

**CERVICAL CANCER RECURRENCE AMONG PATIENTS TREATED
WITH EXTERNAL BEAM AND INTRACAVITARY RADIOTHERAPY
AT OCEAN ROAD CANCER INSTITUTE.**

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**MMed (Clinical Oncology) Dissertation
Muhimbili University of Health and Allied Sciences
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By

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**A Dissertation submitted in (Partial) fulfillment of the Requirements for the Degree
of Master of Medicine in Clinical Oncology of
Muhimbili University of Health and Allied Sciences**

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October, 2014**

CERTIFICATION

The undersigned certifies that he has read and hereby recommends for acceptance of dissertation entitled; **“Cervical cancer recurrence among patients treated with external beam and intracavitary radiotherapy 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.

Dr Khamza Y. Maunda

(Supervisor)

Date

DECLARATION AND COPYRIGHT

I, **Dr. Caroline R. Swai**, declare that this **dissertation** is my own 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

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I would like to thank my supervisor Dr Khamza Maunda for his corporation, dedication to educate, inputs and advice towards development and completion of this study.

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DEDICATION

This study is dedicated to my lovely family.

ABSTRACT

Cervical cancer still represents a significant public health problem with increased incidence of new cases worldwide. Cervical cancer occurs as malignant changes in the squamo-columnar junction in the uterine canal. It is the most common malignancy among Tanzanian women and leading cause of cancer related deaths. Cervical cancer is the first among the top ten cancers at Ocean Road Cancer Institute (ORCI) for the past five years and accounted for 36% of all patients seen at the hospital in 2011. Delayed hospital presentation with advanced disease has led to poor results of treatment. Cervical cancer recurrence after radical treatment has been a major problem to our patients and medical care providers at the institute for the past several years. Percentage of recurrence is still a challenge depending on different risk factors. Unfortunately there is no exact data that show the trend of recurrence in patients.

Objective; to determine cervical cancer recurrence among patients treated with external beam and intracavitary radiotherapy at ORCI.

Methodology; it is a retrospective cross-sectional study design to determine the recurrence among cervical cancer patients after treatment and factors related to it, where retrospective secondary data was obtained from patient medical files and filled into data collection form. The data was collected from September to December 2013. The study was conducted at Ocean Road Cancer Institute, Dar es Salaam the only cancer centre in the country.

Results: 230 patients were studied with a median age of 52 years (range 30-92). Most of them 90(39.10%) were referred to ORCI with disease stage IIB. Disease recurrence was seen in 92 patients (41.1%), the most recurrence site was pelvic area (98.9%). The recurrence rate was significantly associated with overall treatment time.

Conclusion: Most of our patients are diagnosed with locally advanced stage a finding that influences treatment results. Receiving radiotherapy in proper time together with chemotherapy and intensive screening methods may improve treatment results.

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ABBREVIATIONS

AP	Anterior posterior
EBRT	External beam radiation therapy
FIGO	International Federation of Gynecologist and Obstetric
HDR-ICT	High dose rate intracavitary therapy
HPV	Human papilloma virus
IAEA	International Atomic Energy Agency
LINAC	Linear accelerator machine
MUHAS	Muhimbili University of Health and Allied Sciences
ORCI	Ocean Road Cancer Institute
PA	Posterior anterior
SSD	Source skin distance
W.H.O	World Health Organization

DEFINITION OF TERMS

Local recurrence is considered if disease is seen during speculum examination or by radiographic findings in the cervix or parametrium within pelvis more than 6 months since last treatment and was confirmed by histology findings.

Distant recurrence is considered if disease occurred elsewhere outside pelvis more than 6 months after last treatment.

Grays is the unit of absorbed dose from ionizing radiation.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Cervical cancer occur as malignant changes in the squamo-columnar junction in the uterine canal (1). Cervix is the lower part of uterus, composed of dense fibro muscular tissue. It is lined by two types of epithelium and measures about 3cm in length and 2.5cm diameter. The upper two-thirds of cervix lie above the vagina and lower one third lies within the vagina. It can be visualized by speculum during vaginal examination. Cervical cancer is the second most common cancer affecting women worldwide but it occurs more commonly in developing countries (2)

Cervical cancer is most common in women above 40 years and rare in women below 30 years of age; with most deaths occurring in patients in their 50s and 60s. Cervical cancer rates have been raising in developing world and falling in most developed world due to screening programs and proper treatment programs (2).

It is the most common malignancy in Tanzanian women and leading cause of cancer related death due to late hospital presentation with advanced disease that is beyond cure. Cervical cancer is the first among the top ten cancers at ORCI for the past five years and accounted for 36% of all patients seen at the hospital in 2011 (22). Lack of proper management with poor health facilities and socio-economic status are some of the contributing factors. Cervical cancer is one of the most preventable and potentially curable as long as it is detected early and managed effectively (2).

Many risks factors have been associated with development of cervical cancer and most of patients tend to have multiple risks. The most common risk is persistent exposure to human papilloma virus (HPV), an oncogenic virus. Others include promiscuous male partners, poor genital hygiene, multiple sexual partners, early age at sexual intercourse, poor socio economic status, multiparity and immunosuppression (1)(3).

Patients usually present to hospital with abnormal vaginal bleeding in the reproductive age, post menopausal or can be with lower abdominal pain and backache.

1.1.1 Staging and treatment of cervical cancer

Cervical carcinoma has several stages, stage I disease is confined to cervix and measured less than 4 cm. For stage II the disease is seen in the upper two thirds of vaginal wall and parametrium. Involvement of lower one third of vaginal wall and pelvic wall it accounts for stage III cervical carcinoma. Stage IV is disease beyond the pelvis which may involve the rectum, bladder or any other site.

At ORCI cervical cancer patients are initially treated with external beam irradiation to the pelvis which is obtained through cobalt 60 unit with SSD 100cm. The field is 15 by 15 cm to 15 by 18 cm with AP/PA parallel opposing ports.

Then high dose rate intracavitary therapy (HDR-ICT) is given either one week after completion of external beam dose or during the course of external beam after receiving the first ten fractions of external beam the patient can get ICT weekly till she had three sessions. On the day she's getting weekly HDR-ICT she won't be able to have external beam together. The HDR-ICT source is Cobalt 60 and the standard dose per fraction is 6.7Gy in three insertions or 9Gy in two insertions are given to point A.

After completion of treatment patient is regularly followed up every 3months for first six months then every six months up to second year then yearly. Clinical examination is usually done, cervical examination by speculum together with chest radiography and abdominal pelvic ultrasound at each follow up visit. Recurrence is detected by development of signs and symptoms related to site or by evidence of metastasis during follow up routine investigation and has to be confirmed by histology.

The treatment course for recurrent cervical cancer depends on many factors including treatment the patient received previously, overall condition of the patient and location of recurrence. Some patients with recurrence within the pelvis can be treated with radiation, if no radiation therapy was used before. Once the patient has received prior radiation therapy to the pelvis, more radiation cannot be given to the same area. Recurrence of cervical cancer outside the pelvis is difficult to treat, as they may receive chemotherapy or radiation to alleviate symptoms.

Published studies suggest that management of locally advanced cervical cancer is radiotherapy, which can be delivered through external beam radiotherapy followed by intracavitary brachytherapy (3). Intracavitary brachytherapy is important element in curative treatment of cervical cancer. The purpose of intracavitary brachytherapy is to deliver high dose radiation to the tumour while sparing the normal surrounding tissues.

The high dose rate intracavitary brachytherapy was installed at ORCI hospital in 2011 for treatment of cervical cancer. As a result a significant number of women have received definitive treatment. It is the only hospital with radiotherapy equipment, planned to serve all patients from all over the country.

1.2 Literature Review

New approaches have been developed for management of cervical cancer which offer benefit in terms of better quality of life and longer survival period. The current approach is non surgical for advanced local cervical cancer, a combination of radiation and chemotherapy. This protocol control local and distance disease and decrease mortality rate and failure rates (4).

A study was done in Japan to evaluate pattern of failure in cervical cancer patients after definitive radiotherapy alone. In this study pelvic failure reported to be the most common site of failure followed by Para aortic lymph nodes (5).

Another retrospective study was done in India to evaluate treatment results after radical radiotherapy in 342 cervical cancer patients. Local recurrence was detected in 18 patients(5.26%) and 27(7.9%) patients had distant metastasis (6).

Predictive factors for local tumour control and early recurrences were evaluated in Sweden. Brachytherapy dose, combined external and brachytherapy dose and number of days of interruption or delay of external radiation were all significant predictive factors of local tumor control. Squamous cell histology, lower FIGO stage, more brachytherapy fractions were favorable risk factors for recurrent disease (7).

One study from Taiwan which used high dose rate brachytherapy to report treatment results concluded that using a three fraction scheme survival rate appeared comparable with the existing results of low dose rate with central regional recurrence and distant metastasis (8).

Treatment results of patients with cervical cancer from Iran were retrospectively evaluated. The most frequent site of recurrence was pelvic area. Recurrence was more frequent if the radiotherapy dose was less than 50 Gy and also in patients treated with four field technique (9).

Another experience from Iran to determine local recurrence and distant metastasis suggested that 50 Gy to the whole pelvis together with three fractions of 10 Gy brachytherapy was an effective schedule in the treatment of locally advanced cervical cancer (10).

Outcome of patients treated at a rural center in India after radical radiotherapy showed 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. Most recurrence were at primary site and recurred within two years of treatment completion (11).

In treatment of cervical cancer patients from USA with radiation therapy alone it was found that higher dose of irradiation delivered to the medial and lateral parametrium with external beam and intracavitary radiation were correlated with a lower incidence of parametrial failures in all stages (12).

A study from USA to determine relationship between radiation field and recurrence showed that most regional recurrence include a component of marginal failure, usually immediately superior to radiation field. Median time to regional recurrence was thirteen months (13).

A retrospective study from India by Saibishkumar et al (14) to find results of radiotherapy alone found that in developing countries, where chemo radiation can be afforded by a minority, judicious use of radiotherapy still produces satisfactory results with acceptable toxicity. The addition of chemotherapy may be beneficial in patients with adverse prognostic factors (14).

A study by Patel FD et al from India to determine high dose rate brachytherapy in uterine cervical carcinoma found that HDR brachytherapy at 9 Gy per fraction is both safe and effective, with good local control and a minimum of normal tissue toxicity (15).

A retrospective study to determine pelvic recurrence rate following three fractions of brachytherapy showed that using a three fraction scheme, HDR brachytherapy is safe and effective in management of cervix cancer (16).

A retrospective study from Italy to determine pattern of failure and value of follow up procedures for cervical cancer found that no statistically significant differences were found in survival of cervical cancer patients between the symptomatic and asymptomatic group. The vast majority of recurrences occurred within the first three years after primary treatment. (17).

The impact of anemia and relapse in cervical cancers was investigated where tumour oxygenation and hemoglobin level at 0Gy and 19.8Gy was measured. It was found that midtherapy hemoglobin level at 19.8Gy has significant impact on local failure rate and the presence of anemia before treatment of cervical cancer had a strongest impact on relapse rate (18).

A systematic review and meta analysis to determine survival and recurrence after concomitant chemo radiation found that it improves overall and progression free survival and reduces local and distant recurrences in selected patients which may give a cytotoxic and sensitization effect (19).

A study done to detect which tools were helpful in detection of recurrent cervical cancer and the percentage which is detected during follow up diagnosed that 45% were due to self referral. Presence of symptoms (87%) was most important first test results that leads to diagnosis of recurrence (20).

A study was done at ORCI to determine treatment outcome of cervical cancer patients. It was found that most patients present late to the hospital with advanced disease and most of them received external beam alone, while a small proportion received combination therapy of radiation and chemotherapy (21).

An American study done to evaluate therapeutic implications of patterns in cervical cancer showed that majority of recurrence occurred within the first two years after treatment. The most common site for recurrent was pelvic. Incidence of tumor recurrence was directly related to initial tumor stage, cell type, and lesion size (23).

Another study was done by Lanciano RM et al to find the influence of treatment time on outcome of squamous cell cancer of uterine cervix treated with irradiation therapy. This study demonstrates a significant adverse effect on pelvic control and survival on prolongation of overall treatment time for stage III in multivariate analysis (24).

The American brachytherapy society recommends the treatment for locally advanced cervical cancer to not exceed eight weeks for better local control of tumor and survival (25)

Another study to find the adverse effects of treatment prolongation in cervical carcinoma recommends avoidance of unnecessary breaks during treatment, possibly use of cytostatic drugs during conventional radiation to improve local control and survival (26).

Treatment time prolongation is still negatively influencing pelvic control as a result done from Chen SW et al. Other prognostic factors found were stage and tumor response to radiation. (27)

The study from Morocco to investigate the factors associated with delayed diagnosis of cervical cancer as measured by stage at diagnosis and delay between first symptom and diagnosis of cancer. It describes different demographic, socioeconomic and medical characteristics of patient and their relation to diagnosis stage (28)

Another study performed to evaluate treatment results, prognostic factors and complication rates in patients with locally advanced cancer of uterine cervix after radiotherapy with high-dose rate brachytherapy. This study suggests that radical radiotherapy with HDR brachytherapy was appropriate for treatment of local advanced cervical cancer. Also overall treatment time and the response after treatment are prognostic factors (29)

The effect of treatment prolongation in treatment of cervical cancer in rural center India concluded that to achieve better treatment outcome avoid treatment prolongation and overall treatment time should be less than 50 days (30)

The IAEA strategy for limited resources centre suggests that for a locally advanced cervical cancer a dose of 45 to 50Gy from external radiotherapy is required. Prolongation of overall treatment time results in increased failure rate of ~1% per day beyond planned treatment for all stages (31).

A study was done in Kenya to analyze factors affecting response and overall survival in cervical patients undergoing radiotherapy. Late presentation, lack of cancer awareness, poor education, absence of regular screening programs, sub optimal diagnosis and treatment were major factors (32)

Treatment results study of radical radiotherapy in uterine cervical carcinoma was done in Korea. Significant factors for disease free survival were age, FIGO, and overall treatment time of less than 55days has positive impact on pelvic control (33)

Anemia is one of the factors influencing local disease control in patients with cervical carcinoma. Anemia itself is defined as having hemoglobin level below 12g/dl as per WHO classification for non pregnant women (34)

Results from Zimbabwe to evaluate factors associated with tumor stage at presentation in invasive carcinoma of cervix found that no history of prior screening was found to be significantly associated with late tumour stage at presentation (35)

A case control study to determine level of knowledge on basic symptoms for cancer of cervix from Tanzania females and causes of late presentation with advance disease among cancer patients. The result was both cases and control had low knowledge of basic symptoms of cervical carcinoma and as a result most of them happen to have disease reported late at advanced stage (36).

A pilot study done in Mexico to learn about factors that may influence cervical cancer screening found that addressing cultural beliefs, and increasing number of female health care providers to increase compliance with cervical cancer screening (38)

1.3 Problem Statement

Cervical cancer is a leading cause of admission at ORCI, but also the incidence of cervical cancer in developing world is increasing. In developed world treatment of cancer is achieved through modern machines like LINAC and early detection of metastasis using modernized equipments. In poor resource countries we still employ the use of Co 60 teletherapy machine together with brachytherapy. Regardless of proper treatment schedules provided, patients have been diagnosed with recurrent cervical disease on follow up visits after treatment. The magnitude of the problem has been increasing without any supportive data. Possible predictors of recurrence being poor socio economic status that patients can't afford chemotherapy, advanced disease at presentation, type of histology, stage, dose of radiation and others. This study provided necessary information on recurrence and the reasons behind it. Improvement in awareness and education of the people about cervical cancer may increase the detection of disease in early stage and proper treatment rather than palliative.

1.4 Study Rationale

Most of our patients present late to health facilities, with inoperable disease. Recurrent cervical cancer is a devastating disease for those unfortunate women who suffer such an event. Treatment options are limited for patients with recurrent cervical cancer and don't survive their disease. Currently the treatment of these patients includes chemotherapy. Unfortunately a small proportion of patients with recurrent disease responded to chemotherapy treatment. There's limited data on recurrence of cervical cancer especially pattern of recurrence, common histology types and if added chemotherapy has influence on recurrence. No such study has been done at our settings and majority of African countries. This study will help to evaluate recurrence rate, furthermore improving treatment schedules.

Early detection of the localized disease that can be treated properly offers the only chance for complete eradication of disease.

1.5 Research Question

What are the reasons for recurrence of cervical cancer after definitive treatment at ORCI?

1.5.1 Broad Objective

To determine the recurrence rate of cervical cancer among patients treated with external beam and intracavitary brachytherapy at Ocean Road Cancer Institute.

1.5.2 Specific Objectives

1. To determine socio demographic factors among cervical cancer patients attending ORCI.
2. To determine the disease profile among cervical cancer patients attending ORCI.
3. To determine treatment modalities among cervical cancer patients attending ORCI.
4. To determine the recurrence rate of cervical cancer after treatment.

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study Design

This is a retrospective cross sectional study design to determine cervical cancer recurrence among patients treated with external beam and intracavitary radiotherapy at ORCI where secondary data obtained from patient's medical records were used.

2.2 Study Setting

The study was conducted at ORCI, the only cancer centre in the country. It serves all cancer patients from all over the country and neighborhood. It is located along the shore of Indian Ocean on eastern side of the specifically in Dar es Salaam region. The hospital can accommodate up to 270 in patients. It runs services for inpatient and outpatient care. The services included are screening clinic, palliative care, follow up and new patient clinic, chemotherapy clinic, radiation and nuclear medicine. From 2006 to 2011 cervical cancer has been number one on the list of top ten diseases, account for 36% of all patients seen per year (22). The hospital has two telecobalt units which have elapsed one half life and two brachytherapy units which up to now are not working due to malfunctioning of portable x-ray machine in brachytherapy room.

2.3 Study Population

Women with cervical cancer who were histological proven, treated at ORCI from January 2011 to December 2011 and followed up for at least one year. These patients received external beam with intracavitary brachytherapy. The recurrence from this study was detected clinically and did not include histopathology result which is highly unreliable.

2.3.1 Inclusion criteria

All women with cervical cancer, histological proven results registered for EBRT plus ICT with or without weekly chemotherapy.

2.3.2 Exclusion criteria

Women who have surgery prior to ORCI referral

Women presented with distant metastatic on first visit to ORCI.

Women who were treated with palliative protocol

2.4 Sample Size and Selection

The estimated number of all patients attending at ORCI was about 5000 per year in 2011, whereby cervical cancer patients accounts for about 1881 patients. The sample size for the study of recurrence of cervical cancer among patients treated at ORCI was calculated using a single proportion formula:

$$n = \frac{z^2 p (100 - P)}{\epsilon^2}$$

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 recurrent among treated cervical cancer patients estimated at 17% based on previous study (20)

ϵ = Margin of error set at 5%

$$n = \frac{(2)^2 \times 17 \times 83}{(5)^2}$$

$$n = 225$$

The number of patients recruited was 225. The sample size was increased to 230 to cater for non-response and lost to follow up. Random selection was done using a table of random numbers to obtain them.

2.5 Data Collection

ORCI has medical records department which stores files of all patients attending the hospital. Principal investigator together with assistant of one trained research assistant was recruited. Filling up of data collection form from patients file data was done by the principal investigator and one assistant. After listing the file numbers from registration book, the research assistant

collect and sort out the files. The files of cervical cancer patients who underwent treatment at ORCI during a period of January to December 2011 were collected from medical records. All needed information was extracted from patient files to data collection form. English data collection form was used for data collection.

The assistant was trained for data collection by principal investigator. Data was collected from Monday to Thursday. Pilot study was done to assess the compatibility of data collection form.

2.6 Ethical Clearance

The ethical clearance was obtained from MUHAS Research and Publication Committee. The permission to do the study was sought from the Executive Director of ORCI. Hospital Administration was informed about the purpose of the study and that all information provided from patients files will be confidential. To ensure confidentiality patients names were not included in the questionnaire. The files were returned to medical records department after data extraction from the files.

2.7 Data Analysis

Data was collected from patient's medical records, data entry and analysis were done using Statistical Package for Social Sciences {SPSS}. Continuous data was presented in number (standard deviation). Categorical data presented as frequency or percentage. The bivariate and multivariate regression analysis was done to determine the association between dependent and independent variables. Association between categorical data was done using Chi-square test. The residents of cervical cancer patient were categorized into zone (37). The Northern zone (Arusha, Kilimanjaro, Manyara, Tanga), Coastal zone (Dare s salaam, Lindi, Morogoro, Mtwara, Pwani), Central zone (Dodoma, Singida, Tabora), Lake zone (Geita, Kagera, Kigoma, Mara, Mwanza, Shinyanga, Simiyu), Southern highlands (Iranga, Katavi, Mbeya, Njombe, Ruvuma, Rukwa) and Zanzibar (Mjini magharibi, Pemba north, Pemba south, Unguja north, Unguja south).

CHAPTER THREE

3.0 RESULTS

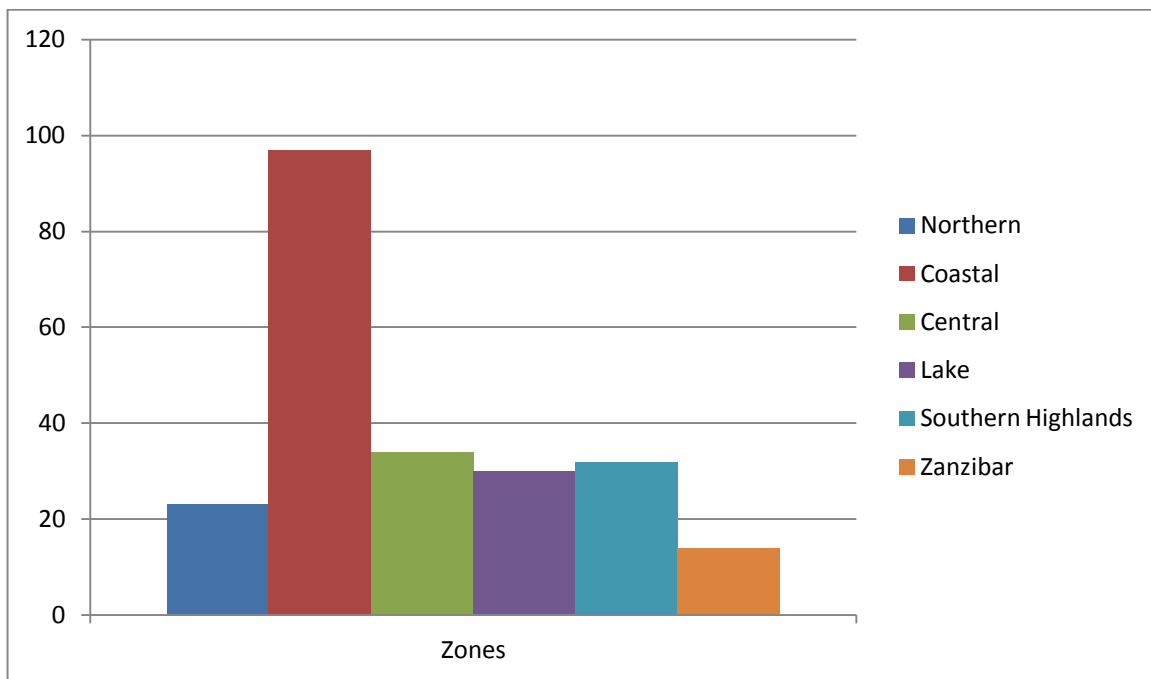
Table1: Socio Demographic Profile of patients with cervical cancer at ORCI (N=230)

Variables	Frequency	Percent(%)
Age group(years)		
21-35	11	4.80%
36-50	108	46.96%
51-65	85	36.96%
≥66	26	11.30%
Religion		
Christian	118	51.30%
Muslim	112	48.70%
Marital status		
Single	5	2.20%
Married	162	70.40%
Widow	33	14.30%
Cohabiting	7	3.00%
Divorced	23	10.00%
Education level		
No formal education	70	30.40%
Primary education	140	60.90%
Secondary education	10	4.30%
College education	10	4.30%
Occupation		
Peasant	138	60.00%
Housewife	45	19.60%
Civil servant	16	7.00%
Self employed	30	13.00%
Unknown **	1	0.40%

**unknown-not documented

A total of 230 women with cervical cancer were enrolled into the study. Majority of these patients were of age group 36 to 50 years, with mean age being 52years (range 30 to 91years). Nearly 70.40% of all women were married. About 60.90% had attained primary education, 30.40% not attended formal education and the rest had secondary and post secondary education. Most of these patients 60% were peasant (Table 1)

Figure 1: Residence of the Cervical Cancer Patients Categorized into Zones in Tanzania



Most of cervical cancer patients seen at ORCI were coming from coastal zone (Dar es salaam, Lindi, Morogoro, Mtwara, Pwani) this could be explained by the fact that all these regions are nearer to Dar es salaam where cancer institute is located so it is easier for referred patients to reach the hospital.

Table 2: Disease Profile among Cervical Cancer Patients at ORCI (N=230)

Variables	Frequency	Percent(%)
Symptoms at presentation		
Abnormal per vaginal bleeding alone	191	83.00%
Post coital bleeding alone	36	15.70%
Foul vaginal discharge alone	69	30.00%
Lower abdominal pain alone	14	6.10%
Disease stage at presentation (FIGO staging)		
IB	13	5.70%
IIA	60	26.10%
IIB	90	39.10%
IIIA	31	13.50%
IIIB	33	14.30%
IVA	3	1.30%
Histology type		
squamouscell	208	90.40%
adenocarcinoma	12	5.20%
adenosquamous	3	1.30%
Others**	7	3.10%
Haemoglobin level		
<12g/dl	145	63.00%
≥12g/dl	85	37.00%

Others**: rare types are anaplastic, mucoepidemoid, neuroendocrine, papillary and small cell carcinoma.

Majority of these patients 90(39.1%) were referred to ORCI with disease stage IIB. The most common pathologic subtypes were squamous cell carcinoma (208 patients, 90.40%) and adenocarcinoma (12 patients, 5.20%). At the time of admission stage IIB (90 patients, 39.10%) and stage IVA (3 patients, 1.3%) had the highest and lowest frequency respectively. The most common presenting symptom was abnormal per vaginal bleeding (191 cases, 83%). All 230 patients had hemoglobin level measured before radiotherapy commencement, 145 cases (63%) had values below 12g/dl and 85cases (37%) had values above 12g/dl with mean value being 11.05 (range 6-19g/dl) (Table 2)

Table 3: Treatment Modalities Received by Cervical Cancer Patients at ORCI

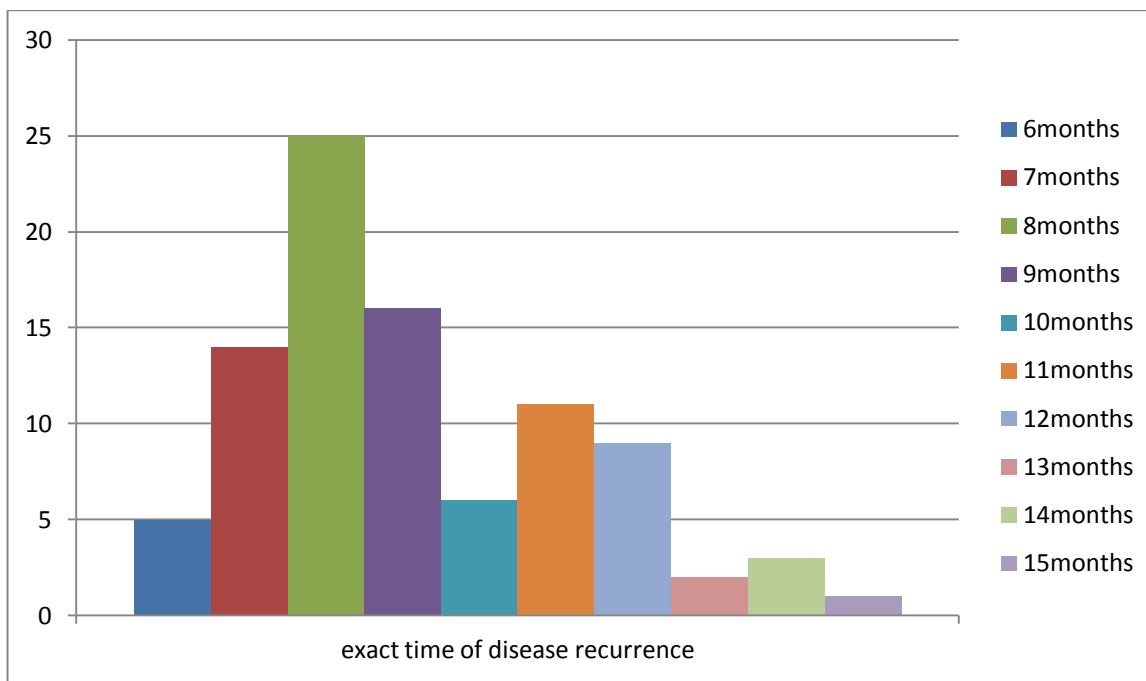
Variables	Frequency	Percent(%)
Prescription of external dose radiation(n=230)		
45Gy/23fractions/4.3weeks	2	0.90%
50Gy/25fractions/5weeks	228	99.10%
Duration to receive external beam radiation(n=230)		
≤35DAYS(or ≤5 weeks)	115	50.00%
>35DAYS(or >5weeks)	115	50.00%
Dose prescription for intracavitary radiation(n=230)		
9Gy in single insertion	4	1.70%
9Gy in two insertions	31	13.50%
6.7Gy in two insertions	13	5.70%
6.7Gy in three insertions	182	79.10%
Overall treatment time(n=230)		
≤8Weeks	27	11.70%
>8Weeks	203	88.30%
Total equivalent dose(n=230)		
60-69Gy	15	6.50%
70-79Gy	215	93.50%
Weeklychemotherapy cycles(n=75)		
Completed 6 cycles	63	84.00%
Not completed 6 cycles	12	16.00%

All 230 patients received the external beam radiation therapy as two opposed field radiotherapy, among them 2 (0.9%) received a prescription dose of 45Gy in 23 fractions for 4.3weeks, and 228 (99.1%) were treated with a dose of 50Gy in 25 fractions for 5weeks. The duration it took for them to receive external beam radiation was either 5 weeks (35 days) or below for 115 cases (50%) and 115 cases (50%) had external beam for more than 35 days. The total equivalent dose was above70Gy for most these cases 93.50%. Among 230 patients, only75 (32.6%) received chemotherapy out of which 69 was cisplatin type of chemotherapy and 6 had carboplatin. Out of 75 who received chemotherapy only 63 had complete 6 cycles of weekly chemotherapy. Most of these cervical cancer patients (203cases, 88.3%) the total number of days spent for both treatment modalities means EBRT and ICT was above 56 days were the mean was 87.22 days (range 44-203 days).(Table 3)

Table 4: Recurrence Rate of Cervical Cancer after Treatment

Variables	Frequency	Percent(%)
RECURRENCE		
YES	92	41.10%
NO	132	58.90%
Pelvic recurrence alone	91	98.90%
No pelvic recurrence	1	1.10%
Lung recurrence alone	5	5.40%
No lung recurrence	87	94.60%
Viscera recurrence alone	7	7.60%
No viscera recurrence	85	92.40%
Brain recurrencealone	1	1.10%
No brain recurrence	91	98.90%
Abdominal lymphadenopathyrecurrence alone	1	1.10%
No abdominal lymphadenopathy recurrence	91	98.90%
Time of recurrence Since last Treatment		
6-9months	60	65.22%
9-12months	26	28.26%
12-15months	6	6.52%

Recurrence rate observed from our study was 92cases (41%). Out of 230 patients, there were 4cases with local residual disease, 2were lost to follow up. The most common site for recurrence was pelvic area 91 cases out of 92, followed by viscera 7 cases. Most of these recurrences occurred during 6 to 9months after completion of treatment. (Table 4)

Figure 2: Exact time of Cervical Cancer Recurrence after Treatment

This figure shows when the recurrence occurred in terms of months from the last treatment time.

Table 5: Disease free Survival, Follow up status, with Pattern of failure (Persistent Disease, Pelvic Recurrence) according to Disease Stage after Radiotherapy

STAGE	TOTAL PATIENTS	DISEASE FREE TILL LAST FOLLOW UP(%)	LOST TO FOLLOW UP	PERSISTENCE DISEASE	PELVIC RECURRENCE AND METASTASIS
IB	13	8 (61.54%)	0	0	5
IIA	60	42 (70%)	0	0	20
IIB	90	55 (61%)	1	0	40
IIIA	31	19 (61.29%)	0	1	14
IIIB	33	15 (45.45%)	1	3	21
IVA	3	0 (0%)	0	0	3

Majority of our patients were in stage IIB. The disease free survival until the last follow up according to stage was good in early stages and decrease as the stage advanced

Table 6: Association between recurrences with Socio Demographic Factors, Disease Profile, treatment Modalities

Variable	Type	Without recurrence (N=132)	With recurrence (N=92)	P value
Level of education(N=224)	No formal education	46	23	0.330
	Formal education	86	69	
Disease stage(N=224)	Stage IB	8	5	0.030
	Stage IIA	42	18	
	Stage IIB	53	36	
	Stage IIIA	16	14	
	Stage IIIB	13	16	
	Stage IVA	0	3	
Hemoglobin level(N=224)	Below 12g/dl	78	63	0.486
	Above 12g/dl	54	29	
Chemotherapy(N=224)	Had weekly chemotherapy	41	33	0.424
	No weekly chemotherapy	91	59	
Duration for external beam radiation(N=224)	≤5weeks	97	18	<0.001
	>5weeks	35	74	
Total equivalent dose(N=224)	<70.1Gy	7	6	0.033
	≥70.1Gy	125	86	
Overall treatment time(N=224)	≤8weeks	24	3	0.006
	>8weeks	108	89	

Table 7: The Multivariate Association Table

	Sig	OR	95% CI
Recurrence			
Duration for external beam radiation ^a	<0.001	0.093	0.048,0.179
Overall treatment time ^b	0.027	0.220	0.058,0.840
Total equivalent dose ^c	0.340	1.968	0.490,7.905

Recurrence=yes, no; Sig = significance; OR = odds ratio; 95% CI = 95% confidence interval;
^a Duration for external beam radiation (< 5weeks,>5weeks); ^b Duration of total therapeutic time (< 8weeks, >8weeks); ^cTotal equivalent dose (<70Gy, >70Gy).

Duration for external beam radiation was found to be significantly associated with recurrence rate. Receiving external beam within five weeks was found to be protective against disease recurrence by 0.093. Overall treatment time of less than 8weeks was significantly found to be protective against cervical cancer recurrence (Table 5)

CHAPTER FOUR

4.0 DISCUSSION

Due to the nature of the study all participants were females who were followed for at least one year after completion of treatment. Majority of patients were of age group 35-50 with a mean age of 52 years. The mean age of study population is inconsistent with many previous studies which showed that the mean age for disease was below 50 years (32)(35)(36).

The most common histology type from our study was Squamous cell carcinoma followed by adenocarcinoma which is in favor with most previous cervical carcinoma studies. Having this type of histology is a good prognosis as it responds well to radiotherapy (7) (21)(35).

At least 60% of these patients had primary level education or below it. Since socio economic status of an individual can be determined by the level of education, these results show that most of these women ended up with early marriages and sexual intercourse, multiparity, poor genital hygiene and poor socioeconomic status as risks factors for development of cervical cancer (1)(3)(28)(32).

The most common site of recurrence was pelvis like other studies shown followed by the viscera as a common extra pelvic site a result from our finding (5)(6)(9).

The recurrence rate was 42% which is high as compared to other studies which is ranging from 5% to 31% (6)(7)(8)(10)(12)(16)(20)(23).

The most important finding from this study was most of our patients presented with locally advanced disease (stage IIB to IVA) at diagnosis which was about 68%. This could be due to poor socio economic status, poor knowledge about the disease and lack of confidence in these poor women that present late to hospital (21)(28)(36).

All of them received external radiation and brachytherapy but the problem was the amount of dose from HDR intracavitary brachytherapy which varied from one insertion of 9Gy, two

insertions of 9Gy, or two to three insertions of 6.7Gy according to prescription from consultant who saw the patient and patient preference. A good percent of cases 215 (93.50%) had total equivalent dose of 70Gy or above but recurrence was high in this group. From this study there was no association between total equivalent dose and recurrence rate although other studies have shown to be significant. This could be corrected by increasing sample size of those who had total equivalent dose of below 70Gy and follow up time and also other factors could be masking the effect like treatment time (7)(8)(15)(16)(29).

Considering the effect of stage on disease recurrence there was no association on recurrence rate from our study. Although more than 39% of patients had locally advanced disease but the distribution of patients was not equally between the groups, this could be a reason for being not significant. This finding can be resolved by the fact that screening program among high risk women could be used as a tool for earlier diagnosis. Most cases present late to hospital. A lot of factors could be attributing to poor screening programs including poor socio economic status, poor access to public health facilities, poor education and lack of knowledge on symptoms and prevention of cervical cancer. Also educating primary caregivers on the risks and symptoms of disease in order to have referrals at earlier stages of disease and that it is curable at earlier stage and disease is also preventable (7)(11)(29)(35)(36)(38).

Since only a few of investigated patients received combination of chemotherapy and radiotherapy 75 cases out of 230 (32.6%) the effect of chemotherapy into recurrence rate was not shown here as many previous studies showed . Since the drugs are provided free by the government at the hospital sometime they run out of stock at the hospital, necessitate the patients to buy the drugs at their own cost. Most of the patients seen at ORCI are coming from poor socio economic status hence most of them cannot afford to buy the chemo drug for treatment (4)(14)(19).

Considering the effect of anemia on the rate of recurrence, the findings from this study shows no significant relation to recurrence. The presence of anemia before treatment has significant impact on relapse rate. Anemia according to WHO definition for non pregnant women means having hemoglobin level below 12g/dl. The severity of anemia ranges from mild (11-

11.9g/dl), to moderate anemia (8-10.9g/dl) and severe anemia (below 8g/dl). From our study the mean value for hemoglobin level was 11.05g/dl and 63% had hemoglobin below 12g/dl.

Tumor hypoxia is a well known factor for response to radiotherapy and poor local regional control. The cancer cells undergo a variety of biological response when placed in hypoxic conditions allowing them to grow and survive. The reason for higher recurrence in anemia is that oxygenation level in cancer tissues becomes lowest hence radiation efficacy becomes lowest also. Lack of proper hemoglobin level data and criteria at our settings are reasons for this (18)(34).

In this study, I found a higher recurrence rate among patients treated with EBRT for more than 35 days or 5 weeks. The same effect was observed for those who had the total therapeutic time more than 56 days or 8weeks, the association was statistically significant which is consistent with many previous studies. The overall treatment time of less than 55days had positive impact on pelvic control and survival rate. Also prolongation of overall treatment time to more than 8 weeks results in an increased failure rate of approximate 1% per day for all stages (7)(24)(25)(30)(31)(33)

From our study most of the cases were followed up for at least a year after completion of treatment and a good recurrence number was seen 6 to 9 months after completion of therapy. Out of 92 recurrences, 60 were seen between six to nine months, which was also seen on other studies were recurrence was within two years after treatment (11)(17)(23).

4.1 Study Limitations

Recurrence was not confirmed by histology, being a poor resource country some other studies need to be done with this confirmation result.

The HIV status was not done to most of my patients hence I couldn't evaluate its role on recurrence.

CHAPTER FIVE

5.0 CONCLUSION

From our study most of the patients present to hospital with locally advanced stage disease (IIB to IVA). A few patients received a combination of chemoradiation. The overall treatment time for most of these cases was above 8weeks which was found to be a significant reason for recurrence.

5.2 Recommendations

The hospital needs proper criteria for recording and correcting anemia before radiotherapy treatment which might have good results in post treatment.

The government must ensure that the screening programs are conducted intensively throughout the country together with mass education. This might improve the stage at presentation or diagnosis to be earlier and might improve the recurrent rate.

Also the government must ensure that the machines available are enough to treat all cancer patients from all over the country. This is the only cancer treatment centre in the country so far with radiotherapy machines. Also must ensure that the chemotherapy drugs are available to patients at hospital and avoidance of unnecessary treatment breakups when the radiation therapy commence.

The institute must make sure that patients start HDR intracavitary brachytherapy after having the first ten fractions from external beam radiation or the booking system for intracavitary therapy should begin as earlier as possible in order to reduce overall treatment time

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APENDIX**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

6. Level of education
 - (a) No formal education
 - (b) Primary
 - (c) secondary
 - (d) College
 - (e) Others.....

7. Occupation
 - (a) Peasant
 - (b) Housewife
 - (c) Student
 - (d) Civil servant
 - (e) Self employed
 - (f) Unknown

8. Symptoms at presentation
 - (a) Abnormal vaginal bleeding
 - (b) Post coital bleeding
 - (c) Foul vaginal discharge
 - (d) LAP
 - (e) Others.....
9. Stage of disease.....
10. Type of histology
 - (a) Squamous cell
 - (b) Adenocarcinoma
 - (c) Adenosquamous
 - (e) others
11. Hemoglobin level at initiation of radiotherapy.....
12. External beam irradiation dose
 - (a) 40-45Gy
 - (b) 46-50Gy
13. Duration of EBRT
 - (a) 25-30 days
 - (b) 31-35days
 - (c) ≥ 35 days
14. Total treatment dose.....
15. A)Duration of total therapeutic time
 - (a) ≤ 8 weeks
 - (b) > 8 weeks

B) If duration more than 8 weeks, state exact number of days.....
16. A)Addition of weekly chemotherapy
 - (a) Yes
 - (b) No

B) if yes which type of chemo.....

c) number of cycles.....

- 17. Time of recurrence since last treatment
 - (a) 6-9 months
 - (b) 9-12 months
 - (c) 12-15 months
 - (d) others.....

- 18. Site of recurrence
 - (a) Pelvis
 - (b) Lung
 - (c) Viscera
 - (d) Others.....

“END”