BRACHYTHERAPY

IN

CANCER OF THE CERVIX: AN AFRICAN PERSPECTIVE.

Longino Kabakiza Mucheusi

National Diploma (Diagnostic) KMTC, BTech (Therapy) CPUT

Student Number: 198094892

Thesis submitted in fulfilment of the requirements for the degree

Master of Technology: Radiography Degree

Faculty of Health and Wellness Sciences

Cape Peninsula University of Technology

14th February, 2012

Supervisor: Prof. Penelope Engel-Hills BSc Med Hon (RT), MSc (Med Physics), D Tech (Rad)

Co-supervisor: Bridget D. Wyrley-Birch MTech (Rad)

External Supervisor: Dr. Catherine Nyongesa MBCHB, FC Rad Onc, MMED Rad Onc

Declaration

I, Longino Kabakiza Mucheusi, declare that the contents of this thesis represent my own unaided work, and that the thesis has not previously been submitted for academic examination towards any qualification. Furthermore, it represents my own opinions and not necessarily those of the Cape Peninsula University of Technology.

Signed  Date 14th February, 2012

Dedication

To my Mother Elizabeth Kabakiza Mucheusi, whose love for me and consistent prayers for my well being is beyond any ordinary measure. This is for you Mama.

Acknowledgments

This research and thesis would not have been possible without the support and sponsorship of the International Atomic Energy Agency, the two hospitals where this research was done and distinguished professors and academicians at Cape Peninsula University of Technology, the University of Cape Town and the University of Nairobi. While it may not be possible to mention all those who gave invaluable support during the conduct and writing of this thesis, a few deserve special mention and thanks:

Professor Penelope Engel-Hills for her encouragement and support right from the initial conception as we thought of this work. Her tremendous insight and understanding of the challenges involved and how they could be overcome will remain a constant reminder to me that surely, nothing is impossible.

Bridget D. Wyrley-Birch for her encouragement and support.

Dr. Anselmy Opiyo for his great vision, foresight, support and encouragement.

Dr Leon van Wijk for the support, teaching and love that he showed towards my research as I worked alongside him in theatre, despite the busy schedules.

Dr Alistair Hunter for always being available for consultation as I did this work. His important contributions in the radiobiology models used in this thesis and statistics, was high value ended knowledge that I will without hesitation, use to teach others.

Kobus Botha, for preparing the excel spread sheets with the difficult radiobiology formulas and date calculators.

Dr. Motasim Badri for always being a friend in research statistics for the many years I have known him.

Dr Catherine Nyongesa for her unquestionable support.

Professor Guantai for her timely efforts in getting my ethics approval through in Nairobi.

My dear wife Emily, and my two sons Martin and Mike, for their sacrifice and understanding during the difficult times of writing this thesis.

Abstract

Introduction: Brachytherapy plays an essential role in the management of patients with cervical cancer. The high cervical cancer burden in Africa presents challenges with regard to provision and sustainability of these services. This study analysed treatment outcomes of two brachytherapy modalities, high dose rate (HDR) and low dose rate (LDR) intracavitary treatment for patients with cervical cancer, and evaluated the problems and challenges of the provision of these services within the African context.

Methodology: The study was conducted using a case study approach with mixed methods at two sites in Africa, one in South Africa (Centre I) and the other in Kenya (Centre II). The study explored factors and issues affecting definitive radiotherapy of the patient with cervical cancer at the two sites with a focus on the brachytherapy treatment. The case study provided an opportunity to collect in-depth data consisting of quantitative and qualitative components that generated numeric and textual data. Treatment outcomes of one site treating with HDR and the other LDR intracavitary brachytherapy were retrospectively analysed for a maximum sample size of 193 (91%) patients in the HDR group and 49 (100%) patients in the LDR group. All patients were treated with external beam radiation therapy (EBRT) using parallel opposed beams (POP) for the patients that received LDR brachytherapy, and four field box technique or POP for those that received HDR brachytherapy. The linear quadratic formula was used to calculate the equivalent dose in 2 Gy fractions (EQD_2) between the two groups. The primary endpoints assessed were pelvic relapse free survival, late radiation complications, and overall survival. Endpoints were estimated using the Kaplan-Meier method. Comparisons between treatment groups were performed using the log-rank test. The results were compared and considered against data from other relevant published research findings. Further to this, the implementation process of the HDR brachytherapy equipment was evaluated. The data was integrated and interpreted to answer the main research question of how well HDR brachytherapy has replaced LDR as an appropriate treatment strategy for cervical cancer within the African context.

Findings: The findings showed several issues in regard to brachytherapy infrastructure, clinical outcomes between patients treated with HDR and LDR, and numerous challenges with regard to HDR implementation and use. The median follow-up for patients treated in the two groups (HDR and LDR) was 42.2 and 12.4 months, respectively. The actuarial 5-year pelvic relapse free survival in the HDR and LDR group was 65.8% and 53.9% ($p = 0.84$), respectively. The 5-year bladder and rectal (grade 3 and 4) complication rates for patients treated with HDR were 3.4% and 3.0%, whereas those treated with LDR were 0% and 25.0%, respectively. The difference in rectal

complications was significant with a p-value of 0.0024. The 5-year overall survival for the HDR group was 50% with a median survival time of 49.2 months. There was no survival data for the LDR group. The evaluation showed management logistics with regard to the supply of HDR sources, lack of experience in HDR use, and technical issues of implementing an HDR programme as strong challenges at Centre II, while issues of machine maintenance were found to be similar for HDR and LDR equipment at both Centres.

Recommendations: The results showed similarities between HDR and LDR treatments with regard to pelvic relapse free survival and bladder complications. This and the findings on overall survival in the HDR group, compared well with published literature. However, a high rectal complication rate was observed in the patients treated with LDR. This suggests that other factors such as the small sample size in the LDR group or the external beam technique might have influenced the outcome, as the results contradict other studies that report similar treatment outcomes between LDR and HDR. Overall, the results were comparable. Therefore based on these findings and the challenges that emerged from the evaluation on HDR implementation process at Centre II, this study recommends LDR/MDR (medium dose rate) brachytherapy as appropriate in this environment where adequate experience is available for this modality. This would be conditional on a strict maintenance programme being initiated with the equipment supplier, as this is no longer the case. A model treatment schedule is proposed that would enable an under-resourced Centre to treat as many patients on LDR as the Centre using HDR intracavitary brachytherapy. Though Co-60 based HDR would be considered better given availability of infrastructure, experience and oncology support systems.

Conclusion: The evidence from Centre I in South Africa shows that HDR has replaced LDR, and can be used in Africa but with certain conditions of: infrastructure and support services, dedicated management and logistics in supply of sources, expertise in its use, and scheduled treatment times. The evidence from Centre II in Kenya shows that HDR has not replaced LDR /MDR, and cannot be used due to: lack of infrastructure and oncology support services, equipment expertise, experience and resources. These challenges encountered in HDR implementation may hinder the use of HDR in dealing with the high cervical cancer burden in Africa, despite its ability to treat many more patients compared to LDR/MDR. Nevertheless, despite these challenges and the statistical difference observed in rectal complications between HDR and LDR, the adequate experience in the use of LDR/MDR that is shown at Centre II, can be exploited to activate brachytherapy services at the Centre. This is due to the overall comparable study results and published literature that show both modalities give similar treatment outcomes. The study aim was to provide in-depth insight into

the African situation through research at the two oncology sites. Suggestions and possible solutions to the challenge of accessibility of definitive radiotherapy treatment for the patient with cervical cancer within the African context are made, in order to contribute to management of the cervical cancer burden on the continent. There is however the question of advancement in technology favouring resource rich countries thereby creating a divide with poor countries such as African countries with limited resources and inadequate support systems. This concern is also raised by the International Atomic Energy Agency (IAEA) and is discussed in this study. Hence, there is the possibility that the findings and issues highlighted in this study may form a basis for further research to unravel the many issues affecting brachytherapy services in Africa. It is also envisaged that the recommendations and suggestions made, may contribute to solutions beyond the two study sites.

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Abbreviations

AAPM	American Association of Physicists in Medicine
ABS	American Brachytherapy Society
AP	Antero-posterior (Coronal view)
CIA	Central Intelligence Agency (United States)
CPUT	Cape Peninsula University of Technology
Cs-137	Caesium 137 radionuclide source
CT	Computerised Tomography
CULINKE	Cultural Link Kenya
EBRT	External beam radiation therapy
EQD_2	Equivalent isoeffective dose in 2 Gray (Gy) fractions
FIGO	International Federation of Gynaecologists and Obstetricians
GCIG	Gynaecologic Cancer Intergroup
Gy_{10}	EQD_2 dose arising from linear quadratic calculation using an alpha- beta ratio of 10 for early effects
Gy_3	EQD_2 dose arising from linear quadratic calculation using an alpha-beta ratio of 3 for late effects
HDR	High dose rate: >12 Gy/hour
HOD	Head of Department
IAEA	International Atomic Energy Agency
ICBT	Intracavitary brachytherapy treatment
ICRU	International Commission on Radiation Unit and Measurements
ICT	Intracavitary therapy
Ir-192	Iridium 192 radionuclide source
LDR	Low dose rate: 0.4 - 2 Gy/hour
LQ	Linear quadratic calculation

MDR	Medium dose rate: 2-12 Gy/hour
MV	Megavoltage
NCI	National Cancer Institute US (United States)
OS	Overall survival
OTT	Overall treatment time
PC	Pelvic control
PDR	Pulsed dose rate
POP	Parallel opposed beams
Pt	Point
REF	Reference
RTOG	Radiation Therapy Oncology Group
Sq	Squamous
S-tube	Stent tube
UN	United Nations
UNICEF	United Nations Children's Fund.
US	United States of America
WHO	World Health Organization
#	A radiotherapy fraction session

Glossary of Terms

Centre I	Represents the oncology centre where data was collected in South Africa
Centre II	Represents the oncology centre where data was collected in Kenya.
Manchester system	A brachytherapy dosimetry system that gives a uniform dose distribution in the paracervical region with dose defined at point 'A'.
Point 'A'	A standard dose prescription point used in cervical cancer brachytherapy treatment. To locate Point A (right and left), a line is drawn to connect the superior aspects of the vaginal ovoids, positioned in the lateral vaginal fornices; from the interception of this line and the midline, this point is established by measuring 2cm superior along the tandem, and 2cm perpendicular in the lateral direction.
Environment	This refers to all the physical, social, and cultural dimensions in the research sites that may have an impact on the research outcome. It includes such factors as the equipment, staffing, evidence of practice, physical space, among others.

Chapter One

Introduction: An African perspective of brachytherapy in cervical cancer

1.1 Introduction

The continent of Africa with a population estimated at one billion people, has the highest cervical cancer burden in the world according to figures released by the world cancer report (WHO, 2008:418-420). The highest incidence rates in the world are reported in Southern and Eastern Africa with 43 per 100,000 women and 37 per 100,000 women, respectively. The corresponding mortality rates are 34 per 100,000 women and 23 per 100, 000 women. This compares dismally with the developed world. In the United States (US), for example, the incidence rate for all races is 8.2 per 100,000 women (Leaver & Labonte, 2010: 31). While Makin & Kamanu (2010) note that reported mortality rates in resource rich countries seldom exceed 5 per 100,000 women. This difference between Africa and the developed world is enormous, and the success in the latter, is attributed largely to wide spread comprehensive cervical cancer screening control programs (WHO, 2008:418) ;(Adewole et al., 2005:S209). In Africa, with a population of 267.9 million women aged 15 years or greater, estimates are that 78,897 women are diagnosed with cervical cancer annually and 61, 671 (78%) die from the disease (Denny, 2010:70). This is due to inadequate resources in Africa, where lack of funding, skilled personnel, and public awareness could be possible reasons. Therefore, an estimated 80% of the patients with cervical cancer in Africa (Adewole, 2005:S209), present at an advanced clinical stage. The only option for these patients is radiation therapy that is administered by external beam radiation therapy (EBRT) in addition to high dose rate (HDR) or low dose rate (LDR) intracavitary brachytherapy. It is within this context that a need arises for strategic approaches to deal with the high number of patients presenting that require treatment with radiation therapy, and the corresponding challenges within the African set-up. Therefore, this study through a case study approach, inquired into the treatment of cervical cancer in Africa. An argument is presented on the strategies that may be used to deal with this significant public health problem. The study conducted in South Africa and Kenya, presents findings and suggestions, many of which may hold for other African countries as well.

This chapter broadly examines the rationale for the study and the clinical context in brachytherapy of cervical cancer.

1.2 Rationale

The definitive treatment for locally advanced cervical cancer involves the use of external beam radiation therapy (EBRT) and brachytherapy. The frequently used gynaecological brachytherapy treatment is intracavitary treatment (ICBT), in which the radioactive source is placed inside the body cavities of the cervix and uterus. The brachytherapy technique employed is treatment with either low dose rate (LDR) or high dose rate (HDR) radionuclide sources following or concurrent with EBRT. The International Atomic Energy Agency (IAEA), through one of its publications, IAEA-TECDOC-1257 (2001), recommends HDR as an alternative to LDR brachytherapy for the management of cervical cancer for developing countries. This study on brachytherapy of cervical cancer was conducted at two Centres in Africa; the one in South Africa, and the other in Kenya, designated as Centre I and II, respectively. Centre I in this study stopped using LDR (radium-226 source) in 1995 and has been using HDR (iridium-192 source) since. Centre II in this study has both LDR (caesium-137 source) and HDR (iridium-192 source) brachytherapy equipment. The HDR implementation process at this centre has not been finalized and is still ongoing since purchase of the equipment in the year 2000. The LDR equipment in use at the centre has frequent technical breakdowns.

The present study therefore aimed to explore the suitability of HDR brachytherapy for treatment of cervical cancer in Africa by exploring the factors and issues surrounding treatment of cervical cancer at the two sites. This included; comparing treatment outcomes between HDR and LDR ICBT and an evaluation of the challenges and problems in the implementation of HDR brachytherapy. The question that guided the study was how well HDR ICBT has replaced LDR as an appropriate treatment strategy in cervical cancer treatment for African countries in terms of treatment outcomes and implementation. Given that Africa has a variety of problems including limited resources, a high cervical cancer burden, and problems of healthcare infrastructure and capacity, then strategies are needed that can be adopted to optimise the treatment of this significant public health problem.

1.3 Research Focus

The study sought to examine the problems and issues surrounding brachytherapy for cervical cancer at two Centres in Africa. Using a case study approach, the study focused on the place of HDR brachytherapy for treatment of cervical cancer by comparing patient numbers, clinical and infrastructural set-up between the two study sites, and investigated treatment outcomes of LDR and HDR ICBT. In addition, the study evaluated the implementation process of HDR brachytherapy at the two sites. This was in order to build understanding on the problems of brachytherapy within the African context. The thesis examines the evidence and presents arguments on whether HDR ICBT

may or may not be the right strategy for dealing with the large number of cervical cancer patients requiring radiation therapy treatment in Africa.

1.4 Research aim

The aim of this research was to explore brachytherapy treatment in cervical cancer at two Centres in Africa. Through an integration of the findings, the aim was to provide strategies and recommendations for treatment of cervical cancer with an African perspective. The strategies in this research, it was thought, might help to activate and sustain brachytherapy treatment, and thereby provide consistent accessibility to many patients with cervical cancer that need these services at one of the study sites.

This case study across two Centres in Africa has the potential to provide a basis for further research on brachytherapy. In addition, the findings may be used to contribute solutions beyond the two sites, since they are derived from a perspective that achieves understanding of the unique conditions that exist in Africa. This research might be of help, in combating the high cervical cancer burden on the continent.

1.5 Research question

The main study question was how well HDR has replaced LDR brachytherapy in cervical cancer treatment within the African context.

1.6 Research objective

The principal objective was to explore LDR and HDR ICBT in cervical cancer by:

1. comparing and analysing brachytherapy treatment factors and the environment at Centre I and II.
2. retrospectively determining the treatment outcomes in terms of 5-year pelvic relapse free survival, 5-year incidence of late radiation complications to bladder and rectum, and 5-year overall survival.
3. utilizing IAEA published advisory recommendations to evaluate and compare implementation of HDR brachytherapy at Centre I and II.

1.7 Background

1.7.1 Historical development of brachytherapy

The discovery of radium in 1898 by Marie Curie opened the doors for the first patients to be treated with radium implanted into their tumours (Aird, 2001:3). This marked the beginning of brachytherapy. The word brachytherapy is derived from the Greek stem word 'brachys' and is described by Coles (2010:82) as short-distance therapy, where the radionuclide source is placed into or immediately adjacent to the region requiring treatment.

Gynaecological brachytherapy began with Margaret Cleaves when using radium rays in 1903, she treated the first patient who had an advanced squamous cell carcinoma of the cervix (Aronowitz, Aronowitz, Robison, 2007: 293-294). Several days after this treatment, the patient had no bleeding, no odour, no discharge, no ulceration, and the vaginal and cervical mucous membrane appeared normal. This technique, intracavitary brachytherapy (ICBT) for gynaecological malignancies, led to the extensive use of the radium radionuclide source, with many applications in cervical cancer treatment. This is evidenced by Stitt (1997:505) quoting a statement by James Larkin in 1939, "the complete destruction of cervical cancer carcinoma in many cases of all types and stages has brought radium to the point where it is the agent of choice in the treatment of all but the early operable cases."

The challenges of radiation safety when using preloaded applicators with radium (hot loading), for example; staff exposure, storage, and an excessively long half-life of 1226 years, resulted in the use of afterloading applicators in the 1950s. These allowed the applicator to be placed in the patient and positioned, before loading the active sources (Stitt, 1997:505). The introduction of these applicators led to the development of alternative sources namely; cobalt-60, caesium-137, and iridium-192 (Joslin, 2001; Aird, 2001: 4). Then in the 1960s, Ulrich Henschke and Basil Hilaris introduced remote afterloading with high dose rate activity sources at the Memorial Hospital in New York (Joslin, 2001:354; Stitt, 1997:506; Fu & Phillips, 1990). This was the beginning of a new era and a whole new dimension in brachytherapy applications emerged. Development of treatment techniques using either low dose or high dose rate intensity sources followed in earnest.

1.7.2 Clinical context of research

Radiation treatment of cervical cancer

The treatment of choice for locally advanced cervical cancer (FIGO stage IIB to IVA) is radiation therapy as surgery is no longer an option due to the potentially unclear resection margins (Ahmed, Tan, & Shafi, 2010:153-156; Koh & Rose, 2004:179-181). Radiation therapy treatment is achieved

by a combination of brachytherapy with external beam radiation therapy (EBRT). This is sometimes referred to as definitive radiotherapy (Gerbaulet, Potter, Haie-Meder, 2002:308). In EBRT, ionizing radiation is produced in a linear accelerator or a cobalt-60 unit and delivered at a distance from the patient. The current study confined itself to the definitive treatment of cervical cancer using radiation therapy. According to the IAEA (2001) and the American Brachytherapy Society (ABS) [Viswanathan & Thomadsen, Undated], LDR ICBT is typically performed after EBRT to the pelvis. However in HDR, the EBRT and ICBT are usually combined, with the HDR beginning after about 2 weeks (or 20 Gy) of EBRT. This combination of EBRT and ICBT forms the radiation treatment strategy for cervical cancer including early cervical cancer (Stage I-IIA), for patients that are unfit for surgical interventions.

Staging of cervical cancer (FIGO clinical staging, 2009)

The International Federation of Gynaecologists and Obstetricians (FIGO) in 2009 revised the staging of cervical cancer. This was to provide uniform terminology between health professionals in terms of assessing extent of disease. This is important in the management of cervical cancer since staging is the most important prognostic factor, followed by bulk of disease (Ahmed et al., 2010:151). Each stage describes the extent of disease and is used to decide on the appropriate treatment that should be applied, either surgery, radiation therapy, or a combination of both, or use of chemotherapy as neo or an adjuvant treatment. The new FIGO staging system adapted from Han & Kohn (2010) and Soeters, Denny, Wijk et al. (2009:9) is described in detail in Table 1.1. The current study included all the FIGO stages presenting at Centre I and Centre II that were within the study period.

Table 1.1: FIGO staging of cervical cancer, 2009.

Stage I	**The carcinoma is strictly confined to the cervix**
1A	Invasive carcinoma identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5mm and no wider than 7mm.
1A1	Measured invasion of stroma no greater than 3mm in depth and no wider than 7mm.
1A2	Measured invasion of stroma greater than 3mm and no greater than 5mm in depth and no wider than 7mm.
Stage 1B	Clinical lesions confined to the cervix or preclinical lesions greater than stage 1A.
IB1	Clinical lesions no greater than 4cm in size.
IB2	Clinical lesions greater than 4cm in size.
Stage II	**The carcinoma extends beyond the cervix, but no extension to pelvic side wall. The carcinoma involves the vagina, but not as far as the lower third.**
IIA	Involvement of up to the upper two thirds of the vagina. No obvious parametrial involvement.
IIA1	Involvement of the upper two thirds of vagina, less than 4cm in greatest dimension.
IIA2	Involvement of the upper two thirds of vagina, greater than 4cm in greatest dimension.
IIB	Obvious parametrial involvement but not onto the pelvic side wall.
Stage III	**The carcinoma extends to pelvic sidewall. The tumour involves the lower third of the vagina. All cases of hydronephrosis or non-functioning kidney should be included unless they are known to be due to other causes.**
IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall.
IIIB	Extension onto the pelvic sidewall, or hydronephrosis /non- functioning kidney.
Stage IV	**The carcinoma extends beyond the true pelvis or clinically involves the mucosa of the bladder and/or rectum.**
IVA	Spread to adjacent pelvic organs and extends beyond the true pelvis.
IVB	Spread to distant organs outside the true pelvis.

Histological classification of cervical cancer

The World Health organisation (WHO:2011) classifies cervical cancer into two major histological types; squamous cell carcinomas which constitute about 85% of all cases and adenocarcinomas which constitute about 10-12% of all cases. Other types of carcinoma, for example, adenosquamous carcinoma, adenoid cystic carcinoma, small cell carcinoma, undifferentiated and metastatic tumours make up the remaining 3-5%. In this study, it was proposed to include all of the above classifications in the sampled patient cohort that received definitive radiotherapy.

Manchester brachytherapy technique

The most common dose specification system still in use for treating cervical cancer with brachytherapy today is the Manchester system that was reported in 1938 and reviewed by Todd and Meredith in 1953 (Joslin, 2001:343; Stitt, 1997:506). The system is based on an intrauterine tube or tandem with two vaginal ovoids circular in shape, or a ring and tandem set (Gerbaulet et al., 2002:313-316). This system originally defined Point 'A' as a point found by drawing a line connecting the superior aspects of the vaginal ovoids, and measuring 2 cm superior along the tandem from the interception and then 2 cm perpendicular to this in the lateral direction (Nag, Erickson, Thomadsen et al., 2000:204). This is the point that was thought to give the most dose to the paracervical region. Ferrigno, Nishimoto,Novaes, et al. (2005:1109) simply define the same point as 2 cm above the vaginal fornix and 2 cm lateral to the midline. Though dose calculation using a single point as a reference point would seem outdated, the system is still considered practical and is widely used worldwide (Toita, 2009: 25). This is because the method is easily applied by using two projection radiographs and most centres can use this method. Toita (2009: 27) notes also that a large amount of clinical experience has been accumulated using this system. The two study sites in this research both prescribe to the Manchester point 'A' dose specification system.

Anatomical topography and brachytherapy applicator insertions

The anatomical topography and position of ring/or ovoid and tandem applicators is shown in the sketch diagrams, Figures 1.1 & 1.2. The picture shows the coronal and sagittal views of the brachytherapy applicators when positioned in the vagina, cervix and uterus during brachytherapy treatment of cervical cancer. All patients within the study period who received these type (ring/or ovoid and tandem) of applicators were analysed in detail and compared between the two Centres with a further comparison with published studies in the literature.

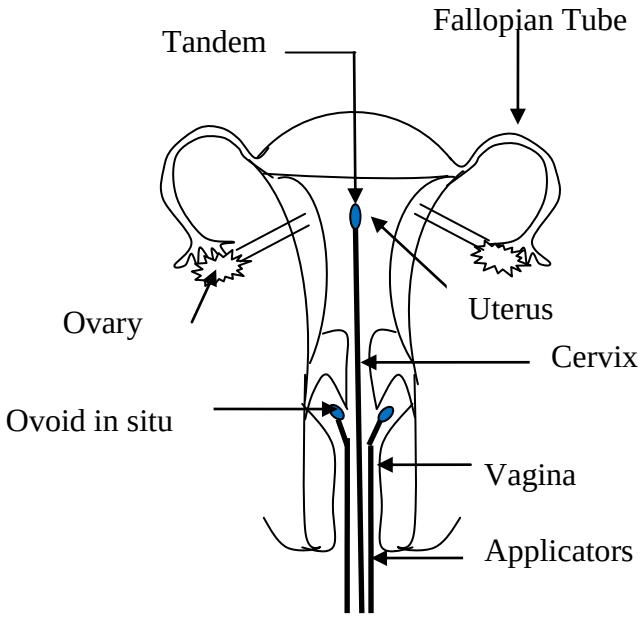

Figure 1.1: Coronal pelvic view with tandem inserted into the uterus and two ovoids positioned in the vaginal fornices.

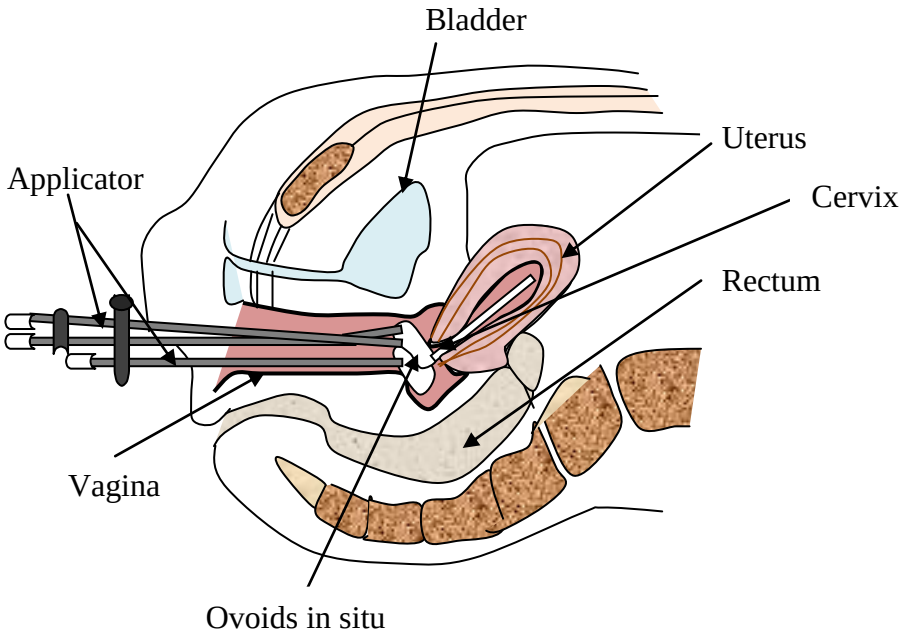

Figure 1.2: Lateral pelvic view showing, tandem and ovoids in situ.

ICRU dose reference points

The International Commission on Radiation Units and Measurements report number 38 (ICRU-38) of 1985 defines the dose reference points for the bladder and rectum when using two perpendicular radiographs, AP (coronal) and lateral. The two study sites both reported dose to the bladder and rectum using the ICRU-38 (1985:11) defined reference points.

Radiobiological considerations

Radiobiology is a science that deals with the use and effects of ionizing radiation in biological tissues and living organs. HDR and LDR ICBT for cervical cancer may result in different effects to the tumour cells and normal tissues (bladder and rectum) in terms of repair, repopulation, reoxygenation and reassortment (Stewart & Viswanathan, 2006:909-910). Therefore to compare the clinical effects of EBRT plus HDR or LDR ICBT, this study used the linear quadratic (LQ) calculation by Bentzen and Joiner (2009:109). Each treatment schedule was converted into an equivalent dose of 2 Gy fractions (EQD_2) in order to compare equivalent biological effect between HDR and LDR ICBT.

1.8 Overview of thesis

Here, a brief overview of the structure of the thesis is presented.

Chapter Two

In the next chapter, the necessary literature on cervical cancer treatment options and brachytherapy in general is reviewed. The chapter further provides the reader with the contextual framework in Africa against which this study is based. Discussion centres around different conditions and situations in a number of African countries highlighting the African perspective and how it would impact on HDR brachytherapy implementation process for treatment of cervical cancer. IAEA recommendations on implementation of HDR brachytherapy for developing countries are discussed.

Chapter Three

Describes the research design and the methodologies used to achieve the objectives of this study. These include data collection methods, procedures on data categorization, integration and analysis.

Chapter Four

The results of the study are documented and displayed in diagrams, tables, pictorials, and graphic form. Comparisons of data between the two centres is analysed and presented. Patterns in the data pertaining to the objectives of the study are outlined.

Chapter Five

The interpretation and integration of the data is discussed. The relevant links between the results and the literature is reviewed, and conclusions which include a summary of the findings and recommendations are presented.

Chapter Two

A review of the literature on brachytherapy of cervical cancer and the African setting.

2.1 Introduction

The review of the literature presented in this section is intended to build a conceptual framework in which to understand and analyse issues surrounding cervical cancer treatment that incorporates HDR or LDR ICBT within the African context. Towards this end, a structured literature search was conducted using appropriate key words to identify literature comparing LDR and HDR ICBT for the treatment of cervical cancer. There was found to be lack of literature relating to studies comparing LDR and HDR ICBT for treatment of cervical cancer in Africa, however a majority of studies done in other developing countries in Asia and South America have been cited as the context has similarities. Literature was selected from the results of the search and relevant books were searched as well as journal articles, academic papers, official publications, newspaper articles, unpublished research and materials on information related to cervical cancer treatment.

The treatment of cervical cancer, clinical experiences of HDR or LDR ICBT and the arguments on which produces better treatment outcomes are discussed. Issues within the African context in particular the high cervical cancer burden, late stage presentation, low levels of health care infrastructure, inadequate resources, and poverty are highlighted. Background information in the literature about South Africa and Kenya is provided in regard to economic disparity and situational analysis on cancer. An argument is presented from the literature on the need for strategies in Africa that may provide a solution in dealing with the high number of patients with cervical cancer that require radiation therapy.

2.2 Treatment of cervical cancer

The researcher evaluated the literature on treatment of cervical cancer and the African setting. The most common type of gynaecological malignancy in Africa was found to be cervical cancer. According to Ahmed, Tani, and Shafi (2010:153); Koh and Rose (2004:175-176), the choice of treatment modality is based on the FIGO stage, pelvic node status at the time of presentation, performance status and the anticipated side effects resulting from the type of treatment intervention that will be given. The authors note that early cervical cancer FIGO stage 1A is treated with surgery due its excellent prognosis. While, FIGO stage IB to IIA is treated by either surgery or radiation therapy depending on the most appropriate choice of management based on side effect profile. They contend that between surgery and radiation therapy for treatment of FIGO stage IB and IIA, there is no difference in survival or recurrence. Makin & Kamanu (2010) confirm the above and point out

that radical radiotherapy is preferred in centres where surgical expertise is not available or in women who are medically unfit for surgery.

With regard to locally advanced cervical cancer (FIGO stage IIB-IVA), Ahmed et al. (2010:156) state that this is treated by radical radiotherapy, consisting of a combination of EBRT and ICBT. The role played by EBRT before ICBT is emphasized by Eifel (2003:702) and Limbergen and Haie-Meder (2002:120) as that of shrinking the volume of central disease such that there is adequate dose distribution coverage of the tumour during brachytherapy, thereby controlling the disease. This is supported by Ahmed et al. (2010: 156) who note that considerable tumour shrinkage can be seen during this initial phase of treatment when EBRT is given to the whole pelvis to encompass the cervix, uterus, upper vagina, parametria, and regional lymph nodes. ICBT is then used to boost the dose to primary tumour while limiting the dose to the bladder and rectum. In the last decade, radiotherapy has been combined with concomitant platinum based chemotherapy in the treatment of advanced cervical cancer (Gerbaulet et al., 2002:301). The addition of cisplatin-based chemotherapy to EBRT has shown to improve survival by 10-17% and the most common single-agent in use now is cisplatin 40 mg/m^2 given on a weekly basis (Ahmed et al., 2010: 156 & 158). However, this study focused on treatment of cervical cancer by definitive radiotherapy combining external beam therapy (EBRT) and intracavitary brachytherapy (ICBT) and the effects of chemotherapy were not considered.

2.3 Brachytherapy

Anatomically, the cervix is a site that is easily accessible to brachytherapy devices manufactured specifically for LDR or HDR machines, making brachytherapy a crucial component for the treatment of cervical cancer. When treatment is administered by EBRT plus intracavitary brachytherapy (ICBT), patient prognosis is better than when compared to EBRT alone (IAEA TECDOC-1257, 2001:3, WHO, 2008:422).

Brachytherapy treatment for cervical cancer can be administered by either HDR or LDR ICBT. However, several authors have described controversies between radiation oncology professionals as to which gives better treatment outcomes with less toxicity to normal tissues (Viani et al., 2009; Stewart & Viswanathan, 2006; Orton, 1998). These controversies, as explained by Viani et al. (2009:1-2), may arise from the fact that HDR has been in use for about 30 years while LDR ICBT has been in use for the treatment of cervical cancer for nearly 100 years. In particular, due to inadequate tumour coverage because of bulk disease, they question whether HDR or LDR ICBT produces better results for FIGO stage III patients, in terms of survival rate, local control rate and treatment complications.

Eifel (1992:384) criticised HDR ICBT because of its narrower therapeutic index, which she argued was more critical for advanced-stage disease in which dose must be maximized to effect local control. Some studies have highlighted the controversy over treatment for FIGO stage III disease. Petereit, Sarkaria, Potter, and Schink (1999) from the University of Wisconsin reported findings that showed a poorer outcome in Stage III disease with HDR therapy, compared with their historical controls. Ferrigno et al. (2005) in their study in Brazil also found poorer outcome for stage III disease for patients treated with HDR brachytherapy as compared to LDR patients. This has led Chen, Liang, Hung, et al. (2009:1335) to question the radiobiological advantages of HDR, and note that despite these, its use has been increasing. The above authors nevertheless agree on the overall statistical equivalency between the two reported by several studies, but they suggest that LDR ICBT may be preferable for large bulky tumours. The role of HDR with concomitant chemotherapy is also noted as being controversial by Stewart and Viswanathan (2006:908-912), though they point out that the existing literature shows no significant increase in complications in patients treated with HDR and concurrent chemotherapy.

2.4 Advantages and disadvantages of HDR and LDR ICBT

In clinical practice, centres use LDR or HDR ICBT depending on their needs and historical perspectives. The advantages of HDR brachytherapy treatment for cervical cancer are documented by Nag (2004:270) as being improved radiation protection for personnel, shorter treatment times, smaller sources, and wider possibilities in treatment dose optimization. Wang, Liu, Ma, et al. (2010:15) add that other potential advantages include rigid immobilization of treatment applicators, patient convenience, outpatient treatment, accuracy of source and applicator positioning, and enhanced individualized treatment. They suggest that HDR ICBT should be considered as standard treatment strategy for developing countries.

The disadvantages are noted by Nag (2004: 270) as; radiobiological (non-repair of sub-lethal damage in normal tissue hence the need for multiple treatments), limited experience in its use (although this is growing), large initial capital expenditure, and increased potential risk in case of machine malfunction or a calculation error. The advantages of LDR brachytherapy are also well enumerated by Dusenbery and Gerbi (1997:472): long history of use, ability to predict rate of late complications, favourable dose rate effect on repair of normal tissue, infrequent replacement of sources because of long isotope half-life. Rogo, Omany, Onyango & Babu (1992) after their experience with the Amersham LDR brachytherapy in Kenya for cervical cancer, noted that although LDR is safe and acceptable, it's not recommended for centres with heavy workloads. The advantages of HDR and LDR ICBT appear to make the two both useful in the treatment of the

patient with cervical cancer. Therefore, if the practitioner is well trained, careful, and respectful of the potential use and limitations of each, both HDR and LDR ICBT would be acceptable (Koh & Rose, 2004:181).

2.5 Clinical experiences of HDR and LDR ICBT

Many radiation oncologists as early as 1991 (Orton, Seyedsadr, & Somnay, 1991) were reluctant to even consider the adoption HDR brachytherapy techniques for cervical cancer treatment. This was probably due to lack of clinical experience in its use, or due to lack of convincing evidence that could show that it can be applied at least as safely and effectively as LDR brachytherapy. In North America for example, many people remained sceptical about the efficacy and potential complications of HDR brachytherapy and continued to use LDR brachytherapy for cervical cancer treatment (Stitt, 1997:506; Fu & Phillips; 1990:791). Only in the last 20 years has the use of HDR been steadily increasing in the North and South America (Viani et al., 2009:2). HDR was more rapidly adopted in Asia and Europe, and in particular Japan, where its clinical applications started in the 1960s and a large number of patients have now been treated using HDR activity sources (Viani et al., 2009:2; Toita, 2009:25; Stitt, 1997:506).

2.6 HDR and LDR ICBT in Africa

Several studies comparing HDR and LDR ICBT of cervical cancer have been done in Asia, South America, and North America, among others, but none in Africa that has been published (Pilani, 2011). Notable studies done in Asia that would have similarities with Africa since they were based in developing countries include: Shrivastava, Dinshaw, Mahantshetty, et al. (2006) in Mumbai, India; Lertsanguansinchai, Lertbutsayanukul, Shotelersuk et al. (2004) in Bangok, Thailand; Okkan, Atkovar, Sahinler et al. (2003) in Istanbul, Turkey, and Kim, Kim, Suh, and Loh, (2001) in Seoul, Korea. All these studies showed overall statistical equivalency in treatment outcomes between the two. In South America, Brazil, a retrospective study by Ferrigno et al. (2005) that could well be replicated in Africa, showed similar overall statistical equivalency. Other studies in the developed world particularly in the US that showed similar treatment outcomes include; Falkenberg, Kim, Meleth, Santos, and Spencer in 2006, in Alabama, Birmingham and a multi-institutional questionnaire survey by Orton, Seyedsadr, and Somnay in 1991. Hareyama, Sakata, Oouchi et al. (2002) in Sapporo, Japan also showed similar treatment outcomes. The lack of such studies and representation of Africa in various world oncology groupings cannot be overemphasized. This is well illustrated in a paper by Gaffney, Bois, Narayan et al. (2007:485). They state that the Gynaecologic Cancer Intergroup (GCIG) is involved in research and treatment of gynaecologic

cancer and is composed of various cooperative groups from Europe, Asia, Australia, and North America, but no representation from Africa or South America.

In a survey on practice patterns of treatment of cervical cancer in member groups, the GICG found that out of the total number of respondents, 23 used HDR and four used LDR brachytherapy (Gafney et al., 2007: 486-487). This confirms that both types of equipment are still being used. A literature search for a similar type of survey in Africa was unsuccessful. Therefore, the need for such studies in Africa might help in analyzing the use of either LDR or HDR ICBT in combination with EBRT in order to conceptualize results from other studies around the world to the African situation. Furthermore, they may highlight the challenges and problems in regard to brachytherapy services for the high number of cervical cancer patients that require radiation therapy in Africa.

The situation in Kenya is best exemplified by the following. Rogo, et al. (1992) in their review of the Amersham LDR afterloading system, state that LDR brachytherapy for cervical cancer treatment was introduced in the country in 1986. Follow-up of patients treated by the above LDR system in the study by Rogo, Omany & Onyango et al. (1990) was characteristically poor and treatment results although difficult to calculate with accuracy, were also poor.

2.7 Cervical cancer burden in Africa

The cervical cancer burden in Africa could be attributed to numerous reasons. Two crucial factors singled out in the world cancer report (WHO, 2008:418) is the lack of effective cervical cancer screening programmes and lower levels of development of cancer related health services. These may lead to advanced clinical stage at presentation coupled with the fact that due to deficiencies in treatment availability, accessibility and affordability, many patients do not avail themselves or complete prescribed courses of treatment.

Adewole (2005: S209) in Nigeria; Wabinga, Ramanakumar, Banura, et al. (2003:68) in Kampala, Uganda; Moodley and Mould (2005:707) in KwaZulu-Natal South Africa, and Moodley, Hoffman, Carrara et al. (2006) in the Western Cape, South Africa, all confirm that a majority of the patients in their studies had late FIGO stage presentation. Adewole (2005:S209) presents an interesting argument that since most cervical cancers present late in his country, Nigeria, there is a great strain on the country's radiotherapy facilities. He therefore postulates that new approaches to radiotherapy, including HDR brachytherapy would be of interest.

The long radiotherapy waiting lists and the fact that follow-up is problematic in the African setting (Moodley & Mould, 2005:709) makes the situation even more difficult. This is because most centres in Africa for management of cervical cancer are found in urban areas and a large number of

the patients are poor and live in rural areas. Therefore the lack of access to facilities and follow-up is a critical factor mitigating against successful treatment. Makin and Kamanu (2010) add that facilities for clinical and surgical interventions for those cases presenting at a stage where such interventions might be successful are often inadequate.

2.8 Inadequate radiation oncology infrastructure in Africa

In Sub-Saharan Africa, statistics indicate that radiotherapy either for curative or palliative intent is not readily available. In Kenya, a recent report to the National Parliament underscores the lack of a proper cancer infrastructure, and notes the unavailability of cancer data due to lack of a national cancer registry (Policy Brief, 2011:4). The report points out that there is only one public oncology Centre for a population estimated at 40 million. In Africa, only 18% (155) of the estimated need of radiotherapy machines (cobalt or linear accelerator) was available in 2002 (Barton, Frommer, & Shafiq, 2006:584). Statistics from Makin & Kamanu (2010) point to low levels in the ability of African countries to provide access to radiotherapy services. In 2003, sixteen (16) countries in Africa did not have a single radiotherapy machine. In 2007, Nigeria with a population of over 140 million people had only five radiotherapy centres. Ethiopia with 60 million people has only one radiotherapy cobalt-60 external beam treatment machine. This approximates to 0.04 radiotherapy machines per million population. This ratio of one machine for several million people according to the IAEA is quite low, and compares poorly with a ratio of one machine per 250,000 people, which is typical of most developed countries (IAEA, 2003).

Therefore; accessing radiation therapy services is a major problem faced by cervical cancer patients requiring radiation therapy in Sub-Saharan Africa, and as noted by Makin & Kamanu (2010), the available facilities are often faced with constant breakdowns due to unavailability of maintenance expertise.

2.9 Transition: LDR to HDR ICBT

The information discussed so far, shows that cervical cancer patients in Africa could have a greater need for radiation therapy services than those in more developed economies. Orton (1998:119) notes that replacing LDR with HDR ICBT may not be cost effective unless the HDR unit is utilized by many patients. This he argues is due to the high initial expenditure of establishing a new HDR programme. The International Atomic Agency (IAEA) through advisory recommendations published in IAEA-TECDOC-1257 (2001:1), for implementation of HDR brachytherapy in developing countries, points out the high versatility of HDR brachytherapy equipment in achieving cure and palliation in many common cancers. Supporting the view of Orton (1998), the IAEA notes

that economic advantages of HDR only become visible when large numbers of patients are treated, but that there are unquantifiable benefits of source and personnel safety.

Institutions planning to switch from LDR to HDR or planning to introduce HDR alongside LDR brachytherapy for treatment of cervical cancer have to take into consideration several factors and issues of concern. Staffing and experience need to be considered and as emphasized by Nag (2004:270), training and expertise is a requirement for proper administration of HDR treatments. He points out that many radiation oncologists who are accustomed to LDR techniques must realize that experience in LDR cannot be automatically translated into expertise in HDR. He advises institutions wishing to introduce HDR brachytherapy to survey the experiences of centres that have been performing HDR.

Technical, clinical and practical factors are involved when making a decision to change to HDR therapy. Infrastructure, source and personnel safety require careful attention (IAEA-TECDOC-1257, 2001:1). The IAEA further recommends the following to be in place before introducing HDR brachytherapy treatments: infrastructure, a supportive budget, specialized training, and quality assurance programmes, all of which require capital expenditure. Hence the need to address availability of resources, technical and staffing requirements, is key to the successful implementation of HDR. These will in turn impact on the sustainability of brachytherapy services. HDR units utilizing the Co-60 isotope have been implemented in Nigeria and Tanzania (Ntekim et al., 2010); Van Wijk, 2010). The effectiveness of this modality in the African situation will need to be evaluated.

2.10 South Africa and Kenya: Comparison

South Africa, one of the countries where this study was conducted, has a population of about 50 million according to 2011 estimates (South Africa, 2011; Times Live, 2011). According to the World Fact Book[1] (2011), South Africa is a middle-income emerging market with an abundant supply of natural resources and modern infrastructure and a 2010 estimated GDP (Gross Domestic Product) of $524 billion. Several EBRT and brachytherapy equipment are available in the country both private and public. IAEA (201I) estimates the ratio to be between 3 and 5 radiotherapy machines per million people. According to Fokazi (2011), in addition to these facilities not being adequate to serve the population, stigma about cancer caused mainly by misinformation, lack of awareness and cultural myths persist. Conversely, Kenya, the other country where this study was conducted in East Africa, is a low-income country with an estimated population of 39.8 million (UNICEF, 2009). It ranks as a country of low human development at 128 out of 182 countries by

the 2010 Human Development Report (Merlin, 2010), and has a 2010 estimated GDP of $66 billion (World Fact Book[2], 2011). The country despite the high population topping nearly 40 million has only one public oncology centre, and recently a private centre was established with two linear accelerators and no brachytherapy equipment (Wekesa, 2011). Available information indicates that the country has only two public EBRT machines and three brachytherapy units. IAEA (2011) estimates the ratio to be less than 1 machine per million people.

Though efforts to address the post apartheid imbalances in South Africa continue, daunting economic problems remain. Unemployment remains high and outdated infrastructure has constrained economic growth (World Fact Book[1], 2011). Approximately 57% of individuals in South Africa were living below the poverty line in 2001, though the Western Cape Province where this study was conducted had the lowest proportion in poverty estimated at 32% (Schwabe, 2004). These may impact on the cervical cancer situation in the country. According to Botha (2009:444), cervical cancer is the most common cancer diagnosed in women in Southern Africa. Analysing data from South Africa that has a population estimated at 50 million, Denny (2010:70) reports that current data for new cervical cancer cases is lacking in South Africa due to the failure to maintain the pathology based cancer registry. Nevertheless, she notes that an average of 3,378 new cases of cancer of the cervix were reported annually, using available data between 1993 and 1995. In addition, she quotes the South African Cancer Registry, which reported on cancer incidence in 1998-1999, with 6,061 and 5,203 new cases of cervical cancer respectively. These figures are quite high when compared with statistics from the US that has a population of over 300 million, where 13,162 women aged 15 years and older, develop new cancer cases per year (Denny, 2010: 70).

In Kenya, poverty remains a critical development challenge and is widespread throughout the country (CULINKE, 2011). According to Capital FM (2010) and Policy Brief (2011), the country has only one public hospital that offers cancer treatment, and is unable to cope with the huge number of cancer patients seeking treatment at the facility. This situation is described by Capital FM (2011) that quoted the head of the cancer unit requesting for support for the Centre that receives about 4,000 patients each year, with cervical cancer topping the list. This he said is followed by breast and head and neck malignancies. He emphasized on the need to develop other cancer units and improve on facilities and manpower development in the area of cancer in the country. The same report quoted the Minister of Medical Services in Kenya stressing the need to develop proper facilities with trained personnel who can treat patients scientifically and effectively. He deplored the little progress that was being made in the country on cancer prevention and treatment.

2.11 Need for strategies for Africa

The need for strategies in the treatment of cervical cancer cannot be overemphasized. The study by Ferrigno et al. (2005), recommended that HDR ICBT be used for developing countries if a proper adequate fractionation scheme protocol is formulated within a proper overall treatment time (OTT). A meta-analysis done by Wang et al. (2010), that reviewed randomised controlled trials done in Asia, showed similarities in treatment outcome between HDR and LDR ICBT. Due the potential advantages of HDR ICBT, they also recommended HDR ICBT as standard treatment modality for patients with cervical cancer instead of LDR ICBT, especially for developing countries. The IAEA-TECDOC-1257, (2001), Ferrigno et al. (2005), and Wang et al. (2010) among others seem to suggest HDR as a better strategy for cervical cancer treatment for developing countries. This study sought to determine how well LDR ICBT has been replaced by HDR, by establishing the place of HDR as a modality and treatment strategy for cervical cancer within the African context, considering the vast challenges that exist in healthcare provision on this continent.

2.12 Summary of Literature Review

The main issues mentioned in this literature review have centred on aspects of cervical cancer and treatment using radiation therapy, in addition to a description of the situation in Africa that might impact on accessibility of these services to the patients that require them. These aspects are relevant to this study, although a broader framework has been provided for studies in Africa that might contextualise the African perspective with regard to cervical cancer and brachytherapy services. The salient points are now summarised to capture the most important aspects before proceeding to the following chapters.

Cervical cancer is the most common gynaecological malignancy. Early cervical cancer (FIGO stage I-IIA) might be treated with surgery, and locally advanced cervical cancer (FIGO stage IIB-IVA) with radiation therapy (Ahmed et al., 2010, Koh & Rose, 2004). Radiation therapy is administered by EBRT followed by HDR or LDR brachytherapy. EBRT plus ICBT results in better patient prognosis than when compared to EBRT alone (IAEA-TECDOC-1257, 2001; WHO, 2008). The role of EBRT is best exemplified by Eifel (2003), Limbergen & Haie-Meder (2002) and Ahmed et al. (2010) as that of shrinking the volume of central disease before application of brachytherapy devices, resulting in adequate tumour coverage.

There have been numerous controversies over the efficacy and safety of HDR brachytherapy. Nevertheless, several studies have shown statistical equivalence between HDR and LDR ICBT including Shrivastava et al. (2006); Lertsanguansinchai et al. (2004) in Asia, Ferrigno et al. (2005) in South America, and Falkenberg et al. (2006) and a multi-institutional questionnaire survey both

in the US (Orton et al., 1991). The use of HDR ICBT is currently on the increase as shown by Viani et al. (2009) and Toita et al. (2009). Some authors suggest the use of LDR ICBT for large bulky tumours (Ferrigno et al., 2005, Petereit et al., 1999). However, the potential limitations of each are noted by Koh and Rose (2004) as being acceptable, on condition that the practitioner is well trained and careful in the handling and application of either modality.

Africa has few radiotherapy machines that are not adequate (IAEA, 2003), and by 2002, this was estimated at 185 of the entire need of the continent (Barton, Frommer & Shafiq, 2006:584). There is a lack of published studies determining the exact number of HDR and LDR machines available in Africa and studies comparing treatment outcomes of the two (Pilani, 2011). Access to these facilities, maintenance challenges, constant breakdowns, and follow-up of patients treated are critical factors mitigating against successful treatment of cervical cancer. Makin & Kamanu (2010) contend that facilities for clinical and surgical interventions at a stage where such interventions might be successful are always inadequate. The high cervical cancer burden is due to lack of effective screening programmes (WHO 2008) and a large number of patients presenting with late stage disease that can only be effectively treated with radiation therapy. Therefore provision and accessibility of brachytherapy services is a key concern in Africa that needs to be evaluated. In Sub-Saharan Africa, statistics indicate that radiotherapy either for curative or palliative intent is not readily available (Makin & Kamanu, 2010; Barton, Frommer, & Shafiq, 2006), and results in long waiting lists (Moodley & Mould, 2005). These put a strain on the few radiotherapy facilities available, and Adewole (2009), notes that new strategies are needed including HDR brachytherapy.

The IAEA through advisory recommendations published in IAEA-TECDOC-1257 (2001) recommends HDR for developing countries. The study is set in two countries in Africa (South Africa and Kenya) that have similar profiles for the cervical cancer patient in terms of late clinical presentation and the high volume of patients with cervical cancer that require radiation therapy. However the economic disparity between the two countries is enormous (World Fact Book[1], 2011; World Fact Book[2], 2011). The successful implementation of an HDR programme may depend on a number of factors. The study therefore evaluated how well HDR ICBT has replaced LDR in the two African settings, in the search for a strategy to deal with the high number of patients with cervical cancer that require radiation therapy on the continent.

Chapter 3

Research methodology

3.1 Introduction

The current chapter provides information on the research design and methods used in conducting this study. This case study employing a mixed method approach identified a number of factors that are associated with brachytherapy treatment of cervical cancer. This was in order to gather data that would answer the initial proposition in this case study of how well HDR brachytherapy has replaced LDR as an appropriate treatment strategy for cervical cancer within the African context.

Two research sites were identified in Africa, one in South Africa with HDR brachytherapy, and the other in Kenya with LDR and HDR brachytherapy equipment, and are designated as Centre I and Centre II, respectively. Quantitative and qualitative data was gathered through a case study inquiry. The chapter explains why the case study with a mixed method research design was adopted, and then gives a description of the research methods applied in the study, explaining the samples, research tools and data collection strategies. The chapter concludes by explaining the processes used by the researcher in data analysis and a discussion of issues relating to ethical considerations, assumptions and delimitations of the study.

3.2 Research design

Yin (2009:41-42, 114-116) and Babbie and Mouton (2001:282-283) argue against the use of single sources of evidence in conducting case studies, and recommend the use of multiple sources of evidence as a way to ensure construct validity. This case study utilizing mixed method research explored brachytherapy service provision at Centre I and II. The qualitative and quantitative data gathered generated both numeric and textual data from various perspectives. The researcher first identified a series of factors at Centre I and Centre II that are associated or may have an impact on the provision of a brachytherapy service. These were: infrastructure, clinical protocols, number of patients, clinical factors, treatment outcomes of LDR and HDR ICBT, and the HDR implementation process.

Quantitative and qualitative data was collected about each factor at both centres. Facts were gathered from various sources that encouraged the development of converging lines of inquiry aimed at corroborating the evidence of whether HDR brachytherapy is an appropriate treatment strategy for cervical cancer within the African setting. These generated a richer and stronger array of evidence that explored the dimensions of the research question

3.2.1 Research questions

The main research question arising from the objective of this case study inquiry was:

How well has HDR replaced LDR brachytherapy in cervical cancer treatment within the African context?

To answer this question, quantitative and qualitative data was collected guided by the following sub-questions:

1) How does Centre I and II compare in terms of brachytherapy set-up and specified factors associated with cervical cancer treatment?
2) How does HDR brachytherapy compare with LDR brachytherapy in terms of 5-year pelvic relapse free survival, 5-year incidence of late radiation complications to bladder and rectum, and 5-year overall survival?
3) How effective was the HDR brachytherapy implementation process at Centre I and Centre II?

3.2.2 Quantitative and qualitative components

The following table gives a description of the detailed quantitative and qualitative data that was collected (Table 3.1).

Table 3.1: A description of quantitative and qualitative components of the case study.

OBJECTIVE OF INQURY	**TYPE OF DATA**
Infrastructure settings	*Qualitative (Observations/pictures)*
Clinical protocols	*Qualitative (Documentation)*
Number of patients	
Numbers at each Centre	*Quantitative / Qualitative (Spread sheet and explanations)*
Number Treated	*Quantitative / Qualitative (Spread sheet and explanations)*
Clinical factors	
FIGO stage,	*Quantitative (Data sheet and spread sheet)*
Histology	*Quantitative (Data sheet and spread sheet)*
Age	*Quantitative (Data sheet and spread sheet)*
Number of fractions	*Quantitative (Data sheet and spread sheet)*
Biological dose	*Quantitative (Data sheet and spread sheet)*
Overall treatment time	*Quantitative (Data sheet and spread sheet)*
Follow-up	*Quantitative (Data sheet and spread sheet)*
Treatment outcomes (HDR & LDR ICBT)	*Quantitative (Data sheet and spread sheet)*
HDR implementation process	*Qualitative (questionnaire/interviews/documents)*

Records of patients treated by radiotherapy for cervical cancer at Centre I and II were retrospectively analysed. The researcher followed up with further lines of qualitative inquiry through interviews and informal conversations with relevant staff members at the two Centres to gain in-depth clarity in enhancing understanding beyond the quantitative data collected. Yin (2009: 101-102) states that a good case study should use as many sources of evidence as possible and describes six: documentation, archival records, interviews, direct observations, participant observation and physical artefacts. Brink, van der Walt and van Rensburg (2006:110) add questionnaires and written accounts by the participants as popular approaches to data collection in case studies. This case study closely followed the above recommendations and gathered qualitative data on HDR brachytherapy implementation process at the two centres through questionnaire techniques and interviews involving key staff members. Information from official letters, purchase and contract documents, equipment manuals, spontaneous conversations and ad hoc conversations was also gathered. Observations by the researcher played a key role in corroborating the evidence gathered.

3.3 Site selection

This study was conducted at two oncology centres, one in South Africa (Centre I), and the other in Kenya (Centre II), between the months of August, 2010 and March, 2011. The two sites were selected to represent the varied African context. Centre I represents the few countries in Africa with a fairly advanced oncology infrastructure, though not yet matching other middle income economies and the developed world, that are estimated by the IAEA (2011) to have 5 or more radiotherapy machines per million people. Centre II is a country in Africa with a limited radiation oncology resource setting typical of the majority of African countries, with less than 1 radiotherapy machine per million people according to the IAEA (2011). Centre I utilizes a HDR Flexitron brachytherapy unit and Centre II conducts treatments with a Caesium 137 Selectron LDR brachytherapy unit. In addition, Centre II has a Nucletron HDR brachytherapy unit that is not yet operationalized.

3.4 Research method

The following methods were used to answer research questions 1, 2 and 3.

3.4.1 Part of question 1

To answer sections of question 1 on brachytherapy set-up at the two Centres on infrastructure settings and clinical protocols, the researcher employed the following methods.

Infrastructure settings

Observations were made and the researcher recorded the brachytherapy infrastructure at the two Centres through documentation and picture images.

Clinical Protocols

The Clinical protocols used at the two Centres were recorded and discussions were held with the relevant radiation oncologists at each site.

3.4.2 Part of question 1 and 2

To record data on the specified factors on the number of patients, clinical factors and treatment outcomes as stated in sections of question 1 and 2, an excel spreadsheet was prepared from the brachytherapy register of all patients who underwent brachytherapy at Centre I from January 1998 to December 2004. This period was selected as the first two years overlap with the period selected for Centre II. Secondly, 1998 is the time Centre I introduced EBRT treatment regimes of 4 fractions (#s) per week rather than 3#s per week. The 4#s per week was considered close to 5#s per week used by Centre II. At Centre II, a spreadsheet of all patients who underwent cervical cancer treatment was prepared from the main records source book from January 1993 to December 1999 as the brachytherapy register had gaps between 1993 and 1998. The year 1999 was selected because that was the period when the planning system malfunctioned resulting in the discontinuation of brachytherapy treatment for patients with cervical cancer. Brachytherapy using the planning system was re-introduced briefly in 2009 but the LDR equipment developed a technical problem that had not been repaired at the time of conducting the study.

Number of patients

To determine the number of patients on brachytherapy over a 7-year period at the two centres, the prepared excel sheets were analysed, and all patients who were for other applications other than gynaecological were excluded.

Clinical factors and treatment outcomes for cervical cancer

To analyse and compare treatment factors and outcomes for patients with cervical cancer who received brachytherapy at the two centres, the following criteria were used:

<u>Inclusion Criteria</u>

All cancer of the cervix patients who received EBRT and brachytherapy treatment using a ring and tandem applicator for Centre I, and ovoids and tandem applicator for Centre II.

Exclusion criteria

All patients

i) that underwent cylinder insertions
ii) that were found to be not suitable for applicator insertions
iii) with incomplete clinical or dosimetric data
iv) whose files were missing or could not be traced

Sample size determination

A systematic random sample of 212 patients for Centre I was selected from the population of 468 patents who underwent radical treatment of EBRT plus brachytherapy using ring and tandem applicators. The sample size of 212 patients was calculated using statistical software OpenEpi-Version 2.3.2 (2009). This is an open source program for use in research and provides a number of statistical tools for summary data, and had its initial development supported by a grant from the Bill and Melinda Gates Foundation (Wikipedia, 2011; OpenEpi, 2010).

To calculate this sample size of 212 patients at Centre I, the hypothesized frequency of outcome factor in the population based on the literature available was put at 50%, and the statistical level of confidence used was 95%, with a 5% maximum allowable error for any differences observed (Moore, 2007:200). The same was applied at Centre II, and a sample size of 44 patients was calculated from the population of 49 patents who underwent radical treatment of EBRT plus brachytherapy treatment using ovoid and tandem applicators, after exclusion factors were applied. This number being small compared to Centre I, the researcher decided to include all the 49 patients in the study.

Research Instrument

The research instrument, a data sheet for question 1 and 2 was first piloted by the researcher. At Centre I, ten (10) files that were not part of the study were assembled by the researcher and the data sheet was used to fill out the required information. Some necessary information was found to be missing and was included in a revised version, while duplicated sections were merged to simplify the data sheet. Following the changes, there was information flow on the data sheet that facilitated easy and accurate data collection (Annexure, A1). For Centre II, the need for additional changes became apparent after the first two folders were analysed, since LDR is administered as a single fraction. The revised data sheet (Annexure, A2), reflects the information gathered for Centre II.

Data Collection

The list of the sample of 212 patients at Centre I was used to retrieve patient folders and data was collected using the research instrument (Annexure A1). For Centre II, data was collected using the research instrument (Annexure A2) from the 49 folders identified. Brachytherapy and EBRT dose to point 'A', rectal and bladder points as defined by the ICRU-38 report (1985) was recorded. Data to assess pelvic relapse free survival was captured by a recording of the first day of treatment by EBRT, to the date of recurrence of disease to the cervix, vagina, parametrium, or loco-regional recurrence. Grade 3 & 4 complications to bladder and rectum were recorded based on the information available in the folders, as for the studies done by Hellenbust, Olsen, & Kristensen (2010:714) and Ferrigno et al. (2005:1111). A completed data sheet at each Centre is attached (Annexure A1A and A2A). The identified late grade 3 & 4 complications were given to an independent radiation oncologist to verify the grading score as assessed by the researcher (Annexure A2B).

Analysis criteria for question 2

a) Treatment outcome in terms of pelvic relapse free survival were confined to recurrences to the cervix, vagina, parametrium and loco-regional disease. Distant metastasis without recurrence to the cervix, vagina, parametrium and pelvic region was considered as pelvic relapse free. The percentage of patients that achieved a complete tumour response to radiotherapy, and were included in this analysis, were recorded for each Centre.
b) Treatment outcome in terms of late radiation complications was confined to grade 3 & 4 toxicity criteria for bladder and rectum as defined by the Radiation Therapy Oncology Group, RTOG (Cox, Stetz & Pajak, 1995). Grade 1 and 2 toxicity plus complications to other anatomical sites were not considered.
c) Survival outcome was confined to 5-year overall survival. Disease specific survival was not considered.

Study assumptions for question 2

The researcher made the following assumptions:

i) That point 'A' was the standard reference and comparison point for all patients at both centres since they both prescribe to the Manchester system.
ii) That the rectal and bladder points marked on radiographs for all patients at the two centres are the ones defined by the ICRU-38 report (1985).

iii) That the contribution of the EBRT dose to point A, ICRU rectal and bladder points, was the dose prescribed to the ICRU reference point at the centre of the planning target volume from the 4 field box pelvic dosimetric plans.

iv) That the contribution of the EBRT dose to point A, ICRU rectal and bladder points, was the calculated midpoint dose from the pelvic parallel opposed (POP) beams.

v) That the entire dose points described above would be assumed to represent dose to the whole volume of the specific organ in question, due to lack of image guided brachytherapy to generate dose volume histograms (DVHs) at the two centres.

Delimitations for question 2

a) The effect of chemotherapy on treatment outcome was not considered as a variable in this study.
b) The effect of HIV on treatment outcome was not considered as a variable in this study.

3.4.3 Question 3

To answer question 3, an evaluation of the HDR implementation process at Centre I and II was considered based on IAEA published advisory recommendations on HDR brachytherapy in developing countries. The IAEA is a United Nations (UN) body that has one of its main functions as that of providing information and supporting scientific and technical exchanges in the various fields of science involved in peaceful applications of nuclear technology, to ensure safety and security (IAEA, 2010). The organisation has published several guidelines and recommendations in the field of radiotherapy. The researcher structured questions (Appendix B and C) to reflect issues surrounding the HDR brachytherapy implementation process derived from the IAEA document: Implementation of microsource high dose rate (mHDR) brachytherapy in developing countries (IAEA-TECDOC-1257: 2001).

Participant selection

Three (3) participants were selected at Centre I and four (4) participants were selected at Centre II. They were purposively selected on their ability to contribute to the information needed; meeting the requirement of case studies to have fewer participants but a detailed level of analysis (Stringer, 2004:12; Brink et al., 2006:110; Becker, Dawson, Devine, Hannum, Hill, *et al*., 2005). The criterion defined by the researcher was a member of staff:

i) involved in brachytherapy treatment of gynaecological malignancies at the Centre.
ii) with the relevant knowledge and experience to inform the study (Stringer, 2004:12).
iii) who will provide a broad perspective of the multidisciplinary team involved in brachytherapy.

The professionals selected at Centre I were a radiation oncologist, a medical physicist, and a mould room technologist. At Centre II, a radiation oncologist, two medical physicists and a radiation therapist were included in the survey. However, other professionals were also interviewed on an adhoc basis to provide clarity on the information gathered.

Data collection & research instruments

Data was sourced by a self-directed questionnaire (Annexure B), and a researcher guided questionnaire interview (Annexure C). The questionnaires were piloted by one staff member in order to ensure correct use of phrases from the workplace. Anomalies found were corrected and the questions were adjusted to make them easy to understand and answer. Additional data was collected by the researcher from follow-up discussions with the radiation oncologist specialized in gynaecological malignancies and the medical physicist at Centre I, and the head of department and the medical physicist in-charge at Centre II. Unsolicited data was also collected by the researcher from spontaneous conversations and informal interviews with other members of staff. Documentary evidence was gathered from official letters, purchase and contract documents, including equipment manuals, available at the two centres. Observations by the researcher were also recorded.

Sources of evidence

The three principles suggested by Yin in collecting evidence for case studies (2009:114-124); multiple sources of evidence, creating a case study data base, and maintaining a chain of evidence were adhered to in this study. Navigation through the case study data base that was created is shown as an annexure (Annexure D). The reference codes (ref code) used that allow for any evidence cited in the discussions or conclusions in this study, to be traced to the database is discussed in the following section.

Data sources and reference codes used in the findings

All the participants and sources of data gathered in the study were given a code. The coding system, developed to identify the participant and data sources, is summarised in the Tables 3.2, 3.3, and 3.4. All information gathered was classified according to the source, for example, CIID2 refers to a document at Centre II coded D2. In addition, the questions developed from the IAEA-TECDOC 1257(2001) provided a basic reference for the textual data sources (Table 3.4). For example, CIPr1AB4-5 refers to a response from Professional 1 at Centre I on question 4 to 5 from questionnaire Annexure B on HDR purchase considerations. However, it's noted that the data sources frequently contributed to information beyond what was planned and information that was not relevant to the objectives of the study was also given, but was excluded from analysis or discussion.

Table 3.2: Reference codes for professionals and data sources at Centre I.

DESCRIPTION	REF CODE
Professional 1	CIPr1
Professional 2	CIPr2
Professional 3	CIPr3
Annexure A	AA
Annexure B questionnaire	CIAB
Annexure C questionnaire	CIAC
Follow-up interview	CIFOIN
Informal Interview	CIADHOC
Research feedback	CIRF
Researcher notes (2010, 2011)	CIRN
Spontaneous conversation	CISC
Document I	CID1
Observations	CIOBS

Table 3.3: Reference codes for professionals and data sources at Centre II.

DESCRIPTION	REF CODE
Professional 1	CIIPr1
Professional 2	CIIPr2
Professional 3	CIIPr3
Professional 4	CIIPr4
Professional 5	CIIPr5
Professional 6	CIIPr6
Annexure A	CIIAA
Annexure B questionnaire	CIIAB
Annexure C questionnaire	CIIAC
Follow-up Interview	CIIFOIN
Informal Interview	CIIADHOC
Spontaneous conversation	CIISC
Document I,2,3,4,5,6,7, & 8	CIID1,CIID2,CIID3,CIID4,CIID5,CIID6,CIID7,& CIID8
Observations	CIIOBS
Researcher notes (2010,2011)	CIIRN

Table 3.4: Data codes for questionnaire B and researcher guided questionnaire interview C.

RESEARCH ACTIVITY (QUESTION ADDRESSED)
Purchase considerations - questionnaire/interview (AB4-5)
Planning for purchase -questionnaire/interview (AB6-21, AC1-2)
HDR ongoing costs - questionnaire guided interview (AC3)
Comparison of LDR & HDR - questionnaire guided interview (AC4)
Challenges of HDR implementation - questionnaire guided interview (AC5)
QA implementation of HDR - questionnaire guided interview (AC6)

3.4.4 Ethical considerations

Information gathered from the patient folders and database was kept in electronic format and could only be accessed by use of a password by the researcher and the supervisor. All departmental records at Centre I and II were kept in a folder that could only be accessed by the researcher and supervisor. This was to maintain confidentiality of patient information and privacy of departmental records at the two centres. All the participants who participated in the study through questionnaires and interviews were requested through an invitation letter and were required to sign a consent form (Annexure E). This ensured that their participation in the study was voluntary, and confirmed that their responses were not to result in judgment of themselves or the Centre. They were also to be kept informed of the results of the research. The participants and all the information accrued in the conduct of this study was allocated a code and reference number as explained in the previous section. This maintains confidentiality of all participants.

The study adhered to all ethical and approval processes as prescribed by the Cape Peninsula University of Technology (CPUT), Centre I and Centre II. All the approvals that were granted are not attached due to confidentiality issues. Permission was first obtained from the head of department at Centre I (dated 3rd June, 2010) on condition that ethics clearance be obtained from the CPUT and the Medical Superintendent of the hospital. Ethics clearance was obtained from CPUT (dated 14th, July 2010, ref: CPUT/HW-REC 2010/007) and permission from the hospital superintendent was sought and granted (dated 26th, July, 2010). At Centre II, permission was sought from the head of department at the Centre (dated 7th, June, 2010) who directed that ethics clearance first be obtained from the joint hospital and university ethics research committee (ERC). This was obtained (dated 17th, November 2010) and handed over to the head of department before data collection at the Centre began.

3.5 Data analysis and presentation

The data analysis followed the initial proposition in this case study of how well HDR ICBT has replaced LDR as an appropriate treatment strategy for cervical cancer within the African setting (Yin, 2009:130). The researcher defined the unit of analysis as, 'appropriateness of HDR in the African setting' (Babbie and Mouton, 2001: 281; Tellis, 1997:3). The researcher categorized the data under the following issues to help provide a focus for the findings:

- Infrastructure setting at Centre I and II.
- Number of patients handled by HDR at Centre I compared to LDR at Centre II.
- Patient profile at the two Centres. Do they represent the African profile described in the literature? Late presentation of disease, and majority being in stage II and III.
- Overall treatment time (OTT) at each Centre.
- Treatment time for each session.
- Biological equivalent dose at the two centres (EQD_2) Gy_{10} and $Gy_{3.}$
- Treatment outcomes of HDR in comparison to LDR, and comparison with results from published literature.
- Challenges of using HDR, and comparisons with LDR.
- Challenges of HDR implementation.

3.5.1 Number of patients

The number of patients treated at the two centres was analyzed by use of an excel spreadsheet, compared and displayed in graphical format.

3.5.2 Patient clinical profile

The FIGO staging of patients with cervical cancer at the two centres was analysed by use of an excel spreadsheet and presented in tabular format. This was followed by pathological classification and age at the time of starting EBRT treatment.

3.5.3 Number of fractions

The number of fractions administered at each Centre was analysed using an excel spreadsheet, and is presented in graphical format.

3.5.4 Overall treatment time (OTT)

The overall treatment time to complete both EBRT and ICBT was analysed between the two Centres and is compared.

3.5.5 Biological dose (EQD2) at the two Centres

Data from Centre I & II on dose was entered into two separate Microsoft excel spreadsheets, specially prepared with the help of an experienced staff member at Centre I, to help minimize calculation errors. Equivalent dose per 2 Gy fractions (EQD_2) was calculated using the linear quadratic formula for isoeffective dose by Bentzen and Joiner (2009:109-112) that had been fed into the excel spread sheets.

For Centre I, the following formula was used:

$$EQD_2 = D\,\frac{d+\alpha/\beta}{2+\alpha/\beta}.$$

where EQD_2 is the dose in 2 Gy fractions,

D is total dose given,

and d is dose per fraction size,

α/β ratio is defined either for acute effects, or late effects.

This formula was used to calculate the equivalent dose contributed by EBRT to point 'A'. The same formula was used to calculate the equivalent dose of HDR ICBT to point 'A', where D was the total dose given, and d was the average dose per fraction given over a number of days.

For Centre II, the formula was adjusted to cater for the influence of incomplete repair for continuous low dose rate irradiation, and is shown below:

$$EQD_2 = D\frac{dg+\alpha/\beta}{2+\alpha/\beta},$$

where D is the total dose prescribed, and d is the same as D for single continuous exposures used at Centre II.

A factor g was added in the above formulae for brachytherapy exposures lasting between 1 hour and 4 days, using values given by Bentzen and Joiner (2009:113). The value of g used was of 0.367 and was derived from the table by Bentzen and Joiner (2009:113), using a repair half time ($T_{1/2}$) of 2.00, that was estimated using values given by Fowler for various pelvic complications (Bentzen & Joiner, 2009:124). An average single LDR ICBT exposure at Centre II was estimated to last 12 hours.

At both Centres, the α/β ratio at point A dose that was used was 10 for acute effects/tumor (Gy_{10}), and 3 for the late effects of bladder and rectum (Gy_3).

The EBRT and brachytherapy dose for each patient was then added together to get the equivalent dose in 2 Gy fractions (EQD_2) for Point 'A', bladder and rectum that could be compared between

the two Centres. The measure of central tendency was calculated for the summative EQD_2 s for EBRT and LDR or HDR, respectively, by using IBM SPSS Statistics Version 19 (2010). Leedy & Ormond (2005: 30) note that descriptive statistics summarize and explain the nature of the data obtained.

The effect of OTT (overall treatment time) of EBRT and ICBT combined was also considered to take into account the estimated effects of repopulation.

3.5.6 Treatment outcomes

Data from question 2 was analysed by descriptive and inferential statistics. The statistical packages used were IBM SPSS Statistics Version 19 (2010), Graphpad Prism Version 3.02 (2000), OpenEpi (2010), and Microsoft Excel Office (2007). The results of HDR ICBT at Centre I and LDR ICBT at Centre II were compared. Endpoints of pelvic relapse free survival, complications and survival were estimated using the Kaplan-Meier method and comparisons between treatment groups were performed using the log-rank test. An overall measure of confidence of 95% was used to see if there is any difference among distributions of treatment outcomes between LDR and HDR ICBT. This was in order to decide which of the outcomes differ and to estimate how large the differences would be (Moore, 2007:554). This being a case study, the focus was not on a universal realizable truth, or cause effect relationship, but emphasis was placed on exploration and description of the data obtained (Becker, 2005). The purpose was to examine the interplay of all variables, in an in-depth analysis over time, in order to provide a complete understanding of HDR ICBT in cervical cancer within African settings (Becker, 2005; Leedy & Ormrod, 2005:135; Creswell, 2007:73). The results obtained are displayed in tabular format, scatter plot and bar graphs in chapter 4. They are then the compared to results from published literature in chapter 5.

3.5.7 Implementation of HDR

The qualitative data generated from evaluation of the HDR implementation process was integrated with the numerical and textual data and analysed. This is described in the following section.

3.6 Data integration and analysis

The data generated from infrastructural settings, clinical protocols, patient statistics and historical records, patient variables, treatment outcomes, and evaluation of the HDR implementation process at both Centres was integrated and analysed. Using both quantitative and qualitative data in case studies leads to a strong analytic strategy (Yin, 2009:132; Flyvbjerg, 2004:432). This data was categorised and coded in line with the initial propositions generated from the objectives of the study, questionnaires and interviews (Babbie & Mouton, 2001:389, 499). To increase reliability,

another expert in the field encoded the same data to assess concurrence (Brink et al., 2006:185). The emerging categories are summarised in Table 3.5.

Table 3.5: Emerging data categories.

CATEGORY	ITEM
1	Number of patients
2	Patient profile
3	Overall treatment time (OTT)
4	Mean treatment time per session
5	Biological equivalent dose at Centre I and II (EQD_2), Gy_{10} and Gy_3.
6	Treatment outcomes of HDR in comparison to LDR (Centre I, II and results from published literature.
7	Challenges of using HDR

The categories were then assessed by the researcher by making connections between them in order to answer the main research question on the appropriateness of HDR brachytherapy within African settings, which was used by the researcher as the main unit of analysis (Yin, 2009:147; Tellis, 1997: 2). A check list and question format adapted and modified from Leedy & Ormrod (2005:173) was used in this exercise. This is shown in Table 3.6.

3.6.1 Assessment of categories

Table 3.6: Method of assessment (Adapted & modified from Leedy & Ormrod (2005:173)

	Is HDR appropriate? (in what ways)	**Is HDR not appropriate?** (in what ways)	**Maybe/Maybe not**	**Evidence /Support Source**
Category 1				
Category 2				
Category 3				
Category 4				
Category 5				
Category 6				
Category 7				

The themes that emerged were subjected to discussion and interpretation by staff and those who provided the data at the two Centres. This is described by Becker et al. 2005 as member check; where the researcher initiates and maintains an active corroboration with the research participants in the study. The categories were refined, with recording of further support data, in order to increase construct validity with multiple sources of evidence through a process of data triangulation and identification of propositions ((Yin, 2009:102-124; Brink et al., 2006: 184; Tellis, 1997:2).

3.7 Interpretation

The information that emerged was interpreted and conclusions and recommendations were drawn, in order to address the main research question. The researcher acknowledges that the unavoidable variation in sample size from two populations, and the different timeframes in this study, could compromise the application of trend analysis. Furthermore, given that the researcher acted in a participant observer status, the possibility of bias in the study was acknowledged and limited as much as possible through interventions such as member checks by interviewees and analysis check by persons not connected to data collection.

In the next chapter, the results of the study are presented. The findings have been summarized in graphical format and tables with explanatory notes as appropriate.

Chapter 4

Findings

4.1 Introduction

This chapter presents the results of this study on HDR brachytherapy in cervical cancer, an African perspective. The case study with mixed methods gathered quantitative and qualitative data that generated both textual and numeric data at the two study sites in Africa. The information on infrastructure, clinical protocols, historical records and patient statistics is first presented. The results of the retrospective data, based on a data sheet (Annexure A1 and A2) are then presented in tables and graphs starting with data on patient variables; disease stage, histology, and age. This is followed up by analysis and presentation of patient follow-up, overall treatment time (OTT), biological dose, and treatment outcomes at the two centres. The second phase, presents results based on data collected through an evaluation assessment survey using questionnaires, interviews, documents and observations on the HDR implementation process at the two centres. These are presented through tables with a description of participant responses and observations by the researcher.

The numeric and textual data generated is then integrated and analysed using a tabulated assessment grid adapted from Leedy and Ormrod (2005), to answer the main research question of how well HDR ICBT has replaced LDR as an appropriate treatment strategy for cervical cancer within the African setting. The nature of the study meant that some data resulted in findings not directly relevant to this study. Variables such as treatment field size, patients' weight, height, haemoglobin status, chemotherapy, time from histological diagnosis to treatment, among others are therefore not presented.

The findings of the study are presented in the next section.

4.2 Clinical infrastructure

The researcher was on site at Centre I during part of the study period. Through observations and documentation, Centre I was found to have one operating theatre for brachytherapy treatment of cervical cancer (Figure 4.1). In addition, a micro-selectron HDR unit employing one iridium-192 (Ir-192) radionuclide source was being used for the treatment procedure (Figure 4.2).

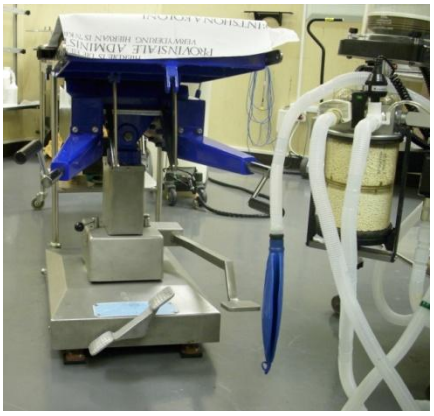

Figure 4.1: Operating theatre suite at Centre I.

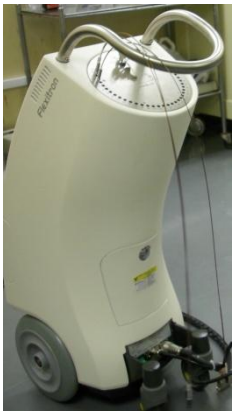

Figure 4.2: Flexitron HDR Unit at Centre I.

At Centre II where the researcher is a staff member, there is one operating theatre for staging of gynaecological malignancies (Figure 4.3), and an LDR brachytherapy treatment ward (Figure 4.4). The equipment used for brachytherapy treatment of cervical cancer is an LDR Selectron unit (Figure 4.5) employing a train of caesium-137 (Cs-137) radionuclide sources. The Centre also has a HDR micro-selectron brachytherapy treatment unit with an Ir-192 source (Figure 4.6).

Figure 4.3: Operating theatre suite at Centre II.

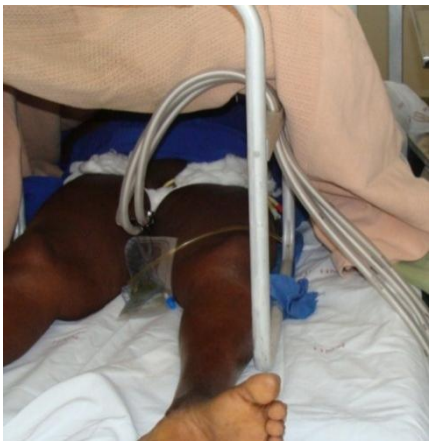

Figure 4.4: Caesium ward at Centre II.

Figure 4.5: Selectron LDR at Centre II.

Figure 4.6: Micro-selectron HDR at Centre II (Nucletron).

The settings at both Centres show similar theatre infrastructure, and similar HDR units. However, the selectron LDR unit at Centre II adds extra capacity in terms of equipment availability compared to Centre I.

4.3 Clinical protocols at Centre I and II

The following (Table 4.1) represents a summary of the clinical protocols employed at the two centres for treatment of cervical cancer.

Table 4.1: Comparison of clinical protocols at Centre I and II.

PROCEDURE ITEM	**CENTRE I**	**CENTRE II**
Modality	EBRT + HDR	EBRT + LDR
FIGO stage	IA2 upwards	I upwards
Dose EBRT	2.30 Gy, 4 #s per week, total 46Gy (4 Field box or POP beams)	2.00 Gy, 5#s per week, total 46 to 50Gy (POP beams)
Dose brachytherapy	5-7 Gy to Manchester point 'A', 2#s per week for 2 weeks, starts during the 4th week of EBRT. Total 20-28Gy	20-30 Gy to point 'A', single # at end of EBRT.
Applicators	Ring and tandem set (see Figure 4.7)	Fletcher-Suit-Delcos tandem and ovoids set (see Figure 4.8)

Imaging	Orthogonal films at 0^{o} and 90^{0} using portable X–ray unit	Semi-orthogonal films at 30^{0} and 60^{0} using simulator
Planning	Standard plans (see Figure 4.9 and 4.10)	Plan for every patient (see Figure 4.11 and 4.12)
Dose constraints	70% to dose at point A for ICRU rectal and bladder points	60% to dose at point A for ICRU rectal and bladder points
Post treatment follow-up	5 years	5 years

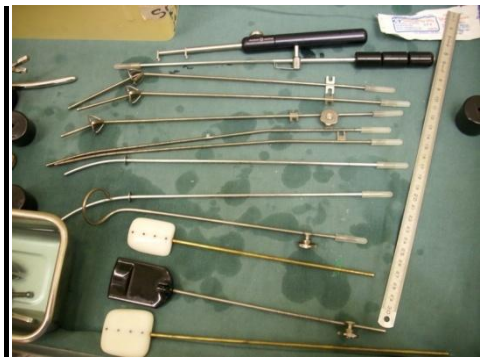

Figure 4.7: Ring and tandem applicators at Centre I.

Figure 4.8: Fletcher suit ovoids and tandem applicators at Centre II.

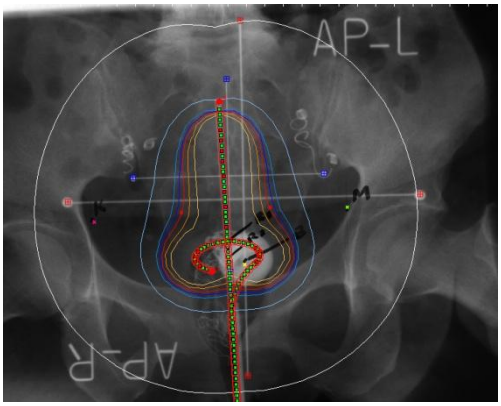

Figure 4.9: AP dosimteric plan at Centre I.

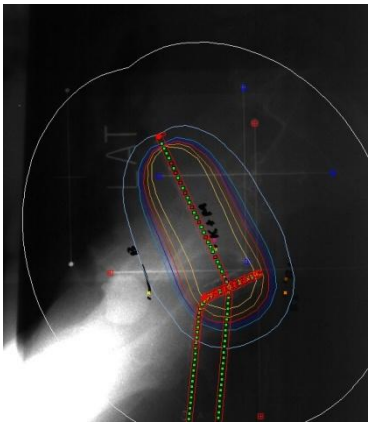

Figure 4.10: Lateral dosimteric plan at Centre I.

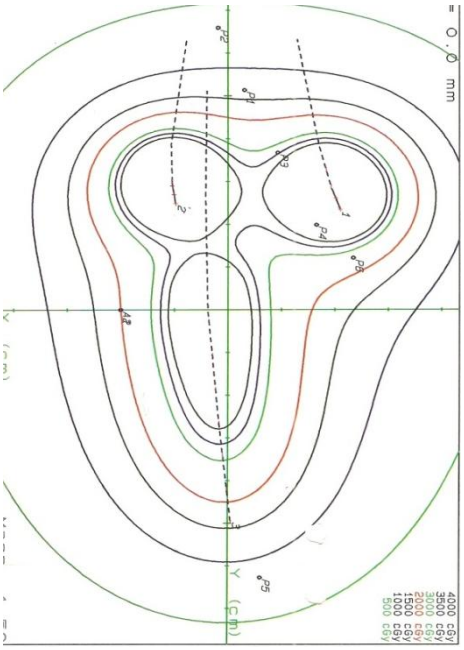

Figure 4.11: AP dosimetric plan at Centre II.

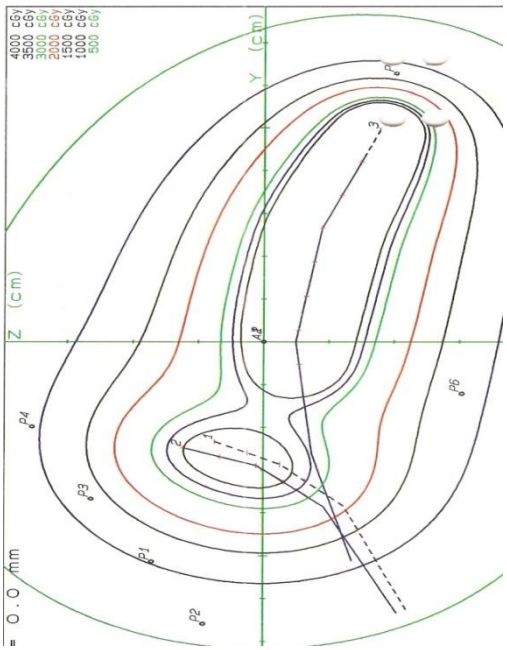

Figure 4.12: Lateral dosimetric plan at Centre II.

The clinical protocols show both centres prescribe to Manchester point 'A', and apply dose constraints to the ICRU-38 (1985:11) defined rectal and bladder points.

4.4 Statistics and historical records

4.4.1 Cervical cancer

Data was gathered from the gynaecological data base at Centre I and the main records register at Centre II. One thousand and fifty seven (1057) patients with cervical cancer were treated at Centre I over a 7 year period, compared to one thousand three hundred and six (1306) at Centre II. This is displayed in Figure 4.13.

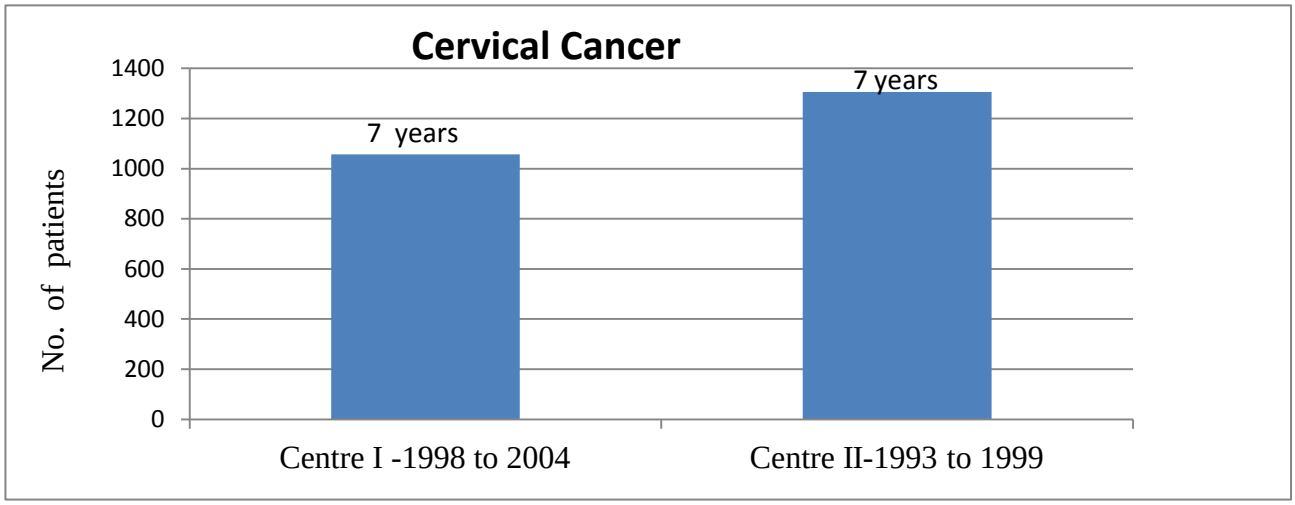

Figure 4.13: Total number of cervical cancer patients at Centre I and II.

4.4.2 Brachytherapy applications

All intracavitary insertions

The brachytherapy register at Centre I had seven hundred and twenty four (724) patients that received HDR ICBT using ovoids or ring and tandem applicators, vaginal cylinders and moulds compared to Centre II with one hundred and forty five (145) patients that received LDR ICBT (Figure 4.14).

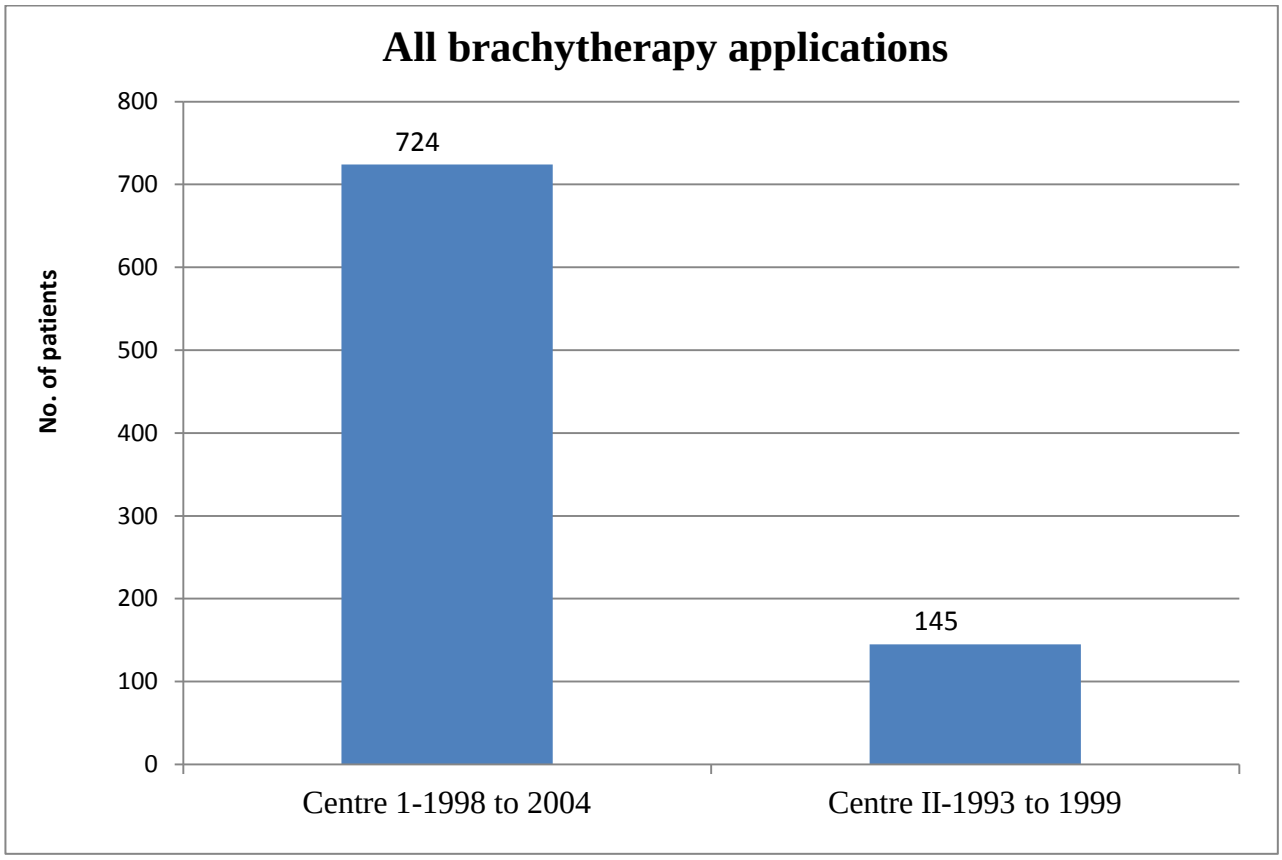

Figure 4.14: Brachytherapy applications at Centre I and II.

Ovoids or ring/tandem procedures

Table 4.2 shows a summary of the type equipment, period, number of patients treated, applicators used, and dose administered, based on information and data found at both centres. Four hundred and sixty eight (468) patients at Centre I were treated with HDR Ir-192 Flexitron brachytherapy equipment using ovoids, or a ring and tandem applicator when procedures using cylinders and moulds were excluded. They received definitive radiotherapy for cervical cancer. At Centre II, seventy seven (77) patients had received ICBT using the Amersham LDR Cs-137 afterloading system between 1993 and 1995, and sixty eight (68) had received ICBT using the Nucletron Selectron LDR Cs-137 remote afterloading system between 1998 and 1999. Another three (3) patients had received HDR brachytherapy elsewhere and were being followed up at Centre II. These are excluded from the study.

Table 4.2: Definitive radiotherapy at Centre I and II.

SITE	CENTRE I	CENTRE II	
Equipment	Flexitron HDR Ir-192	Amersham LDR Cs-137	Selectron LDR Cs-137
Period	1998-2004	1993-1995	1998-1999
No of patients (All ICBT applications)	724	77	68
No of patients (excluding cylinders & moulds)	468		49
Applicators	Nucletron	Gallos (Cervifix)	Nucletron
EBRT dose	1.80-2.30 Gy per # Total 50.40-56.70 Gy 22 to 28#s	2.00 Gy per # Total 46 - 48Gy 23-24#s	1.80 - 2.00 Gy per # Total 48 -50.40 Gy 24-28#s
Total ICBT dose to point A	28 Gy in 4 #s Time per # 4-20 minutes	20-35 Gy single #, Time 50-64 hours	20-30 Gy single #, Time 8-16 hours

4.4.3 The Amersham low dose rate afterloading system

The case study explored the workings of the Amersham low dose rate system and the Cervifix applicator devices. Documents were reviewed, and conversations with key staff members at the Centre showed that between 1993 and 1995, patients were treated using Cervifix afterloading devices developed by Mario Gallo of Italy. Some of the information that emerged is described below:

"...In 1985, a team, underwent training in Egypt....on the application of the Amersham low dose rate afterloading system....the use in Kenya commenced in 1986.....in 1987...two cervifix semi-remote afterloading devices (Mario Gallo, Italy) were introduced and connected to the already established Amersham devices..."(CIID1).

"...We used to use Gallos applicators, before the TPS.....these applicators were plastic...they were donated to the department by Mario Gallo an Italian - the one who designed them for use in developing countries. They brought in 3 Mario Gallo machines (Cervifix)..." (CIIPr3ADHOC).

The brachytherapy dose to point 'A' for the 77 patients treated with the Amersham equipment ranged between 20-35 Gy, and the time per insertion lasted between 50 to 64 hours (Table 4.2). There was no record of dose to ICRU rectal or bladder points in the folders. The researcher could not distinguish between cylinder and ovoid applications using the information in the folders, due to the unfamiliarity of the type of applicators used (Gallos). Therefore, a breakdown of those who received cylinders, or ovoid and tandem applicators was not done for this group.

Reasons for time lapse: 1996 to 1997

The researcher opened up lines of inquiry as to the reasons why brachytherapy treatments were not traced in the records between 1996 and 1997 at Centre II. It emerged from the data collected that there was a lack of supply of Gallos plastic applicators, and in two of the informal interviews; this is how it was explained:

"...I think at that time 1996-1997, Amersham had stopped making the plastic applicators. You know we never used to plan - there were charts. Cs-37 was loaded onto the plastic applicators..." (CIIPr3ADHOC).

"...The applicators were obsolete. The Physicists had a booklet to use for 10 years. After that, they were to work on (calibrate) a new dose rate for Cs-137 and not use the charts-they didn't do it..." (CIIPr1FOIN).

Impressions of using the Amersham LDR system

Though a document (CIID1) found at Centre II that had been published (Rogo et al., 1992:193), patients, nurses, and physicians expressed their impressions of using this system (Table 4.3).

Table 4.3: Impressions of using the Amersham LDR brachytherapy system at Centre II (Rogo et al. 1992:193).

Users	**Impressions**
Patients	Major complaint was the long hours of isolation during treatment
Nurses	The prolonged treatment period in which patients needed feeding and nursing.
Physicians	Appreciated the safety and ease of application of the system. However they made strong recommendations for reduction in treatment times and concern over the reliance of X-rays in the assessment of applicator positions. This they felt increased the cost of the procedure noting that when it was not available in the treatment room, patients had to be wheeled to the radiology department causing considerable delays before onset of treatment, inconveniencing the anaesthesiology department.

4.4.4 Time delays: dosimetry procedures

Similar sentiments were expressed by staff at Centre I complaining about the time it took to undertake dosimetry procedures. They suggested that if dosimetry procedures could be eliminated, then they would treat many more patients. One key staff member gave a description of a technique that is performed in another hospital in South Africa where they do not undertake dosimetry procedures resulting in many more patients being treated:

"... After EBRT (50 Gy), selected patients are sent to theatre, on the Monday under GA/Spinal anaesthesia...an S-tube is inserted. Then on Tuesday to Friday patients are treated...no sedation, no planning. They use a straight applicator...a straight tandem inserted into a Foleys catheter..." (RN 2010).

"...The dose distribution is like for a **Maize Cob**, not **Pear shaped**. The professor who started this technique did several CT scans/plans and established that it gives adequate dose distribution to the cervix, paracervical region and upper vagina. Unlike the pear shape distribution which concentrates dose to the cervix and uterus..." (RN 2010).

"...One obvious advantage: in-cases where vagina is small, difficult to insert ring or ovoids, this technique serves well..." (RN 2010).

"...But for cases of lower vaginal involvement (FIGO stage IIIA)-then they are forced to do a second insertion using a cylinder. There is then the inconvenience of two procedures and nobody knows what happens to the junction of the two dose distributions..." (RN 2010).

"...They treat many patients, Tuesday to Friday using this technique..." (RN 2010).

Therefore the sentiments expressed show that the time taken to do dosimetry procedures for brachytherapy applications has a negative impact on the number of patients that can be treated, both for HDR and LDR ICBT procedures.

4.5 Patient variables

4.5.1 Sample size selection

To answer sections of question 1 and 2, a sample size of 212 patients (Figure 4.15) was calculated from the population of 468 patients that received ovoid, or a ring and tandem applicator at Centre I. The statistical software OpenEpi-Version 2.3.2, (2009) was used to calculate the sample size. The 212 patients were then selected from the population of 468 through a systematic random sampling procedure. Using this list, one hundred and seventy three (81.6%) patient folders were retrieved. In addition, a gynaecological patient database for patients with cervical cancer was also found at the Centre. The data sheet (Annexure A1) was then used to extract the information requested from the folders and from the patient database. However, not all the information required was found in one place. In some cases where the folder was missing, some of the required information was found in the database. Therefore because of this, some patient variables may have a higher patient sample than the 173 folders indicated. The study also found some categories of information missing altogether in the folders and the database for some cases. The patient sample (n) therefore varies for some information categories and is indicated accordingly. At Centre II, from the population of 145 patients, the 77 patients that received treatments using the Amersham equipment were excluded

(Table 4.2). The remaining 68 patients, 19 received cylinder applications and were also excluded. A sample of 44 patients was calculated from the remaining 49. This number being small compared to Centre I, the researcher included all the 49 (100%) patients in the study (Figure 4.15). Each folder was then analysed and the results are presented in the following sections.

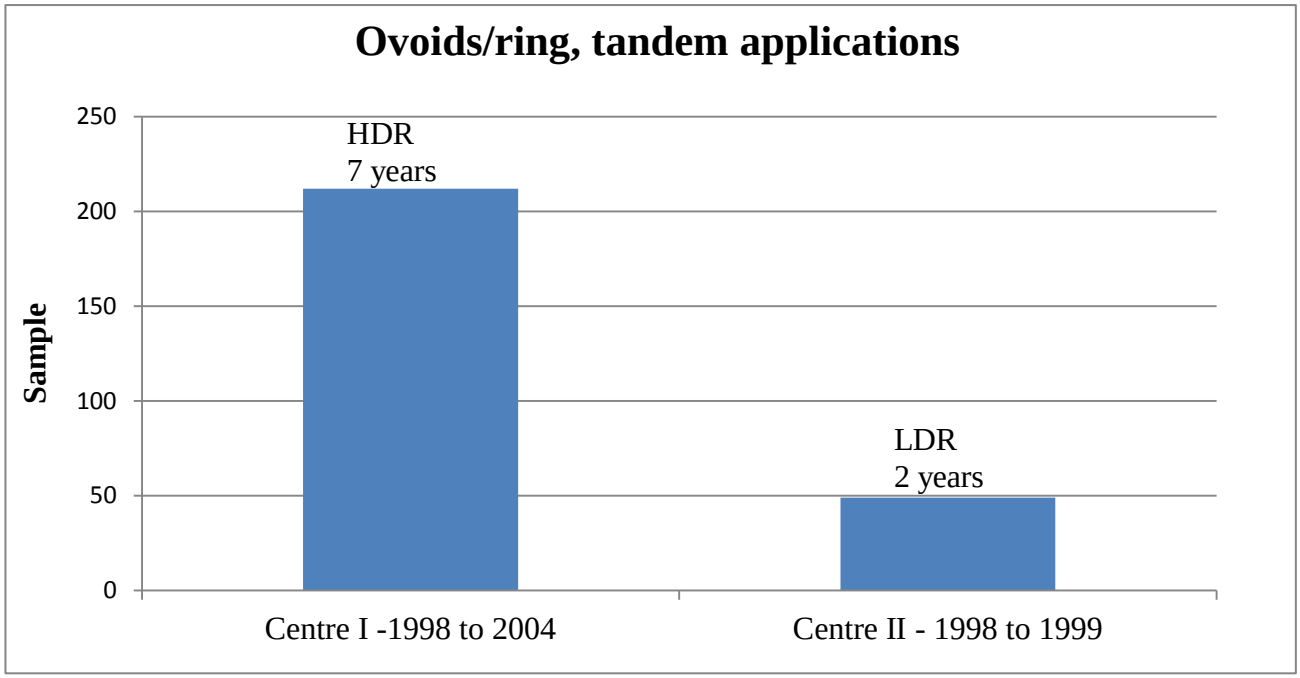

Figure 4.15: Number of patients sampled at Centre I and II (Ovoids/ring and tandem applications).

4.5.2 FIGO stage

Centre I - HDR

The information found for FIGO stage at Centre I comprised of a sample size of 193/212 (91.0%) patients. Some information was found in the database for files that were missing. The various FIGO categories found (IB1 to IIIB) are tabulated in Table 4.4. Grouping the categories into FIGO stage I to III and excluding the unavailable information; 9.3% (18/193) were found to be in stage I, 41.5 % (80/193) in stage II, 49.2 % (95/193) in stage III and none in stage IV. This is summarised in Table 4.5.

Table 4.4: FIGO stage categories at Centre I (sampled ICBT patients).

STAGE	**PATIENTS (n) CENTRE I**
IB1	4
IB2	14
IIA	4
IIB	76
IIIB	95
IV	0
Unavailable information	19 (excluded)
TOTAL	**212**

Table 4.5: Summary of FIGO stage at Centre I after exclusion of missing information (sampled ICBT patients).

Stage	No. of patients (n=193)	%
I	18	9.3%
II	80	41.5%
III	95	49.2%
IV	0	0 %
Total	**193**	**100%**

Centre II - LDR

At Centre II, information for FIGO stage was found in 48/49 (98.0%) folders for patients who underwent LDR ICBT (n=48). The various FIGO categories found (IB to IVB) are tabulated in Table 4.6 and summarised in Table 4.7.

Table 4.6: FIGO staging categories at Centre II (ICBT patients).

STAGE	PATIENTS (n) CENTRE II
Stage IB	3
Stage IIA	4
Stage IIB	22
Stage 3A	7
Stage 3B	11
Stage IVB	1
Unavailable information	1 (excluded)
Total	**49**

Table 4.7: Summary of FIGO stage at Centre II after exclusion of unavailable information (ICBT patients).

Stage	No. of patients (n=48)	%
I	3	5.9%
II	26	56.9%
III	18	35.3%
IV	1	2.0 %
Total	**48**	**100%**

This being a small sample size, an analysis of FIGO stage for all the one thousand, three hundred and six (1306) patients treated for cervical cancer treatment between 1993 and 1999 whose records were retrieved at Centre II is also presented. After excluding the folders with missing information, a total of one thousand two hundred and three cases (N=1203) were analysed and the information is presented in Table 4.8.

Table 4.8: FIGO stage for all cervical cancer cases at Centre II.

Stage	**No. of patients (N=1203) Centre II**	**%**
I	72	6.0%
II	498	41.4%
III	573	47.6%
IV	60	5.0%
Total	**1203**	**100%**

The FIGO stage distribution at Center II for N=1203, and n=48 is similar (Tables 4.7, 4.8). Overall, the majority of the patients presented in FIGO stage II and III at both centres. Data shown in Table 4.9 gives a cross-range comparison of these information.

Table 4.9: Comparison of FIGO staging at Centre I & II.

FIGO	**Centre I (**n=193)	**Centre II (**n=48)	**Centre II (**N=1203)
Stage I	9.3%	5.9%	6.0%
Stage II	41.5%	56.9%	41.4%
Stage III	49.2%	35.3%	47.6%
Stage IV	0%	2.0%	5.0%

4.5.3 Histological classification

Centre I - HDR

The information on histological pathology at Centre I was found on 193/212 (91%) patients. A majority 165/193 (85.5%) were squamous cell carcinomas. 24/193 (12.4%) were adenocarcinomas, and 4/193 (2.1%) were adenosquamous carcinoma (Table 4.10 and 4.11).

Table 4.10: Histological classification at Centre I.

HISTOLOGY	PATIENTS (n) CENTRE I
Squamous carcinoma	165
Adenocarcinoma	24
Adenosquamous	4
Unavailable info	19
Total	**212**

Table 4.11: Histological distribution Centre I, after exclusion of unavailable information.

Histology	No. of patients (n=193)	%
Squamous cell carcinoma	165	85.5%
Adenocarcinoma	24	12.4%
Adenosquamous	4	2.1 %
Total	**193**	**100%**

Centre II - LDR

At Centre II, the forty nine (n=49) patients who received LDR ICBT with tandem and ovoid applicators were analysed, and the histological type is presented in Tables 4.12 and 4.13.

Table 4.12: Histological classification at Centre II.

HISTOLOGY	PATIENTS (n) CENTRE I
Squamous carcinoma	31
Adenocarcinoma	4
Anaplastic	3
Unavailable information	11
Total	**49**

Table 4.13: Histological distribution at Centre II after exclusion of unavailable information.

Histology	No. of patients (n=38)	%
Squamous (Sq) cell carcinoma	31	79.5%
Adenocarcinoma	4	10.3%
Anaplastic	3	7.7%
Total	**38**	**100%**

The histological distribution at the two centres was comparable (Table 4.14).

Table 4.14: Comparison of histological classification at Centre I & II.

HISTOLOGY	**CENTRE I** (n=193)	**CENTRE II** (n=38)
Sq Cell carcinoma	85.5%	79.5%
Adenocarcinoma	12.4%	10.3%
Adenosquamous	2.1%	0%
Anaplastic	0%	7.7%

4.5.4 Age analysis

Centre I - HDR

Data on age was found in 152/212 (71.7%) folders at Centre I and the age range and percentage distribution are shown in Table 4.15.

Table 4.15: Age of patients who received HDR ICBT at Centre I.

Age range	**No. of patients** (n=152)	**%**
20-29	6	3.9%
30-39	18	11.8%
40-49	43	28.3%
50-59	42	27.6%
60-69	34	22.4%
70-79	9	5.9%
Total	**152**	**100%**

Centre II - LDR

The age distribution for Centre II is shown in Table 4.16 for 48/49 (98.0%) patients who received LDR ICBT. One patient had missing information and was excluded.

Table 4.16: Age of patients who received LDR ICBT at Centre II.

Age range	**No. of patients** (n=48)	**%**
20-29	3	6.3%
30-39	17	35.4%
40-49	11	22.9%
50-59	8	16.7%
60-69	8	16.7%
70-79	1	2.1%
Total	**48**	**100%**

Due to the small sample size at Centre II, a further age analysis was done for one thousand two hundred and eighty two (N=1282) patients at Centre II after excluding missing information. The age range distribution was comparable at Centre II between the small sample size (n=48) and the large population (N=1282) shown in Tables 4.16, 4.17.

Table 4.17: Age analysis for all cervical cancer cases at Centre II.

Age range	**No. of patients** (N=1282)	**%**
20-29	58	4.5%
30-39	310	24.2%
40-49	403	31.4%
50-59	256	20.0%
60-69	193	15.1 %
70-79	48	3.7%
80-89	12	0.9%
90-99	2	0.2%
Total	**1282**	**100%**

Comparison: Centre I and II

The results at the two centres were compared (Table 4.18). The mean age at Centre I was 52.1 years and the median age 51 years with a standard deviation of 12.41. At Centre II, the mean age for patients treated with LDR ICBT (n=48) was 45.7 years and the median age 41.5 years with a standard deviation of 12.04 (IBM SPSS version 19: 2010). The two means were compared using the two sample independent t-Test, and no significant difference was shown between the two groups with a p value of 0.83 (Soe & Sullivan, 2011). When the larger patient population at Centre II (N=1282) was considered, the mean age was 47 years and the median age 45 years, implying no statistical differences would be observable when a large sample size at Centre II is considered.

Table 4.18: Comparison of age distribution at Centre I and II.

Age Range	**Centre I** (n=152)	**Centre II** (n=48)	**Centre II** (N=1282)
20-29	3.9%	6.3%	4.5%
30-39	11.8%	35.4%	24.2%
40-49	28.3%	22.9%	31.4%
50-59	27.6%	16.7%	20.0%
60-69	22.4%	16.7%	15.1%
70-79	5.9%	2.1%	3.7%
80-89			0.9%
90-99			0.2%

Nevertheless, these comparative data (Table 4.18) shows a higher number of patients presenting at age 30-39 at Centre II of 35.4% (n=48) compared to Centre I of 11.8% (n=152). The figure still remains higher when the larger patient population at Centre II is considered (24.2%, N=1282). Likewise, a higher number of patients presented at Centre I between the ages of 50-59 (27.6%, n=152) compared to Centre II (16.7%, n=48). Comparatively, this figure at Centre II remains lower when the larger population is considered (20.0%, N=1282). These seems to show that a majority of the patients at Centre I present at postmenopausal age compared to Centre II where they present at premenopausal age, though no statistical differences were shown between the overall age groups at the two centres.

4.6 Brachytherapy technical and clinical factors

4.6.1 Type of equipment used and dose rate

Information was gathered on the type of equipment used at both centres and a dose rate was calculated from the available data.

Centre I - HDR

The equipment used at Centre I was a Flexitron HDR Ir-192 unit, Figure 4.2. This is how it was described in the manual:

"...afterloading system that enables an operator to apply by remote control a radionuclide source (Flexisource) of different isotopes into the body, or to the surface of the body for radiation therapy..." (CIDI).

The treatment time ranged from 4 minutes to 20 minutes per # (fraction), and a majority of the patients received a dose of 7 Gy to point 'A'. The researcher then worked out an average dose rate at 'point A':

Dose/Time: 7/4, and 7/20. The calculated average dose rate was 2.10 Gy/minute = 126 Gy/hour.

This falls within the high dose rate range defined by the ICRU report (1985: 4-5) of greater than 12 Gy/hour. Though the report notes that for most HDR applications, this usually refers to dose rates as high as 120 to 300 Gy/hour.

Centre II - LDR

When analysing the sampled data at Centre II, the researcher came across a conflict in nomenclature of the Selectron LDR unit, Figure 4.5. The mean treatment time for a single LDR treatment at

Centre II was 12 hours, and the dose delivered ranged between 20 to 30 Gy. The time for treatment insertions ranged between 8-16 hours. Calculating the dose rate at point 'A':

Dose (Gy) /Time (hours), 20/12, and 30/12. The average dose rate was 2.09 Gy/hour.

The researcher then carried out an inquiry on whether this equipment was an LDR or MDR (Medium dose rate) unit. This was because everybody called the unit LDR. The following are the responses the researcher got from the question of whether it was an LDR or MDR unit:

"...LDR..... Not MDR!..." (CIIPrIFOIN).

"...Note that Cs is usually regarded as MDR!!We have to sort this out..." (CIPr1RF).

From the equipment manual, it was described as;

"...The Selectron LDR-137 Cs is a remote afterloading system for low and medium dose rate brachytherapy treatments using Caesium 137 sources..." (CIID2).

Though the equipment supplier and all the professionals referred to the unit as LDR unit, the applications at Centre II based on the calculated dose rate were in the range of medium dose rate (MDR) as proposed by the ICRU-38 (1985:5) report: "Some radiotherapists are now exploring intermediate dose rates, between 2 and 12 Gy per hour and we propose to refer to such dose rates as medium dose rates."

4.6.2 Number of fractions (#s)

The number of fractions (#s) given for a complete dose of brachytherapy was evaluated. At Centre I where patients were treated with HDR ICBT, the number of #s given over the 7 years was analysed. Out of the one hundred seventy three (173) folders found, one hundred and sixty one (n=161) had doses recorded for point 'A'. 55/161 (34.2%) had received four (4) fractions, 100/161 (62.1%) three (3) fractions, 1/161 (0.6%) two (2) fractions, and 5/161 (3.1%) one (1) fraction (Figure 4.16).

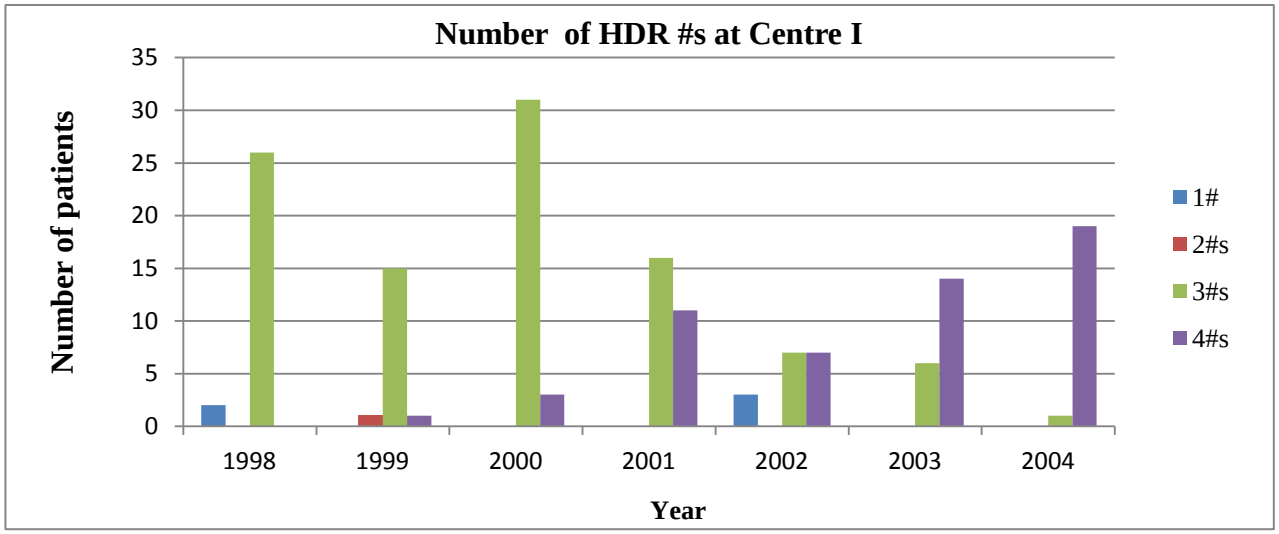

Figure 4.16: HDR fractions (#s) at Centre I.

The majority of the patients received 3#s, and by the end of the study period (2004), this had largely been replaced by four (4) fractions. When this was compared to Centre II, information from the patient folders indicated only one single # was administered per patient for a complete dose of LDR ICBT.

4.6.3 Overall treatment time (OTT*)*

Overall treatment time (OTT) was calculated from the date of the first treatment by EBRT to the date of completion of LDR or HDR ICBT. One hundred and fifty eight (n=158) cases were analysed for Centre I. The median OTT was 48 days (29 to 211days). While forty six (n=46) cases were analysed for Centre II and the median OTT was 169 days (57 to 576 days). One (1) patient at Centre I had a 6 months gap between EBRT and ICBT resulting in an OTT of 211 days. The rest of the patients ranged between 29 and 81 days. At Centre II, the OTT range was; 10 patients (57 to 98 days), 15 patients (105-198 days), 15 patients (211 to 576 days).

Patients at Centre II took longer to complete the definitive treatment for cervical cancer (combination of EBRT and brachytherapy), compared to Centre I.

4.6.4 Biological dose

Centre I - HDR: Summative dose at point A

For patients treated with HDR ICBT at Centre I between 1998 to 2004 , the brachytherapy dose to point 'A' and the dose contribution from the EBRT treatment was added together after conversion to equivalent dose in 2 Gy fraction (EQD_2) using the linear quadratic equation for isoeffective dose by Bentzen & Joiner (2009:109-119). Out of the 173 patient folders that had dose to point 'A' recorded, 162 had the teletherapy dose recorded in the external beam treatment sheet at Centre I. This is because some patients had been referred at Centre I from elsewhere to receive only brachytherapy, and detailed information on external beam dose was not available. Therefore 162 patients were considered for EQD_2 conversion. The Median EQD_2 dose to point A for 162 patients at Centre I was 82.8 Gy, with a mean of 81.8 Gy, for acute effects.

Centre II - LDR: Summative dose at point A

At Centre II, information to point 'A' dose was found for the 49 patients treated with the Selectron LDR unit using tandem and ovoid applicators between 1998 to 1999. The median dose at point A was 88.0 Gy, with a mean of 87.7 Gy. The resultant summative EQD_2 dose of EBRT and brachytherapy to point 'A' for both centres is illustrated in Figure 4.17.

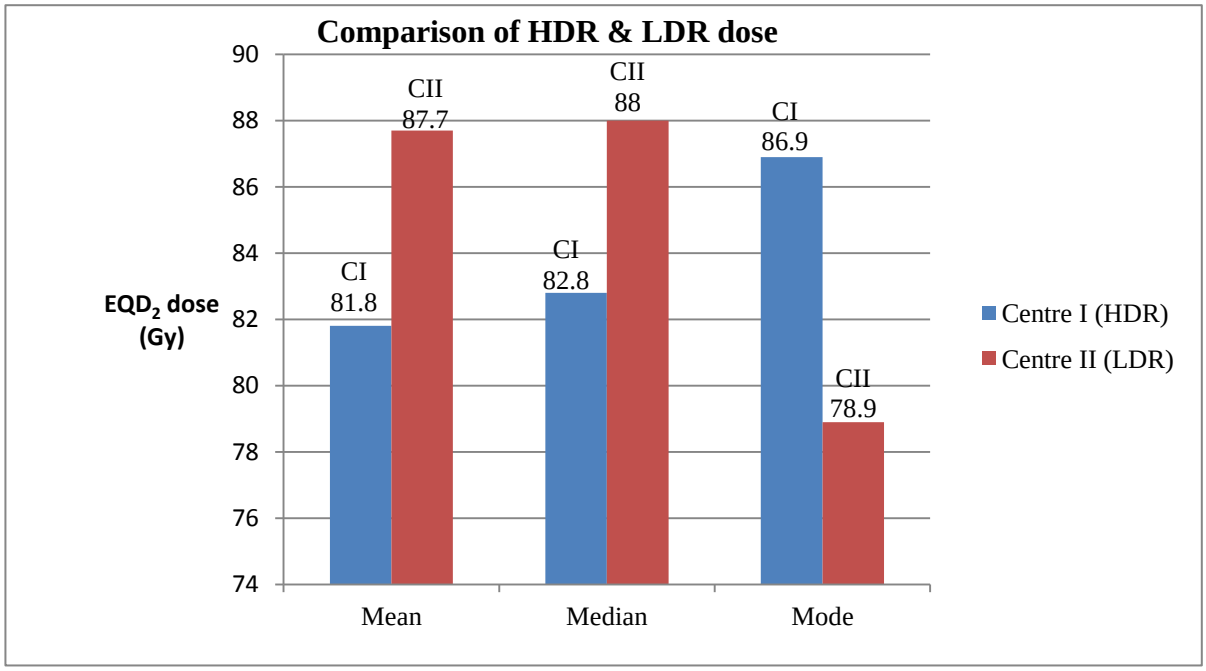

Figure 4.17: EQD_2 at Centre I and II (Point 'A').

The difference in EQD_2 dose to point 'A' is not statistically significant with a p-value of 0.88, using the two sample independent t-Test (Soe & Sullivan, 2011). The most commonly administered EQD_2 dose to point 'A' is 86.9 Gy and 78.9 Gy at Centre I and II respectively, and is displayed as a mode function in Figure 4.17.

Effect of OTT on biological dose at Point 'A'

The EQD_2 at Point 'A', was subjected to the formulae by Bentzen & Joiner, (2009: 125), taking into account the estimated effects of repopulation.

$EQD_{2,T} = EQD_{2,t} - (T-t)\, D_{prolif}$, where,

$EQD_{2,T}$ is the isoffecive dose delivered when OTT is factored,

$EQD_{2,t}$ is the dose derived from the basic linear quadratic formulae (Bentzen & Joiner, 2009: 109,112),

T is the overall treatment time,

t is the repair kick off time, and

D_{prolif} is the dose in Gy lost per day due to proliferation.

This study used t of 28 days and D_{prolif} of 0.5Gy (Gasinska, Fowler, Lind, Urbanski, 2004). A majority of the patients at Centre II resulted in $EQD_{2,T}$ values of 0 (zero) since they had large gaps between EBRT and ICBT treatment. Excluding those who had OTTs of more than 100 days as the treatment may not have been effective, 10/46 (22%) patients had OTTs of between 57 and 98 days compared to 157/158 (99%) with OTTs of between 29 and 81 days at Centre I. Thus Centre II had too few patients to make reliable conclusions. Therefore for further discussion, the researcher will

revert to the EQD_2 s derived from the basic linear quadratic equation by Bentzen & Joiner (2009: 109,112).

EQD_2 trends at both Centres.

The calculated EQD_2 dose per year at both centres is displayed in the scatter plot, Figure 4.18.

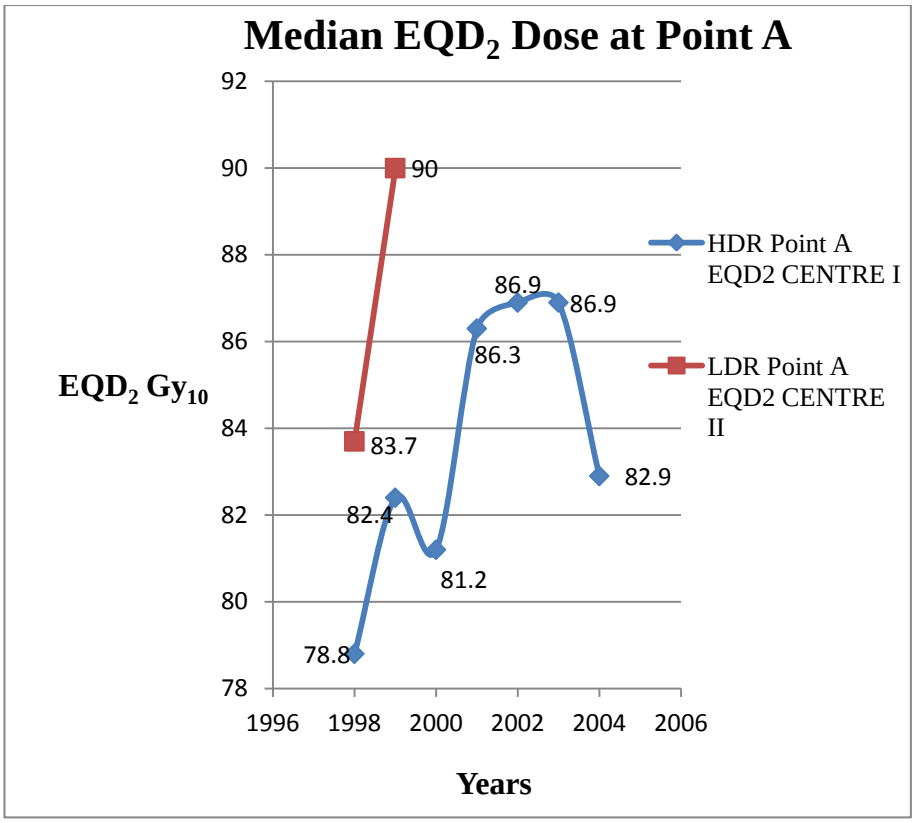

Figure 4.18: Trends in yearly median EQD_2 at both Centres.

A similar dose range of between 82 Gy to 87 Gy is shown in Figure 4.18, when extreme high and low figures are excluded. However, there is a slightly higher dose for Centre II (LDR) than Centre I (HDR) for dose administered to point 'A',

Summative EQD_2 dose at bladder and rectal points

ICRU Bladder point

One hundred and thirty seven folders (n=137) had brachytherapy dose recorded for the ICRU bladder point at Centre I (HDR). The resultant total EQD_2 dose at this point was calculated, including the contribution from the EBRT beam. This was done for the 137 patients. The median dose to the bladder point was 67.7 Gy and the mean 68.7Gy. For Centre II (LDR), out of the 49 patients, one had dose to the bladder point missing. The median and mean for the 48 patients was calculated as 66.3 Gy and 66.8 Gy, respectively. These were similar between the two centres. This information is tabulated in Table 4.19.

ICRU rectal point

The dose to the ICRU rectal point was recorded in one hundred and forty folders (n=140) at Centre I (HDR). After conversion and summation with the contribution from the EBRT beam, the median and mean EQD_2 dose to the rectal point was 68.9 Gy and 68.2 Gy, respectively, for late effects. At Centre II, the median and mean for 48 patients was 58.4 Gy and 59.8 Gy, respectively. The two means for rectal dose were compared between the two centres using the two sample independent t-Test. The standard deviation was 8.07 and 6.19, for Centre I and II respectively. The difference was found to be statistically significant with a p-value of 0.04 (Soe & Sullivan, 2011). The results are shown in Table 4.19 and displayed in Figure 4.19.

Table 4.19: EQD_2 at rectal and bladder point.

	EQD_2 at ICRU Bladder point		**EQD_2 at ICRU Rectal point**	
	Median (Gy)	Mean (Gy)	Median (Gy)	Mean (Gy)
Centre I (HDR) n=137 (bladder), n=140 (rectal)	67.7	68.7	68.9	68.2
Centre II (LDR) n=48	66.3	66.8	58.4	59.8

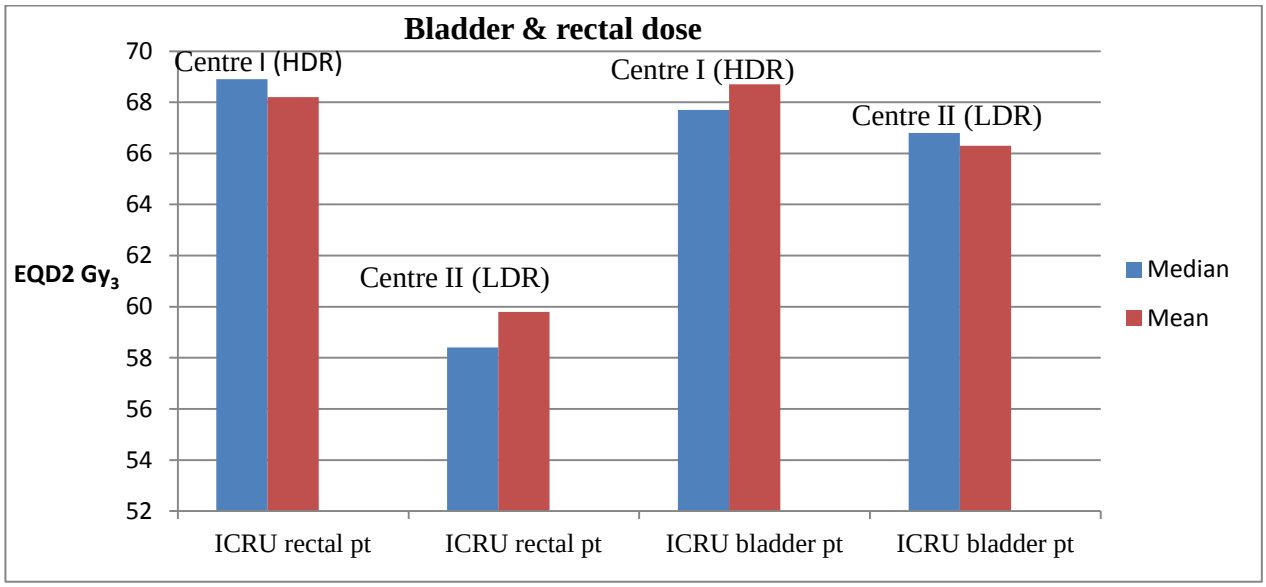

Figure 4.19: EQD_2 at rectal and bladder point at Centre I and II.

The findings show similar dose to ICRU bladder point at both Centre I & II. However, the dose to the ICRU rectal point at Centre I is higher than for Centre II and the difference is statistically significant.

4.6.5 Follow-up time

The researcher gathered information of 176 patients followed up till the time of death or date of last follow-up at Centre I (HDR). The median follow-up time was 42.2 months. At Centre II, the median follow-up time to the date of last follow-up was 12.4 months based on the information gathered for the 49 patients. There was no indication of date of death in all the folders analysed at Centre II.
The median follow-up time at Centre II was poor compared to Centre I.

4.7 Treatment outcomes

The clinical outcomes measured were pelvic relapse free survival, late grade 3 to 4 complications, and overall survival. The following sections present the findings at the two centres.

4.7.1 Pelvic relapse free survival

Pelvic relapse free survival was calculated from the date of first treatment by EBRT. Persistent disease or non-responsive tumours were excluded from the analysis, 9.0% (19/212) for Centre I, 10.2% (5/49) for Centre II. Some of the information contained in the folders that were missing was found in the database. Table 4.20 summarises the information that was found at Centre I. Information was analysed for 170 patients using the Kaplan-Meier method. An event was defined at the date of pelvic recurrence (cervix, vaginal, parametrial, or loco-regional recurrence). Event status was defined for 47 patients and 123 were censored up to their last time of follow-up, or death.

Table 4.20: Information for pelvic relapse at Centre I.

PATIENT STATUS	**NUMBER OF PATIENTS**
Pelvic relapse	47
Censored	123
Persistence disease / No response	19 (excluded)
Ineligible information	1 (excluded)
Unavailable information	22 (excluded)
Total	**212**

Information for pelvic relapse free survival was analysed in the 49 folders available at Centre II. Event status was defined for 8 patients and 35 were censored up to their last time of follow-up (Table 4.21).

Table 4.21: Information for pelvic relapse at Centre II.

PATIENT STATUS	NUMBER OF PATIENTS
Pelvic relapse	8
Censored	35
Persistence disease / No response	5 (excluded)
Non definitive information	1(excluded)
Total	49

The pelvic relapse free actuarial rates for Centre I and II are illustrated in Figure 4.20. For patients treated with HDR at Centre I and LDR at Centre II, the pelvic relapse free survival rate was 65.8 % and 53.9%, respectively (p=0.84). This difference is not statistically significant, and the survival curve shows similar pelvic relapse rates at 4 years of 67.8 % and 67.4%, Centre I and II, respectively.

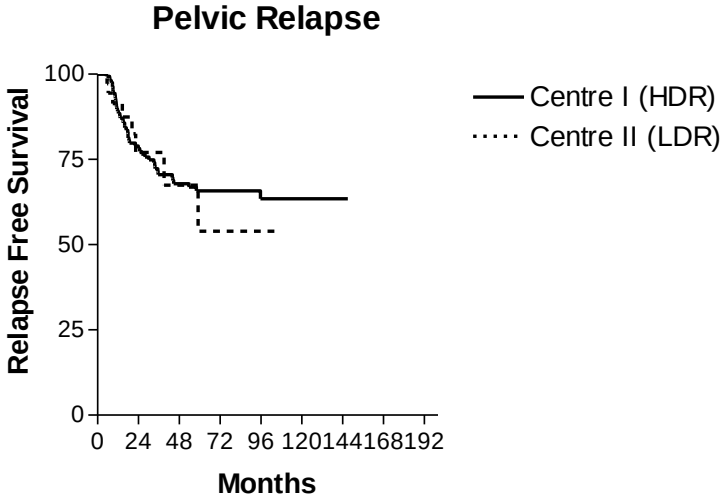

Figure 4.20: Pelvic relapse free survival rates, Centre I and Centre II.

4.7.2 Radiation late effects

Late grade 3 and 4 radiation complications to the bladder and rectum was analysed in 174 and 175 patients, respectively, from the folders and database at Centre I. All grade 3 and 4 late radiation complications had been recorded in the database. This was cross-checked against the patient folders. Four (4) patients developed grade 3 bladder complications. Out of the 4 patients, one folder was unavailable; hence time to the event could not be calculated and was excluded from the analysis. Therefore 171 patients were censored up to the time of last follow-up or death. The same was done for rectum. Out of 175 patients analysed, 3 had grade 3, and 1 had grade 4 rectal complications. An evaluation of the 49 patient folders at Centre II was also done to assess the same. An independent radiation oncologist also assessed the follow-up notes for patients at Centre II to

increase reliability of the findings (Annexure A2B). Out of the 49 patients, one had grade 3 and one had grade 4, bladder and rectal complications, respectively. The rest of the patients were censored up to the time of their last follow-up. The results are summarised in Table 4.22 and the 5-year actuarial complication rates displayed in Figure 4.21 and 4.22.

Table 4.22: Rectal & bladder complications rates (Grade 3 and 4) at Centre I and II.

Site	Bladder (Grade 3 /4)	Rectal (Grade 3/4)
Centre I	3 (3.4%) n =174	4 (3%) n =175
Centre II	1 (0%) n =49	4 (25%) n=49

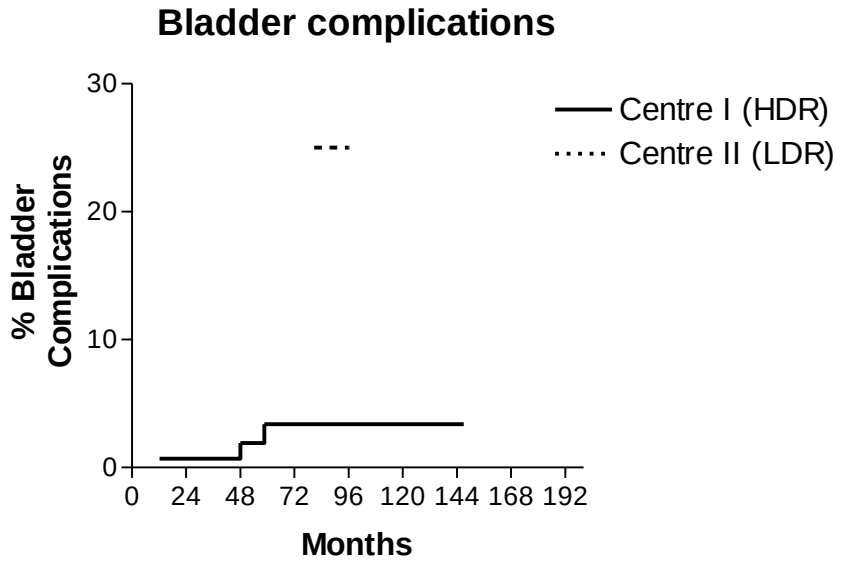

Figure 4.21: Late grade 3 and 4 bladder complications, Centre I and II.

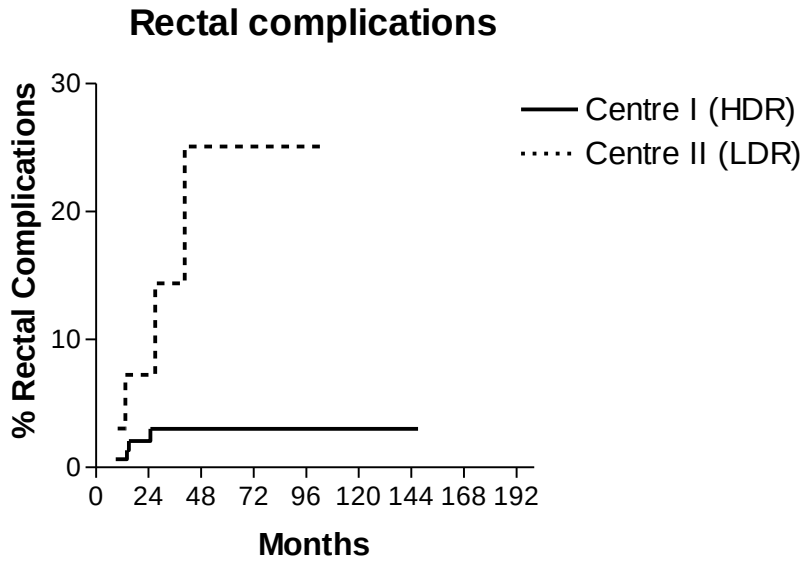

Figure 4.22: Late grade 3 and 4 rectal complications, Centre I and II.

The difference in bladder complications between Centre I and II was not statistically significant, p value 0.30. However, the difference in rectal complications was statistically significant with a p-value of 0.0024.

4.7.3 Overall survival

Overall survival was plotted for the patients at Centre I (HDR). Using the Kaplan-Meier method, all patients, whose status of death was not known, were assumed to be alive at the time of their last follow-up and were censored. Out of 173 patients, the number of events (death) was 105, and 65 patients were censored. The 5-year overall survival was 50% at a median survival time of 49.2 months (Figure 4.23).

The overall survival for Centre II (LDR) was not calculated as data for patients' death status was not available. This is well expressed in one of the conversations and ad hoc interviews conducted by the researcher:

"... For patients who die at home, some relatives bring back the information out of good will, and we put a + on the patients file, not date..." CIIPr6ADHOC.

"...In the hospital folder if the patient is admitted...there is a form where its indicated date of death....the doctors do not transfer this information to the radiotherapy folder but write in the hospital file....that is why all these radiotherapy folders have no dates of death..." CIIPr6ADHOC.

The researcher then conducted a search for the hospital folders, but all folders before the year 2000 could not be traced.

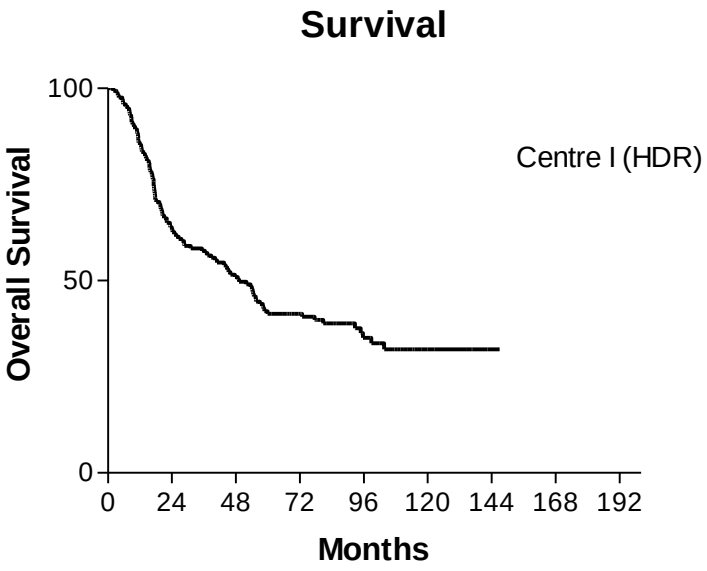

Figure 4.23: Overall survival for patients with cervical cancer at Centre I treated by HDR ICBT.

4.8 Implementation of HDR

4.8.1 Introduction

The researcher carried out an evaluation of the implementation process of HDR brachytherapy at each centre. The case study gathered data through a self-directed questionnaire (Annexure B), and a researcher guided questionnaire interview (Annexure C). One key staff member at Centre I did not return the questionnaire and was not available for follow-up interview. Additional data was collected by the researcher through the following activities:

i) Follow-up discussions with the radiation oncologist specialized in gynaecological malignancies and the medical physicist at Centre I. The same was also conducted with the head of department and the medical physicist in-charge at Centre II. Discussions and spontaneous conversations were also held with other key staff members involved in brachytherapy treatments; a medical physicist, a therapy radiographer, an oncology nurse and a medical records officer.

ii) Unsolicited data from spontaneous conversations and ad hoc interviews with the specified key staff members.

iii) Documentary evidence gathered from official letters, purchase and contract documents including equipment manuals available at the two centres.

iv) Observations by the researcher that played a key role in corroborating the evidence gathered.

4.8.2 Findings

HDR Purchase considerations

Patient volume was the reason why the purchase of HDR brachytherapy equipment was considered at both centres. In addition, available infrastructure, human resources, cost related issues, and problems with LDR sources were key factors at Centre I. At Centre II, an interesting factor that emerged was:

"...Availability of funds..." (CIIPr3AB5)

"...A last minute decision to buy HDR due to availability of funds..." (CIIPr1AC1-2)

A summary of the responses are tabulated in Table 4.23.

Table 4.23: Purchase considerations at Centre I and II.

ITEM	CENTRE I	REF CODE	CENTRE II	REF CODE
Purchase considerations	Future patient volume.	CIPr1AB4-5,	High current patient volume.	CIIPr1AB4-5, CIIPr4AB5
	Existing infrastructure-availability of theatre, it was already there for LDR work.	CIPr1AB4-5AC2	Availability of funds...was for purchase of LDR unit, but a last minute decision to buy HDR due to availability of funds.	CIIPr3AB5
	Available human resources.	CIPr1AB4-5 CIPr2AB4-5		CIIPr1AC1-2
	LDR sources (radium tubes) were becoming unsafe.	CIPr1AB4-5		CIIPr3ADHOC
	Outpatient treatment.	CIPr1AC2		
	Availability of anaesthetist.	CIPr1AC2		
	Cost of unit	CIPr1AC2		
	Cost of sources yearly	CIPr1AC2		
	Same LDR staff to be used for HDR.	CIPr1AC2		
	Savings-no patients to be admitted, while for LDR all patients had to be admitted.	CIPr1AC2		

Planning for HDR installation

Adequate preparations and plans were made at Centre I for the installation of the HDR equipment. The last minute decision to buy the HDR equipment seems to have complicated the situation at Centre II. The Centre did plan for a one year maintenance contract and procured and paid for the supply of fifteen (15) Ir-92 sources. The document CIID3 at Centre II confirmed these findings. Some of the responses were expressed in this way:

"...No prior preparation when ordering HDR. When LDR was ordered previously, there was no problem; there was a good plan when it was being procured. Everything was ready-building, rooms, and all the infrastructure plus training in place.....when HDR came, then we became aware we needed all these things, i.e. room plus other infrastructure. Then we started planning where the HDR was to be installed..." (CIIPr2FOIN).

"...I remember there was a meeting to discuss conversion from LDR to HDR, and we were told the usefulness of HDR: treat many patients in a short time, easy to handle, can be intertwined with EBRT treatments, that is treat patient with HDR while the patient is still undergoing EBRT...I think why the HDR didn't work was lack of awareness/training. It was formalised without preparation..." (CIIPr5ADHOC).

More detailed responses are presented in Annexure F (CIIPr1AC1-3, CIIPr3AB5, and CIIPr2A1b3c).

Technical preparation on the ground

The availability of an existing bunker at Centre I played a major role in the installation of the HDR equipment compared to Centre II. And the available oncology infrastructure in South Africa helped Centre I one to achieve successful installation of the HDR equipment. One of the professionals had this to say:

"....checked with what other centres do here in South Africa: the procedures they have put in place and we customize or adapt to here..." (CIPr2FOIN). The technical preparations at both Centres are summarised in Table 4.24.

Table 4.24: Technical preparation.

CENTRE I	**REF CODE**	**CENTRE II**	**REF CODE**
Availability of bunker/theatre	CIPr1AC2	No HDR brachytherapy bunker available.	CIIPr4AB14
Same applicator placement room/treatment room.	CIPr1AB8-18 CIPr2AB8-18	Different applicator placement/treatment room.	CIIPr4AB9 CIIPr2AB9
Available portable X-ray		No X-ray equipment installed in treatment room, imaging to be done in simulation.	CIIPr4AB9
Adequate space in treatment room.			
Space for planning computer next to treatment console.		Planning computer installed next to treatment console, but currently no planning being done.	CIIPr4AB14
Treatment room with concrete wall 35cm Closed circuit TV installed.		Currently HDR installed in EBRT cobalt-60 bunker - shielding more than adequate for brachytherapy	CIIPr4AB14

Personnel training

The researcher noted from the responses that key staff at Centre II had undergone more training in the use of HDR equipment compared to Centre I. Staff at Centre I had only undergone in-service training and courses organized by the supplier of the equipment. The responses are shown in Table 4.25. Though there were no responses to indicate whether some staff had been trained by the equipment supplier at Centre II, a document available (CIID4) showed Nucletron had conducted training at the Centre in July 2002 on: 'Micro Selectron HDR Application Training Course'. Documents (CIID5 & CIID6) available also show the contract for the supply and delivery of the new HDR was drawn in March 2000 and installation was completed in February 2001. The contract included brachytherapy training and microselectron HDR technical training (CIID3). These show a one and half year gap between installation and training by the supplier.

In addition, documentary evidence (CIID7) showed the equipment was not commissioned after installation. Observations by the researcher also revealed that the equipment had not been used by the time of conducting the study.

Table 4.25: Responses on personnel training at Centre I and II.

Centre I	Ref code	Centre II	Ref code
In-service training, not specific courses.	CIPr1AB21	2 doctors trained, one in Japan, and the other in South Africa for 3 months. A medical physicist also trained in South Africa.	CIIPr1AC3b
Diagnostic radiographers not trained-only take the X-ray then leave.	CIPr1AB21		
Contacted various hospitals for their procedures	CIPr2AC6	Oncologists, physicists, radiographers & two oncology nurses have already been trained by the IAEA	CIIPr2AC3b
Verbal training	CIPr2AC6		
Training by supplier	CIPr2AC6	Personnel available but not utilising the HDR unit at present	CIIPr4AB20E
There is a treatment protocol	CIPr1AB8-18		

HDR ongoing costs

Maintenance of the equipment and supply of Ir-192 sources was a major recurring cost that emerged at Centre I. Costs of personnel training and the sources that were paid for were the major costs highlighted at Centre II. A maintenance contract for the equipment is ongoing at Centre I, while Centre II only procured a one year maintenance contract. Anaesthesia was cited as readily available at both centres and affordable. These are presented in Table 4.26.

Table 4.26: HDR ongoing costs at Centre I & II.

Centre I	Ref code	Centre II	Ref code
Have a maintenance contract with supplier	CIPr2AC1b	Costs of training personnel.	CIIPr1AC3b
If things go wrong we have agents in Cape Town who are quickly available and are familiar with the unit.	CIPr1AC2	Contract elapsed, so no maintenance costs.	CIIPr1AC3c
Existing maintenance in place and essential.	CIPr2AC2	Source replacement procured and paid for.	CIIPr1AC3a CIIPr2AC3a
Keeping the supply of sources going.	CIPr14a	Anaesthesia service is available and well maintained during applicator insertions	CIIPr2AC3f
Anaesthesia is small cost and is available-drugs are cheap.	CIPr1AC3f		

The findings at both sites show the cost of sources is a major recurring expenditure, in addition to contract maintenance.

Comparison of HDR and LDR

There was agreement at both centres that it was difficult to keep HDR running compared to LDR. Some of the key responses highlighted are:

- Need of dedicated staff to keep supply of sources going for HDR
- LDR easier and cheaper to run in terms of management, ease of use and staffing.
- Costs associated with buying HDR and supply of sources is very high.
- LDR source lasts longer translating into lower running costs.

However, in terms of HDR being able to treat a high patient load, concurrence of thought was not so clear. At Centre I, where they have experience treating with HDR, one response was:

"... More patients in theory to be treated with HDR..." (CIPrIAC4e).

At Centre II, where they have no experience treating with HDR, it was clear to them that HDR treats more patients than LDR. Some of the responses were:

"...Though numbers on waiting list could be cleared faster using an HDR service..." (CIIPr2AC4).

"...However due to high dose rate (HDR); a high number of patients can be treated..." (CII2Pr1AC4).

"....And we were told the usefulness of HDR: treats many patients in a short time..." (CIIOPr5ADHOC).

The detailed responses are shown in Annexure G.

Challenges of HDR implementation and use

The Challenges of HDR implementation and use at both centres were more explicit. They are shown in Annexure H. A summary of the key issues were:

Centre I

- The challenge of managing and maintaining a seamless supply of sources every 3 months.
- Difficult to sustain dosimetry for every fraction (#) in HDR. Leads to time wastage and is labour intensive, thereby causing few patients to be treated.
- Occasional technical and hardware failure. This was never experienced with the LDR because it had a manual system.

Centre II

- Lack of a dedicated bunker for HDR
- The operational aspects of the unit have not been understood since installation, due to non-usage.
- Logistical and bureaucratic issues have prevented HDR use.
- Radiation safety issues which have not been addressed.
- Breakdown of supporting equipment; planning software and simulator

Observations by the Researcher at Centre I and II

During the course of the study, the researcher made the following observations:

- The HDR unit was placed in a functioning brachytherapy suite.
- The unit was being used to treat patients twice a week, every Tuesday and Friday.
- Treatments were scheduled from 8am to 1pm.
- Total number of brachytherapy fractions was four (4) for the entire dose of HDR ICBT.
- On a given day, when the Ir-192 radionuclide source is still new, the maximum number of HDR insertions would be 8.

- Time for anaesthesia: First insertion for a new patient, the spinal anaesthesia procedure would take about 30 minutes. X-rays and dosimetry would take about 15 minutes. For repeat insertion 2, 3, and 4, local anaesthetic procedure would take about 10 minutes.
- No X-rays were done during repeat insertions.
- Treatment time ranged from 4 to 20 minutes depending on the activity of the source, and 5 minutes for the patient to get on and off the bed.
- When they had a new source, they would start 2 new patients and do up to 6 repeat insertions, to a total of 8 patients. During low source activity, the number of patients to be treated would be reduced. They would do 2 new insertions and up to 3 or 4 repeat insertions.
- Patients were began HDR ICBT treatments during their last week of EBRT and this was not given during the day of ICBT.

This works out to an average of 6 patients treated per day, using an average treatment time of 12 minutes if a time allowance is given for anaesthesia and dosimetry procedures. Conversations with staff concurred with these observations.

At Centre II, the researcher observed that the HDR unit was not being utilized and was installed in the cobalt-60 treatment room. The following observations were made:

- The simulator room, the planning room, and the HDR unit were quite a distance from each other.
- The brachytherapy planning computer was placed next to the cobalt-60 room where the HDR unit is installed.

Conversations with staff revealed that the intention was to use the cobalt-60 room for the HDR treatment on some days of the week. Though, the researcher observed that the cobalt-60 treatment room was being used daily from 6am to midnight for EBRT sessions from Monday to Friday on overlapping shifts.

This showed that technical and logistical issues were involved in actualizing the use of the HDR equipment at Centre II.

Experience in use of HDR

The issue of experience with HDR was best exemplified by one key staff member at Centre II, as he refused to answer the rest of the questions in Annexure B and C. He only answered the first few in Annexure B: This is how his sentiments were expressed:

"...our experience is in LDR, why are you asking us about HDR..." (CIIPr3SPCON)

Another staff put it explicitly as follows:

"....HDR is available at our centre but has not been put into use due to...a dedicated bunker has not been built for HDR and... the operational aspects of the unit have not been understood since installation for it has not been used..." (CIIPr4AC5).

4.9 Data integration and analysis

4.9.1 Integration

The data generated was integrated, categorised and coded in line with the initial propositions generated from the objectives of the study, questionnaires, and interviews (Babbie & Mouton, 2001:389, 499). To increase reliability, another expert in the field encoded the same data to assess concurrence (Brink et al., 2006:185). The researcher envisaged that using both quantitative and qualitative data would lead to a strong analytic strategy (Yin, 2009: 132; Flyvbjerg, 2004:432).

Categories identified

A: Patients' clinical profile.

B: Patient numbers and clinical factors associated with brachytherapy.

C: Africa context: Challenges & difficulties of HDR implementation.

D: Africa Context: Type of equipment, experience and availability of infrastructure.

Assessment of categories

A check list and question format adapted and modified from Leedy and Ormrod (2005:173) was used to assess each of the categories identified.

Category A was subdivided into subcategories and assessed to find out if the clinical profiles identified in these patients were amenable to LDR or HDR ICBT based on the evidence available.

Table 4.27: Patients' amenability to ICBT combined with EBRT based on clinical factors.

Sub-category	Amenable to HDR or LDR ICBT. **Yes.** In what ways?	Is not amenable to HDR or LDR ICBT. **No.** In what ways?	Evidence/ support
FIGO Stage	Majority of patients in stage II & III.		**Study results:** High pelvic relapse free survival rates at both Centres, hence good pelvic control. **Studies in literature:** Comparable results in Ferrigno et al. (2005), Lertsanguansinchai et al. (2004) and Eifel (1997).
Histology	Majority are Squamous cell carcinomas followed by adenocarcinomas		Follows trends worldwide: WHO (2011) and National cancer institute, US (2011). **Studies in literature:** Comparable results in Ferrigno et al.(2005) and Lertsanguansinchai et al. (2004)
Age	Majority in age 30-60 years		**Study results**: High pelvic relapse free survival rates at both Centres, hence good pelvic control **Studies in literature:** Comparable results in Ferrigno et al.(2005), Lertsanguansinchai et al. (2004).

The theme identified in this assessment was:

The majority of the patients in the study are amenable to definitive radiotherapy of HDR or LDR ICBT combined with EBRT (Table 4.27). No evidence emerged to the contrary.

In category B, the unit of analysis was, "Is HDR appropriate?" (Yin, 2009:147; Tellis, 1997:2). The subcategories were analysed to find out if HDR or LDR ICBT were appropriate in dealing with the patient numbers and clinical factors identified in the study (Table 4.28).

Table 4.28: Assessment of patient numbers and clinical factors at Centre I and II.

Sub-category	Is HDR appropriate? **(Yes).** In what ways?	Is HDR not appropriate? (**No)**. In what ways?	Same with LDR**(Yes)**	Evidence/Support
Patient numbers	Centre I (HDR) treated more patients compared to Centre II(LDR)			Many patients reported at both Centres (Figure 4.13). 68.5 % (724/157) treated at Centre I (HDR) compared to 11.1 %(145/1306) at Centre II (LDR) [Figure 4.14]. Patients seen at Centre II (LDR) constitute about 50% of all patients presenting at the Centre... (CIIPr4 AC4).
Number of fractions(#s)		Several visits to hospital - inconvenience to patient.		**Study finding:** Currently Centre I uses a minimum of 4 #s for radical treatment. At Centre II only a single # is used.
Biological dose			Slight variation in range between Centre I(HDR) and Centre II(LDR)	**Study finding:** Calculated EQD_2 dose has an almost similar range at both Centres using HDR or LDR
Overall Treatment time (OTT)	Short overall treatment time seen at Centre I(HDR) compared to long treatment time at Centre II(LDR)			Median OTT at Centre I was 48 days. Median time at Centre II was 169 days Recommendation from American Brachytherapy Society (ABS): 56 days.
Treatment outcomes			Similar results with LDR, therefore cannot say HDR is better than LDR	**Study findings:** Similar Pelvic free survival rates results and bladder complications. Comparable to literature. The 5-year overall survival was 50% at Centre I (HDR) which compared to published literature on LDR. Literature: Falkenberg et al. (2006) and Ferrigno et al. (2005).

Using Table 4.28, the five (5) subcategories were analysed:

Is HDR appropriate? (HDR is better) 2/5 (40%).

Is HDR not appropriate? (LDR is better) 1/5 (20%).

Same with LDR (HDR similar with LDR) 2/5 (40%).

Table 4.29: Analysis of appropriateness of HDR in dealing with patient numbers and identified clinical factors.

HDR is better	**LDR is better**	**HDR same with LDR**
2/5 (40%)	1/5 (20%)	2/5 (40%)

In a number of sub-categories, HDR and LDR ICBT were the same at 40% (Table 4.29). Though HDR ICBT emerged better in dealing with patient numbers and having a short overall treatment time (40%) compared to LDR ICBT at 20%.

In category C, appropriateness of HDR was assessed based on the various categories identified from the study (Table 4.30). Where the issues identified were the same for both HDR and LDR, comments were also made in the box, *'maybe the same'*.

Table 4.30: Assessment of African context: Challenges and difficulties of HDR implementation at Centre I and II.

Sub-category	Is HDR appropriate? **Yes**. In what ways?	Is HDR not appropriate? **No**. In what ways?	Maybe the same with LDR**(Yes)**	Evidence/Support
Sources		Costly sources, Difficult to maintain supply in terms of management. LDR, only one source required.		...Cost of regular source replacement is high...(CIIPr4AC4). ...Challenges of keeping supply of sources going...CIPr1AC5,3a
Technical Preparation	Same preparation required as for LDR-similar amounts of investment & preparation as for LDR		Same preparation required as for HDR-similar amounts of investment and preparation as for HDR.	Technical preparations adequate for Centre I. (Table 4.24). Technical preparations not adequate for Centre II. (Table 4.24).

Shielded radiation treatment bunker		Requires a dedicated bunker, cash strapped African countries may not afford.	One may argue that LDR also needs a Bunker	...Existing infrastructure-availability of theatre, it was already there for LDR work...CIPr1AB4-5AC2 ...No HDR brachytherapy bunker available...CIIPr4AB14
Ongoing costs		Cost of sources every 3-4 months. LDR source costs only once for 30 years.		...LDR source lasts longer, translating into low running costs...(CIIPr4AC4)
Maintenance		Maintenance contract a must but costly to sustain in Africa due to logistics & support	LDR also needs a maintenance contract.	...small technical failures, solved by local agents. Big technical failures by senior people from Johannesburg or overseas (rare)...CIPr1AC5. ...Lack of a maintenance contract for HDR...contract was only for one year which elapsed...CIIPr1AC5. ...LDR maintenance sourced overseas...(CIIPr4AC4) ...we have a local hospital biomedical team who perform minor repairs on LDR....CIIPr2AC1b3c.
Training		In African countries without several oncology centres that can provide support, it's very costly to train staff, like at Centre II.		...checked other Centres' procedures: customize or adapt to here...CIPr2AC6 & FOIN All key staff trained at Centre II, overseas and local (Table 4.25). Can use LDR staff, though have to be trained...(CIPr1AC2)
Savings	No inpatient costs for HDR.			... no patient admission, while for LDR all patients have to be admitted... (CIPrIAC2). ...Outpatient treatment...CIPr1AC2). LDR/MDR- average time was 12 hrs-single treatment at Centre II, logistics, maybe overnight stay.

Analysing the 7 sub-categories:

Is HDR appropriate: Y (Yes)

Is HDR not appropriate: N (No)

Same with LDR: S (Same)

- Sources- HDR not appropriate compared to LDR (N)
- Shielded radiation treatment bunker- Same requirement with LDR (S)
- Technical preparation-similar requirement with LDR (S)
- Ongoing costs-HDR not appropriate compared to LDR (N)
- Maintenance-Similar issues with LDR (S)
- Training-HDR not appropriate in African countries without oncology centres that can provide support (N)
- In-patient savings- HDR is appropriate, no inpatient hospital costs for HDR compared to LDR ICBT(Y)

Is HDR appropriate: In-patient savings. Scores (Y): 14% (1/7)

Is HDR not appropriate: Sources, ongoing costs, training. Scores (N) 43 % (3/7)

Same with LDR: Shielded bunker, technical preparation, maintenance. Scores (S) (43%) 3/7.

Table 4.31: Analysis of appropriateness of HDR in implementation and use based on the specified subcategorise in the study.

Is HDR appropriate?	Is HDR not appropriate?	HDR same with LDR
1/7 (14%)	(3/7) 43%	3/7 (43%)

The finding here was that HDR was not appropriate in terms of regular source replacement, ongoing costs and training (43%), but appropriate in terms of in-patient savings due to outpatient treatment (14%) [Table 4.31].

For Technical preparation and maintenance, LDR and HDR scored the same (43%), implying they would require about the similar engagement and preparation.

Through observations and reflections, the researcher noted that the problem at Centre II was lack of brachytherapy treatment for patients with cervical cancer. Reflecting upon the entire data collected, the following question emerged: What would solve this problem at Centre II?

Therefore, category D analysed type of equipment at Centre II, experience and availability of infrastructure (Table 4.32).

Table 4.32: Type of equipment at Centre II, experience and availability of infrastructure.

	Experience, available?	Infrastructure availability?	No of patients to treat?	Evidence/source
Nucletron HDR	No	No	Several but with repeat fractions	CIIPr3SC, CIIPr4AC5, CIIPr4AB14, Table 4.24, Blank answer scripts AC6 (Annexure N), Figure 4.6.
Selectron LDR/MDR	Yes	Yes	One patient per day single fraction (#)	CIIPr3SC, CIIPr2FOIN, Figure 4.3, Figure 4.4, Tables 4.1, 4.2.
Amersham LDR	Yes	No	One patient per week.	Tables 4.2, 4.3.

Among the three equipment types, LDR/MDR emerged the most favourable in terms of experience, and availability of infrastructure (Table 4.32).

4.9.2 Interpretation

The themes that emerged were then assessed by the researcher by making connections between them in order to answer the main research question on the appropriateness of HDR brachytherapy within African settings. This exercise was guided by the unit of analysis, "appropriateness of HDR brachytherapy" (Tellis, 1997:3).

- Category A: Majority of the patients in the study are amenable to definitive radiotherapy of HDR or LDR ICBT combined with EBRT (Table 4.27).

- Category B: HDR ICBT emerged better in dealing with patient numbers and having a short overall treatment time (40%) compared to LDR ICBT at 20% (Table 4.29).

- Category C: HDR was not appropriate in terms of regular source replacement, ongoing costs and training (43%), but appropriate in terms of in-patient savings due to outpatient treatment (14%) [Table 4.31].

- Category D: Among the three types of equipment, LDR/MDR emerged the most favourable in terms of experience, and availability of infrastructure at Centre II (Table 4.32).

In a number of subcategories, the score was the same for either equipment.

The resulting connections were subjected to discussion and interpretation by staff and those who provided the data at the two centres. This is described by Becker et al. (2005) as member check; where the researcher initiates and maintains an active corroboration with the participants in the study. The resulting themes were refined, with recording of further support data in order to increase construct validity with multiple sources of evidence through the process of data triangulation (Yin, 2009:102-124; Brink et al., 2006:184; Tellis, 1997:2).

These results from the quantitative and qualitative data will be discussed in the following chapter.

Chapter 5

Discussion and conclusions

5.1 Introduction

Drawing on the findings of this case study, this chapter presents a discussion on cervical cancer burden in Africa, patient profile, factors with regard to brachytherapy treatment at Centre I and II, comparison of treatment outcomes between HDR and LDR ICBT, and implementation of HDR brachytherapy treatment within the African setting. The chapter concludes with recommendations on possible strategies that may be sustainable for treating the high number of cervical cancer patients in Africa.

5.2 Findings

The final finding was that HDR is not generally considered an appropriate treatment strategy within the African context although there are notable exceptions. The focus of the discussion will be to develop a recommendation for a suitable treatment strategy for brachytherapy of cervical cancer within the African context where HDR is not considered appropriate. The African context in terms of cervical cancer treatment using brachytherapy was explored using a case study approach. The findings highlighted the following at the two Centres:

i) The high number of patients with cervical cancer
ii) The clinical profile of the patient with cervical cancer
iii) Type of brachytherapy applications employed.
iv) Factors associated with regard to brachytherapy treatment.
v) Similarities in treatment outcomes of HDR and LDR ICBT.
vi) The challenges in the use and implementation of HDR brachytherapy in Africa.
vii) Possible solutions and strategies in treatment of cervical cancer within the African context.

5.3 Cervical cancer burden

This study shows a high number of cervical cancer patients, 1057 and 1306, at Centre I & II, respectively (Figure 4.13). This study conducted in South Africa and East Africa, gives an indication of the high number of cervical patients in Africa. Nigeria with a population of 32 million women (of reproductive age), and only four radiotherapy Centres, would be expected to treat approximately 8000 new cases of invasive cervical cancer annually (Adewole et al. 2005: S209). At Centre II, one of the professionals had this to say:

...the number of patients with cervical cancer constitute approximately 50% of all cancer patients at our Centre... (CIIPr4AC4). In this study, 69% (724/1057), and 11% (145/1306) of the

patients presenting at Centre I and II, respectively, received brachytherapy applications over a 7 year period (Figure 4.13 & 4.14). The above figures show a high number did not receive brachytherapy with as high as 89% at Centre II, despite EBRT plus ICBT being the standard treatment modality for cervical cancer (Dobbs, Barret, Morris & Roques, 2009:371). Multiple reasons could account for the above situation. IAEA estimates in 2003 showed that 15 countries in Africa did not have a single radiotherapy machine. The figure does not change much in the current estimates (IAEA, 2011). These calls for solutions. The ratio of 1 machine and 3 to 5 machines per million people in Kenya and South Africa respectively is one the reasons denying the many patients with cervical cancer access to these services. In particular, Kenya with only one public oncology Centre (Parliamentary Brief, 2011), is an indicator of the difficult decisions that must be made by governments regarding priorities for their limited budgets in limited resource settings. Poverty, awareness, and low levels of literacy, among other reasons, may also account for the high numbers not receiving brachytherapy services. Despite this reasons, studies show that investment in programmes that include; prevention, early diagnosis, treatment, and palliative care are highly successful in developed countries as they result in 45% of all cancers cured (IAEA, 2003). Therefore investment in brachytherapy services should be considered a high priority area by African governments to be able to deal with the high cervical cancer burden.

5.4 Late FIGO stage presentation

Gerbaulet et al. (2002:305) note that indications for brachytherapy will be divided according to stage with careful considerations between early and locally advanced cervical cancer. The majority of the patients at both Centres presented with Stage II and III disease. Most of the patients in FIGO stage II were in IIB with 76/193 (39.4%) at Centre I, and 22/48 (45.8%)] at Centre II, respectively (Tables 4.4 and 4.6). The prognosis for these patients is better when treatment is administered by EBRT and ICBT as stated by the IAEA (2001) and WHO (2008:422). Less than 10% of the patients in this study were in FIGO stage I, that usually benefits from surgery, and the distribution compares well with other reported series in Africa except for the study by Wabinga et al. (2003), Table 5.1.

Table 5.1: Reported FIGO stage I series in Africa compared to Centre I and II.

CENTRE / STUDY	STAGE I
Centre I (South Africa)	9.3%
Lomalisa et al.(2000) Johannesburg, South Africa	8.4%
Centre II (Kenya)	5.9%
Rogo et al. (1990) Kenya	6%
Ntekim et al. (2010) Nigeria	4%
Wabinga et al. (2003) Kampala, Uganda	27.9%

Though the distribution of FIGO stage I in the study that was conducted in Kampala Uganda was 27.9%, they reported that 45% of the cases in this category had been treated with radiotherapy. This would imply that due to other competing health care needs and lack of adequate health care infrastructure for surgical interventions, coupled with overall socioeconomic conditions of the patients, many in Africa with early stage disease would still benefit from radiotherapy. Therefore the many patients reported in this study would be treated with radiotherapy treatment that combines EBRT and HDR or LDR ICBT from stage I onwards. Unlike the normal practice, for example, stage IA that is treated with surgery due to its excellent prognosis (Ahmed et al., 2010:153). This implies many patients with cervical cancer in Africa require radiation therapy services, compared to the developed countries.

5.5 Histological classification

The findings in this study, despite the small sample size at Centre II, confirm the representation of squamous cell carcinoma and adenocarcinoma in cervical cancer patients given by the WHO (2011) and the National Cancer Institute (2011) of the US (Table 5.2). The majority of the cases were squamous cell carcinomas that respond well to radiation therapy. The five year survival in all FIGO stages for squamous cell carcinoma of the cervix is approximately 10% greater than for other common histological types due to its low incidence of distant metastasis (Ahmed et al., 2010:151). Hence, the majority of the patients in this study and elsewhere in Africa where radiation therapy services (EBRT +HDR or LDR ICBT) would be available would benefit, thereby prolonging overall survival rates for patients with cervical cancer in Africa.

Table 5.2: WHO and US pathological classification compared with Centre I and II.

PATHOLOGICAL CLASSIFICATION	**SITE/ORGANIZATION**			
	Centre I	**Centre II**	**WHO 2011**	**NCI 2011(US)**
Squamous Cell carcinoma	85.5%	79.5%	85%	90%
Adenocarcinoma	12.4%	10.3%	10-12%	10%

5.6 Age

A policy brief to the national parliament in Kenya, points out that more young Kenyans seem to be affected by cancer unlike in the past when it was considered a disease of the old (Policy Brief, 2011). The mean age in this study was 45.7 years with a median age of 41.5 years for Centre II in Kenya, and 52.1 years with a median age of 51 years for Centre I in South Africa. The difference was not statistically significant with a p-value of 0.8315. Nevertheless, the figures show that the disease was being detected at a much younger age (premenopausal) at Centre II compared to Centre I (postmenopausal). This confirms the above policy brief to parliament and the findings of the study by Rogo et al. (1990:251) in Kenya on carcinoma of the cervix in the African setting, that showed 70% of the patients were premenopausal and despite their young age, the majority reported with late stage disease (FIGO). Other studies in Nigeria showed age distributions of between 24 and 80 with an aggregated mean age of 48 (Adewole, 2005:S209). One particular study that had patients treated with HDR ICBT in Nigeria using a Cobalt-60 radionuclide source showed patients to have a median age of 45 years and a range 25-69 years (Ntekim, Adenipekun, Akinlade and Campbell, 2010). These findings show the situation in Africa to be that many patients present at a time when they are in the most productive years of their life. Several factors like poverty and low standard of living may influence this. Kenya may therefore be a country in Africa representative of a majority of countries in Sub Saharan Africa with similar standards of living. Though according to the World Fact Book[1&2] (2011), life expectancy which is a measure of overall quality of life in a country and summarizes the mortality at all ages, was similar in 2003 at 45 and 46 years, in Kenya and South Africa respectively. Therefore, other factors may influence the above trends and indicate the need for further studies.

5.7 Factors influencing treatment outcomes

5.7.1 Overall treatment time (OTT)

The overall treatment time at Centre II was high compared to Centre I with a median time of 169 days (57 to 576 days) and 48 days (29 to 211 days), respectively. Follow-up records at Centre II showed patients who had persistent disease were considered for ICBT long after completion of their EBRT sessions resulting in long OTTs. A possible reason for the long OTTs is the lack of integration of EBRT and ICBT from the start. There is only one public oncology Centre in Kenya (Policy Brief, 2011:4), and all possible efforts are made to start as many patients as possible on EBRT with the consequent effect that patients have to wait for ICBT. The data at Centre II shows that there was a time-period in the two years preceding 1998 with no brachytherapy applications (Table 4.2). The data shows several patients waiting for over 6 months after EBRT with one particular patient who had EBRT in May 1997 and who was treated with ICBT in December 1998,

resulting in an OTT of 576 days. This represents a typical African situation of too many patients for the limited available resources. The American Brachytherapy Society (ABS) recommends LDR ICBT for patients with cervical cancer to commence after EBRT with one treatment per week (Viswanathan & Thomadsen, Undated). While for HDR ICBT, they suggest that this may be initiated earlier, but not earlier than the administration of at least 20 Gy of EBRT. Therefore, regardless of the factors influencing OTT, if these guidelines are followed, HDR would still produce a lower OTT than LDR ICBT. This will influence treatment outcomes (Chen, Liang, & Yang et al., 2003). Though in the current study, the effect was not observable in the pelvic relapse rates at 4 years post follow-up, probably due to the small sample size at Centre II. Nevertheless, Stewart & Visawanathan (2006: 909) and the ABS advise that all treatment, HDR or LDR ICBT plus EBRT, should be completed within 56 days. The findings from this research show that Centre I meets this standard, and Centre II does not.

5.7.2 Follow-up

The study recorded a median follow-up time of 42.2 months (3 to 147 months) and 12.4 months (2 to 105 months) at Centre I and II, respectively. Compared to other published studies (Table 5.3), the Centre II follow-up time was extremely short. This reflects the problems of follow-up in Africa. Rogo et al. (1990:249) notes that follow-up in Africa is extremely poor and treatment results are therefore difficult to calculate. The situation in Kenya conforms to a majority of African countries. The poor infrastructure, poverty, lack of proper address and record systems may impact on data collection systems and reported follow-up patterns in the two countries. Therefore calculation of treatment outcomes may not be accurate due to unavailable data. For example, Kenya currently lacks a National Cancer Registry (Policy Brief, 2011). In South Africa, data from the National Cancer Registry has been unavailable since the last published report in 1999 (Denny, 2010: 70).

Table 5.3: Median follow-up time at Centre I, II, and published studies.

CENTRE / STUDY	MEDIAN FOLLOW-UP TIME
Centre I (HDR)	42.2 months (3 to 147months)
Centre II (LDR)	12.4 months (2 to 105 months).
Falkenberg et al., 2006 (HDR)	59 months (0 to 136 months)
Falkenberg et al., 2006 (LDR)	48 months (2 to 104 months)
Ferrigno et al., 2005 (HDR)	33 months (4 to 117 months)
Ferrigno et al., 2005 (LDR)	70 months (8 to 127 months)
Lertsanguansinchai et al., 2004 (HDR)	37.2 months
Lertsanguansinchai et al., 2004 (LDR)	40.2 Months

5.7.3 Biological dose

The treatment protocol at Centre I gives guidance on the total EQD_2 at Point 'A' when EBRT is combined with ICBT to range between 75 and 85 Gy, for acute effects. The results in the study show a mean of 81.8 Gy and a median of 82.8 Gy at point 'A' (Figure 4.17). This dose is analysed over a 7-year period and has a median range of 78.8Gy to a peak of 86.9Gy (Figure 4.18). The EQD_2 at point 'A' for Centre II has a mean of 87.7 Gy and a median of 88 Gy (Figure 4.17). The median range over a 2-year period was 83.7 to 90 Gy (Figure 4.18). Despite the short period of analysis at Centre II, the EQD_2 s at both Centres are comparable and dose to a single point ('A') using two projection radiographs is widely used and a lot of clinical experience has been accumulated using this system (Toita, 2009:27), that inevitably boosts research efforts. Therefore dose to point 'A' still remains a good prognostic factor for treatment outcomes. Though for accurate reporting, the effect of dose to point 'A' should be ruled out by considering other factors. These include improvement in EBRT practice, tumour volume, extension of parametrial invasion, presence of hydronephrosis, lymph node metastasis, and extension of vaginal involvement (Falkenberg et al., 2006 & Ferrigno et al., 2005).

Despite the study results indicating a similar biological dose to point 'A' for LDR and HDR at Centre I and II respectively, with a p-value of 0.88 that is not statistically significant, numerically there is a slightly higher dose for Centre II than for Centre I (Figures 4.17, 4.18). The study by Ferrigno et al. (2005:1113) in Brazil attributed the poorer outcome in FIGO stage III patients in their study to a lower biologic effective dose to point 'A' delivered by HDR ICBT, compared to LDR ICBT. The fractionation schedule was 4 fractions of 6 Gy to point 'A', which they later noted was not effective for treating large tumours. In another study, Falkenberg et al. (2006:51-52) reported similar outcomes for the HDR and LDR group for FIGO stage III patients using the single point 'A' dosimetry system. Though sub group analysis was not done in this study that had too few patients at Centre II to allow for reliable conclusions, the slightly different biological dose between Centre I and II may not necessarily be the cause of any differences in treatment outcomes between the two Centres. This is because this study shows a majority of the patients had locally advanced cervical cancer with probable bulky disease. Therefore the conventional point 'A' may not be consistent with individual tumour extent. 3D image-based treatment planning might have been better in ensuring adequate tumour coverage that could be correlated with treatment outcomes (Wang et al., 2010:15).

5.8 Similarities in treatment outcomes

5.8.1 Pelvic relapse free survival

The study found similar actuarial rates for pelvic relapse free survival at 5 years post follow-up for Centre I compared to Centre II, 65.8% and 53.9 %, respectively (p = 0.84), Figure 4.20. These results were compared with other studies in published literature (Table 5.4). All showed similar pelvic relapse free (pelvic control) survival rates, and although the differences were not significant with p values greater than 0.05, the trend from published literature seemed to show slightly higher pelvic relapse free rates for LDR than HDR ICBT. Figures in Table 5.4 show the reverse being the case in this study. The small sample size at Centre II notwithstanding, one most likely reason is the effect of the long OTTs that cannot be ruled out, where only 20% (10/49) received treatment within 57 and 98 days, despite the recommended being 56 days. Though the statistical similarities in pelvic relapse outcome could have been a result of the exclusion in analysis of the patients with persistent disease 5/49 (10%), who according to data available had extraordinary long OTTs that might not have resulted in effective treatment. Wang et al. (2010) in a meta-analysis compared the results of Lertsanguansinchai et al. (2004); Harayema, Sakata, Oouchi, et al. (2002), and other randomized control trials in Asia using statistical methods and found no significant difference in rates of pelvic relapse free survival, recurrence and metastasis between HDR and LDR patients. The evidence in this study and others that are published (Table 5.4), seems to show that LDR ICBT posts similar pelvic relapse free survival rates when treating patients with cervical cancer.

Table 5.4: Published studies comparing LDR and HDR ICBT for cervical cancer.

Site / Study	**Total number of patients (n)**	**Pelvic relapse free or pelvic control (PC)**	
		HDR	**LDR**
Centre I(HDR) and Centre II(LDR)	213	65.8% (5-year PC)	53.9% (5-year PC)
Falkenberg et al. (2006)	160	76% (3-year PC)	78% (3-year PC)
Ferrigno et al. (2005)	308	65.0% (5-year PC)	74.0% (5-year PC)
Lertsanguansinchai et al. (2004)	206	85.6% (3-year PC)	90.2% (3-year PC)
Patel et al. (1994)	482	75.8% (5-year PC)	79.7% (5-year PC)

5.8.2 Late complications

The study results showed similar late grade 3 & 4 bladder complications with a p value of 0.29 at Centre I and II (Tables 4.22, 5.5, Figure 4.22). The occurrence of grade 3 and 4 rectal complications was higher at Centre II than Centre I with a significant p value of 0.002. When the bladder and rectal complications at Centre I (HDR) and Centre II (LDR) were further compared with the other published data in the literature (Table 5.5), the rectal complications at Centre II were found to be quite high. Several factors could have caused this difference. The small sample size used at Centre II would result in higher calculated rates. The effect of the EBRT technique employed at Centre II, where all patients were treated with POP beams, compared to Centre I where a majority of the patients received the 4 field pelvic box technique, with only a few receiving the POP beam arrangement (Table 4.1). These probably resulted in higher doses to the rectum and bladder at Centre II, despite the small EQD_2 recorded (Table 4.19, Figure 4.19). This is because, the dose specification based on the ICRU-38 (1985:11) report, defines dose at a point, and this is not representative of the entire organ. In addition, the study analysis did not include grade 5 at Centre I and II, unlike the figures by Wang et al., 2010 (Table 5.5), though the figures at Centre I were very similar. This indicates other factors need to be ruled out, including calibration and dosimetry, which would require another study.

Table 5.5: Comparison of late complications at Centre I and II with the meta-analysis by Wang et al., 2010.

	Centre I (HDR) **Grade 3 &4**	**Centre II (LDR)** **Grade 3 & 4**	**Wang et al., 2010 (HDR)** **Grade 3-5**	**Wang et al., 2010 LDR** **Grade 3-5**
Bladder	3.4 % (3/174)	0 % (1/49)	1.8% (12/668)	3.0% (18/597)
Rectum	3 % (4/175)	25 % (4/49)	1.3% (8/597)	2.0% (14/668)

Nevertheless, the results by Wang et al. (2010) suggest that there was no significant difference in the reporting of severe bladder and rectal complication between HDR and LDR ICBT. The figures by Wang et al. (2010) were derived from very large numbers and therefore more likely to be accurate, since they are actuarial rates. This implies that LDR ICBT is as good as HDR ICBT and can continue being used safely with minimal or acceptable complications.

5.8.3 Overall survival

The survival figures at Centre I (HDR) were compared with other results from published literature (Table 5.6). The unavailability of survival figures at Centre II highlights some of the difficulties in data records and follow-up of patients in Africa. The Centre I overall survival results were calculated using the Kaplan Meier method to cater for those patients whose status of death was not known. The trend shows LDR ICBT giving higher overall survival figures compared to HDR in all the studies. Nevertheless, statistical tests done in the published studies show the difference not being significant, and conclude that the two are comparable. Therefore LDR ICBT gives similar overall survival figures when compared with HDR ICBT.

Table 5.6: Centre I (HDR) overall survival compared with published data.

Site / Study	**Total number of patients (n)**	**Overall survival (OS)**	
		HDR	**LDR**
Centre I(HDR)	173	50.0% 5-year OS	
Ferrigno et al. (2005)	308	55.0% 5-year OS	69% 5-year OS
Patel et al. (1994)-stage I, II & III	482	I - 78% II - 64.0% III - 43% 5-year OS	I - 73.0% II - 62.0% III - 50.0% 5-year OS
Falkenberg et al. (2006)		55% 3-year OS	60% 3-year OS
Lertsanguansinchai et al. 2004	206	66.3% 3-year OS	69.6% 3-year OS

5.8.4 Implications

Overall, the results of treatment outcomes in this study and published data in the literature seem to suggest that HDR would give similar treatment outcomes when compared to LDR ICBT. A study by Tanaka, Rhoong, Yamada et al. (2003) also showed no differences in clinical outcomes between MDR (Cs-137) and HDR (Ir-192) ICBT for patients treated for cervical cancer. Therefore, although the worldwide trend is to convert to HDR ICBT treatments for cervical cancer, LDR or MDR ICBT if available can continue being used and the clinical results will be equivalent to using HDR ICBT. Use of HDR ICBT is on the increase due to its ability to treat more patients and the short treatment times administered per session. The following section discusses the results of this study on implementation and the use of HDR brachytherapy equipment at the two African centres.

5.9 Implementation and use of HDR

The high volumes of patients with cervical cancer who need radiation therapy treatment, is a key factor in deciding to purchase and install HDR brachytherapy equipment. This is evidenced in the results of this study by the number of patients presenting at Centre I and II (Figure 4.13), and reports from the world cancer report (WHO, 2008:418-420) that Africa has the highest cervical cancer burden in the world. Previous problems with leaky radium sources were also instrumental in making Centre I shift to HDR. The long hours associated with the LDR Amersham afterloading system made Centre II initially shift to the Selectron LDR with an MDR option. Remote afterloading systems associated with HDR and Selectron LDR units give better radiation protection to staff and patient, compared to the old LDR systems using radium or the Cs-137 Amersham afterloading units (Wang et al., 2010:3 & Glenn, Bourland, Grigsby et al., 1993:1).

The shift to HDR involves technical and practical factors including well laid down maintenance schedules. Therefore when making a decision to change to HDR infrastructure, source and personnel safety require careful attention (IAEA-TECDOC-1257, 2001:1). In developing countries, the cost of establishing health infrastructure is weighed against other competing but equally essential needs. From this study, Centre I appears to have made a complete shift to HDR, and therefore was able to convert the existing infrastructure of LDR to HDR use. In contrast, Centre II planned to run the new HDR unit, alongside the existing Selectron LDR/MDR option, hence the available infrastructure for LDR was not available for use with HDR. Therefore when the room earmarked to house the HDR unit was found to have inadequate shielding (CIIPr3SC), the unit was shifted to the cobalt-60 treatment room. One response gives a situation analysis at Centre II:

"...No prior preparation when ordering HDR. When LDR was ordered previously, there was no problem; there was a good plan when it was being procured. Everything was ready-building, rooms, and all the infrastructure plus training in place. When HDR came, then we became aware we needed all these things i.e. room plus other infrastructure. Then we started planning where the HDR was to be installed..." (CIIPr2FOIN).

Hence the technical need to address shielding requirements for the new unit, led to the need of a radiotherapy bunker, which had not been addressed. This is likely due to insufficient resources and other competing needs. This is in contrast to Centre I where they overcame this obstacle by making use of the existing infrastructure.

The importance of practical support when implementing HDR brachytherapy is emphasized by (Nag, 2004:270) in his advice to institutions wishing to introduce HDR brachytherapy. He states that they should survey the experiences of Centres that have been performing HDR, and cautions against translating LDR experience automatically into HDR use. South Africa has a number of

radiation oncology centres that are well established with skilled and experienced personnel. This is well exemplified in this study:

"...checked with what other centres do here in South Africa: the procedures they have put in place and we customize or adapt to here..." (CIPr2FOIN).

The study shows that Kenya with only one public oncology centre therefore cannot benefit from this kind of support. Hence, planning and implementation of an HDR programme may be more complicated and challenging as evidenced in this study.

Regular maintenance is essential for sustainable use of any HDR brachytherapy system. Therefore, the need of a proper maintenance contract with the supplier is crucial for successful implementation and sustainable use of HDR brachytherapy equipment. The evidence accrued showed that between 1996 and 1997, there were no brachytherapy treatments at Centre II using the LDR Amersham afterloading system (Table 4.2), due to technical issues. The findings also show no brachytherapy treatments after 1999 at Centre II due to technical issues with the Selectron LDR/MDR. The study highlights several issues that might have to do with maintenance services. At Centre I where they have managed to keep brachytherapy treatments going with the HDR unit:

- They have an existing maintenance contract with the supplier (CIPr1AC1b, CIPr1AC2, CIPr2AC2, Table 4.26.
- They have agents in Cape Town who are quickly available and familiar with the unit. CIPr1AC1b, CIPr1AC2, Table 4.26.
- Big technical failures were solved by senior people from Johannesburg or overseas but have been rare (CIPr1AC5), Annexure H.

At Centre II, difficulties in accessing maintenance services, lack of locally available skilled personnel, and lack of sufficient resources to sustain long service contracts and upgrades seemed to be the main issue:

"..Lack of a maintenance contract for HDR... contract was only for one year which elapsed..." (CIIPr1AC1b3c) [Annexure H].

"...Had initial service contract. Though we have a local (hospital) biomedical engineering team who perform minor repairs..." (CIIPr2AC1b3c, CIIPr2AC3) [Annexure F].

"...LDR has been in use for some time now in our department and has provided good service with minimal servicing. However, maintenance is challenge as it has to be sourced from outside the country, which is costly..." (CIIPr4AC4), Annexure G.

Therefore, regardless of the type of equipment, maintenance emerged as a major factor disabling sustainability of brachytherapy services at Centre II.

In addition, service contracts that are embedded with training components would be preferable. The cost of training embedded in the contract (CIID3) at Centre II was technically a good decision, as it ensured training was delivered, despite the contract being only for one year (CIIPr1AC5); (CIID8). The available evidence shows there was a delay of one and half years between installation and training at Centre II. The evidence further shows that no practical experiential training with actual patients was done on site (CIID4, CIID6, and CIIPr3SC), as the training was largely theoretical. This lack of practical applied training with real patients is proposed as one of the factors that could be associated with the unsuccessful implementation of HDR at Centre II. The in-service training at Centre I, in addition to other oncology support systems in the country seems to have enabled successful implementation of HDR brachytherapy at Centre I (CIPr1AB21; CIPr2AC6).

The use of HDR Ir-192 brachytherapy has its own challenges as shown by this study. These arise largely from ongoing costs and management logistics for the continuous supply of Ir-192 sources. This may hinder successful use of this equipment in countries with limited resource settings. The findings indicate the ongoing costs of HDR are high, compared to the Selectron LDR/MDR:

"... LDR source lasts longer translating into low running costs..." (CIIPr4AC4), Annexure G.

"...Much cheaper to run LDR than HDR in terms of: management, ease of use, staffing..." CIIPr2AC4, Annexure G.

"...for HDR, more management to keep supply of sources going. Dedicated staff to see this happen....." CIPr14a, Annexure G.

The high costs associated with HDR Ir-192 brachytherapy are confirmed by Wang et al. (2010:3). He notes that HDR is more expensive than LDR, and that source changes are required every three months.

Despite this study confirming that HDR ICBT can treat more patients with cervical cancer compared to Amersham LDR and the Selectron LDR/MDR (Table 4.2, Figure 4.14), there appear to be challenges with its implementation and sustained use, making this a hard reality, more so at Centre II. One of the key study findings is that HDR is not appropriate in terms of regular source replacement, ongoing costs and training (Table 4.31), and that experience with HDR is not available at Centre II (Table 4.32). These highlight the challenges within the African context. Kenya represents the environment of a majority of African countries with limited resources, hence these types of problems might be found in a number of African countries, especially in Sub-Saharan Africa. This creates problems with the sustainable use of HDR brachytherapy as a technique to deal with the cervical cancer burden in Africa.

5.10 Experience and reflections by the researcher

The issue of experience is one of the important factors in the implementation and use of HDR as pointed out by Nag (2004). The study shows that while HDR experience is lacking at Centre II, the evidence available points to the Centre having adequate experience with the Selectron LDR/MDR (Table.4.32). These made the researcher reflect on his research strategy.

"... Why ask them about HDR and they have not used it!..."

Analysing further the questionnaire answer scripts, question 6 on QA implementation (Annexure C) was not answered by all the respondents at Centre II, though it was answered by staff at Centre II (Annexure I). This implied and confirmed that HDR has not been used at Centre II, since no procedures had been implemented. However, on second thoughts after looking at the entire spectrum of the data collected, the researcher reflected:

"...Lack of HDR experience...could this be the solution to the problem at Centre II..." (Researcher notes CIIRN-2011). Therefore the suggestions and recommendations made in this study are largely based on the experience available at Centre II and are discussed in the following sections.

5.11 Use of LDR/MDR: Considerations

The findings in this study when compared to other studies that have been published, confirm that the use HDR and LDR ICBT for patients with cervical cancer result in similar treatment outcomes (Tables 5.4, 5.5 & 5.6). Numerically, the study and all the other published data referred to in this study, show slightly higher figures for clinical outcomes with LDR compared to HDR ICBT, though statistical tests performed do not show any significant differences. In terms of radiobiological considerations, LDR is superior to HDR brachytherapy (Chen et al., 2009:1335; Stewart & Viswanathan, 2006:909-910; Stitt, 1997:507). A comparative radiobiological dose was calculated at Centre I and II with HDR and LDR, respectively. The LDR dose is higher for tumour, but less for the bladder and rectum, compared to HDR (Figures 4.19 & 4.20, & Table 4.19). Though this dose is referenced at Point 'A' and ICRU-38 (1985) reference points, it strongly indicates the clinical advantages of LDR ICBT.

Viani et al. (2009:2) and Dusenbery & Gerbi (1997:471) state that worldwide, a lot of data and experience has been accumulated treating with LDR brachytherapy. Therefore, with the high number of patients at the Centre (Table 4.1), the challenge is to combine the worldwide clinical experience in the use of LDR, the favourable radiobiological factors, and experience in its use at the Centre, to evolve an innovative strategy that may treat more patients, and thereby enable many patients access brachytherapy services. The following section discusses a suggested strategy based on the findings in this study.

5.12 A model treatment schedule

This study provided data on the number of fractions administered at Centre I using HDR ICBT (Figure 4.16), and Centre II using LDR ICBT. The optimal fractionation schedule of HDR ICBT in the management of cervical cancer is still unclear and not yet determined (Wang et al., 2010; Wong, Tung, Leug, et al., 2003). The study showed that by 2004, Centre I had moved from a 3 to four fractions schedule (Figure 4.16). Hence repeat fractions have to be contended with as they have an impact on the number of new patients that could be started on HDR ICBT (Figure 5.1). In addition, the patient suffers the inconvenience of several hospital visits. This is in contrast to Centre II where the LDR ICBT was administered as a single fraction, and lasted for only a day. This is because the dose rate at Point 'A' was calculated to an average 126 Gy/hour and 2.09 Gy/hour at Centre I and II, respectively. The MDR mean time of 12 hours at Centre II implies that patients could be treated in a day and discharged if treatments are started early.

New patients at Centre I

The number of new patients starting and finishing HDR ICBT at Centre I based on the findings in this study, is simulated and displayed in the flow diagram, Figure 5.1.

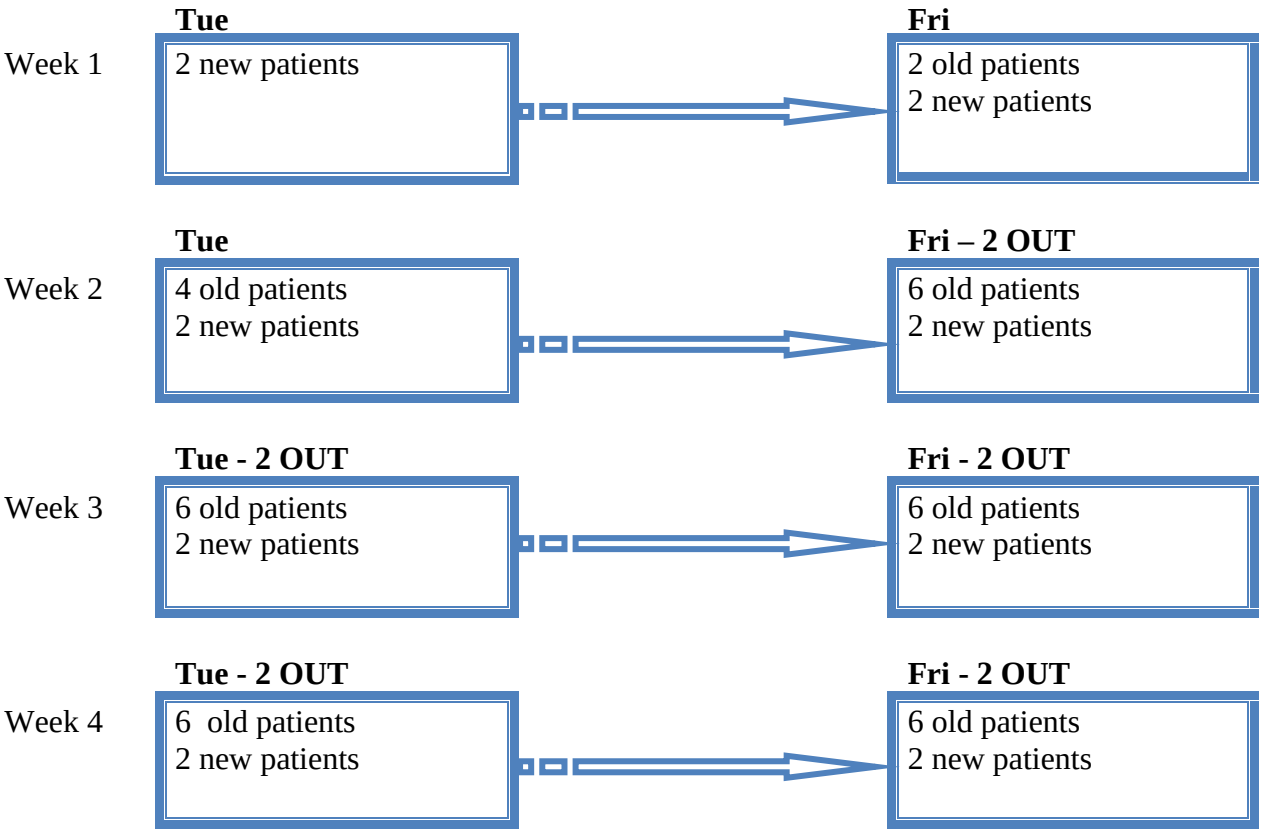

Figure 5.1: Flow chart showing number of new patients and those completing treatment at Centre I (HDR).

The pattern at Centre I (Figure 5.1) shows that theoretically, 4 new patients can be started in a week. There is an integration of EBRT and ICBT treatment such that only 4 new patients can be started on EBRT per week for eventual absorption in the HDR ICBT schedule. This integration ensures all patients with cervical cancer started on EBRT are eventually absorbed in the HDR schedule unlike at Centre II. Though the number of new patients started at Centre I is limited by the few working hours and time taken for dosimetry and anaesthetic procedures (CIPr1SPCON). The technique with the straight tandem (RN, 2011) could be adopted to speed up the procedures and hence treat more patients.

Simulated treatment schedule at Centre II

Centre II could adapt this model from Centre I, since the time taken to complete a single dose treatment at Centre II with the Selectron LDR/MDR will determine how many patients can be started in a week (EBRT +ICBT). Though the numbers as shown in this study with only one public oncology centre are overbearing (Figure 4.13). The mean ICBT time in this study was 8 hours. The researcher also observed that the nurses at the Centre are called upon to work night shift and weekend duties to accommodate patients on iodine therapy (RN 2011). Therefore, based on these findings, a model treatment schedule is suggested for Centre II (Table 5.7) to help manage the cervical cancer burden at the Centre.

Table 5.7: A model treatment schedule suggested for Centre II for LDR/MDR ICBT.

Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Weekend**
MDR ICBT		MDR ICBT		MDR ICBT	Weekend coverage (for unforeseen extra work)
Single dose #	Preparations / Off days	Single dose	Preparations / Off days	Single dose #	
Mean time 12 hours		Mean time 12 hours		Mean time 12 hours	

A potential implication of this is that Centre II can treat one patient per day with ICBT, 3 times a week if all other conditions permit; adequate staffing, timely dosimetry procedures, service and maintenance. As a patient undergoes only a single fraction and as many as 5 patients can be treated per week, though the study recommends 3 patients per week on a trial basis. Due to availability of nursing staff, any extra work can be handled over the weekend in-case of unforeseen circumstances during the week, with off days arranged during the week, as is currently the practice with Iodine

therapy at the Centre (RN, 2011). Therefore to enable effective treatments with a less OTT as recommended by Viswanathan and Thomadsen (Undated-ABS); Stewart and Viswanathan (2006:909), only 3 patients should be started on radical EBRT treatment per week for eventual integration with ICBT, though there could be exceptions.

Comparisons

A historical perspective from this study shows that between 1993 and 1995 when the Amersham LDR system was being used, 77 patients were treated in total, averaging 25 patients per year (Table 4.2). The Selectron LDR/MDR treated 68 patients between 1998 and 1999 (Table 4.2), averaging 34 patients per year, an annual increase of 36%. If the theoretical treatment schedule suggested by this study is adopted, then approximately 132 patients or more can be treated in a year, an increase of 288%. When this is compared with Centre I using the theoretical flow diagram, Figure 5.1 and Table 5.8, the number of insertions at Centre II will be less implying more patients could be added in the suggested schedule, all other conditions permitting. A comparison of the three brachytherapy units highlighted in this study at Centre I and II (the Amersham LDR system, the Selectron LDR/MDR, and the Felxitron HDR), is shown in Table 5.8.

Table 5.8: Assessment of Amersham LDR, Selectron LDR/MDR and Flexitron HDR.

	Amersham LDR system	**LDR/MDR Centre II**	**Flexitron HDR Centre I**
New patients	1 or 2 patients per week - Single # takes 50-64 hours (Table 4.2)	3 per week on Monday, Wednesday, Friday. Single # to last in a day say, 11am to 8pm (see Table 5.7)	4 per week for ICBT. For historical reasons cannot work 5 days a week (CIPr1SP)
Hospitalization	2-3 days (see Table 4.2)	Within a day (study results)	Outpatient treatment - a few minutes. (see Tables 4.1,4.2)
Radiation protection	Semi-remote afterloading (see CIID1)	Remote afterloading (see CIID2)	Remote afterloadaing (see CID1)
Maintenance	Same issues of contract maintenance & support- though its appropriate technology for developing countries (Rogo et al.1992)	Same issues of contract maintenance & support (see Tables 4.30, 4.31)	Same issues of contract maintenance & support (see Tables 4.30, 4.31)

Experience	Experience readily available at Centre (see Table 4.3). Staff have no experience with HDR (see Table 4.32)	Experience readily available at Centre. Staff have no experience with HDR (see Table 4.32)	Experienced staff with oncology support infrastructure in the country(see Table 4.23, CIPr1AB4-5) & Table 4.25, CPr2AC6)
Nursing staff	Can work over weekend (RN, 2011)	Can work over weekend (RN, 2011)	Work half a day twice a week at brachytherapy suite (CIPr1SP)
No of patients that could be treated in a year	Assumption: 8 weeks allocated for maintenance & servicing, 2X44 weeks =88 patients	Assumption: 8 weeks allocated for maintenance & servicing, 3X 44=132 patients per year.	Assumption: 8 weeks allocated for maintenance & servicing, 4X44= 176 patients per year.
Insertions	Workload=88 insertions, single #	Work: 132 insertions, single #	Work: 704 insertions, 4 #s per patient (See Figure 4.16)
During study period	Treated 77/3=25 patients per year	Treated 68/2=34 patients per year	Treated 724/7=103 patients per year.
Insertions per year during study period	25 insertions	Only 34 insertions	103x4=413 413 insertions

The comparison shows that the Selectron LDR/MDR could still do well at Centre II in terms of treating more patients than were treated previously as reported in this study. The evidence available is highlighted below:

- Availability of infrastructure (Figures 4.3 & 4.4)
- Staff with adequate experience (Table 4.32)
- High number of patients with cervical cancer requiring the brachytherapy service (Figure 4.13).

However, the researcher notes that this can only be possible if the issues of equipment maintenance and repairs are addressed comprehensively on a sustainable basis through a well structured maintenance contract. Furthermore, a simple economic analysis in Table 5.9 showing patients being treated 5 days per week 8 hours per day, indicates that HDR (using Ir-192 or the Co-60 isotope) can treat many more patients than either MDR or LDR.

Table 5.9: Analysis showing the number of patients that can be treated utilizing different brachytherapy sources.

	LDR/MDR (Cs-137)	HDR (Ir-192)	HDR (Co-60)
Working days per week	5	5	5
Working hours per day	8	8	8
Working hours per week	40	40	40
New patients per day	1 patient on alternate days (each patient takes an average of 12 hours more than the 8 working hours allocated)	3	3
New patients per week	3	15	15
Number of new patients that could treated in a year	Assumption: 8 weeks allocated for maintenance & servicing, 3X44 weeks =132 patients	Assumption: 8 weeks allocated for maintenance & servicing, 15X44= 660 patients per year.	Assumption: 8 weeks allocated for maintenance & servicing, 15X44= 660 patients per year.
Nursing staff	Will result in additional working hours and nursing shifts.	Normal day working hours and shifts	Normal day working hours and shifts
Hospitalization	Possible if delays occur (delays in start of procedure would result in hospitalization)	Outpatient treatment	Outpatient treatment
Logistics in supply of sources	Once every 10 years	Once every 3 months	Once every 5 years
Maintenance	Same issues	Same issues	Same issues

5.13 Study conclusions & recommendations

The high number of patients with cervical cancer highlighted by this study (Figure 4.1) that require radiation therapy demands a solution. The study presents a simulated model treatment schedule for Centre II, based on the technical and clinical factors available, in comparison to Centre I. Local attempts using adaptable solutions may be sustainable compared to copying interventions, trends and technological advances from the developed world. The issue of experience is of great importance (Table 4.35) and could be exploited to address some of the issues at Centre II.

Nevertheless, the trend by the IAEA as highlighted in this study and the clinical thinking in many oncology Centres is to promote the use of HDR ICBT in treatment of cervical cancer in developing countries. This approach is commendable and may work in other developing countries in Asia and South America. However, this may not always be the case in Africa, as shown at Centre II in this study. Nevertheless, the IAEA might have realized these challenges of HDR Ir-192 implementation and use in Africa, and has recently donated a HDR brachytherapy unit with a Co-60 source for use in Ibadan Nigeria and Dar es Salaam in Tanzania (Ntekim et al., 2010; Van Wijk, 2010). The analysis in Table 5.9 shows Co-60 based HDR is better in terms of logistics of source and supply management. The half-life of 5.26 years for Co-60 is advantageous over the regular replacement of Ir-192 sources every 3 months, and hence its use might address some of the issues raised in this study. Equipment companies also point to the fact that Co-60 based HDR is the only alternative to HDR Ir-192 as they no longer manufacture MDR brachytherapy equipment. A source from the Nucletron Elekta Company points to the fact that the last MDR devices were sold in the early 1990s and have been out of service for the last 10 years (Rotink, 2012). Though the advantage of Iridium-192 is the low energy and high dose gradient with a rapid fall off dose. This may spare the bladder and rectum if the brachytherapy applicators are well positioned. The high energy of Co-60, 1.25MV (1.17-1.33MV), may give a higher dose to bladder and rectum compared to the average energy of 0.380 KV of Ir-192 (Meertens & Briot, 2002:25).

In regard to impressions from use of the Amersham LDR system Cs-137 (Table 4.3), this equipment compares dismally to HDR despite its ease of use. Therefore, HDR is technically superior in the number of patients that can be treated when compared with this equipment. Though according to Rogo et al. (1992:194), the technology of the Amersham system is appropriate and only requires modest expenditure during installation. These include minimal staff training and hence the machine is suitable for oncology centres in developing countries. Therefore, equipment manufactures should try to understand the African situation, and for that matter, upgrade and adapt their equipments to withstand the hard realities in less developed countries, where the majority of the patients that need these services live. This is well exemplified by the IAEA deputy director

general for the department of nuclear science and applications in his challenge to equipment manufacturers:

"...Making radiotherapy accessible is a key component in any comprehensive cancer control programme - to make this a reality, it would be heartening to see the development of sturdier and lighter equipment that can be used not only in hospitals in large urban centres, but also in resource-poor settings in the field..." (Burkart, 2009). He therefore challenged manufacturers to make equipment that is robust, portable, easy to use and more affordable. This is timely and could provide solutions for the high cervical cancer burden in Africa.

Furthermore, the profile of the patient with cervical cancer in Sub-Saharan Africa is that of early age with locally advanced disease. This has been shown in this study and other studies (Ntekim et al., 2010; Rogo et al., 1990). This is worrying as it has a direct bearing on the economy. This is because it impacts on women in their prime working phase, affecting families and children, and thus tearing away the fabric of the society including established social structures. This calls for an urgent solution. The study suggests a multi-prong process that involves, early screening, programmes that are cost effective, treatment strategies that take into consideration practical experiences in Africa, and sustainable support from more affluent nations. For developing countries, the WHO (2008:418-420) advocates for cost effective early screening methods by visual inspection using acetic acid, as opposed to cytology screening. This may be due to the socio-economic status of patients especially in Africa, and the lack of accessibility to such services. The same kind of strategy needs to be adapted as regards treatment for those found with locally advanced cervical cancer disease. Therefore:

- equipment that is easy to repair and handle with locally trained personnel would assist in the cause of cost-effective management of cervical cancer for patients requiring radiation therapy. An example is the Co-60 used for EBRT treatments. This equipment has been effective in Africa because it is easy to operate, maintain, and repair.
- the trend by the suppliers of constantly upgrading, though important for commercial reasons, does not help the cause of managing and treating cancer cost effectively especially in developing nations. Research through special research units, should focus on integrating the old and new technology to adapt for conditions in Africa and other developing countries. This might as well be part of supplier's socio-corporate responsibility.

These together with public awareness of the importance of early screening, may form part of the strategies for reducing the high cervical cancer burden on the continent.

This study therefore, based on the findings, recommends the following:

1. Centre II could treat a considerable number of patients with the Selectron LDR/MDR. (Tables 5.7 & 5.8) if the unit was functional and maintained by the manufacturers, which is not the case. Therefore it is recommended that any funds allocated should be utilised for the purchase of or upgrading this unit to operate as a PDR (pulsed dose rate) brachytherapy system. According to the Director of Nucletron Elekta Company for Europe and Emerging Markets, Arjen van Hooft, (2012): "MDR technique can still be used with our PDR systems as average dose rate can be programmed as desired". It is noted that this is the preferred option since the existing infrastructure (Tables 4.3 & 4.4) and the Centre staff are experienced in the use MDR techniques (Table 4.32). In contrast, the use of the HDR will require heavy investment to provide new infrastructure. This is in addition to inadequate user experience by the staff at the Centre and the unavailability of oncology support systems in the country.

2. The study shows the HDR unit at Centre II was purchased 10 years ago, and while the Centre is pursuing a comprehensive review of this equipment on site (CIIPr2FOIN), clinical, technical and practical experience is required before this system can be safely used. The advancement in computer technology may make upgrading the unit quite expensive. Therefore, a sell back to the supplier company may be considered, who may be able to rehabilitate the unit and provide a replacement with an HDR unit utilizing the Co-60 isotope which is advantageous in this context as compared to the Ir-192 based HDR brachytherapy unit. This is especially due to logistics of source and supply management in Africa.

3. The key issue of maintenance highlighted by this study should be solved by a strict maintenance contract that involves in-service training, and a penalty clause to the supplier in case of machine downtime beyond a certain specified time. Regular local training of biomedical engineering staff should also be catered for in the contract. This should be applicable to all equipment supplied to the hospital.

4. Extended working hours, for example up to 8-10 hours a day, 5 days per week, should be introduced as necessary to enable all patients with cervical cancer to access brachytherapy services. It is noted that at Centre I, the reduced working hours accommodates all patients who require brachytherapy.

The findings in this study should enable Centre II to revive brachytherapy services for patients with cervical cancer on a more sustainable basis, and Centre I to undertake further audit reviews of the patients treated to enhance further research in this important field of cervical cancer. The evidence from Centre I in South Africa shows that HDR has replaced LDR and can be used in Africa but with certain conditions of: infrastructure and support services, dedicated management and logistics in supply of sources, expertise in its use, and scheduled treatment times. The evidence from Centre II in Kenya shows that HDR has not replaced LDR /MDR and cannot be used due to: lack of infrastructure and oncology support services, equipment expertise, experience and resources. Nevertheless, the researcher realizes that the in-depth analysis of this case study provides ground for more enquiries, questions and further research, for example, the use of HDR Ir-192 or HDR Co-60 brachytherapy. Though the following limitations might have impacted on these findings and recommends studies involving many more countries in Africa, to shed light on how well HDR has replaced LDR ICBT.

5.14 Limitation of the study:

- The advantages of HDR ICBT in terms of applicator rigidity, dose optimization because of the single stepping source were not analysed in this study. This may require another study in a place in Africa.
- The study only analysed information at two Centres in Africa, and may therefore not have provided the entire brachytherapy situation for patients with cervical cancer on the continent. Therefore a more detailed case study may have to be carried out involving many more Centres than was the case in this study.
- The sample size at Centre II was a major limitation in getting accurate clinical outcomes that would have enabled inferential statistics and parametric tests to be carried out between Centre I (HDR) and Centre II (LDR).
- The study did not consider chemotherapy usage for the patients analysed and their HIV status, hence these might have had a bearing on clinical outcomes.

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Annexure A1

Revised data Source sheet for research question 1 and 2 (Centre I)

Instruction: To be filled by Researcher: Centre.....I.....

Patient RT No:.....Age: ..... DOB.....

Patient Characteristcs							
Staging		HB		Histology		Date of hist	
Weight		Height			HPV		Urea	
Creat		CXR		Hydronephrosis			
GT		ALP		Cytoscopy		CIN	

Brachytherapy Dosimetric Data					
Source Type	Source Activity				Average activity
Ir-192					

Dates &Type of Procedures					
EBRT 1st date	EBRT Completion date	4 F Box or POP	ICBT 1st Date	ICBT Completion Date	OTT

Tumor Dose (TD) in Gy administered						
EBRT 4F	Daily	Total TD	No. of #s per week	Total #s	Sep	Rad Modality
POP						

ICBT Point A	Dose per Single #				No of #s	Total ICBT Dose to Point A

Dose to ICRU Bladder Point						
Bladder Dose	**ICBT # 1**	**ICBT #2**	**ICBT # 3**	**ICBT #4**	**Total**	**Total ICBT + EBRT contribution**

Dose to ICRU Rectal Point						
Dose	**ICBT # 1**	**ICBT #2**	**ICBT # 3**	**ICBT #4**	**Total**	**Total ICBT + EBRT contribution**

Calculated EQD_2	**Point A (Gy_{10})**	**Bladder(Gy_3)**	**Rectum(Gy_3)**
Chemotherapy			

Clinical Data

Pelvic Control

Recurrence (Tick)	**Cervix**	**Vagina**	**Parametrium**
Indicate date recorded			
No recurrence (blank)	**Date:**	**Date:**	**Date:**

Complications (Bladder Grade 3)

Bladder Grade 3 (tick)	**Severe freq / Dysuria**	**Severe generalised Telengiectasia**	**Haematuria**	**Red bladder cap.(<150cc)**
Indicate date recorded				
No complic. (blank)	**Date:**	**Date:**	**Date:**	**Date**

Complications (Bladder Grade 4)

Bladder Grade 4 (tick)	**Necrosis**	**Contracted Bladder (< 100cc)**	**Severe Haemorrhagic cystitis**
Indicate date recorded			
No complic. (blank)	**Date:**	**Date:**	**Date:**

Complications (Rectum Grade 3)

Rectum Grade 3 (tick)	**Obstruction (requiring surgery)**	**Bleeding (requiring surgery)**

Indicate date recorded **No complic. (blank)**	**Date**	**Date**
Complications (Rectum Grade 4)		
Rectum Grade 4 (tick)	**Necrosis**	**Perforation/ Fistula**
Indicate date recorded **No complic. (blank)**	**Date**	**Date**
Overall Survival		
Date of last follow-up	**Date of death if recorded patient died**	

Follow up comments in file:

Annexure A1A

A completed data source sheet for research question 1 and 2 (Centre I)

Instruction: To be filled by Researcher: Centre.....1.....

Patient RT No:.....Age: ..... DOB.....10/06/1947.....

Patient Characteristcs							
Staging	2B	HB	12.8	Histology	Sq Ca	Date of hist	27/11/2001
Weight		Height			HPV		Urea
Creat	48	CXR	Normal	Hydronephrosis		No	
GT	15	ALP	103	Cytoscopy	Neg	CIN	

Brachytherapy Dosimetric Data

Source Type	Source Activity				Average activity
Ir-192	5.00	4.82	4.68	4.51	

Dates &Type of Procedures

EBRT 1st date	EBRT Completion date	4 F Box or POP	ICBT 1st Date	ICBT Completion Date	OTT
14/01/2002	25/02/2002	4F	15/02/2002	26/02/2002	

Tumor Dose (TD) in Gy administered

EBRT 4F	Daily	Total TD	No. of #s per week	Total #s	Sep	Rad Modality
	2.30	50.60	4	22	21	16X
POP						

ICBT Point A	Dose per Single #				No of #s	Total ICBT Dose to Point A
	6.40	6.40	6.40	6.40		

Dose to ICRU Bladder Point						
Bladder Dose	**ICBT # 1**	**ICBT #2**	**ICBT # 3**	**ICBT #4**	**Total**	**Total ICBT + EBRT contribution**
	3.82	**3.82**	**3.82**	**3.82**		

Dose to ICRU Rectal Point						
Dose	**ICBT # 1**	**ICBT #2**	**ICBT # 3**	**ICBT #4**	**Total**	**Total ICBT + EBRT contribution**
	3.00	**3.00**	**3.00**	**3.00**		

Calculated EQD_2	**Point A (Gy_{10})**	**Bladder(Gy_3)**	**Rectum(Gy_3)**
Chemotherapy	**Cisplatin Jan/Feb 2002**		

Clinical Data

Pelvic Control

Recurrence (Tick)	**Cervix**	**Vagina**	**Parametrium**
Indicate date recorded			
No recurrence (blank)	**Date:**	**Date:**	**Date:**

Complications (Bladder Grade 3)

Bladder Grade 3 (tick)	**Severe freq / Dysuria**	**Severe generalised Telengiectasia**	**Haematuria**	**Red bladder cap.(<150cc)**
Indicate date recorded				
No complic. (blank)	**Date:**	**Date:**	**Date:**	**Date**

Complications (Bladder Grade 4)

Bladder Grade 4 (tick)	**Necrosis**	**Contracted Bladder (< 100cc)**	**Severe Haemorrhagic cystitis**
Indicate date recorded			
No complic. (blank)	**Date:**	**Date:**	**Date:**

Complications (Rectum Grade 3)

Rectum Grade 3 (tick)	**Obstruction (requiring surgery)**	**Bleeding (requiring surgery)**

Indicate date recorded **No complic. (blank)**	**Date**	**Date**
Complications (Rectum Grade 4)		
Rectum Grade 4 (tick)	**Necrosis**	**Perforation/ Fistula**
Indicate date recorded **No complic. (blank)**	**Date**	**Date**
Overall Survival		
Date of last follow-up **15/02/2010**	**Date of death if recorded patient died**	

Follow up comments in file:

11/07/2002- V/V-fibrosis. PV/PR- no nodules, no nodes, difficult to visulaise.

PR- thickened. PSW-normal,

Rectal mucosa-normal.

10/10/2002- PV/PR- V=V- Normal. No vaginal lesions on Speculum.

Whitish PV-discharge.

30/01/2003- PV/PR- Normal V+V. Vault flush with cx, No identifiable cervix. Rectal mucosa normal. A: No evidence of recurrence.

9/2/2004- ???? sigmoid stenosis from RT .

11/02/2004: Underwent laparotomy for Bowel obstruction 4 years after RT for Stage 2B cervical cancer. Procedure: Perfortaion sigmoid on mobilizing sigmoid off uterus. – Resection of sigmoid colon containing perforation and primary hand sewn anastomosis with 3/0 Vicryl. Closure: 1 Nylon for sheath. 3/0 Nylon for skin. Drainage: Nil. Difficulty: Massively dilated bowel loops.

Note: I have classified this as late radiation complication, Grade 4. GSH database concurs.

2/12/2004- PV/PR-Clear

19/05/2005- No PV bleeding/ D/C

PV+Spec—NAD

31/11/2005- Alive, B&D.

15/02/2010. B&D Ticked-alive. Repeat Feb 2016.

Annexure A2

Revised data source sheet for research question 1 and 2 (Centre II)

Instruction: To be filled by Researcher: Centre.....2.....

Patient RT No:.....Age: ..... DOB.....

Patient Characteristcs											
Staging		**HB**		**Histo logy**		**Date of hist**					
Weight		**Height**			**HPV**		**Urea**				
Creat		**CXR**		**Hydronephrosis**							
GT		**ALP**		**Cytoscopy**			**CIN**				

Brachytherapy Dosimetric Data

Source Type	Source Strength(mCi)		Average activity
Cs-137			

Dates &Type of Procedures

EBRT 1st date	EBRT Completion date	4 F Box or POP	ICBT Treatment Date	OTT

Tumor Dose (TD) in Gy administered

EBRT 4F	**Daily**	**Total TD**	**No. of #s per week**	**Total #s**	**Sep**	**Rad Modality**
POP						
ICBT Point A	**Dose Single #**		**Time of ICBT(hrs)**	**Total ICBT Dose to Point A**		

Dose to ICRU Bladder Point			
Bladder Dose	**Received**	**Total**	**Total ICBT + EBRT contribution**

Dose to ICRU Rectal Point			
Dose	**Rectum 1**	**ICRU Rectal dose**	**Total ICBT + EBRT contribution**

Calculated EQD_2	**Point A (Gy_{10})**	**Bladder(Gy_3)**	**Rectum(Gy_3)**

Chemotherapy	

Clinical Data

Pelvic Control

Recurrence (Tick)	**Cervix**	**Vagina**	**Parametrium**
Indicate date recorded			
No recurrence (blank)	**Date:**	**Date:**	**Date:**

Complications (Bladder Grade 3)

Bladder Grade 3 (tick)	**Severe freq / Dysuria**	**Severe generalised Telengiectasia**	**Haematuria**	**Red bladder cap.(<150cc)**
Indicate date recorded				
No complic. (blank)	**Date:**	**Date:**	**Date:**	**Date**

Complications (Bladder Grade 4)

Bladder Grade 4 (tick)	**Necrosis**	**Contracted Bladder (< 100cc)**	**Severe Haemorrhagic cystitis**
Indicate date recorded			
No complic. (blank)	**Date:**	**Date:**	**Date:**

Complications (Rectum Grade 3)

Rectum Grade 3 (tick)	**Obstruction (requiring surgery)**	**Bleeding (requiring surgery)**

Indicate date recorded **No complic. (blank)**	**Date**	**Date**
Complications (Rectum Grade 4)		
Rectum Grade 4 (tick)	**Necrosis**	**Perforation/ Fistula**
Indicate date recorded **No complic. (blank)**	**Date**	**Date**
Overall Survival		
Date of last follow-up	**Date of death if recorded patient died**	

Follow up comments in file:

Annexure A2A

A completed data source sheet for research question 1 and 2 (Centre II)

Instruction: To be filled by Researcher: Centre.....2.....

Patient RT No:.....Age: ...65..... DOB.....

Patient Characteristcs									
Staging	2B	HB	12.8	Histology	Invasive anaplastic carcinoma	Date of hist	5/03/1999		
Weight		Height			HPV		Urea		
Creat		CXR		Hydronephrosis					
GT		ALP		Cytoscopy		CIN			

Brachytherapy Dosimetric Data			
Source Type	Source Strength(mCi)		Average activity
Cs-137	34.795		

Dates &Type of Procedures				
EBRT 1st date	EBRT Completion date	4 F Box or POP	ICBT Treatment Date	OTT
18/03/1999	07/05/1999	POP	19/08/1999	

Tumor Dose (TD) in Gy administered						
EBRT 4F	Daily	Total TD	No. of #s per week	Total #s	Sep	Rad Modality
POP	2.00	50	5	25	22	Co-60(16X15)
ICBT	Dose Single #		Time of ICBT(hrs)	Total ICBT Dose to Point A		

Point A	**30.00**	**10.89**	

Dose to ICRU Bladder Point

Bladder Dose	**Received**	**Total**	**Total ICBT + EBRT contribution**
	20.395		

Dose to ICRU Rectal Point

Dose	**Rectum 1**	**ICRU Rectal dose**	**Total ICBT + EBRT contribution**
	7.465	**9.274**	

Calculated EQD_2	**Point A (Gy_{10})**	**Bladder(Gy_3)**	**Rectum(Gy_3)**

Chemotherapy	

Clinical Data

Pelvic Control

Recurrence (Tick)	**Cervix**	**Vagina**	**Parametrium**
Indicate date recorded	**Date:**	**Date:**	**Date:**
No recurrence (blank)			

Complications (Bladder Grade 3)

Bladder Grade 3 (tick)	**Severe freq / Dysuria**	**Severe generalised Telengiectasia**	**Haematuria**	**Red bladder cap.(<150cc)**
Indicate date recorded	**Date:**	**Date:**	**Date:**	**Date**
No complic. (blank)				

Complications (Bladder Grade 4)

Bladder Grade 4 (tick)	**Necrosis**	**Contracted Bladder (< 100cc)**	**Severe Haemorrhagic cystitis**
Indicate date recorded	**Date:**	**Date:**	**Date:**
No complic. (blank)			

Complications (Rectum Grade 3)		
Rectum Grade 3 (tick) **Indicate date recorded** **No complic. (blank)**	**Obstruction (requiring surgery)**	**Bleeding (requiring surgery)**
	Date	**Date**
Complications (Rectum Grade 4)		
Rectum Grade 4 (tick) **Indicate date recorded** **No complic. (blank)**	**Necrosis**	**Perforation/ Fistula**
	Date	**Date**
Overall Survival		
Date of last follow-up 04/12/2002	**Date of death if recorded patient died**	

Follow up comments in file:

21/3/2001- HB 7.4g/dl. Referred for Transfusion.

20/6/2001- Rectal bleeding, has reduced now much better. VE-stenosis-no recurrence. 26/09/2001- Stll has occasionally Pv bleeding. NAD

19/12/2001- rectal bleeding has stopped, but has radiation fibrosis.

20/02/2002- No evidence of recurrence.

21/08/2002- c/o epigatric pain, easy fatigability and on and off per rectal bleed. Noted to be pale with epigastric tenderness.

2/10/2002- Has slight PR bleeding especially on defecation. Transfused 3 units 3 weeks ago. VE-Neg. Vaginal length 3.5cm.

4/12/2002 - Still has scanty per rectal bleed. No PV discharge. Not pale.

Annexure A2B

Independent assessment script of late grade 3 and 4 radiation complications

(Centre II)

6.Patient RT No:....21379.....Age: ...65.....DOB.....

Patient Characteristcs							
Staging	2B	HB	12.8	Histology	Invasive anaplastic carcinoma	Date of hist	5/03/1999

EBRT 1st date	EBRT Completion date	4 F Box or POP	ICBT Treatment Date	OTT
18/03/1999	07/05/1999	POP	19/08/1999	

Follow up comments in file:

21/3/2001- HB 7.4g/dl. Referred for Transfusion.

20/6/2001- Rectal bleeding, has reduced now much better. VE-stenosis-no recurrence. 26/09/2001- Stll has occasionally Pv bleeding. NAD

19/12/2001- rectal bleeding has stopped, but has radiation fibrosis.

20/02/2002- No evidence of recurrence.

21/08/2002- c/o epigatric pain, easy fatigability and on and off per rectal bleed. Noted to be pale with epigastric tenderness.

2/10/2002- Has slight PR bleeding especially on defecation. Transfused 3 units 3 weeks ago. VE- Neg. Vaginal length 3.5cm.

4/12/2002 - Still has scanty per rectal bleed. No PV discharge. Not pale.

Assessment for research purposes: Grade:... Rectal late (grade 3)

Radiation Oncologist Signature..... Date.....5/9/11.....

Annexure B

Data source sheet for research question 3 (Based on IAEA-TECDOC-1257:2001)

Self directed questionnaire to oncology staff involved in cancer of the cervix treatment at Centre I and II

Instructions to Participants.

Thank you for agreeing to participate in this research. Please read the following:

1. The answers to the following questions will be kept strictly confidential and will only be used for research purposes.
2. Participant confidentaility is assured.
3. Carefully read each question and give factual and honest answers.
4. Tick in the appropriate brackets or write your answer as directed.
5. Incase you do not know the answer to any of the questions listed below, leave it blank.

Name: **Position:**

Institution: **Date:**

1. What type of brachytherapy machine does the institution have?

   A. Both HDR and LDR [ ] B. HDR [ ] C. LDR [ ]

   If your Centre has HDR continue answering the questions below.

2. What components does it consist of?

   A. HDR source [ ] B. Afterloader device (treatment unit) [ ] C. Applicators [ ]

   D. Treatment planning system [ ] E. Other [ ] Specify……

3. What is the type source? A.Iridium -192 [ ] B. Co-60 [ ] C. Other……

4. Were the following factors considered in purchasing the HDR unit?

   A. Current patient volume [ ] B. Future projected patient volume [ ]

   C. Case mix [ ] Existing infrastructure [ ] D Available human resources [ ]

5. Are there any other reasons that could be advanced for the decision to purchase the HDR unit?

. …….

6. Were the following treatment procedure (relating to Ca Cx brachytherapy treatment) considered?

   A. Applicator/catheter placement [ ] B. Imaging (simulation & localisation) [ ]

   C. Treatment Planning [ ] D. Treatment delivery [ ]

7. Any other options that were considered?……

8. Is the treatment room separate from the applicator placement room? A. Yes [ ] B. No. [ ]

9. If your answer is [Yes] above, is the shielded treatment room adequate to allow localisation images to be obtained on the treatment table, in order to minimise patient movement?

A. Yes [ ] B. No [ ] Please comment …….....

10. What imaging equipment was installed in the treatment room?

A. Portable X-ray unit [ ] B. Dedicated X-ray equipment (C-Arm) [ ]

C. X-ray equipment not installed [ ]

11. If your answer is C above, where is the imaging done?
.....

12. Is there adequate space in the treatment room?

A. Adequate [ ] B. Inadequate Please comment……..…

13. In addition to the X-ray equipment, is there a device (simulation box) available if orthogonal films are used for the dosimetry?

A. Yes [ ] B. No [ ]

Incase your answer is [No] above, other imaging options (please specify)

…….

14. Where is the hardware for brachytherapy treatment planning placed?

A. Adjacent to the control console [ ] B. In a separate room [ ]

Please comment……..

15. Does the treatment planning system have a device for uninterrupted power supply (UPS) with a voltage regulator?

A. Yes [ ] B. No [ ]

16. Is the shielding for the HDR room appropriate? That is:

A. a concrete wall 35cm, equivalent to 4cm Lead (Pb) [ ] B. or it is based on local regulations [ ]

C. Others specify…….

17. If your answer is none of the above, any other shielding modifications considered for: A. staff [ ] B. patient [ ]

18. At the control console of the treatment room, is there a direct vision or closed circuit observation system?

A. Yes [ ] B. No [ ]

19. Is a multidisciplinary team organised to carry out the Ca Cx brachytherapy procedure using the HDR unit?

A. Yes [ ] B. No [ ]

Please comment……

20. Based on your answer in question 19, please tick below the available staff

A. Radiation Oncologist [ ] B. Medical Physicist [ ] C. Radiographer [ ] D. Nurse [ ]

E. Other, Please specify.....

21. Have the staff above been trained in using the HDR unit? A. All [ ] B. Some [ ]

C. None [ ] Please specify…….....

Annexure C

Data source sheet for research question 3 (Based on IAEA-TECDOC-1257:2001)

A researcher guided questionnaire interview to oncology staff involved in cancer of the cervix treatment at Centre I and II

Instructions to Participants.

Thank you for agreeing to participate in this research. Please read the following:

1. The answers to the following questions will be kept strictly confidential and will only be used for research purposes.
2. Participant confidentiality is assured.
3. Carefully read each question and give factual and honest answers.
4. The researcher will be present to take notes and guide you through the questions.
5. Provide answers in the blank sheets provided by the researcher.

Name: **Position:**

Institution: **Date:**

1. How did you consider the following radiation safety factors when purchasing the HDR unit?
   a) Authorization for the source b) Maintenance of the unit c) Double checks in the QA programme
   d) Prevention from accidental exposure e) Emergency plan and response f) Investigation of accidental exposure
   g) Identification of causes and contributing factors to accidental exposure in radiotherapy
2. How did you consider initial costs and cost operational factors when purchasing and setting up the HDR unit?
3. What are the ongoing costs in terms of:
   a) Source replacement b) Training personnel c) Maintenance contract d) Applicator replacement
   e) Staffing f) Anaesthesia

Others, please elaborate.

4. How do you compare LDR and HDR remote afterloading practice in terms of associated?
   a) ongoing costs b) management c) ease of use of equipment d) staffing
   e) number of patients on the waiting list f) other, please specify and elaborate
5. What other challenges or difficulties have you encountered as a Centre in HDR implementation and operations?

HDR Quality Assurance Programmes

Treatment unit QC

6. How did you implement the following daily QC programme for the HDR treatment unit?

a) Emergency procedures

b) Interrupting power supply

c) Source positioning

d) Room radiation monitors

Other, please specify and elaborate.

7. How did you implement the following monthly QC programme on the HDR treatment unit?

a) Source activity against predicted radioactive decay

b) Integrity of applicators in regard to internal shields, wells, and joints

Other, please specify and elaborate.

8. How did you implement the following quarterly QC programme on the HDR treatment unit?

a) calibration of source strength using well type chambers or Farmer-style ion chambers.

b) testing of source positional accuracy.

Other, please specify and elaborate.

QC on the Planning unit

9. How did you implement the following QC programme on the treatment planning unit?

a) Verification of the reconstruction quality

b) the accuracy of calculated dose

c) measures to prevent error during dose input before commencement of treatment.

Other, please specify and elaborate

QC on the patient treatment procedure

10. How did you implement the following QC programme for cancer of the cervix treatment procedure when using the HDR unit?

a) Consistency

b) Applicator placement

c) Simulation & localisation

d). Treatment planning and calculations

e) Treatment delivery

f) Documentation

Annexure D

Chain of evidence: Navigation

CENTRE I

Data description	Data storage	Codes
Infrastructure Clinical profiles Treatment outcomes	CD -FOLDER 1 -pictorials. -Ms-word- CI raw data -Excel spread sheet CI transferred data. -Excel spread sheet - CI HDR & LDR EQD_2 calculations -Excel spread sheet-data analysis.	**Data from Annexure A1:** CIAA1
Implementation of HDR	Box file- CI Data	**Data from Annexure B:** CIAB **Data from Annexure C:** CIAC **Additional data- CI** Follow-up interview: FOIN Informal interview-ADHOC Research feedback: RF Spontaneous conversation-SC Document 1-2 D1to D2 Observations-OBS

CENTRE II

Infrastructure Data clinical profiles, Data treatment outcomes	CD 2 –FOLDER II -pictorials. -Ms-word- CII raw data -Excel spread sheet-CII transferred data. -Excel spread sheet CII- HDR & LDR EQD_2 calculations -Excel spread sheet-data analysis.	Data from Annexure A2: CIIAA2
Implementation of HDR	Box file- CII Data	Data from Annexure B: CIIAB Data from Annexure C: CIIAC **Additional data- CII** Follow-up interview: FOIN Informal interview-ADHOC Spontaneous conversation-SC Documents 1- D1 to D4 Observations-OBS

Annexure E

Invitation letter to participants & consent form

INVITATION LETTER & CONSENT EXPLANATION

I am a MTech (Radiography) student at Cape Peninsula University of Technology. The title of my research is: **Brachytherapy in Cancer of the Cervix: An African Perspective.** The main objective is to explore low and high dose rate brachytherapy in cancer of the cervix treatment at two African oncology centres and thereafter advice on appropriate strategies and recommendations for treatment with an African perspective. Participants will be drawn from the two centres to include a radiation oncologist, a medical physicist and a radiographer involved in brachytherapy treatment of cancer of the cervix, to answer a self directed questionnaire and a researcher guided questionnaire interview. You are assured that you may withdraw from the research process at any time without consequence.

If you agree with the information below, please sign the consent form:

I understand that:

1. My participation is voluntary and I have the right to withdraw at any time without consequence.
2. I will be asked to give responses on issues related to the research and that these responses will not result in any judgment of me.
3. I will be kept informed of the results of the research
4. Participant confidentiality is assured.
5. Confidentiality of all data gathered will be maintained during collection and analysis of the research.

Thank you.

Researcher: Longino Mucheusi**,** **Student No**: 198094892 **E-mail:** mucheusil@yahoo.com

Mobile Phone: 0761016868-South Africa and 0722385053-Kenya.

Supervisor: Prof Penelope Engel-hills: **E-mail**: engelhillsp@cput.ac.za

Institution: Cape Peninsula University of Technology.

CONSENT FORM

I.....consent to participate in the research

study outlined above.

Position:…… **Institution:…….**

Signature of participant:…… **Date:……..**

Annexure F

Planning for HDR installation: Questionnaire/Interview responses

	Centre I	Ref code	Centre II	Ref code
Planning for installation	Authorisation of source obtained.	CIPr2AC1-2	Planning was for purchase of LDR unit, but a last minute decision	CIIPr1AC1-2
	Maintenance contract signed.	CIPr2AC1-2	to buy HDR due to availability of funds.	CIIPr3AB5
	Comprehensive QA programme drawn up.	C1Pr2AC1-2	No maintenance contract was only for 1 year which elapsed.	CIIPr1AC1b 3c.
	Interlocks and radiation monitor in place.	CIPr2AC1-2	Had initial service contract. Though we have a local (hospital)	CIIPr2AC1b3c
	Emergency program in place.	CIPr2AC1-2	biomedical engineering team who perform minor repairs.	
	Emergency kit in treatment room.	CIPr2AC1-2	Authorisation of the source obtained.	CIIPr2AC3
	Studied IAEA report on accidents in radiotherapy.	CIPr2AC1-2	Hospital had initially deposited funds for 10 (ten) sources and the	CIIPr2AC3a
	Source replacement-hospital to commit itself, otherwise it becomes a problem (I suggest you use Co-60 source if upgrading to HDR)	CIPr1AC2	other costs were to be prepaid on a yearly basis.	
			A 5 year source supply was procured and paid for.	CIIPr1AC3a
			No prior preparation when ordering HDR. When LDR was ordered previously, there was no problem; there was a good plan when it was being procured. Everything was ready-building, rooms, and all the infrastructure plus training in place.	CIIPr2FOIN
			When HDR came, then we became aware we needed all these things i.e. room plus other infrastructure.	CIIPr2FOIN

			Then we started planning where the HDR was to be installed We approached the Hospital Engineer with a suggestion on renovation of the intended room to include an increase in wall thickness which was to act as a bunker. Proposal was taken to Hospital Engineer and you know how Finance & Supplies work. Still waiting for Hospital to make a proper room. I remember there was a meeting to discuss conversion from LDR to HDR, and we were told the usefulness of HDR: treat many patients in a short time, easy to handle, can be intertwined with EBRT treatments, that is treat patient with HDR while the patient is still undergoing EBRT.	CIIPr2FOIN CIIPr2FOIN CIIPr5ADHOC

Annexure G

Comparison of HDR and LDR

Centre I	Ref code	Centre II	Ref code
For HDR, more management to keep the supply of sources going. Dedicated staff to see this happen. Having Co-60 HDR source will be less of an issue.	CIPr1PrAC4a	Much cheaper to run LDR than HDR in terms of: Management, ease of use, staffing.	CIIPr2AC4
		Though numbers on waiting list could be cleared faster using an HDR service.	CIIPr2AC4
More patients in theory to be treated with HDR	CIPr1AC4e	Cost of purchasing HDR and regular source replacement is high, however due to high dose rate; a high number of patients can be treated. Though LDR source lasts longer translating into low running costs.	CIIPr4AC4
LDR had a manual system incase of technical failure	CIPr1AC5		
Only used HDR	CIPr2AC4	LDR has been in use for some time now in our department and has provided good service with minimal servicing. However, maintenance is challenge as it has to be sourced from outside the country, which is costly.	CIIPr4AC4
		All staff earmarked for HDR have had exposure with LDR brachytherapy treatment	CII2Pr4C4
		Many patients could benefit from HDR ICBT due to the fact that the number patients with cervical cancer constitute approx 50% of all cancer patients at our Centre.	CII2Pr4AC4

Annexure H

Challenges of HDR implementation

Centre I	Ref code	Centre II	Ref code
Challenges of keeping supply of sources going	CIPr1AC5, 3a	HDR is available at our centre but has not been put into use due to: i) a dedicated bunker has not been built for HDR and ii) the operational aspects of the unit have not been understood since installation for it has not been used.	CII2Pr4AC5
Difficult to sustain dosimetry for every fraction in HDR, can lead to time wastage, labour intensive, and therefore leads to treating fewer patients. Before we did X-rays for dosimetry per insertion, now we only do one X-ray per initial insertion.	CIPr1AC5 CIPr1AC5AC2	HDR has not been put to use due to logistical/bureaucratic issues	CII2Pr4AC4
Occasional hardware and software failure of the unit. Only once we had a spectacular technical failure. This was never experienced with the LDR because it had a manual system.	CIPr1AC5	Lack of a maintenance contract. Difficult... but the main issues were on radiation safety which has not been addressed.	CIIPr1AC5 CIIPr1AC5
For small technical/software failures, they are normally solved with the local agents. Big technical failures are solved by senior people from Johannesburg, or overseas agents (rare).	CIPr1AC5	The machine has not been commissioned. The supporting equipment were lacking/or not working, i.e. planning software/simulator broken down/lack of standard plans-therefore planning would take long Planning unit was not working, only recently started working. Of late the hospital has put the machine in the old simulator room. So efforts are underway to renovate /rectify old simulator room to suit HDR.	CIIPr1AC5 CIIPr1AC6 CIIPr2FOIN

Annexure I

HDR QA Implementation Question 6 (Researcher guided question interview: AC)

Centre I	Ref code	Centre II	Ref code
Integrity of the Applicator is checked by the Oncologist.	CIPr2AC6	Blank questionnaire/interview sheets	
Emergency procedure notification: Is placed on the wall outside and inside the treatment room.	CIPr2AC6		
There is a cluster of data from the company/Supplier to compare with.			
Checked with what other centres do: the procedures they have put in place and customize or adapt to here.	CIPr2AC6		
Placed TLDs on a phantom & simulate.	CIPr2AC6		
Check that all the points B, R1, R2 and (K & N) Nodal points coincide on the AP and Lateral film.(Accept only if its within 2mm).			
Time/True cross-check	CIPr2AC6		