PREVALENCE OF UTERINE CERVICAL CANCER PROGRESSIVE AND PERSISTENT DISEASE AMONG PATIENTS TREATED WITH CHEMO-RADIATION AT OCEAN ROAD CANCER INSTITUTE

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By

Faraja C. Kiwanga

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, 2019

CERTIFICATION

The undersigned, certifies that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled*:* "**Prevalence of Uterine Cervical Cancer Progressive and Persistent Disease among Patients Treated with Chemo-radiation at Ocean Road Cancer Institute",** in (partial) fulfillment of the requirements for the degree of Master of Medicine (Clinical Oncology) of Muhimbili University of Health and Allied Sciences.

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Date

DECLARATION AND COPYRIGHT

I, Dr. Faraja C. Kiwanga, 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 similar or any other degree award.

Signature: …… **Date:** ……

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DEDICATION

I dedicate this research study to my lovely husband, Dr. Alick Kayange and my lovely daughters; Alice-Elizabeth, Jane-Rose and Doreen-Faith. May the Lord God Almighty keep and bless you always!

To my lovely father, the Late Prof. Christopher A. Kiwanga. You were my powerful influence and I can't forget all your efforts to raise and support me. *May your soul rest in eternal peace, AMEN!!*

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ABSTRACT

Background: Uterine cervical cancer is the second most commonly diagnosed cancer and third leading cause of cancer death among women in less developed countries. It remains the most common cancer of public health concern in women in Eastern and Middle Africa, Tanzania inclusive. At Ocean Road Cancer Institute (ORCI), it is the leading diagnosis for all malignancies. Though progressive and persistent cancer of cervix post treatment is a major problem at the Institute, exact data on the trends is desperately needed.

Objective: To determine prevalence of progressive and persistent cervical cancer disease among patients treated with chemo-radiation at Ocean Road Cancer Institute (ORCI).

Materials and methods: A descriptive cross-sectional study was conducted among patients received treatment from January through December 2014 at ORCI based in Dar es Salaam. Two-hundred thirty-nine women with uterine cervical cancer disease meeting the predetermined inclusion criteria were included in the study. Retrospective secondary data obtained from the patients' medical files included socio-demographic profile, clinical profile, pre-treatment assessment as well as 3months and six months post treatment were filled into a well-structured data collection form, and were compiled and analyzed using statistical package for social sciences (SPSS) software version 21. Socio-demographic and clinical factors were analyzed by using frequency and percentage as well as mean and standard deviation. The univariate and multivariate regression analysis were performed to determine the association between dependent variables and independent variables. An association was regarded as statistical significance when the p-value was less than the significance level of 0.05 i.e. $P < 0.05$.

Results: About half of the 239 patients studied were 45-67 years old and 34.7% came from the coastal zone. Approximately, 68.2% patients were referred to ORCI with International Federation of Gynecologist and Obstetric (FIGO) disease stage IIB-IIIB. Among patients studied, progressive disease was seen in 43(18%) patients while persistent disease was observed in 111(46.4%) patients. Progressive disease rate was statistically significantly

associated with disease stage (p=0.001), Hb level before therapy (p=0.001)and time taken from the diagnosis of the patient to initiation of therapy (p=0.021). Moreover, mid-therapy Hb level of less than 9gm/dl (p=<0.0001), overall treatment time of more than eight weeks (p=<0.0001), the use of weekly concurrent chemo-radiation (p=<0.0001) and increased time taken from the diagnosis to initiation of radiotherapy (p=<0.0001) were the main factors that contributed to the development of persistence disease for cervical cancer patients received chemo radiation during the stated period.

Conclusions and recommendations:

This study found that progressive disease had significant association with increased waiting time from the diagnosis of the patient to initiation of therapy and advanced disease stage. Moreover, Persistent disease had significant association with increased waiting time from the diagnosis of the patient to initiation of therapy, lower level of mid-therapy hemoglobin and use of concurrent chemo radiation.

Due to high rate of progressive disease found, this can be addressed by early diagnosis and referral to consultant hospital, as well as improving infrastructure and equipments used for cancer treatment.

However the prevalence of persistent disease can be intervened by correction of anemia during the course of the therapy, use of concurrent chemo radiation, and giving adequate doses in a proper time.

TABLE OF CONTENTS

CERTIFICATION i
DECLARATION AND COPYRIGHT ii
ACKNOWLEDGEMENTS iii
DEDICATION iv
ABSTRACT v
TABLE OF CONTENTS vii
LIST OF TABLES x
LIST OF FIGURES x
ABBREVIATIONSAND ACRONYMS xi
DEFINITION OF KEY TERMS xii
CHAPTER ONE 1
1.0 INTRODUCTIONAND LITERATURE REVIEW 1
1.1Background 1
1.1.1 Staging of cervical cancer 3
1.1.2 Prognosis 4
1.1.3 Treatment of cervical cancer 5
1.1.4 Follow-up 6
1.1.5 Assessment of progressive disease and persistent disease 6
1.2 Literature review 7
1.3 Problem statement 9
1.4 Rationale of study 9
1.5 Hypotheses 9
1.6 Objectives 10
1.6.1 Broad objective 10
1.6.2 Specific objectives 10
CHAPTER TWO 11
2.0 MATERIALS AND METHODS 11
2.1 Study design 11

2.2 Study setting 11
2.3 Study population 11
2.3.1 Inclusion criteria 12
2.3.2 Exclusion criteria 12
2.4 Study variables 12
2.4.1Exposure variables 12
2.4.2 Outcome variables 12
2.5 Sample size calculation 13
2.6 Data management 13
2.6.1 Data collection 13
2.6.2 Data quality control 14
2.6.3 Data analysis 14
2.7 Dissemination plan 15
2.8 Ethical clearance 15
CHAPTER THREE 16
3.0 RESULTS 16
3.1 Socio-demographic characteristics of patients 16
3.2 Disease characteristics of patients with uterine cervical cancer 18
3.3 Treatment modalities received by patients 20
3.4 Prevalence of progressive disease 21
3.5 Prevalence of persistent disease 21
3.6 Progressive disease and associated factors 22
3.7 Persistent disease and associated factors 24
chapter four 27
4.0 DISCUSSION 27
4.1 Study limitations 31
chapter five 32
5.0 CONCLUSIONS AND RECOMMENDATIONS 32
5.1 Conclusions 32
5.2 Recommendations 33

REFERENCES 34
APPENDICES 38
Appendix I: Data Collection Form 38
Appendix II: Ethical Clearence 40

LIST OF TABLES

Table 1: Socio-demographic characteristics of patients 17
Table 2: Disease characteristics of patients with uterine cervical cancer 19
Table 3: Treatment modalities received by patients 20
Table 4: Prevalence of progressive disease 21
Table 5: Prevalence of persistent disease 21
Table 6: Progressive disease and associated factors 23
Table 7: Progressive disease and associated factors (multivariate analysis 24
Table 8: Persistent disease and associated factors 25
Table 9: Persistent disease and associated factors (multivariate analysis) 26

LIST OF FIGURES

Figure 1: Residence distribution of patients 18

ABBREVIATIONSAND ACRONYMS

BED	Biological Effective Dose
CBC	Complete Blood Count
CCRT	Concurrent Chemo-Radiotherapy
EBRT	External Beam Radiotherapy
FIGO	International Federation of Gynecologist and Obstetric
HDR	High Dose Rate
Hb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
ICBT	Intra-Cavitary BrachyTherapy
KPS	Karnofsky Performance Status
MUHAS	Muhimbili University of Health and Allied Sciences
ORCI	Ocean Road Cancer Institute
OR	Odds Ratio
OTT	Overall Treatment Time
RECIST	Response Evaluation Criteria in Solid Tumours
RT	Radiotherapy
SCC	Squamous Cell Carcinoma
SPSS	Statistical Package for Social Sciences
WHO	World Health Organization

DEFINITION OF KEY TERMS

Transformation zone: The point place where the two main types of cells covering the cervix (squamous cells on the exocervix and glandular cells on the endocervix).

Radiotherapy: Therapy using ionizing radiation to treat cancer so as to control or kill malignant cells.

Chemo-radiation (CRT): The form of treatment that combines both chemotherapy and radiotherapy so as to improve/control of the disease.

Response criteria: The criteria used to determine objective solid tumor response to treatment.

Complete response: The disappearance of gross lesion one month after the completion of radiotherapy and the absence of any viable tumor cells on biopsy.

Partial response: A greater than 50% reduction of tumor size one month after completion of radiotherapy and absence of new lesions.

Residual tumor: This may be localized in the area of the primary tumor or a distant metastasis.

Persistent disease: The presence of gross tumor or less than 50% reduction of tumor size within 3-6months after radiation therapy.

Progressive disease: The appearance of new lesion during therapy or a greater than 25% increase in size of local tumor (an absolute increase of at least 5mm) or a persistent lesion within 3-6months after the radiation therapy.

Recurrent disease: The tumor occurring one-two years after complete remission. **Performance status:** is an attempt to quantify cancer patients' general well being and activities of daily life. This measure is used to determine whether they can receive chemotherapy, whether dose adjustment is necessary and as measure for the required intensity of palliative care.

CHAPTER ONE

1.0 INTRODUCTIONAND LITERATURE REVIEW

1.1Background

Cancer of uterine cervix is the malignant growth that arises from the uterine cervix, which is the lower end of the uterus that contacts the upper vagina. It is the second most common type of cancer (17.8 per 100,000) and third cause of cancer death (9.8 per 100,000) among all types of cancer in women in less developed countries (1).

It accounted for an estimated 527,600 new cancer cases worldwide and for 266,000 death in 2012 (1). Global incidence and mortality rates depend upon the availability of screening programs for the uterine cervix pre-cancerous lesion and cancer lesion and of human papilloma virus (HPV) vaccination which are available in developed countries. As a result of these interventions there has been a 75% reduction in incidence and mortality in developed countries over the past 50 years (2). However in Africa and Central America, it is the leading cause of cancer-related mortality among women. Despite different campaign advocated for early screening, cervical cancer remains the most common cancer of public health concern in women in Eastern and Middle Africa with mortality rate of 34 deaths per 100,000 women per year compared to only nine deaths per 100,000 women per year worldwide (3).

Uterine Cervix is the part that is at the lower third of the uterus. In a non-pregnant woman of reproductive age, it measures about 3 cm in length and 2.5 cm in diameter. Ectocervix is the lower part of the cervix that lies within the vagina and is visible with a speculum; the upper two thirds of the cervix (endocervix) lie above the vagina and is not visible. Most cervical cancers originate in the area where the endocervix and ectocervix join (transformation zone). It is composed of dense fibro-muscular tissue. The cervical canal passes all the way through the centre of the cervix from the internal os the opening at the entrance to the cavity of the uterus and to the external os the opening in the cervix seen with a speculum (4).

The primary cause for developing uterine cervical cancer is following persistent infection with Human papilloma virus (HPV) types 16 and 18, where their main spread is through sexual contact (5). On the other hand there are several risks factors that contribute to the development of uterine cervical cancer including early onset of sexual activity, multiple sexual partners, having high risk sexual partner, sexually transmitted disease, immunosuppresion, early age at first birth, multiparity, smoking and low socio-economic status (6). The peak age for emergent of uterine cervical cancer is 47 years and about 47% of women with invasive cervical cancer are less than 35 years old at diagnosis. Cervical cancer primarily affects women from lower socio-economic status and those with poor access to routine medical care (3).

There are several steps in cervical cancer development; infection by the oncogenic HPV on the metaplastic epithelium at the cervical transformation zone (the junction between the squamous epithelium of the ectocervix and the glandular epithelium of the endocervical canal), persistence of the HPV infection, development of a clone of epithelial cells from persistent viral infection to pre-cancer, and development of carcinoma and invasion through the basement membrane (7).

Initially uterine cervical cancer is frequently asymptomatic, however the most common symptoms at presentation include irregular or heavy vaginal bleeding or postcoital bleeding. Otherwise some women present with a vaginal discharge that may be watery, mucoid, or purulent and malodorous. In advanced disease it may present with pelvic or lower back pain, which may radiate along the posterior side of the lower extremities. The other symptoms related to bowel or urinary complaints like, hematuria, hematochezia, or vaginal passage of urine or stool, are not common and when they present they suggest an advanced disease. In asymptomatic women, cervical cancer may be discovered as a result of cervical cancer screening or incidentally, if a visible lesion is discovered upon pelvic examination (8).

The diagnosis of uterine cervical cancer is made after pelvic examination and speculum examination for women with symptoms suggestive of cervical cancer. Thereafter the diagnosis is confirmed by histology. Any abnormal lesion whether raised, friable, or has the look of condyloma has to be biopsied, regardless of previous benign cervical cytology results.

Detailed examination has to be done to ascertain extent of local invasion of the tumor or distance metastasis (9).

Different uterine cervical cancer histological features have been identified, one being squamous cell carcinoma which comprise of about 90% of all cases. This is further subdivided into: large cell non-keratinizing (with better prognosis of 75% for 5 year survival), large cell keratinizing and small cell non-keratinizing which is usually regarded as poorly differentiated. The other histological types are adenocarcinoma contributing10 to 15%cases with 20% 5year survival, and adeno-squamous carcinoma (2 to 3% cases). Rare types are sarcoma, lymphoma and verrucous carcinomas (10).

1.1.1 Staging of cervical cancer

According to the International Federation of Gynecologist and Obstetric (FIGO), staging (AJCC 7TH ED., 2010 / FIGO 2008) (11).

Primary Tumour		
TNM categories	FIGO Stages	
Tx		Primary tumour can not be assesed
T0		No evidence of primary tumour
Ts		Carcinoma in situ (pre-invasive carcinoma)
T1	I	Cervical cancer confined to uterus
T1a	IA	Invasive carcinoma diagnosed with only by microscopy.Stromal invasion with a maximum depth of 5mm measured from the base of the epithelium amd a horizontal spread of 7.0mm or less. Vascular space involvement, venous or lymphatic, does not affect classification.
T1a1	IA1	Measured stromal invasion of 3.0mm or less in depth and 7.0mm or less in horizontal spread.
T1a2	IA2	Measured stromal invasion more than 3.0mm and not more than 5mm with a horizontal spread of 7.0mm or less
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/T1a2

T1b1	IB1	Clinically visible lesion 4.0cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0cm in greatest dimension
T2	II	Cervical carcinoma invades beyond uterus, but not to pelvic wall or to loer third of vagina.
T2a	IIA	Tumor without parametrial invasion.
T2a1	IIA1	Clinically visible lesion 4.0cm or less in greatest dimension.
T2a2	IIA2	Clinically visible lesion more than 4.0cm in greatest dimension.
T2b	IIB	Tumour wiwth parametrial invasion.
T3	III	Tumour extend to pelvic wall and/or involve lower third of vagina and/or causes hydronephrosis or non functioning kidney.
T3a	IIIA	Tumor involve lower third of vagina, no extension to pelvic wall.
T3b	IIIB	Tumour extends to pelvic wall and/or causes hydronephrosis or non functional kidney.
T4	IVA	Tumour invades mucosa of bladder or rectum and/ or extends beyond true pelvis
Regiona lymph nodes (N)		
TNM categories	FIGO Stages	
Nx		Regional lymph nodes cannot be assesed
N0		No regional lymph node metastasis
N1	IIIB	Regional lymph node metastasis

1.1.2 Prognosis

Prognostic factors for uterine cervical cancer include lymph node metastasis, tumor size, stage uterine extension of the disease and the level of hemoglobin (< 10g/dl). The risk of pelvic lymph node involvement increases as the disease stage increase. They include 15%, 30% and 45% for stage I, II and III respectively. Apart from pelvic lymph node metastasis, the other common sites for metastasis include the lungs and para-aortic nodes (11).

1.1.3 Treatment of cervical cancer

Depending on the stage of disease, modalities of treatment for carcinoma of the cervix are surgery, radiotherapy, chemotherapy or combination of them. In general, surgical series tend to be more highly selective and are indicated for stage I and IIA cancers. An important advantage of surgery is the definition of a true state of spread, which should allow more accurate overall planning of treatment. For patients presenting with more advanced stage IIB - IV of disease, radiotherapy is the treatment of choice (11).

Patients with pre-invasive cervical lesion are treated by conization or loop electrosurgical excisional procedure, cryotherapy ablation or simple hysterectomy. For women with micro-invasive disease (stage IA_1) who have no evidence of intermediate- or high-risk features, suggested treatment modalities are conization or extrafascial hysterectomy rather than radical hysterectomy. For stage IA_2 lesion preferably methods are radical hysterectomy or brachytherapy alone (LDR 65-75Gy) or (HDR 7Gy× 5-6fractions).For women with stage IB1the reasonable treatment options are radical hysterectomy with pelvic lymph node dissection or definitive radiation therapy (External Beam Radiation Therapy (EBRT) plus Brachytherapy). Stage IB_2-IIA can be given concurrent chemo-radiation with Cisplatin where by whole pelvis radiation of 45Gy and Brachytherapy (HDR/LDR) can be given. For women with locally advanced uterine cervical cancer from stage IIB-IVA recommended modalities of treatment include primary concurrent chemo-radiation with Cisplatin rather than primary surgery or radiation therapy. Women with stage IVB can be given combination chemotherapy (11).

In our setting most of our patients come with advanced disease whereby they are treated initially with external beam irradiation to the pelvis using cobalt 60 and the field size to be used will be determined due to the extent of disease during simulation with parallel opposing fields(anterior-posterior/posterior-anterior). Then high dose rate Intra-Cavitary Therapy (HDR-ICT) is given in the third, fourth and fifth week during the course of external beam radiation. The HDR-ICT source is Cobalt 60 and the dose per fraction that is used is 6.7Gy per week in three insertions or 9Gy per week in two insertions (8).

It is recommended for all woman diagnosed with cervical cancer to start treatment immediately depending on the stage of the cancer, type of cervical cancer, patient's desire to have children and patient’s age.

Despite radiotherapy being the gold standard treatment of cervical cancer, pelvic radiotherapy by itself has failed to control the progression of cervical cancer in 35% to 90% of patients with locally advanced disease. Despite improvements in radiation equipment and techniques, the results of treatment of advanced stages remain suboptimal (12).

Local disease control of uterine cervical cancer disease differs according to stage, for stage IA-95-100%, IB1-90-95%, IB2-60-80%, IIA-80-85%,IIB-60-80%,IIIA-60%, IIIB-50-60% and IV-30% (11).

With radical radiation therapy alone 5 year survival rates for locally advanced carcinoma of the cervix vary in range of 50 to 76% (4). The sites of failure in these patients are pelvis only in 12 to 18%, pelvis and distant metastasis in 11 to 27% and distance metastasis in 15-20% (5).

1.1.4 Follow-up

After completion of treatment, the schedule involves monthly assessment for three months, three monthly assessments for nine months, four monthly for one year, six monthly for two years and then annually for the rest of the years (13).

In our setting, patient is regularly followed up every 3months for the first six months then every six months up to the second year then yearly up to ten years.

1.1.5 Assessment of progressive disease and persistent disease

Progressive and persistent disease is detected by presence of symptoms clinically three months post treatment and confirmed through clinical examination and routine investigations.

In our setting progressive disease and persistent is assessed through pelvic and speculum examination as well as abdominal-pelvic ultrasound during follow up post treatment.

1.2 Literature review

A hospital based study retrospective analysis of patients with cervical cancer receiving radiotherapy between January 2005-December 2006 done in India showed 12% had residual disease and 16% patients had progressive disease of cervical cancer after radiotherapy and majority were associated with liver and bone metastasis (14).

There was a study done on Short term persistence of carcinoma of the cervix after radiation by Jacobs et al revealed that persistent disease was found for patient who had tumors of more than 5cm and had higher stages of more than stage III (15).

In new response evaluation criteria of solid tumor by Eisenhauer et al at least a 20% increase in the sum of diameters of target lesions, an absolute increase of at least 5 mm (or appearance of one or more new lesions) was referred to as progressive disease (16).

Liu et al did a study on analysis of patients with persistent disease after concurrent chemo radiation where a persistent lesion or new lesion was seen to occur within six months after concurrent chemo-radiation and it was taken as the key for persistent disease (17).

Yale University School of Medicine conducted the research on risk factors associated with cervical cancer and revealed that rapidly progressive invasive cervical cancer occurs in a younger populations <54years old. The presence of cervical cancer progressive disease was accounted for the presence of gynecological disorders prior diagnosis. Results reported that women with rapidly progressive disease had gynecologic disorders like uterine leiomyomata and vaginitis prior cervical cancer diagnosis (18).

Progressive disease was seen among women who were screened and monitored and found to have HPV positive that was high risk type (5).

The use of concurrent chemotherapy is an important component for better clinical outcome for cervical cancer. In the study done at the National Institute of Health on chemo-responsive to Cisplatin and outcome in cervical cancer, the clinical outcome was best for those whose tumor tested responsive for Cisplatin. This emphasize the importance of cytotoxic chemotherapy in the control of the subclinical disease (19).

An Indian study on outcome of patients after radical radiotherapy revealed that overall outcome was poor in advanced stage disease, but might be improved by increasing the total dose, decreasing overall duration of treatment, and by adding chemotherapy in patients with disease limited to pelvis (20).

Several clinical factors may have influence on disease progression such as initial hemoglobin level, cancer stages, tumor size and volume, type of tumor, patient performance status, type of treatment, overall treatment time, radiation dose and co-morbidities (21).

A study done by Juergen Dunst et al on impact of anemia in cervical cancer revealed that the presence of anemia before treatment had strong impact on the rate of pelvic relapse. It also showed that hemoglobin level at mid-therapy (19.8Gy) had the strongest impact on local failure rate and survival (22).

In a study done by Sheiban et al in Iran on Clinical manifestation and treatment result of patient with cervical cancer ,it revealed that the improvement of treatment results can be due to proper and timely duration of external beam radiation therapy and brachytherapy (23).

A study in Taiwan revealed that prognostic factors for pelvic treatment failure were tumor stage, tumor response to radiation and overall treatment time. However, the daily decrease of pelvic control rate was higher in stage III patient with 0.73% and lower for stage I patients with 0.43% (24).

A study done by Majinge et al on treatment outcome of patients receiving treatment at ORCI revealed that late presentation of the disease was the main factor causing poor treatment outcome resulting to death of the patients (25).

A study in India by Singh K.K et al evaluated treatment results, prognostic factors and complication rates in patients with locally advanced cancer of uterine cervix after radiotherapy with high-dose rate brachytherapy and suggested that radical radiotherapy with HDR brachytherapy was appropriate for treatment of local advanced cervical cancer. Also, overall treatment time and the response after treatment were prognostic factors (26).

1.3 Problem statement

In follow up of the patient with uterine cervical cancer treated at ORCI, it has been observed that most patients still have similar symptoms as those at presentation before treatment. These symptoms either happened immediately or within a short time after completion of treatment.
It is not known whether this symptoms are due to progression of disease or persistence of the disease.

This study aimed at determining the magnitutde of this problem as well as the factors which are associated with it.

1.4 Rationale of study

The study will help to identify the factors predicting the progression or persistence of the uterine cervix cancer in patients treated with chemo radiation at our institution.

The results obtained will be used in improving planning and individualizing treatment for the patients with this disease.

Moreover, it can also be used to improve our local cancer treatment protocol as well as influencing cancer control policy change.

1.5 Hypotheses

Null Hypothesis: There is no difference in socio-demographic and clinical factors among patient with cervical cancer progressive and persistent disease after chemo-radiation compared to those with complete response.
Alternative Hypothesis: There is a difference in socio-demographic and clinical factors among patient with cervical cancer progressive and persistent disease among patients treated with chemo radiation at ORCI.

1.6 Objectives

1.6.1 Broad objective

1. To determine the prevalence of progressive and persistent cervical cancer disease among patients treated with chemo radiation at Ocean Road Cancer Institute (ORCI).

1.6.2 Specific objectives

1. To determine socio-demographic characteristics of patients with cervical cancer.
2. To determine the prevalence of cervical cancer progressive disease after chemo-radiation.
3. To determine the prevalence of cervical cancer persistent disease after chemo-radiation.
4. To determine clinical factors associated with cervical cancer progressive disease.
5. To determine clinical factors associated with cervical cancer persistent disease.

CHAPTER TWO

2.0 MATERIALS AND METHODS

2.1 Study design

This was a cross-sectional study designed to determine prevalence of uterine cervical cancer progressive and persistent disease among patients treated with chemo radiation therapy at ORCI.

Patients information regarding detailed clinical history, complete clinical examination and investigations (haematological, biochemical and radiological) performed during treatment were extracted from available records.

2.2 Study setting

The study was conducted at Ocean Road Cancer Institute (ORCI) which is the leading specialized institute for cancer management. It is located along the Indian Ocean in Dar es Salaam, Tanzania and the facility was founded in1895 by the German colonial government.

The hospital has two Cobalt 60 machines, one conventional simulator and two high dose rate brachytherapy units.

In the year 2014, the institute received 5900 patients, among which 34% had the diagnosis of uterine cervical cancer. Most patients are referred to ORCI from other zonal consultant hospitals or normal hospital after a histopathological diagnosis of uterine cervical cancer. When patient attend ORCI, they are clinically staged by a medical doctor and then further investigations are done to elicict spread of the disease in the body by doing abdominal and pelvic ultrasound, chest xray, hematological,metabolic,renal and hepatic profiles.

2.3 Study population

Women who were referred to ORCI for treatment and were diagnosed to have uterine cervical cancer with confirmed histological features that were treated in the period of January 2014 to December 2014.All women meeting the eligibility criteria below were included in the study.

2.3.1 Inclusion criteria

1. Patients with uterine cervical cancer that has been confirmed histologically.
2. Patients that were treated with EBRT plus ICBT with or without weekly chemotherapy from January to December 2014.
3. Patients with cervical cancer FIGO stage I-IIIB.

2.3.2 Exclusion criteria

1. Patients who had previous surgery.
2. Patients with poor and deteriorating health condition.

2.4 Study variables

2.4.1Exposure variables

1. Socio-demographic (age, education, occupation).
2. FIGO stage of the disease.
3. Histological type of the disease.
4. Clinical manifestations (signs and symptoms).
5. HIV status.
6. Hemoglobin level before treatment.
7. Hemoglobin level at mid-therapy.
8. KPS performance status.
9. Chemotherapy (Cisplatin) received.
10. Total dose (radiotherapy) received.
11. Overall treatment duration.
12. Waiting time before initiation of treatment.

2.4.2 Outcome variables

1. Progressive disease, persistent disease.

2.5 Sample size calculation

The sample size of the study on prevalence of cervical cancer progressive and stable disease among patients with uterine cervical cancer after chemo-radiation was calculated using the formula:

$$n = \frac{z^2\, p\, (100 - p)}{\varepsilon^2}$$

Where:

n = Minimum sample size designed.

z = the point on standard normal deviation corresponding to 95% Confidence Interval which is 1.96 (Z_x of 1.96 approximated to 2).

p = the proportion of progressive disease among treated cervical cancer patients estimated at 16% based on the previous study (18).

ε = Margin of error set at 5%.

$$n = \frac{(2)^2 \times 16 \times (100 - 16)}{(5)^2} = 215.04$$

For adjusting non response; cross-sectional study done a couple of years on cervical cancer; response was 95%. For follow up study respond rate may decrease to 90%. Then, N = n/R 215.04/0.90 = 238.93

The number of patients to be recruited was 215. However, the sample size was adjusted to 239 to minimize non-response bias.

2.6 Data management

2.6.1 Data collection

Retrospective secondary data were obtained from the files that were stored at the Medical Records Department of ORCI. The information collected were socio-demographic characteristics of age, sex, marital status, education level and occupation, histological type, stage of the disease, pre-treatment assessment, Principal Investigator (PI) recruited two

research assistants who were then trained to fill the data that were available in the patient's files. PI oversaw the whole process of the data collection and also at times participated in data collection from patient sites. Pre-testing of the well structured data collection form was done for assessment of the compatibility of data collection form.

Each individual patient was assessed at three months post treatment and six months post treatment for the clinical outcome of progressive or persistent disease. The patient with progressive disease was categorized as the patient with the appearance of a new lesion during therapy or increase in size of local tumor at least 5mm within three to six months after the radiation therapy. However the patient with persistent disease was categorized as the presence of the gross tumor or less than 50% reduction of the tumor size within three to six months after radiation therapy. The research assistant identified all the files from the medical records of patients treated from January 2014 to December 2014. All needed information was extracted from the patients' files into the data collection form during working from Monday to Thursday.

Data were recorded and stored in a computer which had a special password for data security and confidentiality. Only supervisors, PI and research assistants were permitted to get access to use the patient's information.

2.6.2 Data quality control

The data obtained were coded, edited and cleaned prior to statistical analysis. Additional internal documentations such as variables and value labels were added and the necessary additional variables were created through algebraic or logical expressions. Data capture sheet was pre-tested to improve consistency. Data were double entered and checked to control errors.

2.6.3 Data analysis

Data entry and analysis were processed using Statistical Package for Social Sciences (SPSS) computer software version 21. Socio-demographic and clinical factors were analyzed by using frequency and percentage as well as mean and standard deviation. The univariate and multivariate regression analysis were performed to determine the association between

dependent variables and independent variables. An association was regarded as statistical significance when the p-value was less than the significance level of 0.05 i.e. $P < 0.05$.

During analysis of association, the dependent variables were persistent disease and progressive disease while the independent variables were socio-demographic factors, FIGO stage of the disease, Histopathological type of the disease, clinical manifestations (signs and symptoms), HIV status, hemoglobin level before treatment, hemoglobin level at mid-therapy, KPS performance status, Chemotherapy (cisplatin) received, total dose of radiotherapy received, overall treatment time and waiting time before initiation of treatment.

The study subjects with uterine cervical cancer were grouped according to zones; Northern (Arusha, Manyara, Kilimanjaro and Tanga), Coastal (Dare es salaam, Morogoro,Lindi, Mtwara, Pwani), Central (Dodoma, Singida and Tabora), Lake (Geita,Kagera, Kigoma, Mara, Mwanza, Shinyanga and Simiyu), Southern-highlands (Iringa, Katavi, Mbeya, Njombe, Ruvuma and Rukwa), and Zanzibar (MjiniMagharibi, Northern Pemba, Southern Pemba, Northern Unguja and Southern Unguja (27).

2.7 Dissemination plan

Results obtained from this study are a part of partial fulfilment of the Masters of Medicine in Clinical Oncology and will be presented to Muhimbili University of Health and Allied Sciences (MUHAS). Moreover, the ORCI Authority will have access to use the result and the study in a proper way whenever deemed necessary to do so. The results may also be presented in scientific meetings and published in local and international peer-reviewed journals.

2.8 Ethical clearance

Ethical clearance was obtained from MUHAS Research and Publications Committee.

The permission to conduct the study was required from the Executive Director of ORCI. The Hospital management was informed about the intention of the study and that information provided from the patients' files were confidential. To make certain confidentiality, the names of the patients were not included in the data collection forms. The files were then sent back to Medical Records Department after data extraction.

CHAPTER THREE

3.0 RESULTS

This chapter provides analysis of the findings in relation to the prevalence of uterine cervical cancer progressive and persistent disease after chemo-radiation. Association of socio-demographic factors and other clinical factors with progression and persistence of uterine cervical cancer has been analyzed.

3.1 Socio-demographic characteristics of patients

A total number of 239 women histologically confirmed with uterine cervical cancer were enrolled into the study. The patients were followed up for six months after completion of chemo-radiation. Fifty-four percent (54%) of the patients were between perimenopausal and post menopausal age (46-67years). About 61.5% of the patients were married. In this study 56.4% of all patients with uterine cervical cancer had no formal education whereas 39.8% had primary level of education and only 0.8% had college education. Majority of the patients (77.8%) were peasants (Table 1).

Table 1: Socio-demographic characteristics of patients

Variables		Frequency (N = 239)	Percent (%)
Age (complete years)	< 45	79	33.1
	46 - 67	129	54.0
	> 67	31	13.0
Religion	Christian	135	56.5
	Muslim	104	43.5
Marital Status	Single	9	3.8
	Married	147	61.5
	Widow	56	23.4
	Divorced	23	9.6
	Cohabiting	4	1.7
Education level	No formal education	134	56.1
	Primary education	95	39.8
	Secondary education	8	3.4
	College education	2	0.8
Occupation	Peasant	186	77.8
	Housewife	21	8.8
	Civil Servant	2	0.8
	Self Employed	30	12.5

Residence

A third of the patients with uterine cervical cancer came from the Coastal zone, followed by Southern (17.2%) and the Lake zones (15.5%) as Figure 1 indicates.

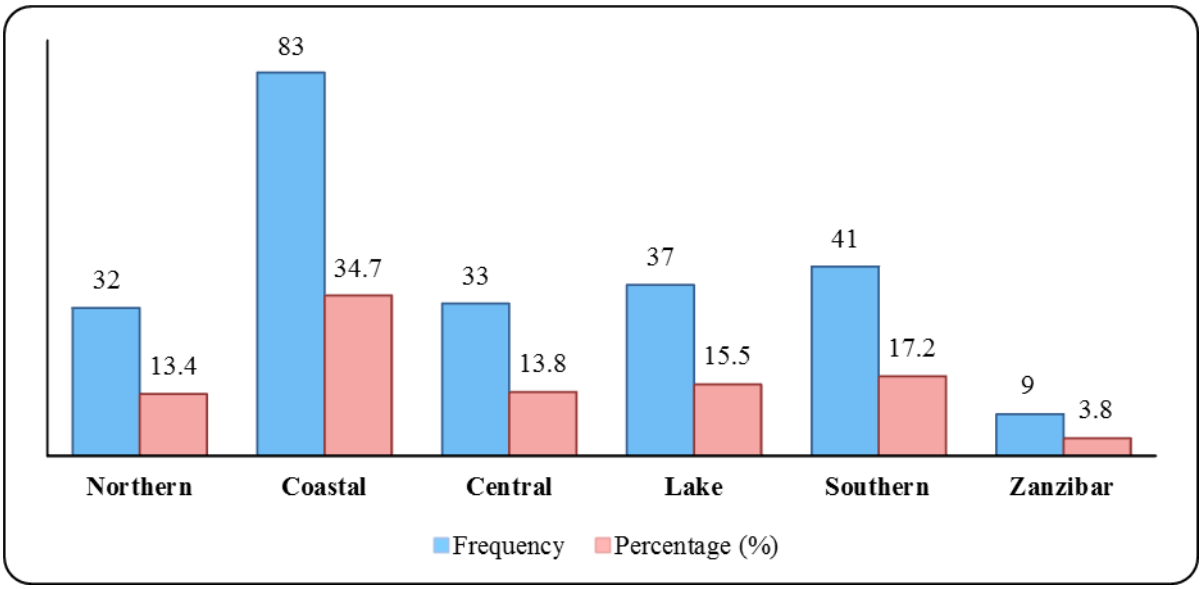


Figure 1: Residence distribution of patients

3.2 Disease characteristics of patients with uterine cervical cancer

Table 2 below presents information on the disease characteristics of patients. Of the 239 patients enrolled, 68.2% presented with disease FIGO stage (II-IIIB) which is an advanced stage and majority had an abnormal vaginal bleeding at presentation (86%). Most (89.1%) of the patients had squamous cell carcinoma as the histological type of cancer. The mean tumor volume was 97.5cm^3 where as the median tumor was 75cm^3. The mean level of hb before therapy was 9.7g/dl, where as the median level was 10g/dl and Most of the patients 64.9% had hemoglobin level of > 9 g/dl before therapy. The mean level of mid-therapy Hemoglobin was 8.9g/dl where as the median level was 8.6g/dl and the majority of the patients 69.3% had Hemoglobin level of < 9g/dl at the mid of therapy. The patients who had hb level of <7g/dl were given blood transfusion and those who had hb level of >7g/dl and <9g/dl were given Iron suppliments.

Approximately 50% of the patients enrolled had good performance status. Of the recruited patients, 51.5% and 30.5% had negative and positive HIV status, respectively. Unfortunately, HIV status was unknown in 18%of patients. The mean time taken from diagnosis to initiation of EBRT was 63days and 54.4% of the patients took more than 45days to the initiation of EBRT.

Table 2: Disease characteristics of patients with uterine cervical cancer

Variable		Frequency(N=239)	Percentage (%)
Presenting symptoms	Abnormal vaginal bleeding	207	86.6
	Post-coital bleeding	14	5.9
	Pelvic pain	2	0.8
	Vaginal discharge	14	5.9
	Dysuria/Incontinence	2	0.8
Disease stage (FIGO)	Early stage (IB-IIA)	76	31.8
	Advanced stage(IIB-IIIB)	163	68.2
Histological types	SCC	213	89.1
	Adenocarcinoma	19	8.0
	Adeno-squamous	7	3.0
Tumor volume	<75 cm^3	121	50.6
	>75 cm^3	118	49.4
Hemoglobin level before therapy	<9 g/dl	84	35.1%
	>9 g/dl	155	64.9%
Hemoglobin level at Mid-therapy	<9 g/dl	160	69.3
	>9 g/dl	79	33.1
Performance status	<80	85	35.6
	>80	154	**64.4**
HIV status	Positive	73	30.5
	Negative	123	51.5
	*Unknown	43	18.0
Time from diagnosis to initiation of EBRT	<45 days	122	51
	>45 days	117	49

**Unknown = Not documented*

3.3 Treatment modalities received by patients

Of the patients included, 96.2% received curative intent of radiation, whereas 3.8% had palliative intent. About 68.2% of the patients who underwent treatment took approximately 35days to complete EBRT, however the mean duration of time taken to complete external beam radiation therapy was 43.5 days. In addition, the intracavitary insertion was performed in 96.7% of patients (6.7Gy per session). The mean BED was 91.3Gy whereby 79.1% of the patients had BED of more than 87Gy. The study revealed that 84.7% patients had received both chemotherapy and radiotherapy whereas 15.9% had received radiotherapy alone, and the number of cycles used was in a range of 3-4cycles, as the addition of more cycles causes more toxicity to the patients.

The mean overall treatment time was 9weeks, where as the median was 6weeks and 2days and about 51.5% had the overall treatment time of more than 8weeks which is the time taken to receive both EBRT and ICT (Table 3).

Table 3: Treatment modalities received by patients

Variables		Frequency (N = 239)	Percent (%)
Radiotherapy dose			
Palliative	30GY/10#/2 weeks	9	3.8
Curative	50Gy/25#/5 weeks	230	96.2
Duration of EBRT	< 35 days	76	31.8
	> 35 days	163	68.2
Intracavitary radiation dose	6.7GY (×3insertions)	231	96.7
	9GY (× 2insertions)	8	3.3
BED	< 87Gy	50	20.9
	> 87Gy	189	79.1
Chemo-radiation	Yes	201	84.1
	No	38	15.9
OTT	< 8 weeks	67	30.5
	> 8 weeks	227	51.5

3.4 Prevalence of progressive disease

Prevalence of progressive disease was 43 (18%) cases and was observed mostly 3-6 months post chemo-radiation (Table 4).

Table 4: Prevalence of progressive disease

Variables		Frequency (N = 239)	Percentage (%)
Progressive Disease	Yes	43	18.0
	No	196	82.0
Time of Progressive Disease post treatment	0-3 months	17	7.1
	3-6months	26	10.9

3.5 Prevalence of persistent disease

Prevalence of persistent disease was 111 (46.4%) cases and was observed at 3 months post chemo-radiation (Table 5).

Table 5: Prevalence of persistent disease

Variables		Frequency (N = 239)	Percentage (%)
Persistent Disease	Yes	111	46.4
	No	128	53.6
Time of Persistent Disease post treatment	0-3 months	111	46.5

3.6 Progressive disease and associated factors

Disease stage, hemoglobin level before therapy and time from diagnosis to initiation of radiotherapy had shown strong association to progressive disease. Patients who had advanced disease (IIB-IIIB) had high incidence of developing progressive disease, (*p-value of 0.001)*, same as patients who had hemoglobin level of < 9g/dl before therapy. Additionally, patients who had more than 45 days from diagnosis to initiation of radiotherapy had high incidence of progressive disease *(p-value = 0.021)*.

The patients who received radiotherapy curative dose of EBRT (50Gy/25#5wks) were found to be protective against progressive disease *(p-value =0.049)*. Age, HIV status, histological types, tumor volume, mid-therapy hemoglobin level, BED, chemo-radiation and OTT were not statistically significant towards attaining progressive disease (Table 6).

Table 6: Progressive disease and associated factors

Variables		Progressive Disease		*p-value*
		Yes (%)	**No (%)**	
Age (in complete years)	< 45	15 (34.9)	64 (32.6)	0.55
	45-67	21 (48.8)	108 (55.1)	
	> 67	7 (16.3)	24 (12.3)	
HIV status	Positive	14 (37.8)	59 (37.1)	1.071
	Negative	23 (62.2)	100 (62.9)	
Histology	S.C.C	36 (83.6)	177 (90.3)	0.122
	Adenocarcinoma	3 (7.0)	16 (8.2)	
	Adeno-squamous	4 (9.4)	3 (1.5)	
Early stage	IB - IIA	7 (16.3)	69 (35.2)	0.001
Advanced stage	IIB - IIIB	36 (83.7)	127 (64.8)	
Tumor volume (cm^3)	< 75	18 (41.9)	103 (52.6)	0.206
	> 75	25 (58.1)	93 (47.4)	
Hb before therapy	< 9g/dl	25(58.1%)	59(30.1%)	
	> 9 g/dl	18(41.9%)	137(69.9%)	0.001
Hb at mid therapy	< 9g/dl	37 (94.9)	107 (61.5)	0.165
	> 9g/dl	2 (5.1)	67 (38.5)	
Time from diagnosis to initiation of Radiotherapy	< 45 days	13 (35.1)	52 (48.6)	0.021
	> 45 days	24 (64.9)	150(51.4)	
EBRT dose	30Gy/10#2wks	4 (10.8)	4 (3.7)	0.049
	50Gy/25#5wks	33 (89.2)	103 (96.3)	
HDR-ICT	6.7Gy × 3	42 (97.7)	189 (96.4)	0.534
	9Gy × 2	1 (2.3)	7 (3.6)	
BED	< 87Gy	12 (27.9)	38 (19.4)	1.61
	> 87Gy	31 (72.1)	158 (80.6)	
CRT	Yes	31 (83.8)	86 (80.4)	0.14
	No	6 (16.2)	21 (19.6)	
OTT	< 8 weeks	6 (16.7)	25 (24.5)	0.056
	> 8 weeks	30 (83.3)	77 (75.5)	

In multivariate analysis, disease stage and time from diagnosis to initiation of radiotherapy were significantly associated with progressive disease; *p-value < 0.05* and *OR* of 2.801 and 4.697 respectively. However, there was no significant association between hb before therapy with progressive disease (Table 7).

Table 7: Progressive disease and associated factors (multivariate analysis)

Variables	OR	95%CI for OR		p-value
		Lower bound	Upper b	
Disease stage	1.991	1.415	2.801	0.000
Time from diagnosis to initiation of radiotherapy	2.265	1.092	4.697	0.028
Hb before therapy	0.347	0.077	1.567	0.169

3.7 Persistent disease and associated factors

Patients with tumor volume of more than 75 cm^3 had high incidence of persistent disease; 70 (63.1%) cases had persistent with 1.934 times to develop persistent disease. The trend shows that the bulkier the disease the high incidence of persistent disease.

The study has reported a strong association between radiotherapy waiting time post diagnosis, overall treatment time and incidence of persistent disease *(p-value =0.000).* This study revealed no association between hemoglobin level before therapy and cervical cancer persistent disease among the patients studied (*p-value of 0.279).* However patients that had mid-therapy Hb of <9g/dl had persistent disease (86.5%) that was highly significant statistically compared to patients that had mid-therapy Hb of >9g/dl *(p-value =0.000).*

The patients who received concurrent chemo-radiation were 0.338 less likely to have persistent disease compared to those who received radiotherapy alone *(p-value =0.004).*

Clinical factors such as disease stage, histology type, HIV status, EBRT prescription dose, biological effective dose and social demographic factors statistically were not significant towards having persistent disease (Table 8).

Table 8: Persistent disease and associated factors

Variables		**Persistent Disease**		***p-value***
		Yes (%)	**No (%)**	
Age (in years)	< 45	35 (30.2)	22 (36.1)	0.352
	45-67	49 (59.0)	34 (55.8)	
	> 67	9 (10.8)	5 (8.1)	
HIV status	Positive	46 (49.5)	27 (26.2)	0.131
	Negative	47 (50.5)	73.8 (73.2)	
Histological type	SCC	114(88.3)	99(89.8)	0.123
	Adenocarcinoma	10 (9.0)	9 (7.0)	
	Adeno-squamous	3 (2.7)	4 (3.2)	
Early stage	IB - IIA	30 (27.0)	46 (35.9)	0.141
Advanced stage	IIB - IIIB	81 (73.0)	82 (64.1)	
Tumor volume (cm^3)	< 7 5	41 (36.9)	80 (62.5)	<0.0001
	> 75	70 (63.1)	48 (37.5)	
Hb before therapy	< 9g/dl	43(38.7)	41 (32.0)	0.279
	>9 g/dl	68(61.3)	87 (68.0)	
Hb at mid therapy	< 9g/dl	95 (85.6)	65 (50.8)	<0.0001
	> 9g/dl	16 (14.4)	63 (49.2)	
Time from diagnosis to initiation of	< 45 days	40 (36.0)	82 (64.1)	<0.0001
	> 45 days	71 (64.0)	46 (35.9)	

radiotherapy				
EBRT dose	30Gy/10#/2wks	6 (5.4)	3 (2.3)	0.228
	50Gy/25#/5wks	105 (94.6)	125 (97.7)	
HDR-ICT	6.7Gy × 3	108 (97.3)	123 (96.1)	1.463
	9Gy × 2	3 (2.7)	5 (3.9)	
BED	< 87Gy	26 (23.4)	24 (18.8)	0.376
	> 87Gy	85 (76.6)	104 (81.2)	
CRT	Yes	85 (76.6)	116 (90.6)	0.004
	No	26 (23.4)	12 (9.4)	
OTT	< 8weeks	16 (15.4)	51 (41.5)	<0.0001
	> 8 weeks	88 (88.4)	72 (58.5)	

Time from diagnosis to initiation of radiotherapy, mid-therapy Hb level, chemo-radiation, and OTT have shown association to persistent disease in multivariate analysis with statistical significance, where *p-value<0.05* and *OR* were 2.21, 0.201, 2.971 and 3.283, respectively. However, there was no association between tumor volume with persistent disease (Table 9).

Table 9: Persistent disease and associated factors (multivariate analysis)

Variables	**OR**	**95%CI for OR Lower bound**	**Upper bo**	**p-value**
Time from diagnosis to initiation of radiotherapy	2.21	1.061	3.919	0.013
Tumor volume	0.043	0.960	3.638	0.066
Mid-therapy Hb	0.201	0.105	0.520	<0.0001
CRT	2.971	1.234	7.281	0.015
OTT	3.283	1.423	7.211	0.002

CHAPTER FOUR

4.0 DISCUSSION

Cervical cancer is one of the leading malignancies in Tanzania, ranking number one in all cancer patients admitted at our institute. This study recruited 239 cases who received chemo radiation between January-December 2014.

The majority 54% of the cases were aged 45-67 years, this was similar to the retrospective study done by Wabanga et al in Kampala and by Nandi et al India whereby majority of the women were middle aged in 4^{th} and 5^{th} decade of their lives (3, 14).

An advanced age has been associated with high morbidity which can result in poor outcome of therapy. However in our study we found no significant statistical association between age and progressive disease *(p-value = 0.550)* or persistent disease (*p-value = 0.352*) in our study. This was contrary to study done by Yale et al that showed those patients who were above 54yrs were more likely to develop progressive disease (18).

One-third of patients came from the Coastal zone while Zanzibar had the lowest (3.8%) number of patients which was similar to the previous studies done at ORCI by Majinge et al (25) and Swai et al (28). The high peak at the Coastal zones could be explained by the effective and specialized cervical cancer screening and treatment at ORCI as well as Muhimbili national Hospital which are located in Dar es Salaam.

This study found that the progressive disease rate was 18% among patients who received chemo-radiation. This findings were similar to a study done by Nandi et al in India that revealed 16% of the cases had progressive disease post chemo-radiation (14).

It was found that progressive disease after chemo-radiation was significantly associated with disease stage and increased waiting time from diagnosis to the initiation of radiotherapy. However, it was seen that tumor volume, hemoglobin level before therapy, mid-therapy hemoglobin level, use of concurrent chemoradiation and overall treatment time was not significantly associated with progressive disease.

On the otherhand, persistent disease rate observed from our study was (46.4%) nearly four-times greater compared to12% reported in a study done Nandi et al (14).

Another study done in India on Radical radiotherapy treatment of cancer of cervix revealed 28.97% had local residual disease after treatment and this was associaed with increased stage (20).

The observed high prevalence of persisent disease in the current study could be attributed to the high proportion of patients presenting with advanced stages in our set up compared to other regions.

Persistent disease was strongly associated with low hemoglobin level at mid-therapy, time from the diagnosis to the initiation of radiotherapy, use of concurrent chemo-radiation as well as overall treatment time. It was seen that disease stage and hemoglobin level before therepy was not significantly associated with persistent disease.

Squamous cell carcinoma was the most common histopathology (89%) reported. Other studies had similar finding (20).

Univariate analysis revealed that histology had no significant statistical difference neither in progressive disease *(p-value=0.122)* nor in persistent disease *(p-value =0.940)*. This finding was contrary to a study done by Hadjimichael et al on histological and clinical characteristics associated with rapidly progressive invasive cervical cancer which revealed more than 50% patients had SCC (18).

Nearly 68.2% of the patients in the study presented with locally advanced stage (stage IIB-IIIB) at the time of diagnosis and was similar to the previous studies where by most of the patients presented to the hospital with stage IIB and stage III (15,25,28). This could be explained by the fact that most affected women were illiterate and they do not understand the diseases process implication, and therefore come to the hospital when the disease is already advanced.

Univariate analysis recorded a strong statistical association between disease stage and progressive disease *(p-value=0.001).*This was also observed in multivariate analysis that demonstrated a significant association between disease stage and progressive disease. The findings were supported via the study done by Nandi et al which revealed those patients who had advanced stages had progressive and residual disease (14). However the current study showed no significant association between disease stage and cervical cancer persistent disease.

Of the respondents, 64.9% had hemoglobin level of more than nine gram per decilitre before therapy. It was seen that hemoglobin level before therapy had no significant association with progressive disease. This was contrary to a study done by Juergen Dunsten et al that revealed the significant impact of pre-treatment anemia and relapse rate of cervical cancer (22).

In the current study 69.3% of the patients had mid-therapy hemoglobin level of < 9g/dl. It found out that mid-therapy hemoglobin level was significantly associated with persistent disease. This was seen in a study done by Juergen Dunsten et al on impact of anemia and pattern of relapse where the mid-therapy hb level of < 11g/dl had the strongest impact the local failure rate and survival of cervical cancer patients post chemo-radiation. It also showed that the local failure was high (67%) in the patient who had mid-therapy Hb level less than 11g/dl (22). However, this finding did not surprise us since oxygenation is an important factor of the tumor microenvironment and has a significant impact on tumor response during therapy. The study revealed that mid-therapy hemoglobin level had no significant association with progressive disease.

In this study majority (96.2%) of patients received the curative radiotherapy. However, there was no association between radiotherapy curative dose and progressive or persistent disease. This was due to the fact that majority of the patients were treated with the same curative dose and very few patients were treated with palliative doses.

Majority (84.1%) of patients had used radiotherapy concurrent with chemotherapy. This finding was also reflected in a previous study done at ORCI where about 84% had used combination of chemotherapy and radiotherapy (28). In the current study there was a

significant association between CRT and persistent disease. The patients who used CRT had 0.338 less likely chance of developing persistent disease compared to those who had radiotherapy alone. This was also seen in an Indian study where CRT has shown to have good pelvic control (19).

Another study done by Morris et al in Massachusetts proved that concurrent chemo-radiation has better clinical outcome for cervical cancer patients (29).

However, the use of CRT was not significantly associated with cervical cancer progressive disease.

Majority 51% took less than forty five days from the diagnosis to initiation of radiotherapy. The mean duration of time taken from diagnosing patients to initiation of treatment was 63 days (2 months). However, time taken from diagnosis to initiation of radiotherapy was significantly associated to both uterine cervical cancer progressive and persistent disease.

Of the respondents 51.5% had the overall treatment time of more than eight weeks (56 days). It was also seen that OTT had significant association with persistent disease. It was supported by a study done by Song et al on the effect of treatment time in locally advanced cervical cancer where treatment time of more than 56 days had contributed to pelvic failure (30). However, OTT had no significant association with progressive disease.

Tumor volume of less than seventy five cubic centimeters was seen in 50.6% of the patients. It was observed that tumor volume was neither statistically significant to cervical cancer progressive disease nor persistent disease. This was supported in a retrospective analysis that was conducted in Japan by Daisuke Endo et al on prognostic factors for patients with cervical cancer after chemo radiotherapy and revealed that tumor diameter of more than six centimeters was associated with poor survival (31).

4.1 Study limitations

The present study had the following limitations:

1. There was no immediate clinical and sonographic assesment one month post radiotherapy,patient evaluation was done three month or more after completion of therapy.This resulted that the persistent lesions could not be picked up early where intervention of therapy could have been done.
2. Ultrasound was the only feasible imaging tool used during staging, restaging and therapy response assessment, which may underestimate the evaluation/detection of the persistence or disease progression
3. Retrospective nature of the study, some of the important information like HIV status and Performance status were missing in the files.

CHAPTER FIVE

5.0 CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Majority of the patients with Uterine cervical cancer who attended ORCI were of more than forty five years of age. However, most of them presented with advanced disease stage and took more time to wait for initiation of radiotherapy ,however hemoglobin level of more than nine gram per deciliter before treatment reduces the risk of developing progressive disease. In this study waiting time from the diagnosis to initiation of radiation was found to be a significant reason for persistent disease. While the overall treatment time with radiotherapy of more than eight weeks significantly contributed to increased incidences of persistent disease, concurrent chemo-radiation with weekly Cisplatin proved to reducing it. It also found that Persistent disease had significant association with low hemoglobin level at the mid-therapy. The lower volume of the tumor was protective for persistent disease.

5.2 Recommendations

1. Emphasize on early cervical cancer screening to pick up the disease at earlier stages as well as strengthening referral system once the diagnosis is reached, so that the patient can reach cancer institute early for therapy.
2. Educating primary health workers on the risks and symptoms of disease so as to transfer patients at earlier stages of disease and that it is curable at earlier stage and disease is also preventable.
3. ORCI needs its own diagnostic imaging tools (CT, MRI, PET / CT) so as to improve diagnosis, disease staging, re-staging and treatment response assessment.
4. Evaluating haemoglobin level before and during the course of the therapy is very important as well as correcting anaemia.
5. Concurrent chemo-radiation should be used along with radical radiotherapy in locally advanced disease to improve outcome.
6. Availability of more cancer treatment machine is crucial in our country to reduce the overall treatment time and waiting time.
7. Further studies are required to analyse treatment outcome and survival of the patients with cervical progressive and persistence disease.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J. Global Cancer Statistics , 2012. CA CANCER J CLIN. 2015;65(2):87–108.

2. Quinn M, Babb P, Jones J, Allen E. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. BMJ. 1999;318(7188):904–8.

3. Wabinga H, Ramanakumar A V, Banura C, Luwaga A, Nambooze S, Parkin DM. Survival of cervix cancer patients in Kampala, Uganda: 1995-1997. Br J Cancer. 2003;89(1):65–9.

4. World Health Organisation. Comprehensive Cervical Cancer Control. WHO Libr Cat Data. 2014;364.

5. Hawes SE, Critchlow CW, Faye Niang MA, Diouf MB, Diop A, Toure P, et al. Increased risk of high-grade cervical squamous intraepithelial lesions and invasive cervical cancer among African women with human immunodeficiency virus type 1 and 2 infections. J Infect Dis. 2003;188(4):555–63.

6. Vincent T. Devita, Samuel Hellman SAR. Principles and practice of Oncology. 6th editio. Lippincont, editor. 1095 p.

7. Sorbe B, Bohr L, Karlsson L, Bermark B. Combined external and intracavitary irradiation in treatment of advanced cervical carcinomas: predictive factors for local tumor control and early recurrences. Int J Oncol. 2010 Feb;36(2):371–8.

8. Hussein Mwinyi H. the United Republic of Tanzania Standard Treatment Guidelines and Essential Medicines List Ministry of Health and Social Welfare Fourth Edition. 2013;42–3.

9. Partridge EE, Abu-Rustum NR, Campos SM, Fahey PJ, Farmer M, Garcia RL, et al. Cervical Cancer Screening. J Natl Compr Cancer Netw. 2010;8(12):1358–86.

10. Lim S, Lee S-H, Lee KB, Park C-Y. The influence of number of high risk factors on clinical outcomes in patients with early-stage cervical cancer after radical hysterectomy and adjuvant chemoradiation. Obstet Gynecol Sci. 2016;59(3):184–91.

11. Hansen EK, Roach M. Handbook of evidence-based radiation oncology. Radiation Oncology. 2010. 57-65 p.

12. Baskar R, Lee KA, Yeo R, Yeoh K-W. Cancer and radiation therapy: current advances and future directions. Int J Med Sci. 2012;9(3):193–9.

13. Spierer MM, Landau EM. CNS Lymphoma. Decision Making in Radiation Oncology volume 2. 2011. 895-922 p.

14. Nandi M, Mandal A, Asthana A. Retrospective analysis of patients with cancer of the cervix attending a radiotherapy outpatient department: experience from a university-based hospital in eastern Uttar Pradesh, India. South African J Gynaecol Oncol. 2015;7(1):5–12.

15. Jacobs AJ, Faris C, Perez CA, Kao MS, Galakatos A, Camel HM. Short-term persistence of carcinoma of the uterine cervix after radiation. An indicator of long-term prognosis. Cancer. 1986;57(5):944–50.

16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours : Revised RECIST guideline (version 1 . 1). Eur J Cancer. 2008;45(2):228–47.

17. Liu S-P, Yang J-X, Cao D-Y, Shen K. Analysis of 30 patients with persistent or recurrent squamous cell carcinoma of the cervix within one year after concurrent chemoradiotherapy. Cancer Biol Med. 2013;10(4):227–31.

18. Hadjimichael O, Janerich D, Lowell DM, Meigs JW, Merino MJ, Schwartz PE. Histologic and clinical characteristics associated with rapidly progressive invasive cervical cancer: a preliminary report from the Yale Cancer Control Research Unit. Yale J Biol Med. 1989;62(4):345–50.

19. Perry W, Grigsby, M.D IZ. In Vitro Chemoresponse to Cisplatin and Outcomes in Cervical Cancer. Gynaecol Oncol. 130(1):188–91.

20. Jain, Vandana; Singh, Kailash; Shrivastava, Rajeev; Saumsundara, KV; Sarje, Mukund; Jain S. Radical radiotherapy treatment (EBRT + HDR-ICRT) of carcinoma of the uterine cervix: Outcome in patients treated at a rural center in India. 2007;3(4).

21. Yoon HI, Cha J, Keum KC, Lee HY, Nam EJ, Kim SW, et al. Treatment outcomes of extended-field radiation therapy and the effect of concurrent chemotherapy on uterine cervical cancer with para-aortic lymph node metastasis. Radiat Oncol. 2015;10(1):18.

22. Dunsten Juergen et al. Images in Anemia in cervical cancers_ Impact on survival, patterns of relapse, and association with hypoxia and angiogenesis - International Journal of Radiation Oncology • Biology • Physics. :59–60.

23. Sheibani KM, Alidoosti A, Motlagh AG, Tabatabaeefar M, Ameri A, Anbiaei R, et al. Clinical manifestations and treatment results of patients with cervical cancer: A report from Iran. Iran J Cancer Prev. 2009;2(3):155–8.

24. Xiao Y, Ren Y-K, Cheng H-J, Wang L, Luo S-X. Modified Glasgow prognostic score is an independent prognostic factor in patients with cervical cancer undergoing chemoradiotherapy. Int J Clin Exp Pathol. 2015;8(5):5273–81.

25. Mapigano P, Majinge C. Treatment outcome of cervical cancer patient at Ocean road cancer institute , Dar es salaam,mmed (obs and Gyn) disertation -MUHAS. 2011;(November):1–43.

26. Radical radiotherapy treatment (EBRT + HDR-ICRT) of carcinoma of the uterine cervix: Outcome in patients treated at a rural center in India Jain VS, Singh KK, Shrivastava R, Saumsundaram K V, Sarje MB, Jain SM - J Can Res Ther.

27. Wikipedia F. Regions of Tanzania. 2016;

28. Swai C, A. Cervical cancer recurrence among patients treated with external beam and intracavitary radiotherapy at ocean road cancer institute . cervical cancer recurrence among patients treated with external beam and intracavitary radiotherapy at ocean road cancer institute. 2014;

29. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med. 1999;340(15):1137–43.

30. Song S, Rudra S, Hasselle MD, Dorn PL, Mell LK, Mundt AJ, et al. The effect of treatment time in locally advanced cervical cancer in the era of concurrent chemoradiotherapy. Cancer. 2013;119(2):325–31.

31. Endo D, Todo Y, Okamoto K, Minobe S, Kato H, Nishiyama N. Prognostic factors for patients with cervical cancer treated with concurrent chemoradiotherapy : a retrospective analysis in a Japanese cohort. J Gynecol Oncol. 2015;26(1):12–8.

APPENDICES

Appendix I: Data Collection Form

1. Form number…….
2. File number…….
3. Age……
4. Residence……..
5. Religion…….
6. Marital status: (a) Single (b) Married (c) Widow(d)Divorced (e) Cohabiting
7. Level of education: (a) No formal education (b) Primary (c) Secondary (d) College (e) Others……
8. Occupation: (a) Peasant (b) Housewife (c) Student (d) Employed (e) Self-employed (f) Unknown
9. KPS……..
10. Symptoms at presentation:
    (a) Abnormal vaginal bleeding (b) Post coital bleeding (c) Pelvic pain
    (d) Foul vaginal discharge (e) Dysuria/incontinence (g) Others (specify)……..
11. HIV status: i) Positive ii) Negative iii) Unknown
12. Presence of co-morbidity: i) Yes ii) No
13. Which co-morbidity? i) HT ii) DM iii) Others (specify).....
14. Type of histology:
    (a) Squamous cell (b) Adenocarcinoma (c) Adeno-squamous(e) others …….
15. Speculum examination: i) beforetreatment.....
    ii) After treatment:.....
16. Tumor size (volume) before treatment (ultrasound):……..mm.
17. Tumor size (volume) after treatment >3momths (ultrasound):…….mm.
18. Disease stage: ……..
19. Hemoglobin level; (a) at initiation of radiotherapy…….g/dl.
    (b) Mid therapy Hb……..g/dl.

20. Patient received blood transfusion: i) Yes (how many units?)..... ii) No

21. Time of initiation of treatment post diagnosis…….(Specify how many days).

22. External beam irradiation dose: (a) 50Gy (b) Others (specify) …….

23. Duration of EBRT…..……. (Specify in days)

24. ICBT dose (Point A): (a) 6.7Gy (b) others (specify)

25. Total treatment dose (EBRT + ICBT):……...Gy

26. Duration of total therapeutic time: (a) 5 weeks (b) 8weeks (c) > 8weeks (specify)……...

27. Weekly Cisplatin: (a) Yes (b) No

28. Other type of chemotherapy used: (a) Yes (b) No

28a.If yes, number of cycles and type of chemotherapy used……..

29. Treatment completed? i) Yes. ii) No iii) If No, reason.....

30. Any treatment breaks? i) Yes b) No

30-i) If Yes, how many days with reasons…….

-ii) Time from EBRT to ICT……..

31. Presence of progressive disease: (a) Yes (b) No

32. Presence of Persistent disease: (a) Yes (b) No

33. Presence of symptoms post treatment: (a) Yes (b) No

34.If yes from above, please specify.....

Appendix II: Ethical Clearence

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9th May, 2017

Dr. Faraja C. Kiwanga
MMed. Clinical Oncology
MUHAS.

RE: APPROVAL OF ETHICAL CLEARANCE FOR A STUDY TITLED "PREVALENCE OF CERVICAL CANCER PROGRESSIVE AND PERSISTENT DISEASE AMONG PATIENTS TREATED WITH CHEMORADIATION AT OCEAN ROAD CANCER INSTITUTE."

Reference is made to the above heading.

I am pleased to inform you that, the Chairman has, on behalf of the Senate, approved ethical clearance for the above-mentioned study. Hence you may proceed with the planned study.

The ethical clearance is valid for one year only, from 10th May, 2017 to 9th May, 2018. In case you do not complete data analysis and dissertation report writing by 9th May 2018, you will have to apply for renewal of ethical clearance prior to the expiry date.

Prof. Andrea B. Pembe
DIRECTOR OF POSTGRADUATE STUDIES

cc: Director of Research and Publication
cc: Dean, School of Medicine