UNIVERSITY OF NAIROBI

Faculty of Health Sciences

Department of Surgery

THE PREVALENCE AND FACTORS ASSOCIATED WITH ACUTE COMPLICATIONS OF EXTERNAL BEAM RADIOTHERAPY AMONG PATIENTS ON TREATMENT FOR ANAL CANCER IN KENYATTA NATIONAL HOSPITAL

A dissertation submitted as Part Fulfillment for the Award of The Degree of Master of Medicine (General Surgery), University of Nairobi

Principal Investigator:
Dr. Lawrence Koli Kioko (MBChB)
Reg No: H58/71556/2007

DECLARATION

I declare that this thesis is my original work and has not been presented for a degree in any other institution or university.

Dr. Lawrence Koli Kioko

MBChB (UON)

Signature.....Date....24/4/2022.....

SUPERVISORS APPROVAL

This dissertation has been submitted for our review

Dr. Elly Nyaim Opot

MBChB, M. Med General Surgery (UON),FCS(ECSA)

Senior Lecturer, Department of Surgery, University of Nairobi

Consultant General Surgeon, Kenyatta National Hospital

Signature.....

Date.....25/4/2022.....

Dr. Marilynn A. Omondi

MBChB, MMed (General Surgery) UON

Consultant General Surgeon, Kenyatta National Hospital

Signature.....

Date.....25/04/22.....

Dr. Catherine Nyongesa

MBChB, M.Med (Radio-Oncology, University of Witwatersrand, S.A)

Consultant Radio-Oncologist, Kenyatta National Hospital

Signature.....

Date.....25/4/22.....

DEPARTMENTAL APPROVAL

This research proposal was submitted at the General Surgery Department meeting at the University of Nairobi held on **8th April 2021** and approved by Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-ERC) on **9th August 2021**. The dissertation is hereby submitted for examination with my approval as the Chairman of, the Department of Surgery

Dr. Julius Kiboi Githinji
Senior Lecturer and Consultant Neurosurgeon
Department of Surgery, Faculty of Health Sciences
University of Nairobi

Signed.....

Date.....26/4/2022

DEPARTMENT OF SURGERY
COLLEGE OF HEALTH SCIENCES
P. O. Box 19676 - 00202 KNH
NAIROBI
2726300, Ext. 43773

LIST OF ABBREVIATIONS

5FU:	5-Fluorouracil
ACA:	Anal Carcinoma
AIDS:	Acquired Immunodeficiency Syndrome
AJCC:	American Joint Committee on Cancer
APR:	Abdominoperineal Resection
CRT:	Chemoradiotherapy
CT:	Computerized Tomography
DRE:	Digital Rectal Examination
EBRT:	External Beam Radiotherapy
HIV/AIDS:	Human Immunodeficiency Virus/Acquired Immunodeficiency Virus
HPV:	Human Papilloma Virus
IARC:	International Association in Research on Cancer
IARC:	International Agency for Research on Cancer
IBD:	Inflammatory Bowel Disease
IGRT:	Image-Guided Radiotherapy
IMRT:	Intensity-Modulated Radiotherapy
KNH:	Kenyatta National Hospital
MMC:	Mitomycin C
MRI:	Magnetic Resonance Imaging
MSM:	Men having Sex with Men
NCCN:	National Comprehensive Cancer Network
NCI:	National Cancer Institute
CTCAE:	Common Terminology Criteria for Adverse Events
OAR:	Organ at Risk
PET:	Positron Emission Tomography
QOL:	Quality of Life
RT:	Radiotherapy
RTOG:	Radiation Therapy Oncology Group
SCC:	Squamous Cell Carcinoma
TD:	Total Dose
OSR:	Overall Survival Rate
WHO:	World Health Organization

OPERATIONAL DEFINITIONS

Acute Complications: Immediate and unfavorable result of a disease, health condition, or treatment.

Adverse Events: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product

Toxicity: The degree to which a chemical substance or a particular mixture of substances can damage an organism.

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ABSTRACT

Background

The treatment of anal carcinoma has tremendously evolved over the last three decades from surgery to the current primary treatment of chemoradiation. However, the use of chemoradiation has often been challenging and fraught with acute toxicity due to the proximity of vulnerable organs in the field of treatment. Data on the impact and prevalence of acute complications together with associated risk factors is limited and has not been sufficiently demonstrated in our setting.

The purpose of the study

This study aimed to determine the prevalence and factors associated with acute complications among patients treated with EBRT for anal carcinomas in Kenyatta National Hospital.

Study Setting and Population

The study was carried out in Kenyatta National Hospital in patients diagnosed with anal carcinoma and receiving definitive radiotherapy treatment at Cancer Treatment Centre, Surgical Outpatient Clinic (SOPC), and adult wards.

Study design and Methodology

This was a prospective cohort study of newly diagnosed anal carcinoma patients undergoing EBRT at KNH who fulfilled the inclusion criteria and gave informed consent. Pretreatment demographic and clinical data of the patients were collected and recorded before the beginning of EBRT and acute complications involving the skin, genitourinary, lower gastrointestinal systems were assessed, graded, and recorded at the mid-session of EBRT and the end of EBRT administration using the NCI-CTC (The National Cancer Institute – Common Terminology Criteria) grading scale.

Data Analysis

Data collected was entered and analyzed using Statistical Package for Social Sciences (SPSS) for Windows Version 21. P values were generated and results were presented in tables, figures, and graphs.

The utility of the study

The data generated will facilitate and develop local management protocols that would mitigate against these adverse events, and optimize clinical outcomes and/or QOL among patients with anal cancer. This study will also form a baseline for future studies on the role of

radiotherapy in the management of cancer particularly with the emergence of newer techniques of its administration.

Results

39 patients met the inclusion criteria, of which 29(85.7%) were female, with a median age at diagnosis of 46 y (min-max: 29-79 y). The median time from the first symptom to diagnosis was 14.5 weeks (min-max: 3-48 weeks). The most common presenting symptom was local pain (n = 13; 41.9%), followed by hemorrhage (n = 11; 35.5%). Only 1(7,7%) patient was HIV-positive. The tumor stage according to the 7th edition of the AJCC manual was distributed as follows: Stage I: 2 cases (5.7%); Stage II: 10 cases (29.4%); Stage IIIA: 8 cases (23.5%), stage IIIB: 14 cases (41.2%), and 4(12,5%) cases were cT4 tumors. Most patients were treated with a dose of 50.4Gy to nodal basins and a total dose between 50.4 and 59Gy to the tumor volume, using 2D-CRT in all. The median treatment duration was 44 days (min-max: 32-90). Radiotherapy delays due to toxicity – that was mostly Skin – occurred in 22 (62.9%) cases. The chemotherapy regimen used was mainly Cisplatin combined with 5-fluorouracil, which was substituted for capecitabine in one patient. Grade 3 or greater acute treatment toxicities occurred in 27(79.4%) cases and there were 2 deaths during treatment due to septicemia. In 8(23.5%) cases, only one cycle of chemotherapy was administered due to toxicity, and 7(20.6%) of patients underwent dose reductions. Febrile neutropenia occurred in 6(17.6%) cases.

Conclusion

In our experience, combined modality treatment with chemotherapy and radiation showed to have similar efficacy to other published studies, despite a high rate of acute toxicities. Due to the rarity of the disease and its complex management, treatment should be done at experienced centers. Strict adherence to treatment guidelines and careful follow-up are mandatory to optimize outcomes.

CHAPTER ONE: INTRODUCTION

1.0: Background

Anal Carcinoma (ACA), although a rare cancer of the distal end of the gastrointestinal tract is associated with substantial disease morbidity and mortality. According to the GLOBOCAN data on cancer incidence and mortality by the International Agency for Research on Cancer (IARC) in 2019, the global incidence of ACA is estimated to be about 0.3% of all cancers and 1%-2% of gastrointestinal cancer(1). In the United States of America, about 8,300 new ACA cases were diagnosed in 2018, and in the last two to three decades, however, there has been an unprecedented increase in the incidence rates from 0.8 to 1.7/100,000 persons/year between 1975 and 2011(2). Locally data on the prevalence of anal carcinoma is limited, but some of the available data obtained from the Kenyatta National Hospital Health Information Department indicate that from2018 to 2020 approximately 528 new cases were diagnosed averaging176 cases annually of anorectal cancer, and approximately36 patients annually of anal carcinoma(Appendix F). However, this data may not reflect the true picture of anal carcinoma and could be higher due to misdiagnosis and the absence of a cancer register.

Table 1: Malignant Neoplasms of Anus and Rectum in KNH

Code	Disease Name	2018	2019	2020	Total
C 20	Malignant Neoplasm of Rectum	187	136	99	422
C 21	Malignant Neoplasms of the Anus and Anal canal	1	2	NR	3
C21.0	Malignant neoplasm of the Anus (unspecified)	21	13	12	46
C 21.1	Malignant neoplasm, Anal canal	3	2	NR	5
C 21.8	Malignant neoplasm, Lesions overlapping Rectum, Anus, and the Anal canal	24	15	13	52
	Total	**225**	**175**	**134**	**528**

*Adapted with permission from KNH, health information department, NR= No Records

Anal carcinoma was historically managed by abdominal-perineal resection (APR) but in the mid-1970s, a study by Nigro et al(3), in a landmark paper, showed that the use of chemoradiation is superior; in terms of outcome, colostomy free survival, and a reduction of morbidity associated with surgery. In this study, three patients were started on radiotherapy at 30Gy but two received 5-fluorouracil while one was given mitomycin –C at the beginning of treatment. After 6 weeks of treatment, no residual disease was found in all three patients, which was validated in the subsequent phase III trials in larger cohort studies(4). Despite this quality-of-life improvement, the use of radiotherapy is associated with significant acute complications also called acute toxicity, which may cause unplanned treatment breaks, unintended dose reduction, and even treatment withdrawal. This often leads to unfavorable disease outcomes and negatively impacts the overall quality of life of patients. This study aimed to evaluate acute toxicity and its predictors in the local setting and quantify them.

1.1: PROBLEM STATEMENT AND STUDY JUSTIFICATION

Anal cancer despite being a rare gastrointestinal malignancy both locally and globally is associated with significant mortality and morbidity. With the emergency of HIV/AIDS in the last three decades, changes in lifestyles, and emerging culture evolution, its prevalence has been on the increase with an annual increase of 2.9% compared to cervical cancer which has been falling by 2.2% despite the main risk factor for both shown to be HPV infection. Further, there has been a paucity of data on treatment-related acute complications as a result of misclassification of anal cancers, difficult histological diagnosis, and complexity of the anal region.

The use of radiotherapy as part of a combined treatment modality has been associated with better clinical responses, albeit not without adverse clinical events. Though there is a demonstrated high potential for clinical benefit in the use of EBRT as a treatment modality, both acute and late adverse events related to therapy can cause increased morbidity, while the quality of life in some patients is often debilitating. The few studies done locally have mainly evaluated complications resulting from EBRT treatment in patients with cervical and prostate cancer but currently none on anal cancer

There is, therefore, a need to assess the prevalence and factors associated with the acute complications of EBRT among patients with anal cancer to ameliorate treatment complications, not to decrease the quality of life more than the disease process would have done. This study will also help facilitate the development of local management protocols that

would better preempt these adverse events, optimize the clinical outcomes and improve the quality of life of patients with not only anal cancer but other cancers where radiotherapy is utilized.

1.2: STUDY OBJECTIVES

1.2.1: General objective

To determine the prevalence and factors associated with acute complications of external beam radiotherapy among patients on treatment for anal cancer.

1.2.2: Specific objectives

1. To determine the prevalence of acute complications of EBRT among patients on treatment for anal cancer.
2. To determine associated factors for the development of acute complications for patients on treatment of EBRT of anal cancer.

CHAPTER TWO: LITERATURE REVIEW

2.0: Background

Anal carcinomas are cancers of the distal part of the gastrointestinal tract arising from the anal canal and anal margin or perianal skin which extends 3-4cm from the anorectal junction to the anal verge(5). There are different histological subtypes of anal carcinoma with the commonest being squamous cell cancer which comprises about 85% and adenocarcinoma less than10% of all diagnoses(6). The rarer subtypes include melanomas, carcinoid sarcomas, lymphomas, neuroendocrine tumors, and gastrointestinal stromal tumors(6).

2.1: Risk Factors

Anal carcinomas are often linked with Human Papillomavirus Infection (HPV) in 80-90% of cases(7). Arbyn et al 2012 showed that HPV serotypes 16 and 18 were most frequent, with HPV 16 accounting for approximately 75%, while HPV 18 was detectable in about 10% of the patients, however, in the vast majority about 80%, demonstrate multiple HPV genotypes(8). It is believed that chronic inflammatory changes in anal mucosa due to HPV infection, followed by epithelial dysplasia or high-grade anal intraepithelial neoplasia that ensues is the possible precursor to anal cancer(9). Additional risk factors include immunosuppression e.g., human immunodeficiency virus (HIV) infection, and patients with organ transplants. High-grade anal intraepithelial neoplasia has been shown to progress to invasive anal cancer in HIV-positive or immunocompromised patients(8). Smoking cigarettes is also linked with the development of anal cancer, much as it is with cervical cancer, though the risk of anal cancer appears to be associated with high pack-years that come with a much higher risk(10). The mechanism of smoking-associated tumors is unclear, but smoking may act as a co-carcinogen in the context of HPV infection. High-risk sexual behaviors such as multiple numbers of sexual partners, receptive anal sex, and men who have sex with men (MSM) have also been linked with a higher risk of anal carcinoma(11).

2.3: Clinical Presentation

Most patients with anal canal carcinoma present when the disease is at advanced stages III or IV, because, this cancer slowly progresses undetected extending to adjacent structures, particularly recto-vaginal septum in females and prostate and /or prostatic urethra in men without eliciting symptoms. Approximately 10-20 percent of cases tend to present early, particularly perianal skin cancer due to their superficial nature(12). The most common presentation of ACA is rectal bleeding occurring in approximately 45% of patients. This is

often misdiagnosed as hemorrhoids since both present commonly with pain and/or discomfort and delay diagnosis of ACA. Pain in the rectal area and/or sensations of rectal fullness and discomfort are reported by 30% of patients, while in 20% the disease is asymptomatic at diagnosis(5). Other signs and symptoms include changes in bowel movements, thin caliber stools, and tenesmus. Condylomata are found in 50% of homosexual men with ACA, while pruritus is a common presentation in tumors of the perianal skin, anal Bowen's and Paget's diseases. In patients presenting with unintentional weight loss, changes in bowel habits, and recurring abdominal distention or abdominal pain may point to advanced disease. In patients presenting with recurring abdominal pain and/or diarrhea, a family history of inflammatory bowel disease (IBD) should be sought(12).

2.4: Diagnosis and Staging

History and physical examination in anal cancer play a significant part in evaluation, diagnosis, and staging because at the presentation about 50% of patients will have superficial mass (i.e. T1 and T2 lesion) while about 25% have nodal involvement(12). History of risk factors such as homosexuality, MSM, HIV status, intravenous drug use, and smoking can be identified from the history. During the physical examination, a digital rectal examination (DRE) is essential to evaluate the anal sphincter function, size, and location of the tumor, as well as the involvement of adjacent organs(13). Also, inguinal lymph nodes should be assessed and a biopsy of the sentinel lymph node of suspected nodes taken in the original work-up of biopsy-proven ACAs(14). In female patients' gynecologic exams to exclude concomitant cervical cancer due to similar etiologic factors, HPV infection, and rule out an extension to the posterior vaginal vault is recommended(13).

Chest and abdominal CT imaging, pelvic CT/MRI, or anoscopy/proctoscopy are critical adjunct modalities for diagnosis, staging, and preparation of treatment. Positron Emission Tomography/CT scan is useful in planning for radiotherapy and in assessing metastatic disease. It is also useful in inguinal nodal detection with specificity and sensitivity rates of 76% and 93% respectively(15). Adjunct testing such as HIV testing (if HIV status is unknown), complete blood count, and the comprehensive metabolic panel is done for workup, treatment prognostication, and identifying metastatic complications of ACA. Lymph node involvement happens in around one-third of cases, primarily inguinal and femoral, while mesenteric and iliac node involvement is rare(13). The staging of anal cancer using the TNM system developed by AJCC is most widely used, and it is based on the size and depth of invasion(T), lymph node involvement(N), and the presence or absence of metastasis(M) as illustrated in Table 2 below(16).

2.5: Management of Anal Cancer

The treatment of anal carcinomas is challenging due to the lack of an easily identifiable landmark between the rectum and the anus, variable histologic appearance of the squamocolumnar transition zone and overlaps of the margin between the anal canal and anal margin while pathologic classification of tumors arising in the anorectal region is often difficult. Furthermore, the anal region is close to multiple organs which are at risk during radiotherapy(17).

Table 2: TNM Staging for Anal Cancer

PRIMARY TUMOUR (T)	
TX	Primary tumor not assessible
T0	Primary tumor not demonstrated
TIS	High-grade squamous intraepithelial lesion (previously termed carcinoma in situ, Bowen disease, anal intraepithelial neoplasia II–III, high-grade anal intraepithelial neoplasia)
T1	Tumor ≤2 cm greatest dimension
T2	Tumor 2 cm - 5 cm in greatest dimension
T3	Tumor > 5 cm in greatest dimension
T4	Tumor any size invading adjacent organ(s) (e.g., vagina, urethra, bladder); direct invasion of the sphincter muscle(s), subcutaneous tissues, perirectal skin or the rectal wall is not classified as T4
REGIONAL LYMPH NODES (N)	
NX	Regional lymph nodes can't be evaluated
N0	No regional lymph node metastasis
N1	Metastasis to regional lymph nodes
	N1a Inguinal, mesorectal, or internal iliac lymph nodes metastasis
	N1b External iliac lymph nodes metastasis
	N1c External iliac with any N1a nodes metastasis
DISTANT METASTASES (M)	
M0	Distant metastasis absent
M1	Distant metastasis present

Adapted from AJCC (18)

Table 3: Simplified Staging and Treatment Algorithm of Anal Cancer (NCCN Guidelines).

Stage	T	N	M	Treatment
0	Tis	N0	N0	Local Excision
I	T1	N0	M0	MMC, 5FU, and RT or MMC, Capecitabine, and RT
IIA	T2	N0	M0	
IIB	T3	N0	M0	
IIIA	T1-T2	N1	M0	
IIIB	T3	N0	M0	
IIIC	T3-T4	N1	M0	
IV	Any T	Any N	M1	Cisplatin-based chemotherapy and RT

Adapted from AJCC, 5FU = Fluorouracil, MMC= Mitomycin C, RT= Radiotherapy(18)

Abdominoperineal resection (APR) was considered the gold standard treatment for anal carcinomas while small lesions were locally excised. APR is a complex procedure with substantial morbidity because it involves removal of the anal sphincter complex necessitating

the need for a permanent colostomy and when performed for anal carcinoma it led to long-term urogenital dysfunctions, wound morbidity, and the five-year overall survival rate (OSR) was only 40% to70%(19). Nigro et al in Wayne University in a landmark report of three patients in 1974 showed that chemoradiation, a combination of chemotherapy and low dose radiotherapy (CRT), showed better outcomes than surgery(20). Subsequent studies showcased CRT superiority in regimens combining radiotherapy with the chemotherapeutic agents 5-fluorouracil and mitomycin-C rather than surgery alone or RT with 5-FU alone when various outcomes such as local recurrence and control, colostomy free survival, or overall survival were evaluated(21).In the follow-up phase III trials, no benefit was demonstrated with regimens replacing MMC with cisplatin, with the 5-year rates of disease-free survival reported to be approximately 65%(22). The use of CRT became the standard treatment of ACAs and in modern times surgery is reserved as a salvage treatment for those with local disease recurrence, patients with dysfunctional anal sphincter function at diagnosis, and excision of small $\leq$2cm anal margin cancers(23). Metastatic ACA is considered incurable and treatment is mainly palliative chemotherapy or radiotherapy for disease control. In patients with tumors after surgery, and the margins are positive, RT is also considered(24).

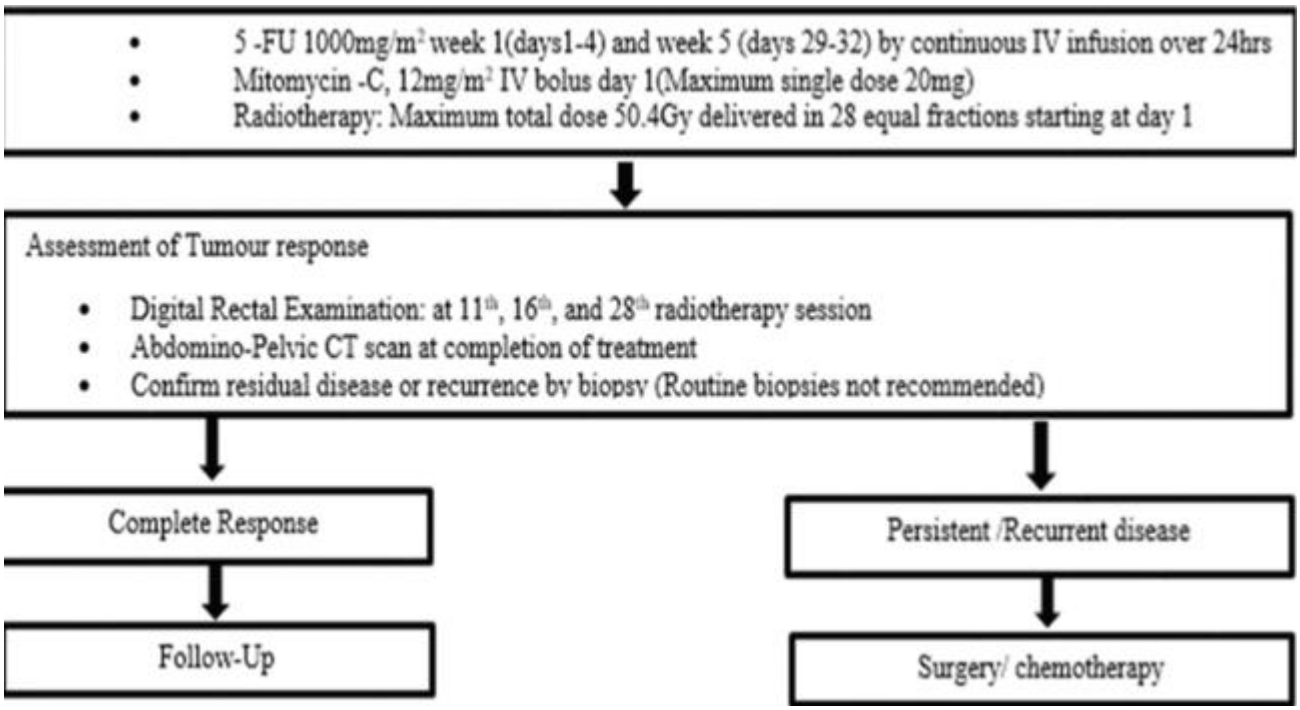

Figure 1: Chemoradiation schedule and assessment of anal carcinoma.

Adapted from NCCN guidelines(25).

2.6: Radiotherapy Technique, Dose, and Treatment Fields

The total radiation dose (TD) and dose per fraction of anal cancer have not been fully defined, however, the minimum dose of 45Gy is recommended. In the study by Ortholan et al in 2005(26), doses of 50-60Gy for T1 tumors were shown to be effective, but other studies suggested that escalation of the doses had a better local control(27). Higher boost radiation doses of up to 70Gy were found not to confer any additional benefit when the end outcomes for colostomy free survival or complete responses as in the ACCORD 03 trial, and thus conventional doses between 50.4 to 59.4 are accepted as the treatment doses for anal carcinomas while the higher doses are used for bulkier disease(28).

EBRT treatment techniques utilized in the treatment of ACAs have been evolving in recent years. Commonly, the use of two- or three-dimensional conformal radiotherapy (2D/3D-CRT) which is the treatment of choice in our local setting is utilized. The EBRT method of inverse planning which uses intensity-modulated radiation therapy (IMRT) improves the therapeutic ratio by reducing the dose to surrounding normal tissues while increasing the conformal dose to the targeted tumor and therefore reducing acute toxicity compared to the conformal methods of delivering radiotherapy(29). Other modes of RT delivery have evolved over the years, but acute complications of anal cancer still exist, albeit in a lesser form, hence the need to study their prevalence in the local setting and ameliorate the poor prognosis and wellbeing of the patients undergoing EBRT for anal cancer.

Lymph node positivity points to a poor outcome and correlates with worse survival and higher colostomy rates(30). Radiation alone controls 70% of involved inguinal nodes, whereas chemoradiation controls 90% of involved inguinal nodes. Therefore, it is important to include mesenteric, iliac, and inguinal lymph nodes within the radiation fields, while augmenting response with the benefit offered by chemotherapy. The radiation dosage delivered can also be modified based on additional factors; such as, when inguinal nodes are cancer-negative the lateral area is decreased, while a booster dose is given to cancer staged T3 or T4, lateral extension of the lateral field of radiation for the lymph node-positive cancers.

2.7: Acute Complications of EBRT

In the treatment of cancer, radiotherapy utilizes ionizing radiation to control cancer cells by mechanisms that work directly or indirectly by interacting with cancer cells. The direct mechanism induces immediate cell death by breaking the DNA double strands and/or tissue protein while the indirect interaction occurs with the release of free radicals by the ionizing radiation producing reactive oxygen species which interferes with enzymatic pathways

leading to cell death and/or mutation(31). These direct and indirect interactions lead to cellular injury by division delay, reproductive failure, and interphase arrest due to activation of certain factors of transcription such as NFκ-β. NFκ-β activation possibly activates some genes which are involved in the pro-inflammatory cytokine production such as Interleukin-6, Interleukin-1,β, and Tumor Necrosis Factor-α(TNF-α)(32). The cytokines are postulated to be responsible for tissue injury and apoptosis, while the cell membranes are hydrolyzed by the chemotherapeutic agents by activation of the ceramide pathway. All these consequences are more frequently encountered in rapidly dividing cells which results in a disproportionate ability to repair more in the cancers cells than normal cells(31).

The desired objective of EBRT is to deliver maximum possible lethal ionizing radiation doses to tumor cells and at the same time spare the organs at risk (OAR). Acute complications result from exposure of the normal tissues adjacent to the tumor during radiation and most prone are the rapidly dividing cells after direct exposure in the radiation field(31). In the treatment of anal cancer, tissues at risk include mucosal epithelium of the gastrointestinal and genitourinary tracts, and local skin, while the hematological toxicity is due to RT exposure to pelvic and/ or femoral bones.

Acute complications range from mild to severe with the majority occurring 7-14 days after initiation of chemo-radiation and mostly resolve 4 to 6 weeks after completion of treatment. There are different grading scales for acute toxicity including the World Health Organization (WHO) system that combines the clinical appearance and function into a single score. In contrast, the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, which is the most widely used in scientific studies, separates the clinical appearance and function into different scores and therefore standardizes reporting of adverse events(33).

Table 4: Grading of adverse Events by CTCAE system

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living**
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to Adverse Event.

Adapted from CTEP(33)

*Refer to cooking, regular shopping, use of telephone, transacting in money, etc.

**Refer to taking showers, self- dressing or undressing, self-feeding, self-toilet care, self-medicating but not bedridden.

Acute complications of EBRT have been reported to occur in approximately 60-80% of patients receiving radiotherapy treatment for pelvic tumors and in about 5-15% necessitating treatment withdrawal(34). The introduction of CRT as the standard treatment improved the local and regional control of anal carcinoma and benefited patients due to the preservation of the sphincter, however, it was noted by clinicians that acute grade three and four toxicity had incidences as high as 80%(34). The dose of radiation is the most likely cause of the adverse events and in the RTOG-87-04 study, it was shown that about 12 % of patients developed acute toxicity or the treatment was altered in its entirety(35).

Thereafter, other schedules of radiotherapy were adopted to reduce toxicity without negatively affecting disease treatment outcomes. Some of these schedules included continuous rather than offering treatment breaks(36), lowering the radiotherapy dose(37), brachytherapy(38), and most recently, the introduction of Intensity Modulated Radiotherapy (IMRT) instead of the conventional 2D-/3D-CRT)(39).

Treatment breaks during EBRT or when used to mitigate against acute complications compromise the efficacy of radiotherapy treatment(40). In RTOG 87-04 study, after about 2 weeks, about 12% of the study participants had unscheduled treatment breaks(41). In the RTOG 92-08 a phase II trial of 46 patients(42), to reduce the unplanned treatment breaks total dose was escalated to TD of 59.4Gy in combination with 5FU/MMC and a mandatory 2-week break in patients diagnosed with anal cancer. In this study the most frequent complication was grade 3-4 skin toxicities in the perianal region in either 2D or 3D-CRT, but more frequent where 2D-CRT was used. The median dose at which treatment was interrupted in this study was 38.7Gy and a range of 12.6Gy to 46.8Gy, while one patient developed severe septicemia and died as a result of multiple GIT complications of radiotherapy and therefore stressing the high toxic level of this protocol. In this study, the prevalence of grade 4 toxicity was 26% (12 patients) while hematological complications leucopenia and, thrombocytopenia of grade 2 occurred in 20% (9 patients). In RTOG 92-08, there was a lower incidence of grade 3 skin toxicity of 34% compared to 55%, but more patients had colostomy rates of 23% versus 6%after one year, while after 2 years the rate of colostomy increased to 30% versus 7% in RTOG 87-04(40). This may be explained by TD escalation in an attempt to achieve local control instead of low TD in a continuous plan.

Some of the studies evaluating acute complications are tabulated below;

Table 5: Second-generation trial outcomes and toxicity profiles

Author	Year	Sample size	Study type	Grade 3-4 acute complications prevalence				
				Skin	GIT	GUS	Hematological	Others
Flam et al(43).	1996	310	Prospective (10Yrs)	7%	-	-	18%	NR
Ajani et al(44).	2008	682	Retrospective (7yrs)	49%	37%	3%	62%	
(22)Gunderson et al(45).	2012							
Bazan et al(25).	2011	45	Retrospective (3yrs)	41%	29%	NR	21%	Treatment break: 88%
Peiffert et al(28).	2012	307	Prospective (7 yrs.)	3%	9%		19%	NR
Chuong et al(46).	2012	37	Prospective (7yrs)	64%	30%		21%	Treatment Break: 30%
James et al(22).	2013	940	Prospective (5yrs.)	48%	16%		Hematotoxicity: 26%, Leucopenia: 24%	Pain: 26%
Kachnic et al(47).	2013	63	Prospective (12 months)	73%	77%	77%	73%	Treatment Break: 49%
Atrash et al(40).	2015	42	Retrospective (9Yrs.)	22.5 %	12.5 %	NR	N/S	NR
Sauter et al(39).	2019	82	Retrospective (6yrs.)	2-3%	68.3 %		17%	

The gastrointestinal tract acute complications include a change in quality and frequency of bowel/incontinence, diarrhea, mucous discharge, rectal and abdominal pain, hematochezia, acute obstruction, and tenesmus. Genitourinary complications are less common compared to gastrointestinal complications. Some of the complications described include hematuria (micro- or macroscopic), urgency, nocturia, dysuria, cystitis, bladder spasms, and urine retention. Acute dermatitis of radiotherapy normally occurs within hours of RT and normally heals after RT is stopped except for mild cutaneous changes(48). The radiation-induced skin reactions are largely due to radiation technique, total dose, volume, and individual variations in treatment. Some of the common acute complications are erythema, epilation, dry and moist desquamation, edema, pain, ulceration, hemorrhage, and necrosis(33).

There are several mechanisms of potential EBRT effects on the bone marrow and they appear to be complementary and not mutually exclusive. These acute complications result from

direct damage to hematopoietic stem cells and are followed by a reduction in their number function, pertinent changes in the surrounding stroma of bone marrow and microenvironment, and damage to the helper cell populations whose function is to regulate hematopoiesis. Since functional bone marrow is situated primarily in the pelvis and vertebrae constituting about 60% of the total volume, and in conventional anal cancer treatment large volume irradiation is delivered to the pelvis or lower spine the likelihood of hematological acute complications is inevitable(49).

Although current EBRT regimens for anal cancer are divided into fractions and generally involve smaller target volumes compared to previous field techniques, the incidence and prevalence of hematological complications increase with the use of combination treatment of chemotherapy and radiotherapy. In one retrospective review of patients who developed severe neutropenia due to EBRT, it was found that the most important predictors are the field of RT and the use of concurrent myelosuppressive chemotherapy(49). Efforts to reduce hematological toxicity by using less myelosuppressive chemotherapy regimens have not been largely successful, an example is the use of cisplatin instead of MMC for the CRT of anal cancer(50).

2.8: Factors associated with Radiation Injury

Acute complications of radiotherapy and their severity often depend on treatment and patient-related factors though little evidence has been adduced to support their role and are summarized below. The treatment-related factors include RT dose, the volume of bowel exposed to radiation, fractionation time, and dose variables. In the initiation of radiotherapy, a large single dose was noted to cause severe or even lethal toxicity, while cumulative doses given as small fractions of the course over several days were better tolerated by the patient. Deore et al demonstrated an increased incidence (8.2-33.3%) of rectal and recto-sigmoid complications when the dose per fraction was increased from 2Gy to 5.4Gy in patients treated for cervical cancer with radiation alone(51).

Table 6: Summary of risk factors for gastrointestinal radiation injury

Risk Factor	
Radiation Technique	Treatment volume, total dose, fractionation dose, and schedules
Combined modality therapies	Previous Surgery Chemotherapy: Particularly concurrent
Medical co-morbidities	Vascular disease, connective tissue disease, inflammatory bowel disease Human Immunodeficiency Virus (HIV)
Genetic susceptibility	Single nucleotide polymorphism, ataxia-telangiectasia

The administration of chemotherapy together with radiation has been shown to correlate with increased incidence of radiation-related toxicity particularly intestinal toxicity which has been postulated to be due to the recall phenomenon, whereby radiation followed by chemotherapy results in recurrence of symptoms of radiation-induced GIT toxicity(52). In a study of patients with cancer of the cervix treated with chemo-radiotherapy, the incidence of Grade 3 intestinal toxicity was found to increase to 26% from 10% when 5-FU alone compared to where 5 -FU and mitomycin C were used together, suggesting a possibility that the chemotherapy used could be a determinant of gastrointestinal toxicity severity(53).
Variations in genetic make -up are also postulated to be a determinant of how normal tissue responds to radiotherapy and may account for about 80%-91%of how different patients' normal tissue responds to radiation treatment(54). This hypothesis was supported in a study of radiotherapy of breast cancer which reported the incidence and time to development of telangiectasia after EBRT and wide-ranging variation between patients although all patients received similar radiotherapy(55). Other studies by Tucker et al in 1992(56), and 1997(57), also supported this hypothesis. Studies by Sharma et al(51), in 2005 and Neelu et al(58), in 2019 identified some of the risk factors for the occurrence of acute complications of pelvic radiotherapy such as; previous abdominal surgery or intraabdominal or pelvic inflammatory outcomes after infections by increasing the risk of radiation enteropathy due to formation of adhesions which fixates parts of the bowel to radiation field(59).
Co-morbidities such as inflammatory bowel disease, diabetes mellitus, hypertension, collagen or vascular disease, and tobacco smoking predispose patients to radiation-related complications due to pre-existing vascular injury and as a result impaired tissue repair after EBRT(60). Other factors implicated include advanced age due to reduced organ function, while the thin body physiques, absence of subcutaneous fat, and reduction in anteroposterior diameter appear to increase toxicity, particularly to fixed organs such as bladder, pelvic

bones, and caecum. In patients with HIV/AIDS, a high viral load has also been demonstrated to offer poorer outcomes and increased risk for acute complications(61).

CHAPTER THREE: MATERIALS AND METHODS

3.0: Study Site

The study was conducted at the Cancer Treatment Centre, Surgical Outpatient Clinic (SOPC), and adult wards in Kenyatta National Hospital (KNH). KNH is the largest and oldest teaching and referral hospital in Kenya established in 1901. KNH has 50 wards, 22 outpatient clinics, 24 theatres (16 specialized), and an Accident & Emergency Department. The total bed capacity is1800, however, due to congestion, the hospital more often hosts between 2000 and 2400 inpatients on any given day. Apart from its environs in Nairobi, KNH serves patients from all over the country and therefore has a large catchment area. The average annual outpatient attendance is 600,000visits while the average annual inpatient attendance is 89,000. Through this study, invaluable information will be obtained to assist in developing protocols in the management of anal cancer patients undergoing radiotherapy and reduce acute adverse effects of this treatment modality.

3.1: Study Design

The study was a prospective cohort study designed to facilitate the description of the acute complications and risk factors of EBRT among patients on treatment for anal cancer.

3.2: Study Population

The study population comprised all patients who were started on EBRT treatment for anal carcinoma.

3.3: Inclusion and Exclusion Criteria

3.3.1: Inclusion Criteria

1. All patients diagnosed with histological diagnosis of anal cancer and started on EBRT as a treatment modality
2. Patients willing to participate in the study and sign an informed consent.

3.3.2: Exclusion Criteria

1. Presence of any other co-existing malignancy other than anal cancer.
2. Patients who have undergone previous pelvic radiotherapy form of treatment for any malignancy.

3.4: Sampling Method

All patients who fulfilled the eligibility criteria were consecutively enrolled until the sample size was achieved.

3.4.1: Sample Size Calculation

This study aimed to describe the relationship between anal carcinoma and other health-related states and the factors of interest as they existed in the specified population at a particular time, without regard for what may have preceded or precipitated the health status at the time of the study.

The sample size was calculated using Fisher's formula:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where;

n=desired sample size of the target population when the population is more than 10,000.

Z=value from the standard normal distribution corresponding to the desired confidence level. The Z value of the 95% confidence interval is 1.96.

d=margin of error, set at 5%.

P=estimated proportion of patients with acute complications after EBRT.

Substituting into the formula;

$$n = (1.96)2(0.05)\ (0.05)(0.05)2 = 384$$

The sample size in this study was more than 10,000 therefore the correction formula for the infinite population was used to calculate the sample size.

$$nf = n/(1 + n/N)$$

Where;

nf = The desired sample size when the population is less than 10,000.

n = The desired sample when the population is more than10,000.

N = From a Kenyatta National Hospital's Health Information department, an average of 176 patients are diagnosed with anorectal cancer annually an average of 15 each month (Table 1). For the duration of the study of 6 months desired population was therefore 90 participants. Substituting in the formula;

$$nf = \frac{384}{1 + \frac{384}{90}} = \frac{384}{1 + 4.267}$$

$$= \frac{384}{5.267} = 72.906 = 73\ participants$$

3.4.2: Data Collection

Data was collected using a structured interview form after consent was sought from the eligible patients. Data was collected by the primary investigator through patient interviews and physical examinations. The eligibility was ascertained by verification from the recorded data and decisions made in the files of the patients, and also information provided by the patient.

The patients who fulfilled the study inclusion criteria were invited into a separate room within the facility. The purpose and objectives of the study were introduced and discussed. Both oral and written consent was sought. A baseline physical examination was performed at the time of recruitment, the study questionnaire was administered in private, and confidentiality was assured. A follow-up examination was performed at the midpoint session of EBRT and the end of EBRT. The participants' or caretakers' telephone numbers were recorded to facilitate ease of follow-up by reminding the patients about their follow-up appointments.

3.4.3: Study Flowchart

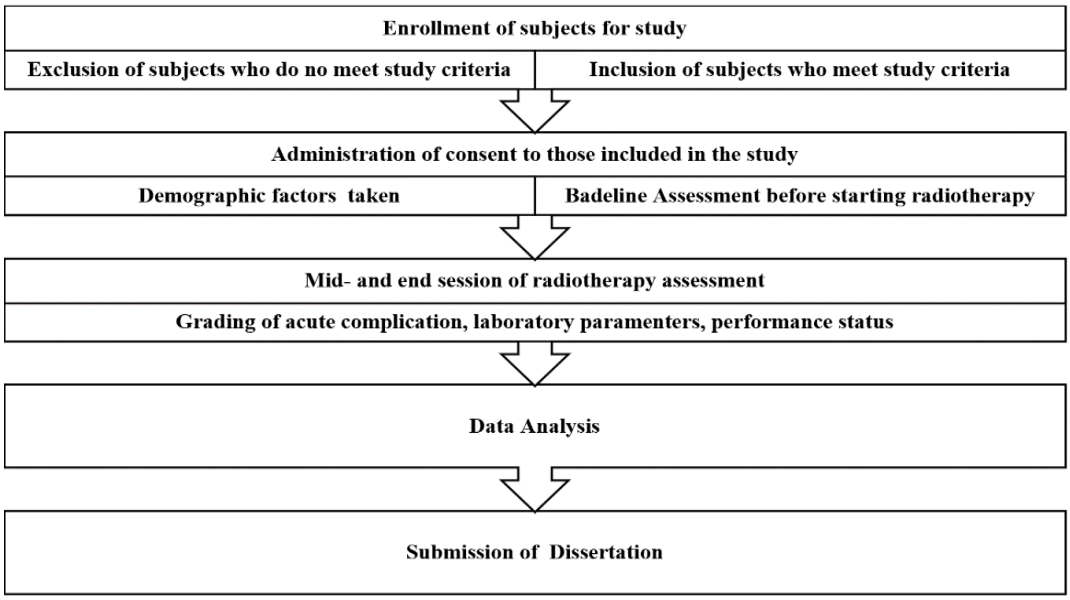

Figure 2: Study flowchart

3.4.4: Study Variables

The study variables were either dependent or independent and are tabulated below:

Table 7: Study Variables

Variable		
	Dependent variables	**Independent Variables**
1	Radiation Dose	Age
2	Acute Complications	Sex
3	Treatment Break	Comorbidity
4	Laboratory Parameters	Previous Surgery
5		Concurrent Chemotherapy

3.4.5: Data Collection Instrument

Data was collected using a structured questionnaire that focused on the following areas based on the objectives of the study:

1. Demographic factors
2. Acute clinical complications
3. Co-Morbidities
4. Treatment dynamics e.g., the total dose of radiation and modality of EBRT
5. Chemotherapy used and dosage
6. Unscheduled treatment breaks and or withdrawal due to acute complication

7. Hematological investigations done

During the follow-up assessments, any acute complications were graded by the primary investigator using the NCI-CTCAE version 5.0 grading scale (Appendix E).

3.4.6: Quality Assurance

All aspects of this study were subjected to strict quality control. There was strict adherence to the inclusion criteria to avoid collecting irrelevant data. Observation of the ethical considerations while handling the study participants was paramount. The primary investigator verified each questionnaire to confirm that the responses were filled correctly.

To ensure the radiotherapy mapping is standardized the radiotherapy treatment card was confirmed by the primary investigator to be countersigned by a radio-oncologist.

3.4.7: Data Management and Analysis

Once data collection is completed, the database was password-protected for security and to prevent tampering or alterations. Regular file backup was done to avoid any loss.

Statistical analysis was performed in SPSS version 21.0. Patients' socio-demographic and clinical information was summarized into percentages and means/medians for categorical and continuous variables respectively. Acute complications of EBRT were analyzed and presented as percentages with 95% confidence intervals. The total dose given to the patient was obtained from the radiotherapy treatment cards and documented. Associations between the total dose of radiation and the modality of EBRT were tested using the Chi-square test for categorical independent variables and Student's t-test to compare means. Statistical tests were interpreted at a 5% level of significance (p-value less or equal to 0.05). Study findings are presented in tables, figures, and graphs.

3.5: Ethical Considerations

This proposal will be subject to review by the KNH/UON ERC. The data collected from this study are to be used to provide information geared towards the development of protocols that would help optimize treatment outcomes for patients who have anal carcinoma.

The study was fully voluntary and affected patients were allowed to drop off without giving any reason or due to the acute adverse effects and did not affect the quality of care that they received.

The findings were treated with utmost confidentiality, for this research only.

3.6: Covid-19 Ethical Considerations

Since Covid-19 is highly infectious, during the study public health obligations were upheld to protect research participants, the general public, and all involved in the study while at the same time ensuring the continued care of patients participating in the study. This included adherence to covid-19 related public health directives and guidelines, including reporting possible covid-19 exposure or symptoms during the study.

The principal investigator ensured clinical examinations were as safe as possible, that good clinical practice was adhered to, social distancing was maintained where necessary, and use of masks, hand washing, and cleaning of surfaces after the examination was done. The principal investigator as part of public health guidelines to mitigate against Covid -19 had taken the two vaccines.

At the study site, the principal investigator ensured appropriate infection control measures are undertaken such as:

1. Temperature checks for all participants
2. Handwashing and using sanitizers after every physical examination
3. Ensured use of 3-ply face masks for participants and investigators during interactions.
4. Social distancing of at least 1.5 meters in the waiting and examination rooms was maintained.
5. Principle investigators used appropriate personal protective equipment as recommended by MOH Infection Prevention and Control guidelines when conducting close contact or handling biological specimens.

Further, all measures as per the Ministry of Health guidelines on Covid-19 were adhered to during this study.

3.7: Management of Adverse Effects

During EBRT, patients who developed acute complications effects were managed at the respective multi-disciplinary units as per the guidelines of KNH, and Cancer Treatment Center.

CHAPTER FOUR: RESULTS AND DISCUSSION

4.1: RESULTS

Data collection for this study was carried out from September 2021 to March 2022. A total of 39 patients were recruited at the Cancer Treatment Centre, Surgical Outpatient Clinic (SOPC), and adult wards in Kenyatta National Hospital (KNH). Of the recruited patients,37 (94.7%) completed treatment prescribed as out-patients 2(5.3%) were inpatients while 2 patients died before the completion of treatment.

4.1.1: Socio-demographic characteristics

Thirty-nine (39) patients undergoing anal cancer treatment were assessed for acute complications resulting from external beam radiotherapy. The mean age of the patients was 46 years (range 29-79 years, SD 13.1years, and a median of 43 years.

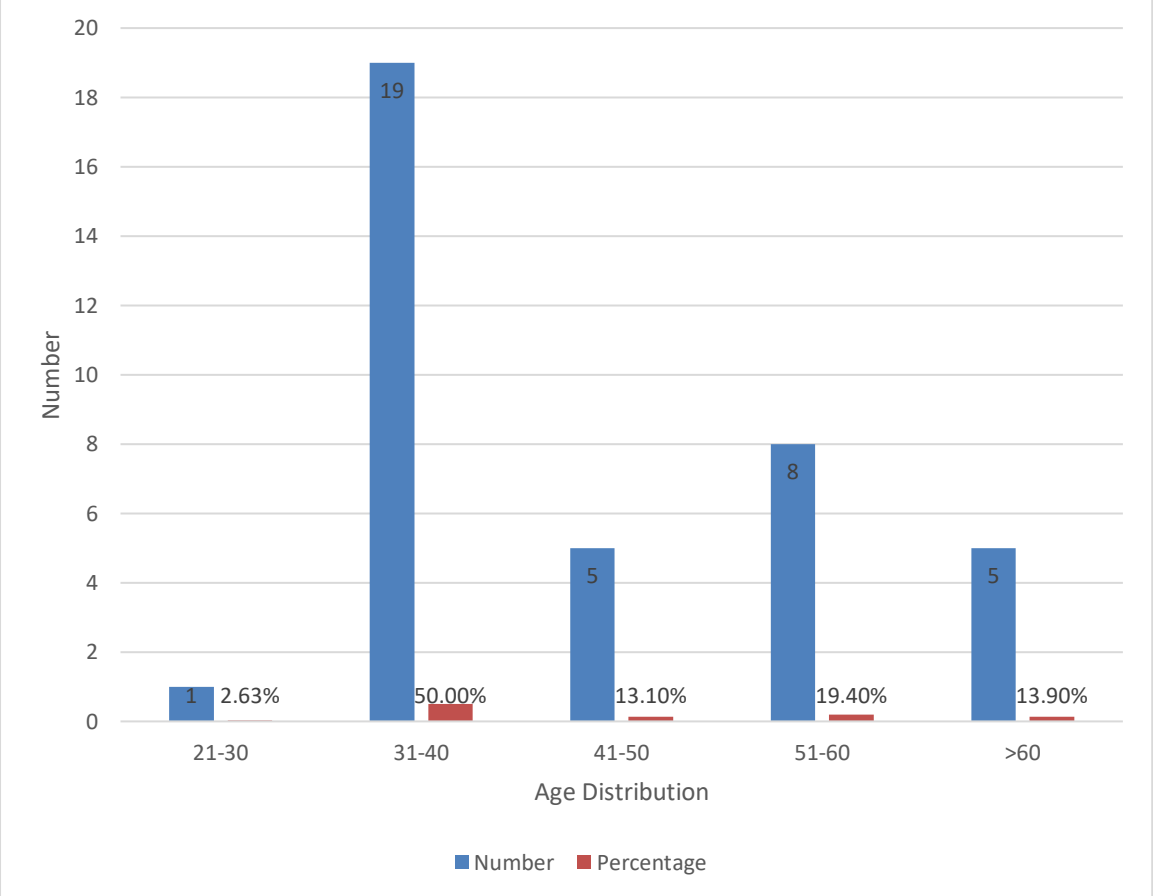

Figure 3: Graph showing age distribution and percentages of patients with anal cancer.

The sex distribution as shown in figure 4, 22 (56.4%) were female while 17(43.6%) were male.

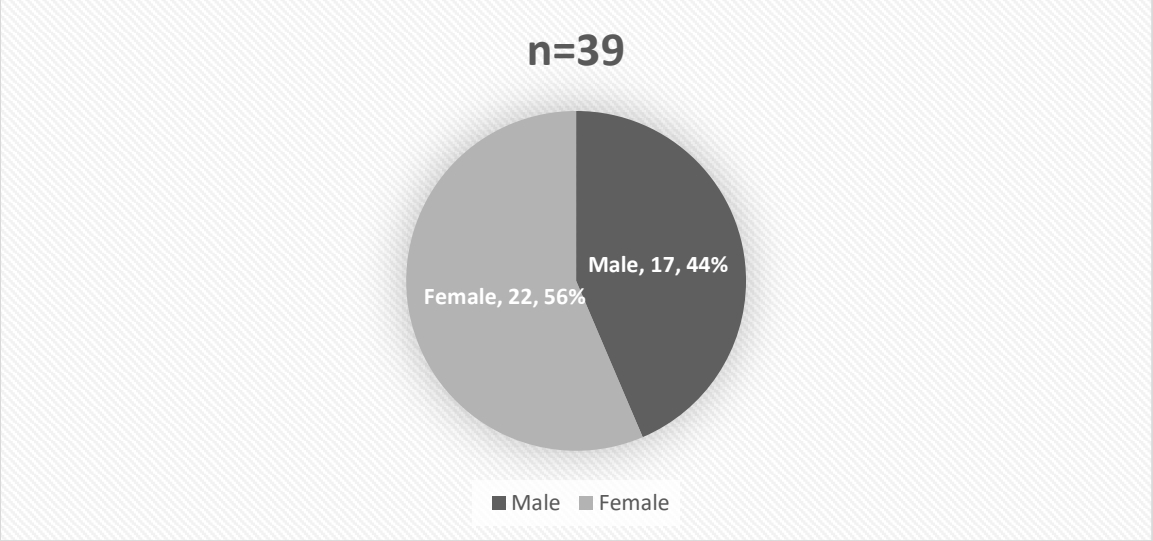

Figure 4: Pie Chart showing sex distribution of patients with Anal Cancer

The majority of the patients had secondary (48.5%) and primary (33.3%) levels of education. The source of the patients was mainly rural (63.6%) and 66.7% were married. More than a third (69.7%) of the patients' cited an immediate family member as their primary caregiver.

Table 8: Socio-demographic characteristics

Variable	**Frequency (%)**
Age in years	
Mean (SD)	46.0 (13.1)
Median (IQR)	43.0 (32.5-56.8)
Min-max	29.0-79.0
Sex	
Male	17 (43.1)
Female	22 (57.9)
Level of education	
No formal education	1 (3.0)
Primary education	11 (33.3)
Secondary education	16 (48.5)
Post-secondary education	3 (9.1)
College	2 (6.1)
Residence	
Rural	21 (63.6)
Suburban	7 (21.2)
Urban	5 (15.2)
Marital status	
Single	2 (6.1)
Married	22 (66.7)
Divorced	2 (6.1)
Separated	2 (6.1)
Widowed	5 (15.2)
Primary home caregiver	

Immediate family member	23 (69.7)
Prisoner	2 (6.1)
Relative	8 (24.2)

4.1.2: Characteristics of the Patients Before Initiation of Radiotherapy

As shown in Table 9, most patients had normal physical characteristics. Comorbidities were identified in 47.4% of the patients with HIV being diagnosed in the majority (83.3%) of the cases. TNM staging was done in 33(86.8%) patients with 31(93.9%) staged at T3 or T4 stage, while 2 had T2 disease.

Table 9: Pre-radiotherapy characteristics

Variable	**Frequency (%)**		
	Abnormal		**Normal**
Blood Pressure	1 (2.6)		38(97.4)
Pulse rate	0		39 (100)
RR	0		39 (100)
Temperature	0		39 (100)
Other Characteristics			
Comorbidities	Present		Absent
	18 (47.1)		21 (53.9)
	Diabetes	1(5.6)	
	HIV	15(83.3)	
	Hypertension	2(11.1)	
Mean hemoglobin (SD)	11.9 (1.9)		
Mean white blood cell count (SD)	8.6 (3.4)		
Mean neutrophil count (SD)	5.6 (2.5)		
Mean platelet count (SD)	327.0 (101.5)		
TNM Staging	Staged	Not Staged	
	33(86.8)	5 (13.2)	

4.1.3: Treatment Modalities

As shown in Table 10, 84.8% of the patients received concurrent chemotherapy and 63.6% had done surgery previously. In this study, only 2 patients received Mitomycin -C with 5-fluorouracil or capecitabine combination, while 16(42.1%) received cisplatin and 5-FU combination. Diversion colostomy was the main surgery performed in 34(87.2%) of the patient, one patient received wide local excision as definitive surgical treatment for anal cancer while one pregnant mother had an elective caesarian section and diversion colostomy. Two patients had hemorrhoidectomy before recruitment in the study, with histology confirming anal carcinoma.

Table 10: Treatment

Variable	Frequency (%)			
Patient planned for Chemotherapy	Yes 33 (86.8)			No 5 (13.2)
	Chemotherapy Received	5FU	1 (3.0)	
		Capecitabine	12 (36.4)	
		Cisplatin + 5FU	16 (48.5)	
		Mitomycin-C+ Capecitabine	1 (3.0)	
		Mitomycin-C + 5FU	1 (3.0)	
Previous surgery done	Yes 24 (63.1)			No 14 (36.8)
	Surgery Done	Diversion Colostomy	21 (87.5)	
		Elective Caesarian Section + Diversion Colostomy	1 (4.2)	
		Wide Local Excision	1 (4.2)	

4.1.4: Assessment During Radiotherapy

As shown in Table 11, the mean SBP was 119.5 mmHg (SD 13.6 mmHg), mean DBP was 76 mmHg (SD 8.8 mmHg), and mean pulse rate was 82.8 beats per minute, and mean respiratory rate was 18.9. The patients who had treatment breaks were 42.4% and the mean duration was 12.5 days.

Table 11: Assessment during radiotherapy

Variable		Frequency (%)	
		Mean (SD)	**Min-Max**
Systolic Blood Pressure		119.5 (13.6)	100.0-158.0
Diastolic Blood Pressure		76.0 (8.8)	57.0-92.0
Pulse rate		82.8 (12.1)	56.0-106.0
Respiratory rate		18.9 (1.6)	14.0-22.0
Temperature		36.6 (0.5)	35.0-38.0
Treatment break		14 (42.4)	19 (57.6)
	Treatment break-in days	12.5 (4.9)	5.0-21.0

4.1.5: Performance of Patients Before and During Radiotherapy

As shown in Table 12, about half of the patients scored between 2 to 4 on their performance status. The performance was not significantly different across the different stages of treatment. Similarly, ECOG status was majorly between 1 and 2 and similar across the 3 stages of interventions.

Table 12: Performance of patients before and during radiotherapy

Variable	Radiotherapy stage

	Pre- n (%)	Mid n (%)	End n (%)	P- Value
Patient's performance status Median (IQR) Category, n (%)	3 (2.5-5)	3 (2.5-5)	3 (2-5)	
0	1 (3.0)	0	1 (3.0)	0.598
1	4 (12.1)	2 (6.1)	6 (18.2)	
2	3 (9.1)	6 (18.2)	7 (21.2)	
3	11 (33.3)	10 (30.3)	3 (9.1)	
4	3 (9.1)	3 (9.1)	7 (21.2)	
5	5 (15.2)	9 (27.3)	3 (9.1)	
6	5 (15.2)	3 (9.1)	4 (12.1)	
7	1 (3.0)	0	2 (6.1)	
ECOG Performance				
1	14 (42.4)	9 (27.3)	12 (36.4)	0.409
2	13 (39.4)	14 (42.4)	12 (36.4)	
3	6 (18.2)	10 (30.3)	7 (21.2)	
4	0	0	1 (3.0)	
5	0	0	1 (3.0)	

[a]Anal cancer limiting patients' daily activities (0 – not at all, 10 – very much)

4.1.6: Prevalence of Acute Complications

As shown in Table 13, 97% of the patients reported gastrointestinal complications associated with radiotherapy and the complications were higher in mid-radiotherapy (93.9%) which reduced significantly to 69.7% at the end of treatment (p=0.021). Similarly, 45.5% had genito-urinary complications with a reduction to 12.1% at the end (p=0.001). Also, all patients experienced skin adverse events and it increased from 75.8% to 97% (p=0.039). Hematological complications were identified in 39.4% of the patients and there was no significant difference between the mid-radiotherapy period and the end of treatment (p=0.227).

Table 13: Prevalence of acute complications

Variable	Overall	Radiotherapy stage		P-value
		Mid n (%)	End n (%)	
Gastrointestinal	32 (97.0)	31 (93.9)	23 (69.7)	0.021
Genito-urinary	15 (45.5)	15 (45.5)	4 (12.1)	0.001
Skin	33 (100.0)	25 (75.8)	32 (97.0)	0.039
Hematological	13 (39.4)	5 (15.2)	10 (30.3)	0.227

4.1.7: RTOG Grade of Acute Complications

As shown in Table 14, Figures 5, the most common and significantly different between mid and end radiotherapy among gastrointestinal complications included diarrhea, incontinence, anorexia, and pain. All patients during the treatment developed one or more acute complications and therefore no association with either of the outcomes could be assessed

adequately. Hematuria was significant in the genito-urinary complications while skin adverse events were more common at the end of radiotherapy.

Table 14: Grade of acute complications

Variable		Grade						P-value
		0	1	2	3	4	5	
Gastrointestinal								
Diarrhea	Mid	12 (36.4)	5 (15.2)	10 (30.3)	5 (15.2)	1 (3.0)	-	0.044
	End	14 (42.4)	11 (36.4)	3 (12.1)	2 (6.1)	1 (3.0)	-	
Incontinence	Mid	22 (66.7)	3 (9.1)	2 (6.1)	6 (18.2)	-	-	0.003
	End	30(90.9)	0	2 (6.1)	1 (3.0)	-	-	
Nausea	Mid	13 (45.5)	8 (24.2)	9 (27.3)	1 (3.0)	-	-	0.123
	End	22 (63.6)	6 (18.2)	5 (15.2)	1 (3.0)	-	-	
Anorexia	Mid	22 (54.5)	4 (15.2)	10 (30.3)	-	-	-	0.049
	End	24 (72.7)	7 (18.2)	3 (9.1)	-	-	-	
Hemorrhage	Mid	31 (97.0)	0	3 (3.0)	-	-	-	0.180
	End	31 (90.9)	1 (3.0)	2 (6.1)	-	-	-	
Ulceration	Mid	35 (97.0)	0	1 (3.0)	-	-	-	0.317
	End	34 (100)	0	0	-	-	-	
Pain	Mid	4 (12.1)	10 (30.3)	8 (24.2)	8 (24.2)	2 (6.1)	1 (3.0)	<0.001
	End	21 (63.6)	2 (6.1)	6 (18.2)	4 (12.1)	0	0	
Genito-urinary								
Hematuria	Mid	22 (66.7)	7 (21.2)	4 (12.1)	-	-	-	0.003
	End	31 (93.9)	1 (3.0)	1 (3.0)	-	-	-	
Urinary incontinence	Mid	33 (100)	-	-	-	-	-	1.000
	End	33 (100)	-	-	-	-	-	
Bladder spasm	Mid	32 (97.0)	0	1 (3.0)	-	-	-	1.000
	End	32 (97.0)	0	1 (3.0)	-	-	-	
Urinary frequency	Mid	31 (93.9)	1 (3.0)	0	1 (3.0)	-	-	0.593
	End	32 (97.0)	0	1 (3.0)	0	-	-	
Urgency	Mid	33 (100)	-	-	-	-	-	1.000
	End	33 (100)	-	-	-	-	-	
Hematological								
Anemia	Mid	30 (90.9)	2 (6.1)	0	1 (3.0)	-	-	0.414
	End	31 (93.9)	2 (6.1)	0	0	-	-	
Neutropenia	Mid	31 (93.9)	0	1 (3.0)	1 (3.0)	-	-	0.347
	End	27 (81.8)	3 (9.1)	2 (6.1)	1 (3.0)	-	-	
Thrombocytopenia	Mid	32 (100)	0	0	-	-	-	0.059
	End	29 (87.9)	3 (9.1)	1 (3.0)	-	-	-	
Skin								
Skin	Mid	8 (24.2)	7 (21.2)	8 (24.2)	9 (27.3)	1 (3.0)	-	0.024
	End	1 (3.0)	5 (15.2)	12 (36.4)	13 (39.4)	2 (6.1	-	

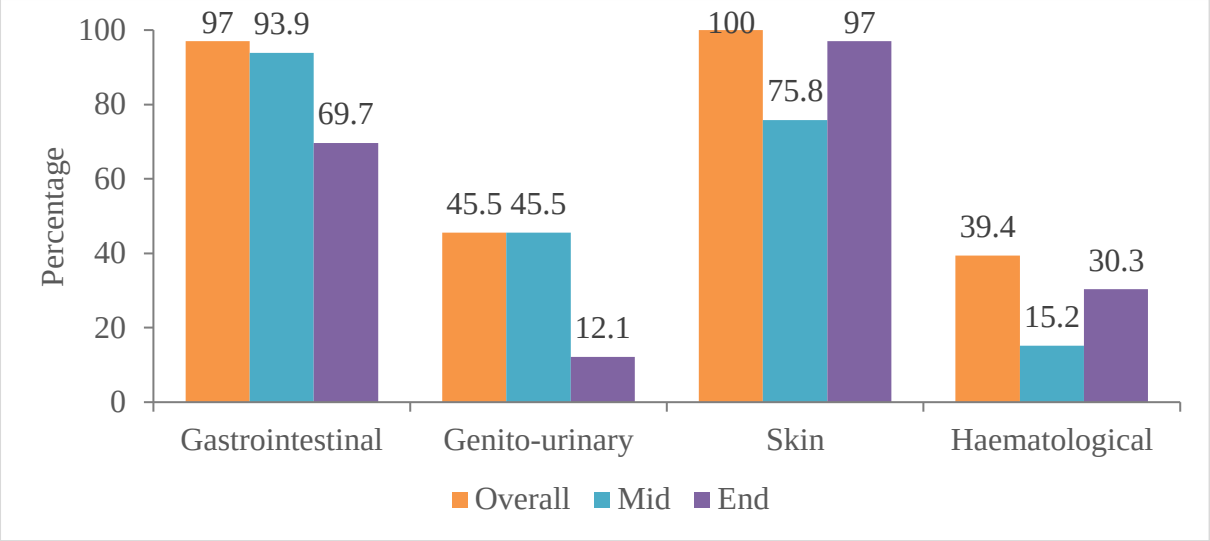

Figure 5: Graph of the Summary of Acute Complications

4.1.8: Factors Associated with Genito-Urinary Complications

As shown Table 15, Genito-urinary complications were more common in males (71.4%) than females (26.3%), OR 7.0 (1.5-32.8), p=0.010. Similarly, the patients who had the complications were more likely to have a treatment break. All the other factors such as baseline clinical characteristics of the patients or their prior treatment interventions were not associated with complications.

Table 15: Factors associated with genito-urinary complications

Variable	**Genito-urinary**		**OR (95% CI)**	**P-value**
	Yes	No		
Age in years Mean (SD)	43.7 (12.3)	44.8 (13.3)	-	0.818
Sex Male Female	10 (71.4) 5 (26.3)	4 (28.6) 14 (73.7)	7.0 (1.5-32.8) 1.0	0.010
Any comorbidities Yes No	7 (50.0) 8 (42.1)	7 (50.0) 11 (57.9)	1.4 (0.3-5.5) 1.0	0.653
Mean hemoglobin (SD)	12.3 (1.7)	11.5 (2.0)	-	0.218
Mean WBC count (SD)	9.0 (4.0)	8.3 (2.7)	-	0.577
Mean neutrophil count (SD)	6.1 (3.0)	5.2 (2.0)	-	0.313
Mean platelet count (SD)	292.5 (85.8)	360.1 (104.4)	-	0.054
Performance score, mean (SD)	3.7 (1.5)	3.5 (1.5)	-	0.654
ECOG status, mean (SD)	2.3 (0.8)	1.8 (0.7)	-	0.108
Received chemotherapy Yes No	13 (46.4) 2 (40.0)	15 (53.6) 3 (60.0)	1.3 (0.2-9.0) 1.0	1.000
Any previous surgery done				

Yes No	10 (47.6) 5 (41.7)	11 (52.4) 7 (58.3)	1.3 (0.3-5.3) 1.0	0.741
Treatment break Yes No	 10 (71.4) 5 (26.3)	 4 (28.6) 14 (73.7)	 7.0 (1.5-32.8) 1.0	 0.010

4.1.9: Factors Associated with Hematological Complications

As shown in Table 16, none of the demographic and clinical features of the patients was associated with the development of hematological complications. However, patients who had the complications were more likely to have a treatment break, OR 6.8 (95% CI 1.4-31.9), p=0.012.

Table 16: Factors associated with hematological complications

Variable	**Hematological**		**OR (95% CI)**	**P-value**
	Yes	No		
Age in years Mean (SD)	 46.4 (13.8)	 43.0 (12.0)	 -	 0.455
Sex Male Female	 8 (57.1) 5 (26.3)	 6 (42.9) 14 (73.7)	 3.7 (0.8-16.2) 1.0	 0.073
Any comorbidities Yes No	 8 (57.1) 5 (26.3)	 6 (42.9) 14 (73.7)	 3.7 (0.8-16.2) 1.0	 0.073
Mean hemoglobin (SD)	11.8 (2.6)	11.9 (1.4)	-	0.900
Mean white blood cell count (SD)	9.2 (3.3)	8.2 (3.3)	-	0.409
Mean neutrophil count (SD)	6.1 (2.6)	5.4 (2.4)	-	0.438
Mean platelet count (SD)	348.9 (115.7)	316.7 (90.8)	-	0.378
Performance score, mean (SD)	3.6 (1.6)	3.6 (1.4)	-	0.977
ECOG status, mean (SD)	2.2 (0.7)	1.9 (0.8)	-	0.234
Received chemotherapy Yes No	 12 (42.9) 1 (20.0)	 16 (57.1) 4 (80.0)	 3.0 (0.3-30.4) 1.0	 0.625
Any previous surgery done Yes No	 10 (47.6) 3 (25.0)	 11 (52.4) 9 (75.0)	 2.7 (0.6-13.0) 1.0	 0.278
Treatment break Yes No	 9 (64.3) 4 (21.1)	 5 (35.7) 15 (78.9)	 6.8 (1.4-31.9) 1.0	 0.012

4.2: DISCUSSION

The treatment of anal cancer has evolved over the years from abdominal-perineal resection to chemoradiotherapy using modern radiotherapy techniques. This chemoradiation protocol, often referred to as Nigro Protocol, has improved the quality of life of many patients with anal cancer. Several important findings have emerged in this study of patients undergoing curative-intent treatment for anal carcinoma in KNH.

In this study 31(86.8%) of the TNM staged patients with anal cancer treatment and recruited for treatment were diagnosed at advanced stages T3 and T4, contrary to other studies 25-40%(12). The current study also found that the incidence of acute complications from radiotherapy in patients in KNH with anal cancer is much higher compared to similar studies conducted elsewhere(22,25,28,40;43). Most of the acute complications were mild grades 1 and 2, mainly GIT which is comparable to RTOG-87-04 study (35). The study also showed that the occurrence of these side effects was not influenced by the age, gender of the patients, or tumor stage consistent with that of Yeoh et.al 1993(60).

The present study has documented for the first time that 42.4% of patients undergoing radiotherapy for anal cancer at KNH had unscheduled treatment breaks due to the severity of acute complications. This is comparable to a study by Kachnic et al 2013(47) where the cumulative doses of radiation at which patients' treatment was interrupted, reflected the individual variability in susceptibility to side effects of radiotherapy. This also suggests that patients who had interruption at lower cumulative doses of radiation had the potential to be interrupted again upon resumption of radiation therapy.

Available data suggest, strongly, that unscheduled and uncompensated prolongation of radical treatment adversely affects local tumor control in patients with anal cancer. The present study has also for the first time documented the number of days treatment has been lengthened due to the interruptions and therefore detrimental to tumor control and survival. If one was to add the days of radiotherapy missed due to machine breakdown, transport problems as the patients commonly reside outside Nairobi, shortage of money to pay for treatment, and lack of treatment because KNH does not work on weekends then the unscheduled gaps in treatment can be unacceptably high. Treatment interruption was confounded by factors such as unplanned public holidays, machine breakdown, stoppage for annual maintenance, or due to patients being unable to afford the treatment costs.

Because of the association between treatment gaps and loss of tumor control, studies need to be conducted to correlate the number of tumor recurrences, distant metastasis, and overall, 5-year survival rates of patients who have undergone unscheduled treatment interruptions at KNH. There appears to be a general lack of awareness, in the radiotherapy department, of the importance of avoiding treatment gaps or lethargy in taking measures to address the issue.

The preceding factors all militate towards a sizeable number of anal cancer patients at KNH having a poor overall prognosis following radiotherapy. Performance statuses are scales and criteria used by doctors and researchers to assess how a patients' disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

Mucositis may propagate contrasting forces; on the one hand, treatment interruption caused by mucositis may drive tumor response lower and on the other hand, the occurrence of severe mucositis may also be a marker for more aggressive treatment, with higher tumor response rates. Since about 42% of the patients in the present study had their treatment interrupted, more efforts should be spent on pre-, mid-and post-treatment health education and supportive therapy to encourage patients to complete their treatment.

During the past 10 years, there has been a significant increase in the incidence of anal SCC, particularly in those who are HIV-positive (61). The literature suggests that patients with HIV are less likely to achieve a complete clinical response to treatment, are more likely to die of their cancer, and have a significantly shorter median time to cancer death (61). Because there were only 15 HIV-positive patients in our cohort, it was difficult to evaluate the impact of HIV on the ability to tolerate therapy, and/or treatment outcomes. Further due to the lack of details about their HIV, studies with more pertinent details (length of time infected with HIV, HAART, CD4 count, human papillomavirus status) are required.

4.3: LIMITATIONS

The results of this study are important to consider in the context of its limitations. Imbalances in unmeasured and unknown prognostic factors also related to treatment decisions may have confounded our results.

- Residual confounding owing to possible unmeasured time-dependent confounders (i.e., changes in cancer severity/overall health from the time of cancer diagnosis to treatment start) should also be considered as a study limitation.
- Although we know the intent of treatment at the time of radiation planning, the original planned radiation dose and the specific volumes/fields prescribed are not known, therefore for this study, chemoradiation was the treatment modality, and the acute complications that may occur were assumed to be primarily due to EBRT rather than chemotherapy. It was also assumed all patients received similar doses of radiotherapy at all sessions.
- Similarly, some treatment protocols call for 2 doses of mitomycin (during week 1 and week 5) and others call for only 1. We cannot ascertain whether some patients were originally planned for 2 doses of mitomycin and only received 1. Thus, our definition of complete chemoradiation may overestimate the rate of planned chemoradiation completion
- Due to the ongoing Covid-19 pandemic, limitations to the number of patients attending anal cancer treatment limited the timely data collection and subject's recruitment to the study. Therefore, patient numbers with anal cancer were few and far between thus achieving less than the required patient size.
- Lack of previous research studies locally on the study area, socio-economic, racial, and environmental factors may have resulted in differences in acute complications which may not be generalizable to all patients with anal cancer. Further, patients' information regarding how their current disease affected them was very subjective.

CHAPTER FIVE: CONCLUSION AND RECOMMENDATIONS

5.1: CONCLUSION

Our study demonstrates that there is a higher prevalence of acute complications, with some often resulting in treatment interruption in about half the patients undergoing anal cancer radiotherapy at KNH. Administering standard EBRT results in the potential for developing acute complications. Major morbidities are relatively rare, however, can cause a significant reduction in quality of life in patients with anal cancer. Presence of co-morbidities particularly HIV and the use of concurrent chemotherapy may play a significant role in the risk of radiation-induced toxicity. This may have grave consequences in terms of tumor control and hence overall patient. Despite these events, EBRT is a relatively safe and effective treatment mode in anal cancer patients, though it is important to recognize the presence of these acute complications to effectively counsel these patients before therapy. The majority of adverse events arising from EBRT are grade 1 and below at a radiation dose of 50.4Gy. A large number of patients undergoing EBRT for anal cancer will get a form of the adverse event i.e., skin-related, gastrointestinal, and/or genitourinary.

Over the past several decades, tremendous strides have been achieved in improving outcomes in the definitive management of anal cancer. However, the current standard of care, CRT with 5-FU/MMC, remains a toxic regimen despite providing high cure rates. Future treatments focusing on mitigating toxicities as well as optimizing survival and individualizing treatment approaches in anal cancer patients are needed in KNH.

5.2: RECOMMENDATIONS

1. Specific anal cancer treatment protocols need to be revised and implemented within the guidelines of Total Quality Management (TQM).
2. There is a need to develop local protocols within the radiotherapy department for patients undergoing EBRT for anal cancer that include a patient information guide as to the type and grade of the adverse events that they should expect with this treatment modality
3. Similar long-term prospective studies for a larger sample than the current one, should be conducted to determine to evaluate the acute adverse events occurring as a result of this modality of treatment, the long-term QoL of post-radiotherapy patients, and the effect of poor QoL on patient survival within Kenya
4. Studies should be conducted to determine the effect of frequent treatment interruption on tumor control at KNH.

5. The radiation delivery system at KNH should be upgraded to allow for the utilization of other superior techniques such as 3DCRT or IMRT which may reduce these risks in some instances.
6. Future diagnostic testing may assist in determining which patients have the greatest risk for toxicity and will benefit most from frequent monitoring and early intervention.

5.3: DISSEMINATION OF STUDY FINDINGS

Findings from this study will be published in medical journals and presented at surgical conferences. The results will also be shared with the Cancer Treatment Centre unit of KNH and contribute to protocol development and policymaking. In addition, copies of the dissertation will be submitted to the University of Nairobi as an e-repository and College of Health Sciences Library where it can be accessed by academic staff and other members of academia.

REFERENCES

1. Bray F, Ferlay J, Siegel R, Soerjomataran I, Torre LA, Jemal A. Global Cancer Statistics. Cancer J Clin. 2018;68(6):394–424.
2. Shiels MS, Kreimer AR, Coghill AE. Anal cancer incidence in the United States, 1977-2011: Distinct patterns by histology and behavior. Cancer Epidemiol Biomarkers Prev. 2015;24(10):1548–56.
3. Nigro N., Vaitkevicius VK, Considine B. Combined therapy for cancer of the anal canal: A preliminary report. Dis Colon Rectum. 1974;17(3):354–6.
4. Sebag-Montefiore D, Meadows HM, Cunningham D, Plowman PN, Hurman DC, Davidson N, et al. Three cytotoxic drugs combined with pelvic radiation and as maintenance chemotherapy for patients with squamous cell carcinoma of the anus (SCCA): Long-term follow-up of a phase II pilot study using 5-fluorouracil, mitomycin C and cisplatin. Radiother Oncol. 2012;104(2):155–60.
5. Lee JM, Kim NK. Essential anatomy of the anorectum for colorectal surgeons focused on the gross anatomy and histologic findings. Ann Coloproctol. 2018;34(2):59–71.
6. Kim SH, Kim HJ, Lee JI, Kye BH, Lee IK, Lee YS, et al. Clinicopathologic characteristics of anal cancer. J Korean Surg Soc. 2010;78(4):219–24.
7. Glynne-Jones R, Saleem W, Harrison M. Background and Current Treatment of Squamous Cell Carcinoma of the Anus. Oncol Ther 4, 2016;135–72.
8. Wang C, Sparano J, Palefsky J. Human Immunodeficiency Virus/AIDS, Human Papillomavirus and Anal Cancer. Surg Oncol Clin N Am. 2017;26(1):17–31.
9. Arbyn M, De Sanjosé S, Saraiya M, Sideri M et al. Roadmap on Prevention and Treatment of HPV-related Disease. Int J Cancer. 2012;131(9):1969–82.
10. Frisch M, Glimellus B, Wohlfahrt J et al. Tobacco Smoking as a Risk Factor in Anal Carcinoma: An Antiestrogenic Mechanism? J Natl Cancer Inst. 1999;91(8):708–15.
11. De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S, Shiels MS, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: A systematic review and meta-analysis. Lancet Oncol. 2012;13(5):487–500.
12. Schraut WH, Wang C -H, Dawson PJ, Block GE. Depth of invasion, location, and size of cancer of the anus dictate operative treatment. Cancer. 1983;51(7):1291–6.
13. Matalon SA, Mamon HJ, Fuchs CS, Doyle LA, et al.. Anorectal Cancer: Critical Anatomic and Staging Distinctions That Affect the Use of Radiation Therapy. Radiographics. 2015;35(7):2090–107.

14. Noorani A, Rabey N, Durrani A, Walsh SR, Davies RJ. A systematic review of sentinel lymph node biopsy in anal squamous cell carcinoma. Int J Surg [Internet]. 2013;11(9):762–6. Available from: http://dx.doi.org/10.1016/j.ijsu.2013.07.005
15. Trautmann TG, Zuger JH. Positron emission tomography for pretreatment staging and posttreatment evaluation in cancer of the anal canal. Mol Imaging Biol. 2005;7(4):309–13.
16. American Cancer Society. Cervical Cancer Early Detection, Diagnosis, and Staging Can Cervical Cancer Be Found Early ? Am Cancer Soc. 2019;1–32.
17. Ryan M, Mayer RJ. Anal Carcinoma: Histology, S, Epidemiology, Staging, and Treatment. Curr Opin Oncol. 2000;12(4):345–52.
18. AJCC. AJCC Cancer Staging Manual 7th Edition. Definitions. 2020;125755.
19. Ryan M., David P, Compton CC, Robert J. Carcinoma Of The Anal Canal. N Engl J Med [Internet]. 2000;342(11):792–800. Available from: http://www.nejm.org
20. Nigro ND, Vaitkevicius VK, Considine B. Combined Therapy for Cancer of the Anal Canal: A Preliminary Report. Dis Colon Rectum. 1974;17(3):354–6.
21. Group UACW. Epidermoid Anal Cancer: Results from UKCCR randomized Trial of Radiotherapy alone versus Radiotherapy, 5-Fluorouracil, and Mitomycin C. Lancet. 1996;348:1049–54.
22. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): A randomized, phase 3, open-label, 2×2 factorial trial. Lancet Oncol. 2013;14(6):516–24.
23. Niederhuber J., Armitage J., Tepper J., Kastan MB. Abeloff's Clinical Oncology. 5th ed. Philadelphia: Elseiver Inc.; 2015.
24. American Cancer Society. External Beam Radiation [Internet]. 2016 [cited 2021 Jan 4]. Available from: https:/www.cancer.org/treatment- and -side-/treatment-types/radiation.htmleffects
25. Bazan JG, Hara W, Hsu A, Kunz PA, Ford J, Fisher GA, et al. Intensity-modulated radiation therapy versus conventional radiation therapy for squamous cell carcinoma of the anal canal. Cancer. 2011;117(15):3342–51.
26. Ortholan C, Ramaioli A, Peiffert D, Lusinchi A, Romestaing P, Chauveinc L, et al. Anal canal carcinoma: Early-stage tumors ≤10 mm (T1 or Tis): Therapeutic options and original pattern of local failure after radiotherapy. Int J Radiat Oncol Biol Phys. 2005;62(2):479–85.

27. Huang K, Haas-Kogan D, Weinberg V et al. Higher radiation dose with a shorter treatment duration improves outcome for locally advanced carcinoma of the anal canal. World J Gastroenterol. 2007;13(6):895–900.
28. Peiffert D, Tournier-Rangeard L, Gerard JP et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. J Clin Oncol. 2012;30(16):1941–8.
29. Kachnic LA, Tsai HK, Coen JJ et al. Dose-painted Intensity Modulated Radiation Therapy for anal cancer: a multi-institutional report of acute toxicity and response to therapy. Int J Radiat Oncol Biol Phys. 2012;82(1):153–8.
30. Hardcastle JD, Bussey HJ. Results of surgical treatment of squamous cell carcinoma of the anal canal and anal margin as seen at St. Mark's Hospital. Proc R Soc Med. 2008;61(6):629–30.
31. Bolus EN. Basic Review of Radiation Biology and Terminology. J Nucl Med Technol. 2001;29(2):67–73.
32. Sonis ST. The biological role Of nuclear factor-Kappa b in Disease and its potential involvement in mucosal injury associated with anti-Neoplastic therapy. Crit Rev Oral Biol Med. 2002;13(5):380–9.
33. Cancer Therapy Evaluation Program (CTEP). Common Terminology Criteria for Adverse Events (CTCAE).v.5.0. Cancer Ther Eval Progr. 2017;155.
34. Ajani JA, Wang XM, Izzo JG et al. Molecular Biomarkers correlate with disease-free survival in patients with anal carcinoma treated with chemoradiation. Dig Dis Sci. 2010;55(4):1098–105.
35. Hauer-Jensen M, Wang J, Boerma M et al. Radiation damage to the gastrointestinal tract: mechanisms, diagnosis, and management. Curr Opin Support Palliat Care. 2007;1(1):23–9.
36. Glynne-Jones R, Sebag-Montefiore D, Meadows HM et. al. Best time to assess complete clinical response after chemoradiotherapy in squamous cell carcinoma of the anus (ACT II): a posthoc analysis of randomized controlled phase 3 trial. Lancet Oncol [Internet]. 2017;18(3):347–56. Available from: http://dx.doi.org/10.1016/S1470-2045(17)30071-2
37. Allal AS, Mermillod B, Roth AD et. a. . Impact of clinical and therapeutic factors on major late complications of radiotherapy with or without concomitant chemotherapy for anal carcinoma. Radiat Oncol Biol Phys. 1997;51(5):1099–105.

38. Gerard JP, Mauro F, Thomas L et. a. . Treatment of squamous cell carcinoma with pulsed dose rate brachytherapy. Feasibility study of a French Cooperative Group. Radiother Oncol. 1999;51(2):129–31.
39. Sauter M, Lombriser N, Keilholz G et. al. Improved treatment outcome and lower skin toxicity with Intensity Modulated Radiotherapy vs. 3D conventional radiotherapy in anal cancer. Strahlentherapie und Onkol. 2020;196:356–67.
40. Atrash F, Kaidar-Person O, Billan S. Toxicity of treatment for anal carcinoma: 2D versus 3D planning. Isr Med Assoc J. 2015;17(7):414–7.
41. Touboul E, Schlienger M, Buffat L, Lefkopoulos D, Parc R, Tiret E, et al. Evolution and Management of Treatment-Related Toxicity in Anal Cancer. Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington, M.K., Gershenwald JE, et al., editors. Int J Radiat Oncol Biol Phys [Internet]. 8th ed. 2017 Oct 1 [cited 2020 Dec 12];14(1):1049–54. Available from: http://www.nicd.ac.za/wp-content/%0Auploads/2017/03/2014-NCR-tables-1.pdf
42. Myerson RJ, Garofalo MC, El Naqa I et. al. Elective Clinical Target Volumes for Conformal Therapy in Anorectal Cancer: A Radiation Therapy Oncology Group Consensus Panel Contouring Atlas. Int J Radiat Oncol Biol Phys. 2009;74(3):824–30.
43. Flam M, John M, Pajak T et . al. Role of mitomycin in combination with fluorouracil and radiotherapy and salvage chemoradiation in definitive non-surgical treatment of epidermoid carcinoma of the anal canal: results of phase III randomized intergroup study. J Clin Oncol. 1996;14(9):2527–39.
44. Ajani JA, Winter KA, Gunderson LL. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA. 2008;299(16):1914–21.
45. Gunderson LL, Winter KA, Ajani JA. Long-term update of US GI Intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol. 2012;30(35):4344–51.
46. Chuong MD, Freilich JM, Weber JM, .al. E. Comparative Outcomes of Intensity Modulated Radiation Therapy Versus 3D Conformal Radiation Therapy for Squamous Cell Carcinoma of the Anal Canal. Int J Radiat Oncol. 2012;84(3): S351.
47. Kachnic LA, Tsai HK, Coen JJ, Blaszkowsky LS, Hartshorn K, Kwak EL, et al. Dose-painted intensity-modulated radiation therapy for anal cancer: A multi-institutional report of acute toxicity and response to therapy. Int J Radiat Oncol Biol Phys.

2012;82(1).

48. Millender LE. Complications of Radiation Therapy. In: Complications in Head and Neck Surgery. Mosby Elsevier; 2009. p. 167–79.
49. Prabhu RS, Cassidy RJ, Landry JC. Radiation therapy and neutropenia. Curr Probl Cancer. 2015;39(5):292–6.
50. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB, Thomas CR, et al. Prognostic factors derived from a prospective database dictate clinical biology of anal cancer: The intergroup trial (RTOG 98-11). Cancer. 2010;116(17):4007–13.
51. Sharma B, Pandey D, Chauhan V et. al. Radiation proctitis. Indian Acad Clin Med. 2005;6(2):146–51.
52. Theis VS, Sripadam R, Ramani V et. al. Chronic radiation enteritis. Clin Oncol. 2010;22:70–83.
53. Rakovitch E, Fyles AW, Pintilie M et . al. Role of Mitomycin C in development of late bowel toxicity following chemoradiation for locally advanced carcinoma of the cervix. Int J Radiat Oncol Biol Phys. 1997;(38):979–87.
54. Ho AY, Atencio DP, Peters S et . al. Genetic predictors of adverse radiotherapy effects: the Gene-PARE project. Int J Radiat Oncol Biol Phys. 2006;(65):646–55.
55. Safwat A, Bentzen SM, Turesson I et al. Deterministic rather than stochastic factors explain most of the variation in expression of skin telangiectasia after radiotherapy. Int J Radiat Oncol Biol Phys. 2002;(52):198–204.
56. Tucker SL, Turesson I, Thames HD. Evidence for individual differences in radiosensitivity of human skin. Eur J Cancer. 1992;28A:1783–91.
57. Tucker SL, Geara FB, Peters LJ, Brock WA. How much could the radiotherapy dose be altered for individual patients based on a predictive assay of normal tissue radiosensitivity? Radiother Oncol. 1996;(38):103–13.
58. Neelu P, John G. Radiation Enteritisands Proctitis [Internet]. Medscape. 2019 [cited 2020 Dec 20]. Available from: http:/emedicine.medscape.com/article/197483
59. Hauer-Jensen M. Late radiation injury of the small intestine: Clinical, pathophysiologic, and radiobiologic aspects. A review. Acta Oncol. 1990;(29):401–15.
60. Yeoh E, Horowitz M, Russo A et. al. Effect of pelvic irradiation on gastrointestinal function : a prospective longitudinal study. Am J Med. 1993;(95):397–406?
61. NCCN. NCCN Clinical Practice Guidelines in Oncology [Internet]. 2020 [cited 2020 Oct 14]. Available from: NCCN.org

APPENDICES

APPENDIX A: INFORMED CONSENT

The Informed Consent is for patients with anal cancer attending radiotherapy treatment and will be administered to those eligible patients or the patient's guardian/ next of kin. We shall request these patients to participate in this research project titled "**The Prevalence and Risk Factors Associated with Acute Complications of External Beam Radiation among Patients on Treatment for Anal Carcinoma in Kenyatta National Hospital"**

Principal investigator: Dr. Lawrence Koli Kioko

Institutional Affiliation: Department of Surgery, School of Medicine, University of Nairobi

This Informed Consent has three parts.

- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)
- A statement of the researcher /person taking consent

You will be given a copy of the full informed consent form.

PART I: INFORMATION SHEET

Introduction

My name is Dr. Lawrence Kioko, a postgraduate student of General Surgery at the University of Nairobi. I am carrying out research to determine the acute complications of external beam radiation therapy among patients on treatment for anal cancer.

Purpose of the research

Anal cancer is a type of malignancy whose prevalence has been on the rise within our country and globally. Among the recommended treatment methods used to manage this disease process is the combination of radiotherapy and chemotherapy which have been shown in studies to be an effective approach. The radiation therapy used may have acute complications during treatment and the purpose of this study is to determine these complications if and as

they occur. I will provide information to you and let me know what you don't understand. After receiving the information concerning the study, you are encouraged to seek clarification in case of any doubt.

Type of Research Intervention

This research will involve asking relevant questions, and examining your body and medical records with your doctor's permission [or their representative] to obtain the symptoms arising from the radiation treatment. This assessment will be done before, during, and immediately after your scheduled radiotherapy sessions.

Voluntary participation

Your participation is entirely voluntary. Whether you choose to participate or not, all the services you receive at this hospital will continue without change. You have a right to refuse or withdraw your participation in this study at any point.

Confidentiality

The information obtained will be treated confidentially and will only be available to the primary investigator and the study team. Your name will not be used and any information about you will have a number on it instead of your name. We will not be sharing the identity of those participating in this research.

Sharing the results

The knowledge that we get from this study will be shared with the policymakers in the Ministry of Health, Kenyatta National Hospital, and doctors through publications and conferences. Confidential information will not be shared.

Benefits

You may not directly benefit from the information you provide for this study; however, the results will greatly contribute to the advancement of health science by providing knowledge of the acute complications of radiotherapy and better management of patients undergoing a similar treatment process such as yours in KNH.

Risks, Cost, and Compensation

There are no direct risks anticipated in this study as it only seeks to describe the acute effects of the treatment that you are receiving. There will be no extra cost incurred for participating in this study, nor will there be any compensation offered. This proposal has been reviewed and approved by UON / KNH Ethics Committee.

PART II: CERTIFICATE OF CONSENT

I have read the above information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction.

I consent voluntarily to participate as a participant in this research.

Signature of Participant _____Date _____

If Non -literate:

Thumbprint of participant

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

Signature of witness: _____Date _____

PART III: STATEMENT BY THE RESEARCHER

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

Refusal to participate or withdraw from the study will not in any way compromise the care or treatment.

All information given will be treated with confidentiality.

The results of this study might be published to facilitate a better understanding of the acute effects of radiotherapy.

I confirm that the participant was allowed to ask questions about the study, and all the questions asked by the participant have been answered correctly and to the best of my ability.

I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this Informed Consent Form has been provided to the participant.

Name of researcher/person taking consent _____

Signature of researcher/person taking consent _____

Date_____

Whom may you contact if need be;

Principal Researcher: Dr. Lawrence Koli Kioko,

P.O. Box 19676- 00202.

KNH, Nairobi

Mobile no. 0727304840

University of Nairobi Supervisors:

Dr. Elly Nyaim Opot, Consultant General Surgeon and Senior Lecturer,

Department of Surgery, University of Nairobi

Tel: +254722714668

Dr. Marilynn A. Omondi Consultant General Surgeon, and Lecturer

Tel: +254722986777

Dr. Catherine Nyongesa Consultant Radio-Oncologist,

Kenyatta National Hospital

Tel: +254723698888

If you have any ethical concerns, you may contact:

Secretary, UON/KNH-ERC,

P.O. Box 20723- 00202, KNH, Nairobi.

Tel: 020-726300-9

Email: KNHplan@Ken.Healthnet.org

APPENDIX B: FOMU YA MAKUBALIANO.

Fomu hii ya makubaliano itaidhinishwa na wagonjwa au jamaa zao, wenye saratani ya mkundu (anal) ambao wanapokea matibabu ya miale ya mionzi (external beam radiotherapy). Tunakusihi kushiriki katika uchunguzi huu wa maarifa ambao anwani yake ni: "**Athari za Utabibu wa Miale ya Mionzi kwa Wagonjwa Waliona Saratani Sehemu ya Mwisho Njia ya Choo Katika Hospitali Kuu ya Kenyatta."**

Mtafiti Mkuu: Dkt. Lawrence Kali Kioko

Chuo Kikuu cha Nairobi, Kitivo cha utabibu.

Fomu hii ina sehemu tatu:

- Habari itakayo kusaidia kukata kauli
- Fomu ya makubaliano (utakapo weka sahihi)
- Ujumbe kutoka kwa mtafiti

Utapewa nakala ya fomu hii.

SEHEMU YA KWANZA: UKURASA WAHABARI

Kitambulizi

Mimi ni daktari Lawrence Koli Kioko, anayesomea uzamili katika idara ya upasuaji Chuo Kikuu cha Nairobi. Ninafanya utafiti Kwa anwani: **"The Prevalence and factors associated with Acute Complications of External Beam Radiation Among Patients on Treatment for Anal Cancer in Kenyatta National Hospital"**

Lengo kuu la utafiti.

Sarataniyapurunamkundukatikasikuyajusiimezidikuongezekakatikanchiyetuna dunia nzima. Kunaoainanyingiyamatibabuasiliaambazohutumikakukabilimaradhihaya, ijapo kwa wakati mwingi hutumika kwa jumuisho. Moja wapo ya aina za tabibu ni miale ya mionzi. Utabibuhuuunawezakuwanaatharizakewakatimgonjwaanapoupokeandiposautafitihuuukaleng akuzipekuakwa kina. Nitakupa ujumbe kuhusu utafiti huu kisha nikupe fomu utakayo ijaza

kama kibali cha kujiunga na utafiti. Iwapo kuna baadhi ya mambo hutaelewa, una uhuru wa kuuliza kwa maelezo zaidi.

Aina ya utafiti.

Utafiti huu utahusu kujibu maswali kupitia kwa dodoso, kukupima hali ya afya kulingana na ugonjwa wako wa saratani na pia kuturusu hifadhi ya jumbe za afya yako kulingana na hiari ya daktari wako. Utafiti utafanywa kabla, kati na baada ya kupokea utabibu wa miale ya mionzi.

Haki ya kukataa utafiti

Kushiriki kwako kwa utafiti huu ni kwa hiari yako. Una uhuru wa kukataa kushiriki, na kukataa kwako hakutatumiwa kukunyima tiba. Unayo haki ya kujitoa katika utafiti wakati wowote unapo amua.

Taadhima ya Siri

Ujumbe kuhusu majibu yako yatahifadhiwa. Ujumbe kuhusu ushiriki wako katika utafiti huu waweza kupatikana na wewe na wanao andaa utafiti na wala siyeyote mwingine. Jina lako halitatumika bali ujumbe wowote kukuhusu utapewa nambari badala ya jina lako.

Hatari unayoweza kupata

Hakuna hatari yoyote ambayo yaweza kutokea kwa sababu ya kuhusishwa kwa utafiti huu. Hatari ambazo zaweza tokana na upasuaji wenyewe zitaelezwa katika fomu ya kibali cha upasuaji, tofauti na hii. Aidha, kukataa au kujitoa katika ushiriki wako kwa huu utafiti kwa wakati wowote ule hakutakuletea hatari yoyote ya matibabu.

Hifadhi ya matokeo.

Matokeo ya utafiti huu yatachapishwa kwa nukuu mbalimbali za sayansi kupitia kwa idhini ya mtafiti mkuu. Nakala za chapisho zitahifadhiwa katika idara ya upasuaji, chuo kikuu cha Nairobi na katika maktaba ya sayansi za Afya, kitivo cha utabibu. Hivyo basi, matokeo ya utafiti huu hayatasambazwa kwa umma au jukwaa lisilo idhinishwa kihalali. Ujumbe ulio kwa dodoso zitahifadhiwa baada ya uchanganuzi wa matokeo.

Kusambaza Matokeo.

Utafiti huu hauta kugharimu zaidi ya matibabu yako ya kawaida. Vilevile, hakuna malipo yoyote au fidia utakayopokea kutokana na kujiunga kwako katika utafiti huu. Muda wako ndio utakao tumiwa wakati wa mahojiano.

SEHEMU YA PILI: FOMU YA MAKUBALIANO

Nimeelezewa utafiti huu kwa kina. Nakubali kushiriki katika utafiti huu kwa hiari yangu. Nimepata wakati wa kuuliza maswali na nimeelewa kuwa iwapo nina maswali zaidi, ninaweza kumwuliza mtafiti mkuu au watafiti walio tajwa hapa juu.

Jina la Mshiriki _____

Sahihi ya mshiriki _____Tarehe _____

Kwa wasioweza kusoma na kuandika:

Nimeshuhudia usomaji na maelezo ya utafiti huu kwa mshiriki. Mshiriki amepewa nafasi ya kuuliza maswali. Nathibitisha kuwa mshiriki alipeana ruhusa ya kushiriki bila ya kulazimishwa.

Jina la Shahidi _____

Alama ya kidole cha gumba cha mshiriki

Sahihi la shahidi _____Tarehe_____

SEHEMU YA TATU: UJUMBE KUTOKA KWA MTAFITI

Nimesomea mshiriki ujumbe kiwango ninavyo weza na kuhakikisha kuwa mshiriki amefahamu ya fuatayo:

Kutoshiriki au kujitoa kwenye utafiti huu hakutadhuru kupata kwake kwa matibabu.

Ujumbe kuhusu majibu yake yatahifadhiwa kwa siri.

Matokeo ya utafiti huu yanaweza chapishwa kusaidia utambuziwa shida zinazotokana utabibu wa miale ya mionzi. Ninathibitisha kuwa mshiriki alipeana nafasi ya kuuliza maswali yote yakajibiwa vilivyo. Nina hakikisha kuwa mshiriki alitoa ruhusa bila ya kulazimishwa. Mshiriki amepewa nakala ya hii fomu ya makubaliano.

Jina la mtafiti: _____

SahihiyaMtafiti: _____Tarehe_____

Anwani za Wahusika

Ikiwa uko na maswali ungependa kuuliza baadaye, unaweza kuwasiliana na:

Mtafiti Mkuu:	Dkt. Lawrence Koli Kioko Idara ya upasuaji, Shule ya Afya, Chuo Kikuu cha Nairobi, SLP 19676 KNH, Nairobi 00202. Simu: 0727304840
Wahadhiri wahusika:	
Dkt. Nyaim Opot,	Consultant General Surgeon and Senior Lecturer, Department of Surgery, University of Nairobi Tel:0722714668
Dkt.Marilynn A. Omondi	Consultant General Surgeon and Lecturer Tel: 0722986777
Dkt Catherine Nyongesa,	Consultant Radio-Oncologist, Kenyatta National Hospital Tel:0723698888

Wahusika wa maslahi yako katika Utafiti:

Karani, KNH/on-ERC

SLP 20723 KNH, Nairobi 00202

Simu: +254-020-2726300-9 Ext 44355

Barua Pepe: uonknh_erc@uonbi.ac.ke

APPENDIX C: QUESTIONNAIRE

SECTION A: PATIENT IDENTIFYING DATA

Name Initials……

Age……Gender: ……

Ward/Unit……

Inpatient Number: ……

Date of admission……

What is your level of formal education?

No formal education ☐

Primary education ☐

Secondary education ☐

Post-secondary education (Certificate, Diploma, Degree, Masters) ☐

What is your usual residence?

Urban ☐

Rural ☐

Marital status

Single ☐

Married ☐

Other –widowed/divorced ☐

Primary home care giver

Immediate family member/s ☐

Relative ☐

Friend ☐

Other(Specify)……... ☐

SECTION B: PRE-RADIOTHERAPY ASSESSMENT

Does the Anal cancer limit the patient's daily activities? (CIRCLE)

Not 1 2 3 4 5 6 7 8 9 10 very

At all much

ECOG performance status classification (Grade 0, 1,2,3,4 or 5)----------

Vital signs

BP: _____ (mmHg) PR: _____ (BPM) Temp._____ (^{0}C) RR _____ (/min)

Presence of other co-morbidities?

No ☐ Yes ☐

If yes, indicate the co-morbidity _____

Previous Surgery

Yes/No

If Yes, Specify…….

On treatment with Chemotherapy?

Yes ☐ No ☐

If yes, indicate Chemotherapy _____

Tumor stage (TNM) _____

Pre-Radiotherapy Local Skin Assessment, Final Grade:

Pre-Radiotherapy Lower Gastrointestinal/Pelvis Assessment: Final Grade:

Pre-Radiotherapy Genitourinary Assessment: Final Grade:

Laboratory Findings:

HB: g/dl WBC: $x10^9$ NEU: $x10^9$ Plts. $x10^9$

SECTION C: MID- RADIOTHERAPY ASSESSMENT

ECOG performance status classification (Grade 0, 1,2,3,4 or 5)----------

Vital signs

BP:_____ (mmHg) PR:_____ (BPM)Temp:_____(^{0}C) RR:_____ (/min)

Mid-Radiotherapy Local Skin Assessment: Final Grade:

Mid-Radiotherapy Gastrointestinal/Pelvis Assessment: Final Grade:

Mid-Radiotherapy Genitourinary Assessment: Final Grade:

Any unscheduled treatment break: Yes/No…… If yes duration in days…….

Laboratory Findings

Hb: g/dl WBC: $x10^9$ Neu: $x10^9$ Plt. $x10^9$

SECTION D:END- RADIOTHERAPY ASSESSMENT

ECOG Performance Status Classification (Grade 0, 1,2,3,4 Or 5)----------

Vital Signs

BP: _____ (mmHg) PR: _____ (BPM) Temp: _____ (^{0} C) RR_____ (/min)

End-Radiotherapy Local Skin Assessment: Final Grade:

End-Radiotherapy Gastrointestinal/Pelvis Assessment: Final Grade:

End-Radiotherapy Genitourinary Assessment: Final Grade:

Any unscheduled treatment break: Yes/No…… If yes duration in days…….

Laboratory Findings

Hb: g/dl WBC: $x10^9$Neu: $x10^9$ Plt. $x10^9$

APPENDIX D: RTOG ACUTE ADVERSE EVENT GRADING

The study variables will be as shown in the table below.

Study Objective	**Outcome Variable**		**Exposed Variable**	**Source of Data**
Immediate adverse clinical effects among patients undergoing EBRT for anal cancer	**Organ Complication**	**Grade**	External beam radiotherapy treatment	Physical examination of patient questionnaire RTOG ACUTE - Radiation Morbidity questionnaire
	1. Genitourinary effects	0,1,2,3,4,5		
	2. Lower Gastrointestinal effects	0,1,2,3,4,5		
	3. Local Skin Changes	0,1,2,3,4,5		

NB: For all: GRADE 0 = no symptoms, GRADE 5 = death directly related to radiation effects.

APPENDIX E: CTCAE ADVERSE EVENTS GRADING

GASTROINTESTINAL GRADING OF ACUTE EVENTS							
	Symptom						
Grade	Nausea	Anorexia	Hemorrhage	Diarrhea	Incontinence	ulceration	Anal Pain
1	Loss of appetite without alteration in eating habits	Loss of appetite without alteration in eating habits	Mild, intervention (other than iron supplements) not	Increase of <4 stools per day over baseline; mild increase in Ostomy output compared to baseline baseline; limiting self-care, ADL	Occasional use of pads required	Asymptomatic, radiographic, or endoscopic findings only	Mild pain
2	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 h	Oral intake, altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Symptomatic and medical intervention or minor cauterization indicated.	Increase of 4 - 6 stools per day over baseline; moderate increase in Ostomy output compared to baseline; limiting instrumental ADL	Daily use of pads required	Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated < 24 h	Moderate pain; limiting instrumental ADL
3	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24 h	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings, or TPN indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site)	Increase of ≥7 stools per day over baseline; Hospitalization indicated; Severe increase in Ostomy output compared to baseline; limiting self-care ADL	Interfering with ADL; operative intervention indicated	Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ≥ 24 h	Severe pain; limiting self-care ADL
4	Life-threatening consequences	Life-threatening consequences	Life-threatening consequences; major urgent intervention indicated	Life-threatening consequences; urgent intervention indicated	Permanent bowel diversion indicated	Life-threatening consequences	

Dermatological Grading of Adverse Events						
Grade	**0**	**1**	**2**	**3**	**4**	**5**
Event	No adverse event	Faint erythema or dry desquamation	Moderate to brisk erythema or patchy moist desquamation, mostly confined to skin folds and creases; moderate erythema	Moist desquamation other than skin folds; pitting edema, bleeding from minor trauma or abrasion	Skin necrosis or ulceration of full-thickness dermis; may have spontaneous bleeding from the affected area	Death

Genitourinary Grading of Adverse Events as per CTCAE						
	Grade					
Adverse Event	**0**	**1**	**2**	**3**	**4**	**5**
Incontinence	No Adverse Event	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self-care ADL	-	Death
Bladder Spasm		Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Urinary Urgency		Present	Limiting instrumental ADL; medical management indicated	-	-	-
Hematuria		Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications, or hospitalization indicated; elective invasive intervention indicated; limiting self-care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death
Urinary Tract Pain		Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Urinary Frequency		Present	Limiting instrumental ADL; medical management indicated	-	-	-
Urinary Retention		Urinary, suprapubic, or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic, or intermittent catheter placement indicated; medication indicated	Elective invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death

Hematologic Adverse Events						
	Grade					
Event	0	1	2	3	4	5
Anemia		Hemoglobin (Hgb) < LLN - 10.0 g/dL; < LLN - 6.2 mmol/L; < LLN - 100 g/L	Hgb < 10.0 - 8.0 g/dL; < 6.2 - 4.9 mmol/L; < 100 - 80g/L	Hgb < 8.0 g/DL; < 4.9 mmol/L; < 80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Neutropenia	-	-	-	ANC <1000/mm3 with a single the temperature of >38.3 degrees	Life-threatening consequences; urgent intervention indicated	Death

				C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour		
Thrombocytopenia	-	-	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death

APPENDIX F: BUDGET AND STUDY TIMELINE

STUDY BUDGET

BUDGET ITEM	COST
Research fee – KNH/ERC	2000
Statistician Consultation Fee	30000
Stationery: a. Printing b. Photocopying c. Binding d. Pens	 5000 5000 10000 500
Research Assistant	20000
Contingency	10000
Total Cost	82, 500

TIMELINES

Activity	January-April 2021	April – July 2021	September 2021– March 2022	March 2022-	April 2022
Proposal Development					
Ethical Approval					
Data Collection					
Data Analysis					
Dissertation Submission					

APPENDIX H: KNH ANORECTAL DISEASE TREND FROM 2014-2020

ANAL RECTAL DISEASE TREND AT KNH - 2014-2020

2014

Disease_code	disease_name	Alive	Dead	Total
C20	Malignant neoplasm of rectum	94	5	**99**
C21.8	Malignant neoplasm, overlapping lesion of rectum, anus and anal canal	11	2	**13**
C21.0	Malignant neoplasm, anus, unspecified	11	2	**13**
	Total	**116**	**9**	**125**

2015

Disease_code	disease_name	Alive	Dead	Total
C20	Malignant neoplasm of rectum	169	5	174
C21.8	Malignant neoplasm, overlapping lesion of rectum, anus and anal canal	15	2	17
C21.0	Malignant neoplasm, anus, unspecified	12	2	14
C21.1	Malignant neoplasm, anal canal	2	0	2
	Total	**198**	**9**	**207**

2016

Disease_code	disease_name	Alive	Dead	Total
C20	Malignant neoplasm of rectum	188	17	205
C21.0	Malignant neoplasm, anus, unspecified	7	0	7
C21.8	Malignant neoplasm, overlapping lesion of rectum, anus and anal canal	6	0	6
	Total	**201**	**17**	**218**

2017

Disease_code	disease_name	Alive	Dead	Total
C20	Malignant neoplasm of rectum	98	10	**108**
C21.0	Malignant neoplasm, anus, unspecified	7	5	**12**
C21.8	Malignant neoplasm, overlapping lesion of rectum, anus and anal canal	4	1	**5**
	Total	**109**	**16**	**125**

2018

Disease_code	disease_name	Alive	Dead	Total
C20	Malignant neoplasm of rectum	172	15	**187**
C21	Malignant neoplasm of anus and anal canal	1	0	**1**
C21.0	Malignant neoplasm, anus, unspecified	21	3	**24**
C21.1	Malignant neoplasm, anal canal	3	0	**3**
C21.8	Malignant neoplasm, overlapping lesion of rectum, anus and anal canal	6	4	**10**
	Total	**203**	**22**	**225**

2019

Disease_code	disease_name	Alive	Dead	Total
C20	Malignant neoplasm of rectum	119	17	136
C21	Malignant neoplasm of anus and anal canal	2	0	2
C21.0	Malignant neoplasm, anus, unspecified	13	2	15
C21.1	Malignant neoplasm, anal canal	1	1	2
C21.8	Malignant neoplasm, overlapping lesion of rectum, anus and anal canal	18	2	20
	Total	**153**	**22**	**175**

2020

Disease_code	disease_name	Alive	Dead	Total
C20	Malignant neoplasm of rectum	84	15	99
C21.0	Malignant neoplasm, anus, unspecified	12	0	12
C21.8	Malignant neoplasm, overlapping lesion of rectum, anus and anal canal	10	3	13
		106	**18**	**124**

Source: Statistics Unit, Health Information Department KNH, 18/03/2021