COMPARATIVE STUDY OF TWO DIFFERENT DOSE FRACTIONATIONS FOR HIGH DOSE RATE BRACHYTHERAPY IN LOCALLY ADVANCED CERVICAL CARCINOM

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Department of Clinical Oncology

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By

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

Muhimbili University of Health and Allied Sciences

October, 2018

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Science a dissertation entitled: "**Comparative study of two different dose fractionations for High Dose Rate Brachytherapy in Locally Advanced Cervical Carcinoma"** in (partial) fulfillment of the requirement for the degree of Master of Medicine (Clinical Oncology) of Muhimbili University of Health and Allied Science.

_____

Dr. Nazima J. Dharsee

(Supervisor)

Date_____

DECLARATION AND COPYRIGHT

I, **Dr. Achille Manirakiza Van Christ** 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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DEDICATION

I dedicate this thesis to my late father, Mr. Etienne Nzohabonayo whose passing at a young age due to cancer inspired the choice of my career path in Oncology.

To my Mother, Mrs. Félicité Nzohabonayo for her support and prayers all through this phase,

To my sister, my nephew, niece and brother in law, who have always believed in me.

ACKNOWLEDGEMENTS

I acknowledge the effort of everyone who has been involved in the conception and the execution of this work. My sincere gratitude goes to the department of brachytherapy at the Ocean Road Cancer Institute for the enthusiasm shown during the data collection of the study, to the nurses, the radiation technologists, physicists and physicians involved in the cancer care of cervical cancer patients on a daily basis.

Special thanks also go to Dr Nazima J.Dharsee, Dr Diwani Msemo for the relentless work in reviewing and guidance to completion of this work.

ABBREVIATIONS

ABS: American Brachytherapy Society

BED: Biologically Effective Dose

CT: Computed Tomography

CTC-AE: Common Terminology Criteria – Adverse Events

EBRT: External Beam Radiotherapy

ECOG: Eastern Cooperative Oncology Group

EQD2: Equivalent Dose in 2Gray

HDR: High Dose Rate

HIV: Human Immuno-deficiency Virus

ICBT: Intra-Cavitary Brachytherapy

LDR: Low Dose Rate

PDR: Pulse Dose Rate

SPSS: Statistical Package for Social Sciences

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ABSTRACT

Background

Cervical cancer is the most common and fatal among other gynecologic malignancies encountered in Low and Middle Income Countries.

Brachytherapy holds a central part in the treatment of locally advanced cervical carcinoma. It has been suggested that smaller doses per brachytherapy insertions were safer and more efficient as attempts to brachytherapy hypofractionation.

This study compares two different dose fractionations of High Dose Rate brachytherapy, kept at the same total Biologically Effective Dose to point A, and to compare the disease control, toxicity and overall survival at 9 months of follow-up.

Materials and Methods

The study was a comparative study, including two groups of patients who underwent concurrent external beam radiation therapy and weekly cisplatin followed by HDR intracavitary brachytherapy. External Beam Radiation Therapy was delivered by a Co-60 teletherapy unit to a prescribed dose of 50 **Gray** with 2 **Gray** per fraction in 25 fractions over 5 weeks, together with weekly intravenous cisplatin at a dose of 40 mg/m^2. The patients were allocated into two groups of either HDR-ICBT dose of either a weekly 8.5**Gray** x 2 insertions (Test Group – Arm A) or a weekly 6.7 **Gray** x 3 insertions (Control Group – Arm B). Patients were then followed-up every 3 months for 9 months, with regular check for toxicity and abdomino-pelvic ultrasound to monitor disease control.

Independent Chi-Square analysis was used to compare local control and toxicity profiles between the two arms. Kaplan-Meier analysis was run to estimate survival.

Results

Our preliminary findings were for the first 65 patients, enrolled between April and August 2017, then followed up until May 2018. Median follow-up time was 9.1 months. Analysis was run for 47 patients with complete data. Over a half of our patients were aged between 41-50 years, 93.6% were Squamous Cell Carcinoma, and 46.8% of the patients had stage IIB disease.

9-months local control was comparable between the two groups of treatment (85.7% Vs 76.9%, p=0.058), and 10.6% patients in the standard arm were found to have grade 2 rectal complications. 9 months overall survival analysis was similar for the two arms (p>0.05).

Conclusions

Our study findings highlight the non-superiority of the standard, smaller dose per fraction (6.7 Gray x 3) to a larger dose (8.5 Gray x 2) per insertion, with a similar Biologically Effective Dose, that can be replicated safely in resource-limited settings.

CHAPTER ONE

INTRODUCTION

1.1. Background

Cervical cancer constitutes a major public health threat worldwide, figuring among the top five most common malignancies in women globally (1). Disparities in incidence are noted between regions, making cervical cancer the most common gynaecologic malignancy encountered in Low and Middle Income Countries, and the same account for the mortality rates. (1–5).

The Eastern Africa region has one of the highest incidence and mortality of cervical cancer, highlighting, with a few other regions of the world. (1–3). Associations between HPV infection, a positive HIV status and a low socioeconomic background with cervical cancer, despite efforts for screening have been long investigated and put on evidence (2,5–7).

Locally advanced cervical cancer status, as defined by the International Federation of Gynecology and Obstetrics confers to the patient a high recurrence and low survival rate risks altogether. Survival rates has been shown to have a decreasing tendency as the cancer stage increase (8).

Although upfront primary surgery followed by adjuvant chemotherapy and radiotherapy has its place in early staged disease, it has gradually lost its place for higher and locally advanced staged diseases. For the latter, a large meta-analysis involving 18 trials has shown a clear-cut advantage for chemo-radiation if compared with radiotherapy only (9). Chemo-radiation with a single agent platinum has shown better toxicity profiles and is associated with higher completion rates (9,10).

The radiotherapy modalities in modern use are generally a combination of External Beam Radiotherapy and Brachytherapy. The latter is used in the quest of local control, and its importance in improving cancer specific survival parameters has been highlighted elsewhere (11).

Brachytherapy, as a part of the radiation scheme is introduced when local tumor reduction is satisfactory. In the era of chemo-radiation use, research has shown that substantial tumor regression, measured with Magnetic Resonance, happens during radiotherapy, between 45-50 **Gray** of Radiotherapy, equivalent to four and five weeks of external beam radiotherapy (12,13). Completion of the full treatment should be aimed to be kept at 8 weeks, overall (14).

Brachytherapy, as defined as the International Commission on Radiation Units, uses three main modalities, namely the Low Dose Rate (LDR), Pulse Dose Rate (PDR) and High Dose Rate (HDR) at differing doses and delivery modes. Uses of Intermediate Dose Rate were also scarcely described in another setting, but this technique seem to be outdated(15) The now current widely-used technique is the Intracavitary brachytherapy with a uterine tandem and vaginal ovoids unlike the two other techniques (Interstitial and PDR brachytherapy).

Modern Intra-Cavitary Brachytherapy finds its source by the methods established with both the Manchester and Paris system. Both systems use adjustable strength and length Iridium-192 sources, irradiating two anatomical sites (Points A and B) defined remotely with the use of imaging (2D or 3D)(16). The work by Tod and Meredith in 1953 in both anatomical redefinition is in use currently, and places the point A at 2 cm from ‘ the end of lowest uterine source – internal os – and then 2 cm, laterally in the frontal plane’(16).

The American Brachytherapy Society recommends a total dose of 80-90 **Gray** to point A, depending on the tumor stage for both Low Dose and High Dose Rate techniques (14,17).

Although recent, comparable results have been shown in terms of control and survival, over the years, between High Dose Rate and Low Dose Rate brachytherapy for cervix carcinoma (18–21). Advantages have been found with the use of HDR in a recent 5 studies meta-analysis, not only because it has an afterloading technology and better toxicity profile, but also could be well applicable in developing countries without necessary hospitalization and extended radiation exposure (18).

Dosing and fractionation pertaining to HDR **Intra-Cavitary** brachytherapy has been evolving, from an institution to another, from a hyper- fractionated method with large time apart between insertions(16) to hypo-fractionation with a generally acceptable week apart between insertions, with 5-6 **Gray** in 5 fractions (17).

Scarce knowledge exist, seeking to provide a hypo-fractionation option to HDR **Intra-Cavitary** brachytherapy, given the same Dose and Biologically Effective Dose (BED) at the tumor location, parametrium and organs at risk, and have shown similar parameters in terms of control, survival and toxicity (22–25). Although a large impact on survival has been found for a

prolonged exposure to **Intra-Cavitary** brachytherapy with hyper-fractionation, this model seem to be associated with a higher toxicity possibility (26).

Of interest, Kehwar and colleagues reported a comparison of two different **Intra-Cavitary** brachytherapy doses (9.5 **Gray** and 7.5 **Gray**) regimen but with the same BED dose to point A of Manchester System, and found similar parameters, but also equal tolerability and effectiveness (27). The pitfall to that study was the variation between the insertions intervals across arms. In a similar study, Patel and colleagues proved the applicability and advantages from fewer insertions (2 insertions, 9 Gray) when compared with a longer exposure (3 insertions, 6.8 **Gray**) (28).

Whether the differences between regimens would cause different extent complications to organs at risk has been tested too and provided encouraging results (24,29,30), provided the BED values are similar.

1.2. Problem Statement

With a high incidence of cervix carcinoma in our settings, subsequent high patients volume, and to minimize radiation exposure, **Intra-Cavitary** brachytherapy insertions and hypothetically increasing overall outcomes, little is known in resource-limited settings on the use of hypo-fractionated brachytherapy while keeping the same Biologically Effective Dose. This study was conducted to provide solutions and alternative dosing in the global realm of efforts towards **Intra-Cavitary** brachytherapy hypofractionation for cervical cancer.

1.3. Rationale and Hypothesis

Our hypothesis consisted in proving the non-inferiority of the hypo-fractionated dose of brachytherapy (8.5 **Gray** in 2 insertions) in cervical carcinoma to the then practiced regimen (6.7 **Gray** in 3 insertions) in terms of short-term (9 months) local control, event free survival and toxicity profile.

The aim of this study was to compare two different doses and insertions of High Dose Rate **Intra-Cavitary** brachytherapy on patients with locally advanced cervical carcinoma, and to seek to determine the differences in short-term event free survival, local control and toxicity profiles.

The results of this study provide new knowledge to ORCI and similar, high patients' volume centers in Low and Middle Income Countries on the benefits of hypofractionation in cervical cancer **Intra-Cavitary** brachytherapy.

1.4. Objectives

Broad Objective:

To compare two different doses and insertions of High Dose Rate **Intra-Cavitary** brachytherapy for patients with locally advanced cervical carcinoma.

Specific Objectives:

- To assess feasibility and safety of hypo-fractionation for HDR **Intra-Cavitary** brachytherapy for patients with locally advanced cervical carcinoma;

- To study the differences in outcomes, namely, event free survival, local control and toxicity profiles pertaining to the two regimens for a period of 1 year.

- To assess the differences across age ranges, disease stage and histology types in response to radiotherapy;

CHAPTER TWO

MATERIALS AND METHODS

2.1. Study Design

The study was a hospital based, open-label, single institution, comparative study. Patients were assigned (1:1), with a consecutive recruitment according to set randomization criteria, to receive two **Intra-Cavitary** brachytherapy insertions of 8.5 **Gray**, one week apart (test group - A) or three **Intra-Cavitary** brachytherapy insertions of 6.7 **Gray**, one week apart (control group - B).

Patients were enrolled then allocated to either group after satisfactory completion of a 5 week-course of both external beam radiotherapy, total dose of 50 **Gray**, on a 2 Gray daily in 25 fractions, combined with a single agent cisplatin for a dose of 40 mg/m^2.

2.2. Study Period

The study had a recruitment phase spanning between April to August 2017 and a follow up phase from April 2017 to May 2018.

2.3. Study Area

Ocean Road Cancer Institute is cancer referral facility, located along the Indian Ocean within the Capital City Dar es Salaam. The health facility is one of the oldest health institutions in Tanzania, having been founded in 1895. The cancer care started in 1980 where by the Radiotherapy Unit of the Faculty of Medicine, University of Dar es Salaam was shifted from Muhimbili Medical Centre to the Ocean Road Hospital. In 1996, the centre became autonomous and was upgraded a national referral facility for comprehensive cancer services accessible by all Tanzanians and patients from neighbouring countries. The centre offers Radiation therapy treatment, Medical oncology, palliative care, cancer prevention and screening programs.

2.4. Study Population

All new cases starting insertions for **Intra-Cavitary** brachytherapy in the specified period (April to August 2017), fitting the inclusion criteria, were re-assessed for enrolment, which was done in a stratification model with set criteria (see randomization criteria below).

2.5. Inclusion Criteria

- A confirmed locally advanced cervical cancer, as per the FIGO classification, patients with disease stage IB to IVA will be included, at the completion of the combined weekly

chemotherapy (cisplatin 40 mg/m^2) cycle for at least 2 weeks (2 cycles) and External Beam Radiotherapy, dose of 50 **Gray** in strictly 5 weeks, on curative intent;

- A clear pathology report;
- An Eastern Cooperative Oncology Group (ECOG) performance status below or equal 2;
- A signed informed consent form

2.6. Exclusion Criteria

- Patients with metastatic disease at presentation;
- Patient with a diarrheal disease, for rectum contrast injection purposes;
- Patients at first **Intra-Cavitary** brachytherapy evaluation presenting with a lesion above 5 centimetres;
- Patients without a clear pathology report, confirming cervical cancer;
- Failure to obtain a signed consent form;

Loss for follow-up either during treatment (absconding during brachytherapy) or any set time for follow up (3, 6, 9 and 12 months) in the post-treatment period

2.7. Randomization Criteria

To ensure data quality and minimize allocation bias between the arms, the randomization followed a 1:1 model, and the patients were allocated in the two arms with these 3 specific stratification criteria:

- Age range (defined in the questionnaire below)
- Disease Stage at first presentation, before any form of treatment
- Histo-pathology results (squamous cell carcinoma, adenocarcinoma, adenosquamous)

2.8. Sample Size

Basing on another similar single institution study[28], whose primary outcome was local control after 3 years, our sample size estimation formula (Formula for prospective comparative studies) would be:

$$n = \frac{2(Z_{\alpha/2} + Z_{\beta})^2 P(1-P)}{(p_1 - p_2)^2}$$

Where Z_α is the Z for a 95% confidence interval, and $Z_{0.05/2} = Z_{0.025} = 1.96$

Z_β for a power of 80% equals 0.842 (from the Z table)

P1-P2, the difference in proportion of events in the two groups of the cohort

P= pooled proportion = (P1+ P2)/2;

In our study of interest, the proportion between the two events are: local control for arm A (9 Gy x2) is 81.35% (0.8135) and local control for arm B (6.7Gy x 3) is 65.18% (0.6518).

Hence the sample size becomes:

1.0. $\frac{2(1.96+0.842)^2\ \ 0.73265(1-0.73265)}{(0.8135-0.6518)^2} = \frac{15.702408x0.1958739775}{0.02614689} = \frac{3.0756931113}{0.0261469}$

$$n = \frac{2(1.96+0.842)^2\ \ 0.73265(1-0.73265)}{(0.8135-0.6518)^2} = 117.63$$

n≈118, as the population in both arms. Accounting for 10% of loss of follow-up, seen in prior similar studies[28], the sample size would be:

$$n = 118 + \frac{118x10}{100}$$

n≈130 -- about 65 participants in each arm.

2.0

2.9: Equation

To find the suitable, equivalent dose to the formerly used **Intra-Cavitary** brachytherapy dose, given in fewer fractions, we considered a α/β ratio dose of 10 for a good responding tissue and an α/β ratio dose of 3 for a poor responding tissue,

With the former dose of 6.7 **Gray** given in 3 insertions (3 fractions) totaling a total dose of 20.1 **Gray**, the two equations to find a Biological Equivalent Dose, considering both sets of tissues (good and poorly responding tissues) would be:

$BED = nd\left(1 + \frac{d}{\frac{\alpha}{\beta}}\right)$, where n is the number of fractions (insertions) and d the dose per fraction.

For α/β ratio of 10, the BED was found to be: 3x6.7 (1+6.7/10) =33.567;

For α/β ratio of 3, the BED was found to be: 3x6.7 (1+6.7/3) = 64.993

To have a similar BED for 2 fractions, for both α/β ratios, the equation was:

BED 10: 34 = 2d (1+ d/10) –> 34= 2d + d^2/5 –> 170 = 10d + d^2

Giving a linear quadratic equation equaling to: d^2+ 10d – 170=0

In this case: $d = \frac{-b \pm \sqrt{b^2-4ac}}{2a}$ $d = \frac{-10 \pm \sqrt{10^2-4(-170)}}{2}$ -- d = 8.96, for a BED accounting for a α/β ratio of 10.

For a BED 3: 65 = 2d (1+ d/3) –> 65= 2d+ 2d^2/3 –> 195= 6d+ 2d^2

Giving a linear quadratic equation equalling to: 2d^2+ 6d – 195 =0

In this case: $d = \frac{-b \pm \sqrt{b^2-4ac}}{2a}$ $d = \frac{-6 \pm \sqrt{36-4(2\ (195)}}{2a}$ – d= 8.48, for a BED accounting for a α/β ratio of 3.

After consultations with the medical physicists at the institution, a minimal dose of 8.5 **Gray** for 2 insertions was agreed upon for use for this study.

2.10. Outcomes

The primary outcome to be tested was:

- Local control of the disease, tested with at regular intervals of three months using both a vaginal examination (with speculum) assessing the status of the cervix and treatment response, abdominal-pelvic ultrasound and was compared with the ultrasound (staging) done at the patient first diagnosis and treatment prescription. The disease size was considered for its largest measured diameter on the ultrasound report, for ease of analysis. Improving disease was defined as a disease reducing in size at the regular 3-month ultrasound report, and disease not improving was defined as a progression (increase in size and/or metastatic disease) or stable (no change in size).

Secondary outcomes will be:

- Early survival and disease status data at follow-up schedules, 3 monthly for a year. For this, a vaginal examination with speculum was done, disease progression, an event free period was assessed and reported at a one-year period (for local control check);
- Rectal and urinary bladder toxicity assessment was done. Toxicity was reported by the patients as having a proctitis, urinary incontinence and dysuria.

2.11. Data Collection Process

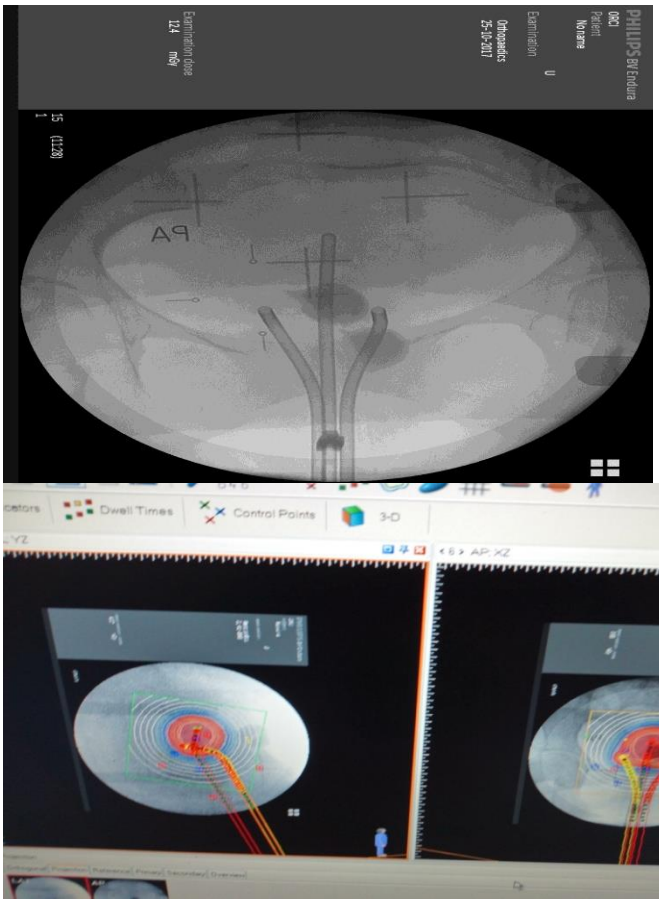
A form of patient information detailing the study in Swahili was given to all study participants and consent was taken prior to enrollment. Preliminary demographical data were recorded by a research assistant.

Clinical data were taken in phases, the first phase being before the **Intra-Cavitary** brachytherapy delivery after signing the informed consent, assigning patients randomly to the two arms, after each delivery of **Intra-Cavitary** brachytherapy to record the findings at the **Intra-Cavitary** brachytherapy insertion and during the follow up time, every three (3) months.

At enrollment and arm assignment, every patient was prepared for imaging for **Intra-Cavitary** brachytherapy planning purposes. A Foley's Catheter was inserted to the bladder and the rectum, and a contrast was injected, prepared with a solution of Iopamidol® with Normal Saline at a concentration of 2:8 for bladder for a total injected volume of 10 milliliters, and 1:4 for the rectum, for a total injected volume of 5 milliliters, after emptying both the bladder and the rectum.

Patients then had an insertion of **Intra-Cavitary** brachytherapy using a set of applicators made by a central tandem and ovoids. The choice of the size of the applicators was done at the treating physician's discretion from one patient to another. Orthogonal imaging was performed using a C-arm X-ray machine after applicators insertions to verify the relative distances from the central tandem with the main organs at risk, the bladder and the rectum. Radiation planning was performed through the HDR basic 2.6 planning software®.

The following images depict the typical imaging and planning processes for all the patients respectively:



A checklist containing specific items regarding the history, physical examination, laboratory and imaging tests at each encounter was provided to all firms involved with the follow up of cervical cancer patients. Toxicity was reported by the patients, and evaluated by the consulting physician, using the CTCAE version 4.0 tool to grade the toxicity.

Data was entered into Excel software (Redmond VA 2012) and analyzed using SPSS V.22. Categorical demographic data and other categorical variables were reported as simple frequencies and/or percentages of the whole. Continuous variables were expressed as median values with inter-quartile ranges or categorized and reported as simple frequencies.

Comparisons related to Local Control, toxicity and Survival data, controlling for the randomization criteria were made between the two arms of treatment with a desired Confidence Interval of 95% and p values will be made to test the hypothesis. The study was powered at 80%. All patients were involved in an Intention to Treat Analysis.

Ethical clearance was sought and approved by the Muhimbili University of Health and Allied Sciences institutional review board.

CHAPTER THREE:

RESULTS

A total of 65 patients were enrolled between April and August 2017. At 9 months, a number of 47 patients were included in the analysis as they had complete full enrolment and follow-up data. Patients were analysed using a 1:1 randomization method, with 15 (31.91%) receiving 8.5 **Gray** to point A, and 32 (68.08%) in the control group (Arm B), receiving 6.7 **Gray**

51.06% of the patients were in the range of 41-50 of age.

Nearly a half of the patients enrolled had a stage IIB (46.8%; n=22) and the majority of the lesions were squamous cell carcinoma at 93.6%, with more malignancies being graded as moderately differentiated (82.98%).

Table 1. Demographic and Clinical Data

<table>
<tr><td>Demographic and Clinical Data</td><td>Details</td></tr>
<tr><td>Age</td><td>
<table>
<tr><th></th><th>Test Group</th><th>Control Group</th></tr>
<tr><td>31-40</td><td>0</td><td>4</td></tr>
<tr><td>41-50</td><td>8</td><td>13</td></tr>
<tr><td>51+</td><td>7</td><td>15</td></tr>
</table>
</td></tr>
<tr><td>Histology Subtype</td><td>
<table>
<tr><th></th><th>Test Group</th><th>Control Group</th></tr>
<tr><td>Adenocarcinoma</td><td>0</td><td>3</td></tr>
<tr><td>Squamous Cell Carcinoma</td><td>15</td><td>29</td></tr>
</table>
</td></tr>
<tr><td>Ultrasound findings prior to brachytherapy (Size in largest Diameter in centimeters)</td><td>No visible cervical mass 14 (29.7%)
Diameter of ≥2 but <3 centimeters 8 (17.6%)
Diameter of ≥3 but <4 centimeters 14(29.7%)
Diameter of ≥4 but <5 centimeters 11(23.4%)</td></tr>
<tr><td>Dose of Brachytherapy</td><td>Test Group (8.5 Gray) 15 (31.9%)
Control Group (6.7 Gray) 32 (68.1%)</td></tr>
</table>

Speculum Findings on 1st insertion per Arm	Test Group No Mass seen Mass seen +/- bleeding	 6 9
	Control Group No Mass Seen Mass seen +/- bleeding	 6 26
Speculum Findings on 2nd Insertion per Arm	Test Group No mass seen Mass seen +/- bleeding	 8 7
	Control Group No mass seen Mass seen +/- bleeding	 12 20
Speculum Findings on 3rd Insertion per Arm	Control Group No mass seen Mass seen +/- bleeding	 22 10

Doses were distributed across the stages as described in Table 2. All patients (n=6) of stage IB received the control dose (6.7 Gray), 60% (n=3) patients who were in stage IIIB were treated with 8.5 Gray as opposed 40% (n=2) who received 6.7 Gray.

Table.2 Treatment dosage delivered to patients by stage of disease

Stage of disease	Test Group n (%)	Control Group n (%)	Total
Stage 1B	0 (0%)	6 (100%)	6 (100%)
Stage 2A	2 (16.7%)	10 (83.3%)	12 (100%)
Stage 2B	10 (45.5%)	12 (54.5%)	22 (100%)
Stage 3A	0 (0%)	2 (100%)	2 (100%)
Stage 3B	3(60%)	2 (40%)	5 (100%)
Total	15 (31.9%)	32 (68.1%)	47 (100%)

Univariate analysis was done with chi-square to determine patient improvement observed by disease stage while controlling the different treatment dosages. Results revealed that patients in Arm A (dose: 8.5 Gray), in stage IIA, stage IIB and stage III B had a response of 50%, 89.9% and 100% respectively accounting for disease improvement. Likewise, results in Arm B shows that stage IB, stage IIA, stage IIB, stage IIIA and stage IIIB patients were respectively 80.0%, 88.9%, 70.0%, 100% and 0.0%, observed to have improvement of their disease condition. However, these results showed no relationship of the stages of disease and improvement of disease condition as were independent variables (likelihood ratio test = 2.432, df = 2, p>0.05). A trend was observed, tending to a better response for late stages (stage III) with the test dose (8.5 Gray). The overall disease control was 85.7% for Arm A vs 76.9% for Arm B, and there was no statistical difference between the two groups (p=0.058).

Table 3: Improvement of disease condition by stage under control of dosage delivery

	stage of disease	**No improvement Observed N (%)**	**Improvement Observed N (%)**	**Total**
Test group Arm A	stage 2A	1 (50%)	**1 (50%)**	**2 (100%)**
	stage 2B	1 (11.1%)	**8 (88.9%)**	**9 (100%)**
	stage 3B	0 (0%)	**3 (100%)**	**3 (100%)**
	Total	2 (14.3%)	**12 (85.7%)**	**14 (100%)**
Control group Arm B	stage 1B	1 (20%)	**4 (80%)**	**5 100%**
	stage 2A	1 (11.1%)	**8 (88.9%)**	**9 (100%)**
	stage 2B	3 (30%)	**7 (70%)**	**10 (100%)**
	stage 3A	0 (0%)	**1 (100%)**	**1 (100%)**
	stage 3B	1 (100%)	**0 (0%)**	**1 (100%)**
	Total	6 (23.1%)	**20 (76.9%)**	**26 (100%)**

**Missing 1 – in Test group and 6 in control group*

Results related to disease improvement, controlling for age, and disease histology for all the patients analyzed showed a statistically significant difference of the control dose between the subset of patients aged between 41-50 (60%) Versus patients aged 51 and older (100%) (p=0.017).

Table 3: Disease Improvement by age and Histology type

Treatment		Variable	Not Improved	Improved	CHISQ Value	DF	P-Value
Test Group	Age of Patient	41-50	1	7	0.049	1	0.825
		51+	1	5			
Control Group		31-40	0	4			
		41-50	6	9	5.72	1	0.017*
		51+	0	11			
Test Group	Disease histology	Moderately differentiated SCC	2	10	0.389	1	0.533
		Poorly differentiated Squamous Cell carcinoma	0	3			
Control Group		Adenocarcinoma	0	3	1.418	2	0.492
		Moderately differentiated SCC	8	16			
		Non Keratinizing SCC	1	4			

The toxicity data was collected during the period of follow-up, both reported by the patients and evaluated by the consulting physician. Over the 9 months of follow-up, there were 12 events (25.5%), categorized into gastro-intestinal and genito-urinary toxicities. Patients in Arm B (dose = 6.7 Gray) were found to have more grade 2 rectal toxicity (10.6%). A non-significant interaction was found (χ^2 (1) = .224, p > .05)

Table 4: Toxicity Profile comparison between the two dose regimens

Toxicity		**Treatment dosage**		**Total**
		Test Group N (%) **Out of 15**	Control Group N (%) **Out of 32**	
Diarrhea	Count	1 (100%)	0 (0%)	1
Proctitis	Count	2 (28.6%)	5 (71.4%)	7
Dysuria	Count	2 (40%)	3(60%)	5
Urine incontinence		0(0%)	3 (100%)	3
	Total Count	5	7	12

The Kaplan Meier was run to compare survival distribution between two treatment arms. Figure 1 summarizes the survival curves, revealing no significant exist in performance between 6.7Gys and 8.5Gys ($\chi 2$ (1) = 3.493, p>0.05).

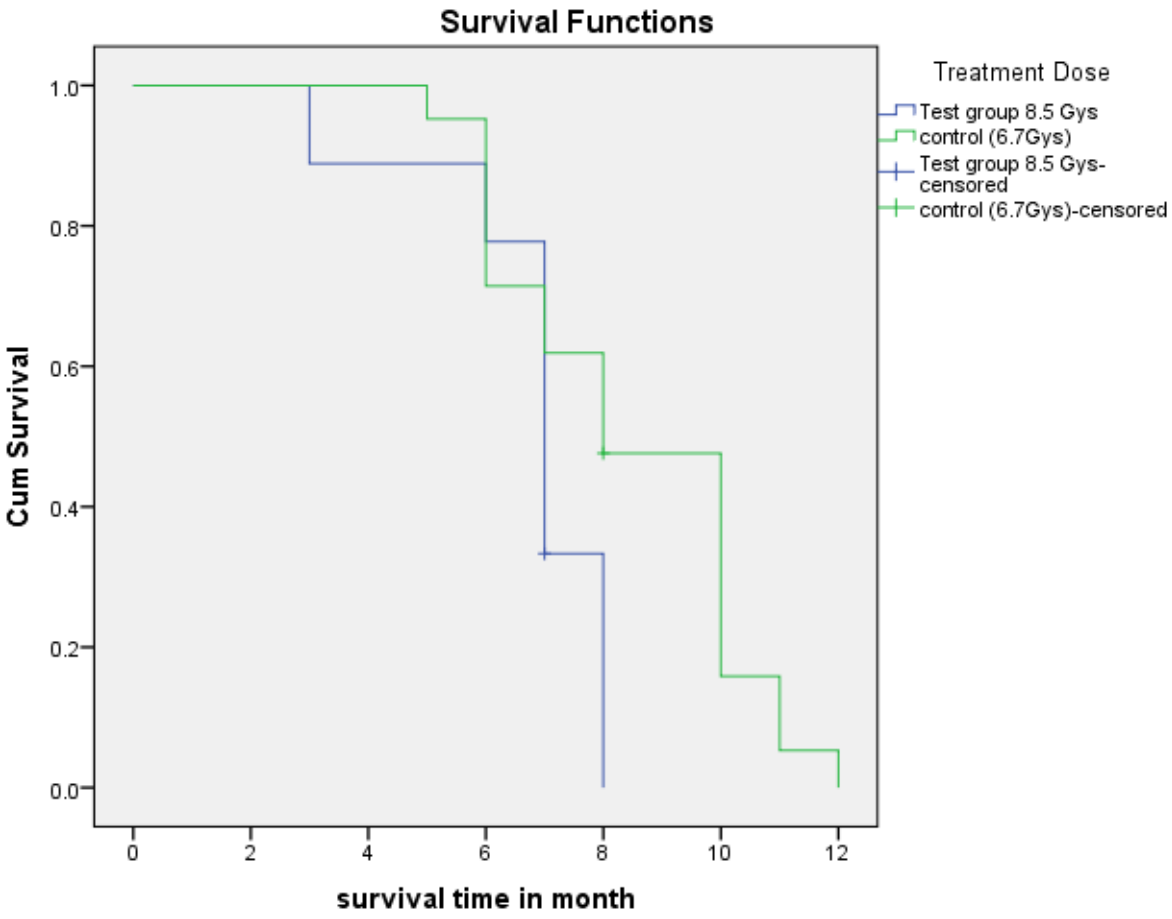


Figure 1: Survival Function compared for the two dose groups

CHAPTER FOUR

DISCUSSION

Cervical cancer is a threatening public health issue in resource-limited settings. The generalities of patients found in other studies are maintained in our findings, in terms of a late presenting disease, an increased percentage of the squamous cell carcinoma histology, with most consulting patients in their late forties(31–34).

The East African region has the highest estimated cervical cancer figures in the world, but radiotherapy practices and changes across the years have not been steadily reported. **Intra-Cavitary** Brachytherapy has been in use for over four decades now, and the first, reported historical data findings relates the introduction of afterload high dose rate brachytherapy in Tanzania (8 **Gray** in 4 insertions). This reported dose differs largely with the institutionally approved dose to point A at the time of our study, namely, 6.7 **Gray** in 3 insertions (35-38).

In the year 2011, a change of practice has been established at the Ocean Road Cancer Institute, shifting the **Intra-Cavitary** brachytherapy delivery from LDR, 10 **Gray** x 2 to HDR 6.7 **Gray** x 3. The newer dose differed from the ABS recommended dose indicated for locally advanced cervical carcinoma (17). The reasoning behind was taking into consideration the burden of patients, while minimizing the toxicity to the patients.

A validated manual developed by the ABS and tested by the Department of Radiotherapy and Radiobiology of the Medical University of Vienna has been in use for the purpose of calculating the Biologically Equivalent Doses, taking in consideration the α/β ratio for slow and fast responding tissues, and the added effect of EBRT. With this tool, an addition of the **Intra-Cavitary** brachytherapy dose of 6.7 Gray on EBRT dose of 50 Gray, would equate to a Biologically Equivalent Dose (BED10) of 93.6 **Gray**, and an Equivalent Dose (in 2 **Gray** fraction) of 78 **Gray** slightly below the recommended point A dose of 80-90 **Gray**. This finding correlates, by extension to our testing dose of 8.5 Gray in 2 insertions.

Our 9-months, preliminary findings have shown similar short term local control rates for both the test and standard doses of HDR **Intra-Cavitary** brachytherapy, when added to chemoradiation. These results were found in similar study settings, reporting a little over 80% of 3year local control rate for test (2 insertions) doses(27,28). Whether these findings could be sustained over 3

years in our setting would require a longer follow-up. Of interest, however a recent trial found a significantly better local controlled conferred by the ABS recommended dose (7 **Gray** in 4 insertions) when compared with the attempted hypofractionation regimen (9 **Gray** in 2 insertions) highlighting the ongoing concern, over a long follow-up period, of a sub-optimal dose delivered to point A (within the ABS recommended dose range, accounting for a BED10 of 89.4)(39)

The toxicity profile in our study reported about 14.8% of early onset of grade 2 rectal complications, for both set of patients, with only 4.2% of the patients treated with the novel dose found with proctitis. The findings differ with key studies' findings, relating of a much lower grade 2 or worse late rectal toxicities profile (2-5%)(27, 39, 40). The same applies to urinary system-related toxicity, which favored the investigative dose arm (8.5 **Gray**) with an overall 25% grade 2 toxicity (urinary incontinence and dysuria), from all patients found with a urinary related toxicity.

Whereas the radiation planning for EBRT and Intra-Cavitary Brachytherapy for all major similar studies was done with three-dimensional conformal planning (3D), with evaluation of disease control done with Computed Tomography (CT) scan imaging (24,27,28,39). The patients enrolled in our study had radiation therapy (EBRT+ ICBT) planned with two-dimensional planning and disease control evaluated with ultrasound, both 3D conformal planning and CT-scan not available and operational at the time of both enrollment and analysis.

CHAPTER FIVE

CONCLUSIONS AND LIMITATIONS

Our preliminary study findings highlight similarities between two High Dose Rate **Intra-Cavitary** brachytherapy dosages, in terms of local control, toxicity profile and overall survival.

A longer follow-up period is needed to track disease control, toxicity and survival, with a large cohort.

With the largest share of cervical cancer figures being in LMICs, the results of this study have shown that a larger dose per fraction given in few insertions is as safe and as effective as a smaller dose in many insertions.

However, the study had major limitations, including:

- The follow-up was done by imaging with ultrasound, without control form a different sonographer, due to lack of CT-scan at our center at the time of patient randomization and follow-up;
- The brachytherapy department experienced a “down time” in the middle of the patient enrolment, leading to a poor accrual and hence a smaller number of patients to analyze;
- The follow-up time was limited to less than 1 year.

CHAPTER SIX

RECOMMENDATIONS

From the accrual, randomization and follow-up, several recommendations related to patient's assessment arise, and are summarized as follows:

- Patient evaluation should be mandatory before brachytherapy sessions by the respective firms, in order to assess disease status, size and general response to concurrent chemo-radiation. During patients assessment, many patients were excluded as they were found with a larger disease, beyond the recommended measurements by the ABS;
- Patient evaluation needs to be done with objective imaging tools – namely a CT scan at least. Better imaging tools help assess nodal spread and staging of the disease;
- With the advent of a newer institutional dose for **Intra-Cavitary** brachytherapy (8 Gray x 3), another study designed as a randomized controlled trial with a longer follow-up should be undertaken to assess feasibility of hypofractionation in brachytherapy for locally advanced cervical cancer.

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