# PREVALENCE AND FACTORS ASSOCIATED WITH LATE EFFECTS OF RADIOTHERAPY AMONGST CERVICAL CANCER PATIENTS AT OCEAN ROAD CANCER INSTITUTE FROM 2016 TO 2019

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**MMed (Clinical Oncology) Dissertation**
**Muhimbili University of Health and Allied Sciences**
**October, 2021**

**Muhimbili University of Health and Allied Sciences**

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# PREVALENCE AND FACTORS ASSOCIATED WITH LATE EFFECTS OF RADIOTHERAPY AMONGST CERVICAL CANCER PATIENTS AT OCEAN ROAD CANCER INSTITUTE FROM 2016 TO 2019

**By**

**Diane Andrea Ndoli**

**A Dissertation Submitted in (Partial) Fulfillment of the Requirements for the Degree of Master of Medicine (Clinical Oncology) of**

**Muhimbili University of Health and Allied Sciences**
**October, 2021**

## CERTIFICATION

The undersigned certifies that he/she has read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled; **"Prevalence and Factors Associated With Late Effects of Radiotherapy Amongst Cervical Cancer Patients at Ocean Road Cancer Institute from 2016 to 2019",** in (partial) fulfillment of the requirements for the degree of Master of Medicine (Clinical Oncology) of the Muhimbili University of Health and Allied Sciences.

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## DECLARATION AND COPYRIGHT

I, **Dr. Diane Andrea Ndoli**, hereby declare that this **dissertation** is my original work and that it has not been presented and will not be presented to any other university for a similar or any other degree award.

**Signature**……. **Date**……

## ACKNOWLEDGMENTS

First and foremost, I thank the Almighty God for the gift of life, protection and daily provision.

My sincere gratitude to the Muhimbili University of Health and Allied Sciences (MUHAS) and Ocean Road Cancer institute (ORCI) for the knowledge and competency I acquired during my postgraduate training.

Special thanks to the ORCI academic team and more to Dr. Nazima Dharsee the head of department, for her mentorship and moral support throughout my training.

Sincere thanks go to Dr. Sikudhani Muya for supervising this project and Dr Emmanuel Lugina the co –supervisor. Their guidance and support were key in this project.

Finally I acknowledge the support from my family, my fellow residents, friends and everyone whose support in one way or the other made this journey worth achievable.

## DEDICATION

I dedicate this work,

To my lovely husband Kayumba Polepole, whose belief in me, moral support and love were of great support during this journey.

To my daughters Simbi Natete Kylie and Berwa Kaze Kaylane, thanks for being the reason for me to never give up, you are my sunshine.

To my late mother Immaculee Uwase Mukakazenga , maman Cherie, I am because you were, thanks for your love and guidance.

## ABSTRACT

**Background:** Cervical cancer prevails as the fourth most common diagnosed female cancer worldwide and the first in incidence and mortality amongst diagnosed cancers in Tanzania. Pelvic radiation therapy including both external beam radiation therapy and brachytherapy remains the main core treatment of cervical cancer. It has been associated with toxicities both acute and late, secondary to irradiation of the normal surrounding tissues. Frequently these effects are under-reported and inadequately addressed, since treatment success is usually defined in terms of tumor control and eradication than the long-term well-being of cervical cancer patients.

**Aim of the study:** This study aimed at determining the prevalence and factors associated with late effects of radiotherapy amongst cervical cancer patients at Ocean Road Cancer Institute (ORCI), Dar es Salaam.

**Material and methods:** This study employed a cross sectional designed study done at Ocean Road Cancer Institute. The study participants were patients with cervical cancer attending follow up clinic, at least six months after finishing curative pelvic radiotherapy. Chi-square test was used to assess factors associated with occurrence of late effects and multiple logistic regression was used to assess for confounding factors.

**Results:** Three hundred and eight patients were recruited in this study. All participants had multiple late effects, the most common late effect was Genitourinary late effects (cystitis) (91.9%),followed by vaginal stenosis (dyspareunia ,vaginal narrowing) (87.3%),sexual dysfunction (79.2%) and Gastro intestinal late effects(proctitis and enteritis) (72.19%) respectively. Majority of late effects were grade1-2(mild to moderate).Vaginal stenosis and sexual dysfunction late effects were significantly associated with age and EBRT field size ($p<0.05$).Smoking showed a statistically significant association with Genital Urinary late effects.

**Conclusion:** The prevalence of radiotherapy induced late effects in cervical cancer patients was high in this study. Majority of participants had mild late effects (grades 1 and 2 ).

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| | |
|---|---|
| 2DRT: | 2-Dimensional Radiation Therapy. |
| 3DRT: | 3Dimensional Radiation Therapy |
| BT: | Brachytherapy |
| CRP: | Chronic Radiation Proctitis |
| EBRT: | External Beam Radiation Therapy |
| EORTIC: | European Organization for Research and Treatment of Cancer |
| FIGO: | International Federation of Gynecology and Obstetrics (Fédération Internationale de Gynécologie et d'Obstétrique) |
| GI: | Gastrointestinal |
| GU: | Genito Urinary |
| IAEA: | International Atomic Energy Agency |
| LINAC: | Linear Accelerator |
| LMICS: | Low- and Middle-Income Countries |
| ORCI: | Ocean Road Cancer Institute |
| QOL: | Quality of Life |
| RT: | Radiation Therapy |
| RTOG: | Radiation Therapy Oncology Group |
| SD: | Sexual Dysfunction |

## DEFINITIONS OF KEY TERMS

**Radiation therapy:** Treatment of cancer with the use of high energy radiation from x-rays gamma rays, protons and neutrons and other sources to destroy cancer cells and shrink tumour (1).

**External beam radiation therapy:** A form of radiation therapy where high energy radiation is given from a machine outside the body aiming at the disease to be treated (2).

**Brachytherapy:** A form of radiation therapy where the radioactive material is placed in the body inside or next to the area that needs to be treated. Commonly used in cervical cancer, prostate cancer and esophageal cancer(3).

2D convention radiation therapy: A form of radiation therapy that uses X-rays films to determine the Position of radiation beams. Beams are designed to only match the height and width of the tumor exposing more healthy tissue to radiation (1).

**3D conformal radiation therapy:** A form of radiation therapy where radiation beams are shaped to match the shape of the tumor (1).

**Side effects of radiation therapy:** Effects secondary to damage of normal tissues in the path of the treatment beams' entrance and exit as the radiation passes in the target region designated for treatment. For example skin reactions during radiation therapy (4).

**Acute/sub-acute effects of pelvic radiotherapy:** There are those side effects that appear within weeks of initiating Treatment to up to 6 months after treatment.

**Late effects of pelvic radiotherapy:** Late effects also known as long term effects of radiation therapy, are effects occurring normally more than six months to years after treatment. These effects are occasionally a continuation of acute effects of pelvic radiation therapy or new side effects developing months or years after pelvic radiation therapy (2).

**Radiation Proctitis:** Damage to lower part of the colon by high energy radiation post pelvic radiation therapy usually presents with mild to chronic bloody stool (4).

# CHAPTER ONE

## 1.0 INTRODUCTION

### 1.1 Background

Worldwide cervical cancer remains the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death in women with an estimation of 604,000 new cases and 342,000 deaths in 2020(5). According to recent estimates, sub –Saharan Africa was the region with the highest incidence and mortality of cervical cancer, with rates increased in the Eastern Africa .Similarly, Tanzania as a country in the eastern part of Africa, according to the GLOBOCAN 2020 estimates, cervical cancer incidence and mortality rate was reported to be at 25.3% and 24.2 % per 100,000 people respectively (6)(7). Cervical cancer is mostly diagnosed at a locally advanced stage and about 7300 Tanzanian women are diagnosed each year for cervical cancer, with more than a half of those diagnosed dying each year (8,9). At the Ocean Road Cancer Institute, the main national cancer hospital in Tanzania, approximately 3,000 new cervical cancer patients are seen every year, ranking cervical cancer as first in incidence and mortality among all diagnosed cancers at this center (10).

Radiation therapy has been the mainstay in the treatment of cervical cancer, either as adjuvant therapy post-surgery, definitive treatment or for palliative intent. Concurrent chemotherapy and radiation therapy followed by brachytherapy is the cornerstone in the treatment of cervical cancer and this has portrayed increase in overall survival of the patients, compared to either radiation alone or surgery alone (11). Newer technologies have evolved in radiotherapy like 3D conformal, IMRT with an aim to give higher dose to the target volume and minimize dose to the organs at risk. In most Lower and Middle Income Countries (LMCIS) though radiation is mostly delivered using cobalt machines that are a lot cheaper and easier to maintain than LINAC (12).

Several effects post pelvic radiation therapy have been reported either as acute ;effects occurring within 6 months of treatment ,or late those occurring from six months on wards after treatment (13).

These effects occur mainly due to patho-physiological changes in normal tissues or organs that are found included in the irradiated volume and they present with toxicities that usually affect the quality of life and day to day activities of the patients (14). Despite available tools to analyze late effects of pelvic radiation therapy, these effects are under reported hence not well managed and followed up (15). Therefore, this study aimed at determining the prevalence of late effects in cervical cancer patients post pelvic radiation therapy and understanding the factors influencing their occurrence and severity.

## 1.2 Problem Statement

Pelvic radiation therapy that includes EBRT and brachytherapy have for long been the mainstay of treatment in cervical cancer. However, these treatment modalities have been associated with adverse effects that compromise the well-being of these patients earlier on or later in the course of their disease(39).

Despite the fact that treatment benefits most of time outweigh its effects in cervical cancer patients, late effects are reported to hinder the wellbeing of patients after treatment, leading to stigma and depression. This lead to increased loss of follow up to treatment hence, the necessity of these late effects to be addressed. In Tanzania, cervical cancer patients receive mainly concurrent pelvic radiation therapy and brachytherapy as treatment of cervical cancer. Late complications associated with this treatment most of the time are under reported hence not addressed. This study aimed at assessing the magnitude of the most common late effects occurring post pelvic radiation therapy.

## 1.3 Conceptual Framework

Fig 1 below shows cervical cancer patients who received radiation therapy as treatment. It describes the relationship between prevalence of common late effects post pelvic radiation therapy in accordance with various types and parameters of radiotherapy treatment, clinical features as well as social demographic influence. Radiotherapy of cervical cancer results to long term effects such as urinary tract, GI, vaginal stenosis and sexual dysfunction.

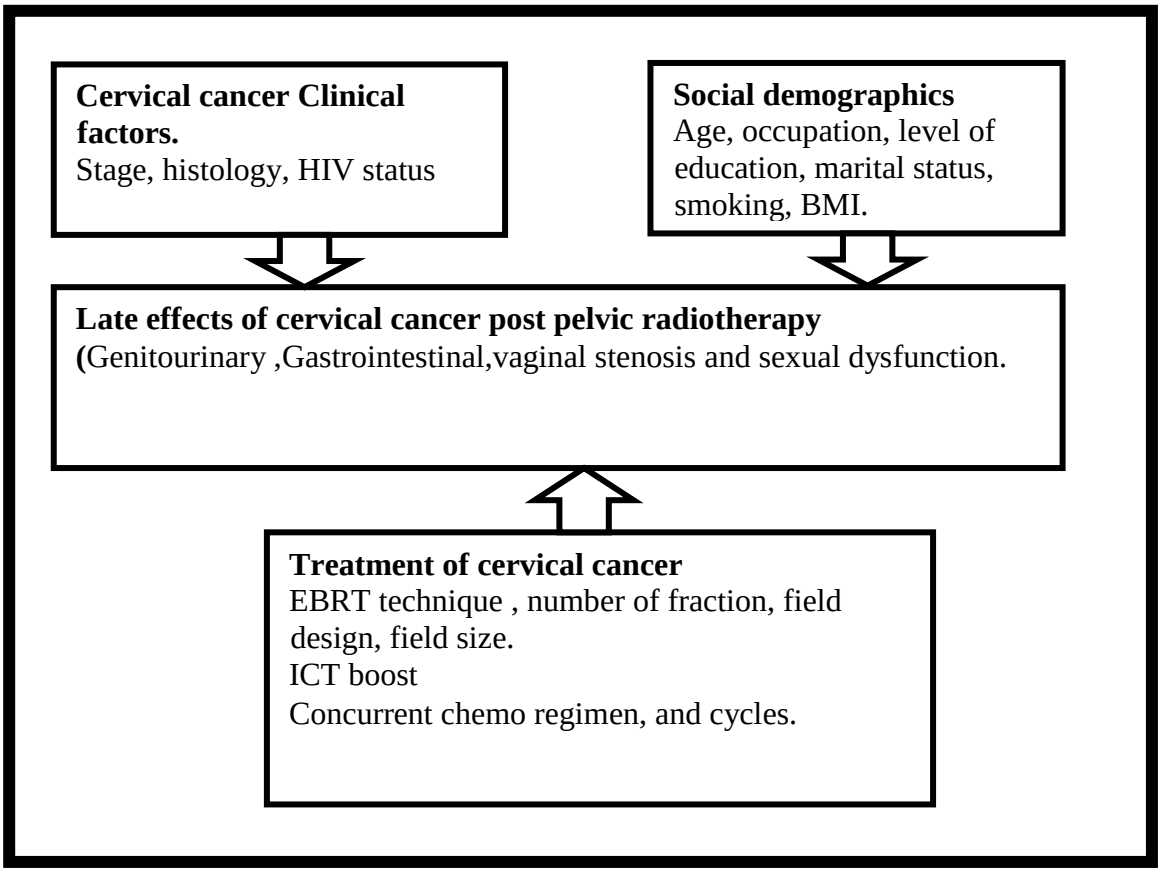


**Figure 1: Conceptual framework. Structure adopted and modified from study that assessed late presentation of cervical cancer, Ghana (16).**

### 1.4 Rationale

The findings of this study helped us understand that, as there is a continuing improvement in treatment of cervical cancer and the oncology care at large in Tanzania, there is necessity for reporting and addressing to the late effects of the treatment modalities that we offer to our patients. Patients with cervical cancer live long after treatment and hence they live with these effects for long.

With scarcity of such study in Africa, this study shed light to the magnitude and severity of late pelvic radiation therapy effects in Tanzania. Besides, the findings may help spearhead the development of institutionalized strategies in an attempt to minimize the occurrence of the late effects.

## 1.5 Research Question

General research question: what is the prevalence and factors associated with late effects of radiotherapy amongst cervical cancer patients at Ocean road cancer institute from 2016 to 2019?

i. What is the prevalence of late effects post pelvic radiation therapy in patients treated for cervical cancer at ORCI from 2016 to 2019?
ii. What are the factors associated with occurrence of radiotherapy induced late effects amongst cervical cancer patients at ORCI from 2016-2019?

## 1.6 Objectives

### 1.6.1 Broad objective

To determine the prevalence and factors associated with radiotherapy induced late effects amongst cervical cancer patients treated at Ocean Road Cancer Institute between the years of 2016-2019.

### 1.6.2 Specific objectives

1. To describe the social- demographic and clinical characteristics of cervical cancer patients with late effects post pelvic radiation therapy at Ocean Road Cancer Institute from 2016 to 2019.
2. To determine the prevalence of late effects in cervical cancer patients post pelvic radiation therapy at 2016 Ocean Road Cancer Institute to 2019.
3. To describe factors associated with late effects post pelvic radiation therapy in cervical cancer patients at ORCI from 2016 to 2019.

### 1.7 Literature Review

Cancer of the cervix uteri remains considerable due to the high morbidity and mortality it causes among women globally, and more pronouncedly in the developing world ,despite being the cancer with the greatest demonstrated potential for secondary prevention (17). According to the World Health Organization (WHO), many of women living with cancer present late when treatment is more difficult and expensive and chances of cure are abysmal (18).

Treatment for cervical cancer which includes radiotherapy as core, has been associated with both acute and late effects (13) acute effects being those seen within weeks of initiating treatment to up to 6 months after treatment and late effects being those that are diagnosed six months after treatment.(19) These effects are mainly due to the damage of normal tissues surrounding the area that is treated in cervical cancer that is mainly; bladder, rectum, vagina, sigmoid colon and small bowel.(19).

#### 1.7.1 Prevalence of late effects post pelvic radiation therapy

The International Atomic Energy Agency human health report series No.6 on management of cervical cancer strategies in LMICs, reported the late effects of pelvic radiation therapy to include; late bowel complications or effects (such as bleeding, and/or bowel obstruction) as the most common late complications in up to 5–15% of treated patients followed by bladder complications (such as urinary dysfunction) (19,20).Vaginal effects that include narrowing and shortening of the vagina is also among the major late effects with an incidence of 1.25% to 88% in patients who received pelvic radiation therapy. This mostly results in dyspareunia associated with or without post-coital bleeding(21).A study by Ferry W. Grigsby et al in 1995 on late injury of cancer therapy on female reproductive tract, reported Sexual dysfunction as one of the major late complication post pelvic irradiation causing a negative impact in the lives of the patients (22).

The true prevalence of late effects of radiation therapy in cervical cancer patients is very poorly reported, as even the incidence is not genuinely reported, yet patients' follow up post treatment is always rigorously done and their evaluation done repetitively. A Systematic Review and Meta-Analysis of Individual Patient Data from 18 Randomized Trials that looked at the uncertainties about the effects of chemo radiotherapy in cervical

cancer patients, showed that only few of the trials in the meta-analysis measured late toxicity. Where only one of the 28 trials that were eligible for inclusion in the meta-analysis reported quality-of-life outcomes(23).

Another study done in south Africa also affirmed the under reporting of late effects of pelvic radiation therapy in cervical and endometrial cancer patients. It highlighted the under reporting of patient reported late effects leading to the underestimation of their impact on patient's life, as the later have been severally portrayed by different quality of life studies (15). Amongst the analysis of Simmonds and her colleagues in the mentioned study, sexual dysfunction was found not documented in developing countries, mainly due to failure of the clinician to address sexuality issues both prior and after radiation therapy. The latter was mainly due to cultural barriers leading to lack of genuine communication between the clinician and the patient.

Late gastrointestinal radiotherapy effect often given the term chronic 'radiation Proctitis (CRP), refers to the damage to the intestinal lining caused by radiation therapy occurring 6 months after pelvic Radiation Therapy (RT) (18,24–26). It is the most frequently diagnosed complication where by 50% of patients treated with pelvic radiation therapy develop CRP(27). CRP has been linked to persistence and severity of acute bowel effects post pelvic RT (28). The first step in the pathophysiology of radiation injury to the GI lining is cell death and cell depletion that leads to the loss of epithelium and villi, causing edema and subsequently inflammation of the mucosa (29). This in turn mostly leads to ulceration of the mucosa and sepsis (30). The combination of ischemia and vascular telangiectasia prompt the bowel to bleeding and ulceration, stricture formation and if injury persist, they cause obstruction, fibrosis, and development of fistulas. (27). These changes usually occur in a period of months or years. Most patients will complain of episodic rectal bleeding and incontinence of bloody diarrhea (31). Patients could also complain of abdominal cramps, constipation, mucoid rectal discharge and fecal urgency and reduced rectal capacity secondary to scarring and fibrosis (31,32).

Late genito-urinary complications post RT develops in about 5 to 10 % of the patients post pelvic radiation therapy (29). GU complications that normally present as radiation induced cystitis develops as a progressive obliteration of small blood vessels of the bladder wall that leads to development of tissue hypoxia, ischemia and tissue damage. The resulting tissue hypoxia and fibrosis, sometimes can progress to necrosis and fistulation, an abnormal opening between a body cavity (33). GU effects may occur after radiation therapy from within 2 months to 2 to 3 years or more than 15 years (34). Patients will mostly complain of urinary urgency, frequency ,dysuria, reduced bladder capacity, hematuria ,sphincter dysfunction and bladder perforation (33).

Vaginal stenosis post RT is among the known but least studied late effect of radiation therapy in cervical cancer patients (35). This stenosis happens as a result of adhesions formation causing circumferential fibrosis of the vaginal vault. The incidence of vaginal stenosis varies highly and ranges from 1.2% to 88% (21,36). Vaginal stenosis is considerable to both the clinician and the patient. It makes it difficult for the clinician to analyze and detect subsequent disease recurrence by vaginal examination because of patient discomfort, as a result of narrowing and complete obliteration of the vaginal canal. Furthermore, fundamentally sexual intercourse post treatment may be painful or even impossible for patients (37).

Sexual dysfunction following pelvic RT occurs in most cervical cancer patients (38). The cause of sexual dysfunction is multifactorial, it may be due to psychosocial or anatomic /physiologic cause (39). Sexual dysfunction usually relates to the desire(libido), frequency and satisfaction, for vaginal intercourse and orgasm (22). In developing countries sexual dysfunction is not documented, mainly due to failure of the clinician to address sexuality issues both prior and after radiation therapy mainly due to cultural barriers leading to lack of genuine communication between the clinician and the patient (15).

Most studies done in Tanzania, focused on the prevalence of early effects of radiotherapy. Currently there is no study published that reported the prevalence of late effects of radiotherapy post treatment among cervical cancer. Consequently, this study will determine the prevalence of cervical cancer late effects post radiotherapy treatment among patients who were previously treated at Ocean. Road Cancer Institute.

### 1.7.2 Social demographics

Some studies done before the era of more conformal radiation therapy treatment, have shown some baseline patient factors like age, tobacco smoking to contribute to the occurrence of late radiation effects of radiation therapy (40,41). Elderly patients with age greater 60 years were prone to higher incidence of late effects (40). However several other studies reported to have found no association between late pelvic radiation therapy effects and age (42,43). Body mass index was found to be associated with effects of pelvic radiation therapy in that, low BMI patients were found to have a higher incidence of pelvic late radiation effects than higher body mass index cervical cancer patients (43). This could be explained by the large fatty tissue in higher BMI patients separating the organs at risk with the target hence sparing the normal tissues.

Smoking has also shown some synergic effect with radiation to normal tissues, correlation was explained to be caused by the combination of the vasculotoxic effects of smoking and radiation combined to increase the severity of late tissue injury (40). The frequency of late side effects of pelvic radiation was seen to be higher in smokers than non-smokers cervical cancer patients treated with radiation therapy (41). In Tanzania, there is currently no study that argued about the association of social demographic factors with occurrence of pelvic late effects post radiotherapy, therefore this study is aimed to find out the association between these social demographic factors with post pelvic radiotherapy late effects.

### 1.7.3 Clinical characteristics

There is a dearth of studies showing the correlation between the stage of the disease, histological subtypes and late complications of treatment however, locally advanced stage cervical disease and squamous cell carcinoma histology were seen to associate with higher incidence of late pelvic radiation therapy effects (43). This might be explained by the greater tumor extension to the adjacent organs at risk, most of the time leading to the increase in the irradiated area, hence more of the organs at risk will be found in the target volume.

Globally there is a paucity of data that describe the association between HIV infection and pelvic radiation late effects, however a study done in South Africa showed that treatment toxicities in HIV positive cervical cancer patients were more compared to HIV negative patients (44). This was also highlighted by several studies, that HIV underlying comorbidities would impact radiation therapy treatment, hence also leading to a higher number of treatment effects seen in this category of patients (45,46). In Eastern Africa region no study could be found that looked into the association of disease clinical characteristics and radiotherapy late effects in cervical cancer patients.

### 1.7.4 Treatment related factors associated with late pelvic radiation therapy

Several treatment related factors have been associated with late effects post pelvic radiation therapy. The total radiation dose,fraction size received and volume of the organs at risk irradiated are reported to influence occurrence of late effects (42,47). Evolution of radiation therapy delivery has been of focus to conform dose to the tumor while sparing normal tissues. The percentage of dose received by the rectum and bladder during brachytherapy has also been highlighted as one the major factors influencing the late GI and GU effects of radiation therapy. Where by improving the technic of intra cavitary applicators insertion and adjusting dose per fraction have been found to reduce late toxicity to the rectum in irradiated cervical cancer patients (48).

Increasing dose and volume of vagina irradiated during pelvic radiation therapy has also been reported in several studies to be associated with all grades of vaginal stenosis (21). Newer highly conformal radiation therapy delivery like 3D conformal radiation therapy, IMRT, VMAT have been reported to minimize effects of radiation therapy simply because of a more conformal dose to the target treated volume sparing the normal tissues adjacent to the target (49).

Several studies have shown that there is a dearth of data on the prevalence of late effects of radiation therapy in cervical cancer patients and factors associated with these effects. This can be explained by the fact that usually disease response is evaluated by tumor reduction than effects of the treatment given.

While these late effects have shown to negatively impact the quality of life of these patients, it appeared that the true prevalence and severity of these effects is under reported and hence underestimated secondary to imperfect scoring systems and lack of prompt communications to patient. A study done at Kenyatta National Hospital in Kenya, that assessed the treatment factors that associated with incidence of late effect among cervical cancer patients, found that patients who were treated with chemo radiation, 48.2% developed late effects (50).

# CHAPTER TWO

## 2.0 MATERIAL AND METHODS

### 2.1 Study Design

This was a hospital based cross-sectional study conducted from January to June 2020 among cervical cancer patients, 6 months post pelvic radiation therapy at Ocean Road Cancer Institute.

### 2.2 Study Setting

This study was conducted at Ocean Road Cancer Institute national referral facility where comprehensive cancer services are accessible to all Tanzanians and patients from neighboring countries. It is located along the Indian Ocean in Ilala municipal, Dar es Salaam region. The health facility is one of the oldest health institutions in Tanzania having been founded in 1895.The cancer care started in 1980.The center offers cancer prevention and cancer screening services, radiotherapy-chemotherapy, and palliative care. In 2018 the institute upgraded its radiation therapy unit with a linear accelerator machine with a capacity to deliver conformal radiation therapy. Ocean Road Cancer Institute receives approximately 1000 new cervical cancer cases each year, around 30% of all new cancer cases received every year. The treatment of cervical cancer at ORCI is mainly radiation therapy (both 2D conventional and 3D conformal) concurrent with chemotherapy together with brachytherapy. Cervical cancer stages (Stage 1 to 4A), patients are treated with concurrent chemo radiation 50GY in 25 fractions, with cisplatin at 40mg/m2 weekly, then HDR brachytherapy at 8GY weekly for 3 weeks. Stage 4B the treatment is a combination of chemotherapy and localized radiation therapy. After completion of treatment patients come for follow up at the clinic on a three monthly basis for the first year,6 monthly from the second year and yearly for the following years.

### 2.3 Target Population

All cervical cancer patients post 6 months of treatment at Ocean Road Cancer Institute.

## 2.4 Study Population

All cervical cancer patients post 6 months of treatment seen at Ocean Road Cancer Institute Ocean Road Cancer Institute (ORCI) and who fulfilled the eligibility criteria.

## 2.5 Inclusion Criteria

- ✓ All patients with a confirmed histological diagnosis of cervical cancer and who received curative treatment comprising of pelvic radiation therapy and brachytherapy.
- ✓ Patients with age more than 18 years old.
- ✓ Patients who gave consent to participate in the study.

## 2.6 Exclusion Criteria

- ✓ Cervical cancer patients diagnosed with a recurrent disease post treatment.
- ✓ Cervical cancer patients who did not complete treatment.
- ✓ Patients who presented with underlying complication of the disease like fistulas at diagnosis.

## 2.7 Sample Estimation

Due to the scarcity of similar studies previously in our region, the estimated median prevalence of 50% of late effect among cervical cancer patients was taken to calculate the sample size.

The sample size for this study was estimated with the use of a population prevalence formula:

$$\frac{Z^2(P)(1-P)}{c^2}$$

With an assumption that the population proportions (p) is 50%, Z score for confidence interval of 95% being 1.96, with margin of error (C) estimated to be 5%.

$$\frac{1.96^2(0.5)(1-0.5)}{0.05^2}$$

Therefore, the projected sample size was 384.

## 2.8 Study Variables

**Dependent variables in this study include:**

Radiotherapy induced late effects such as:

Gastro Intestinal (GI) characterized by chronic radiation proctitis and enteritis.

Genito Urinary (GU) characterized by chronic cystitis.

Vaginal Stenosis (VS) characterized by dyspareunia and vaginal canal narrowing.

Sexual Dysfunction characterized by decreased sexual desire (libido).

These were estimated/ measured by the RTOG/EORTC toxicity grading scale and CTCAE v4 tool in 2.10 and 2.11

**Independent variables**

**Group…**

Social demographics: Age, occupation, education level, marital status and smoking.

Clinical pathological characteristics: Disease histology, stage of the disease and HIV status.

Treatment parameters: technique XRT, number fractions, field size, and total dose, chemotherapy regimen and number of chemo cycles.

## 2.9 Sampling Procedure

This study employed consecutive sampling technique. The principal investigator and research assistant were stationed at the clinics and recruited cervical cancer patients who met the eligibility criteria visiting clinics for follow up at least 6 months after treatment. Once patients were recruited then their files were retrieved from the medical record database to trace the social demographics, clinical and treatment related parameters.

## 2.10 Data Collection Tool

This study used a structured questionnaire. The questionnaire consisted of three parts, the first part comprised of patient social demographics and clinical profile, the second part

comprised of parameters of treatment received by the patients and the third section was consisted of late effects assessment Checklist, that was involved in grading of these late effects.

### 2.11 Reliability and Validity of the Questionnaire and Checklist

Principle investigator formulated the questionnaire in line with specific objective of this study. This questionnaire was reviewed by two consultants in the field of clinical oncology and one epidemiologist to ensure that it gathers the sufficient information that answers specific objectives of this study. The checklist of this study was adopted from RTOG/EORTC toxicity grading scale and CTCAE v4 tool. This tool is consistent with cancer patients treated with radiotherapy and therefore was used to score the patients complaints into definite experienced radiation induced late effects grades. During translation from English to Swahili, simple language was used without losing the intended meaning from the former original version hence ensured that linguistic versions are equivalent to each other. Principal investigator cross checked the questionnaire before data entry.

### 2.12 Data Collection

Data collection started after ethical review board approval of the study. During the collection process, a dedicated research assistant passed through four clinics (clinic 1, 2, 3, 4) that are run every day by oncologists. In each clinic cervical cancer patients were seen during follow up or newly diagnosed cases. The research assistant and PI recruited patients attending these clinics on basis of the inclusion and exclusion criteria. Eligible patients' files were retrieved to trace treatment related factors and other clinical pathological characteristics of the patient while some social demographics information were retrieved from the patient. Vaginal stenosis was assessed by vaginal canal examination (visualization with help of a lamp and speculum examination), by a medical doctor either the PI or research assistant.

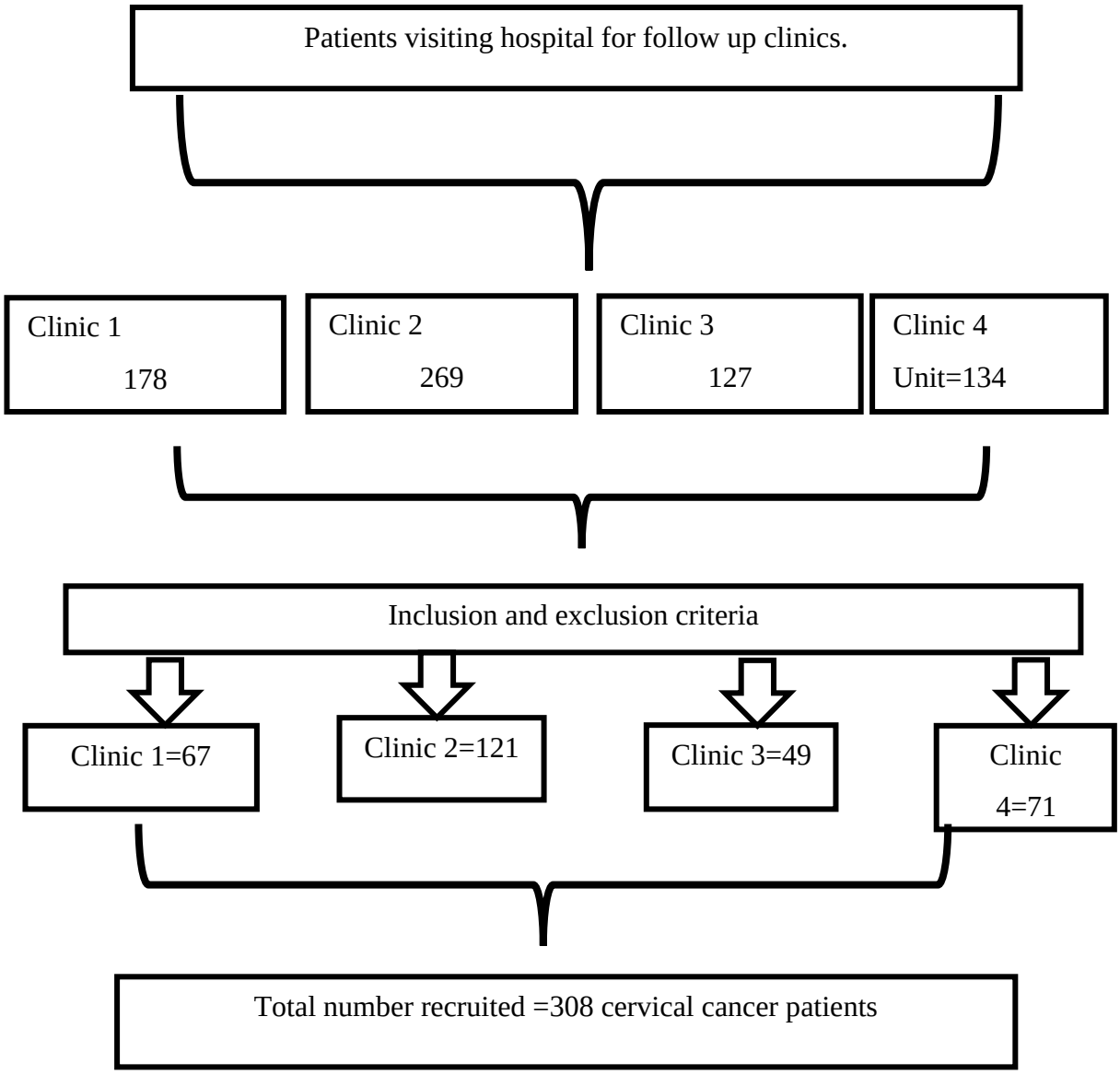


**Figure 2: Flow chart above, illustrate the recruitment process of the study participants**

Patient's social demographic and late effects information was obtained by interviewing the patient at the time of clinic visit for follow up. Clinical pathological characteristics and treatment related parameters were extracted from medical records. Pelvic examination was also done to assess for vaginal stenosis.

### 2.13 Data Analysis and Quality Plan

Data was entered into Excel and analyzed using IBM SPSS version 23 software. The Data collected from extraction forms was double-checked, corrected and entered in a coded format. Then the data in SPSS file, was cleaned and recorded. Continuous data was summarized using mean/standard deviation or median/range whereas categorical data was summarized using frequency/percentage. The summarized data was then presented in tables, figures and text. Chi-square test was used to check for association between dependent variable and independent variables. Multiple logistic regression was done to assess for possible confounding factors. p value of less than 0.05 was considered statistically significant.

**Table 1: Analysis plan per specific objective**

| Specific objective | Analysis plan |
|---|---|
| 1. To determine the social-demographic characteristics of patients with late effects post pelvic radiation therapy in cervical cancer patients at ORCI from 2016 to 2019. | Frequency and percentage. Mean/standard deviation or median/range |
| 2. To determine clinical characteristics of patients with late effects post pelvic radiation therapy in cervical cancer patients at ORCI from 2016 to 2019. | Frequency and percentage. |
| 3. To determine the prevalence of late effects in cervical cancer patients post pelvic radiation therapy at ORCI 2016 to 2019. | Proportion. |
| 4. To determine factors associated with occurrence of with late effects post pelvic radiation therapy in cervical cancer patients at ORCI from 2016 to 2019. | The $\chi^2$ test was used to compare the association of the demographic clinical characteristics of patients with late effects. Multiple logistic regression was done to assess for possible confounding factors. |

### 2.14 Ethical Consideration

The study's ethical approval was sought from the institutional review board (IRB) of Muhimbili University of health and allied sciences and Ocean Road Cancer Institute review board before the start of the study. Patients' choice to participate in the study was ensured through signed consent forms after thorough explanation to the participant on the purpose of the study and ensuring confidentiality. Eligible patients signed a well standardized consent form, confirming their willingness to the participation of the study.

### 2.15 Dissemination Plan

The study results will be part of the partial fulfillment of the Masters of Medicine in Clinical Oncology at Muhimbili University of Health and Allied Sciences. After successful completion and acceptance of the dissertation, it will be disseminated to the institute management. It will be submitted for publication in local and international journals.

# CHAPTER THREE

## 3.0 RESULTS

This study recruited 308 patients, which was the response rate of 80.2% of the anticipated sample size.

### 3.1 Social Demographic Characteristics of The Study Participants

The Mean age was 54.2 years and standard deviation was 12.1. The HIV prevalence in this study was 14%.Smoking rate in this study was 13.3%. Majority (50.8%) had BMI of 18.6-25Kg/m2 with the mean BMI of 24.4 and standard deviation of 4.5. Table 2.

**Table 2: Social demographic characteristics of the study participants (n=308)**

| Variables | Categories | Frequency | Percent's |
|---|---|---|---|
| Age | <40 | 36 | 11.7 |
| | 41-60 | 173 | 56.2 |
| | 61+ | 99 | 32.1 |
| Marital Status | Married | 170 | 55.2 |
| | Single | 138 | 44.8 |
| HIV status | Positive | 57 | 18.5 |
| | Negative | 207 | 67.2 |
| | Unknown | 44 | 14.3 |
| Education | Primary school and less | 191 | 62.0 |
| | Secondary school | 88 | 28.6 |
| | College/university | 29 | 9.4 |
| Occupation | Peasant | 110 | 35.7 |
| | Petty business | 106 | 34.4 |
| | Employed | 69 | 22.4 |
| | House wife | 23 | 7.5 |
| BMI | <18.5 | 20 | 6.5 |
| | 18.6-25 | 167 | 54.2 |
| | >25 | 121 | 39.3 |
| Smoking | Yes | 41 | 13.3 |
| | No | 267 | 86.7 |

### 3.2 Clinical-Histopathological Characteristics of the Study Participants

The most common histology was squamous cell carcinoma (94.5%) and most of the participants had stage 2 (70.8%) cervical cancer. Table 3.

**Table 3: Clinical-histopathological characteristics of the study participants (n=308)**

| Variable | Categories | Frequencies | Percent's |
|---|---|---|---|
| Histology | | | |
| | Squamous | 291 | 94.5 |
| | Adenocarcinoma | 17 | 5.5 |
| Stage | | | |
| | Stage I | 46 | 14.9 |
| | Stage II | 218 | 70.8 |
| | Stage III | 44 | 14.3 |

### 3.3 Treatment Information of the Study Participants

All study participants received EBRT concurrent with cisplatin. All patients received 50Gy of EBRT and all had received 3 insertions 8Gy per each fraction of ICT. Table 4

**Table 4: Treatment information of the study participants (n=308)**

| Variables | Categories | Frequency | Percent's |
|---|---|---|---|
| Field size | <15x15cm | 160 | 51.9 |
| | >15x15cm | 148 | 48.1 |
| Field design | Four field/box | 1 | 0.3 |
| | AP/PA | 307 | 99.7 |
| Chemo cycles | 1 | 38 | 12.3 |
| | 2 | 45 | 14.6 |
| | 3 | 75 | 24.4 |
| | 4 | 97 | 31.5 |
| | 5 | 53 | 17.2 |

### 3.4 Prevalence of Radiation Induced Late Effects

The most common late effect was GU.

Severe frequency and dysuria, intermittent/frequent diarrhea and bleeding, dyspareunia and Decrease in frequency of intercourse / decrease in the desire were most common effects of GU, GI, VS and sexual dysfunction late effects respectively.

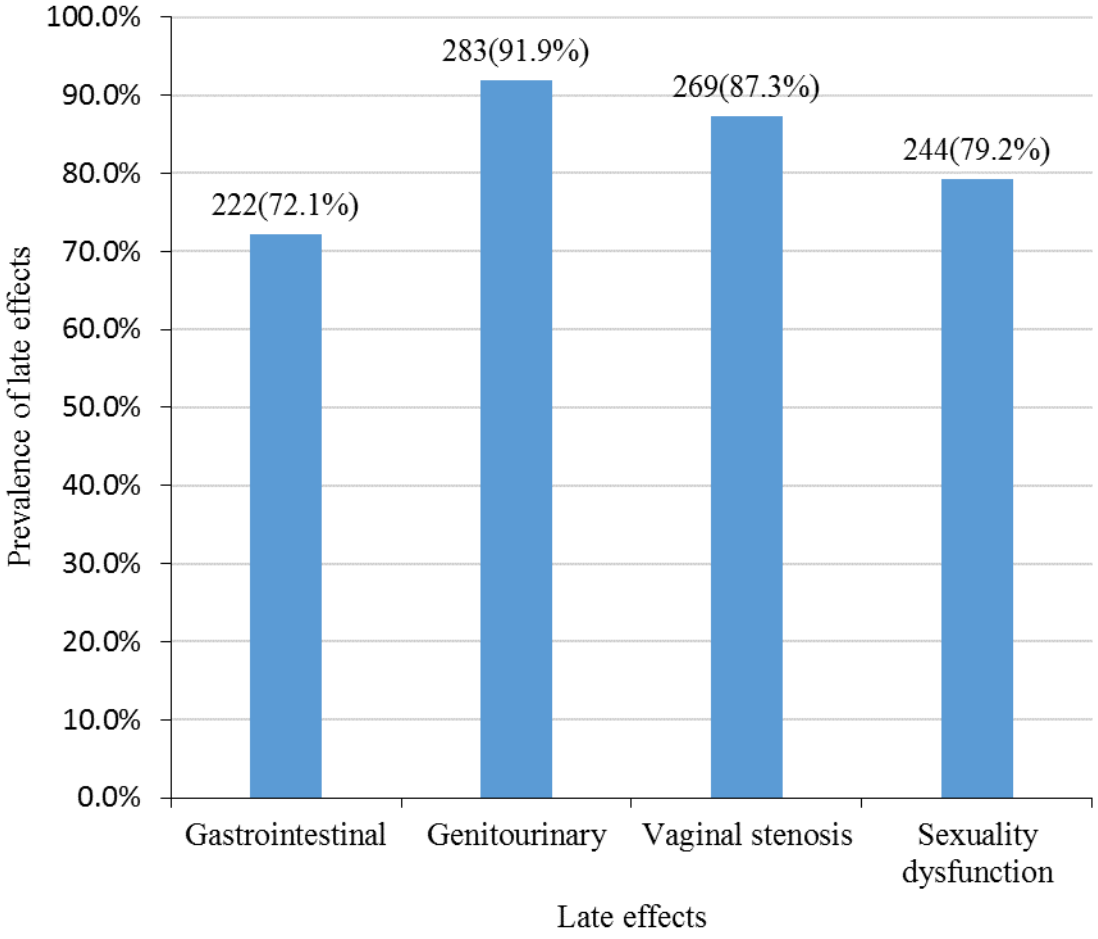


**Figure 3: Distribution of late effects**

### 3.5 Distribution of Late Effects by Grades

Majority of the participants had grade one, two and three late effects.

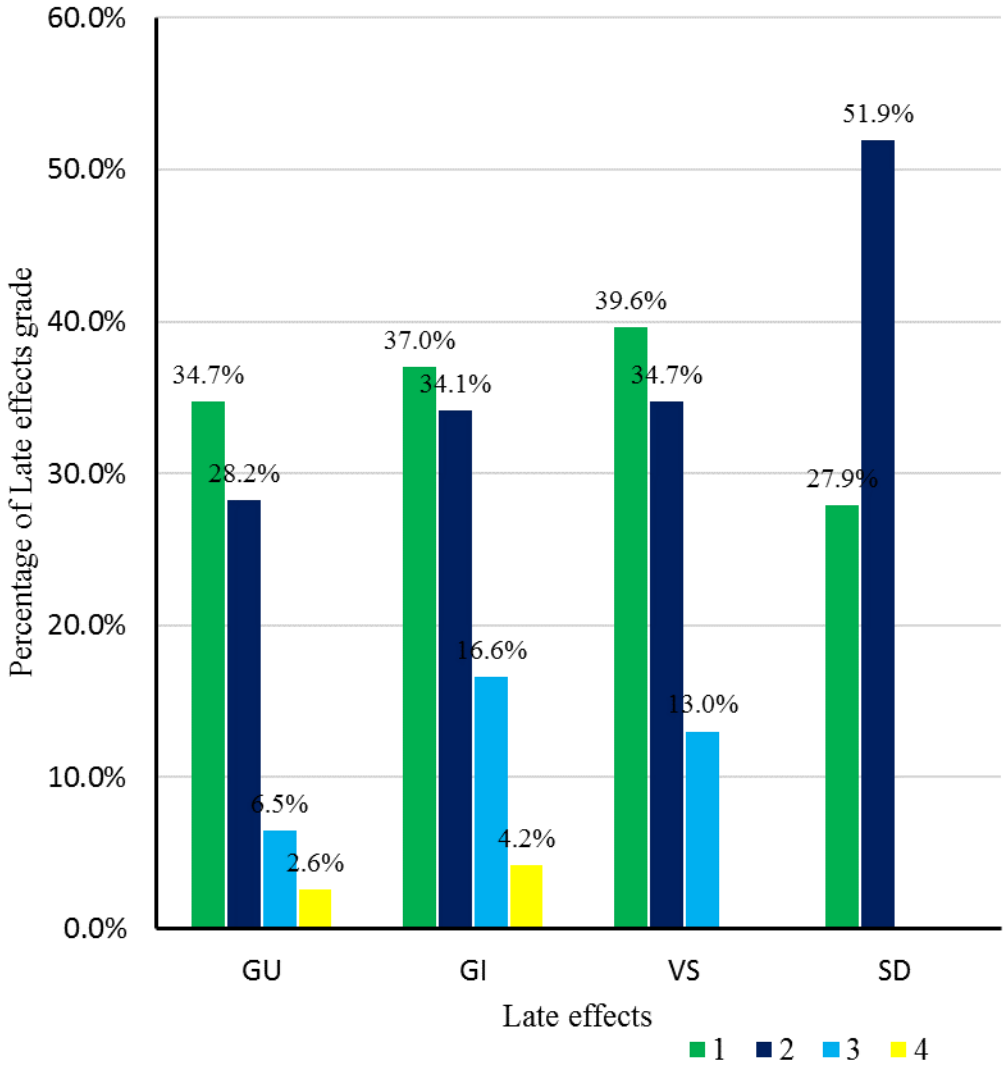


**Figure 4: Distribution of grade of late effects grades**

**GU = Genito Urinary GI = Gastro Intestinal VS=Vaginal stenosis SD=Sexual dysfunction**

### 3.6 GI Late Effect vs Social Demographics, Clinical-Pathological and Treatment Parameters

Participants who were treated with field size >15x15cm experienced more GI effects than patients treated with field size <15x15cm. No patient treated with four field/box got GI effects while 72.3% of patients treated with AP/PA fields reported GI effects.These findings were not statistically significant.

**Table 5: Cross tabulation table of GI vs social demographics, clinical-pathological and treatment parameters**

| variables | Categories | GI | | |
|---|---|---|---|---|
| | | Yes | No | |
| | | N (%) | N (%) | P value |
| Age | <40 | 28(77.8) | 8(22.2) | 0.715 |
| | 41-60 | 123(71.1) | 50(28.9) | |
| | 61+ | 71(71.7) | 28(28.3) | |
| Marital Status | Married | 116(68.2) | 54(31.8) | 0.095 |
| | Single | 106(76.8) | 32(23.2) | |
| HIV Status | Positive | 42(73.7) | 15(26.3) | 0.51 |
| | Negative | 151(72.9) | 56(27.1) | |
| | Unknown | 29(65.9) | 15(34.1) | |
| Education | Primary school and less | 145(75.9) | 46(24.1) | 0.097 |
| | Secondary school | 60(68.2) | 28(31.8) | |
| | College/university | 17(58.6) | 12(41.4) | |
| Occupation | Peasant | 79(71.8) | 31(28.2) | 0.997 |
| | Petty business | 76(71.7) | 30(28.3) | |
| | Employed | 50(72.5) | 19(27.5) | |
| | house wife | 17(73.9) | 6(26.1) | |

*Continue to the next page*

**Continuation of table 5: Cross tabulation table of GI effects vs social demographics, clinical-pathological and treatment parameters**

| variables | Categories | GI | | |
|---|---|---|---|---|
| | | Yes | No | |
| | | N (%) | N (%) | P value |
| BMI | <18.5 | 14(70.0) | 6(30.0) | 0.616 |
| | 18.6-25 | 117(70.1) | 50(29.9) | |
| | >25 | 91(75.2) | 30(24.8) | |
| Smoking | Yes | 30(73.2) | 11(26.8) | 0.867 |
| | No | 192(71.9) | 75(28.1) | |
| Histology | Squamous | 211(72.5) | 80(27.5) | 0.486 |
| | Adenocarcinoma | 11(64.7) | 6(35.3) | |
| Stage | Stage I | 38(82.6) | 8(17.4) | 0.072 |
| | Stage II | 149(68.3) | 69(31.7) | |
| | Stage III | 35(79.5) | 9(20.5) | |
| Field size | ≤15x15cm | 111(69.4) | 49(30.6) | 0.212 |
| | >15x15cm | 111(75.0) | 37(25.0) | |
| Field design | Four field/box | 0(.0) | 1(100.0) | 0.108 |
| | AP/PA | 222(72.3) | 85(27.7) | |
| Chemo cycles | 1 | 26(68.4) | 12(31.6) | 0.754 |
| | 2 | 33(73.3) | 12(26.7) | |
| | 3 | 53(70.7) | 22(29.3) | |
| | 4 | 26(68.4) | 12(31.6) | |
| | 5 | 33(73.3) | 12(26.7) | |

### 3.7 GU Late Effect vs Social Demographics, Clinical Pathological and Treatment Parameters

Smoking and HIV status were found to statistically significantly associate with GU with p values of 0.041 and 0.044 respectively. Majority 92.7% of participants who smoked experienced more GU late effects compared to 91.8% who did not smoke. All participants (100%) who were HIV+ experienced GU late effects compared to 89.9% of participants who were HIV-.HIV status and smoking were entered into multivariate binary logistic regression, however, HIV status was rejected by the model. Therefore, the only factor that was found to associate with occurrence of the GU late effect was smoking (p=0.041).

**Table 6: Cross tabulation table of GU vs social demographics, clinical pathological and treatment parameters.**

| Variable | Categories | GU | | P value |
|---|---|---|---|---|
| | | Yes | No | |
| | | N (%) | N (%) | |
| Age | <40 | 33(91.7) | 3(8.3) | |
| | 41-60 | 160(92.5) | 13(7.5) | 0.899 |
| | 61+ | 90(90.9) | 9(9.1) | |
| Marital Status | Married | 153(90.0) | 17(10.0) | 0.179 |
| | Single | 130(94.2) | 8(5.8) | |
| HIV status | Positive | 57(100.0) | 0(.0) | |
| | Negative | 186(89.9) | 21(10.1) | 0.044 |
| | Unknown | 40(90.9) | 4(9.1) | |
| Education | Primary school and less | 177(92.7) | 14(7.3) | |
| | Secondary school | 80(90.9) | 8(9.1) | 0.79 |
| | College/university | 26(89.7) | 3(10.3) | |
| Occupation | Peasant | 100(90.9) | 10(9.1) | |
| | Petty business | 98(92.5) | 8(7.5) | 0.966 |
| | Employed | 64(92.8) | 5(7.2) | |
| | house wife | 21(91.3) | 2(8.7) | |
| BMI | <18.5 | 19(95.0) | 1(5.0) | |
| | 18.6-25 | 152(91.0) | 15(9.0) | 0.778 |
| | >25 | 112(92.6) | 9(7.4) | |

**Continuation of table 6: Cross tabulation table of GU vs social demographics, clinical pathological and treatment parameters.**

| Variable | Categories | GU | | P value |
|---|---|---|---|---|
| | | Yes | No | |
| | | N (%) | N (%) | |
| Smoking | Yes | 38(92.7) | 3(7.3) | 0.041 |
| | No | 245(91.8) | 22(8.2) | |
| Histology | Squamous | 267(91.8) | 24(8.2) | 0.729 |
| | Adenocarcinoma | 16(94.1) | 1(5.9) | |
| Stage | Stage I | 43(93.5) | 3(6.5) | 0.896 |
| | Stage II | 200(91.7) | 18(8.3) | |
| | Stage III | 40(90.9) | 4(9.1) | |
| Field size | ≤15x15cm | 149(93.1) | 11(6.9) | 0.407 |
| | >15x15cm | 134(90.5) | 14(9.5) | |
| Field design | Four field/box | 1(100.0) | 0(.0) | 0.766 |
| | AP/PA | 282(91.9) | 25(8.1) | |
| Chemo cycles | 1 | 35(92.1) | 3(7.9) | 0.749 |
| | 2 | 40(88.9) | 5(11.1) | |
| | 3 | 70(93.3) | 5(6.7) | |
| | 4 | 89(91.8) | 8(8.2) | |
| | 5 | 49(92.5) | 4(7.5) | |

**Chi-square test**

### 3.8 Vaginal Stenosis vs Social Demographics, Clinical-Pathological and Treatment Parameters

Age and field size of the treatment were associated with occurrence of vaginal stenosis and the association was statistically significant. Participants aged ≤40 years reported more vaginal stenosis (97.2%) compared to participants of age >40 years. Majority of the participants (91.2%) treated with a field size of >15x15cm had Vaginal stenosis compared to participants who were treated with a field size of ≤15x15cm (83.8%).

**Table 7: Cross tabulation table of vaginal stenosis vs social demographics, clinical-pathological and treatment parameters.**

| Variables | Categories | Vaginal stenosis | | P value |
|---|---|---|---|---|
| | | Yes | No | |
| | | N (%) | N (%) | |
| Age | <40 | 35(97.2) | 1(2.8) | 0.011 |
| | 41-60 | 155(89.6) | 18(10.4) | |
| | 61+ | 79(79.8) | 20(20.2) | |
| Marital Status | Married | 150(88.2) | 20(11.8) | 0.599 |
| | Single | 119(86.2) | 19(13.8) | |
| HIV status | Positive | 50(87.7) | 7(12.3) | 0.977 |
| | Negative | 181(87.4) | 26(12.6) | |
| | Unknown | 38(86.4) | 6(13.6) | |
| Education | Primary school and less | 173(90.6) | 18(9.4) | 0.068 |
| | Secondary school | 71(80.7) | 17(19.3) | |
| | College/university | 25(86.2) | 4(13.8) | |
| Occupation | Peasant | 95(86.4) | 15(13.6) | 0.931 |
| | Petty business | 93(87.7) | 13(12.3) | |
| | Employed | 60(87.0) | 9(13.0) | |
| | house wife | 21(91.3) | 2(8.7) | |
| BMI | <18.5 | 17(85.0) | 3(15.0) | 0.874 |
| | 18.6-25 | 145(86.8) | 22(13.2) | |
| | >25 | 107(88.4) | 14(11.6) | |
| Smoking | Yes | 37(90.2) | 4(9.8) | 0.548 |
| | No | 232(86.9) | 35(13.1) | |

*Continue to the next page*

**Continuation of table 7: Cross tabulation table of vaginal stenosis vs social demographics, clinical-pathological and treatment parameters.**

| Variables | Categories | Vaginal stenosis | | P value |
|---|---|---|---|---|
| | | Yes | No | |
| | | N (%) | N (%) | |
| Histology | Squamous | 255(87.6) | 36(12.4) | 0.525 |
| | Adenocarcinoma | 14(82.4) | 3(17.6) | |
| Stage | Stage I | 43(93.5) | 3(6.5) | 0.248 |
| | Stage II | 190(87.2) | 28(12.8) | |
| | Stage III | 36(81.8) | 8(18.2) | |
| Field size | ≤15x15cm | 134(83.8) | 26(16.3) | 0.049 |
| | >15x15cm | 135(91.2) | 13(8.8) | |
| Field design | Four field/box | 1(100.0) | 0(.0) | 0.703 |
| | AP/PA | 268(87.3) | 39(12.7) | |
| Chemo cycles | 1 | 35(92.1) | 3(7.9) | 0.778 |
| | 2 | 39(86.7) | 6(13.3) | |
| | 3 | 67(89.3) | 8(10.7) | |
| | 4 | 82(84.5) | 15(15.5) | |
| | 5 | 46(86.8) | 7(13.2) | |

**Chi-square test**

### 3.9 Multivariate Analysis of the Factors Associated with Prevalence of Vaginal Stenosis Effects

A multivariate logistic regression was run to discern the effect of participant's age and treatment field size, on likelihood that participants would have developed vaginal stenosis. The logistic regression model was statistically significant, $\chi 2$ (3) = 14.343, p <0.002). The model explained 8.5% (Nagelkerke R2) of the variance in vaginal stenosis and correctly classified 87.3% of cases. The probability that participants with age 41-60 and 61+ to get vaginal stenosis was 89.3% (Odds ratio 0.107; 95% Confidence interval 0.014 to 0.831; P value: 0.033) and 56.5% (OR: 0.435 ; CI 0.216 to 0.876; P value: 0.020) lower than those who were aged below 40 respectively. The chance of participants who were treated with >15x15cm field sizes to develop vaginal stenosis was 2.158 times higher than those patients treated with ≤15x15cm field sizes.

**Table 8: Multivariate analysis of the factors associated with prevalence of vaginal stenosis.**

| | | | | 95% C.I.for AOR | |
|---|---|---|---|---|---|
| **variables** | **Categories** | **P value** | **AOR** | **Lower** | **Upper** |
| Age | <40 | 0.014 | | | Ref |
| | 41-60 | 0.033 | 0.107 | 0.014 | 0.831 |
| | 61+ | 0.020 | 0.435 | 0.216 | 0.876 |
| | ≤15x15cm | | | | Ref |
| Field size | >15x15cm | 0.036 | 2.158 | 1.050 | 4.437 |

### 3.10 Sexual Dysfunction vs Social Demographics, Clinical-Pathological and Treatment Parameters

Age, smoking and field size were associated with occurrence of sexual dysfunction and the association was statistically significant ($p<0.05$).Majority of the participants ≤40 years reported more (86.1%) sexual dysfunction compared to (84.4%) of participants aged 41-60 years and (67.7%) of participants aged 61+. Most (81.6%) of the participants who did not smoke experienced sexual dysfunction compared to 6.4% of those who were smokers. Participants who were treated with a field size of>15x15 had more (85.8%) sexual dysfunction compared to 73.1% of those who were treated with a field size of <15x15. Although marital status's association with sexual dysfunction was not found to be statistically significant ($p>0.05$), majority of the married participants (80.6%) complained of sexual dysfunction compared to 77.5% of unmarried participants.

**Table 9: Cross tabulation table of sexual dysfunction vs social demographics, clinical-pathological and treatment parameters.**

| Variables | Categories | Sexual dysfunction | | |
|---|---|---|---|---|
| | | Yes | No | |
| | | N (%) | N (%) | |
| Age | <40 | 31(86.1) | 5(13.9) | 0.003 |
| | 41-60 | 146(84.4) | 27(15.6) | |
| | 61+ | 67(67.7) | 32(32.3) | |
| Marital Status | Married | 137(80.6) | 33(19.4) | 0.511 |
| | Single | 107(77.5) | 31(22.5) | |
| HIV status | Positive | 48(84.2) | 9(15.8) | 0.097 |
| | Negative | 157(75.8) | 50(24.2) | |
| | Unknown | 39(88.6) | 5(11.4) | |
| Education | Primary school and less | 150(78.5) | 41(21.5) | 0.622 |
| | Secondary school | 69(78.4) | 19(21.6) | |
| | College/university | 25(86.2) | 4(13.8) | |
| Occupation | Peasant | 81(73.6) | 29(26.4) | 0.121 |
| | Petty business | 89(84.0) | 17(16.0) | |
| | Employed | 58(84.1) | 11(15.9) | |
| | house wife | 16(69.6) | 7(30.4) | |
| BMI | <18.5 | 13(65.0) | 7(35.0) | 0.132 |
| | 18.6-25 | 138(82.6) | 29(17.4) | |
| | >25 | 93(76.9) | 28(23.1) | |
| Smoking | Yes | 26(63.4) | 15(36.6) | 0.007 |
| | No | 218(81.6) | 49(18.4) | |
| Histology | Squamous | 232(79.7) | 59(20.3) | 0.367 |
| | Adenocarcinoma | 12(70.6) | 5(29.4) | |
| Stage | Stage I | 41(89.1) | 5(10.9) | 0.147 |
| | Stage II | 167(76.6) | 51(23.4) | |

**Continuation of table 10: Cross tabulation table of sexual dysfunction vs social demographics, clinical-pathological and treatment parameters.**

| Variables | Categories | Sexual dysfunction | | |
|---|---|---|---|---|
| | | Yes | No | |
| | | N (%) | N (%) | |
| | Stage III | 36(81.8) | 8(18.2) | |
| Field size | ≤15x15 | 117(73.1) | 43(26.9) | 0.006 |
| | >15x15 | 127(85.8) | 21(14.2) | |
| Field design | Four field/box | 1(100.0) | 0(.0) | 0.608 |
| | AP/PA | 243(79.2) | 64(20.8) | |
| Chemo cycles | 1 | 30(78.9) | 8(21.1) | 0.744 |
| | 2 | 37(82.2) | 8(17.8) | |
| | 3 | 58(77.3) | 17(22.7) | |
| | 4 | 74(76.3) | 23(23.7) | |
| | 5 | 45(84.9) | 8(15.1) | |

**Chi-square test**

### 3.11 Multivariate Analysis of the Factors Associated with Prevalence of Sexual Dysfunction

A multivariate logistic regression was run to discern the effect of participant's age, treatment field size and smoking status on likelihood that participants would have developed sexual dysfunction. The logistic regression model was statistically significant, $\chi 2$ (5) = 23.329, p <0.0001). The model explained 11.4% (Nagelkerke R2) of the variance in vaginal stenosis and correctly classified 79.2% of cases. The risk of participants with age 41-60 and 61+ to get sexual dysfunction was 68% (Odds ratio, 0.32; 95% confidence interval[CI] 0,111 to 0.921; P value: 0.035) and 62% (Odds ratio, 0.379; CI 0,206 to 0.696; P value: 0.002) less than those who were aged below 40 respectively. The chance that participants who were treated with >15x15cm field to develop sexual dysfunction was 2.225 times higher than that of patients treated with ≤15x15cm fields.

**Table 11: Multivariate analysis of the factors associated with prevalence of sexual dysfunction effects**

| Variables | categories | Sig. | AOR | 95% C.I.for AOR | |
|---|---|---|---|---|---|
| | | | | Lower | Upper |
| Age | <40 | | | | Ref |
| | 41-60 | 0.035 | 0.320 | 0.111 | 0.921 |
| | 61+ | 0.002 | 0.379 | 0.206 | 0.696 |
| | ≤15x15 | | | | Ref |
| Field size | >15x15 | 0.010 | 2.225 | 1.214 | 4.077 |
| | Smoking | | | | Ref |
| Smoking status | Not smoking | 0.076 | 1.963 | 0.932 | 4.136 |

# CHAPTER FOUR

## 4.0 DISCUSSION

Majority of cervical cancer patients in sub Saharan Africa and Tanzania inclusive are diagnosed at a young age. Most of these patients present with locally advanced disease that leaves pelvic radiation therapy as the mainstay of their treatment. Late effects of pelvic RT are less well described yet they continue to accumulate with time, hence most of these patients live with the effects of the disease and treatment for many years. This study looked at the prevalence of common late effects (GI, GU, vaginal stenosis and sexual dysfunction) post-pelvic radiation therapy and factors associated with them in cervical cancer patients in Tanzania.

The main findings in our study was that, majority of our patients reported with more than one late effect and this presentation was highlighted in several studies(15)(51)(52). The results from our study showed that GU effects (91.9%) were the most common late effects followed by vaginal stenosis(87.3%), sexual dysfunction(79.2%) and GI effects (72.1%) respectively. Some studies though ,report these effects from grades 3 to 4(severe), with a reason that grades 1-2 were mild to moderate symptoms that resolved simultaneously or with conservative treatment (53)(19).

In this regard, the results of our study showed that most common grades 3- 4(severe) late effects were GI (20.8%) followed by vaginal stenosis (13%) and GU (9.3%). Differences in grading and reporting systems of late effects make it hard for us to compare our findings with other studies however, these findings were similar to the IAEA report series on management of cervical cancer (19) ,where late bowel and bladder complications were reported to be the most common grade 3-4 late complications in up to 5–15% of treated patients.( assessed by CTCAE V4 toxicity score). Our findings slightly differs to that of .L.T.TAN et al in that GU grade 3-4 late effects were the most predominant (8.5%) followed by GI late effects at (7%) (54).

Contrary to our results still, in a national UK audit published by Vale et al , 1075 cervical cancer patients who received radiation therapy as adjuvant or definitive treatment were evaluated, and the majority of grade 3-4 late effects (5-4%) were found to be vaginal (55).

This study used a different grading and reporting systems (Franco-Italian glossary) and this could explain different results from our study.

Despite the fact that most of GU late effects are reported to be low grade with a continual accumulation with time ,late GU effects are reported to be the most commonly seen after prostate, bladder and cervical cancer RT. This finding is keeping with the findings from this study .The high prevalence of GU late effects could be related to higher doses of RT used and/or the anatomic proximity of the urinary system to these tumors compared to the uterus and rectum(56). This is the reason why more conformal radiotherapy techniques are recommended in order to reduce the doses to these organs.

According to our findings vaginal stenosis and sexual dysfunction were most commonly low grades 1-2 (mild) late effects, (39.6% -34.7% and 27.99 -51.9%) respectively. This correlated with a study done by Martins et al in Brazil that retrospectively looked at the incidence of vaginal stenosis. Most women in their study had mild vaginal stenosis where 69.1% had grade 1 and 0.7% had grade 2 vaginal stenosis after RT(57). Similarly, Brandt et al showed that vaginal stenosis was found to occur in mainly the first year post treatment in approximately 38% of patients post pelvic RT ,with low grades 1 and 2 predominating at 27% and 11% respectively(58).

Sexual dysfunction was highlighted in different QOL studies to be under reported by clinicians. In our study, most patients reported decrease in interest to sexual activity that was not affecting their relationship. These results correlated with a study done in Singapore, where approximately 85% of their patients reported low or no sexual interest ,55% had mild to severe dyspareunia, and 30% were dissatisfied with their sex life or lack of sex with most of these effects happening within 2 years after treatment (15,59–61)

Univariate analysis in the index study showed that age and different EBRT field sizes were significantly associated with sexual dysfunction and vaginal stenosis late effects ($p<0.05$) where as smoking was associated with sexual dysfunction and GU late effects ($p<0.05$). HIV status showed a trend to be associated with GU late effects but this association was not statistically significant. Our study found no statistical significant association between GI late effects and all other factors in the univariate analysis.

In multivariate analysis, age showed a significant association with sexual dysfunction and vaginal stenosis late effects. Participants whose age were more than 61 years had a lower risk of sexual dysfunction and vaginal stenosis than those whose age was less than 40 years. These findings differed from other studies where ,age more than 50 years was reported to be a major risk factor for vaginal stenosis(21) (39).With regards to sexual dysfunction our findings were in agreement with other studies, in that younger patients were prone to early menopause secondary to irradiation of the ovaries. One can deduce that the increased risk of developing sexual dysfunction and vaginal stenosis in younger cervical cancer patients in our study, may be related to the fact that SD was assessed using questions related to sexuality , it is likely that younger patients for whom this is more of a concern would report SD. For VS decreased knowledge and use of vaginal stenosis preventive measures; like use of vaginal dilators or early resumption of sexual intercourse post treatment may have contributed to these findings.

Despite the fact that the current study did not show any association between BMI and late effects of RT in cervical cancer patients, KIZER e al in his 2010 study revealed that underweight patients (BMI <18.5 kg/m2) with locally advanced cervical cancer would develop more complications post treatment than normal weight and obese patients (62). Most of our study participants fell in the category of normal weight.

Nicotine has been reported to increase occurrence of adverse effects post radiation therapy in different cancer sites. In our study the association of smoking and GU late effects was significant ($p<0.05$).Kucera e al reported an increase in effects of pelvic radiation therapy in cervical cancer patients who were smokers compared to non smokers (41). This finding was in correlation with our study though our study did not define well the characteristic of the smokers. Additional studies could look into this association.

EBRT Field size showed a significant association with occurrence of vaginal stenosis and sexual dysfunction. Patients who were treated with a field size greater than 15 x15cm had more of SD and VS than those who were treated with field sizes less or equal to 15x15 cm ($p<0.05$). Since field size is directly proportional to the radiation dose. This means that patients who were treated with a larger field size received a higher radiation dose. Also a larger amount of normal tissue is irradiated in larger field sizes.

This association was reported by Viswanathan et al where by vaginal stenosis and sexual dysfunction were associated with a high radiation doses(39). The EMBRACE study that looked at among others , the relationship between dose -effect and vaginal stenosis, reported that EBRT dose more than 45GY/25 fractions contributed to an increased risk of vaginal stenosis(63).

Different stages of cancer entails different field sizes of treatment hence different volume of normal tissues irradiated. The index study did not show any significant association of late effects with stage of the disease. The influence of FIGO stage in occurrence of late effects is controversial. Kapp et al in his study revealed a positive association between occurrence of late effects and FIGO stage (p=0.015), with early stage disease patients reporting less effects than locally advanced ones(64). Other studies did not show this association(65)(57).In our study most patients were treated with similar field sizes.

Both old and modern literature have shown that the varying external beam techniques for pelvic radiation like(type of RT machine, treatment position, 2 vs 4 fields technique, fractionation and daily dose) and doses ranging from 40 to 65 Gy, influence the nature and likelihood of complications/effects of radiation therapy(52)(66)(67). Even in brachytherapy, similar considerations have shown to apply, where distinct difference in maximum doses distributed to adjacent normal tissues irradiated, differed in choice of isotope used, applicators used ,and different loading techniques (52)(68)(69). Contrary though, a study by Kapp e al failed to reveal this correlation(64).

# CHAPTER FIVE

## 5.0 STUDY LIMITATION, CONCLUSION AND RECOMMENDATION

### 5.1 Limitations

- Different studies used different toxicity grading systems, this made it difficult to adequately compare our findings with other researchers' findings
- This study used patient reported symptoms and physical assessment. Due to limited funds and resources, hormonal analysis, and tools for assessing some of late effects like vaginal stenosis and sexual dysfunction were not fully tested.

### 5.2 Conclusion

There is a high prevalence of late effects post treatment in our patients, GU late effects had the highest prevalence in our study, with as common complaints, severe frequency and dysuria. Vaginal stenosis and sexual dysfunction had the highest mild to moderate effects (grade 1-2).Despite various grading and reporting systems of these late effects, our results correlated with several other studies.

Several factors were associated to some late effects, correlating with other studies done elsewhere.

Treatment related parameters that are reported to influence effects of radiation therapy were not adequately analyzed in our study, hence the discrepancy in our findings compared to others.

There is need of putting much emphasis on assessing, recording and reporting these late effects as health care providers since they have shown to hinder our patients' survivorship journey.

### 5.3 Recommendations

- For the future, it will be of major importance to register late treatment side effects consistently with proper grading incorporated in patients' medical charts. Since the challenge in managing late effects is to first, recognize them.
- Development of harmonized institutionalized tools designed to screen for late effects during follow up of cervical cancer patients post radiation therapy, is of great importance.
- A comparative study with aim to analyze difference in the prevalence of late effects in patients treated with 2D conventional vs 3D conformal, is of great importance to upgrade our practice and individualize cancer care to our patients.
- Studies directed at looking into each particular late effect separately and different treatment parameters would help give specific insights on the trend, follow-up and management of these effects.
- QOL studies on sexual dysfunction and vaginal stenosis would be of great importance to help us analyze their impact on our patients and hence know how to best serve them.
- Establishment of support groups for cervical cancer patients will help the clinician capture and address these effects.
- Clinicians to emphasize on counselling patients on late effects of radiation therapy prior to start of the treatment and during treatment,this will enable easy diagnosis and reporting of these effects during follow-up.

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# APPENDICES

## Appendix I: Informed consent form-English version

TITLE OF STUDY: Prevalence and factors associated with Late Effects Amongst Cervical Cancer Patients at ORCI Between 2016-2019.

PRINCIPAL INVESTIGATOR
Dr. Diane Andrea Ndoli
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### Purpose of study

You are being asked to take part in a research study. Before you decide to participate in this study, it is important that you understand why the research is being done and what it will involve. Please read the following information carefully. Please ask the researcher if there is anything that is not clear or if you need more information. The purpose of this study is to determine the prevalence of late effects in cervical cancer patients post pelvic radiation therapy and understanding the factors influencing their occurrence and severity.

### Study procedures

This study will require you to answer the question that you will be asked by principle investigator or research assistant. Then your response will be written down in the prepare questionnaire and choosing not to participate will not affect your treatment.

### Risks

No any risk is expected for you participating in this study. You may decline to answer any or all questions and you may terminate your involvement at any time if you choose.

### Benefits

There will be no direct benefit to you for your participation in this study. However, we hope that the information obtained from this study may improve standard of care at our institute.

**Confidentiality**

Your responses to this study will be anonymous. Participant data will be kept confidential except in cases where the researcher is legally obligated to report specific incidents.

**Contact information**

If you have questions at any time about this study, or you experience adverse effects as the result of participating in this study, you may contact the researcher whose contact information is provided on the first page. If you have questions regarding your rights as a research participant, or if problems arise which you do not feel you can discuss with the Primary Investigator, please contact

Dr. Bruno Sunguya: Director of research and publication, Muhimbili University of health and allied sciences P.O. BOX 65001, Dar es salaam, Tanzania, Tel 255222-150-302-6/252489.

**Voluntary participation**

Your participation in this study is voluntary. It is up to you to decide whether or not to take part in this study. If you decide to take part in this study, you will be asked to sign a consent form. After you sign the consent form, you are still free to withdraw at any time and without giving a reason. Withdrawing from this study will not affect the relationship you have, if any, with the researcher. If you withdraw from the study before data collection is completed, your data will be destroyed.

**Consent to take part in research**

- ✓ I.....voluntarily agree to participate in this research study.
- ✓ I understand that even if I agree to participate now, I can withdraw at any time or refuse to answer any question without any consequences of any kind.
- ✓ I understand that I can withdraw permission to use data from my interview within two weeks after the interview, in which case the material will be deleted.
- ✓ I have had the purpose and nature of the study explained to me in writing and I have had the opportunity to ask questions about the study.
- ✓ I understand that I will not benefit directly from participating in this research.

- ✓ I understand that all information I provide for this study will be treated confidentially.
- ✓ I understand that in any report on the results of this research my identity will remain anonymous. This will be done by changing my name and disguising any details of my interview which may reveal my identity or the identity of people I speak about.
- ✓ I understand that I am free to contact any of the people involved in the research to seek further clarification and information.

---------- ----------

Signature of participant Date

I believe the participant is giving informed consent to participate in this study

---------- ----------

Signature of researcher Date

**Appendix II: Consent form-swahili version**

Fomu ya idhini ya kujulishwa

**Mada**

Uthibitishaji wa athari za matibabu ya mionzi tiba kwa wagonjwa wa saratani ya shingo ya kizazi.

**Mtafiti mkuu.**

Dk . Diane Andrea Ndoli
Oncology ya Kliniki
Simu: +250)788856738- +255683479942
Barua pepe: *androli.ljc@gmail.com*

**Malengo ya utafiti**

Utafiti huu unalenga kuamua kuongezeka kwa athari kwa wagonjwa wa saratani ya shingo ya kizazi baada ya tiba ya mionzi ya pelvic na kuelewa sababu zinazoathiri kutokea kwao na ukali wa athari.

**Taratibu za utafiti**

Utafiti huu utakuhitaji kujibu swali ambalo utaulizwa na mpelelezi wa kanuni au msaidizi wa utafiti. Halafu majibu yako yataandikwa chini kwenye dodoso la kujiandaa. Utafiti huu pia utahusisha mbinu ya kufikiria ambayo itasaidia kutambua ikiwa kuna metastasis yoyote. Kukataa kwako kushiriki katika utafiti huu hauta athiri Matibabu yako kwa njia yeyote.

**Athari**

Hakuna hatari yoyote inayotarajiwa kwako kushiriki katika utafiti huu. Unaweza kukataa kujibu maswali yoyote au yote na unaweza kumaliza kuhusika kwako wakati wowote ikiwa utachagua.

**Faida**

Hautakuwa na faida yoyote moja kwa moja kwako kwa ushiriki wako katika utafiti huu. Walakini, tunatumai kuwa habari inayopatikana kutoka kwa utafiti huu inaweza kuboresha nitolewa nakala ya fomu hii ya idhini. Ninakubali elimu kwa hiari katika eneo hili.

**Namba za mawasiliano**

Kama utakuwa na swali lolote muda wowote kuhusu utafiti huu, au umepatwa na madhara yoyote kwa kushiriki kwako katika utafiti huu, unaweza kuwasiliana na mtafiti mkuu kwa number zilitolewa hapo juu katika ukurasa wa kwanza. Kama pia utakuwa na swali lolote kuhusu haki zako kama mshiriki katika utafiti huu au tatizo lolote limetokea ambalo unaona hauwezi kumshirikisha mtafiti mkuu, tafadhali wasiliana na dokta. Bruno Sunguya: Mkurugenzi wa maswala ya utafiti na uchapishaji wa tafiti katika Chuo kikuu cha afya na sayansi shirikishi cha Muhimbili, S.L.P 65001, Dar es salaam, Tanzania, Simu namba: 255222-150-302-6/252489.

**Uhuru wa kushiriki**

Ushiriki wako katika utafiti huu ni wa hiari. Ni juu yako kuchagua kushiriki katika utafiti huu. Ikiwa utaamua kushiriki katika utafiti huu, unatahitajika kutia saini fomu ya idhini. Baada ya kusaini fomu ya idhini, bado uko huru kujiondoa wakati wowote bila kutoa sababu. Kujiondoa kutoka kwa utafiti huu hakuathiri uhusiano ulionaona mtafiti. Ukijiondoa kwenye ushiriki katika utafiti huu kabla ya ukusanyaji wa data kukamilika, data yako itaondolewa katika kumbukumbu ya data za washiriki.

KUKUBALI

- ✓ Mimi _____Kukubali kushiriki katika utafiti
- ✓ Ninakubali kwa hiari kushiriki katika utafiti huu.
- ✓ Ninaelewa kuwa hata kama nakubali kushiriki sasa, naweza kujiondoa wakati wowote au kukataa kujibu swali lolote bila tatizo la aina yoyote.
- ✓ Ninaelewa kuwa naweza kuondoa ruhusa ya kutumia data kutoka kwa mahojiano yangu ndani ya wiki mbili baada ya mahojiano.
- ✓ Nimepata kusudi na asili ya utafiti ulivyonielezea kwa maandishi na nimepata nafasi ya kuuliza maswali juu ya utafiti.

- ✓ Ninaelewa kuwa sitafaidika moja kwa moja kwa kushiriki katika utafiti huu.
- ✓ Ninaelewa kuwa taarifa zote nitakazozitoa kweny utafiti huu zitatunzwa kwa usiri mkubwa
- ✓ Ninaelewa kuwa katika ripoti yoyote juu ya matokeo ya utafiti huu kitambulisho changu kitabaki bila majina. Hii itafanywa kwa kubadilisha jina langu na kuficha maelezo yoyote ya mahojiano yangu ambayo inaweza kufunua kitambulisho changu au kitambulisho cha watu ninaozungumza nao.
- ✓ Ninaelewa kuwa niko huru kuwasiliana na mtu yeyote aliyehusika katika utafiti ili kutafuta ufafanuzi zaidi kuhusu utafiti huu.

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*Sahihi ya mshiriki* Tarehe

I believe the participant is giving informed consent to participate in this study

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Sahihi ya mtafiti Tarehe

**Appendix III: Data extraction form.-English version.**

**IDENTIFICATION**

File Registration number……

**PATIENT CHARACTERISTIC**

1. Age in years……
2. Marital status
    a) Married
    b) Single
    c) Divorced Separated
    d) Widowed……
3. HIV status
    a) Negative
    b) Positive
    c) Unknown
4. Education level
    a) primary level
    b) secondary level
    c) higher education level
    d) None formal.
5. Occupation
    a) Peasant
    b) Petty trader Business
    c) Employed
    d) others: explain
6. BMI weight_____ Height_____
7. Diabetes…YES……NO…….
8. Smoking ……YES……NO…….
9. Disease histology
    a) Squamous cell carcinoma
    b) Adenocarcinoma……

10. Disease Grade
    a) grade 1( well differentiated)
    b) grade 2(moderate differentiated)
    c) grade 3( poorly differentiated)

11. stage of the disease
    a) stage I
    b) stage II
    c) stage III
    d) stage IV

**TREATMENT RECEIVED**

12. Radiotherapy
    a. EBRT

        Total dose given in (Gray): 1. 50GY ……2. >50 GY …….

        Field size 15X15CM 2) >15X15CM 3) <15X15CM ……

        Number of fields given

        Four fields (4 box) 1.YES…… 2. NO…….

        Two fields (AP/PA) 1.YES……. 2. NO…….

    b. Brachytherapy
        a) Yes……
        b) No…….

    IF YES, number of insertions: 1)1…. .2)2……3)3…….

Bladder point: Rectal point:

13. Chemotherapy
    a. Type of chemotherapy ……
    b. Number of cycles received……

**LATE TOXICITY ASSESSEMENT**

14. Grading: Yes……No……

Type of toxicity:

a. Gastrointestinal: grading yes:… No….

If yes what grade.1)1... 2)2… 3)3….4)4…..

b. Genitourinary: grading Yes…… …..No….

If yes what grade.1)1... 2)2… 3)3…. 4)4…..

c. Vaginal stenosis: grading Yes….. …..No…..

If yes what grade.1)1... 2)2… )3…. 4)4…..

d. Sexuality dysfunction: grading Yes…. ……..No…..

If yes what grade.1)1... 2)2… 3)3…. 4)4…..

RTOG/EORTC Late Radiation Morbidity Scoring Scheme/CTCAE V4

| **GRADE** | | | | | |
|---|---|---|---|---|---|
| TOXICITY | 0 | 1 | 2 | 3 | 4 |
| Bladder-<br>Late RT Morbidity Scoring | No change from baseline | Mild/frequency Slight epithelial atrophy/minor telangiectasia (microscopic hematuria) | Moderate frequency/ generalized telangiectasia/ intermittent macroscopic hematuria | Severe frequency and dysuria/severe generalized telangiectasia (often with petechial); frequent hematuria; reduction in bladder capacity (< 150 cc) | Necrosis/contracted bladder (capacity < 100 cc)/severe hemorrhagic cystitis. |
| Small/Large intestine-<br>Late RT Morbidity Scoring | No change from baseline | Mild diarrhea; mild cramping; bowel movement 5 x daily slight rectal discharge or bleeding | Moderate diarrhea and colic; bowel movement > 5 x daily; excessive rectal mucus or intermittent bleeding | Obstruction or bleeding, requiring surgery | Necrosis/ perforation fistula |
| Vaginal stenosis | | | | | |

| | | | | | |
|---|---|---|---|---|---|
| Vaginal dryness | normal | mild | requiring treatment and/or interfering with sexual function, | - | - |
| Dyspareunia | none | mild pain not interfering with function | moderate pain interfering with sexual activity | severe pain preventing sexual activity | - |
| Vaginal stenosis | none | Asymptomatic; mild vaginal shortening or narrowing | Vaginal narrowing and/or shortening not interfering with physical examination | Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination | - |
| Sexual/Reproductive Function:<br><br>Libido | none | Decrease in interest but not affecting relationship; intervention not indicated | Decrease in interest and adversely affecting relationship; intervention indicated | - | - |

**Appendix IV: Data Extraction Form: Swahili version**

**UTAMBULISHO**

Namba ya Usajili wa Faili……

**WASIFU WA MGONJWA**

1. Umri(katika miaka) ……
2. Hali ya ndoa
    a) Nimeoa/nimeolewa
    b) Niko mwenyewa
    c) Mtalaka/Tumetengana
    d) Mjane/Mgane……
3. Hali ya mambukizi ya VVU.
    a) Hasi
    b) Chanya
    c) Haijulikan
4. Kiwango cha elimu
    a) Elimu ya shule
    b) Elimu ya sekondari
    c) Elimu ya chuo
    d) Sikwenda shuleni
5. Shughuli
    a) Mkulima mdogo
    b) mfanya biashara mdodgo
    c) Nimeajiriwa
    d) Nyingine (taja)_____

**TABIA ZA UGONJWA**

6. BMI uzito_____ kimo_____
7. kisukari……NDIO ……HAPANA…….
8. Taarifa za uvutaji sigara ……NDIO……HAPANA…….
9. Histolojia ya ugonjwa
    a) Squamous cell carcinoma
    b) adenocarcinoma……
10. Gredi ya ugojwa
    a) Gredi 1
    b) Gredi 2
    c) Gredi 3
11. Hatua ya ugonjwa
    a) Hatua ya kwanza
    b) Hatua ya pili
    c) Hatua ya tatu
    d) Hatua ya nne
    e) Umesambaa

**HUDUMA ALIYOPOKEA**

12. Tiba Ya Mionzi
    a. Mionzi ya nje

    Jumla ya dozi zilizotolewa (Gray): < 45GY ……45GY…….> 45GY

    Ukubwa wa field ……

    Idadi ya field zilizotolewa

    Field nne (4box) NDIYO…… HAPANA……..

    Field mbili (AP/PA) NDIYO…….. HAPANA…….

b. Mionzi ya ndani

Ndio……Hapana……..

IKIWA NI NDIYO,

Taja Idadi ya michomeko: 1….. .2……3……..

13. Kemotherapia

a. Aina ya kemotherapi……

b. Idadi ya mizunguko uliyopata ……

**TATHMINI YA MADHARA YA BAADAE**

Upatikanaji Wa Nyaraka : Ndiyo……Hapana……

Upangaji Wa Kiwango: Ndiyo……..Hapana…….

<u>Aina ya madhara:</u>

Njia ya chakula: kiwango:

if yes what grade.1)1.. 2)2… 3)3….4)4…..

Njia ya mkojo: kiwango

if yes what grade.1)1.. 2)2… 3)3….4)4…..

Kusinyaa njia ya uke: kiwango :

if yes what grade.1)1.. 2)2… 3)3….4)4…..

Matatizo ya tendo la ndoa: kiwango:

if yes what grade.1)1.. 2)2… 3)3….4)4…..

RTOG/EORTC Late Radiation Morbidity Scoring Scheme:

| KIWANGO | | | | | |
|---|---|---|---|---|---|
| MADHARA | 0 | 1 | 2 | 3 | 4 |
| Kibofu - Late RT Morbidity Scoring | Hakuna mabadiliko kutoka hali ya awali. | Kukojoa mara kwa mar,Kusinyaa kidogo kwa epithelium/kutuna kidogo kwa mishipa ya damu(damu kwenye mkojo isyoonekana kwa macho) | Kukojoa Mara nyigi kiasi/mishipa yote ya damu kutuna/kukojoa dam umara kadhaa. | Kukojoa mara nyingi sana na maumivu/kutuna kwa mishipa yote ya dam una kwa kiasi kikubwa(pamoja na kuvilia damu chini ya ngozi). Kukojoa dam mara nyingi; kupungua kwa ujazo wa kibofu(<150cc) | Kuharibika/kibofu kusinyaa kwa kibofu( ujazo(ujazo< 100cc)/ kuwasha kwa kibofu pamoja kutoka damu. |
| Utumbo mpana/mwembamba- Late RT Morbidity Scoring | Hakuna mabadiliko kutoka hali ya awali. | Kuharisha kidogo; maumivu kidogo ya tumbo; kuharisha mara 5 kwa siku. Kutoka | Kuharisha kiasi na maumivu ya tumbo; kuharisha Zaidi ya mara 5 kwa siku; kutoka uteute | Kuziba auu kutokwa damu kunako hitaji upasuaji. | Kuoza/kutoboka fistula. |

| | | | | | |
|---|---|---|---|---|---|
| | | uchafu au damu kwenye haja kubwa. | mwingi sana kila siku au kutoka damu mara kadhaa | | |
| Hali ukavu ukeni | kawaida | Kidogo | Inahitaji matibabu pia inaathiri tendo la ndoa., maumivu wakati wat endo la ndoa. | - | - |
| Maumivu wakati wat endo la ndoa | hakuna | Maumivu kidogo ambayo hayaathiri utendaji kazi | Maumivu kiasi mbayo yanathiri ufanayji tendo la ndoa | Maumivu makali ambayo yanazuia ufanyaji tendo la ndoa. | - |
| Shughuli za uzazi au tendo la ndoa-Nyingine(taja) | Hakuna | Kidogo | Kiasi | Makali | Kupindukia |