledge-Smith		EORTC-GCG		Querleu & Morrow	
Class I	Simple extra-fascial hysterectomy	Type I	Simple hysterectomy	Type A	Simple hysterectomy, uterosacral and cardinal ligaments resected very close to the corpus uteri, < 10mm of vaginal cuff margin
Class II	Modified Radical hysterectomy (Wertheims) Ureters dissected in the paracervical region but not resected from pubocervical ligament. Uterine art ligated beside and medial to the ureter. Medial half of uterosacral and cardinal ligaments resected. Removal of upper 1/3 vagina. PLND	Type II	Modified Radical hysterectomy Ureters dissected in the paracervical region and pubocervical ligament upto entry into the bladder. Uterine art are ligated in the medial half of parametria Medial half of uterosacral and cardinal ligaments resected. Removal of upper 1/3 vagina. PLND	Type B	Modified Radical hysterectomy BI: ureters de-peritonized to lateral side. No removal of lateral paracervical nodes. Medial half of uterosacral and cardinal ligaments resected. Removal of >10mm vagina margin(tumor/cervix) + PLND B2: AS ABOVE + removal of lateral cervical nodes
Class III	Classical radical hysterectomy(Meigs) Complete dissection of ureter & pubocervical ligaments upto entry into the bladder. Resection of cardinal and uterosacral ligaments at insertion on pelvic wall. Uterine artery ligated at origin from internal iliac art. Removal of upper 1/3 vagina + PLND	Type III	SAME AS CLASS III Piver-Rutledge- Smith	Type C	SAME AS CLASS III Piver-Rutledge- Smith Plus atleast 15-20mm vaginal margin C1: with preservation of autonomic nerves C2: with no preservation of autonomic nerves
Class IV	Like Class III plus Ligation of umbilical artery(superior vesical) and resection of upper ¾ of vagina		SAME AS CLASS IV	Type D	D1: All paracervical tissue together with hypogastric vessels excised up to pelvic bone with exposure of sciatic nerve roots. Ureter completely freed. D2: Excision of adjacent muscle and fascia
Class V	Resection of terminal ureter plus portion of bladder with ureteric reimplantation	Type V	SAME AS CLASS V		

CHAPTER 2. LITERATURE REVIEW

2.1 History of radical hysterectomy

Although, the first description of radical hysterectomy as a surgical procedure for cancer of the cervix was by Clark, a resident gynecology student of Howard Kelly at John Hopkins University in 1895; the procedure is linked in perpetuity to Wertheim of Vienna. In 1905, Wertheim published the outcomes of his first 270 patients who had radical hysterectomy and pelvic node dissection. The operative mortality rate in his series was 18% and significant surgical morbidity rate was 30%. This was mainly attributed to the laparotomy approach for pelvic and para-aortic node dissection; poor patient selection, lack of safe anesthesia, antibiotics and critical care support (16).

There were attempts at a retroperitoneal approach to node dissection. In 1901, Schauta described the vaginal radical hysterectomy with excellent parametrial dissection but this approach was found to be technically challenging at achieving complete pelvic and para-aortic node dissection (16, 17).

Following the advent of radiotherapy with the discovery of radium in early 1900, radical hysterectomy was abandoned in favor of radiation therapy as primary management for cancer of the cervix.

In 1950, Meigs of United States of America and Okabayashi of Japan re-popularized the procedure of radical hysterectomy after 50 years of inactivity (16).

Progressive Changes over the years

The advent of gynecologic oncology fellowships in the 1970s was associated with improved outcomes of radical hysterectomy as primary treatment for cervical cancer due to improved surgical skills.

Advances in technology and minimal access surgery has seen the development of laparoscopic and robotic radical hysterectomy as alternatives to the open abdominal approach. Recent meta-analysis of minimally invasive radical hysterectomy versus open approach has reported an increased incidence of recurrence and less progression free survival with the minimally invasive approach (17,18,19).

Today, proficient performance of radical hysterectomy is the benchmark of the gynecologic oncology surgeon (17).

Results of metanalysis on overall survival after surgery show that primary surgery for early stage cervical cancer is comparable to primary chemoradiation. Surgery however offers the benefit of reduced toxicities associated with pelvic radiation as well as preservation of ovarian endocrine function in women of reproductive age (12). Recent metanalysis shows that primary radical hysterectomy followed by complementary chemoradiation when indicated is associated with better progression free survival as well as overall survival in stage IB2-IIA disease (15).

2.2 Safety of Radical Hysterectomy and associated Complications

Radical hysterectomy has been associated with significant surgical morbidity. The rate of surgical complications has however declined over the years due to improved surgical safety, better patient selection and surgical skill competency. Bladder autonomic dysfunction is the commonest morbidity (16%), urinary infection (5.9%), lymphocyst formation (6.4%) and wound sepsis (3.5%). Surgical mortality is rare at 0.3%

Other acute complications are ureteric/ bladder injury, major pelvic vessel injury, hemorrhage and venous thrombosis. Late complications observed are ureteric obstruction, urinary fistulae and lymphedema of the lower limbs (23,24,25)

2.3 Preoperative Assessment and Case Selection

Bulky exophytic tumors which are confined to the cervix or upper third of vagina present a special challenge during primary surgical treatment. Bulky exophytic early stage cervical cancer has been defined as cervical disease FIGO stage ≥ IB2 to IIA; with greatest dimension of ≥4centimeters. The recognition of this entity has led to the revision of FIGO clinical staging 2009. Cervical cancer stage IB2 disease has been split to IB2 and IB3, while stage IIA now has IIA1 and IIA2(12).

Endophytic growth pattern is another entity that may present with deeply infiltrating tumor of the endocervix but with minimal visible tumor on the ectocervix on speculum examination. Primary surgical treatment of bulky early stage exophytic or endophytic tumors is technically more challenging. Histopathological examination of radical hysterectomy, pelvic and para-aortic node dissection specimens of these cases show a higher rate of close and positive margins, parametrial as well as node involvement (26). Evidence to support primary surgery or primary chemoradiation remains limited and more research is needed (27,28)

The use of imaging by CT SCAN, MRI and even PET CT SCAN where feasible, to determine the local and distant extent of the cervical disease is highly recommended (11).

The inclusion of findings on imaging in staging of the disease and in selecting cases for surgery is advisable.

2.4 Neo-adjuvant chemotherapy (NACT) followed by surgery in bulky early stage cervical cancer

A number of studies including randomized controlled trials (RCT) have shown the beneficial effect of NACT in management of cervical cancer. Use of NACT has been associated with reduced gross tumor size, micro-metastasis and improved vascularity in all stages of the disease. There is also improved surgical operability for bulky early stage cervical cancer when radical hysterectomy is considered as primary treatment after a course of NACT (29,30,31).

When NACT is considered for bulky early stage cervical cancer, three cycles of Cisplatin/Paclitaxel doublet every 21 days is the preferred regimen (32).

This approach is also particularly beneficial in settings where there are delays and limitations in initiating primary chemoradiation as a higher number of women with cervical disease are able to benefit from primary surgical treatment.

Where patients with bulky early stage cervical cancer opt for primary surgical treatment, consideration for NACT should be made by the primary surgeon.

2.5 Adjuvant (Complementary) Chemoradiation after Radical Hysterectomy

Chemoradiation is recommended after radical hysterectomy for early stage cervical cancer where intermediate and high-risk factors for disease recurrence are identified on histopathology.

88% of stage IB3 tumors treated by surgery are associated with risk factors for recurrence and require complementary chemoradiation (26).

The intermediate risk-factors associated with disease recurrence after surgery have been summarized in the Sedli's criteria for adjuvant chemoradiation after primary surgery for cancer of the cervix (Table 5)

Positive margins, parametrial and node involvement are termed as high-risk factors for disease recurrence and progression after radical surgery. The finding of any high-risk factor on histopathology merits the use of adjuvant chemoradiation as part of definitive treatment (5,13, 14,)

2.6 Survival after radical hysterectomy for invasive cervical cancer

Radical hysterectomy for early stage ICC is associated with very good outcomes. Overall five-year survival exceeds 90% in most of the studies for squamous and adenocarcinoma histologic types. Survival is however poor for the non-squamous/adenocarcinoma histologic types. These include small cell, neuroendocrine, clear cell, serous and sarcomatoid tumors. The survival in these cases ranges between 61%-67% (34,35,36,37)

The overall survival is dependent on stage. Five-year survival for stage I patients treated by radical hysterectomy approaches 100% while for stage III and IV patients treated by radiotherapy alone it is 49% and 25% respectively.

Lymph node status is the most important predictor of survival. Stage I patients with 1 positive node have an 85% five-year survival, this reduces to 75% with two positive nodes which is same as IIA2 with no nodes. Bulky tumors are also associated with increased risk of recurrence and poor survival (26,37).

2.7 Radical hysterectomy in Kenya

Radical hysterectomy as definitive primary treatment of cancer of the cervix has been practiced at KNH since the early 1970s. Itsura et al (38) reporting on their experience at Moi Teaching and Referral Hospital in Eldoret noted that; radical hysterectomy for operable early stage cervical cancer in HIV positive and negative women in Kenya is well tolerated with no increase in complications. Survival data was not reported.

In a prospective descriptive study on survival of women with cancer of the cervix managed by radiotherapy at KNH, Maranga et al reported a very low overall survival even for early stage disease. These poor outcomes were attributed to suboptimal administration of radiation therapy and disease under-staging (6). The survival of women treated primarily by surgery including radical hysterectomy at this institution remained unknown.

2.8 CONCEPTUAL FRAMEWORK

2.8.1 Conceptual Framework: Narrative

Survival after radical hysterectomy is influenced by many factors including individual patient characteristics and clinical stage of disease. Elderly patients with medical comorbidities tolerate surgery poorly as opposed to the younger women.

Good surgery begins with skillful patient selection.

In this study we describe the pre-operative assessment given to women with invasive cervical cancer treated primarily by radical hysterectomy during the study period. Using the data abstraction form, we determined the individual patient characteristics, clinical stage of disease before surgery as well as imaging done in selecting cases of invasive cervical cancer managed by radical hysterectomy. Data on the immediate and delayed complications of radical hysterectomy was also obtained.

We also reviewed the histopathology report to determine the proportion of patients in need of complementary chemoradiation after surgery and the overall uptake of this treatment.
The use of neoadjuvant chemotherapy (NACT) in bulky early-stage invasive cervical cancer to reduce the surgical operative morbidity noted with the increased tumor size is also described.
We also describe survival of the study participants.

2.8.2 Conceptual Framework: Diagrammatic Presentation

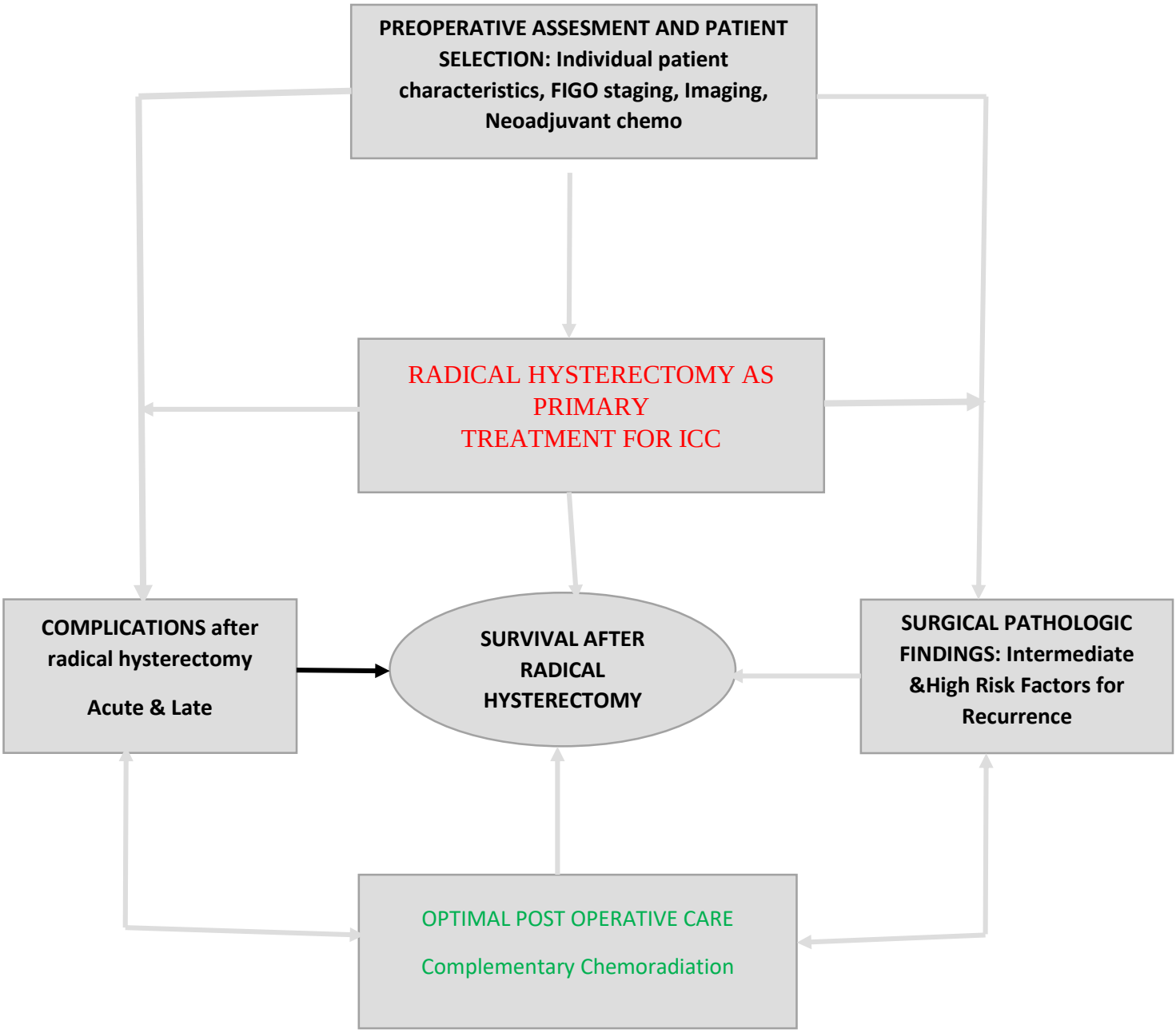


Figure 1: *Diagrammatic presentation of conceptual framework*

2.9 STUDY JUSTIFICATION

Although research on cervical cancer in Africa has increased steadily over the years, most of it has focused on screening and management of premalignant lesions. Studies on tertiary prevention (effective disease treatment and quality of life) are severely lacking (40). A study of survival of women with invasive cervical cancer treated by radiotherapy at KNH noted very poor outcomes even for stage I disease. This was attributed to inaccuracy of clinical staging and suboptimal treatment (6).

Clinical audits and reviews of previous surgeries are important process improvement tools for enhanced surgical safety and positive outcomes.

In this study we describe the preoperative assessment, operative complications and survival of cervical cancer patients treated primarily by radical hysterectomy at KNH between January 2013 to December 2018. We hope that the findings of this study will be useful in reviewing hospital preoperative standard operating procedures (SOPs) and in development of evidence based approaches that aid gynecologic oncologists and other clinical care providers while triaging patients to primary chemoradiation or surgery for early stage cervical cancer.

2.10 STUDY QUESTION

What is the preoperative assessment, surgical outcomes and survival of women treated by radical hysterectomy for early stage cervical cancer at KNH between January 2013 to December 2018?

2.11 STUDY OBJECTIVES

2.11.1 Broad Objective

To evaluate the preoperative assessment, complications, complementary therapies and survival of patients treated primarily by radical hysterectomy for early stage cervical cancer at KNH between January 2013 to June 2018.

2.11.2 Specific objectives

Among patients with early stage cancer of the cervix managed by radical hysterectomy as primary treatment between January 2013-December 2018:

1. To determine the preoperative clinical assessment and imaging
2. To establish the complications associated with radical hysterectomy
3. To determine the histopathologic findings on specimen of radical hysterectomy and pelvic node dissection
4. To describe the proportion of women who received adjuvant chemoradiation and neoadjuvant chemotherapy
5. To determine the two-year and five-year survival

CHAPTER 3. METHODOLOGY

3.1 STUDY DESIGN

This was a descriptive retrospective cohort study. The study population comprised of women with cancer of the cervix treated primarily by radical hysterectomy between January 2013 to June 2018. Files of these patients were retrieved and reviewed using a questionnaire to determine the preoperative assessment, surgical outcomes and survival of cases.

3.2 STUDY SITE AND SETTING

The study was conducted at the Information and Records Department, Kenyatta National Hospital (KNH) in Nairobi, Kenya between June 2020 to December 2020.

KNH is the largest referral hospital in Kenya and serves as the teaching hospital of the University of Nairobi and Kenya Medical Training College. Its catchment area is drawn from all over the country.

Female patients with reproductive and genital tract malignancies are managed by the Gynecologic Oncology Unit. The staff compliment of the unit is comprised of one gynecologic oncologist, eight gynecologic oncology fellows, obstetrics and gynecology residents plus the nursing staff. A multidisciplinary team approach is employed in patient care. Auxiliary services that form part of the Gynecologic Oncology unit include Departments of General Surgery, Anesthesia, Plastic Surgery, Urology, Urogynecology, Pathology, Nutrition and Psychosocial support.

The hospital also has a Cancer Treatment Centre (CTC) manned by medical and radiation oncologists which offers radiation therapy and chemotherapy services. This center is an important partner to the Gynecologic Oncology unit.

The Gynecologic Oncology Unit runs a gynecologic oncology outpatient clinic every Friday and a colposcopy clinic twice a week. New patients with gynecologic malignancy (confirmed and suspect) are seen in these clinics. Old patients with gynecologic malignancies on follow up are also reviewed.

An average of 340 cancer of the cervix are admitted annually to the units' inpatient wards (Ward 1B and 1D). Majority (>90%) have locally advanced disease with acute complications like anemia, deep venous thrombosis, acute infections, renal failure and per vaginal bleeding. Chemotherapy for gynecologic malignancies is offered in the unit as inpatient service while primary and complementary chemoradiation is offered by the Cancer Treatment Centre.

Patients with early stage cancer of the cervix stage IA2-IIA2 scheduled for radical hysterectomy are usually admitted to ward IB after diagnosis is made and confirmed. A preoperative examination under anesthesia for disease staging is routinely done while imaging for local and metastatic work up is at the discretion of the surgical team. The hospital has Ultrasound, CT SCAN and MRI services offered by the Diagnostic Radiology and Imaging Department. These services are covered by the National Hospital Insurance Fund (NHIF) for those patients who are registered members.
Case selection for surgery is by the gynecologic oncology team during the preoperative ward review. Listed patients for surgery are reviewed by the anesthesiology team and mandatory preoperative total blood count, urea and electrolyte testing are done.

Intra-operatively, standard abdominal preparation and draping is done. The open abdominal approach through midline incision is used for abdominal access. The Class II or Class III radical hysterectomies with pelvic lymphadenectomy are the commonly done operative surgical procedures for ICC. A few minimally invasive radical hysterectomy procedures have been done by visiting gynecologic oncologists during laparoscopy training workshops.
All specimens of radical hysterectomy and pelvic node dissection are submitted for pathology at the Laboratory and Pathology services Department. This department is ISO certified and all reports of confirmed malignancy are signed off by a registered consultant pathologist.

Post operatively, the urinary catheter is retained for 48-72 hours for bladder drainage; but this could be extended to a week if urine retention is noted. Prophylactic antibiotics are offered and feeding allowed on the first post-operative day. On account of delay in reporting by our pathology laboratory which is sometimes experienced; the histology reports may be processed outside the KNH laboratory. Usually the neighboring Pathologists Lancet and Nairobi Hospital laboratory which are ISO certified are used.

Early ambulation and non-pharmacologic therapies are used for thromboprophylaxis. Majority of patients are discharged on the fourth or fifth post-operative day after wound exposure.

A scheduled fortnight review in the gynecologic oncology outpatient clinic is given. During the visit, the wound is examined and any other complications post operatively are documented. The histopathology report of all specimens submitted to pathology after surgery is reviewed for surgical pathologic staging. Intermediate and high-risk factors for disease recurrence are noted and a decision on complementary chemoradiation made. Clients requiring complementary chemoradiation are counselled and referred to the radiotherapy unit.

After completion of all indicated definitive treatments, all the clients are then put on life-long follow up although the loss to follow up is high. Patients with disease recurrence are managed by salvage radiotherapy or palliative chemotherapy.

The KNH Department of Information and Health records keeps all the files of patients seen as outpatient and inpatient. Approximately twelve radical hysterectomies are done annually giving a finite population of approximately 72 cases over the study period.

3.3 STUDY POPULATION

Patients with early-stage cancer of cervix treated primarily by radical hysterectomy at Gynecologic Oncology Unit KNH between January 2013 to December 2018 formed the study population.

3.3.1 Inclusion Criteria

Women with histologically confirmed invasive cervical cancer stage IA1 – IIA managed by radical hysterectomy as primary definitive treatment at KNH between January 2013 to December 2018

3.3.2 Exclusion Criteria

The following women with cervical cancer were excluded from the study:

1. Women who had surgery other than radical hysterectomy e.g conization, trachelectomy and simple hysterectomy
2. Women operated outside KNH

3. Women whose files could not be accessed.
4. Women with undocumented clinical disease stage

3.4 SAMPLE SIZE JUSTIFICATION

A representative sample size for the study was calculated using the formulae for Yamane.T (1967) as given in equation below

$$n = {Z^2 \times (P) \times (1 - P)}/{C^2}$$

Where,

n – the required sample size,

p – 90% reported survival rate of patients with early stage cervical cancer treated primarily by radical hysterectomy (35, 37)

c 2 - confidence interval set at 5%, expressed as decimal, Z = Z value (e.g. 1.96 for 95% confidence level).

Substituting the values into the equation above we got,

n = 138.2976 ≈ **139** patients.

Since in this case we had a finite population (N is known), we further used the equation below to adjust the sample size to the finite population,

$$n = \frac{n_0 N}{n_0 + (N - 1)}$$

This gave us,

= 46.778

≈ **47** patients.

If we use the lower survival rate of 65% for FIGO stage IIA2 disease and atypical histologic types, adjusted to the same finite population of 70, we got a sample size 59 patients.

Considering the distribution of patients in stage I and II is about 50:50, a final sample size of 55 cases was thought to be reasonable.

3.5 SAMPLING PROCEDURE

All files of patients who had radical hysterectomy as primary treatment for early stage cancer of the cervix between January 2012- June 2018 were retrieved.

Since the adjusted sample size closely approximated the finite population, a census of eligible cases for data extraction was conducted over the study period.

3.6 DATA COLLECTION AND MANAGEMENT

Data from eligible cases and files was collected using a data abstraction form (Appendix I).

Two research assistants plus a health records officer trained by the Principal Investigator on the research objectives and data abstraction form were involved in the study. Files of cervical cancer patients managed surgically between January 2013 to December 2018 were retrieved from archives by the health records officer. Eligible cases were anonymously summarized as per inclusion and exclusion criteria. Data of interest was obtained from the eligible files and entered into a soft copy of the data extraction form in microsoft office. When the information documented in the file was uncertain with regard to survival and uptake of complementary chemoradiation after radical hysterectomy, the principal investigator (PI) made a phone call to the client or next of kin using the contact telephone number indicated on the admission registration form in the file. The PI introduced himself, obtained verbal consent to participate in the study and the information required was obtained and entered in the respective data abstraction form.

Quality assurance: The data extraction form was piloted on five eligible cases before the commencement of the study in order to assess for any gaps. Quality assurance was implemented at all phases of the study under guidance of the principal investigator. Prior to data collection, a standard operating procedure for data management was developed based on

the data extraction form. Training of research assistants on operational terms and definitions was conducted by the PI. A data dictionary to help in the archiving and documenting all study data was also developed. Random cross checking of the entries made by the research assistants on the data abstraction form was conducted by the PI to ensure accuracy of the data collected. Corrections for wrong entries was done.

Data was then cleaned and exported into Stata v13 (Stata Corp, College Station, TC, USA) for analysis.

3.7 DATA ANALYSIS

De-identified data was analyzed and summarized as per objective.
Data with descriptive statistics was summarized. Continuous data like age was presented as means (SD), while categorical data is described in proportions. A p-value of <0.05 was considered statistically significant along with the associated 95% confidence interval.

Objective (1): Data on social demographics, baseline clinical status plus preoperative imaging is categorized and presented in proportions.

Objective (2, 3 and 4): Data on complications associated with radical hysterectomy, histopathology report after surgery, as well as uptake of complementary treatments is categorized and presented in proportions.

Objective 5: Determining the 2-year survival: Kaplan Meier curves were used to determine 2- year survival. Correlation between disease stage and survival was also determined. Patients lost to follow up were censored in the survival analysis

3.8 ETHICAL CONSIDERATIONS

Permission to carry out this study was granted by the Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee after submission of study proposal. The study was of minimum risk due to its retrospective nature. Although no informed consent was required for this study because of its retrospective nature, a verbal consent to participate in the study was obtained by the Principal Investigator whenever a telephone call was made to study

participants or next of kin seeking clarification on uptake of complementary chemoradiation or survival.

3.9 STUDY LIMITATIONS AND DELIMITATIONS

This a retrospective cohort study and the accuracy of the results is limited to the face value of the medical notes in the files reviewed.

The following study limitations were encountered during this study:

Missing data: Some of the information and data of interest was either missing from the eligible files or was not well documented. This was mitigated by comparing data across different reports (medical notes, nurses notes, laboratory findings and referral letters) to ensure that the most appropriate inference is made regarding the abstracted data. In case the data was missing completely but the case file is eligible, only the available variables were analyzed.

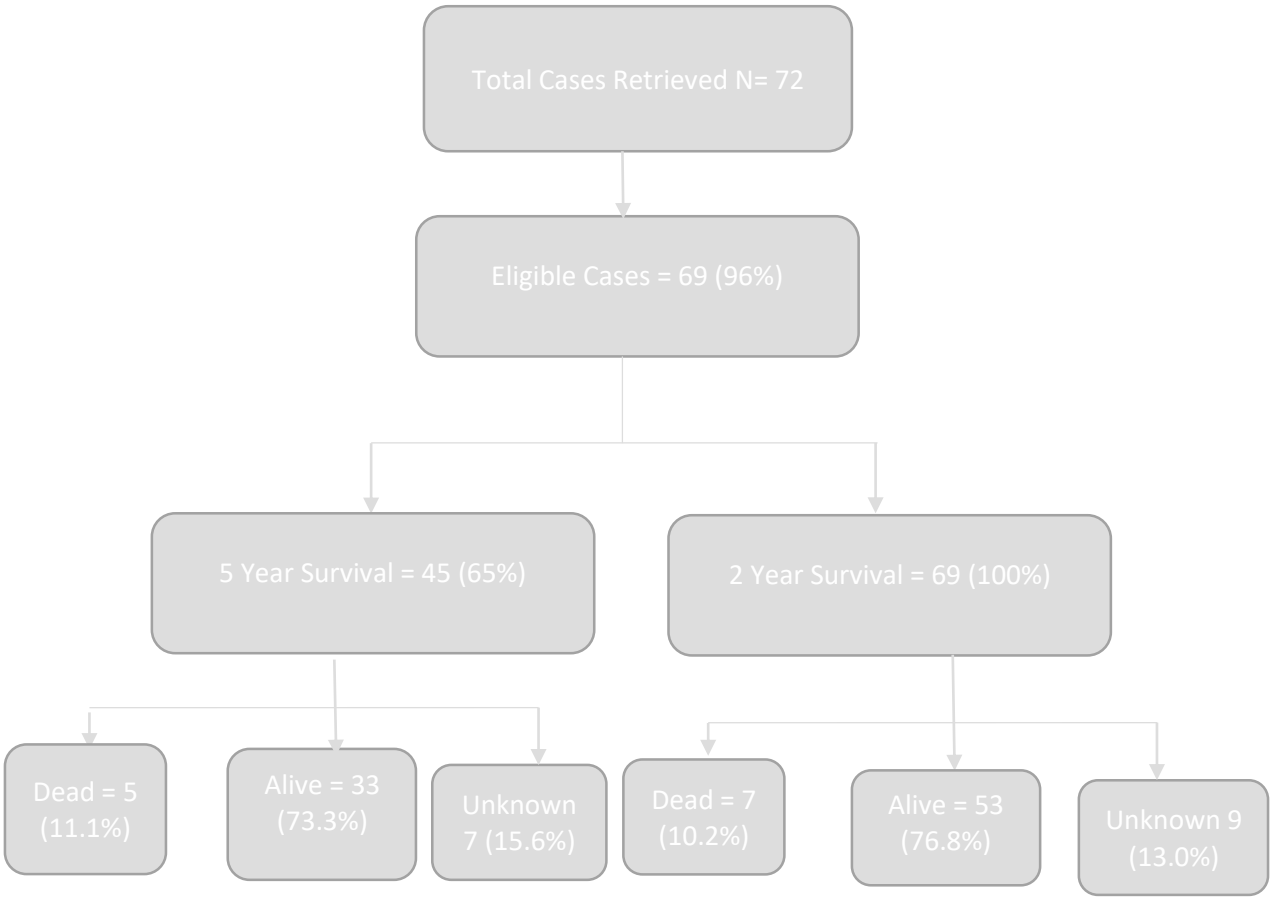
Loss to follow up: It was difficult to tell the outcome of patients who were lost to follow up. To mitigate this shortcoming, a phone call by the PI was made and verbal consent obtained. Uncertain data on survival and complementary treatment was clarified when the call was answered. However, some calls went unanswered or were reported as out of service by the mobile provider. Such cases were marked as missing data. Though data on mortality was collected for survival analysis, it included those who may have died of other obvious causes other than cervical cancer.

CHAPTER 4. STUDY RESULTS

A total of 72 files of women who had radical hysterectomy between January 2013 to December 2018 were retrieved.

Of the 72 files retrieved, 69 were found to be eligible for study while three were ineligible as the surgery was done in another facility or failure to comply as per inclusion/exclusion criteria.

Figure 2: Patient Flow Chart



4.1 Social Demographic Characteristics

Characteristics	Statistics	n	%
Age (in complete years)			
Mean	44.9		
Median	44.0		
Range [Min-Max]	26 - 76		
IQR [25-75%]	38.5-50.0		
< 30		5	7.2
30 – 39		14	20.3
40 – 49		29	42.0
50 – 59		15	21.7
≥ 60		6	8.7
Marital Status			
Single		15	21.7
Married		51	73.9
Separated		0	0.0
Widowed		2	2.9
Divorced		1	1.4
Parity			
Mean	3.6		
Median	3.0		
Range [Min-Max]	1-10		
IQR [25-75%]	2-5		
≤ 3		36	52.2
≥ 4		33	47.8
Religion			
Christian		68	98.6
None		1	1.4
Employment			
Employed		36	52.2
Unemployed		33	47.8
Education			
Not Indicated		8	11.6
Primary		29	42.0

Secondary	25	36.2
College/University	7	10.1
NHIF Registration		
Registered	47	70
Not Registered	21	30

Table 2: *The social demographic characteristics of study participants*

The mean age of the study participants was 44.9 years. Majority (73.9%) were married and of high parity. Most were of primary and secondary school level of education. Seventy percent were registered with National Hospital Insurance Fund. There was no significant age difference at the time of presentation between HIV positive and HIV negative women. The mean waiting from first visit to surgery was 136 days with a median of 79 days

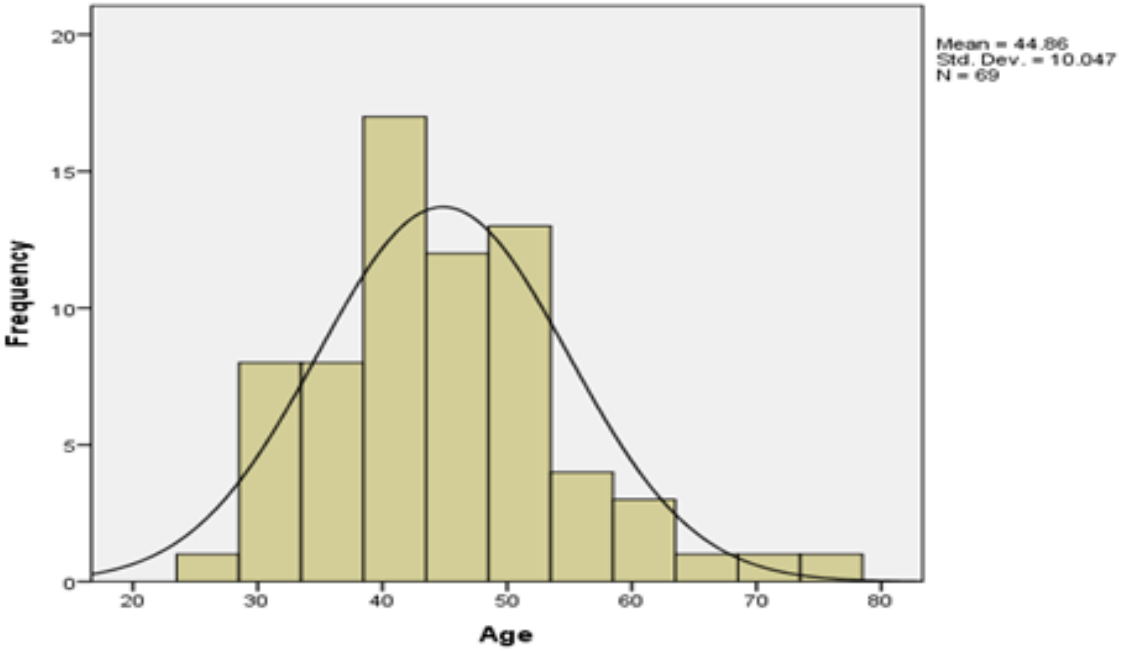


Figure 3: *Age Distribution of eligible cases- normal plot*

Age Distribution (in Years)	**HIV Status**		**OR (95% CI)**	**P-Value**
	+ VE, n (%)	**- VE, n (%)**		
Mean	43	45		
Median	43	44		
• < 30	1 (3.8)	3 (9.1)	1.9 (0.2-	0.243
• 30 – 39	5 (19.2)	8 (24.2)	23.4)	-
• 40 – 49	17 (65.4)	9 (27.3)	Ref.	0.109
• 50 – 59	3 (11.5)	9 (27.3)	0.3 (0.1-1.3)	0.471

• 60+	-	4 (12.1)	1.5 (0.3-10.5) -	-

Table 3: *Age Distribution V/S HIV Status*

	Mean	Median	Range
Waiting time to surgery	136.12	79.00	6-993

Waiting Time: *1st Visit to Surgery in Days*

4.2 Preoperative Assessment

4.2.1 Clinical Characteristics

Majority (98.6%) of the study participants had an optimal preoperative hemoglobin of >10.0g/dl with hypertension and HIV as the most common comorbidities. Of those who were HIV positive, 92% were on HAART. Fifty percent of the women who had radical hysterectomy for invasive cervical cancer were of Stage IB1 and IB2.

Parameters	Statistics	n	%
HB			
Mean	13.2		
Median	13.3		
Range [Max - Min]	8.8-17.7		
IQR [25 - 75] delete this row	123.-14.0		
≥ 10		68	98.6
8 - < 10		1	1.4
HIV Status			
Unknown		10	14.5
-VE		33	47.8
+VE		26	37.7
On HAART (n=26)			
Yes		24	92.3
No		2	7.7
Other Comorbidity			
Diabetes		2	2.9
Hypertension		9	13.0
TB		1	1.4

Cancer of Vulva	1	1.4
Lymphoma	1	1.4
FIGO Procedure		
Examination under Anesthesia at KNH	36	52.2
Examination under Anesthesia outside KNH	19	27.5
Examination without Anesthesia at KNH	14	20.3
FIGO Clinical Staging		
IA1	2	2.9
IA2	9	13.0
IB1	20	29.0
IB2	17	24.6
IB3	7	10.1
IIA1	7	10.1
IIA2	7	10.1

Table 4: *Preoperative clinical characteristics of women who had radical hysterectomy at KNH 2013-2018*

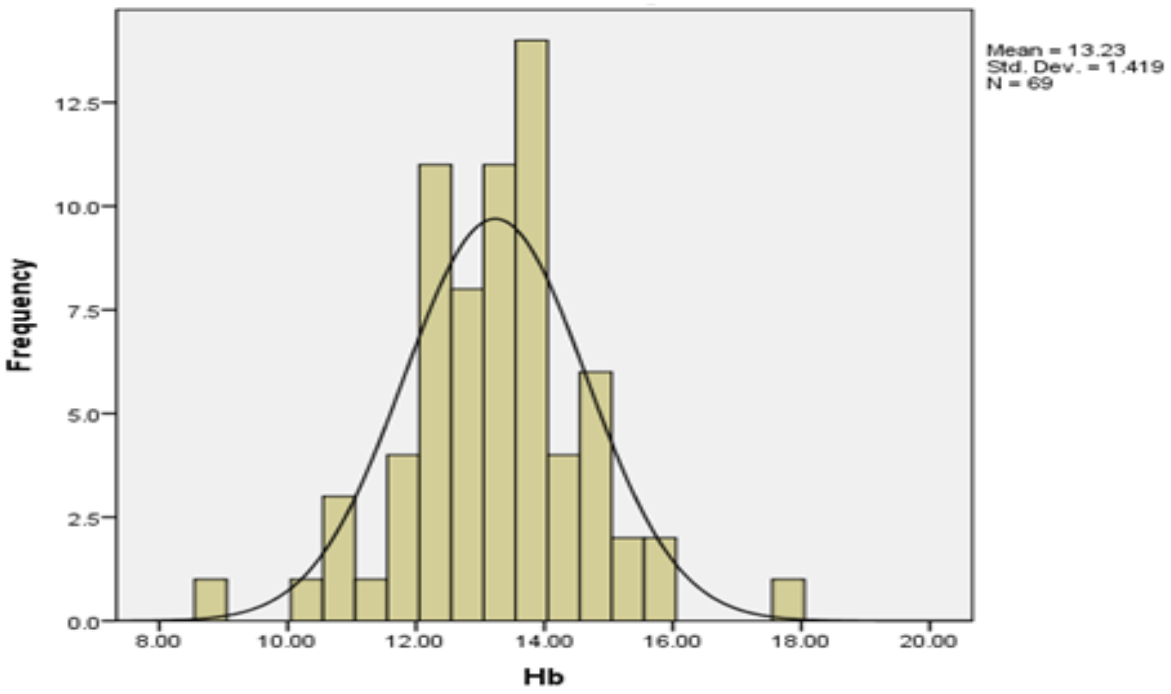


Figure 4: *Hemoglobin Distribution- Normal Plot*

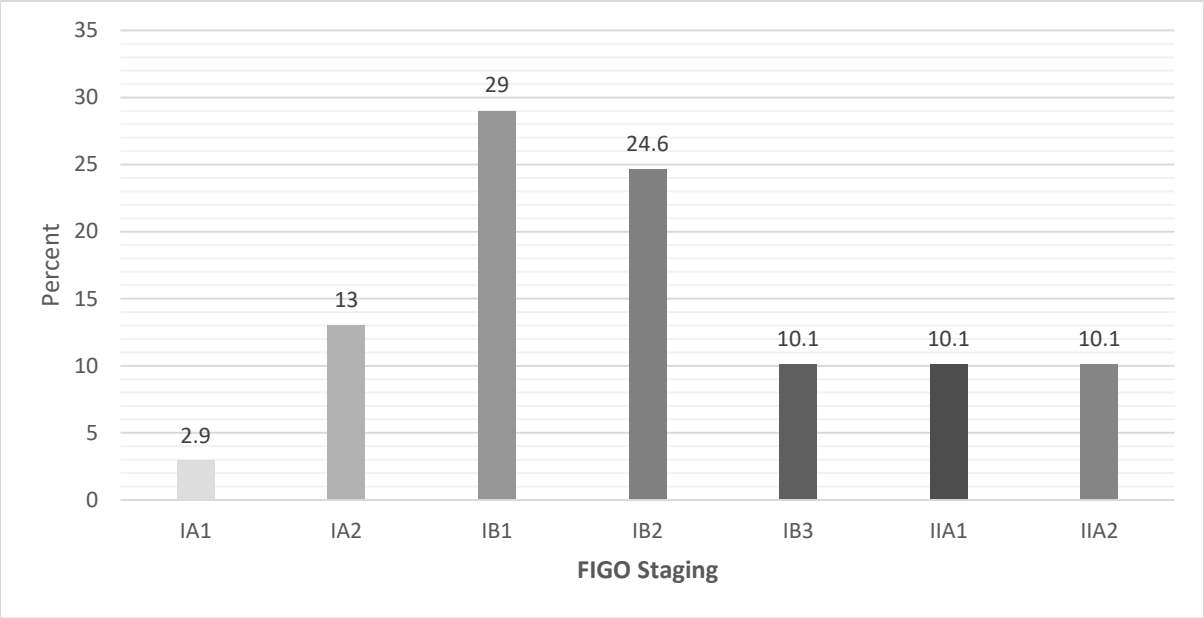


Figure 5: *Disease distribution by FIGO clinical stage*

4.2.2 Preoperative Imaging

With regard to preoperative imaging, pelvic ultrasound scan was the most frequently used imaging modality.

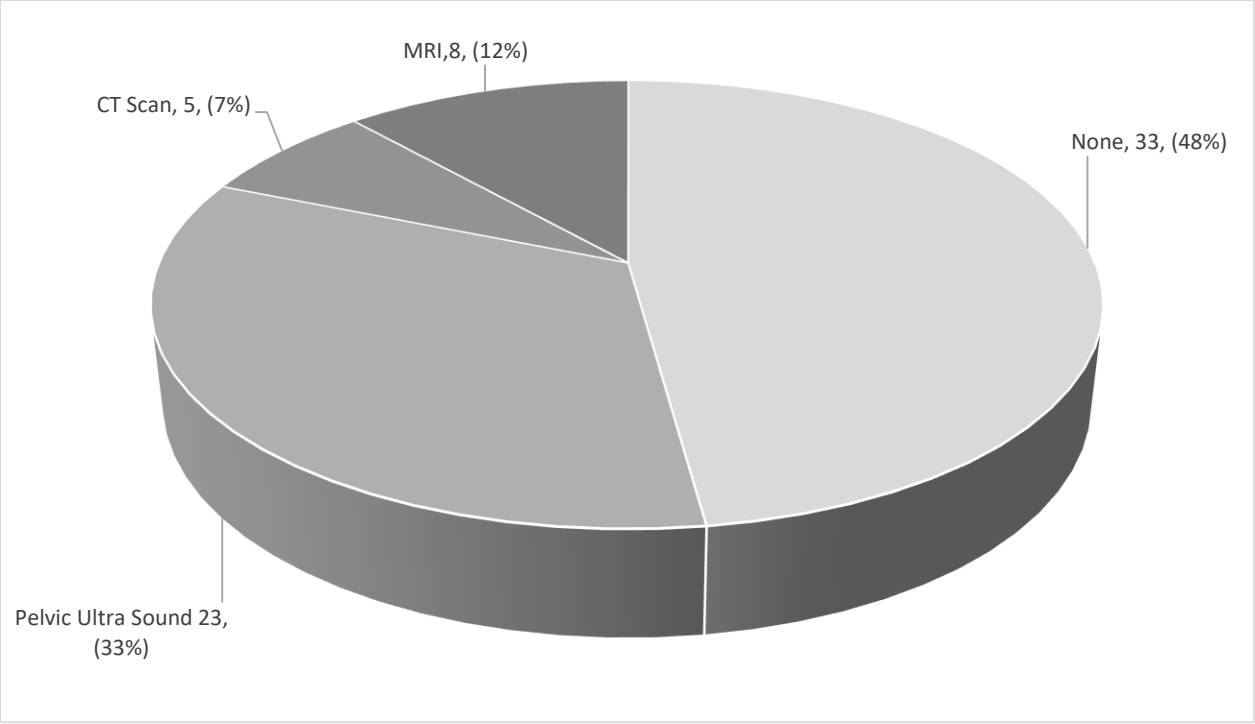


Figure 6: *Pre-operative imaging and metastatic work up*

FIGO Clinical Staging	Pre-Operative Imaging				
	None	Pelvic ultra sound	CT Scan	MRI	Total
IA1	1	0	1	0	2
IA2	4	4	0	1	9
IB1	9	5	3	3	20
IB2	7	6	1	3	17
1B3	5	2	0	0	7
IIA1	3	4	0	0	7
IIA2	4	2	0	1	7

Table5: *Imaging Modality with Disease stage*

4.3 SURGICAL OUTCOMES

4.3.1 Surgical Approach & Complications

Most of the women had an open abdominal radical hysterectomy with no acute (59.4%) or chronic complication (88.4%). Operative hemorrhage requiring transfusion was observed in 33.3% of the cases. This was followed by surgical site infection and ureteric injury at 2.9 %. Mortality from surgery was rare at 1.4%. Urinary and rectal fistulae were the most common chronic complications though rare at 7.2% and 1.7% respectively.

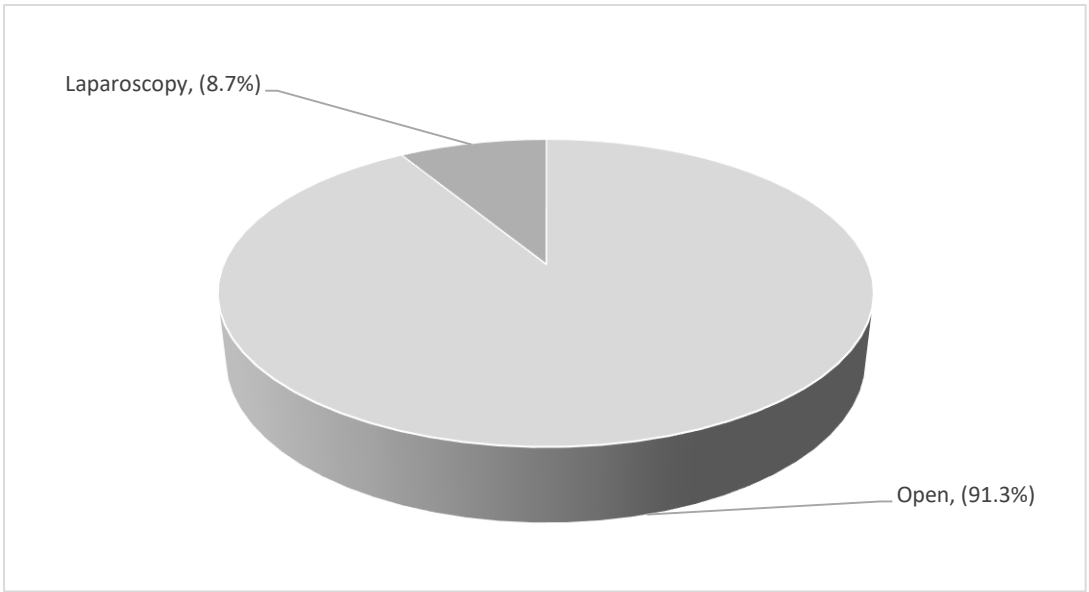


Figure 7: *Open versus laparoscopic approach for radical hysterectomy at KNH (2013-2018)*

Acute	**n**	**%**
None	41	59.4
Surgical Site Infection	2	2.9
Transfusion	23	33.3
Ureter Injury	2	2.9
Death	1	1.4
Late	**n**	**%**
None	61	88.4
Rectal Fistula	1	1.4
Urinary Fistula	5	7.2
Other	2	2.9

Table 6: *Complications after radical hysterectomy for ICC at KNH (2013-2018)*

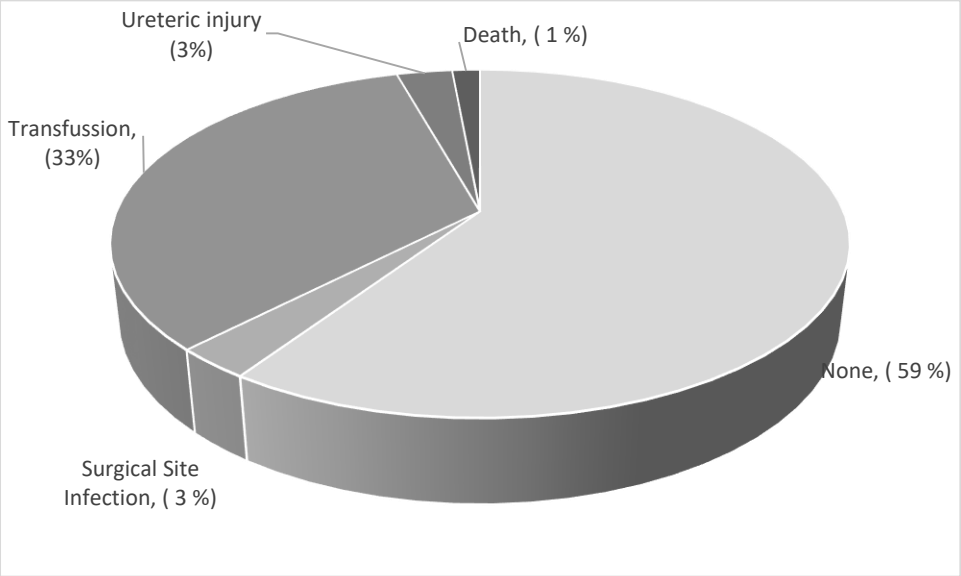


Figure 8*: Rate of acute complications after radical hysterectomy for ICC at KNH 2012-2018*

4.3.2 Histopathologic findings after radical hysterectomy

Squamous cell carcinoma was the most common histologic type (63.8%) followed by adenocarcinoma at 13%. Stage IB2, IB3, IIA1 and IIA2 had the highest prevalence of intermediate and high-risk factors for disease recurrence.

Histologic Type	**n**	**%**
No Cancer	2	2.9

SCC	44	63.8
Adenocarcinoma	9	13.0
Anaplastic	1	1.4
Missing Data	2	2.9
Cervical Intraepithelial Neoplasia (CIN)	10	14.5
Hyperplasia	1	1.4

Table 7: *Histologic types after radical hysterectomy for ICC at KNH (2013-2018)*

Risk Factor	**n**	**%**
Intermediate Risk Factors		
A.Capillary & Lymphovascular Space Involvement	13	18.8
B. Stromal Involvement		
Not Indicated	22	31.9
Superficial	16	23.2
Middle	6	8.7
Deep	25	36.2
C. Tumor Size (in CM)		
> 2 - < 4	18	56.3
> 4	14	43.8
High Risk Factors		
None	56	81.2
Positive Nodes	10	14.5
Positive Margins	3	4.3

Table 8: *Proportion of women with risk factors for disease recurrence after radical hysterectomy for ICC at KNH (2012-2018)*

	High Risk Factors		
FIGO Clinical Staging	None	Positive Nodes	Positive Margins

	n	%	n	%	n	%
IA1	2	100	0	0.0	0	0.0
IA2	9	100	0	0.0	0	0.0
IB1	18	90	1	5	1	5
IB2	14	82	3	17.6	0	0.0
1B3	5	71	2	28.5	0	0.0
IIA1	4	57.1	1	14.2	2	28.5
IIA2	4	57.1	3	42.8	0	0.0

Table 9: *Proportion of women with high-risk factors for disease recurrence by disease stage*

FIGO Clinical Staging	Capilary				Strom								Size			
	Yes		No		Not Indicated		Superficial		Middle		Deep		> 2 - < 4		> 4	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
IA1	0	0.0	2	3.6	2	9.1	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
IA2	0	0.0	9	16.1	6	27.3	3	18.8	0	0.0	0	0.0	0	0.0	0	0.0
IB1	1	7.7	19	33.9	9	40.9	8	50.0	2	33.3	1	4.0	3	16.7	0	0.0
IB2	7	53.8	10	17.9	2	9.1	4	25.0	2	33.3	9	36.0	6	33.3	5	35.7
1B3	1	7.7	6	10.7	2	9.1	0	0.0	0	0.0	5	20.0	4	22.2	1	7.1
IIA1	1	7.7	6	10.7	0	0.0	1	6.3	1	16.7	5	20.0	5	27.8	2	14.3
IIA2	3	23.1	4	7.1	1	4.5	0	0.0	1	16.7	5	20.0	0	0.0	6	42.9

Table 10: *Proportion of women with intermediate risk factors for disease recurrence and FIGO clinical stage*

4.3.3 Complimentary treatment after radical hysterectomy

Complimentary adjuvant chemoradiation was indicated after radical hysterectomy in half (52.2%) of the cases as per Sedli's criteria. However, only 44% of these women actually received this treatment. Most of them (45%) were not informed about the need for adjuvant pelvic chemoradiation, while 10% declined. Only one client out of fourteen clients with bulky early-stage cervical cancer received neoadjuvant chemotherapy.

Complimentary chemoradiation treatment	**n**	**%**
Not indicated	33	47.8
Indicated as per Sedlis criteria	36	52.2

If indicated was it given (n=36)?		
Yes	16	44.4
No	20	55.6
If NOT given, reason		
Declined	2	10.0
Distance	1	5.0
Not Informed	9	45
Cancelled	2	10
Not affordable	1	5
Reason not Given	5	25
NEOADJUVANT CHEMOTHERAPY		
Offered	1	7.1
Not offered	13	92.9

Table 11: *Complimentary treatment- proportion of women with indication as per Sedli's criteria and percent offered*

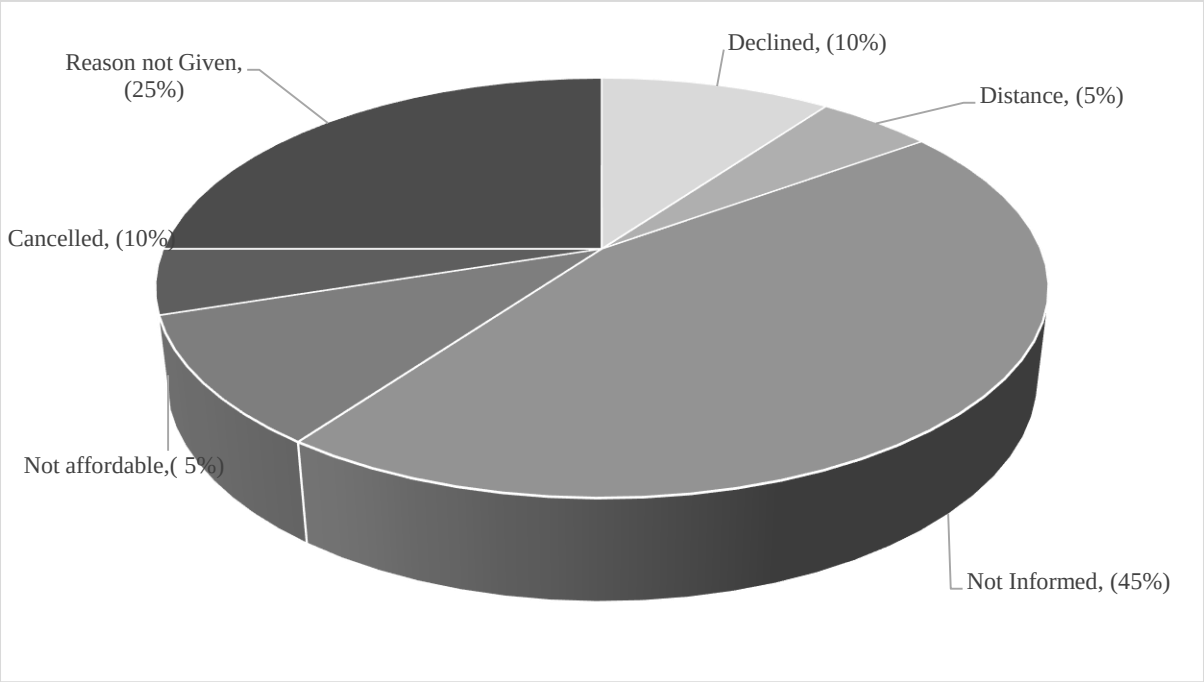


Figure 9: *Reasons for failed uptake of complimentary chemoradiation when indicated*

4.4 SURVIVAL ANALYSIS

Seven deaths were reported during the study period out of sixty women on whom data on survival was available. Nine cases were censored out of analysis for missing data.
Survival declined steadily over the period of time till 48 months when no death was reported thereafter. Our mean follow-up time was 56.6 months, median of 60.5 months, range 0.3-75 months.

	n	%

Survival	Alive	53	76.8
	Dead	7	10.1

4.4.1 TWO-YEAR SURVIVAL ANALYSIS

Data on two-year survival after radical hysterectomy for early-stage invasive cervical cancer at KNH (2012-2018) was available for sixty women out of the cohort of 69 cases. Two-year overall survival was calculated at 93.3%. The earliest mortality was recorded on the third post-operative day in a woman with advanced retroviral disease.

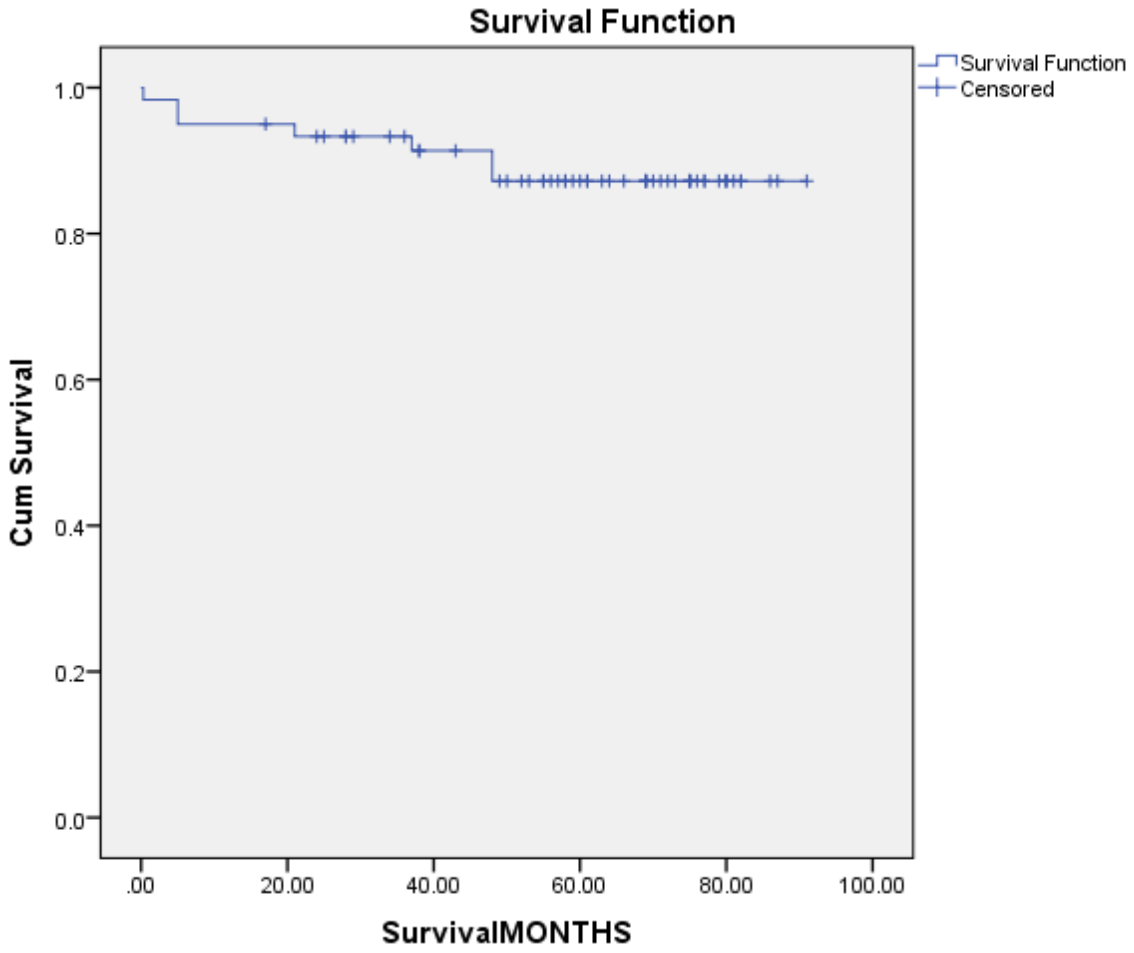


***Figure 10**: Kaplan-Meyer Overall Survival curve after radical hysterectomy for ICC at KNH 2012-2018*

4.4.2 Survival by FIGO clinical stage

Overall survival by FIGO clinical stage after radical hysterectomy at KNH was best for women with invasive cervical cancer stage IA1, IA2 and IB1. Women with disease stages IB2, IB3 and IIA1 had the most mortalities.

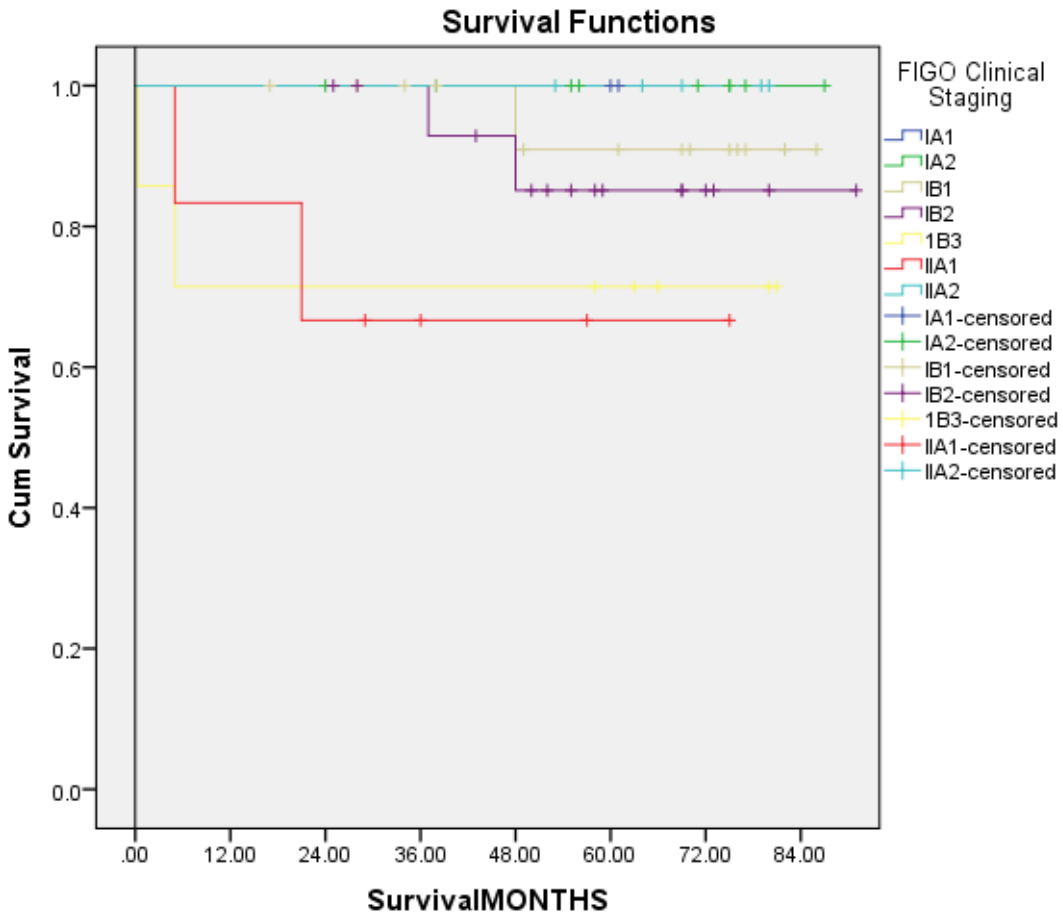


Figure11: *Kaplan-Meyer 2-year Survival curve by clinical stage of disease after radical hysterectomy for ICC at KNH (2012-2018)*

4.4.3 FIVE YEAR SURVIVAL ANALYSIS

Data on five-year survival after radical hysterectomy for early-stage invasive cervical cancer was available for thirty eight women out of the cohort of 69 cases. This included women who had radical hysterectomy between 2012-2015. Women who had radical hysterectomy from January 2016 were censored out of the five-year survival analysis. The five-year survival was calculated at 86.8%.

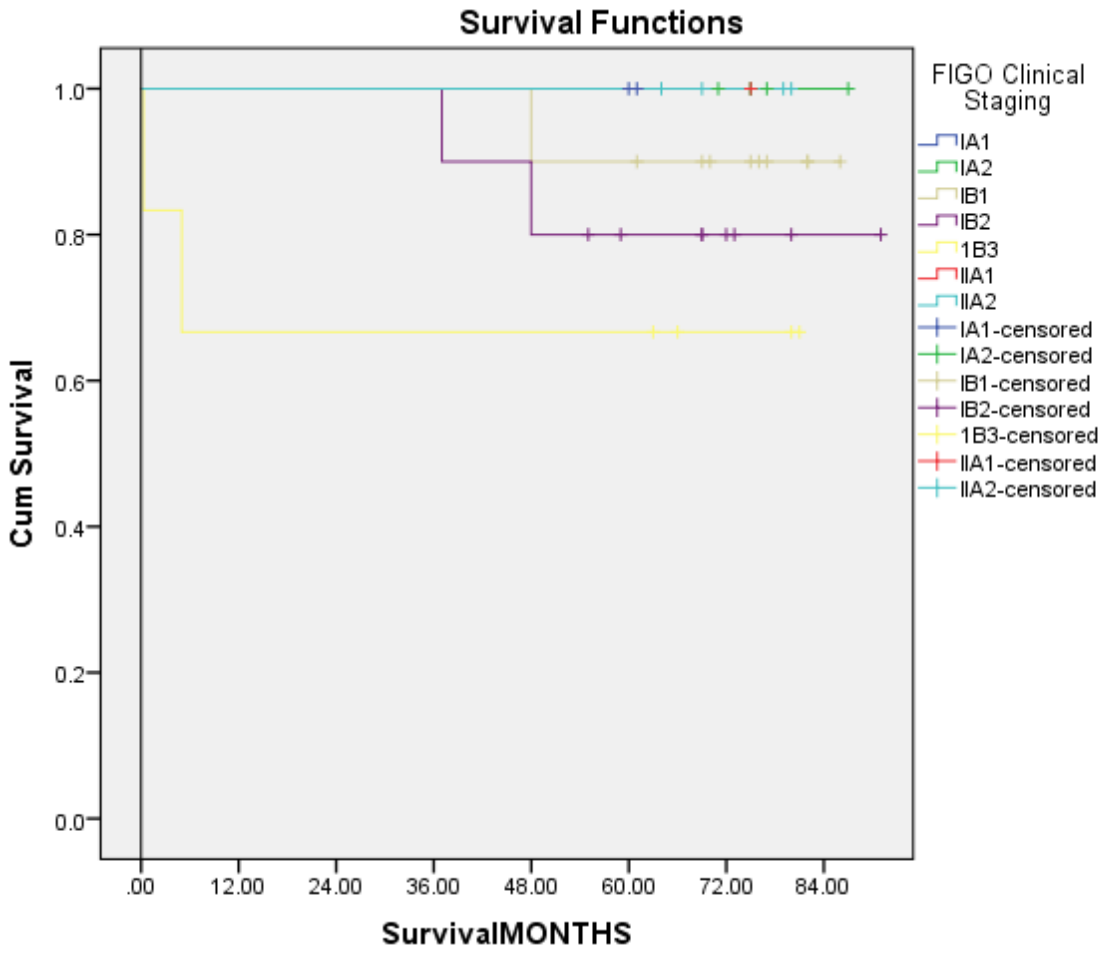


Figure11: *Kaplan-Meyer 5-year Survival curve by clinical stage of disease after radical hysterectomy for ICC at KNH (2012-2018)*

4.4.3 SURVIVAL BY HIV STATUS

There was no significant difference in overall survival between HIV negative and HIV positive women who had radical hysterectomy for invasive early stage cervical cancer at KNH between January 2012 to December 2018 (p value= 0.746)

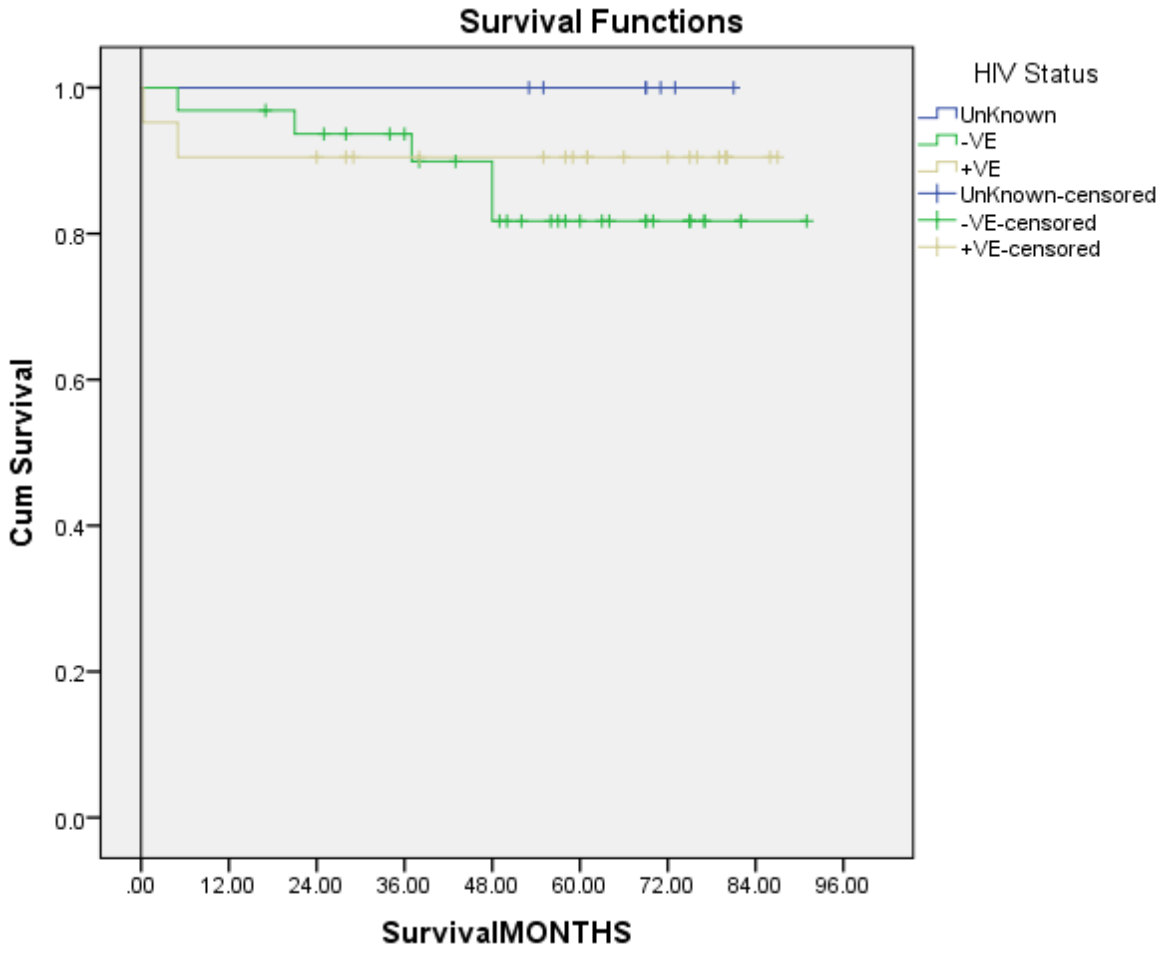


Figure11: *Kaplan-Meyer overall survival curve by HIV status after radical hysterectomy for ICC at KNH (2012-2018)*

CHAPTER 5. DISCUSSION

A total of 69 cases out of 70 women who had radical hysterectomy as primary treatment for invasive early-stage cervical cancer at KNH between January 2013 to December 2018 were found to be eligible for inclusion into this study. The mean and median age of the participants was 44.9 years and 44.0 years respectively. Globally, the average age at diagnosis of women with invasive cervical cancer is 53 years. Maranga et al in earlier study reported a mean age of 49 with a peak incidence at age 47 years (5). Gichangi et al reported a mean age of 48 years at presentation (10). This shows that the fourth decade is the peak age of presentation for invasive cervical cancer in the Kenyan setting. The lower age of peak incidence in Kenya and Africa may be attributed to early age of sexual debut, high parity, high prevalence of HIV infection, limited screening services and poverty. The net effect is early exposure to high-risk human papilloma virus with development of premalignant lesions and progression to invasive cervical cancer.

Although, HIV positivity has been associated with early age of presentation and diagnosis of this disease; in this study, there was no significant age difference between those who were HIV positive and HIV negative. We attribute this finding to the limitation of the cases to early-stage disease as those who are HIV positive are reported to more likely have locally advanced disease at diagnosis (10).

Anemia is a known adverse effect of cervical cancer disease. Maroie Barkati et al reports that hemoglobin levels in cervical cancer are a surrogate marker of disease severity and that low hemoglobin levels are associated with a more infiltrative disease status with possible nodal involvement (41). Patients with low hemoglobin show poor response to treatment with high recurrence rate

A normal hemoglobin therefore signifies less disease morbidity and possibly optimal health status before surgery. The mean preoperative hemoglobin in our study was 13.3g/dl with a range of 8.8-17g/dl. This may be attributed to the early stage of disease at presentation in majority of our study cohort with 70% of cases staged as IB2 and below.

Majority of our clients had HIV and hypertension as the most common comorbidities. Among those who were HIV positive, 92% had been initiated on HAART thus optimizing their health status and tolerance for surgery. Two clients had concurrent malignancies of cancer of the vulva and lymphoma thus requiring multidisciplinary approach to care for optimal outcome.

Radiological imaging to assess disease status is recommended by FIGO and has been incorporated in the 2018 FIGO disease staging guidelines. Charis Bourgioti el in a review of imaging in patients with cancer of cervix, reports that pelvic MRI is the preferred imaging modality for assessment tumor size, parametrial invasion and pelvic node involvement (42). In this study, trans-abdominal ultrasound scanning was commonly used (33%) to evaluate the disease status. No transrectal or transvaginal scanning was used. Majority of the cases (48%) were assessed clinically with no radiological imaging. There was limited use of CT SCAN (7%) and MRI (12%). Women with microinvasive disease stage IA1 and IA2 had advanced imaging while those with bulky lesions of stage IB3 had no imaging. This may be attributed to lack of institutional guidelines to rationalize choice of optimal imaging modality as an aid to more accurate disease staging. With the inclusion of imaging in the comprehensive National Health Insurance Fund cover, we expect an increase in proportion of clients offered CT SCAN

and MRI services for metastatic work up as 70% of the study participants were using this medical insurance for payment services.

Radical hysterectomy is a formidable gynecological procedure with significant risk of morbidity (23,24). John R van Nagell et al reports that lymphocyst formation as well as bladder autonomic dysfunction are the commonest complications at 5-15% (43). Kun Wu et al reports similar findings with bladder dysfuction (10%), lymphocyst (10%) and surgical site infection at 6.8% (44). In this study, we had a 3% prevalence of ureteric injury and surgical site infection. One mortality was reported, on the third postoperative day, in a patient who had advanced retroviral disease and had not started treatment with HAART. Intra-operative hemorrhage requiring transfusion was the commonest surgical complication. Emma et al in a study on surgical morbidity after open radical hysterectomy in low income and middle income countries reports similar findings (25). The low complication rate in our study may be attributed to the young age of our study population. In a study looking at safety and tolerance of radical hysterectomy in elderly women, George E M et al found that perioperative mortality was substantially greater in women aged more than 60 years and that non-surgical treatments should be considered in such groups (45).

Squamous cell carcinoma (60-80%) and adenocarcinoma (10-15%) are the most common histologic types of invasive cervical cancer. The two are closely associated with high-risk Human Papilloma Virus (HPV16,18) infection which results in development of premalignant lesions that progress to malignancy due to individual host factors (46). Atypical histologic types of small cell (neuro endocrine), sarcoma and anaplastic types have also been reported. They are associated with more aggressive disease; often presenting with locally advanced disease, metastasis and poor response to treatment as well as recurrence. These atypical types are often not HPV related.

In this study, squamous cell carcinoma and adenocarcinoma were the most common pathologic subtypes at 63.8% and 13% respectively. One case of anaplastic carcinoma was reported.

Ten percent of the women initially diagnosed to have invasive cancer after preoperative biopsy were reported to only have premalignant lesions on pathologic examination of the radical hysterectomy specimens. We do believe that the initial biopsy reports were accurate but postulate that complete excision of invasive cancer lesions was achieved by the biopsy procedure. This is because all were very early-stage disease of less than or equal to IB1 with either very small gross lesions or micro-invasive disease. Such pathologic findings are useful and may be used in counselling young women with micro-invasive cervical cancer desirous of fertility on local fertility sparing excisional procedures for this disease.

The low number of atypical histologic types reported in this study may be attributed to the small sample size.

Recurrence of invasive cervical cancer may occur after radical hysterectomy as primary treatment for early-stage cervical cancer in up to 10% of cases. Tumor size, lymph node status, positive margins and parametrial involvement have all been correlated with disease recurrence (47,48).

Although there is no consensus on complementary treatment after surgery, Sedli's criteria has been widely accepted by many radio-oncologists and gynecologic oncologists as an acceptable

tool for assessing the risk of recurrence and triaging of cases for complementary adjuvant chemoradiation after surgery.

In this study 52.2% of the cases were assessed to have met the criteria for complementary chemoradiation. The pathology reporting of cancer of cervix was however not standardized and hence it is possible that the prevalence could be higher but missed due to non-reporting.

Most (95%) of the women with risk factors for disease recurrence were of disease stage IB2, IB3, IIA1 and IIA2 (FIGO 2018).

Women with microinvasive disease stage IA1 and IA2 had no risk factors for recurrence. Only 5% of stage IB1 cases were noted to have high risk factors for recurrence. Radical hysterectomy is therefore adequate treatment in such cases but life long follow up is mandatory.

Large tumor, deep stromal invasion plus positive margins were the most commonly seen risk factors for disease recurrence. In a study on outcomes after radical hysterectomy according to tumor size, Park J Y et al concluded that tumor size is an independent prognostic factor for recurrence and correlates well with other risk factors for disease recurrence (26). Positive margins which are commonly seen with bulky early-stage disease (tumor >4cms) was only reported in one case.

Less than half (44.4%) of the women eligible for complimentary treatment after radical hysterectomy were offered adjuvant chemoradiation. Majority (55.6%), did not receive this treatment for varied reasons, mostly for not being informed. Neo-adjuvant chemotherapy was rarely used. Only one client was offered neoadjuvant chemotherapy from the whole study population.

The low uptake of adjuvant chemoradiation and other complementary therapies in this study may be due lack of awareness on Sedli's criteria among the service providers and weak institutional guidelines on complementary chemoradiation and neoadjuvant chemotherapy.

Radical hysterectomy for early-stage cancer of the cervix has been associated with a five-year survival of over 90% for squamous and adenocarcinoma types and 65% for atypical histologic types. The FIGO clinical stage of disease, histologic type, age and cor-morbidities are important determinants of survival (21,25,35). In this study, we report a comparable and acceptable two-year overall survival of 93.3%. The five-year survival was 86%.

There was no statistical difference in survival among those who were HIV positive and those who were HIV negative (p value = 0.746). This may be attributed to the young age of the study population as well as use of HAART among those who were HIV positive. One peri-operative mortality was reported in a patient with advanced retroviral disease who had not been initiated on HAART signifying the importance of this treatment in those with the disease.

These survival findings are comparable to earlier studies by Emma et al who in a systematic review of morbidity and survival after radical hysterectomy in middle and low income countries reported a 5-year progression free survival of 83% after laparotomy with an overall survival of 85% (25).

In this study, patients with stage IA1, IA2 and IB1 had the best outcomes. Stage IB2, IB3 and IIA1 were associated with most of the mortalities. Stage IIA2 was not associated with any mortality in this study possibly due to the small sample size.

5.1 CONCLUSIONS

Radical hysterectomy at KNH as primary treatment for early-stage ICC during the period 2012-2018 was safe with comparable and acceptable outcomes to those from other more resourced treatment centers. The number of women operated is however low, considering the high prevalence of the disease in Kenya.

During the study period, majority of cases were young women with HIV and hypertension as the commonest comorbidities. Most women were staged clinically with limited and non-rationalized utilization of imaging to augment clinical findings.

There is limited uptake of complimentary chemoradiation and minimal use of neoadjuvant chemotherapy possibly due to lack of awareness among service providers and patients on the need for same when indicated.

The two-year and five-year survival rate of women undergoing radical hysterectomy estimated at 93% and 86% respectively is good and much better than that reported for primary chemoradiation from the same institution.

5.2 RECOMMENDATIONS

- More efforts should be made to improve access to radical hysterectomy at KNH and the country at large as only a small number of women with invasive cervical cancer are treated primarily by radical hysterectomy compared to chemoradiation.
- Factors contributing to this low numbers should be determined and addressed.
- The gynecologic oncology unit at KNH should rationalize preoperative imaging of early-stage cervical cancer and work towards improvement of uptake of complementary chemoradiation through institutional guidelines that are accessible to service providers and patients.
- More studies should look at actual disease recurrence rate as this study only focused on risk estimation using Sedli's criteria.

STUDY BUDGET

The study budget was Ksh 270600. The principal investigator received limited funding from his sponsor (KNH) for fellowship program and supplemented this at personal cost.

***Table 15**: Study Budget (Activity Description and Cost)*

Description	**Quantity**	**Amount (Ksh)**	**Total (Ksh)**
Research assistants	2	50000	100,000
Statistician	1	60,000	60,000
Proposal printing	55 pages X 3 copies	-	3000
Final report printing	100 pages X 3 copies	-	10000
Data collection from photocopy	3 page X 60copies	-	1000
Airtime and bundles	3 months	10,000	30,000
Training of research team	2	20000	40,000
Submission to ERC			2,000
Contingency cost (10% of the total)			24600
TOTAL			**270600**

TIMELINES AND WORKPLAN

Table 16: *A schedule of Study Activities and Time*

Activity	**June-July 2020**	**Aug-Sept 2020**	**Oct-Nov 2020**	**Dec2020-Jan2021**	**Feb-March 2021**	**April 2021**
Concept Development	xxxxxxxx xxxxxxxx xxxxxxxx xxxxxxxx					
Proposal Development		Xxxxxxxxx Xxxxxxxxx xxxxxxxxxx	Xxxxxxxx Xxxxxxxx xxxxxxxx			
Ethical Approval			Xxxxxx xxxxxxx	Xxxxxxx xxxxxxx		
Data Collection				Xxxxxxxx xxxxxxxx		
Data Analysis				Xxxxxxx xxxxxxxx		
Results Presentation					Xxxxxxx Xxxxxxxx xxxxxxxxx	
Study Publication						xxxxxxx

CHAPTER 6. REFERENCES

1. International Agency for Research on Cancer. GLOBOCAN 2018; WHO Geneva. Accessed online on https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf
2. Marc A, Elisabete W, Laia B et al. Estimates of Incidence and Mortality of cervical cancer in 2018: A Worldwide analysis. The Lancet Global Health vol 8, issue 2, E 191-E203, Feb 2020
3. International Agency for Research on Cancer: GLOBOCAN Report 2018 Kenya, WHO Geneva. Accesed online https://gco.iarc.fr/today/data/factsheets/cancers/23-Cervix-uteri-fact-sheet.pdf
4. Kinyanjui R M, Ojwang S B O, Kosgei J R, Okemwa P.O. Four-year trend and follow up of women aged more than 15 years with reproductive tract cancers in Kenyatta National Hospital (2008-2011). University of Nairobi Repository.
5. Maranga I.O, Lynne H, Anthony W.O et al, 2013: Analysis of Factors Contributing to Low Survival of Cancer Patients Undergoing Radiotherapy in Kenya. PLoS one 8(10):e78411.doi.101371/journal.pone.0078411
6. Fatima O, Zaki H, Bouchra H R et al. Determinants of patient delay in seeking diagnosis and treatment among Moroccan women with cervical cancer; Obstetrics and Gynecology International Nov 2016. Accessed on line on https://www.hindawi.com/journals/ogi/2016/4840762/
7. Dunyo P, Kofi E, Emilia A U et al. Factors associated with Late Presentation of Cervical Cancer cases at a district Hospital: a retrospective study, BMC Public Health 2018 18:1156. Accessed online https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-018-6065-6
8. Chan C K, Aimagambetova G, Ukybassova T et al. Human Papillomavirus Infection and Cervical Cancer: Epidemiology, Screening and Vaccination -Review of Current Perspectives. J Oncol 2019: 2019:3257939
9. Bruni L, Albero G, Serrano B et al, Information on HPV and Cancer (HPV Information Centre). Human Papilloma and Related Diseases in Kenya: Summary Report June 2019. Accessed online https://hpvcentre.net/statistics/reports/KEN.pdf
10. Gichangi P, De Vuyst H, Estambale B et al. HIV and Cervical Cancer in Kenya. International Journal of gynaecology Obstetrics 2002: 76(01):55-63
11. Bhatla N, Jonathan S. B, Mauricio C F et al. Revised FIGO staging for carcinoma of cervix uteri; International Journal of Obstetrics and Gynaecology January 2019,145(1)

12. Cibula D, Potter R, Planchamp F et al. ESGO-ESTRO-ESP Guidelines for the Management of Patients with Cervical Cancer. International Journal of Gynaecological Cancer. 28(4), May 2018.
13. Ministry of Health (GOK). Kenya National Cancer Treatment Protocols July 2019. Accessed online https://www.health.go.ke/wp-content/uploads/2019/09/National-treatment-Protocols-2019.pdf
14. Nadeem R A, Catheryn M Y, Sarah B et al. NCCN Clinical Practice Guidelines in Oncology. Cervical Cancer Version4.2019. Accessed online https://www2.tri-kobe.org/nccn/guideline/gynecological/english/cervical.pdf
15. R. Yan, Zeng Z, Fang L et al. Primary Radical Hysterectomy Vs Chemoradiation for Cervical Cancer Stage IB2-IIA, A systematic review and meta-analysis. Medicine January 2020. 99(5)
16. Polat D, Murat G, Ali A et al. The History of radical hysterectomy. Journal of Lower Genital Tract Disorders. 2011(3):235-245
17. John A R, Howard W J et al. Te linde's Operative Gynecology, 10th edition page 1238-1239
18. Roni N, Pedro T R, Michael F et al. Survival after MIS vs Open Radical hysterectomy for early stage cervical cancer, A systematic review and meta-analysis JAMA Oncology 2020;6(7):1019-1027
19. Ramirez PT, Michael F, Rene P et al. MIS vs open abdominal radical hysterectomy for cervical cancer. N England J Med 2018; 379: 1895-1904 PubMed
20. Marin F, Plesca M, Bordea C I et al. Types of Radical hysterectomy; Journal of Medicine and Life 2014 June15;7(2):172-176
21. Noriaki S, Tatsuya K, Chisa S et al. Oncological outcomes after radical Okabayashi-Kobayashi radical hysterectomy for early and locally advanced cervical cancer JAMA network open 2020; 3(5).
22. Marcin M, Marek N, Marian S et al. Classical radical hysterectomy and nerve sparing radical hysterectomy in the treatment of cervical cancer; Menopause review June 2014; 13(3):180-185
23. Ayhan A, Tuncer Z S et al. Complication of Radical hysterectomy; European Journal of Surgical Oncology 1991 Oct;17(5):492-4
24. Wu K, Zhang R, Li H et al. Analysis of post-operative complications of radical hysterectomy for 219 cervical cancer patients Zhonghua Zhong Liu Za Zhi. 2006;(4):316-319

25. Emma R A, Cohen P, Aime P et al (2019). Morbidity after surgical management of cancer of cervix in middle and low income countries: A systematic review and meta-analysis. PLoS ONE 14(7):e0217775
26. Park J-Y, Kim D-Y, Kim J-H et al: Outcomes after radical hysterectomy according to tumor size divided by 2-cm interval in patients with early cervical cancer; Annals of Oncology January 2011 22(1):59-67

27. Vivek N, Georgios A, Jeremy T et al: Type II or III radical hysterectomy compared to chemoradiotherapy as primary intervention for stage IB2 cervical cancer; Cochrane Systematic Review 12 October 2018. Accessed online https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011478.pub2/full

28. Landoni F, Allesandro C, Rodolfo M et al. Randomized study between surgery and radiotherapy for treatment of stage IB-IIA cervical cancer: 20-year update; Journal of Gynecological Oncology 2017;28(3)
29. Yue W, Guang W, Li-Hui W et al. Neoadjuvant chemotherapy for locally advanced cervical cancer reduces surgical risks and LVSI: Chinese Journal of Cancer September 2011; 30(9):645-654.
30. Yi Shen, Lu Y, Zehua W et al. Treatment of early bulky cervical cancer with neoadjuvant paclitaxel, carboplatin and cisplatin prior to laparoscopic radical hysterectomy. Oncology Letters March 2012; 3(3):641-645
31. Hui Zhao, Yue H, Shu-Li Y et al. Neoadjuvant chemotherapy with radical surgery vs radical surgery alone for cervical cancer: a systematic review and meta-analysis; Onco Targets and Therapy March 2019;12:1881-1891
32. Qin T, Zhen J, Zhou M et al. Efficacy of neoadjuvant chemotherapy plus radical hysterectomy in patients with bulky stage II cervical carcinoma: a retrospective cohort study; International Journal of Surgery June 2016; 30:121-125
33. Scandurra G, Scibilia G, Luigi Banna G et al. Efficacy and tolerability of paclitaxel, ifosfamide and cisplatin as neoadjuvant chemotherapy in locally advanced cervical carcinoma; Journal of Gynaecologic Oncology April 2015; 26(2): 118-124
34. National Cancer Institute of NIH; Surveillance, Epidemiology and End Results Program; Cancer Stat Facts: Cervical Cancer 2020. Accessed online https://seer.cancer.gov/statfacts/html/cervix.html

35. Sonika A, Kathleen M, Pedro T R et al. Outcomes of Patients Treated by Radical hysterectomy for high risk histologic subtypes; Int Journal of Gynaecological Cancer 2011 Jan 2011; 21(1):123-127
36. Ding-Ding Y, Qui T, Jian-Hong C et al. Prognostic Value of the 2018 FIGO staging system for cervical cancer patients with surgical risk factors: Cancer Management Research June 2019; 11: 5473-5480
37. Nam J H, Park J Y, Kim D Y et al. Laparoscopic Vs Open radical hysterectomy in early stage cervical cancer: long term survival outcomes in a matched cohort study. Annals of Oncology April 2012; 23(4)903-911
38. Itsura M P, Rachel N D, Omenge O et al; Radical hysterectomy for operable cervical cancer in HIV-positive and HIV-negative women in western Kenya; International Journal of Gynaecology and Obstetrics 2019; 148(3):1-2
39. Loehrer J Sr, Barry R, Omenge E O et al. Capacity building in sub-Saharan Africa: models of care; The Lancet Global Health special issue March 2018; 6:17-18
40. Sarak F K, Catherine W, Maloba M et al. Cancer Prevention and Treatment research in Africa: A systematic review from a public health perspective, BMC Womens Health 16, Article:29(2016)
41. Maroie B, Israel F, Linda M et al. Haemoglobin level in cervical cancer: A surrogate for an infiltrative phenotype. International Journal of Gynecological Cancer. 2013 May;23(4): 724-9
42. Bourgioti C, Chatoupis K, Moulopoulos LA et al. Current imaging strategies for the evaluation of uterine cervical cancer. World Journal of Radiology 2016 April 28; (4):342-54
43. Rachael A. W, John RN. Radical hysterectomy with pelvic lymph node dissection: Indications, Technique and Complications. Obstetrics and Gynecology International vol 2010, article ID 587610
44. Wu K, Zhang WH, Zhang R. Analysis of postoperative complications of radical hysterectomy for 219 cervical cancer patients. Zhongua Zhong Liu Za Zhi. 2006 Apr;28(4): 316-9
45. George E M, Tergas AI, Anath CV et al. Safety and tolerance of radical hysterectomy for cervical cancer in the elderly. Gynecologic Oncology 2014 July; 134(1):36-41
46. Gulisa T et al. Cervix: Squamous cell carcinoma and Variants. Pathology Outlines; 24 September 2020

47. Dan L, Xiaoxian X, Dingding Y. Prognostic factors affecting survival and recurrence in patients with early cervical squamous cell cancer following radical hysterectomy. SAGE journals 31 December 2019
48. Sittidilokratna K, Cheewakriangkrai C, Khunamornpong S. Recurrence patterns after radical hysterectomy in stage IB1- IIA cervical carcinoma. Asian Pacific journal of cancer prevention. 2010; 11(2): 499-502

CHAPTER 7. APPENDICES

APPENDIX I: DATA ABSTRACTION FORM

RADICAL HYSTERECTOMY AS PRIMARY TREATMENT FOR EARLY STAGE CERVICAL CANCER AT KNH 2012-2018

SECTION A: IDENTIFIERS

STUDY NO.

SECTION A: ELIGIBILITY TO STUDY

1.) File available in Records Department
( )Yes move to 2
( ) No. exclude from study
2.) Confirmed diagnosis of invasive cervical cancer, dated histopathology report available

( ) Yes move to 3

( ) No. exclude from study

3.) FIGO Staging Indicated as 1A -IIA
( ) Yes move to 4
( ) No exclude from study
4.) Had radical hysterectomy at KNH as primary treatment
( ) Yes move to section B
( ) No exclude from study

NOTE, MOVE TO SECTION B ONLY IF HAD RADICAL HYSTERECTOMY AND STAGE 1A-IIA

SECTION B : SOCIAL DEMOGRAPHIC DATA

1. DATE OF BIRTH DD/MM/YY
--/--/-- ( ) Not indicated
2. Age in years ……..( ) Not indicated
3. Marital status
( )Single
( )Married
( )Separated
( )Widowed
( )Others(specify
( )Not indicated
4. Parity ……+…….( )Not indicated
5. Religion
( ) Christian
( )Muslim
( ) Others(specify)……
( ) None
6. Occupation
( )None
( )Casual laborer

( ) Self employed
( ) Formal employment
( ) Not indicated

7. Education Level
   ( ) No formal education
   ( ) Primary Level
   ( ) Secondary Level
   ( ) College/University
   ( ) Not indicated
8. NHIF Registered
   ( ) Yes
   ( ) No
   ( ) Not indicated

SECTION C: CLINICAL CHARACTERISTICS

PREOPERATIVE CLINICAL ASSESMENT

1.Pre-operative Hb……..g/dl

2.HIV status

( ) Seronegative

( ) Seropositive

3.Use of HAART

( )YES ( )NO…..

4. Last viral load count ……..( ) Not indicated
5. Last CD4 Count…….. (.) Not indicated
6. Other cormorbidities
   ( ) Diabetes Mellitus
   ( )Hypertension
   ( ) Others (specify)…….
7. FIGO Clinical staging Procedure
   ( ) Examination under anesthesia at KNH
   ( ) Examination under anesthesia outside KNH
   ( ) Examination without anesthesia at KNH
8. FIGO clinical stage
   ( )Stage IA1
   ( )Stage IA2
   ( )Stage IB1
   ( )Stage IB2
   ( )Stage IB3
   ( )Stage IIA1

( )Stage IIA2

9. PREOPERATIVE IMAGING AND METASTATIC WORK UP

( )None

( )Pelvic Ultrasound

( ) CT SCAN

( )MRI

( )PET CT

( )Chest Xray

SECTION D: TIME OF EVENTS

1. Date of diagnosis as indicated on histopathology report of biopsy--/--/-- DD/MM/YY
2. Date of first clinic visit at KNH --/--/-- DD/MM/YY
3. Date of surgery as indicated in the operations notes---/--/-- DD/MM/YY
4. Date of last clinic visit as indicated in the file notes ---/---/--- DD/MM/YY
5. Total time of follow up after surgery…….months

SECTION E : SURGICAL OUTCOMES

Surgical approach: Open abdominal( ) Laparoscpic ( )

1.0 COMPLICATIONS AFTER RADICAL HYSTERECTOMY

1.1 ACUTE COMPLICATIONS

( ) None

( )Major Vessel Injury

( )Transfusion

( )Ureteric Injury
( )Bladder injury
( )Bowel injury
( )Deep Venous Thrombosis/ Pulmonary Embolism
( )Death

1.2 LATE COMPLICATIONS

( ) None

( )Urinary fistulae

( )Rectal fistulae

( )Lymphedema of the Lower Limbs

( )Others(specify)……..

2.0 HISTOPATHOLOGIC FINDINGS AFTER RADICAL HYSTERECTOMY

2.1 HISTOLOGIC TYPE AND GRADE(Tick all that applys)

( )SQUAMOUS CELL CARCINOMA

( ) Well differentiated

( ) Moderately differentiated

( ) Poorly differentiated

( ) Keratinizing

( ) Non -keratinizing

( ) Large cell

( )Small cell

( )ADENOCACINOMA

( )Well differentiated

( )Moderately differentiated

( )Poorly differentiated

( ) Sarcoma

( ) Anaplastic

( )Other Histologic Types(Specify)…….

2.2 SURGICAL OUTCOMES: RISK FACTORS FOR RECURRENCE

INTERMEDIATE RISK FACTORS(Tick all that apply)

( )Capillary & Lymphovascular space Involvement(LVI)

Stromal involvement

( )Superficial

( )>1/3 (middle)

( )>1/3 (deep third)

Tumour size

( )> 2cms <4cms

( )>4cms

( )>5cms

HIGH RISK FACTORS

( )Positive Margins

( )Parametrial involvement

( )Positive nodes

3.0 SURGICAL OUTCOMES: COMPLEMENTARY TREATMENT

3.1 ADJUVANT CHEMORADIATION

( )Indicated as per sedlis criteria

( )Not indicated

3.2 If indicated, please state if

( )Indicated and given

( )Indicated and NOT given

3.3 If indicated and NOT given, give reason

( ) Declined

( ) Not informed

( )Radiotherapy not affordable

( ) Long Distance to the radiotherapy unit

( )Long waiting list

( )Others (specify)

3.2 NEOADJUVANT CHEMOTHERAPY

( )Offered

( )Not offered

4.0 Survival

( )Alive at end of study

……months

( ) Dead

( ) unknown

If dead, months alive after radical hysterectomy……..months

APPENDIX II: DUMMY TABLES

Table 1: Socio-Demographic Characteristic among Radical Hysterectomy Patients.

Characteristics	n (%), 95% CI	Statistical Parameter
Age (in 1 Years)		
Mean	-	Mean Age
Median	-	Median Age
Range	-	Min-Max
• 19-29 • 30-39 • 40-49 • 50-60 • 65+		***Proportion/Percentage***
Parity		
Mean	-	Mean Age
Median	-	Median Age
Range	-	Min-Max
• Zero • 1-2 • 3-4 • 4+		***Proportion/Percentage***
Marital Status • Married • Single • Divorced • Window/Widower		***Proportion/Percentage***
Education • None • Primary • Secondary • Tertiary • College/University		***Proportion/Percentage***
Religion • Christian • Muslim • Others • None		***Proportion/Percentage***
Occupation • None • Casual laborer • Formal Employment • Not indicated		***Proportion/Percentage***

NHIF Registered • Yes • No		***Proportion/Percentage***

Table 2: Clinical Characteristic among Radical Hysterectomy Patients.

Characteristics	n (%), 95% CI	Statistical Parameter
Hemoglobin Level • >10g/dl • 8-10g/dl • <8g/dl		***Proportion/Percentage***
HIV Status • +VE • -VE		***Proportion/Percentage***
On HAART • Yes • No		***Proportion/Percentage***
FIGO Stage • Stage IAI • Stage IA2 • Stage IB1 • Stage IB2 • Stage IB3 • Stage IIAI • Stage IIA2		***Proportion/Percentage***

Table 3: Pre-Operative imaging and Metastatic Work up among Radical Hysterectomy Patients.

Characteristics	n (%), 95% CI	Statistical Parameter
• None • Pelvic Ultrasound • CT Scan • MRI • PET CT • Chest X-ray		***Proportion/Percentage***

Table 4: Surgical Outcomes among Radical Hysterectomy Patients: Complications

Characteristic	n (%), 95% CI	Statistical Parameter

A:- Acute Complications • *Major Vessel Injury* • *Ureteric Injury* • *Bladder Injury* • *Bowel Injury* • *Deep Venous Thrombosis* • *Death* **B:- Late Complications** • *Urinary Fistula* • *Rectal Fistula* • *Lymphedema of Lower limp*		***Proportion/Percentage***

Table 5: Surgical Outcomes among Radical Hysterectomy Patients: Histopathology

Characteristic	**n (%) 95% CI**	**Statistical Parameter**
A: Histologic Type and Grade **Squamous Cell Carcinoma** • Well Differentiated • Moderately Differentiated • Poorly Differentiated **Adenocarcinoma** • Well Differentiated • Moderately Differentiated • Poorly Differentiated **Others** (Specify)		
B: Risk Factors for Disease Recurrence		
Intermediate Risk Factors **Stromal involvement** • Superficial • >1/3 (middle) • >1/3 (deep third) **Tumour size** • 2cms <4cms • >4cms • >5cms		
High Risk Factors • Positive Margins		

• Parametrial involvement • Positive nodes		

Table 6: Surgical Outcomes among Radical Hysterectomy Patients: Complementary Treatment

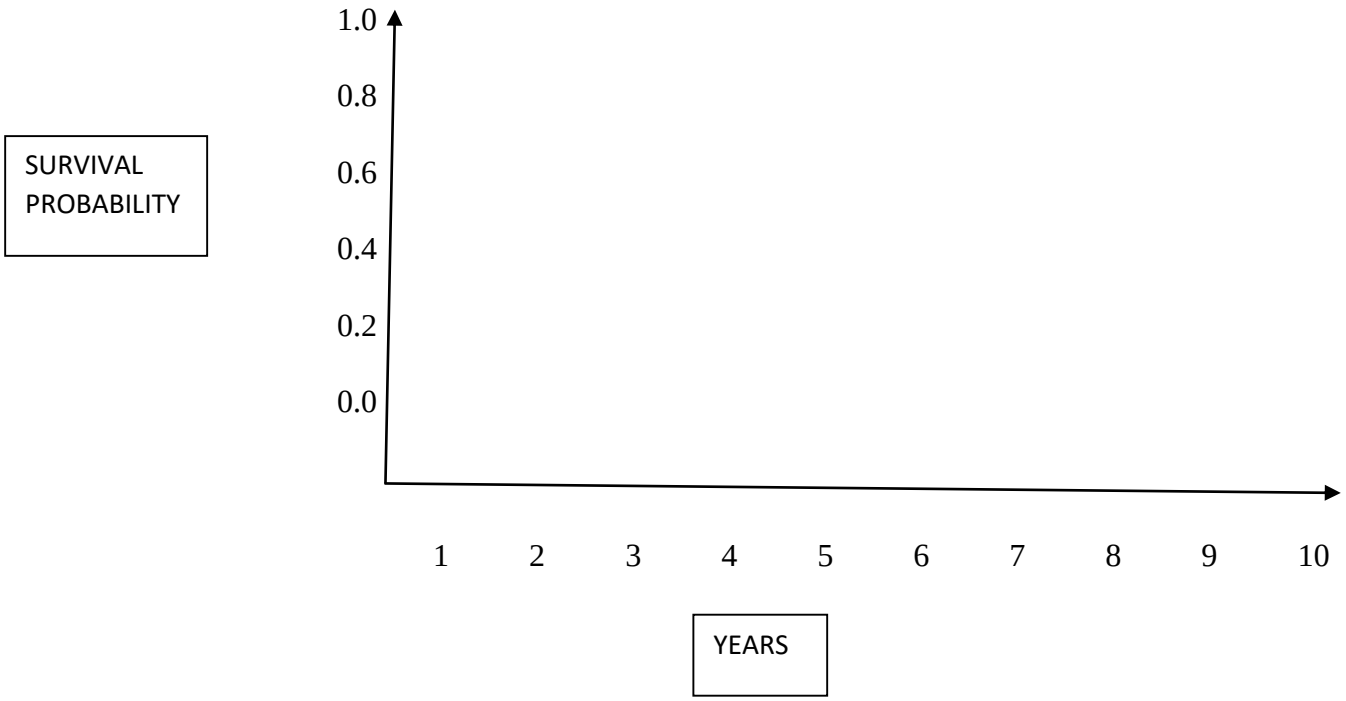
Characteristic	**n (%) 95% CI**	**Statistical Parameter**
Complementary Chemoradiation • Not Indicated • Indicated • Indicated and given • Indicated and Not given		
Neoadjuvant Chemotherapy • Offered • Not offered		

Table 7: Survival

Characteristic	**n (%) 95% CI**	**Statistical Parameter**
Survival in Months		
• 6 months • 6-12 months • 12-18months • 18-24 months		

Figure 1:
Kaplan Meir survival curves for patients with invasive cervical cancer after radical hysterectomy

Figure 2: DUMMY KAPLAN-MEIER CURVE



APPENDIX III: (A)FIGO STAGING OF INVASIVE CERVICAL CANCER 2009

STAGE	DESCRIPTION
STAGE I	**Cancer confined to the cervix (extension to the corpus disregarded)**
IA	Invasive cancer diagnosed by microscopy, maximum depth of invasion< 5mm greatest dimension < 7mm • IA1: stromal invasion < 3mm, • IA2: stromal invasion >3<5mm
IB	Invasive cancer with stromal invasion > 5mm but confined to cervix • IB1: Invasive cancer > 5mm depth of stromal invasion and < 4cms greatest dimension • IB2: Invasive cancer >4cms in greatest dimension but confined to cervix
STAGE II	**Cancer extension to upper vagina (1/3) and parametria (but not to pelvic wall or lower 1/3 vagina)**
IIA	Involvement of upper 1/3 of vagina, no parametrial extension IIA1: Invasive cancer < 4cms greatest dimension IIA2: Invasive cancer > 4cms greatest dimension
IIB	Parametrial extension but not to pelvic sidewall
STAGE III	**Carcinoma involves the lower 1/3 of vagina and extends to pelvic side wall and/or causes hydronephrosis, non-functioning kidney,**
IIIA	Cancer extends to the lower 1/3 of vagina, no pelvic sidewall involvement
IIIB	Extension to pelvic side wall and/or causes hydronephrosis, non-functioning kidney
STAGE IV	**Biopsy proven bladder or rectal involvement and spread beyond true pelvis**
	IVA: Bladder involvement IVB: Rectal or distant organs

APPEDIX III: (B)REVISED FIGO STAGING OF CERVICAL CANCER 2018

STAGE	DESCRIPTION
STAGE I	**Cancer confined to the cervix (extension to the corpus disregarded)**
IA	Invasive cancer diagnosed by microscopy, maximum depth of invasion< 5mm *a • IA1: stromal invasion < 3mm • IA2: stromal invasion >3<5mm
IB	Invasive cancer with stromal invasion > 5mm but confined to cervix*b • IB1: Invasive cancer > 5mm depth of stromal invasion and < 2cms greatest dimension • IB2: Invasive cancer > 2cms but <4cms in greatest dimension • IB3: Invasive cancer >4cms in greatest dimension but confined to cervix
STAGE II	**Cancer extension to upper vagina (1/3) and parametria (but not to pelvic wall or lower 1/3 vagina)**
IIA	Involvement of upper 1/3 of vagina, no parametrial extension IIA1: Invasive cancer < 4cms greatest dimension IIA2: Invasive cancer > 4cms greatest dimension
IIB	Parametrial extension but not to pelvic sidewall
STAGE III	**Carcinoma involves the lower 1/3 of vagina and extends to pelvic side wall and/or causes hydronephrosis, non-functioning kidney, and/or pelvic or paraaortic nodes*c**
IIIA	Cancer extends to the lower 1/3 of vagina, no pelvic sidewall involvement
IIIB	Extension to pelvic side wall and/or causes hydronephrosis, non-functioning kidney
IIIC	Involvement of pelvic or para-aortic nodes irrespective of tumor size and extent (with r and p notations) *c • IIIC1: pelvic node involvement • IIIC2: para-aortic node involvement
STAGE IV	**Biopsy proven bladder or rectal involvement and spread beyond true pelvis**
	IVA: Bladder involvement IVB: Rectal or distant organs

***a:** Imaging and pathology can be used to supplement clinical findings

*b: Lympho-vascular space involvement does not change the stage

*c: Adding notation of r(imaging) and p(pathology) to indicate findings that were used to allocate stage IIIC. Technique of imaging should be documented.

When in doubt with imaging, allot the lower stage.

Areas in red highlight the new changes to the staging system with greater emphasis on imaging and node involvement in stage determining the disease stage

APPENDIX IV: SEDLIS CRITERIA FOR POSTOPERATIVE RADIOTHERAPY AFTER RADICAL HYSTERECTOMY FOR INVASIVE CERVICAL CANCER

INTERMEDIATE RISK FACTORS ELIGIBILTY TABLE

CLS*	Stromal Invasion	**Tumor size**
Positive	Deep 1/3	**Any**
Positive	Middle 1/3	**2cms**
Positive	Superficial 1/3	5cms
Negative	Deep or middle 1/3	>4cms

*****capillary lymphatic space involvement with tumor

At-least 2 intermediate factors are needed to justify adjuvant complimentary chemoradiation

HIGH RISK FACTORS: ANY

Lymph node metastasis

Parametrial invasion

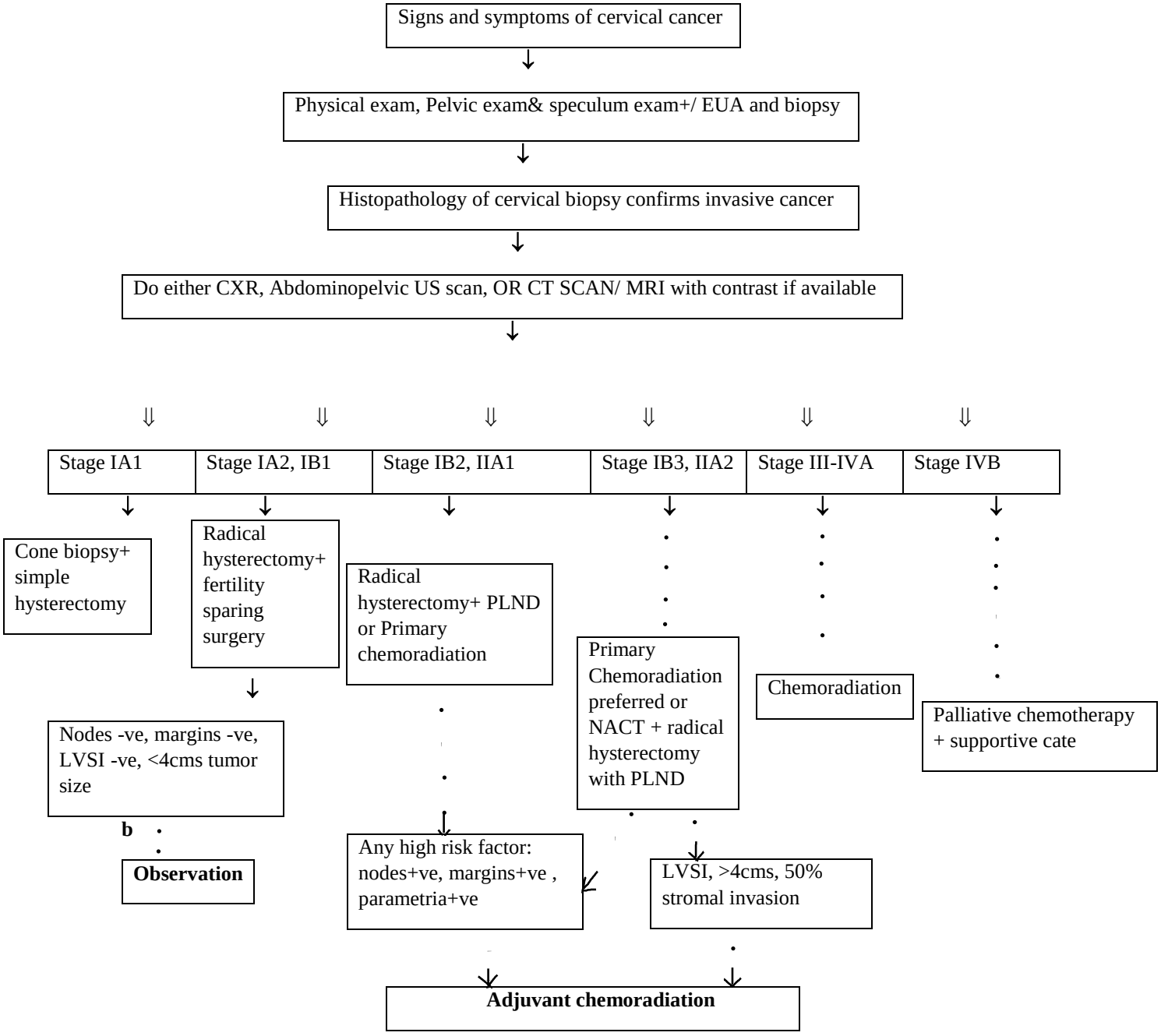
Positive margins

Sedlis et al, Gynecologic Oncology1999

TABLE 1: CLASSIFICATIONS OF RADICAL HYSTERECTOMY

Piver-Rutledge-Smith		EORTC-GCG		Querleu & Morrow	
Class I	Simple extra-fascial hysterectomy	Type I	Simple hysterectomy	Type A	Simple hysterectomy, uterosacral and cardinal ligaments resected very close to the corpus uteri, < 10mm of vaginal cuff margin
Class II	Modified Radical hysterectomy (Wertheims) Ureters dissected in the paracervical region but not resected from pubocervical ligament. Uterine art ligated beside and medial to the ureter. Medial half of uterosacral and cardinal ligaments resected. Removal of upper 1/3 vagina. PLND	Type II	Modified Radical hysterectomy Ureters dissected in the paracervical region and pubocervical ligament upto entry into the bladder. Uterine art are ligated in the medial half of parametria Medial half of uterosacral and cardinal ligaments resected. Removal of upper 1/3 vagina. PLND	Type B	Modified Radical hysterectomy BI: ureters de-peritonized to lateral side. No removal of lateral paracervical nodes. Medial half of uterosacral and cardinal ligaments resected. Removal of >10mm vagina margin(tumor/cervix) + PLND B2: AS ABOVE + removal of lateral cervical nodes
Class III	Classical radical hysterectomy(Meigs) Complete dissection of ureter & pubocervical ligaments upto entry into the bladder. Resection of cardinal and uterosacral ligaments at insertion on pelvic wall. Uterine art are ligated at origin from internal iliac art. Removal of upper 1/3 vagina + PLND	Type III	SAME AS CLASS III Piver-Rutledge- Smith	Type C	SAME AS CLASS III Piver-Rutledge- Smith Plus atleast 15-20mm vaginal margin C1: with preservation of autonomic nerves C2: witn no preservation of autonomic nerves
Class IV	Like Class III plus Ligation of umbilical artery(superior vesical) and resection of upper ¾ of vagina		SAME AS CLASS IV	Type D	D1: All paracervical tissue together with hypogastric vessels excised up to pelvic bone with exposure of sciatic nerve roots. Ureter completely freed. D2: Excision of adjacent muscle and fascia
Class V	Resection of terminal ureter plus portion of bladder with ureteric reimplantation	Type V	SAME AS CLASS V		

APPENDIX VI: KENYA CERVICAL CANCER MANAGEMENT ALGORITHM



APPENDIX VII
VERBAL CONSENT FORM: CERVICAL CANCER RESEARCH

Dear Respondent,

I am Dr. Wycliffe Akikuvi Musalia, a cancer researcher from the University of Nairobi and Kenyatta National Hospital.

I am conducting research on women who had cancer of the cervix and had surgery to remove the uterus at KNH between 2012-2018 as treatment for the cancer. This research has been approved by the University of Nairobi and KNH Ethical review committee.

Your/her file (…patients name……..) was among those we selected from our Records Department for obtaining information useful to this study. While going through it, we were unable to tell what happened to you/her after surgery because we did not this information in the file.

In order to complete this study, I need your assistance with regard to clarifying some of the information that is missing/unclear from your/her file. I wish to state at this point that the information you provide will only be used for the purpose of this study, and it will be treated with utmost confidentiality and privacy.

The correctness and sincerity of your responses will be highly appreciated and critical to the integrity of the study findings. A recording of this phone call may be done for future reference. The phone call may take about five minutes.

Kindly understand that you are not under any obligation to comply with this request. And your non participation will NOT influence the care you receive from KNH now or in future in any way.

If you wish to proceed, kindly say YES and if you are not willing to proceed say NO.

May we proceed? YES….. NO…….

Thankyou for your time.

KISWAHILI VERSION

KIBALI KWA SIMU YA RUNUNU: UTAFITI KWA SARATANI YA UKE

Mpendwa mhojiwa,

Mimi ni Daktari Wycliffe Akikuvi Musalia, mtafiti wa saratani kutoka chuo kikuu cha Nairobi na Hospitali ya Kitaifa ya Kenyatta.

Ninafanya utafiti kuhusu wanawake waliotibiwa kwa upasuaji na kutolewa kizazi kama tiba ya kwanza ya saratani ya uke kuanzia mwaka wa 2012 hadi 2019.

Utafiti huu umeidhinishwa na Hospitali ya Kitaifa ya Kenyatta / Kamati ya Maadili na Utafiti ya Chuo Kikuu cha Nairobi. Faili yako ni kati ya zile tulizo zichagua kwa sababu ya utafiti.

Ninapiga simu kwa sababu ninahitaji msaada wako kufafanua baadhi ya habari ambayo haipo au haijulikani wazi kutoka faili yako. Habari hii itatusaidia kumaliza utafiti na kuelewa jinsi ya kusimamia wagonjwa walio na saratani ya uke. Ningependa kukuhakishia ya kwamba hakuna habari yako ya kutambua itakusanywa. Habari iliyokusanywa itatumika tu kwa madhumuni ya utafiti huu. Habari yako itahifadhiwa kwa siri. Tafadhali kumbuka kuwa simu inaweza kurekodiwa kwa sababu za kumbukumbu. Simu itadumu kwa dakika tano.

Iwapo utachagua kutotoa habari yoyote au kuacha kutoa habari wakati wowote, haitaathiri utunzaji unaopewa wewe au mpendwa wako katika Hospitali ya Kitaifa ya Kenyatta.

Je! Una maswali / ufafanuzi wowote? Ningefurahi kujibu maswali au kufafanua wasiwasi wowote.

Je! Uko tayari kushiriki katika utafiti na kujibu maswali kadhaa kwa simu?

NDIO ( ) LA ( )

ASANTE SANA KWA MUDA WAKO.

APPENDIX V: SURVIVAL DATA TABLES 12-14

***Table12**: Overall survival with time in months after radical hysterectomy*

	Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	.300	Dead	.983	.017	1	59
2	5.000	Dead	.	.	2	58
3	5.000	Dead	.950	.028	3	57
4	17.000	Alive	.	.	3	56
5	21.000	Dead	.933	.032	4	55
6	24.000	Alive	.	.	4	54
7	25.000	Alive	.	.	4	53
8	28.000	Alive	.	.	4	52
9	28.000	Alive	.	.	4	51
10	29.000	Alive	.	.	4	50
11	34.000	Alive	.	.	4	49
12	36.000	Alive	.	.	4	48
13	37.000	Dead	.914	.037	5	47
14	38.000	Alive	.	.	5	46
15	38.000	Alive	.	.	5	45
16	43.000	Alive	.	.	5	44
17	48.000	Dead	.	.	6	43
18	48.000	Dead	.872	.046	7	42
19	49.000	Alive	.	.	7	41
20	50.000	Alive	.	.	7	40
21	52.000	Alive	.	.	7	39
22	53.000	Alive	.	.	7	38
23	55.000	Alive	.	.	7	37
24	55.000	Alive	.	.	7	36
25	56.000	Alive	.	.	7	35
26	57.000	Alive	.	.	7	34
27	58.000	Alive	.	.	7	33
28	58.000	Alive	.	.	7	32
29	59.000	Alive	.	.	7	31
30	60.000	Alive	.	.	7	30
31	61.000	Alive	.	.	7	29
32	61.000	Alive	.	.	7	28
33	63.000	Alive	.	.	7	27
34	64.000	Alive	.	.	7	26
35	66.000	Alive	.	.	7	25
36	69.000	Alive	.	.	7	24

37	69.000	Alive	.	.	7	23
38	69.000	Alive	.	.	7	22
39	69.000	Alive	.	.	7	21
40	70.000	Alive	.	.	7	20
41	71.000	Alive	.	.	7	19
42	72.000	Alive	.	.	7	18
43	73.000	Alive	.	.	7	17
44	75.000	Alive	.	.	7	16
45	75.000	Alive	.	.	7	15
46	75.000	Alive	.	.	7	14
47	75.000	Alive	.	.	7	13
48	76.000	Alive	.	.	7	12
49	77.000	Alive	.	.	7	11
50	77.000	Alive	.	.	7	10
51	79.000	Alive	.	.	7	9
52	80.000	Alive	.	.	7	8
53	80.000	Alive	.	.	7	7
54	80.000	Alive	.	.	7	6
55	81.000	Alive	.	.	7	5
56	82.000	Alive	.	.	7	4
57	82.000	Alive	.	.	7	3
58	86.000	Alive	.	.	7	2
59	87.000	Alive	.	.	7	1
60	91.000	Alive	.	.	7	0

Means and Medians for Overall Survival during follow-up calculated as a percentage

Mean[a]				Median			
		95% Confidence Interval				95% Confidence Interval	
Estimate	Std. Error	Lower Bound	Upper Bound	Estimate	Std. Error	Lower Bound	Upper Bound
82.599	3.048	76.624	88.574	.	.	.	.

a. Estimation is limited to the largest survival time if it is censored.

***Table14**: Two-year survival in months by FIGO clinical stage of disease after radical hysterectomy for ICC at KNH (2012-2018)*

FIGO Clinical Staging		Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
				Estimate	Std. Error		
IA1	1	60.000	Alive	.	.	0	1
IA2	1	24.000	Alive	.	.	0	8
	2	38.000	Alive	.	.	0	7
	3	55.000	Alive	.	.	0	6
	4	56.000	Alive	.	.	0	5
	5	71.000	Alive	.	.	0	4
	6	75.000	Alive	.	.	0	3
	7	75.000	Alive	.	.	0	2
	8	77.000	Alive	.	.	0	1
IB1	1	17.000	Alive	.	.	0	14
	2	28.000	Alive	.	.	0	13
	3	34.000	Alive	.	.	0	12
	4	38.000	Alive	.	.	0	11
	5	48.000	Dead	.909	.087	1	10
	6	49.000	Alive	.	.	1	9
	7	61.000	Alive	.	.	1	8
	8	69.000	Alive	.	.	1	7
	9	70.000	Alive	.	.	1	6
	10	75.000	Alive	.	.	1	5
	11	76.000	Alive	.	.	1	4
	12	77.000	Alive	.	.	1	3
	13	82.000	Alive	.	.	1	2
	14	82.000	Alive	.	.	1	1
	15	86.000	Alive	.	.	1	0
IB2	1	25.000	Alive	.	.	0	15
	2	28.000	Alive	.	.	0	14
	3	37.000	Dead	.929	.069	1	13
	4	43.000	Alive	.	.	1	12
	5	48.000	Dead	.851	.097	2	11
	6	50.000	Alive	.	.	2	10
	7	52.000	Alive	.	.	2	9
	8	55.000	Alive	.	.	2	8

	9	58.000	Alive	.	.	2	7
	10	59.000	Alive	.	.	2	6
	11	69.000	Alive	.	.	2	5
	12	69.000	Alive	.	.	2	4
	13	72.000	Alive	.	.	2	3
	14	73.000	Alive	.	.	2	2
	15	80.000	Alive	.	.	2	1
	16	91.000	Alive	.	.	2	0
1B3	1	.300	Dead	.857	.132	1	6
	2	5.000	Dead	.714	.171	2	5
	3	58.000	Alive	.	.	2	4
	4	63.000	Alive	.	.	2	3
	5	66.000	Alive	.	.	2	2
	6	80.000	Alive	.	.	2	1
	7	81.000	Alive	.	.	2	0
IIA1	1	5.000	Dead	.833	.152	1	5
	2	21.000	Dead	.667	.192	2	4
	3	29.000	Alive	.	.	2	3
	4	36.000	Alive	.	.	2	2
	5	57.000	Alive	.	.	2	1
	6	75.000	Alive	.	.	2	0
IIA2	1	53.000	Alive	.	.	0	4
	2	64.000	Alive	.	.	0	3
	3	69.000	Alive	.	.	0	2
	4	79.000	Alive	.	.	0	1

***Table14**: Five-year survival in months after radical hysterectomy for ICC at KNH (2012-2018)*

	Time	Status	Cumulative Proportion Surviving at the Time		N of Cumulative Events	N of Remaining Cases
			Estimate	Std. Error		
1	.300	Dead	.974	.026	1	37
2	5.000	Dead	.947	.036	2	36
3	37.000	Dead	.921	.044	3	35
4	48.000	Dead	.	.	4	34
5	48.000	Dead	.868	.055	5	33
6	55.000	Alive	.	.	5	32
7	59.000	Alive	.	.	5	31
8	60.000	Alive	.	.	5	30
9	61.000	Alive	.	.	5	29
10	61.000	Alive	.	.	5	28
11	63.000	Alive	.	.	5	27
12	64.000	Alive	.	.	5	26
13	66.000	Alive	.	.	5	25
14	69.000	Alive	.	.	5	24
15	69.000	Alive	.	.	5	23
16	69.000	Alive	.	.	5	22
17	69.000	Alive	.	.	5	21
18	70.000	Alive	.	.	5	20
19	71.000	Alive	.	.	5	19
20	72.000	Alive	.	.	5	18
21	73.000	Alive	.	.	5	17
22	75.000	Alive	.	.	5	16
23	75.000	Alive	.	.	5	15
24	75.000	Alive	.	.	5	14
25	75.000	Alive	.	.	5	13
26	76.000	Alive	.	.	5	12
27	77.000	Alive	.	.	5	11
28	77.000	Alive	.	.	5	10
29	79.000	Alive	.	.	5	9
30	80.000	Alive	.	.	5	8
31	80.000	Alive	.	.	5	7
32	80.000	Alive	.	.	5	6
33	81.000	Alive	.	.	5	5
34	82.000	Alive	.	.	5	4
35	82.000	Alive	.	.	5	3
36	86.000	Alive	.	.	5	2
37	87.000	Alive	.	.	5	1
38	91.000	Alive	.	.	5	0