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An analysis of dose effectiveness and incidence of late rectal complications of high dose-rate brachytherapy in the radical treatment of cervical cancer

DEIRDRÉ LONG

AN ANALYSIS OF DOSE EFFECTIVENESS AND INCIDENCE OF LATE RECTAL COMPLICATIONS OF HIGH DOSE-RATE BRACHYTHERAPY IN THE RADICAL TREATMENT OF CERVICAL CANCER

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Mei 2007

DECLARATION OF INDEPENDENT WORK

I, DEIRDRÉ LONG, do hereby declare that this project submitted for the degree MASTER TECHNOLOGIAE; RADIOGRAPHY (ONCOTHERAPY) in the SCHOOL OF HEALTH TECHNOLOGY, FREE STATE, is my own independent work that has not been submitted before, to any institution by me or anyone else as part of any qualification.

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Signature of student Date

Dedicated to my father:
Reginald Margin Ellerbeck

Blessed is the man who trusts
In the Lord,
And whose hope is the Lord.

For he shall be like a tree
Planted by the waters,
Which spreads out its roots
by the river,
And will not fear when heat comes;
But its leaf will be green,
And will not be anxious in the year
of drought,
Nor will cease from yielding fruit.

Jeremiah 17: 7,8

To my husband, Michael

And our son Jason –

Thank-you.

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Soli deo Gloria

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CHAPTER 1

AN OVERVIEW OF THE STUDY

1.1 Introduction

The first reference to the practice of gynaecology as a field of medicine is found in the Kahun papyrus from 2000 B.C. In a description of women`s diseases, Hippocrates, who is considered to be the father of both medicine and oncology, referred to cancer of the uterus as a disease with a poor prognosis. He recommended the following treatments for cancer: "Regular evacuation of the bowels; the patient is to be given a bath each day with lukewarm water; narcotics such as opium given internally or injected into the uterus for pain relief; the application of leeches or red-hot irons or other caustic agents to the cervix" (Werner 1990). Since the discovery of X-rays by Wilhelm Conrad Roentgen in 1895, the treatment of uterine cervical cancer by means of radiotherapy has developed immensely.

Radiotherapy is a clinical modality that uses ionising radiation in the treatment of patients with malignant neoplasias. The aim of radiotherapy is to deliver a precisely measured dose of radiation to a defined tumour volume with as little damage as possible to surrounding healthy tissue, resulting in eradication of the tumour, a high quality of life and prolongation of survival at a competitive cost (Halperin, Schmidt-Ulrich, Perez & Brady 2004: 3). The current study will look at radiotherapy as treatment modality for patients diagnosed with uterine cervical cancer.

Uterine cervical cancer occurs in women around the world, irrespective of their age and race. The South African cervical cancer screening program implemented since 2001 are an attempt to facilitate early detection of cervical cancer through the Papanicolaou (PAP) smear (Mqoqi, Kellet, Sitas & Jula 2004: 22). Through the screening policy it has become evident that cervical cancer is the leading cancer among South African women. It is thus crucial to treat patients who have been diagnosed with uterine cervical cancer with the best modality currently available.

This current study will look at radiotherapy as the treatment modality administered to patients at the Department of Oncotherapy, Bloemfontein, diagnosed with uterine cervical cancer, since a new modality of high dose-rate (HDR)-intracavitary brachytherapy (ICBT) was implemented in 1994. Treatment results are quantified and analysed in terms of tumour control and late rectal complications. This chapter provides an overview of the incidence of uterine cervical cancer, the development of treatment protocols at the Department of Oncotherapy, Bloemfontein, and the dose effectiveness of HDR-ICBT as an introduction to the problem statement and objectives for this study.

1.2 Worldwide incidence of cervical cancer

Worldwide, uterine cervical cancer is one of the most frequently occurring cancers in women, with more than 80% occurring in developing countries (Stewart & Kleihues 2003: 215). Carcinoma of the uterine cervix is the sixth most common malignant neoplasm amongst women in the world, after carcinoma of the breast, lung, colorectum, endometrium and ovary (Perez & Kavanagh 2004: 1800). From a worldwide perspective, uterine cervical cancer remains one of the biggest causes of cancer death in women. Globocan 2000 estimated that in the year 2000, the number of patients diagnosed with this disease was 470 606, of whom 233 372 died

as a result (Parkin, Bray, Ferlay & Pisani 2001: 153). The American Cancer Society estimated that in 2001 there were 12 900 new cases of invasive uterine cervical cancer in the United States and 4 400 deaths from the disease, in addition to over 50 000 cases of carcinoma in situ (Perez & Kavanagh 2004: 1800).

The epidemiology of uterine cervical cancer is strongly related to the standard of living of populations from the different world regions (Parkin et al. 2001: 153). It follows then that for developed countries, in addition to a lower incidence of the disease, most cases of uterine cervical cancer are detected at a pre-invasive stage where the rates of cure approach 100% with local therapies. On the other hand, developing countries present a different picture, with most cases being diagnosed with locally advanced disease. This requires a much more aggressive treatment approach and, in general, the survival prospects are not very encouraging (Duenas-Gonzalez, Cetina, Mariscal & De la Garza 2003: 390). Nag et al. (2002) reported that cervical cancer is the commonest type of cancer in many developing countries (Nag, Dally, de la Torre, Tatsuzaki, Kizilash, Kurusun, Pinillos, Pokrajac, Sur & Levin 2002: 298). Developing countries with a high incidence of cervical cancer are Zimbabwe, Uganda, South Africa, Gambia and Algeria. Black Zimbabwean women have the highest incidence rates of 55 per 100 000 (Mqoqi et al. 2004: 22).

1.3 Cervical cancer in South Africa

In South Africa, a total of 6 061 and 4 944 uterine cervical cancer cases were reported to the National Cancer Registry (NCR) in 1998 and 1999 respectively. The NCR (established in 1986) is the main cancer data source, which publishes pathology-based cancer incidence data in South Africa. These are the most recent statistics available and comprise 20% and 17% respectively of all cancer cases reported in females over two

years. Consequently, uterine cervical cancer was the leading cancer in women in 1998 and the second leading cancer in 1999 (Mqoqi et al. 2004: 22). The incidence of uterine cervical cancer also differs among the different population groups in South Africa. Statistics indicate that in 1999 a total of 4 944 cases were observed, of whom 4 127 were black, 390 coloured, 371 white and 56 Asian. The statistics for 2000 – 2004 at the Department of Oncotherapy, Bloemfontein, has indicated that Black South African women were the most affected by this disease (Doman 2006).

1.4 Cervical cancer at the Department of Oncotherapy, Universitas Annex, Bloemfontein

The incidence rate of cervical cancer at the Department of Oncotherapy, Universitas Annex, Bloemfontein (Free State, South Africa) is high according to the statistics (Doman 2006). The statistics from 2000 to 2004 in Table 1.1 indicate that a total of 6 285 female patients received treatment for cancer over a five year period from January 2000 to December 2004. Of these, 2 117 patients (33.7%) were diagnosed with cervical cancer (FIGO stages I-IV) and were treated accordingly.

Table 1.1 Female patients treated for cancer at the Department of Oncotherapy, Bloemfontein (Doman:2006)

		White	% of whites	% of females	Black	% of blacks	% of females	Total	% of Total	% of females
2004	cervix	29	4.25	8.92	389	24.13	43.37	418	18.21	34.21
	Females	325			897			1222		
2003	cervix	26	4.70	7.78	402	23.52	46.26	428	18.92	35.58
	Females	334			869			1203		
2002	cervix	36	5.57	11.39	351	22.43	37.70	387	17.50	31.03
	Females	316			931			1247		
2001	cervix	38	9.69	10.83	412	27.23	42.13	450	20.41	33.86
	Females	351			978			1329		
2000	cervix	43	6.44	12.50	391	24.15	41.60	434	18.89	33.80
	Females	344			940			1284		
Total	cervix	172			1945			2117		
	Females	1670			4615			6285		
Average		34	6.13	10.29	389	24.29	42.21	423	18.79	33.70

Treatment modalities for uterine cervical cancer differ according to the disease. Surgery, chemotherapy and radiotherapy, or a combination thereof, are currently being used to treat patients diagnosed with uterine cervical cancer. Radiotherapy plays an important role in the treatment of uterine cervical cancer. A combination of megavoltage external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) is the accepted definitive mode of treatment of International Federation of Gynecologists and Obstetricians (FIGO) stages I-III cervical cancer. The curative potential of radiotherapy in the management of carcinoma of the cervix is enhanced by the use of intracavitary brachytherapy, which delivers a high radiation dose directly to the tumour while sparing the surrounding normal tissues (Patel, Rai, Mallick & Sharma 2005: 125). The choice of radiation modality depends on the efficacy, disease site, equipment availability, treatment duration, expertise and radiation safety considerations (Nag et al. 2002: 298).

How often HDR brachytherapy is used depends on how common a particular cancer is in that country and whether that site can be effectively treated by HDR brachytherapy. Currently, more than 1 000 units exist in the world, including almost 400 in developing countries. The use of HDR-ICBT for uterine cervical cancer patients is the most common indication for brachytherapy, and gynaecological brachytherapy can account for up to 100% of the brachytherapy practice in some developing countries (Nag et al. 2002: 298-299).

The statistics shown in Table 1.1 therefore clearly indicate the need to introduce HDR-ICBT into the treatment schedule for FIGO stages I-III cervical cancer patients with curative intent. In April 1994 the standard prescribed protocol for FIGO stages I-III cervical cancer patients at the Department of Oncotherapy, Bloemfontein, South Africa, changed with the

installation of a high dose-rate (HDR) Ir^{192} brachytherapy afterloading unit, described in the next section.

1.5 Development of treatment protocols at the Department of Oncotherapy, Bloemfontein

Radiotherapy treatment was started in Bloemfontein during 1960 by a diagnostic radiologist, Dr R Tahan. A kilovoltage apparatus for teletherapy (RT 250, Philips) and radium sources (Radium-226) for brachytherapy were the main treatment units during those years. The duration of the brachytherapy (Radium-226) was 72 hours and the patient received three fractions (Friedrich 1996: 16). The treatment protocols from 1966 to 1990 for stages IIb and III cervical carcinoma are summarised in Tables 1.2 & 1.3 respectively (Friedrich 1996: 17).

Table 1.2 Treatment protocols at Universitas Annex, stage II cervical carcinoma: 1986-1990 (Friedrich 1996).

YEAR	TEATMENT PROTOCOLS	DOSE (Gy)	TOTAL DOSE (Gy)
1966	Opposing fields Planned fields Brachytherapy LDR (one application 24 hours) or Surgery Opposing fields followed by Planned fields	2 2.5 2 2 2	14 10 30 10 30
1967	Opposing fields Brachytherapy (2 applications 50/54 hours each) Supplementary fields to pelvic wall	2, 2.5 or 3 variation	12 10 12-15 depended on brachytherapy dose

1969	Fractionation 3 x per week		
1970	Double dose	3.5 to 7	45 - 54
1972 to 1990	Opposing fields Brachytherapy (2 x 50 h) Surgery or supplementary fields or Opposing fields, treatment plan and brachytherapy LDR booster	3 3	12 -15 54 - 60

Table 1.3 Treatment protocol stage III cervical carcimoma: 1996-1990

YEAR	TREATMENT PROTOCOLS	DOSE (Gy)	TOTAL DOSE (Gy)
1966	Opposing fields Planned field length = 15cm Brachytherapy LDR booster or booster plan	2 2	10 30
1972	Field length (planned fields)=12cm	3 or 3.5	57 -60 42 -45
1973 – 1974	Field length (planned fields)=10cm		
1975 – 1990	Field length (planned fields)=8cm	3	57 - 60

In April 1994, the Department of Oncotherapy, Bloemfontein, implemented a high dose-rate (HDR) brachytherapy treatment system, an $Ir\text{-}^{192}$ Nucletron Microselectron afterloading source, using the ring applicator. After careful analysis of the available data on fractionation schedules, the standard prescribed protocol for treating patients for uterine cervical cancer (FIGO stages I-III) was established. The advent of HDR brachytherapy in the department, which has the advantages of individualised dosimetry, outpatient treatment and elimination of radiation exposure of medical personnel, brought a convenient treatment option for

patients with uterine cervical cancer, permitting treatment of a large number of patients (10-15 patients weekly).

The fractionation schedule applicable to the study is shown in Table 1.4. Patients with FIGO stages I-III uterine cervical cancer are treated with a combination of EBRT- 2 Gy/fraction x 25 fractions (50Gy to whole pelvis) and HDR-ICBT given in 4-6 fractions, once weekly (2 Gy/fraction, normalized to the highest rectum dose point), to achieve a minimum total dose of 15 Gy to point A, as opposed to the previous protocols mentioned. Point A is defined as a geometric point in relationship to the cervical os and uterine axis.

Table 1.4 Treatment protocol for FIGO stages I-III cervical cancer patients treated at the Department of Oncotherapy, Universitas Annex, Bloemfontein, from 1994 up to the time of writing

EBRT- Dose per fraction (Gy)	EBRT- No. of fractions	EBRT- WholePelvic Dose (Gy)	HDR- ICBT- Dose per fraction (Gy)	HDR- ICBT- No. of fractions	HDR-ICBT- Total dose to tumour –min.15Gy
2	25	50 Gy	2 (2Gy to highest rectum dose point)	4-6	Cumulative recorded dose to point A

1.6 High dose-rate brachytherapy

Since Margaret Cleaves first performed intracavitary brachytherapy for cancer of the cervix in 1903, the radiotherapy of cervical cancer has traditionally been based on low dose-rate (LDR) intracavitary brachytherapy. HDR brachytherapy was developed to overcome some potential disadvantages of LDR brachytherapy, especially in the treatment of cervical cancer (Ferrigno, Nishimoto, Dos Santos Novaes, Pellizzon, Maia, Fogarolli & Salvajoli 2005: 1108). High dose-rate brachytherapy

allows for shorter treatment times, resulting in reduced hospitalisation costs owing to outpatient therapy, a reduced risk of applicator movement during therapy, and a larger throughput of patients in a busy department (Nag, Erickson, Thomadsen, Orton, Demanes & Petereit 2000: 202).

Studies reported by Falkenberg, Kim, Meleth, De Los Santos & Spencer (2006: 50) and Nag et al. (2000: 202) have compared LDR brachytherapy to HDR brachytherapy and have demonstrated comparable local control, survival and morbidity. To achieve disease control equivalent to that with LDR brachytherapy, changes in the dose/fraction schedule and strict attention to normal tissue doses when using HDR brachytherapy are mandatory. The biological disadvantage of HDR-ICBT in the treatment of cervical cancer is that short treatment times of HDR-ICBT do not allow for the repair of non-lethal damage in normal tissue, or the redistribution of cells in the cell cycle, or reoxygenation of the tumour cells. Multiple treatments are thus required (Nag 2004: 620). These radiobiological disadvantages of HDR-ICBT can, however, be overcome through adequate fractionation (Nag et al. 2000: 201).

The primary concern of using HDR brachytherapy is a potential late toxicity due to large doses per fraction (5 - 9 Gy/fraction). Late responding tissues such as the rectum and bladder have a greater capability of repair than tumour or early responding tissues, but this repair does not occur as fully as that of the same tissues treated with low doses. Fractionation and dose adjustments of the total dose are crucial factors in lowering the frequency of late radiation complications to the rectum, such as rectal bleeding, without compromising the treatment (Patel et al. 2005:125).

1.7 Fractionation and dose effectiveness

Although a large number of fractionation schedules are used worldwide for HDR brachytherapy, the optimal schedule has yet to be decided. Petereit and Pearcey (1999: 364) analysed the fractionation schedules of 24 published articles and came to the conclusion that there is no optimal fractionation schedule available, but suggested that reasonable fractionation schedules should be based on single institutional experience with accurate reporting. Members of the American Brachytherapy Society (ABS) with expertise in HDR cervical brachytherapy conducted a literature review, and, supplemented with their clinical experience and biomathematic modeling, formulated guidelines for HDR brachytherapy for cervical carcinoma. These recommendations are based on the Patterns of Care studies which showed that recurrences and complications decreased when brachytherapy was used in addition to EBRT (see Literature Review, Nag et al. 2000: 202). The International Atomic Energy Agency (IAEA) has also published recommendations specifically for implementing HDR, Ir^{192} brachytherapy in developing countries (Nag et al. 2002: 298).These recommendations correlate with those of the ABS and were thus relevant to the implementation of some of the recommendations into the EBRT and HDR-ICBT treatment at the Department of Oncotherapy, Bloemfontein.

Although there is a marked variation among institutions in the dose and fractionation used for cervical HDR-ICBT, most centers use a schedule of approximately 1.8 to 2 Gy per fraction for 25 fractions EBRT and 6-8 Gy per fraction for HDR in four to six fractions (Orton, Seyedsadr & Somnay 1991: 1425). Analysing different treatment schedules emphasizes the need to deliver biologically effective doses of radiation to ensure the highest probability of tumour control in the pelvis, because the salvage rate in patients who fail with isolated pelvic recurrences are less than optimal even after pelvic exenteration (Perez & Kavanagh 2004: 1858).

Consequently, because of a lack of personal or documented experience, radiation oncologists frequently resort to the use of bio-effect dose models to convert from LDR to HDR (Nag 2004: 610). This is the best available model for the quantitative assessment of clinical problems, primarily because it allows a distinction to be made between the fractionation and dose-rate sensitivities of early and late responding tissues (Clark, Souhami, Roman, Chappell, Evans & Fowler 1997: 989). Calculating the biologically effective dose to point A using the linear quadratic formula with an α/β of 10 is critical to compare fractionation schedules (Petereit & Fowler 2003: 1159). In general, the α/β values for tumour and early-responding tissues are approximately 10 (Gy_{10}), and for late-responding tissues 3 to 5 (Gy_{3-5}) (Petereit & Pearcey 1999: 360). The values derived are not actual doses, but biologically effective ones that take into consideration dose-rate and impact of fraction size.

In uterine cervical cancer, the response to radiotherapy is clearly dose-dependent. As the dose increases, so too does the probability of tumour control. However, the risk of damage and late complications in normal tissues also increases with the dose (Stewart & Viswanathan 2006: 908). The lower the dose-rate of radiation a cell is exposed to, the greater the likelihood of repair. Late-reacting normal tissues seem more capable of repair than tumours; at a given therapeutic dose, the tumour is preferentially killed over normal tissue. The duration of LDR treatment (several days) allows for non-lethal damage repair. The short treatment time of HDR brachytherapy prohibits this repair during the actual irradiation. However, if an interval of more than 24 hours is maintained, normal tissues can undergo full repair. Therefore, LDR may allow recovery of more normal tissues during treatment, but HDR may offer the advantage of increased cytotoxicity to the tumour (Stewart & Viswanathan 2006: 909).

1.8 Problem statement

The radiation treatment protocol for carcinoma of the uterine cervix stages I-III had to be adjusted at the Department of Oncotherapy, Universitas Annex, Bloemfontein, in April 1994 to incorporate HDR-ICBT with EBRT. The standard prescribed treatment protocol implemented at Universitas Annex since 1994 has thus not been evaluated or analysed for dose effectiveness and late radiation complications considering the biologically effective dose (BED) administered to cervical cancer patients. As a wide range of fractionation schedules exists worldwide with as yet no optimum schedule, there is a need to deliver biologically effective doses of irradiation to ensure the highest probability of tumour control in the pelvis with minimum late rectal complications.

The aim of the current study was to calculate the biologically effective dose for the fractionation schedule implemented at the Department of Oncotherapy, Universitas Annex, Bloemfontein, since 1994, to determine whether the fractionation schedule delivered BED`s that lead to local tumour control without severe late rectal complications. These cumulative BED`s, calculated for the combination of EBRT and HDR-ICBT, to the tumour Gy_{10} and the rectum Gy_3 for cervical cancer patients will enable the Department of Oncotherapy, Universitas Annex, Bloemfontein, for the first time to compare the fractionation schedule results with those of other institutions worldwide.

Analysis of the current treatment schedule, regarding the calculated BED, will indicate whether the total dose given to the planned tumour volume (PTV) by means of EBRT and the gross tumour volume (GTV) by means of HDR-ICBT has led to local tumour control with negligible late toxicity to the rectum.

1.9 The objectives of the current study

(i) To analyse the dose effectiveness of the fractionation schedule retrospectively by calculating the cumulative biologically effective dose (Total BED) of the combination of EBRT and HDR-ICBT for FIGO stages I-III uterine cervical cancer patients treated at the Department of Oncotherapy, Bloemfontein from January 1998 to December 2003.

(ii) To analyse retrospectively the incidence of late radiation complications as a result of the particular fractionation schedule used, by utilising the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) grading system, grade 0-5 (0 means an absence of radiation effects and 5 means the effects led to death). See Table 2.2.

1.10 The motivation and significance of the study

As the incidence of cervical cancer is high in developing countries such as South Africa it is essential to treat those affected with the best modality currently available (Mqoqi et al. 2004: 22). Radiotherapy plays an important role in the treatment of carcinoma of the uterine cervix and a combination of EBRT and HDR-ICBT is the accepted definitive mode of treatment (Patel et al. 2005).

Establishing BED values for the first time to the tumour (Gy_{10}) and the rectum (Gy_3) by using the LQ model in the fractionation schedule applicable to the study will be significant in enabling the Department of Oncotherapy, Universitas Annex, to compare the results of this study with those reported in the literature worldwide. Whether the BED values obtained could be used as a predictor of local tumour control and of rectal toxicity in the current treatment protocol for cervical cancer will be indicated after statistical analyses have been done. The outcome of the

study will thus clearly indicate whether the total dose given to the planned tumour volume (PTV) and gross tumour volume (GTV) has been a biologically effective dose for local tumour control with negligible late toxicity.

Other studies were done on patients with cervical carcinoma at the Department of Oncotherapy, Universitas Annex (Friedrich 1996). The focus of Friedrich`s study was to calculate LQ (Linear Quadratic) values for early and late responding tissues, using larger doses per fraction (3 Gy). This study will be unique in calculating the cumulative biologically effective dose of the fractionation schedule applicable to the study, and analysing the tumour control and late radiation complication rate according to the cumulative dose and calculated BED for FIGO stages I-III cervical carcinoma.

1.11 Methodology

1.11.1 Patient selection

A list of patients treated with EBRT and HDR-ICBT for cervical cancer FIGO stages I-III was obtained from the department's HDR-ICBT patient treatment book. All patient treatment files from 1998-2003 were analysed so as to include in this retrospective study only patients with complete dosimetric data and a minimum follow-up period of two years.

1.11.2 Calculations

The linear quadratic model was used to calculate the biologically effective doses for all the patients who met the inclusion criteria for this retrospective study. It is a mathematically simple way to quantify biological responses to different fractionation schedules (Clark et al. 1997: 989).

1.11.3 Research tool

A data source form was designed as a research tool to capture the relevant data from the patient treatment files (Appendix **IA**). Patient demographics, fractionation schedule details, tumour control, late radiation complications, metastatic disease and patient survival details were obtained from the patients treatment files and follow-up notes.

1.12 Data analysis

The data collected for this retrospective study was processed by the Department of Biostatistics, University of the Free State, Bloemfontein.

Results were summarised by frequencies and percentages (categorial variables) and means, standard deviations, minima and maxima (numerical variables). The software used was SAS 9.1.3 Service Pack 3.

1.13 Ethics

The proposal for this retrospective study was presented to the Ethics Committee at the University of the Free State at the meeting held on 14 March 2006 and attained the necessary approval. **ETOVS NR 31/06.** A letter of consent (Appendix **IB**) permitting the use of patient records for the retrospective study was obtained from the Head of Clinical Services, Universitas Annex.

1.14 Outcome of the study

The results obtained from this study of patients treated for FIGO stages I-III cervical cancer by using a combination of EBRT and HDR-ICBT are applied as follows:

- Documentation of the biologically effective dose (BED) values for future use in treating cervical cancer patients and comparison of the

BED values to the tumour Gy_{10} and rectum Gy_3 with those of other international institutions.

- Implementation of a RTOG/EORTC scoring sheet in the patient follow-up files for future research on the crude incidence of late radiation complications
- Use of the data to compile a report for a thesis for M.Tech. qualification.
- Presentation of the results of the thesis at congresses and/or seminars.
- Publication of data in relevant medical journals.

1.15 Arrangement of the dissertation

CHAPTER 1: An overview of the study

This chapter contains an introduction to the relevance of the study, incidence of cervical cancer, development of treatment protocols, HDR-ICBT, fractionation and dose effectiveness, the problem statement, objectives, motivation and the outcome of the study.

CHAPTER 2: Literature review

The literature review covers the epidemiology of uterine cervical cancer, staging, radiation therapy, ABS recommendations, biology of HDR brachytherapy, time-dose models, treatment techniques, late radiation complications and future developments of HDR brachytherapy.

CHAPTER 3: Methodology

The methodology of the study discusses the methods and materials used for patient selection, EBRT, HDR-ICBT insertion technique and treatment planning, calculations of the biologically effective dose, the research tool, scoring of late radiation complications, statistical analysis and follow-up examinations of uterine cervical cancer patients.

CHAPTER 4: Results

The results of the current study are shown in this chapter. The results as well as other information gathered by the data source form regarding patient selection, patient demographics, tumour characteristics, tumour control, metastases and survival are reflected in this chapter.

CHAPTER 5: Discussion and conclusion

The dose effectiveness and the incidence of late radiation complications of the fractionation schedule of EBRT and HDR-ICBT used in treating uterine cervical cancer patients at the Department of Oncotherapy, Bloemfontein are discussed.

1.16 Conclusion

HDR-ICBT for carcinoma of the cervix is widely used because of its advantages over LDR brachytherapy. Although a large number of fractionation schedules are in use for HDR-ICBT, the optimal schedule has yet to be decided (Patel et al. 2005: 125). Because there are few established guidelines for its clinical use the American Brachytherapy Society (ABS) formed a committee to issue guidelines specifically for the use of HDR-ICBT for cervical carcinoma (Nag et al. 2000: 202). The literature review in chapter 2 focuses on these recommendations and other published studies regarding the use of EBRT and HDR-ICBT for cervical carcinoma.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Fletcher and his co-workers stated over 55 years ago: “We are still in an empirical era in the use of radium therapy in cancer of the cervix” (Fletcher, Shalek, Wall & Bloedorn 1952: 935). In the same way, Orton (1986) stated 21 years ago that apart from a change from radium to cesium, they were still in that empirical era regarding the many innovations that have occurred in the use of external beam radiotherapy in comparison to the treatment philosophies concerning intracavitary cervix treatments. The latter were dictated primarily by tradition and well-established convention. Unfortunately, there was evidence indicating that many of these established conventions were by no means optimal in terms of late complications (Orton 1986: 37). Orton also stated that there is a temptation to judge treatment “success” by avoiding complications rather than by long-term survival. He proclaimed that because fractionation and dose rate patterns to the vulnerable pelvic organs vary considerably from patient to patient, doses need to be expressed in terms of some type of “biologically effective dose” units and not simply Gy (Orton 1986: 37).

Treating patients who have been diagnosed with uterine cervical cancer in the most effective manner requires extensive research of the most recent literature on the subject. This literature review scrutinises the appropriate evidence supporting the use of HDR-ICBT in combination with EBRT as the accepted definite mode of treatment for uterine cervical cancer and

correlates it with the dose effectiveness and late radiation complications found in the study. This literature study entailed reviewing the relevant literature in textbooks and published articles to ascertain the work being done in this field and the relevant methods being used. Key words such as “HDR brachytherapy” and “uterine cervical cancer” were used to retrieve the relevant data from the Internet. The epidemiology of patients diagnosed with uterine cervical cancer provides a background to the study.

2.2 Epidemiology

The incidence of uterine cervical cancer differs among different population groups in South Africa. Since the beginning of the National Cancer Registry (NCR) in 1986, uterine cervical cancer has been the leading cancer in black women. A total of 5 069 cancers were reported on black females in 1998, with 4 342 reported in 1999, comprising, on average, about 84% of all uterine cervical cancer cases reported in the two years. The second highest rates of 29 per 100 000 and 26.4 per 100 000 in the two consecutive years were recorded among coloured women. Asian women had the lowest cervical cancer incidence rates of 11 per 100 000 in 1999. Uterine cervical cancer in white women peaked at a significantly lower Age-Specific Incidence Rate (ASIR) of 34.5 per 100 000 and at a younger age (60-64) than in black and coloured women where ASIR peaked between the ages of 65 and 69 (Mqoqi et al. 2004: 22).

According to Perez (1998) the incidence of uterine cervical cancer is substantially higher among women in low socio-economic classes. Uterine cervical cancer is more frequent in women who had first sexual intercourse at an early age, have a history of sexual promiscuity, or have had a large number of pregnancies (Perez 1998: 1734). Considering the epidemiology of uterine cervical cancer in South Africa, it is thus of utmost

importance to treat women who have been diagnosed with uterine cervical cancer with the best curative modality available.

The initial staging system of uterine cervical cancer proposed in 1929 by a subcommittee of the League of Nations was revised in 1937 and 1950. These functions were taken over by International Federation of Gynecologists and Obstetricians (FIGO) in collaboration with the World Health Organization (WHO) and the International Union Against Cancer. The staging recommendations were last revised in 1995 (Shepherd 1995: 319). See Appendix **IIA** for the FIGO staging classification: Cervical Carsinoma. This FIGO staging (being refined e.g. IIIb1R) is used at the Department of Oncotherapy, Universitas Annex, Bloemfontein. The FIGO staging system is based on clinical evaluation (inspection, palpation, colposcopy), roentgenographic examination of the chest, kidneys, and skeleton, and endocervical curettage and biopsies.

Different stages have different local control outcome as indicated by a study done by Patel et al. (Patel et al. 2005: 125). They reported on 121 patients with stages I-III uterine cervical cancer who were treated with EBRT and HDR-ICBT. The actuarial local control rate at 5 years was 100% for stage I, 80% for stage II and 67,2% for stage III uterine cervical cancer patients. Toita et al. (2003) also stated that in their study on uterine cervical cancer patients treated with EBRT and HDR-ICBT, the 5-year local control rate for stage II was 87% and stage III was 50% (Ferrigno et al. 2005: 1113). Thus it seems as if the local tumour control of a patient diagnosed with uterine cervical cancer is influenced by the FIGO staging. The probability of rectal complications shows a correlation for dose-response, while clinical stage is not associated with increased risk of late rectal sequalae (Chen, Liang, Yeh, Yang, Shiau & Lin 2004: 667).

2.3 Radiation therapy

Since the introduction of the first remote afterloading machine in 1962, designed by Rune Walstam at the Radiumhemmet in Stockholm, with a three 50 mg and one 9 mg radium tubes, modern brachytherapy techniques of afterloading and dosimetry optimisation have made revolutionary strides in treating cancer patients (Mould, Batterman, Martinez & Speiser 1994: 8).

Radiation therapy of uterine cervical cancer patients has traditionally been based on low dose-rate (LDR) intracavitary brachytherapy for almost 100 years. However, concerns about its disadvantages, such as the exposure of medical staff to radiation, prolonged treatment time, risk of applicator movement and mandatory hospitalisation, led to the development of HDR brachytherapy (Shakespeare, Lim, Lee, Back, Mukherjee & Lu 2006: 277). Because of the high incidence of uterine cervical cancer in developing countries, it is the most common indication for gynecological brachytherapy and can account for up to 100% of the brachytherapy practice (Nag et al. 2002: 298). Due to the short treatment times needed, HDR machines are capable of treating larger numbers of patients than LDR techniques. The shorter treatment times of HDR brachytherapy also reduce the risk of applicator movement and reduce hospitalisation costs because of using outpatient therapy instead. Additionally, in HDR brachytherapy, late tissue complications might be minimised more effectively than in LDR brachytherapy, because greater normal tissue displacement (e.g. bladder anteriorly and rectum posteriorly) is possible because of the short treatment times and available retraction devices (Nag et al. 2000: 202).

Other advantages of HDR-ICBT treatment include eliminating radiation to care givers and visitors. HDR brachytherapy also eliminates the need for source preparation and transportation and because there is only one

source, there is minimal risk of losing a radioactive source (Nag 2004: 620). HDR sources are of smaller diameter than the cesium sources that are used for intracavitary LDR brachytherapy and therefore reduce the need for dilatation of the cervix, thus reducing the need for heavy sedation or general anesthesia. HDR brachyhterapy also improves treatment dose distribution optimisation. Technical advances in HDR brachytherapy and its advantages over LDR brachytherapy made this treatment modality, in combination with EBRT, an essential component of the curative treatment of uterine cervical cancer (Nag et al. 2002: 299).

2.4 Recommendations of the American Brachytherapy Society (ABS)

A literature analysis was done by Petereit et al. (1999) of the University of Wisconsin, USA, on the fractionation schedules of 24 articles published using the linear quadratic model to determine if doses can be correlated with local control and complications. Their conclusion was that a dose response relationship could not be identified for tumour control or late tissue complications, mainly because most of the HDR publications reported inadequate details of the dose fractionation schedules. It was also reported that the optimal fractionation schedule for treating uterine cervical cancer using HDR brachytherapy is still unknown, and presently can be based on single institutions with significant experience (Petereit, Sarkaria, Potter & Schink 1999: 359).

In order to address this problem, in 2000, the American Brachytherapy Society (ABS) published recommendations regarding the treatment of patients diagnosed with uterine cervical cancer with fractionation schemes which utilises the combination of EBRT and HDR-ICBT (Nag et al. 2000: 202). A retrospective study was done by Shakespeare et al. (2006) to assess the suggested ABS guideline tolerability in an Asian population. The study indicated good local control and survival outcomes. The

conclusion of the study was that it is reasonable and safe to follow the guidelines laid out by the ABS (Shakespeare et al. 2006: 281). The following are some recommendations and guidelines given by the ABS:

General recommendations

The ABS recommends that brachytherapy be included as a component of the definitive radiation therapy for uterine cervical carcinoma, based on the Patterns of Care studies that show that recurrences and complications are decreased when brachytherapy is used in addition to EBRT (Nag et al. 2000: 202). Nag et al. reported that the relative doses given by EBRT compared to brachytherapy depend upon the initial volume of disease, the ability to displace the bladder and rectum, the degree of tumour regression during pelvic irradiation and institutional preference. Patients with larger tumour volumes receive 20-30 Gy of EBRT before HDR-ICBT treatment is initiated to allow for tumour shrinkage of tumor and a more favourable anatomic geometry for applicator placement. Because the overall treatment duration would be unduly prolonged if HDR treatments were begun after completion of EBRT, the HDR-ICBT is interdigitated during the course of EBRT. However, EBRT is not given on the day of a HDR-ICBT treatment. Typically, if the vaginal geometry is optimal, HDR brachytherapy begins after 2 weeks of EBRT. HDR-ICBT is given once a week, with the EBRT continued on the other four days of the week. These recommendations have been implemented at the Department of Oncotherapy, Universitas Annex, Bloemfontein.

External beam radiotherapy

The ABS recognises that the whole pelvic EBRT dose varies from institution to institution. The HDR fraction size and number depends on the EBRT dose (Nag et al. 2000: 203). Some institutions prefer to limit the whole pelvis dose for patients with early disease and to perform the first intracavitary insertion after 20 Gy, with further EBRT delivered with a

central block in place. If a lower EBRT dose is chosen for patients with early disease, the ABS recommends increasing the HDR fraction size and number of fractions. However, the individual fraction size should be kept to less than 7.5 Gy due to reports of higher toxicity with larger fractions. Most institutions, which include the Department of Oncotherapy, Bloemfontein, prefer to deliver 40-50 Gy of EBRT to the entire pelvis. In these cases, the brachytherapy dose is decreased. If EBRT doses greater than 45-50 Gy are to be given, the treatment fields should be coned down after the initial 45-50 Gy in an effort to exclude small bowel (Nag et al. 2000: 203).

Dose specification

Ideally, the dose should be prescribed to the individual patient`s target volume. Unfortunately, many facilities lack the capability to determine the volume at risk, nor is there sufficient information in the literature to establish a better delineated target volume than the customary, Manchester System defined Point A. For HDR brachytherapy, the ABS has provided an applicator-based definition of point A that has been named point H (Nag et al. 2000: 204). Point H was created by the ABS to standardise the dosimetry process in the computerised treatment planning era by defining point A in relation to the applicator as seen on radiographs, as apposed to the cervical os.

Dose recommendations

The ABS recommends that the goals are to treat uterine cervical cancer with a combined EBRT and HDR dose to point A, to at least a total LDR equivalent of 80-85 Gy for early stage disease and 85-90 Gy for advanced stage disease (Nag et al. 2000: 201-211). The pelvic sidewall dose recommendations are 50-55 Gy for early lesions and 55 -65 Gy for advanced ones. Every attempt should be made to keep the bladder and rectal doses below 80 Gy and 75 Gy LDR equivalent doses, respectively.

While recognizing that many efficacious HDR fractionation schedules exist, the ABS has developed suggested tables for combining the EBRT with HDR brachytherapy for patients with early and advanced stages of uterine cervical cancer, respectively (Table 2.1) (Nag 2004: 621).

Table 2.1 ABS suggested doses of EBRT and HDR-ICBT (Nag 2004: 621)

EARLY STAGE			**ADVANCED STAGE**		
EBRT (Gy) at 1.8 Gy/fraction	**No. of HDR fractions**	**HDR Dose per fraction (Gy)**	**EBRT (Gy) at 1.8 Gy/fraction**	**No. of HDR fractions**	**HDR Dose per fraction (Gy)**
19.8	6	7.5	45	5	6.5
19.8	7	6.5	45	6	5.8
19.8	8	6	50.4	4	7.0
45	5	6	50.4	5	6.0
45	6	5.3	50.4	6	5.3

Treatment schedules integrating external beam radiation therapy and brachytherapy were initially designed with regard to the disease stage and volume (Perez & Kavanagh 2004: 1840). In most centers, as the tumour volume or stage increases, the external beam dose plays a more prominent role in the total dose, whereas the number of HDR fractions and the dose per HDR fraction are decreased.

Although there is a marked variation in the dose and fractionation used for cervical HDR-ICBT, most centers use a schedule of approximately 1.8/2 Gy per fraction for 25 fractions EBRT and 6-8 Gy per fraction in four to six fractions (Orton et al. 1991: 1425). The fractionation schedule applicable to this retrospective study, used at the Department of Oncotherapy, Bloemfontein, is 2Gy/fraction for 25 fractions of EBRT and a dose of 2 Gy prescribed to the highest rectum dose point, administered in 4-6 fractions of HDR-ICBT. The dose to point A varies for each HDR-ICBT treatment given as a result of the changes in the rectum position for each treatment.

The standard prescribed protocol for the HDR-ICBT treatment requires a minimum total dose of 15 Gy to point A, achieved in 4-6 fractions.

2.5 Dose effectiveness of fractionation schedules

The use of HDR brachytherapy initially faced criticism and concerns with regard to its effectiveness and late toxicity. However, over the past few years, numerous published studies have demonstrated comparable local control, survival and morbidity with HDR when compared with LDR (Shakespeare et al. 2006: 278). A study on HDR vs. LDR by Falkenberg et al. (2006) confirmed equivalence in pelvic control, cause-specific survival and overall survival, as well as late morbidity between LDR and HDR brachytherapy (Falkenberg et al. 2006: 54). The following are some results reported in the literature on the clinical outcome of different institutions when using HDR-ICBT in combination with EBRT in their treatment schedule for uterine cervical cancer patients.

In 1991, Lanciano et al. (1991) reported their findings on pre-treatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix (Lanciano, Won & Coia 1991: 667-676). Lanciano et al. (1991) compared the outcome of the 1973 and 1978 Patterns of Care surveys. It indicated that on 1558 patients treated using EBRT with or without low dose-rate brachytherapy at different institutions throughout the United States, no dose-response relationship was seen to a dose at point A of < 75, 75-85, or > 85Gy in stage I and II disease. Although a dose-response relationship was seen with a dose > 85 Gy in stage III disease, a dose > 85 Gy was also associated with higher rate of complications.

A retrospective study was done by Chen et al. (2000) to see whether patient, treatment and dosimetric factors could be correlated to the risk of

developing late rectal complications in patients with uterine cervical cancer. The fractionation schedule consisted of EBRT of 40-44 Gy/20-22 fractions given within 4-5 weeks to the whole pelvis, after which the dose was boosted up to 54-58 Gy with central shielding. HDR-ICBT consisted of 3-4 insertions at doses of 5-7.2 Gy and the cumulative rectal biologic equivalent dose was calculated. The study indicates that patients who have stages IIb-IVa disease, a cumulative rectum dose greater than 65 Gy, or who are of 70 years of age and older, are at risk for late rectal sequelae and should be adequately assessed so that the treatment dose can be adjusted to prevent late rectal complications (Chen, Liang, Yang, Liu & Lin 2000: 960).

The Brazilian Experience of Ferrigno et al. (2001) is based on the analysis of dose effectiveness and late radiation complications. One hundred and thirty-eight patients with FIGO stages II and III were treated with 45 Gy of EBRT in 25 fractions and HDR brachytherapy was performed during EBRT with a dose of 24 Gy in 4 weekly fractions of 6 Gy to point A. The overall survival, disease-free survival and local control at 5 years was 53.7%, 52.7%, and 62%, respectively. The five-year actuarial incidence of rectal, bladder and small bowel late complications was 16%, 11% and 14%, respectively. Patients treated with a cumulative BED at rectum points above 110 Gy_3 had a higher but not statistically significant five-year actuarial rate of complications at these organs (Ferrigno, dos Santos, Pellizon, Maia, Fogarolli, Gentil & Salvajoli 2001: 1123).

Sood et al. (2002) reported on the predictive value of the linear quadratic model in the treatment of cervical cancer using HDR brachytherapy. In this retrospective study 49 patients were treated with EBRT of 45 Gy (1.8 Gy/fraction) to the whole pelvis and HDR-ICBT consisting of a total of 18-19 Gy given in 2 fractions of 9-9.5 Gy. Twenty-three patients received concomitant cisplatin-based

chemotherapy. The report indicated that in patients treated with radiotherapy alone, a BED10>89 Gy indicated a trend toward a better local control rate. This difference was not observed in patients receiving chemotherapy. A BED3<100 Gy_3 was associated with negligible late toxicity. The 4-year local control rate was 80% and 83% and disease-free survival rate of 75% and 70% with and without chemotherapy, respectively (Sood, Garg, Advadhani, Gorla, Malhotra, Guha, Deore & Vikram 2002: 1377)

Another analysis was performed by Toita et al. (2003) on dose effectiveness and fractionation schedule. Eighty-eight patients with cervical cancer were treated with EBRT of 2 Gy/fraction to a total dose of 40 Gy, and HDR-ICBT was performed once a week with a total point A dose of 18 Gy. The three-year actuarial pelvic control rate was 82% for all 88 patients: 96% for early stage and 76% for advanced disease. No significant dose-response relationship was observed by the treatment schedule and cumulative BED at point A for both early and late disease. All patients treated with 86.4 Gy_{10} at point A suffered both proctitis and enterocolitis. Patients with cumulative BED at rectal point ≥ 100 Gy_3 had a significantly higher incidence of proctitis (Toita, Kakinohana, Ogawa, Adachi, Moromizato, Nagai, Maehama, Sakumoto, Kanazawa & Murayama 2003: 1344).

The report published by Wang et al. (2004) compared two linear quadratic model-based iso-effect fractionation schemes of HDR brachytherapy for cervical cancer. Five hundred and forty-one women were categorised into two groups according to the two iso-effect schemes used. Group 1 consisted of 254 patients treated with EBRT plus 7.2 Gy HDR-ICBT to point A for three fractions. Group 2 consisted of 284 patients treated with EBRT plus 4.8 Gy HDR-ICBT for five fractions. Overall, 66 patients developed pelvic recurrence. Of these, 53 patients had central recurrence:

24 (9.4%) were in group 1 and 29 (10.1%) in group 2. The actuarial survival rate for Groups 1 and 2 was 63.5% and 56.1% at five years and at ten years 47.8% and 49.3%, respectively. The incidence of high-grade complications remained unchanged, 8% vs. 7%. Multivariate analysis revealed that the fractionation scheme (three fractions vs. five fractions) was a significant factor influencing the proctitis rate, but not the local pelvic control rate, overall survival rate, or cystitis rate. The report concluded that the treatment results of the two groups showed similar outcomes while the complications decreased, and that the linear quadratic model correctly predicted the outcome. Biologically, the manipulation of the fraction size in their study suggested that the sensitivity of the late responding tissue to the fractional change from 7.2 Gy to 4.8 Gy in HDR-ICBT is high and detectable clinically (Wang, Huang, Sun, Chen, Fang, Hsu, Changchien & Leung 2004: 179). The cumulative BED for these published studies correlates well for local tumour control Gy_{10} (range: 80-100 Gy_{10}) and for negligible late toxicity Gy_3 (range: 100-120 Gy_3).

Although HDR brachytherapy has been used for more than 30 years in the treatment of uterine cervical cancer, the optimal time, dose and fractionation have yet to be established through systemic clinical trials (Sood et al. 2002: 1377). Toita et al. also stated that an optimum treatment schedule has not yet been clearly determined (Toita et al. 2003 : 1344). Regarding the results reported by all the above-mentioned authors on dose effectiveness of the different fractionation schedules for EBRT and HDR-ICBT, it is still unclear as to which schedule is the optimum fractionation schedule.

2.6 Biology of HDR brachytherapy

The primary disadvantage of HDR brachytherapy is of radiobiological concern. The high dose-rate leading to short treatment times does not

allow for the repair of non-lethal damage in normal tissue, or the redistribution of cells in the cell cycle, or re-oxygenation of the tumour cells; hence, multiple treatments are required (Nag 2004: 620). The radiobiological disadvantage can, however, be overcome through adequate fractionation, e.g. 4/5 fractions of 2 Gy/fraction prescribed to the highest rectum dose point, which is the treatment protocol used in this retrospective study.

Radiobiologically, the change from low dose rates to HDR requires a reduction in overall dose and the introduction of fractionation. Fractionation introduces logistic problems for brachytherapy because multiple treatment exposures of HDR radiation, 24 hours apart, require either repeat implant procedures or a very stable, carefully verified implant remaining in situ for the duration of the fractionated treatment. Appropriate dose reductions have also been required, and the considerable range of schedules used for HDR brachytherapy reflects the uncertainty in this area (Hoskin & Bownes 2006: 209).

To achieve tumour control with HDR equivalent to that with LDR brachytherapy, attention to the dose/fraction schedule and to normal tissue doses is mandatory. In general, the α/β values for tumour and early-responding tissues are approximately 10 (Gy_{10}) and for late-responding tissues 3-5 (Gy_{3-5}). The values derived are not actual doses but biologically effective ones that take into consideration dose-rate and impact of fraction size (Perez & Kavanagh 2004: 1839).

Figure 2.1 illustrates late damage, which is proportional to log cell kill, and the relationship of late damage to the number of HDR treatment fractions. Each full curve is calculated assuming the same log cell kill. Late damage rises sharply as the number of HDR fractions is decreased. When these curves are above the dashed lines that represent the maximum late effect

of 70 Gy of LDR brachytherapy given at 0.5 Gy/h, the risk of late complications increases. Displacing the bladder and rectum away from the HDR sources for the short duration of brachytherapy can offset the radiobiological disadvantage of using a few brachytherapy fractions (Perez & Kavanagh 2004: 1839).

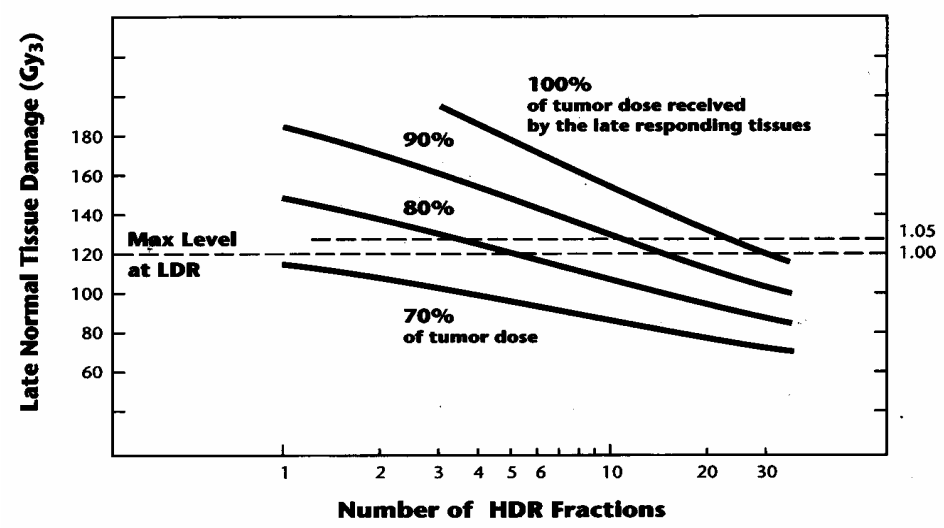

Figure 2.1 Relationship between number of HDR fractions and late normal tissue effects (Perez & Kavanagh 2004: 1839). (Permission to use above figure has been duly granted.)

Each center has developed unique HDR treatment schedules, dose specification systems and time-dose fractionation protocols that reflect their understanding of radiobiological issues and their patient population base (Perez & Kavanagh 2004: 1840). To achieve tumour control with HDR equivalent to that with LDR brachytherapy, attention to the dose/fraction schedule and to normal tissue doses is mandatory (Hall & Brenner 1991: 1403). An analysis of 1 054 patients showed that patients exhibiting complete tumour regression within 30 days after completion of radiation therapy had not only a substantially lower number of pelvic recurrences but fewer distant metastases (Perez & Kavanagh 2004: 1858). The analysis emphasises the need to deliver biologically effective doses of irradiation to ensure the highest probability of controlling the

tumour in the pelvis because the salvage rate in patients who present with isolated pelvic recurrences is not optimal even after pelvic exoneration.

In parallel with the technical developments in intracavitary brachytherapy, advances have been made in the understanding of how tissues respond when altered by radiotherapy treatments. Work in the field of radiobiology has produced mathematical models which attempt to predict the response of tissues to changes in treatment (Deehan & Donoghue 1994: 21).

2.7 Time-dose models

Various formulas for the comparison and effectiveness of different radiation regimes have been developed with clinical experience as guideline. These formulas were an attempt to quantify the influence of dose fractionation, dose-rate and total treatment time on tolerance doses of various normal tissues (Ellis 1969: 2). Early iso-effect models such as the Nominal Standard Dose (NSD), Time Dose Factors (TDF) or the Cumulative Radiation Effect (CRE) models, which did not distinguish between acute and late reactions, have given way to a more sophisticated formulae, for example, the linear quadratic (LQ- model) (Fowler 1992: 16-21).

Since the 1980`s the NSD approach has been largely replaced by the LQ approach, which is based on a biophysical model relating cellular survival to absorbed dose (Williamson & Brenner 2004: 520). These new models reflect the fact that different tissues react in different ways to changes in treatment schedules. The LQ model has proved to be a reliable means of comparing different schedules in both fractionated and continuous radiotherapy (Deehan & Donoghue 1994: 21). This is the best available model for the quantitative assessment of clinical problems, primarily because it allows distinction to be made between the fractionation and

dose-rate sensitivities of early and late responding tissues (Clark et al. 1997: 989).

The linear quadratic model, originally applied to fractionated radiotherapy by Fowler and Stern in 1960, was refined and expanded by Barendson in 1982 and Dale in 1985, and its use has been reviewed by Fowler (Fowler 1992: 16). The basic equation defines the amount of radiation damage, E, resulting from *n* high dose-rate fractions of size *d* **- equation 1:**

$$\mathbf{E = \mathit{n}\,(\alpha \mathit{d} + \beta \mathit{d}^{2})}$$

where two coefficients, α and β are constant and their ratio, α/β, is an inverse measure of fractionation sensitivity or recovery capacity, characteristic of a particular tissue (Clark et al. 1997: 990). The biologically effective dose (BED) is defined by the **equation 2:**

$$\mathbf{BED = E/\alpha = \mathit{nd}\,(1 + \frac{d}{\alpha/\beta})}$$

In general, the α/β values for tumour and early-responding tissues is approximately 10 (Gy_{10}), and for late-responding tissues 3 to 5 ($Gy_{3\text{-}5}$) (Petereit & Pearcey 1999: 360). The values derived are not actual doses, but biologically effective ones that take into consideration dose-rate and impact of fraction size.

The dose effectiveness in this study is analysed retrospectively according to the calculated BED values of the combination of EBRT and HDR-ICBT for FIGO stages I-III uterine cervical cancer patients. In the determination of total BED, the EBRT and HDR-ICBT components have been summed with all calculations using the same value of the ratio α/β. The BED values to the tumour Gy_{10} and the rectum Gy_3 is calculated by using the LQ-model.

For a prescribed tumour dose of 46 Gy EBRT in 23 fractions and 30 Gy HDR-ICBT in 3 fractions, the total BED to the tumour corresponds to 115 Gy_{10} where the subscript is the value of α/β used in the calculation, emphasising that, although the dimensions are those of dose, this value is an effective dose rather than an absolute dose. If the rectal reference point also received the prescribed tumour dose, the total BED to this point would be 207 $Gy_{3,}$ reflecting that in this tissue, the response is characterised by an α/β of 3 Gy. The variation in the dose received at the rectal reference point amongst the 43 patients analysed in a study arose almost entirely from the HDR-ICBT insertions as a result of variation in individual anatomy (Clark, Souhami, Roman & Evans 1994: 1243-1250).

According to the LQ model, the natural logarithm of cell-surviving fraction of cells irradiated at a dose-rate R (Gy hr) in time t (hours) is given by the formula: ln S = (Rt) + G (Rt), where α and β are parameters that present the probabilities of irrepairable (α-type) and repairable (β-type) damage. The parameter G signifies the reduction in β-type damage resulting from repair during or immediately after an exposure. Rearranging this equation and dividing both sides by α leads to the formula for the biologically effective dose (BED), where the single parameter α/β represents the curviness of the log cell-survival curve. The α/β parameter indicates the sensitivity of a given tumour or organ to changes in dose per fraction or dose-rate. The parameters α and β (the linear and quadratic sensitivity coefficients in the LQ equation) respectively determine the initial slope and degree of downward curvature of the underlying cell survival curve (Joiner & van der Kogel 1993: 106-122). A cell-survival curve with a large curvature means that the dose in the equation mentioned is very important. If, β is relatively high, the α/β is low. This is typical of late-responding normal tissue cells, for which α/β values are usually in the range of 1 to 4 Gy (Nag 2004: 610). However, if the log cell-survival curve is fairly straight, α-type damage predominates and α/β is large. This is

typical of tumour and early responding normal tissue cells, for which α/β values are usually in the range of 5 to 20 Gy.

2.8 Treatment techniques and dose specifications

Based on clinical experience, different systems have been proposed for the treatment of uterine cervical cancer. Three basic systems have been developed: the Stockholm system (Kottmeier, 1964), the Paris system (Lamarque and Coliez, 1951) and the Manchester system (Patterson, 1948).

At the Department of Oncotherapy, Bloemfontein, the HDR-ICBT planning is based on the Manchester system to treat patients diagnosed with uterine cervical cancer. The Manchester system (Patterson & Parker 1934) derived from the original Paris system, initiated in about 1920, was designed to deliver a constant dose to defined points near the cervix, irrespective of variation in size and shape. An application was specified in terms of the "dose" in roentgens delivered at specific points such as point "A" and "B" Figure 2.3.

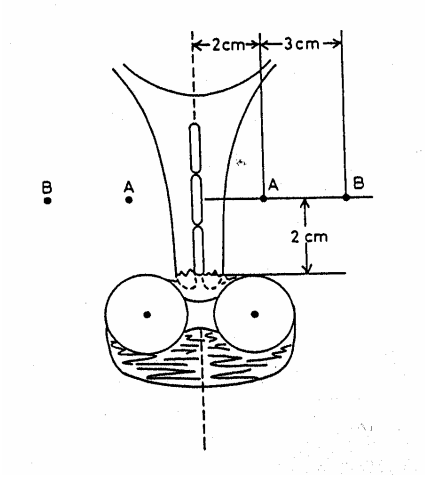

Figure 2.2 Manchester system definition of points "A" and "B" (ICRU 1985: 2).

Originally point A was defined as a point 2 cm superior to the lateral vaginal fornix and 2 cm lateral to the cervical canal. It was later redefined as 2 cm superior to the external cervical os (or cervical end of the tandem) and 2 cm lateral to the cervical canal. Points “A” and “B” are still widely used throughout the world, although their exact meaning and their definition have not always been interpreted in the same way in different centers and even in a given center over a period of time. The International Commission on Radiation Units and Measurements (ICRU 1985: 2) defines point A as 2 cm lateral from central canal of the uterus and 2 cm superior from the mucous membrane of the lateral fornix of the cervix, in the axis of the uterus. Point B is defined in the transverse axis through point A, 5 cm from the midline (3 cm lateral from point A (ICRU 1985: 2).

In particular, some centers relate point A to anatomical references in the patient, others to the geometry of the sources. At the Department of Oncotherapy, Bloemfontein, treatment planning of HDR-ICBT is done by prescribing 2 Gy/fraction to the highest rectum dose point and normalising it to point “A” which is an anatomical reference point in the patient. Thus the dose to clinical points A would vary as a function of the distance to the maximum rectum dose point. The standard prescribed protocol for this study for HDR-ICBT was a minimum total dose of 15 Gy to point A in 4-6 treatments of 2 Gy/fraction. Point A is defined as a point 2 cm lateral to the central canal of the uterus and 2 cm superior from the mucous membrane of the lateral fornix, in the axis of the uterus.

Computer-generated isodose curves provide the best means of determining the doses to point A, point B, bladder and rectum. The rectum position of every fraction given will thus determine the dose to point A for each treatment fraction. Special attention should be paid to obtaining as symmetrical and homogenous dose distribution as is technically allowed by the geometry of the cervix/vagina and the configuration of the tumour

with the use of a rectal retractor in the vagina. Computerised optimisation of source position and the dwell time for each position is an advantage of HDR brachytherapy in that it can provide customised treatment planning on a case-by-case basis. Achieving an optimal dose distribution with HDR-ICBT requires both accurate insertion of the appliance and accurate optimisation. It should be realized that incorrect optimisation is worse than no optimisation at all (Nag et al. 2000: 205). The advantages of computer-aided planning at ICRU reference points are that calculations are available before HDR-ICBT treatment and that they can still be taken into account for treatment planning (ICRU 1985: 5). The ICRU made the recommendation for absorbed-dose patterns and volumes that information should include type of applicator used during brachytherapy, type of source, how it was loaded and the verification film of the application.

With HDR-ICBT treatment the dose is at its maximum adjacent to the source and at the centre of the treatment volume and it falls off continuously with distance from the sources. Consequently, the size of the treatment volume cannot be deduced from a simple inspection of the isodose pattern. Therefore, the radiotherapist has to indicate which dose level defines the treatment volume (ICRU 1985: 5).

Assuming that the Manchester definition of point A is used, this will be the location where there is least variation in the dose-rate from one source arrangement to another one. In the classical Manchester system, point A is defined (as previously mentioned) as a point 2 cm lateral to the central canal of the uterus and 2 cm superior from the mucous membrane of the lateral fornix, in the axis of the uterus. In clinical practice, dose calculations are often made from radiographs and point A is taken 2 cm superior from the flange of the intra-uterine source and 2 cm lateral from the central canal as indicated in Figure 2.3 (ICRU 1985: 2).

2.9 Late complications of organs at risk

Organs at risk are those radiosensitive organs in or near the target volume that would influence treatment planning and/or the prescribed dose. In an intracavitary application for uterine cervical cancer, the main organs at risk are the rectum, bladder, ureters and possibly sigmoid colon (ICRU 1985: 8).

The sites of radiation-related complications which are most frequently noted in uterine cervical cancer radiotherapy are: (a) rectum – the anterior rectal wall most commonly; (b) bladder – the posterior bladder wall most commonly; (c) vaginal vault; (d) sigmoid colon; (e) small bowel – the terminal ileum or multiple sites may be affected; (f) abdomen – diffuse multistructure problems may be encountered; (g) ureters – stenosis my occur in the paracervical region; (h) skin and (i) bone and hip (Maruyama, Van Nagell, Utley, Vider & Parker 1974: 700). In each of these sites, advancing tumour stage greatly increases the likelihood of complications. It is difficult to define tolerance dose when a combination of external and brachytherapy is used. Although stage, age and other disease will naturally modify the number and frequency of complications, it should be expected to increase as a function of delivered dose (Maruyama et al. 1974: 700).

Rectal complications have long been the major concern when applying radiation therapy to treat patients with uterine cervical cancer. Efforts are underway to determine the dose to the rectum to reduce the incidence of such complications. However, the risk analysis of rectal complications is difficult because of the variations in the combined EBRT and HDR-ICBT, the multitude of dosimetric descriptions and the complexity of the anatomy. The highly inhomogeneous dose distribution within the pelvis renders the definition of certain doses difficult, and reliable estimates of tolerance levels have not been established. The distance between the

applicators and the recto-sigmoid region may vary with each insertion as a result of individual technical skills and various motilities of the bowel (Cheng, Peng, Chen, Huang, Wu & Jian 2003: 1016).

The ICRU Report 38 recommends a reference point for specification of the absorbed dose to the rectum (ICRU 1985: 11). According to the ICRU report the rectal reference point is defined in the lateral projection of the applicators on an AP line drawn from the distal end of the uterine source or the middle of the ovoid sources. However, several authors have demonstrated the maximal rectal dose points to be located at positions other than the ICRU reference point.

Chung et al. calculated both the maximal rectal dose to the anterior rectal mucosa identified by contrast medium and the ICRU reference rectal dose. They obtained a significant relationship between the occurrence of late rectal complications and both types of rectal doses. The maximal rectal point dose estimated by contrast medium was greater and correlated better with late complications than did the strictly defined ICRU rectal dose (Chung, Kim & Suh 1996: 319). Therefore the maximal rectal dose point estimated by contrast medium is used at the Department of Oncotherapy, Bloemfontein.

Cheng et al. reported in 2003 on the unique role of the proximal rectal dose in late complications for patients with uterine cervical cancer undergoing HDR-ICBT in combination with EBRT. They concluded that the radiation dose to the proximal rectum plays a more prominent role in predicting late rectal complications in patients with uterine cervical cancer undergoing HDR-ICBT. The importance was established by the greater dose at the proximal rectal point, as estimated by use of rectal contrast medium, than at the ICRU reference rectal point in 89% of patients. The use of contrast medium to delineate the rectal wall up to rectosigmoid

level should be emphasised. Cheng et al. (2003) recommend rectal dose constraints of ≤ 62 Gy in the direct sum of EBRT dose and HDR-ICBT, ≤ 110 Gy for the BED, and a maximal rectal dose/point A dose ratio of ≤ 0.9 (Cheng et al. 2003: 1016).

To evaluate the crude incidence of late complications of organs at risk after radiotherapy, the Late Morbidity Scoring Criteria were developed as a joint effort between physicians with renewed interest in fast neutron therapy and Radiation Therapy Oncology Group (RTOG) staff. Investigators from the European Organisation for Research and Treatment of Cancer (EORTC) wished to have common toxicity criteria in anticipation of joint studies. RTOG Protocol 7929, an international registry of patients treated with heavy particles, was started in 1980. Winchester and Cox published an abbreviated version of the RTOG/EORTC toxicity criteria in 1992 (Cox, Stetz & Pajak 1995: 1341). Table 2.2 shows the RTOG/EORTC Late Radiation Morbidity Scoring Scheme which will be used in this retrospective study to grade the late radiation complications of organs such as the rectum and the bladder of uterine cervical cancer patients.

Table 2.2 Crude incidence of late complications according to RTOG/EORTC-late radiation morbidity scoring scheme (Cox et al. 1995) (0 means an absence of radiation effects and 5 means the effects led to death)

SITE	**RECTUM**
GRADE 0	None
GRADE 1	Increased stool frequency, Occasional blood-streaked stool, or Rectal discomfort (including haemorrhoids)
GRADE 2	Increased stool frequency, Bleeding, mucus discharge, or Rectal discomfort and anal fissure
GRADE 3	Increased stool frequency/diarrhoea, Rectal bleeding, mucus discharge
GRADE 4	Perforation, bleeding or necrosis Or other life-threatening complication

SITE	BLADDER
GRADE 0	No change from baseline
GRADE 1	Slight epithelial atrophy/minor Telangiectasia (microscopic haematuria)
GRADE 2	Moderate frequency/ Generalised telangiectasia/ Intermittent macroscopic haematuria
GRADE 3	Severe frequency and dysuria/severe Generalised telangiectasia; frequent Haematuria; reduction in bladder capacity
GRADE 4	Necrosis/contracted bladder/ Severe hemorrhagic cystitis

2.10 Future developments

The dramatic advances in technology in the last 2 decades have impacted on the practice of brachytherapy in 2 main areas; viz. treatment delivery and treatment planning.

Changes in brachytherapy treatment delivery have evolved partly through changes in the source availability and through a wide-spread move from manual systems to remote afterloading brachytherapy systems. In developed countries, radium is no longer used, and cesium sources are increasingly being decommissioned to be replaced by high dose-rate (HDR) iridium 192 afterloading machines (Hoskin & Bownes 2006: 209). The change from low and medium dose-rate systems delivering a radiation dose at dose rates of around 1 to 1.5 Gy/h to HDR systems delivering doses at a dose-rate similar to a modern linear accelerator, around 1 Gy/min, has resulted in important changes in the way in which brachytherapy is used (Hoskin & Bownes 2006: 209).

Until recently, brachytherapy planning and dosimetry was based on fixed rules and fixed source geometries to achieve dose homogeneity within a planned volume. This was often based on the traditional schools of Manchester dosimetry and the Paris rules for interstitial therapy, which

had served well for many years (Hoskin & Bownes 2006: 2100). Often, however, they could not be fulfilled completely and even the most experienced brachytherapist will not always achieve a perfect implant with consequent adverse effects on dosimetry. The basis of gynaecological brachytherapy has for many years been the use of point A prescription points and organ-at-risk dosimetry limited to the ICRU rectal and bladder point estimates. Although a pragmatic approach, this is now seen to be anachronistic in the modern era of three-dimensional imaging. The conventions of EBRT, that define clinical target volumes and the organs at risk, and plan the target volumes, are slowly being embraced by brachytherapy (Hoskin & Bownes 2006: 210).

As fixed rules have been replaced by cross-sectional and three-dimensional planning, software systems and algorithms have become increasingly sophisticated. Computer-assisted dose calculations around a brachytherapy implant are generally now based on the American Association of Physicists in Medicine Task Group 43 formalism. Another recent technological advance is the development of three-dimensional image-based treatment planning systems. The more advanced systems on the market allow full image-based manipulation, contouring tools, and automated catheter reconstruction. Three-dimensional imaging using computed tomography (CT) scans, magnetic resonance imaging (MRI), ultrasound, or a combination of 2 modalities through image fusion has allowed for accurate target and critical organ delineation and improved applicator or source localisation (Hoskin & Bownes 2006: 210).

2.11 Conclusion

The literature review supports the use of HDR-ICBT in combination with EBRT as a curative modality in the management of uterine cervical cancer. The potential late toxicity of large doses per fraction can be

overcome through adequate fractionation. Studies have shown a reduction in the doses to sensitive structures such as the rectum and bladder make the probability of late complications with HDR brachytherapy comparable to that of LDR brachytherapy. A study done by Ferrigno et al. (2005), however, reported that fewer late rectal complications were observed in the HDR brachytherapy group than in the LDR brachytherapy group. These findings were probably the result of the relatively low HDR brachytherapy dose delivered to point A (Ferrigno et al. 2005: 1108). Analysis of world-wide reviews (retrospective studies as well as prospective randomised clinical trials) suggests that LDR and HDR treatments are probably equivalent in terms of survival, local control and morbidity. The methodology of the retrospective study used in treating uterine cervical cancer patients at the Department of Oncotherapy, Bloemfontein is discussed in Chapter 3.

CHAPTER 3

METHODOLOGY

3.1 Introduction

This is a retrospective study and a quantitative analysis of data captured by means of a data source form of patients treated at the Department of Oncothererapy, Bloemfontein for FIGO stages I-III uterine cervical cancer from January 1998 to December 2003. The methodology described in this chapter involves patient inclusion, the research tool that was designed and utilised, the calculations of the BED to the tumour and the rectum, the retrospective scoring of the late radiation complications and the statistical analysis of the retrospective study. The context of EBRT, HDR-ICBT and treatment planning describes the generic treatment procedure that was followed for each patient in the study. The sequence of events is described to illustrate the background to the methodology of this study.

3.2 Research design

This research design is a formal study which involves precise procedures and data source specifications, but it also has an element of exploration in calculating the biologically effective doses for the treatment schedule. The study was based on an *ex post facto* design, which means that the researcher can only report on the results of the analysis of those data which were captured by the radiation oncologists, medical physicists and radiation therapists during patients` radiotherapy treatment. Analytically, the study has a longitudinal design, given that the efficiency is analysed for specific years, as well as over a period of time (Cooper & Schindler 2005: 146-149). It is a statistical study that will generate results that can

be incorporated into the current treatment schedule (EBRT & HDR-ICBT) for cervical cancer patients.

3.3 Patient selection

A list of patients that were treated with EBRT and HDR-ICBT for cervical carcinoma (FIGO stages I-III) was obtained from the HDR-ICBT statistics book at the Department of Oncotherapy, Bloemfontein. Between January 1998 and December 2003, 696 patients with histologically proven carcinoma of the cervix were treated with curative intent at the Department of Oncotherapy, Bloemfontein. These patients` files were analysed to select the patients who would fit the inclusion criteria for the study. Tables 3.1 & 3.2 show the criteria used for patient inclusion and exclusion.

Table 3.1 Criteria for patient inclusion

1. Patients treated at the Department of Oncotherapy, Universitas Annex, Bloemfontein, for cancer of the cervix.
2. Patients who received only radiotherapy (EBRT & HDR-ICBT) as treatment modality.
3. Patients with FIGO stages I-III.
4. Patients with a minimum of a two year follow-up record for analysis of late radiation complications.

Table 3.2 Patient exclusion details

1. Patients with no positive histology and/or uncertainty about the treatment received.
2. Patients not treated in Bloemfontein and whose treatment details were unavailable, incomplete or impossible to interpret.

Table 3.2 continues

3. Patients who had a hysterectomy before radiotherapy.
4. Patients who were treated from 2002 with radiotherapy and chemotherapy or were part of clinical trials.
5. Patients without a two-year follow-up examination.
6. Patients who had their follow-up examinations in other provinces e.g. Northern Cape & Lesotho.
7. Patients whose EBRT- CT plans were not stored on CD records/ tapes.
8. Patients who received no therapy at all, because they stayed away or because of the advanced stage of the disease.
9. Patients excluded for non-medical reasons, refused treatment, or did not complete radiotherapy because they disappeared and could not be traced.

After applying the exclusion criteria, the initial 696 patients of the study were reduced to a sample of 94 patients (See the reasons in Table 4.2).

3.4 External beam radiotherapy

The technique used was by four-field-box with anterior, posterior and two lateral planned fields with classic limits. The field extended superiorly to the L5-S1 interspace level and inferiorly to the obturator foramen. Laterally, the field extended 1cm beyond the bony margin of the pelvis at its widest point. The anterior and posterior borders of the radiation field is the plane of the anterior third of the symphisis pubis and the junction of S2/3, respectively. The radiation field size was determined and verified with simulation (AP-and LAT radiographs) and the patients were taken for computerised tomography. In patients treated with EBRT the dosimetry of the box field was calculated using computer-based software. Computerised isocentric planning was done on the CADPLAN Treatment

Planning System by using the computerised images of the patient`s pelvis so as to determine the planned-tumour-volume (PTV) for treatment Figure 3.1.

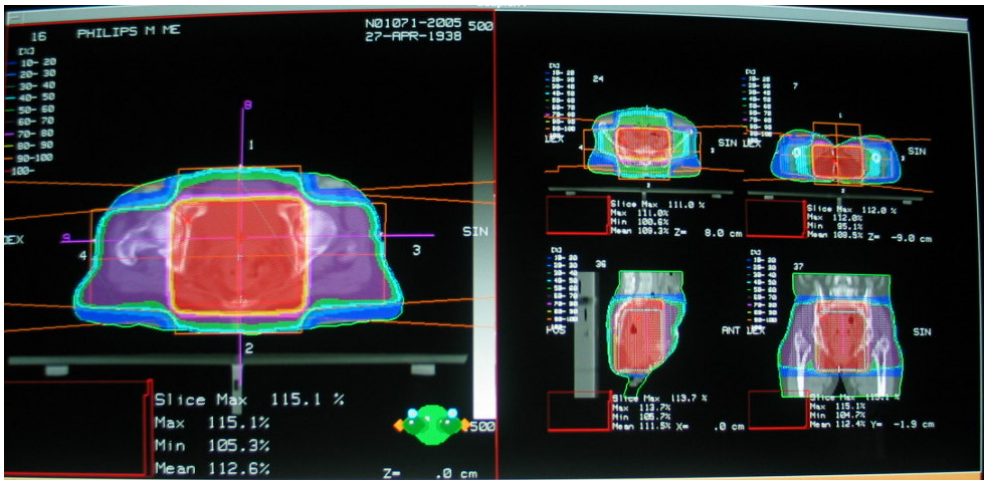

Figure 3.1 The "four field box" technique (Permission to use above figure has been duly granted.)

The relative doses given by EBRT vs. brachytherapy depend upon the initial volume of disease, the ability to displace the rectum, the degree of tumour regression during pelvic irradiation and institutional preference (Nag et al. 2000: 202). The standard prescribed treatment for EBRT at the Department of Oncotherapy, Bloemfontein, is shown in Table 3.3

Table 3.3 Treatment protocol for EBRT at the Oncotherapy Department, Bloemfontein (n=94)

EBRT-Dose per fraction	EBRT-no. of fractions	Total dose of EBRT
2 Gy/fr.	25 fr.	50 Gy

Abbreviation: fr = fraction

All the patients were treated with a dose of 50 Gy in 25 daily fractions of 2 Gy/fraction in 6 weeks. The total treatment duration was kept to less than eight weeks, because prolongation of total treatment duration can adversely affect local control and survival (Nag et al. 2000: 202). The

overall treatment duration would be unduly prolonged if the HDR-ICBT was started only after completion of EBRT, because multiple insertions are required for HDR-ICBT. Therefore, it was necessary to interdigitate the implants during EBRT (but EBRT was not given on the day of HDR-ICBT). Typically, if the vaginal geometry was optimal after two weeks of EBRT, HDR-ICBT was commenced once weekly.

3.5 High dose-rate – Intracavitary brachytherapy

All 94 patients were evaluated after the second week of pelvic EBRT regarding the anatomic and geometrical conditions of the cervix for HDR-ICBT treatment. If it was optimal, the patient could start with HDR-ICBT. A Nucletron Microselectron device delivering HDR-ICBT was used with an Ir^{192} source with a nominal activity of 10 Ci.

3.5.1 Insertion technique

Ideally the applicator insertion, simulation and treatment should take place in a dedicated brachytherapy suit to avoid unnecessary patient movement (Nag et al. 2000: 203). However, because of financial implications and the structural layout of the Department of Oncotheapy, Universitas Annex, the best option was to transfer patients from the simulator to the HDR-ICBT treatment room via a trolley. Every effort was made to minimise patient and applicator movement so that the dosimetry performed on treatment-planning radiographs matched patient and applicator position during treatment.

The insertion of the ring applicator was done at the simulator by an oncologist, assisted by a professional nurse and is the treatment procedure followed by the Department of Oncotherapy, Universitas Annex (and for this study). The patients were positioned in a supine position on the simulator-table on top of a pat slide. A pat slide (Figure 3.2) is an

apparatus used to assist in moving the patients from the simulator bed to a trolley, with minimum patient and applicator movement. Every attempt was made to minimise patient movement when transferring them to the treatment room.

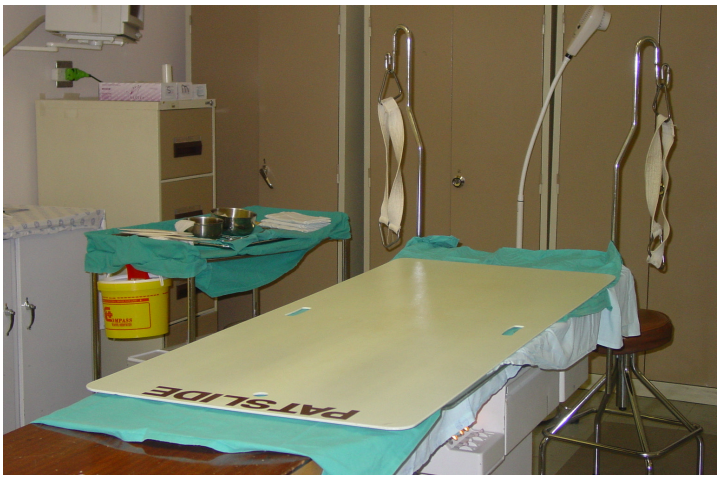

Figure 3.2 " Patslide "– Patient transfer apparatus

Conscious sedation was administered to the patients by the oncologist, whereafter the patients were positioned in the lithotomy position. Patient discomfort can lead to suboptimal packing and the inability to place the optimal applicator size, therefore conscious sedation was used for HDR-ICBT whenever possible and was administered by individuals who were properly trained and familiar with this approach. If the applicator position is not optimal, it can be very difficult to make applicator adjustments when the patient is not sedated and cannot be positioned in stirrups.

It was important to choose an applicator that could optimally treat the disease and could be placed in an anatomically distorted vagina. The applicator used for HDR-ICBT consisted of the ring applicator, which is available in two different angles, 60^{o} (Figure 3.3) and 45^{0} sets. Each ring applicator set consists of three components, inserted separately, and attached via connecting screws. The central applicators used are available in different lengths (2, 4 and 6 cm) and the ring applicators come in

different ring sizes (2.4, 3 and 3.4 cm) with plastic caps. It was important that the plastic caps of the ring applicator were in place with each insertion, because excessive vaginal mucosal doses would be delivered without them. Displacement of the rectum away from the applicator by means of an in-built rectal retractor prevented high doses being delivered to the rectum and thus minimised late complications to the rectum.

The applicator size for each insertion was determined by the vaginal geometry and tumour shrinkage of each patient. The applicator positioning and packing would be adjusted from fraction to fraction if there were any deficiencies in the initial insertions. Optimum applicator placement was critical in maximising local control and minimising complications. The ring applicator had to be positioned by the oncologist at the cervical os of each patient, because HDR-ICBT treatment planning was done to point A which is 2 cm lateral and 2 cm superior from the cervical os of each patient. The ring applicator was particularly useful when the vaginal fornices were asymmetric or absent and was easy to use because it has a reproducible geometry and was easy to insert.

A Foley`s catheter was inserted into the rectum and 20-40 ml of contrast medium (Barium) was slowly instilled into the rectum to demonstrate the anterior wall up to the rectosigmoid junction before radiographs were obtained. The patients were then positioned in the supine extended position in which the radiographs were taken. To avoid any discrepancy in normal tissue doses between patient positions, it was important to treat the patients in the same position as that in the localisation radiographs. The applicator device was fixed to the patient and the patslide via masking tape.

Anterior- (AP) and lateral (LAT) radiographs (Figures 3.3 & 3.4) were taken at the simulator with the patient in the supine extended position for

receiving HDR-ICBT. Good quality radiographs had to be obtained for treatment planning and dosimetry with each fraction. The position of the contrast outlined rectum was drawn in by the oncologist on the lateral radiograph, after which the patients were transferred from the simulator bed to a trolley and taken to the nearby HDR-ICBT treatment room where the Ir-192 Nucletron Microselectron afterloading system (nominal activity of 10 Ci) was connected to the applicators.

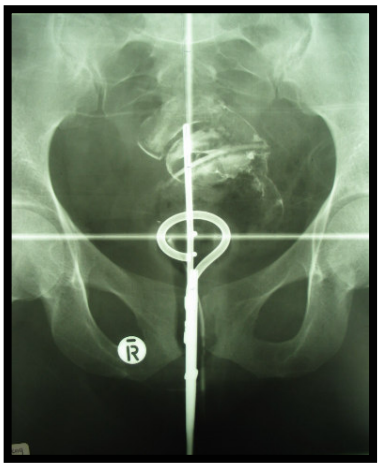

Figure 3.3 AP-radiograph

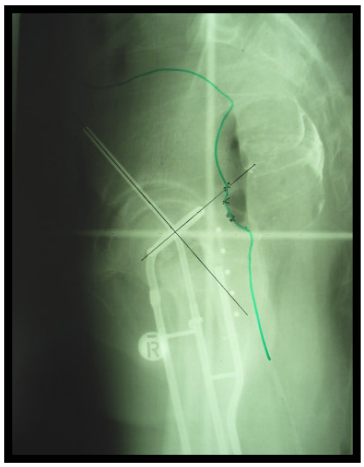

Figure 3.4 LAT-radiograph

3.5.2 Treatment planning

HDR-ICBT treatment planning was done by a medical physicist at the Department of Oncotherapy, Universitas Annex, using the computerised planning program PLATO SYSTEM 3.3.1, version 2, developed by Nucletron International BV, The Netherlands. The standard prescribed protocol of 2 Gy/treatment to the highest rectum dose point was prescribed by the oncologist. These rectum dose points were thus defined on the lateral radiograph and translated to the treatment planning system. The dose to point A was then normalised to the highest rectum dose point. Point A was defined on the radiographs as being 2 cm superior (along the central applicator) to the flange abutting external cervical os and 2 cm lateral from the axis of the central applicator (Figure 3.5).

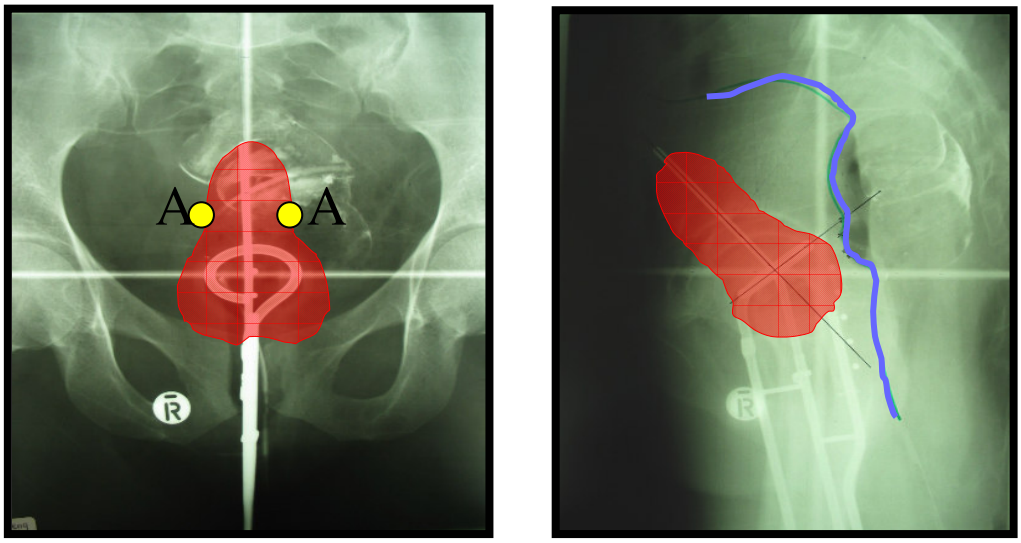

Figure 3.5 Point "A "

The dose to point A differed for each patient due to different rectum positions during each HDR-ICBT treatment. Thus the dose to clinical points A would vary as a function of the highest rectum dose point for each fraction given. Figure 3.6 demonstrates the change in rectum positions for each fraction given.

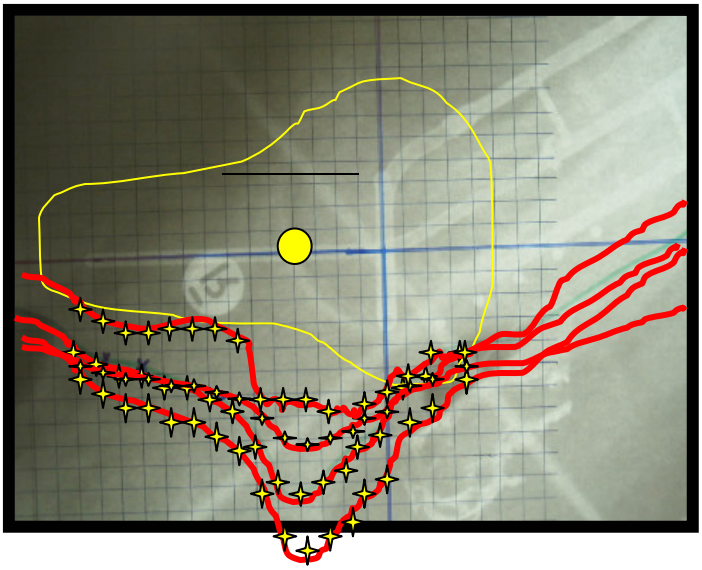

Figure 3.6 Different rectum positions drawn in by the Oncologist for every fraction given

The dose prescription for HDR-ICBT treatment protocol for all 94 patients is shown in Table 3.4. The total dose to point A was obtained by addition of the recorded doses to point A for each fraction given. A minimum total dose of 15Gy to point A was achieved through multiple HDR-ICBT fractions (4-6).

Table 3.4 Treatment protocol for HDR-ICBT at the Oncotherapy Department, Bloemfontein (n=94).

Dose per fraction	Number of fractions	Total dose to point A
2 Gy (2Gy/fr. normalised to the highest rectum dose point)	4-6 fr.	Cumulative recorded dose to point A (min. of 15 Gy)

Abbreviations: fr = fraction: GTV = gross tumour volume

Dosimetric planning of HDR-ICBT was performed in each application for all patients by a standard plan template, which is based on the definition of the Manchester System of point A. Standard plans were developed for each of the ring applicator sets (45^0 or 60^0 degree sets) in use, and source dwell times and positions were adjusted to suit the dose distribution required for each individual patient.

The position of the rectum relative to the ring applicator was defined on the lateral radiograph by the oncologist at the Department of Oncotherapy, Universitas Annex, and the dose distribution, calculated by the medical physicist for each individual patient, was normalised with respect to the maximum rectal dose. The rectal reference point according to the guidelines in the ICRU Report 38 (1985) was therefore not used. The lateral X-ray film, which verified the placement of the ring applicator in regard to the barium-outlined rectum, was used by the physicist to portray the rectum dose points in a 2D-projection, with the applicator shapes used in the standard plan templates to perform the dosimetric plan. Pear-shaped distributions were required, therefore manual optimisation was

done. No planned optimisation was thus done and the prescribed dose was computed to point A. However, in some cases the dwell positions were altered from the standard plan template because of a dose escalation to the rectum caused by its position in regard to the central applicator. Figure 3.7 shows the standard calculated isodose distribution.

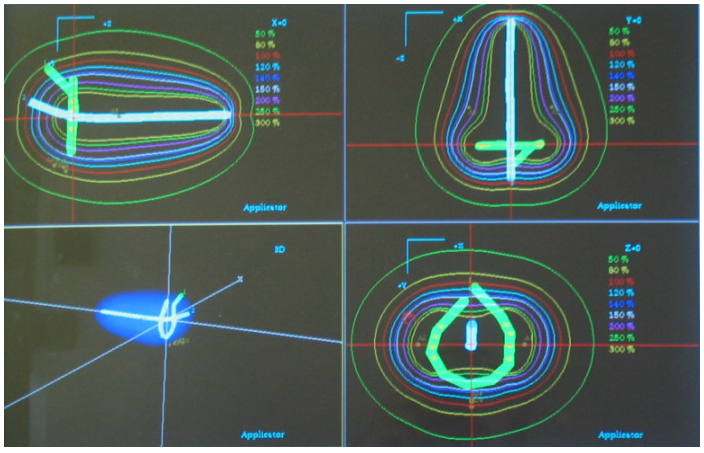

Figure 3.7 Isodose curves generated with fixed relative dwell weighting based on the Manchester System (Permission to use above figure has been duly granted.)

3.6 Calculations

The dose effectiveness of the fractionation schedule was analysed retrospectively by calculating the cumulative biologically effective dose (BED) of the combination of EBRT and HDR-ICBT for FIGO stages I-III cervical cancer patients.

Calculations of the biologically effective dose of the fractionation schedule were done by the Department of Biostatistics. On the basis of the LQ model, the cumulative biologic effective dose (BED) to the tumour and the rectum, generated from the contribution of EBRT and HDR-ICBT, was calculated for all patients. The biological effective dose was calculated to the tumour ($\alpha/\beta = 10$) and the rectum ($\alpha/\beta = 3$) for both EBRT and HDR-ICBT. The cumulative BED to the tumour for each patient was the sum of

the total EBRT midline dose (50 Gy) and the total point A dose of HDR-ICBT. The cumulative BED to the rectum for each patient was the sum of the EBRT dose, determined by dose-volume-hystograms (DVH), and a dose of 2 Gy/fraction prescribed to the highest rectum dose point for HDR-ICBT. The cumulative BED for the tumour (Gy_{10}) and the rectum (Gy_3) were calculated by using **equation 2** (See Chapter two – Time-dose models).

3.7 Research tool

A patient data source form was designed as a research tool to retrieve the relevant data for this study from the patients` radiotherapy treatment files and their follow-up notes (Appendix IA). All the necessary information was categorised under specific headings, making it easier to retrieve the relevant data for statistical analysis.

The data source form contained the patients` demographics; pre-treatment details such as FIGO staging; radiotherapy and brachytherapy details; the tumour and rectum doses; calculated BED values for EBRT and HDR-ICB. The follow-up details included the following: tumour recurrence and control, treatment received, scoring of late radiation complications according to the RTOG/EORTC scoring criteria; metastases and survival. Survival was measured from the first day of radiotherapy treatment to the last follow-up date/death.

A pilot study, using the designed data source form as research tool, was conducted on twenty patients` radiotherapy treatment files and follow-up notes to see if the data source form would be effective in retrieving the relevant information needed for analysis. The original data source form was altered after the pilot study was conducted. The FIGO stages of the patients were adjusted to accommodate all stages of the 94 patients

included in the study. Second and third late radiation complications were also added to the data source form. The data source form was proof-read by a statistician and an oncologist and no alterations were required.

3.8 Scoring criteria for late radiation complications

The retrospective scoring of the late radiation complications was done by the researcher using the information notes captured by the radiation oncologists during the patients` follow-up examinations. Late radiation complications were scored according to the RTOG/EORTC – late radiation morbidity scoring scheme (Cox et al. 1995). The criteria for scoring the late complications of the patients are summarised in Table 2.2.

3.9 Statistical analysis and follow-up

Statistics have a contribution to make in all phases of a research project from the planning, through the data analysis, the interpretation and discussion of the results, to their publication (Katzenellenbogen, Joubert & Abdool Karim 1999: 101). The researcher consulted a statistician to discuss the statistical aspects of the research project in the planning phase, as well as the analysis and writing phase of the thesis.

Results were summarised by frequencies and percentages (categorial variables) and means, standard deviations, median, minima and maxima (numerical variables). The software used was SAS 9.1.3 Service Pack 3. Survival analysis was used to determine the probability of recurrence, late complications and metastases at various time points. The cumulative BED values of the combination of EBRT and HDR-ICBT were investigated using the log-rank test based on survival analysis. The data collected for this retrospective study was processed by the Department of Biostatistics, University of the Free State, Bloemfontein.

The patients were followed-up by radiation oncologists by means of a clinical examination one month after radiotherapy had been completed. After that the patients were followed-up every three months for the first year and every four months for the second and third year. Follow-up procedures included a clinical (pelvic) examination and cervical Papanicolaou smears. When central and/or parametrial recurrence was suspected by pelvic examination and/or Papanicolaou smears, a biopsy was taken for confirmation. A chest radiograph was taken annually. Other imaging studies such as computer tomography, ultrasonography and bone scintigraphy were not routinely performed.

3.9 Conclusion

Although HDR brachytherapy for cervical cancer has been implemented for more than 30 years, there are still controversies regarding its efficacy and long-term side effects. Each institution should follow a consistent treatment policy, including complete documentation of treatment parameters and correlation with clinical outcome (pelvic tumour control, survival and complications) (Nag et al. 2000: 202). Chapter 4 shows the results obtained for this retrospective study using the fractionation schedule of EBRT and HDR-ICBT in treating patients with uterine cervical cancer at the Department of Oncotherapy, Bloemfontein.

CHAPTER 4

RESULTS

4.1 Introduction

This is a retrospective analysis of the dose effectiveness and the incidence of late radiation complications in the radical treatment of patients diagnosed with uterine cervical cancer. The objectives of the study were to calculate the BED values to the tumour and the rectum and to score the incidence of late radiation complications according to the RTOG/EORTC scoring criteria. These results, as well as other information gathered by the data source form regarding patient selection, patient demographics, tumour characteristics, tumour control, metastases and survival are reflected in this chapter. The layout of the results follows that of the data source form.

4.2 Patient selection

From January 1998 to December 2003, 696 patients diagnosed with FIGO stages I-III cervical cancer completed their radiotherapy treatment (EBRT and HDR-ICBT) at the Department of Oncotherapy, Bloemfontein. The treatment and follow-up details of these patients were analysed to select only those who would fit the patient selection criteria for this retrospective study (chapter 3). Table 4.1 shows the number of files with complete treatment and follow-up details which could be used for the study.

Table 4.1 Patient treatment files suitable for study

Year	Patients treated	Files of patients not suitable	Files of patients suitable
1998	70	62	8
1999	115	100	15
2000	157	147	10
2001	114	93	21
2002	100	88	12
2003	140	112	28
Total	**696**	602	**94**

From the information in the 696 patients` files which were analysed, 348 patients did not have their follow-up examinations in the Free State, 196 had follow-up periods of less than two years and 58 patients did not have complete dosimetric data. Therefore, 94 patients who had complete treatment and follow-up documentation and a minimal follow-up period of two years were included in the current study. The reasons for patient exclusion are shown in Table 4.2.

Table 4.2 Reasons for patient exclusion

Number of Patients	Reasons for exclusion
196	Follow-up < 2 years
348	Follow-up at other clinics in other provinces (Lesotho/Kimberley)
58	Incomplete dosimetric data

4.3 Patient demographics

The mean age of the 94 patients was 55 years (Std Dev. 9.5), the youngest patient being 26 years and the oldest 76 years of age. Table 4.3 illustrates the race groups involved of the 94 patients treated for uterine cervical cancer. The black population group dominated with 93 patients (98.94%).

Table 4.3 Summary of race groups treated (n=94)

Race	Number of patients	Percent
Black	93	98.94
Coloured	1	1.06
Total	94	

All 94 patients were tested for HIV/AIDS, of whom 87 (92.55%) were HIV-negative, while 7 (7.45%) patients were HIV-positive (Figure 4.1). Only one of the seven HIV-positive patients developed tumour recurrence (CD4-count = 480), while the remaining 6 patients had no tumour recurrence. The 7 patients who were HIV-positive had a median CD4-count of 398.5 (range: 60-720).

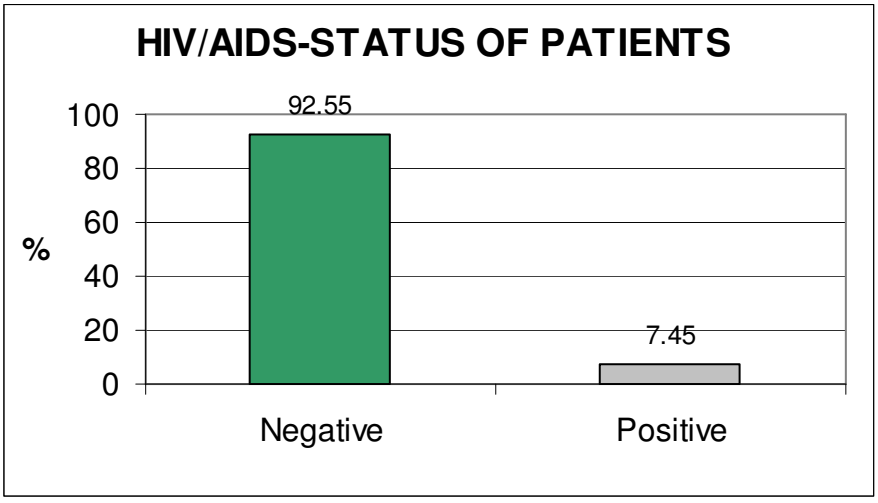

Figure 4.1 HIV/AIDS status of patients (n=94)

4.4 Tumor characteristics

All patients were staged according to the FIGO staging for uterine cervical cancer. The histology of cervical cancer is shown in Figure 4.2. Squamous carcinoma was dominant in 87 (92.55%) of the patients treated.

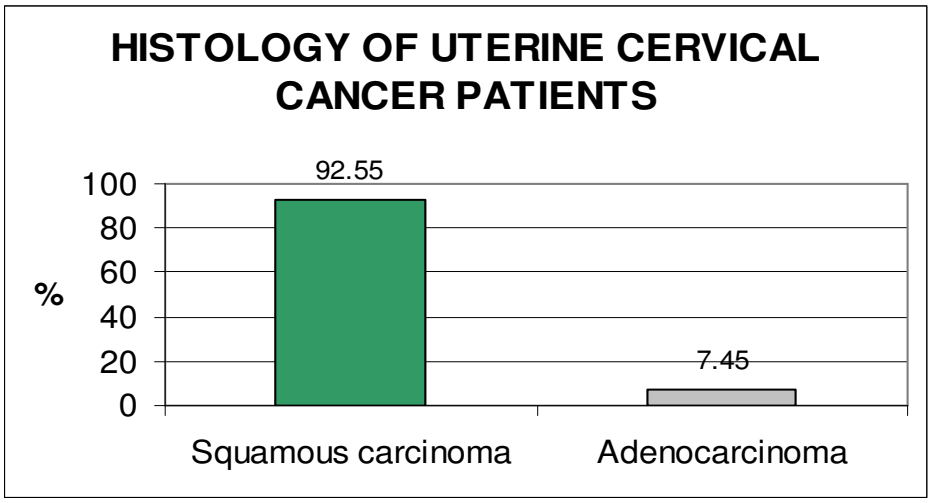

Figure 4.2 Histology of uterine cervical cancer (n=94)

Thirty-nine of the 94 cervical cancers were poorly differentiated, 33 moderately differentiated, 8 well differentiated and in 12 patients the tumour differentiation was not stated (Figure 4.3).

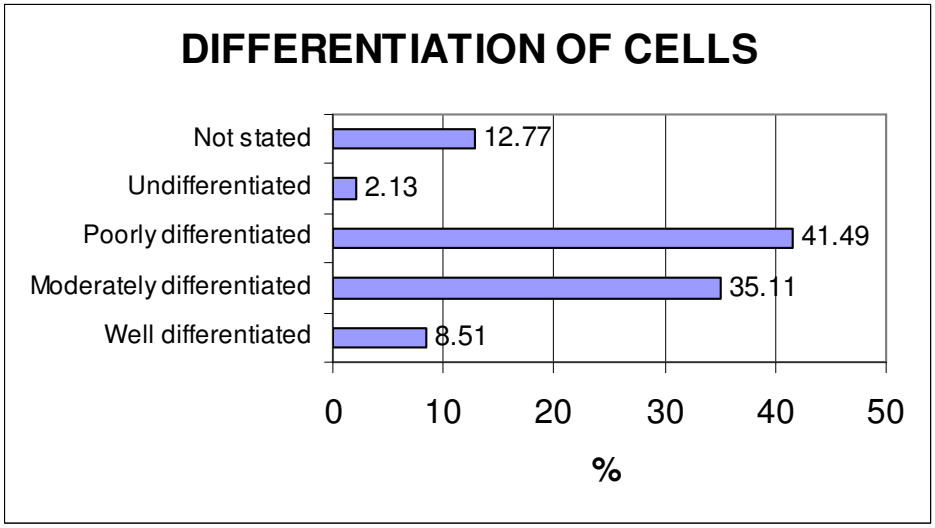

Figure 4.3 Differentiation of uterine cervical cancer cells (n=94)

The cervical carcinoma was also analysed according to the endophytic or exophytic appearances. Exophytic type of tumours were dominant in 52 patients and in 12 patients the tumour type was not stated (Figure 4.4).

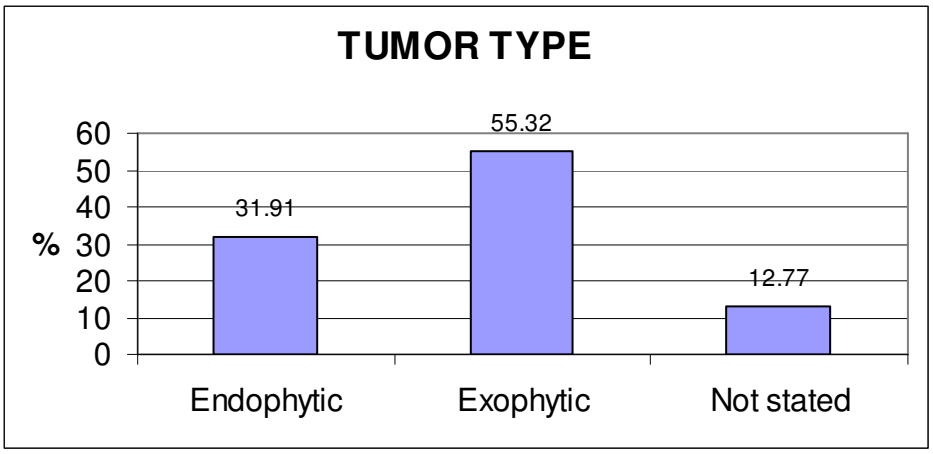

Figure 4.4 Endophytic/exophytic type of tumours (n=94)

The FIGO staging for the 94 cervical cancer patients is illustrated in Figure 4.5. Of the 94 patients, 43 were stage IIIb1, 27 stage IIb2, 12 stage IIb1 and only 1 patient was stage Ib. Clinically stage distribution of patients according to the FIGO criteria was as follows: Ib - 1 (1.05%), Ibl - 2 (2.13%), IIb - 3 (3.19%), IIbl - 12(12.77%), IIb2 - 27 (28.72%), IIIbl - 43 (45.74%) and IIIb2 - 6 (6.38%).

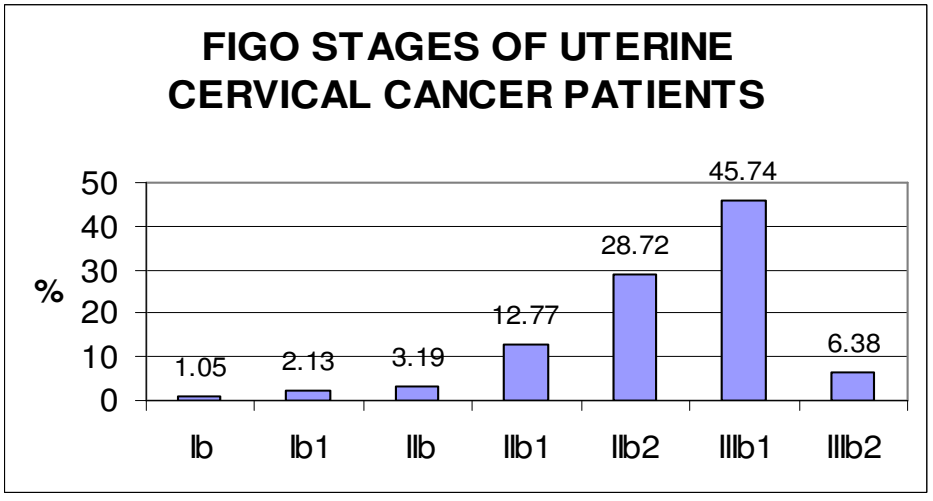

Figure 4.5 FIGO staging of uterine cervical cancer patients (n=94)

The cumulative BED values for EBRT and HDR-ICBT for all FIGO stages I-III cervical cancer patients is shown in Table 4.4. The majority of the

patients had a FIGO IIIb1 staging with a median cumulative dose of 86.01 Gy_{10} to the tumour and a median cumulative dose of 105.43 Gy_3 to the rectum.

Table 4.4 FIGO staging vs. cumulative BED values to the tumour and the rectum (n=94)

FIGO stage	Observations	Cummulative TUMOR BED_{10}	Cummulative Rectal BED_3
		Median	Median
Ib	1	88.5965	113.6959
Ib1	2	85.4123	107.4882
IIb	3	92.0848	109.0957
IIb1	12	89.1473	108.2454
IIb2	27	89.0645	105.6285
IIIb1	43	86.0190	105.4339
IIIb2	6	86.7146	105.5069
TOTAL	94		

4.5 Radiation therapy treatment

Radiation therapy consisted of a combination of EBRT and HDR-ICBT. The EBRT was given over a six week period and the 4-6 fractions of HDR-ICBT were interdigitated (once weekly) into the EBRT treatment schedule. The overall duration of treatment ranged from 32 to 60 days (mean, 41 days). The energy chosen to treat the patients for EBRT depended on the pelvic separation of the patients (larger patients-higher energy). Figure 4.6 illustrates that most of the patients (56) received their EBRT treatment via the 6-MV photon beam accelerator (ELEKTA SL 75/6).

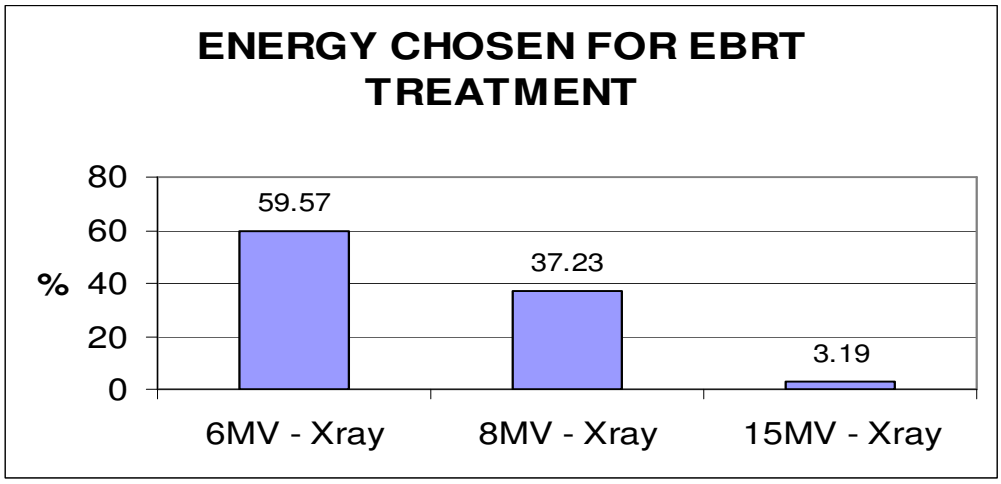

Figure 4.6 Energy chosen for EBRT treatment (n=94)

Patients received 4-6 fractions of HDR brachytherapy to obtain a minimum dose of 15 Gy to point A. Table 4.5 shows that (of the 94 patients) 70 patients had received 4 fractions of HDR-ICBT to attain a minimum total dose of 15 Gy to point A, with only one patient receiving six fractions of HDR-ICBT treatment. The point A dose differs for each fraction given, because of the change in the rectum position for each HDR-ICBT treatment.

Table 4.5 Number of fractions received for HDR-ICBT (n=94)

Number of HDR fractions	Number of patients	Percent
4	**70**	**74.19**
5	**23**	**24.73**
6	**1**	**1.08**
Total	**94**	

The standard prescribed dose for each HDR-ICBT treatment was 2 Gy/fraction, normalised to the highest rectum dose point. Therefore the dose to point A varied between fractions, because the position of the rectum was different with every fraction given. The position of the rectum was determined on the lateral control films for each HDR brachytherapy treatment administered. The median dose to point A for the 94 patients was 3.66 Gy (Std Dev 1.03) ranging from 2.55 Gy – 6.68 Gy (given in 4-6

fractions). The cumulative recorded mean dose at point A for the 94 patients who received HDR-ICBT treatment, was 17.96 Gy.

4.6 Biologically effective doses (BED)

The linear quadratic model was used to calculate the BED for the fractionation schedule used in treating the uterine cervical cancer patients of the study.

4.6.1 BED values of EBRT

The BED values for the tumour (Gy_{10}) and the rectum (Gy_3) for EBRT are shown in Table 4.6. Both these values were used to calculate the cumulative BED for the combination of EBRT and HDR-ICBT.

Table 4.6 EBRT- BED values to the tumour Gy_{10} and the rectum Gy_3 (n=94)

	TUMOR Gy_{10}	**RECTUM Gy_3**
Mean BED	66.5	92.01
Standard deviation	1.15	3.07
Median BED	66.38	92.19
Minimum BED	63.45	79.12
Maximum BED	69.05	97.30

4.6.2 BED values of HDR-ICBT

The BED values for the tumour (Gy_{10}) and the rectum (Gy_3) for HDR-ICBT are shown in Table 4.7. These values were used to calculate the cumulative BED for the combination of EBRT and HDR-ICBT.

Table 4.7 HDR-ICBT-BED values to the tumour Gy_{10} and the rectum Gy_3 (n=94)

	TUMOR Gy_{10}	RECTUM Gy_3
Mean BED	21.09	14.18
Standard deviation	4.31	1.62
Median BED	20.33	13.33
Minimum BED	4.15	10.00
Maximum BED	34.30	20.00

4.6.3 The cumulative BED values of EBRT and HDR-ICBT

Calculations were made using the LQ model to determine the cumulative BED values for the tumour (Gy_{10}) and the rectum (Gy_3) respectively. The **cumulative tumour** BED of EBRT & HDR-ICBT had a median value of 87.27 Gy_{10} and the **cumulative rectum** BED of EBRT + HDR-ICBT had a median value of 106.26 Gy_3 (Table 4.8).

Table 4.8 Cumulative BED values for EBRT & HDR-ICBT(n=94)

	TUMOUR Gy_{10}	RECTUM Gy_3
Mean BED	87.59	106.20
Standard deviation	4.36	3.55
Median BED	87.27	106.26
Minimum BED	72.98	93.71
Maximum BED	101.18	113.86

4.7 Follow-up results

The median follow-up time for all 94 patients was 40 months (3.3 years), (range: 20-93 months).

4.7.1 Tumour recurrence

Eleven (11.7%) of the 94 patients had tumour recurrence, while 83 patients (88.3%) had no tumour recurrence (Figure 4.7).

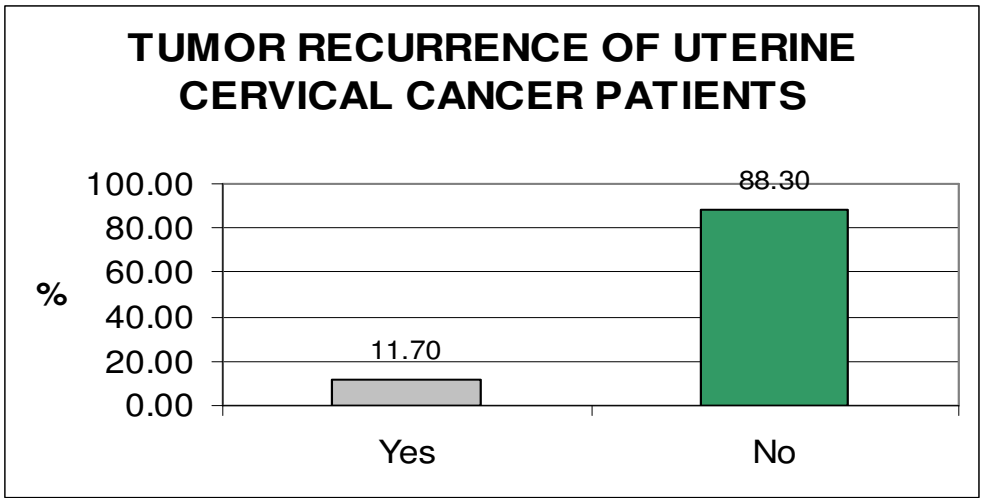

Figure 4.7 Tumour recurrence of uterine cervical cancer patients (n=94)

The histology results of the 94 uterine cervical cancer patients showed that three of the seven patients (42.9%) with adenocarcinoma had tumour recurrence, while eight of the eighty-seven patients with squamous carcinoma (9.2%) presented with tumour recurrence. Between the two types of tumours, patients with adenocarcinoma have a significantly greater chance of developing tumour recurrence than patients diagnosed with squamous carcinoma (p=0.03). Only one of the 11 patients who developed tumour recurrence was HIV-Positive (CD4-count=480).

The probability of tumour recurrence at various time points (using survival analysis) is shown in Table 4.9.

Table 4.9 Probability of tumour recurrence (n=94)

TIME SPAN	PROBABILITY
6 months	0.01
1 year	0.03
2 years	0.09
3 years	0.09
4 years	0.13

Of the 11 patients with tumoUr recurrence (FIGO stages IIb2-IIIb2), five patients had stage IIIb1 and four patients had stage IIb2 cervical cancer (Table 4.10).

Table 4.10 FIGO staging of patients with tumour recurrence (n=11)

FIGO STAGE	Number of patients	Percent
Stage IIb2	4	36.36
Stage IIIb1	5	45.45
Stage IIIb2	2	18.19
Total	11	

Of the 11 patients with tumour recurrence, 6 patients had local infiltration, while the remaining 5 patients showed none (Table 4.11).

Table 4.11 Summary of local infiltration (n=11)

Local infiltration	Number of patients	Percent
Yes	6	54.55
No	5	45.45
Total	11	

Figure 4.8 shows that of the six patients with local infiltration, five had bladder infiltration and only one had rectum infiltration.

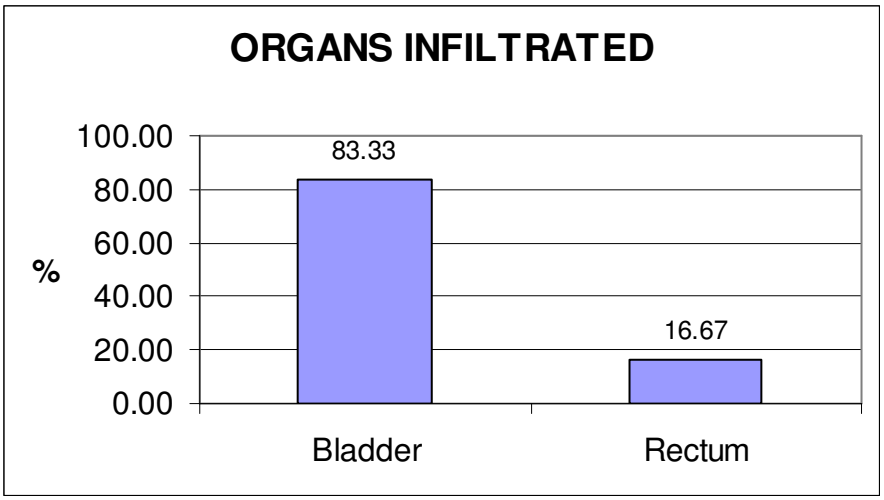

Figure 4.8 Organs infiltrated (n=6)

The 11 patients with tumour recurrence were treated with either one or with a combination of modalities. Nine of the patients received chemotherapy, eight patients received supportive care and two patients received HDR-ICBT (Figure 4.9).

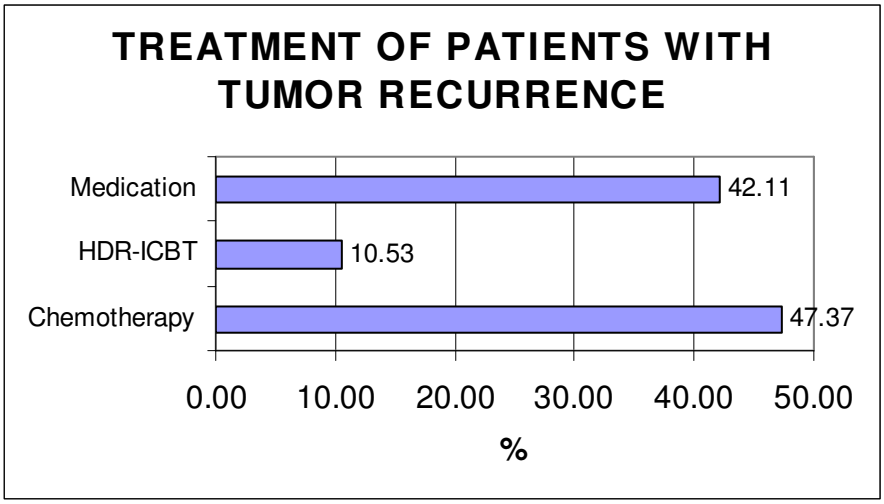

Figure 4.9 Treatment of patients with tumour recurrence (n=11)

The cumulative BED values for EBRT and HDR-ICBT for the patients with or without tumour recurrence is shown in Table 4.12. The cumulative median BED_{10} for the 11 patients with tumour recurrence was 86.02 Gy_{10} and 87.62 Gy_{10} for the 83 patients who did not have tumour recurrence. These cumulative median BED_{10} values did not differ statistically (p=0.68).

Table 4.12 Tumour recurrence vs. BED_{10} (n=94)

Tumour recurrence	Frequency	Cummulative tumour BED_{10}
		Median
Yes	11	86.0251
No	83	87.6183
TOTAL	94	

4.7.2 Late radiation complications

The incidence of late radiation complications was retrospectively analysed according to the RTOG/EORTC scoring criteria. Of the 94 patients in this study, 15 had RTOG/EORTC Grade 1-4 late rectal/bladder complications

(Table 4.13). These late radiation complications occurred at a median time interval of 12.36 months (range: 1-31 months) after completion of radiotherapy treatment.

Table 4.13 Incidence of late radiation complications (n=94)

LATE RADIATION COMPLICATION(S)	Number of pateints	Percent
Yes	15	15.96
No	79	84.04
Total	94	

The FIGO staging of the 15 patients who presented with late radiation complications is illustrated in Table 4.14. Most patients were stages IIb2 and IIIb1 uterine cervical cancer, respectively.

Table 4.14 FIGO staging of patients with late radiation complications (n=15)

FIGO STAGE	Number of patients	Percent
Stage IIb	1	6.67
Stage IIb1	3	20
Stage IIb2	4	26.66
Stage IIIb1	6	40
Stage IIIb2	1	6.67
Total	15	1

Of the 15 patients who presented with late radiation complications, 10 had late radiation complications of the bladder and 5 patients had rectum radiation complications (Table 4.15). Two of the 15 patients who presented with late radiation complications were HIV-positive (CD4-counts of 550 & 480, respectively).

Table 4.15 Site of late radiation complications (n=15)

SITE OF RADIATION COMPLICATIONS	Number of patients	Percent
Rectum	5	33.33
Bladder	10	66.67
Other	0	0
Total	15	

Most of the patients with bladder complications presented with RTOG/EORTC grade I/II late radiation complications. The median time for the development of rectal complications was 6 months (range: 1-10 months), whereas that for bladder complications was 17 months (range: 3-31 months). Table 4.16 shows the crude incidence (grading) of first late radiation complications (RTOG/EORTC scoring of these organs). The late rectal complications varied from blood streaked stool and rectal bleeding to proctitis. Bladder complications were teleangiectasia, intermittent macroscopic haematuria and severe frequency and dysuria.

Table 4.16 Crude incidence of first late radiation complications according to the RTOG/EORTC scoring (n=15)

Site	Grade I	Grade II	Grade III	Grade IV	GradeV
Rectum (n=5)	3	1	1	0	0
Bladder (n=10)	6	3	1	0	0

These 15 patients received either one or a combination of treatments for the late radiation complications. Most of these patients received medication or hyperbaric oxygen (Figure 4.10).

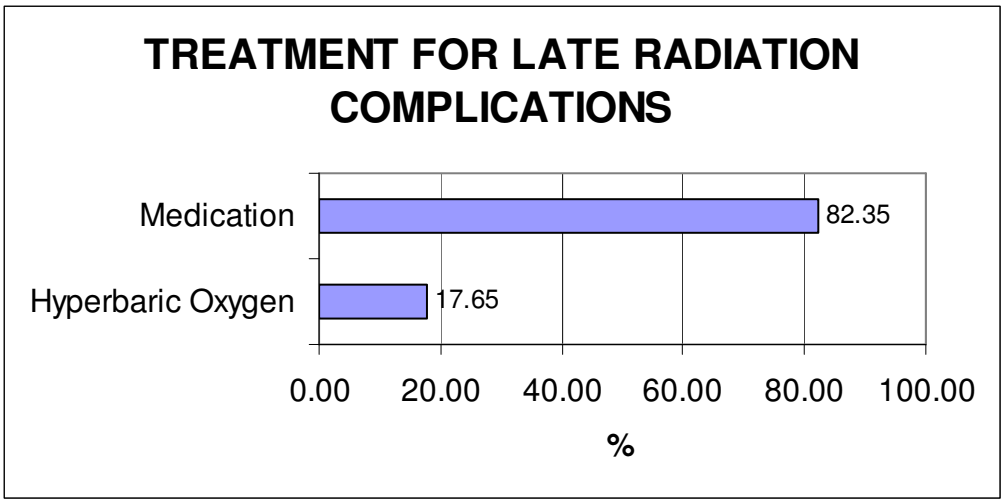

Figure 4.10 Treatment for patients with late radiation complications (n=15)

Three of the 15 patients with late radiation complications also presented with a second late radiation complication. These patients first presented with late radiation complications of the rectum, followed by second late radiation complications of the bladder(2) and rectum (1). Table 4.17 shows the RTOG/EORTC scoring of the second late radiation complication of these patients. Of the three patients who presented with a second late radiation complication, one patient presented with a grade II rectum complication (increase stool frequency and bleeding) and the other two had grade III bladder complications (severe frequency and dysuria).

Table 4.17 Crude incidence of second late radiation complications according to RTOG/EORTC scoring (n=3)

Site	Grade I	Grade II	Grade III	Grade IV	Grade V
Rectum (n=1)	0	1	0	0	0
Bladder (n=2)	0	0	2	0	0

All of these patients were treated medically according to the symptoms.Only one of the three patients with a second late radiation complications developed a third, late radiation complication. The patient had a third, late radiation complication of the rectum (proctitis) and the bladder (cystitis). The patient received palliative treatment (medication). Table 4.18 shows the probability of late radiation complications at various time points (using survival analysis).

Table 4.18 Probability of late radiation complications (n=94)

TIME SPAN	PROBABILITY
6 months	0.05
1 year	0.07
2 years	0.11
3 years	0.16
4 years	0.19

The cumulative rectum (BED_3) values of EBRT and HDR-ICBT for the patients with or without late radiation complications is shown in Table 4.19. The cumulative median BED for the rectum Gy_3, of the 15 patients with late radiation complications was, 106.62 Gy_3 and of the remaining 79 patients, 105.89 Gy_3. These doses also did not differ significantly (p=0.17).

Table 4.19 Late radiation complications vs. BED_3 (n=94)

Late complications	Number of patients	Cummulative median rectum BED_3
Yes	15	106.6285
No	79	105.8964
TOTAL	**94**	

4.8 Metastases

Of the 94 patients whose treatment details were analysed in this retrospective study, 7 patients (7.45%) developed metastases (Table 4.20). Of these 7 patients, 6 also presented with tumour recurrence.

Table 4.20 Patients with metastases at last follow-up (n=94)

Metastases	Number of patients	Percent
Yes	7	7.45
No	87	92.55
Total	94	

The areas where the cancer had spread to are illustrated in Figure 4.11. In some patients the cancer had spread to more than one site. The most common site was the para-aortic lymph nodes, followed by bone infiltration, lungs, liver and brain. These patients with metastases were treated with medication, radiation and/or chemotherapy.

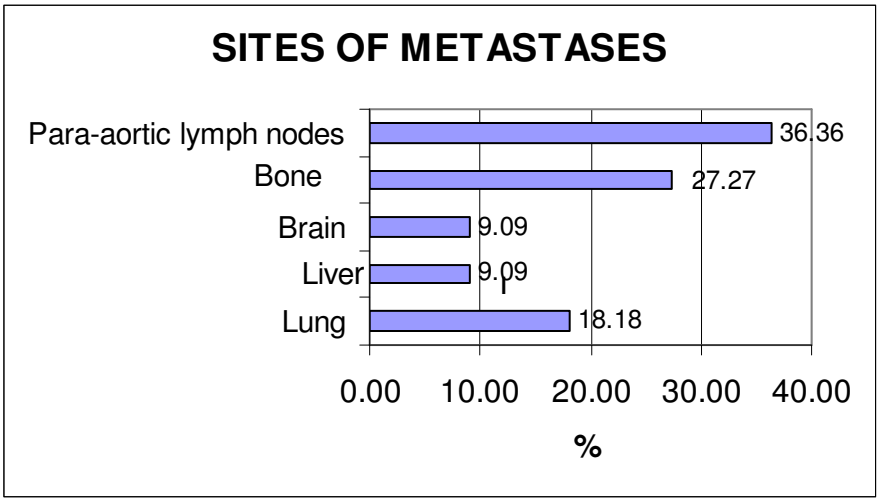

Figure 4.11 Sites of metastases for patients with uterine cervical cancer (n=7)

The probability of metastases at various time points (using survival analysis) is shown in Table 4.21.

Table 4.21 Probability of metastases (n=94)

TIME SPAN	PROBABILITY
6 months	0
1 year	0
2 years	0.01
3 years	0.01
4 years	0.04
5 years	0.09

4.9 Survival

Among the 94 patients who were analysed in this retrospective study, the 3.3-year cause specific survival was 100% for all FIGO stages I-III.

4.10 Conclusion

The results have shown the cumulative median BED_{10} values to the tumour and the BED_3 values to the rectum of patients treated with a combination of EBRT and HDR-ICBT at the Department of Oncotherapy, Bloemfontein for the first time. Although the cumulative median BED_{10} value of 87.27 Gy_{10} to the tumour could not be correlated to tumour recurrence of the patients, only 11.7% of the 94 patients treated presented with tumour recurrence. The median BED_3 value of 106.26 Gy_3 to the rectum could not be correlated to the incidence of late radiation complications, but only 15 of the 94 patients presented with late radiation complications. The results relevant to the objectives of this retrospective are discussed in chapter five.

CHAPTER 5

DISCUSSION & CONCLUSION

5.1 Introduction

This research study was undertaken to analyse retrospectively the dose effectiveness of the applicable fractionation schedule and the incidence of late radiation complications in the radical treatment of uterine cervical cancer. The dose effectiveness was analysed according to the calculated BED values obtained by using the LQ formula. The median BED values to the tumour (87.27 Gy_{10}) and the rectum (106.26 Gy_3) were then correlated to tumour control and incidence of late radiation complications. This chapter discusses the significance of the data source form as research tool, the advantages of implementing HDR-ICBT in combination with EBRT as treatment modality for uterine cervical cancer patients, the dose effectiveness and incidence of late radiation complications of the fractionation schedule used, as well as recommendations and shortcomings of the study.

5.2 High dose-rate brachytherapy

Use of HDR-ICBT in combination with EBRT in the treatment of uterine cervical cancer patients has increased worldwide, especially in developing countries, in many of which the incidence rates exceed 30/ 100 000 (Nag et al. 2002: 299). Considering the statistics of uterine cervical cancer patients treated at the Department of Oncotherapy, Bloemfontein (mentioned in Chapter One), the implementation of HDR-ICBT in 1994 into the fractionation schedule was justified. The advantages of this

treatment modality in comparison to LDR brachytherapy include outpatient treatment, potential cost saving, shorter treatment time, elimination of personnel exposure, dose optimisation and maintenance of better applicator geometry, all of which make this procedure the treatment modality of choice (Nag 2004: 620).

Recent studies published on HDR vs. LDR brachytherapy by Wong et al. (2003: 1254-1264), Ferrigno et al. (2005: 1108-1116) and Falkenberg et al. (2006: 49-55), have reported comparable results in terms of tumour control and toxicity using either LDR brachytherapy or HDR brachytherapy (HDRB). Falkenberg et al. (2006: 49-55), compared 103 LDR brachytherapy patients to 57 HDR brachytherapy patients and reported that for all uterine cervical cancer stages combined and stage for stage in both groups, there was no statistically significant difference in loco-regional control, cause-specific survival and overall survival for LDR therapy compared with HDR therapy. Loco-regional control and overall survival were 78% and 60% for LDR compared to 76% and 55% for HDR at 3 years, respectively. The advantages of HDR-ICBT in comparison to LDR brachytherapy make it the definitive mode of treatment for uterine cervical cancer patients, with curative intent, at the Department of Oncotherapy, Bloemfontein.

5.3 Dose effectiveness

The main objective of this retrospective study was to analyse the dose effectiveness of the fractionation schedule implemented since 1994 at the Department of Oncotherapy, Bloemfontein, by calculating the biologically effective dose (BED) for the combination of EBRT and HDR-ICBT to the tumour Gy_{10} and the rectum $Gy_{3,}$ using the linear quadratic model. This was the appropriate model to use in the study, because it allowed distinction to be made between the fractionation and dose-rate

sensitivities of early and late responding tissues such as tumour tissue (early) and rectum (late). The results of this theoretical study were significantly dependent on the linear quadratic parameters used. The BED_{10} results obtained after analysis of the fractionation schedule for dose effectiveness at the Department of Oncotherapy, Bloemfontein, are summarised and compared to those of other fractionation schedules, Table 5.1. These results compare well with those of HDR brachytherapy fractionation schedules in recently published studies.

Table 5.1 BED_{10} values of the Department of Oncotherapy, Bloemfontein (1998-2003) and HDR fractionation schedules for recently published studies (Petereit & Fowler 2003: 1160).

	Whole-pelvis dose	**HDR FX**	**BED Gy_{10}**
Dept. of Oncotherapy,Bloemfontein (1998-2003).	50 Gy 25 Fx	Median of 4 Gy x 4-6 Fx	87
Wong	40 Gy 20 Fx	7 Gy x 3	86
		6 Gy x 4	88
Sood	45 Gy 25 Fx	9 Gy x 2	89
Ferrigno	45 Gy 25 Fx	6 Gy x 4	92
Pearcey (NCIC trial)	45 Gy 25 Fx	8 Gy x 3	96
GOG standard	45 Gy 25 Fx	6 Gy x 5	101
ABS recommendations	45 Gy 25 Fx	5.3-7.5 Gy x 5-8 Fx	98-109

Abbreviations: HDR = high-dose-rate; Fx = fractions; BED = biologically effective dose; NCIC = National Cancer Institute of Canada; GOG = Gynecologic Oncology Group; ABS = American Brachytherapy Society.

In a literature analysis of 24 articles on HDR brachytherapy fractionation schedules, publiched by Petereit and Pearcey (1999: 359-361), the median BED_{10} was 96 Gy_{10}. The local control rate for uterine cervical

cancer stage Ib, IIb and IIIb disease was 91%, 82% and 71% respectively with a disease-free survival rate of 85%, 68% and 47% at 5 years respectively. No correlation was identified between point A BED and either survival or local control.

Petereit et al. (1999: 1267-1274), reported on 173 uterine cervical cancer patients treated with 40-50 Gy of EBRT and five HDR-ICBT fractions of 3.7-9.9 Gy each. The BED_{10} in their current schedule varied from 96 Gy_{10} for nonbulky stage I/II disease to 109 Gy_{10} for stage IIIb. The 3-year local control and disease-free survival rate was 71% and 62% respectively.

Sood et al. (2002: 1377-1387), reported on 49 uterine cervical cancer patients with cervical cancer treated with a combination of 45 Gy (1.8 Gy/fr) of EBRT and 2 HDR-ICBT treatments of 9-9.5 Gy prescribed to point A. A BED_{10} > 89 Gy indicated a trend toward a better local control rate than patients who received < 89 Gy_{10}. The 4-year control rate was 83% and disease-free survival rate 70%.

Toita et al. (2003: 1344-1353), reported on 88 uterine cervical cancer patients treated with 40 Gy of EBRT and 3 HDR-ICBT treatments of 18 Gy (point A dose of 6 Gy). The median cumulative biologically effective dose (BED) at point A (EBRT + ICBT) was 64.8 Gy_{10} for early disease and 76.8 Gy_{10} for advanced disease. Their conclusion after analysing their fractionation schedule was that, in view of the therapeutic ratio, cumulative BED 70-80 Gy_{10} at point A was appropriate for uterine cervical cancer patients treated with a combination of EBRT and HDR-ICBT.

The median BED_{10} for all 94 patients treated between 1998-2003 at the Department of Oncotherapy, Bloemfontein, was 87.27 Gy_{10} to the tumour. The median BED_{10} in the schedule varied from 88.85 Gy_{10} for nonbulky stage I/II disease to 86.36 Gy_{10} for stage IIIb patients. Although the BED_{10}

value in this study was about 10-15 Gy_{10} less than the studies reported by Petereit & Pearcey (1999), Petereit et al. (1999), Sood et al. (2002) and Toita et a. (2003), the 3.3-year local control rate of 88.3% for all stages and a hundred percent overall survival compared well with these reported studies in the literature. Patients who developed local recurrence received a median of 86.02 Gy_{10}, while those who did not developed tumour recurrence received a median of 87.62 Gy_{10}. These BED_{10} values did not differ significantly ($p=0.68$). Thus BED_{10} values could not be correlated with local control.

The histology results of the 94 uterine cervical cancer patients showed that three of the seven patients (42.9%) with adenocarcinoma had tumour recurrence, while eight of the eighty-seven patients (9.2%) with squamous carcinoma presented with tumour recurrence. Between the two types of tumours, patients with adenocarcinoma have a significantly greater chance of developing tumour recurrence than patients diagnosed with squamous carcinoma ($p=0.03$). The FIGO staging results of the eleven patients with tumour recurrence showed that two patients (18%) were stage IIIb2; four patients (36%) were stage IIb2 and five patients (45%) were stage IIIb1.

Although the patients of this study received EBRT & HDR-ICBT as treatment modality in a pre-chemotherapy era, the American Brachytherapy Society (ABS) recommends the addition of cis-platinum based chemotherapy during pelvic EBRT. Five prospective randomised trials have recently demonstrated a 10-15% increase in local control and survival without increase in complications when concurrent chemotherapy was added to radiation therapy. However, it is not advisable to administer chemotherapy concomitantly with brachytherapy, unless it is in the context of a controlled clinical trial. Increased complications have been reported with concomitant chemotherapy and brachytherapy (Nag et al. 2000: 203).

5.4 Late radiation complications

Similarly, some studies have tried to establish a correlation between BED_3 and late rectal toxicity. Chen et al. (2000: 955-961) reviewed 128 patients with uterine cervical cancer. These patients were treated with 40-44 Gy of EBRT and 3-4 HDR-ICBT fractions of 5-7.2 Gy each. After 30-75 months of follow-up, 38 patients (29.7%) had late rectal complications. When 110 Gy_3 was used as the cutoff value, 19.6% (10 of 51) of patients whose cumulative BED_3 was less than 110 Gy_3 had rectal complications, while 36.4% (28/77) of patients whose BED_3 was greater than 110 Gy_3 developed rectal complications.

The Brazilian Experience, as reported by Ferrigno et al. (2001: 1123-1135), is one of the most concise HDR brachyhterapy papers written to date because the authors provided adequate fractionation details, calculated and correlated biologically effective doses to the tumour and late responding tissues and prospectively studied their patients. One-hundred and thirty-eight patients were treated with 45 Gy EBRT and four HDR-ICBT treatments of 6 Gy prescribed to point A. Patients treated with cumulative BED at rectum points above 110 Gy_3 had a higher but not statistically significant five-year actuarial rate of complications. Sood et al. (2002: 1377-1387) reported on 49 patients with cervical cancer treated with a combination of 45 Gy (1.8 Gy/fr) of EBRT and 2 HDR-ICBT treatments of 9-9.5 Gy prescribed to point A. The median BED_3 at the rectal point in their study was 95.5 Gy_3 (range 79.9-110.2). They suggested that the low rate of rectal complications in the study could be attributed to the low BED_3 at the rectal point, although the point A doses were achieved as prescribed.

Chung et al. (1996: 319) calculated both the maximal rectal dose to the anterior rectal mucosa identified by contrast medium and the ICRU report

38 (1985) reference rectal dose. They obtained a significant relationship between the occurrence of late rectal complications and both types of rectal doses. The maximal rectal dose estimated by contrast medium was greater and correlated better with late complications than did the strictly defined ICRU report 38 (1985) rectal dose.

In the current retrospective study the fractionation schedule did not include the ICRU report 38 rectal reference point, but the maximal rectal dose to the anterior rectal mucosa identified by contrast medium. The standard prescribed protocol at the Department of Oncotherapy was 2 Gy/fraction, normalised to the highest rectum dose point to achieve a minimum total dose of 15 Gy to point A. The dose to point A therefore varied from patient to patient, and fraction to fraction. Point A is a geometric point in relationship to the cervical os and uterine axis and the rectal doses can be significantly different depending on the geometry of the implant, size of applicators, amount of packing, source of activity and optimisation with HDR-ICBT. The median dose per fraction to point A was 3.66 Gy/fraction and the total median dose to point A was 18 Gy.

The median BED_3 at the rectal point in this retrospective study was 106.2 Gy_3 (range 93.7 Gy-113.9 Gy). Patients who developed late radiation complications received a median of 106.62 Gy_3, while those who did not develop complications received a median of 105.89 Gy_3. These BED_3 values did not differ significantly ($p=0.17$), thus BED_3 values could not be correlated with late radiation complications. The incidence and severity of late radiation complications was analysed and graded according to the RTOG/EORTC scoring scheme. Severe late rectal and bladder complications were uncommon in this retrospective study. One patient presented with Grade IV complications (proctitis and systitis). Ten of the fifteen patients with late radiation complications had late radiation complications of the bladder (grade I-III). This was expected, because the

HDR-ICBT treatment did not include bladder shielding. A study reported by Toita et al. (2003: 1344) suggest that cumulative BED_3 at the rectal point should be kept below 100-120 Gy_3 to prevent late rectal complication. At the Department of Oncotherapy, Bloemfontein the cumulative BED_3 at the rectal point (106.2 Gy_3) was within the above mentioned values and therefore only 16% of the 94 patients presented with late radiation complications.

The incidence of late radiation complications occurred at a median time interval of 12.36 months (range: 1-31 months) after completion of radiotherapy treatment. Amongst the 15 patients who presented with late radiation complications (grade I-III), three had second late radiation complications (2 bladder- grade III and one rectum- grade II complications), and one of them had a third late radiation complication of the bladder and the rectum-grade IV.

The probability of metastases at a five-year time point is 0.09, therefore making it negligible. Seven of the 94 uterine cervical cancer patients (7.45%) presented with metastases and of these seven, six presented with tumour recurrence.

5.5 Recommendations

The BED_3 and BED_{10} values calculated for the fractionation schedule of this retrospective study at the Department of Oncotherapy, Bloemfontein, are adequate and the available data indicate that it is not necessary to adapt the prescribed treatment protocol for patients diagnosed with stages I-III uterine cervical cancer.

Regarding the RTOG/EORTC scoring of the late radiation complications, the researcher would suggest that these scoring sheets should be included in the patients` follow-up files and should be completed by the radiation oncologist after every follow-up examination for future research purposes on late radiation complications.

All 94 patients of the retrospective study were tested for HIV/AIDS and the analyses showed that 7 patients (7%) were HIV-Positive. Only one of the 11 patients who developed tumour recurrence was HIV-Positive (CD4-count=480). The influence of the HIV status of patients on the dose effectiveness of a fractionation schedule could be an interesting research study for the future.

The study had a three-year follow-up period, but according to Petereit et al. (2003: 1159-1161), longer follow-up results would be required to determine if lower BED_{10} values compromise pelvic control rates. The researcher would thus suggest looking at five-year follow-up results to determine whether or not BED_{10} values in this study compromise pelvic control rates.

The current fractionation schedule places a lot of emphasis on the rectum dose, while the dose delivered to the bladder has been ignored. Considering that 10 of the 15 patients who presented with late radiation complications had bladder complications, it may be necessary for the future to take the total dose to the bladder of this schedule into account.

5.6 Shortcomings of the study

The original data source form was altered after the pilot study was conducted. The FIGO stages of the patients were adjusted to accommodate all stages of the 94 patients included in the study. Second-

and third late radiation complications were also added to the data source form. However, the patient data source form designed by the researcher for this retrospective study was very useful as a research tool and it provided detailed and summarised information of the patients` radiotherapy treatment details and follow-up notes. At no stage was it necessary to refer to patient files to retrieve extra data for analysis. This research tool made the calculations of the BED values done at the Department of Biostatistics quick and efficient.

From January 1998 to December 2003, 696 patients diagnosed with uterine cervical cancer received radiotherapy treatment at the Department of Oncotherapy, Bloemfontein. Of these, only 94 patients met the patient selection criteria of this retrospective study. One-hundred and ninety-six patients had a follow-up period of less than two years, 348 patients had their follow-up examinations at clinics in other provinces and 58 patients did not have complete dosimetric data. The outcome of the study might have been different if 80% of the 696 patients could have been included into this study.

5.7 Conclusion

This retrospective study suggests that 50 Gy EBRT to the whole pelvis combined with HDR-ICBT with a median total dose of 18 Gy to point A, administered in 4-6 fractions, is an effective and safe fractionation schedule in the treatment of FIGO stages I-III uterine cervical cancer patients, if undertaken in a mean treatment period of 40.69 days.

The cumulative median BED_{10} of 87.27 Gy_{10} to the tumour indicated acceptable local tumour control (88.3%). These BED_{10} values did not differ significantly ($p=0.68$), and so BED_{10} values could not be correlated with

local control. The cumulative median BED_3 of 106 Gy_3 to the rectum could also not be correlated to late radiation complications (p=0.17). The incidence of late radiation complications of the 94 patients treated was only 15.96%. Although this schedule appears to be both safe and effective, it is only a preliminary step to establishing windows of opportunity for BED_{10} to tumours and BED_3 to rectal tissues.

6. SUMMARY

A retrospective study was undertaken to determine if the fractionation schedule, which entails EBRT and HDR-ICBT, delivered acceptable biologically effective doses in treating FIGO stages I-III cervical cancer patients. The purpose of the calculated BED values was to see whether the cumulative biologically effective dose could be used as a predictor of local control and of rectal toxicity in the treatment of patients with cervical cancer. This study endeavoured to provide adequate fractionation details and calculated and correlated biologically effective dose to the tumour (Gy_{10}) and late responding tissues e.g. the rectum (Gy_3). The incidence of late radiation complications was analysed according to the RTOG/EORTC scoring criteria.

The study was conducted on 94 patients (mean age of 55 years), from January 1998 to December 2003, with FIGO stages I-III cervical cancer treated with a combination of EBRT and HDR-ICBT. A data source form was designed to retrieve information from the patients` radiotherapy treatment files and follow-up notes for analysis. The standard prescribed dose for EBRT was 2 Gy/fraction for 25 fractions with a total dose of 50 Gy administered to the whole pelvis in a six week period. The HDR-ICBT treatment was delivered with an Ir^{192} Nucletron Microselectron and ring applicator. HDR-ICBT was interdigitated into the treatment only after two weeks of EBRT to allow for tumour shrinkage. The standard prescribed dose for HDR-ICBT was 2 Gy/fraction with the dose to point A normalised to the highest rectum dose point with a minimum total dose of 15 Gy to point A. A median total dose of 18 Gy to point A was achieved in 4-6 fractions. The mean overall treatment time was 41 days.

The mean follow-up time was 40 months (3.3 years) and the overall survival of all 94 patients FIGO stages I-III was 100%. Tumour control for all stages was

88.3% and the incidence of late radiation complications was 15.96%. Five patients had late rectal complications (Grade I-III) and ten patients had late bladder late complications (Grade I-III). One patient had grade IV (proctitis and cystitis). The median cumulative biologically effective dose was calculated to the tumour Gy_{10} and the rectum Gy_3 by using the Linear quadratic model. The 94 patients had a median cumulative BED_{10} of 87.27 Gy_{10} and a median cumulative BED_3 of 106.26 Gy_3. The median cumulative BED_{10} value for the tumour of 87.27. Gy_{10} was 10-15% below those values reported in the literature, but delivered good tumour control. Longer follow-up results will, however, be required to determine if these lower Gy_{10} values comprise pelvic control rates.

The median cumulative BED_3 value for the rectum of 106.26 Gy_3 was within the range of BED_3 values (100-120 Gy_3) reported in the literature. The eleven patients who presented with tumour recurrence had a median BED_{10} of 86.02 Gy_{10} and those with late radiation complications had a median BED_3 of 106.62 Gy_3. These BED_{10} and BED_3 values could, however, not be correlated to tumour control ($p=0.68$) and late radiation complications (0.17) respectively.

This retrospective study has indicated that the fractionation schedule of EBRT and HDR-ICBT as a radical treatment modality for FIGO stages I-III cervical cancer patients, with curative intent, had delivered acceptable pelvic control rates and a low incidence of late radiation complications at the Department of Oncotherapy, Universitas Annex, Bloemfontein.

7. OPSOMMING

`n Retrospektiewe studie is onderneem om te bepaal of die fraksionasie skedule van eksterne bundel bestraling en intrakavitêre bragiterapie aanvaarbare biologiese effektiewe dosisse (BED) lewer in pasiënte wat gediagnoseer is met FIGO stadiums I-III servikale kanker. Die doel van die berekende BED waardes was om te sien of dit gebruik kan word as `n voorspelling vir lokale tumor beheer en laat rektale bestralings komplikasies. Die studie poog om voldoende fraksionasie besonderhede en berekende BED waardes aan die tumor en die laat responderende weefsel (bv. rektum) te verskaf. Die insidensie van laat rektale bestralings komplikasies is geanaliseer deur gebruik te maak van die RTOG/EORTC gradiëring sisteem.

Dié studie fokus op die radioterapie behandeling van 94 pasiënte in die tydperk van Januarie 1998 tot Desember 2003. `n Inligtingsvorm is deur die navorser ontwerp om die relevante inligting van die pasiënte se bestralingslêers en opvolgnotas te versamel vir analise.

Die voorgeskrewe protokol vir die eksterne bestraling sluit in 25 fraksies van 2 Gy elk tot `n totale dosis van 50 Gy wat oor `n tydperk van ses weke toegedien word. Die bragiterapie behandeling word toegedien deur gebruik te maak van `n $Ir^{192}$ Nucletron Mikroselektron na-ladings apparaat en ring applikators. Die voorgeskrewe dosis vir bragiterapie behels 2 Gy/fraksie wat voorgeskryf word aan die hoogste rektale dosis punt, met `n minimum dosis van 15 Gy aan punt A. Met bragiterapie is `n gemiddelde totale dosis van 18 Gy by punt A verkry in 4-6 fraksies. Die gemiddelde behandelings tydperk was 41 dae.

Die gemiddelde opvolgtyd van die 94 pasiënte was 40 maaande (3.3 jaar). Die lokale tumor beheer vir al die pasiënte was 88.3%, terwyl die insidensie van laat bestralings komplikasies 15.96% was. Vyf van die 94 pasiënte het laat bestralings komplikasies (Graad I-III) ontwikkel an tien pasiënte het laat bestralings komplikasies (Graad I-III) van die blaas ontwikkel. Een pasiënt het met beide graad IV blaas en rektum komplikasies gepresenteer (proktitis & sistitis).

Die Linêer kwadratiese model is gebruik om die BED van die tumor en die rektum te bereken. Die median totale BED_{10} van die 94 pasiënte was 87.27 Gy_{10} en die mediane totale BED_3 was 106.26 Gy_3. Alhoewel die BED_{10} waarde van die tumor 10-15% minder was as dié van sommige gepubliseerde studies, is voldoende lokale tumor beheer verkry. Dit is egter nodig om na `n langer opvolg periode te kyk (5-10 jaar) om te bepaal of die laer BED_{10} waardes voldoende lokale tumor beheer gelewer het.

Die mediane totale BED_3 waarde aan die rektum van 106.26 Gy_3, soos bepaal in die studie, vergelyk goed met die BED_3 waardes (100-120 Gy_3) wat in die literatuur gepubliseer is. Die 11 pasiënte wat met tumor herhaling gepresenteer het, het `n median $BED_{10}$ waarde van 86.02 $Gy_{10}$ gehad, terwyl die 15 pasiënte wat met laat bestralings komplikasies gepresenteer het, het `n mediane BED_3 waarde van 106.62 Gy_3 gehad. Die BED_{10} en BED_3 waardes het ongelukking nie gekorreleer met respektiewelik lokale tumor beheer ($p=0.68$) en laat bestralings komplikasies ($p=0.17$) nie.

Hierdie retrospektiewe studie demonstreer dus dat die fraksionasie skedule wat vanaf April 1994 by die Onkoterapie Departement, Universitas Annex, Bloemfontein geïmplementeer is, aanvaarbare resultate lewer met betrekking tot lokale tumor beheer en die insidensie van laat bestralings komplikasies.

8. REFERENCES

CadPlan, Varian Medical Systems Oy, Finland 1993

Chen S.W., Liang J.A., Yang S.N., Liu R.T & Lin F.J. 2000. The prediction of late rectal complications following the treatment of uterine cervical cancer by high dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys*, Vol. 47, no.4, 955-961

Chen S.W., Liang J.A., Yeh L.S., Yang S.N., Shiau A.C & Lin F.J. 2004. Comparitive study of reference points by dosimetric analyses for late complication after uniform external radiotherapy and high dose-rate brachytherapy for cervical cancer. *Int J Radiat Biol Phys*, Vol.60, no. 2, 663-671

Cheng J.C., Peng L., Chen Y., Huang D.Y.C., Wu J & Jian J.J. 2003. Unique role of proximal rectal dose on late rectal complications for patients with cervical cancer undergoing high dose-rate intracavitary brachytherapy. *Int J Radiat Oncol Biol Phys,* Vol. 57, no. 4, 1010-1018

Chung E.J., Kim G.E & Suh C.O. 1996. Risk of late rectal complications following definitive external radiotherapy and high dose-rate intracavitary irradiation for FIGO STAGE IIB carcinoma of the uterine cervix (Abstract). *Int J Radiat Oncol Biol Phys*, Vol.38 (Suppl.), 319

Clark B.G., Souhami L., Roman T.N & Evans M.D.C. 1994. Rectal complications in patients with carcinoma of the cervix treated with concomitant cisplatin and external beam irradiation with high dose-rate brachytherapy : a dosemetric analysis*. Int J Radiat Oncol Biol Phys,* Vol. 28*,* 1243-1250

Clark B.G., Souhami L., Roman N., Chappel R., Evans M.D.C. & Fowler J.F. 1997. The prediction of late rectal complications in patients treated with high dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys*, Vol. 38, no. 5, 989-993

Cooper D.R. & Schindler P.S. (eds) 2005. Business Research Methods. Eighth edition. McGraw Hill: Singapore

Cox J.D., Stetz J. & Pajak T.F. 1995. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys,* Vol. 31, no. 5, 1341-1346

Deehan C. & O`Donoghue J.A. 1994. Biological equivalence of LDR and HDR brachytherapy in *Brachytherapy- from Radium to Optimization. Edited by* Mould R.F. Batterman J.J., Martinez A.A & Speiser B.L. 1994. Nucletron International B.V., Waardgelder 1, 3905 TH Veenendal, The Netherlands, 1-8

Doman M.J. 2006. Statistics of uterine cervical carcinoma. Department of Oncotherapy, Universitas Annex, Bloemfontein, 2000-2004

Duenas-Gonzalez A., Cetina L., Mariscal I. & De la Garza J. 2003. Modern management of locally advanced cervical carcinoma. *Cancer Treatment Reviews*, Vol. 29, 389-399

Ellis F. 1969. Dose, time and fractionation. A clinical hypothesis. *Clinical Radiobiology*, 20: 1-7

Falkenberg E., Kim R.Y., Meleth S., De Los Santos J. & Spencer S. 2006. Low dose-rate vs. high dose rate intracavitary brachytherapy for carcinoma of the cervix: The University of Alabama at Birmingham (UAB) experience. *Int J Radiat Oncol Biol Phys*, Vol. 5, 49-55

Ferrigno R., Dos Santos P.E.R., Pellizon A.C.A., Maia M.A.C., Fogarolli R.C., Gentil A.C. & Salvajoli J.V. 2001. High dose-rate brachytherapy in the treatment of uterine cervix cancer. Analysis of dose effectiveness and late complications. *Int J Radiat Oncol Biol Phys,* Vol. 50, no. 5, 1123-1135

Ferrigno R., Nishimoto I.N., dos Santos Novaes P.E.R., Pellizzon A.C.A., Maia M.A.C., Fogarolli R.C & Salvajoli J.V. 2005. Comparison of low and high dose-rate brachytherapy in the treatment of uterine cervix cancer. Retrospective analysis of two sequential series. *Int J Radiat Oncol Biol Phys*, Vol. 62, no. 4, 1108-1116

Fletcher G.H., Shalek R.J., Wall J.H & Bloedorn F.G. 1952. A physical approach to the design of applicators in radium therapy of cancer of the cervix uteri. *Am J. Roentgenol*, Vol. 68, 935-949

Fowler J.F. 1992. Brief summary of radiobiological principles in fractionated radiotherapy. *Semin. Radiat. Oncol,* Vol. 2, 16-21

Friedrich H. 1996. A clinical radiobiological analysis of the treatment of carcinoma of the uterine cervix in Bloemfontein, 1967-1990. Unpublished Master Thesis, Bloemfontein, 16-17

Hall E.J., Brenner D.J. 1991. The dose-rate effect revisited: Radiobiological considerations of importance in radiotherapy. *Int J Radiat Oncol Biol Phys*, Vol. 21, 1403-1414

Halperin E.C., Schmidt-Ulrich R.K., Perez C.A. & Brady L.W. 2004. The Discipline of Radiation Oncology in *Principles and Practice of Radiation Oncology.* Edited by Perez C.A., Brady L.W., Halperin E.C & Schmidt Ullrich R.K. (eds). Fourth edition,Philadelphia: Lippincott Williams & Wilkins, 3

Hoskin P.J. & Bownes P. 2006. Innovative technologies in Radiation Therapy: Brachytherapy. *Semin Radiat Oncol*, Vol. 16, 209-217

ICRU (International Commission on Radiation Units and Measurements) Report 38. 1985. *Dose and Volume Specification for Reporting Intracavitary Therapy in Gyneacology*., Bethesda, Maryland, USA., 1-19

Joiner M.C. & van der Kogel A.J. 1993. The linear-quadratic approach to fractionation and calculation of isoeffect relationships. In: Steel G.G, ed. *Basic clinic radiobiology*. London: Edward Arnold, 106-122

Katzenellenbogen J.M., Joubert G & Abdool Karim S.S. (eds) 1999. Epidemiology: A Manual for South Africa. Oxford University Press Southern Africa, N1 City, South Africa

Kottmeier H.L. 1964. Surgical and radiation treatment of carcinoma of the uterine cervix. *Acta Obst. Gynec. Scand*. 43, Suppl. 2,1

Lamarque P. & Coliez R. 1951. Les cancers des organs genitaux de la femme. Electro-radiotherapy, Delherm L (ed), Masson , Paris

Lanciano R.M., Won M. & Coia L.R. 1991. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: A final report of the 1973 and 1978 patterns of care studies. *Int J Radiat Oncol Biol Phys*, Vol. 20, 667-676

Maruyama Y., Van Nagell J.R., Utley J., Vider M.L. & Parker J.C. 1974. Radiation and small bowel complications in cervical carcinoma therapy. *Therapeutic Radiology*, Vol. 7, 699-703

Mould R.F. 1994. Radium brachytherapy: historical review in *Brachytherapy-from Radium to Optimization.* Edited by Mould R.F. Batterman J.J., Martinez A.A. & Speiser B.L. (eds). 1994. Nucletron International B.V., Waardgelder 1, 3905 TH Veenendal, The Netherlands, 1-8

Mqoqi N., Kellet P., Sitas F. & Jula M.(eds). 2004. Incidence of histologically diagnosed cancer in South Africa. *Cancer in South Africa,* 1998- 1999: 22-23

Nag S., Erickson B., Thomadsen B., Orton C., Demanes J.D & Petereit D. 2000. The American Brachytherapy Society recommendations for high dose-rate brachytherapy for carcinoma of the cervix. *Int J RadiatOncol Biol Phys*, Vol. 48, no. 1, 201-211

Nag S., Dally M., De la Torre M., Tatsuzaki H., Kizilbash N., Kurusun S., Pinillos L., Pokrajac B., Sur. R. & Levin V. 2002. Recommendations for implementation of high dose rate ^{192} Ir brachytherapy in developing countries by the Advisory Group of International Atomic Energy Agency. *Radiotherapy and Oncology*, Vol. 64, 297-308

Nag S. 2004. Clinical aspects of High dose-Rate Brachytherapy in *Principles and Practice of Radiation Oncology*. Edited by Perez C.A., Brady L.W., Halperin E.C & Schmidt-Ullrich R.K. 2004. Fourth edition,Philadelphia: Lippincott Williams & Wilkins, 610-620

Nucletron Microselectron, Ir^{192} , Nucletron International BV, The Netherlands 1994

Orton C.G. 1986. Dose dependence of complication rates in cervix cancer Radiotherapy. *Int J. Radiat Oncol Biol Phys*, Vol. 12, 37-44

Orton C.G., Seyedsadr M & Somnay A. 1991. Comparison of high and low dose remote afterloading for cervix cancer and the importance of fractionation. *Int J Radiat Oncol Biol Phys*, Vol. 21, 1425-1434

Parkin D.M., Bray F., Ferlay J. & Pisani P. 2001. Estimating the world cancer burden: Globocan 2000. *Int J Cancer*. Vol 94, 153-156

Patel F.D., Rai B., Mallick I. & Sharma S.C. 2005. High dose-rate brachytherapy in uterine cervical carcinoma. *Int J Radiat Oncol Biol Phys*, Vol. 62, no. 1, 125-130

Patterson R. 1948. The treatment of malignant disease by radium and X-rays. Edward A, London

Patterson R. & parker H.M. 1934. A dosage system for gamma ray therapy. *Br. J. Radiol.* VII, 592

Perez C.A. 1998. Uterine Cervix in Perez C.A. & Brady L.W. (eds). 1998. *Principles and Practice of Radiation Oncology.* Third edition. Philadelphia: Lippincott Williams & Wilkins, 1734

Perez C.A. & Kavanagh B.D. 2004. Uterine Cervix in *Principles and Practice of Radiation Oncology*. Edited by Perez C.A., Brady L.W., Halperin E.C., Schmidt-Ullrich R.K. (eds). 2004. Fourth edition,Philadelphia: Lippincott Williams &Wilkins, 1800-1864

.

Petereit D.G. & Pearcey R. 1999. Literature analysis of high dose brachytherapy fractionation schedules in the *treatment of cervical cancer:* is there an optimal fractionation schedule *? In J Radiat Oncol Biol Phys*, Vol. 43, no. 2, 359 – 361

Petereit D.G., Sarkaria J.N., Potter D.M. & Schink J.C. 1999. High dose-rate versus low dose-rate brachytherapy in the treatment of cervical cancer: Analysis of tumour recurrence-the University of Wisconsin experience. *Int J Radiat Oncol Biol Phys*, Vol. 45, no. 5, 1267-1274

Petereit D.G. & Fowler J.F. 2003. High dose-rate brachytherapy – High-dose, high-tech, and high results. *Int J Radiat Oncol Biol Phys*, Vol. 55, no. 5, 1159-1161

Shakespeare T.P., Lim K.H.C., Lee K.M., Back M.F., Mukherjee R. & Lu J.D. 2006. Phase II study of the American Brachytherapy Society guidelines for the use of high dose-rate brachytherapy in the treatment of cervical carcinoma: is 45-50.4 Gy radiochemotherapy plus 31.8 Gy in six fractions high-dose rate brachytherapy tolerable? *Int J Gynecol Cancer*, 16, 277-282

Shepherd J.H. 1995. Staging announcement FIGO staging of gynecologic cancers: cervical and vulva. *Int J Gynecol Cancer*, Vol. 5, 319

Sood B., Garg M., Advadhani J., Gorla G., Malhotra H., Guha C., Deore S. & Vikram B. 2002. Predictive value of linear-quadratic model in the treatment of cervical cancer using high dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys,* Vol. 54, no. 5, 1377-1387

Stewart A.J. & Viswanathan A.N. 2006. Current controversies in high dose-rate versus low dose-rate brachytherapy for cervical cancer. *Cancer*, Vol. 107, 908-915

Stewart B.W. & Kleihues P. 2003. World cancer report. Lyon: IARC Press, 215-222

Toita T., Kakinohana Y., Ogawa K., Adachi G., Moromizato H., Nagai Y., Maehama T., Sakumoto K., Kanazawa K. & Murayama S. 2003. Combination external beam radiotherapy and high dose-rate intracavitary brachytherapy for uterine cervical cancer: Analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys*, Vol. 56, no. 5, 1344-1353

Wang C.J., Huang E.Y., Sun L., Chen H.C., Fang F.M., Hsu H.C., Changchien C.C. & Leung S.W. 2004. Clinical comparison of two linear-quadratic model-based isoeffect fractionation schemes of high dose-rate intracavitary brachytherapy for cervical cancer. *Int J. Radiat Oncol Biol Phys,* Vol. 59, no. 1, 179-189

Werner I.D. 1990. *Cancer – A Historic Overview*. Inaugural lecture at the third National Congress of SASCRO and SASMO, 22-26 April 1990. Thaba Nchu Sun

Williamson J.F. & Brenner D.J. 2004. Physics and biology of brachytherapy in *Principles and Practice of Radiation Oncology*. Edited by Perez C.A., Brady L.W., Halperin E.C., Schmidt-Ullrich R.K. 2004. Fourth edition,Philadelphia: Lippincott Williams & Wilkins, 520

Wong F.C.S., Tung S.Y., Leung T.W., Sze W.K., Wong Y.W., Lui C.M.M., Yuen K.K. & Ki-O S. 2003. Treatment results of high dose-rate remote afterloading brachytherapy for cervical cancer and retrospective comparison of two regimens. *Int J Radiat Oncol Biol Phys,* Vol. 55, no. 5, 1254-1264

APPENDICES

Appendix I A – Data source form

PATIENT DATA SOURCE FORM

A RETROSPECTIVE STUDY OF PATIENTS DIAGNOSED WITH FIGO STAGES I-III CERVICAL CARCINOMA (1998-2003), DEPARTMENT OF ONCOTHERAPY, UNIVERSITAS ANNEX, BLOEMFONTEIN.

INSTRUCTIONS
Mark the appropriate block with a X or write your answer on the space provided

For Office Use ☐☐☐ 1-3

1. Oncotherapy RT.no.....

2. Age (with registration at Oncotherapy)..... ☐☐ 4-5

3. Race: [1] White [2] Black ☐ 6

[3] Coloured [4] OTHER

PRE-TREATMENT DETAILS:

4. HIV-Status : [1] Negative [2] Positive: CD4-count=.... ☐ 7
[3] Unknown

5. Histology: ☐ 8

[1]= SQUAMOUS CARCINOMA, NOS

[2]= ADENOCARCINOMA, NOS

6. Differentiation: ☐ 9
[1]= WELL DIFFERENTIATED
[2]= MODERATELY DIFFERENTIATED
[3]= POORLY DIFFERENTIATED
[4]= UNDIFFERENTIATED
[5]= NOT STATED

7. Tumor type: [1] Endophytic [2]Exophytic [3]Not stated ☐ 10

8. FIGO STAGE ☐☐ 11-12
[1]= I [2]= Ia [3]= Ib
[4]= Ib1 [5]= IIb [6]= IIb1
[7]= IIb2 [8]= III [9]= IIIa
[10]=IIIb [11]=IIIb1 [12]=IIIb2

RADIATION THERAPY
EXTERNAL BEAM RADIATION THERAPY (EBRT):

9. Source: ☐ 13
[1]6MV-XRay [2]8MV-Xray
[3]10MV-Xray [4]15MV-Xray

10. Date EBRT started(dd/mm/yy)..... ☐☐☐☐☐☐ 14- 19
d d m m y y

11. Mean Tumor dose =..... % ☐☐☐☐☐☐ 20-25

12. Median Tumor dose =.....% | 26-31

13. BED value for Tumor=.....Gy 10 | 32-37

14. Mean Rectum dose =.....% | 38-43

15. Mean Rectum dose = ...Gy | 44-49

16. Median Rectum dose = ...% | 50-55

17. Median Rectum dose = ...Gy | 56-61

18. BED value for Rectum.....Gy3 | 62-67

HIGH-DOSE-RATE (HDR) - INTRACAVITARY BRACHYTHERAPY (ICBT):

19. Number of fractions: [1]3 [2]4 [3]5 [4]6 | 68

20. Dose at point A1=.....Gy | 69-73
A2=.....Gy | 74-78
A3=.....Gy | 1-5
A4=.....Gy | 6-10
A5=.....Gy | 11-15
A6=.....Gy | 16-20

21.Tumor Total dose (TD)=.....Gy | 21-25

22. BED value for Tumor=.....Gy10 | 26-31

23. BED value for Rectum=.....Gy3 | 32-37

24. Date radiation completed (dd/mm/yy)...../...../..... | 38-43
d d m m y y

25. Cummulative Tumor BED of EBRT +HDR-ICBT=.....G10 | 44-49

26. Cummulative Rectum BED of EBRT + HDR-ICBT=.....Gy3 | 50-55

FOLLOW-UP DETAILS:

27. Tumor recurrence: [1] Yes [2] No | 56

28. Date of recurrence (dd/mm/yy).../.../... | 57-62
d d m m y y

29. Treatment received for recurrence:

[1] Chemo	63
[2] HDR-ICBT	64
[3] Palliative radiation	65
[4] Medication	66
[5] Other.....	67
[6] None	68

30. Local infiltration: [1] Yes [2] No ☐ 69

31. Site of infiltration: [1] Bladder ☐ 70
[2] Rectum ☐ 71
[3] Other ☐ 72

32. Crude incidence of late radiation complications: ☐ 73
[1] Yes
[2] No

33. Date of First radiation complication(s):(dd/mm/yy).../.../... ☐☐☐☐☐☐ 74-79
d d m m y y

34. Site of radiation complication (s): ☐ 80
[1] Rectum
[2] Bladder
[3] Rectosigmoid
[4] Other.....

35. RTOG/EORTC grading: ☐ 1
[1] O [2] I [3] II [4] III [5] IV
[6] V

36. Treatment received for abovementioned:
[1] Chemo ☐ 2
[2] Hyperbaric Oxygen ☐ 3
[3] Surgery ☐ 4
[4] Medication ☐ 5
[5] Other..... ☐ 6
[6] None ☐ 7

37. Second radiation complication(s): ☐ 8
[1] Yes
[2] No

38. Date of SECOND radiation complication(s):(dd/mm/yy) ☐☐☐☐☐☐ 9-14
d d m m y y

39. Site of radiation complication(s): ☐ 15
[1] Rectum
[2] Badder
[3] Rectosigmoid
[4] Other.....

40. RTOG/EORTC grading: ☐ 16
[1] O [2] I [3] II [4] III [5] IV
[6]V

41. Treatment received for abovementioned:
[1] Chemo ☐ 17
[2] Hyperbaric Oxygen ☐ 18
[3] Surgery ☐ 19
[4] Medication ☐ 20
[5] Other..... ☐ 21
[6] None ☐ 22

42. Third radiation complication(s): ☐ 23

[1] Yes
[2] No

43. Site of radiatin complication(s): ☐ 24

[1] Rectum
[2] Bladder
[3] Rectosigmoid
[4] Other.....

44. RTOG/EORTC grading: ☐ 25

[1] O [2] I [3] II [4] III [5] IV
[6]V

45. Treatment received for abovementioned:

[1] Chemo ☐ 26
[2] Hyperbaric Oxygen ☐ 27
[3] Surgery ☐ 28
[4] Medication ☐ 29
[5] Other..... ☐ 30
[6] None ☐ 31

46. Metastases: [1] Yes ☐ 32
[2] No

47. Date of metastases (dd/mm/yy).../.../... ☐☐☐☐☐☐ 33-38

48. Site of metastases:

[1] Lung ☐ 39
[2] Liver ☐ 40
[3] Brain ☐ 41
[4] Bone ☐ 42
[5] Para-aortic lymph nodes ☐ 43
[6] Other..... ☐ 44

49. Treatment for metastases:

[1] Chemo ☐ 45
[2] Radiation ☐ 46
[3] Surgery ☐ 47
[4] Medication ☐ 48
[5] Other..... ☐ 49
[6] None ☐ 50

50. Local tumor control at last follow-up(According to cytology) ☐ 51

[1] Unknown
[2] Recurrence of tumor
[3] No recurrence of tumor

51. Survival(Date of last follow-up): ☐☐☐☐☐☐ 52-57
d d m m y y

52. Death: ☐ 58

[1] Yes
[2] No

53. Date of death (ddmmyy).../.../... ☐☐☐☐☐☐ 59-64
d d m m y y

54. Cause of death: ☐ 65

[1] Unknown
[2] Cervix cancer
[3] Radiation complication
[4] Other primary
[5] Metastases
[6] Other disease.....

Appendix I B – Letter of consent

FREE STATE PROVINCE

Ref nr: H5/1

14 February 2005

Me. D Long
Department Oncotherapy
Universitas Annex Hospital

Dear Me. Long

RE: AUTHORISATION FOR ACCESS TO PATIENT RECORDS

We acknowledge you letter dated 13 February 2006 regarding the abovementioned.

Herewith permission for the mentioned access to patient records on condition that no information is published without permission of the CEO.

Yours sincerely

DR NIC VAN ZYL
HEAD: CLINICAL SERVICES

DR NRJ VAN ZYL
2006 -02- 14
HEAD: CLINICAL SERVICES
UNIVERSITAS ACADEMIC HOSPITAL

Department of Health ▪ Departement van Gesondheid ▪ Lefapha La Bophelo Bo Botle

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Universitas Tertiary Hospital, Bloemfontein

Appendix II A- FIGO STAGING Perez et al 1998: 1741

TABLE 61.8. STAGING OF CARCINOMA OF THE UTERINE CERVIX

AJCC	FIGO	
Primary tumor (T)		
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
Tis		Carcinoma *in situ*
T1	I	Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
T1a	IA	Preclinical invasive carcinoma, diagnosed by microscopy only
T1a1	IA1	Minimal microscopic stromal invasion
T1a2	IA2	Tumor with an invasive component 5 mm or less in depth taken from the base of the epithelium and 7 mm or less in horizontal spread
T1b	IB	Clinical lesions confined to the cervix or preclinical lesions greater than IA
	IB1	Clinical lesions no greater than 4 cm in size
	IB2	Clinical lesions greater than 4 cm in size
T2	II	Cervical carcinoma invades beyond uterus but not to the pelvic wall or to the lower third of vagina
T2a	IIA	Tumor without parametrial invasion
T2b	IIB	Tumor with parametrial invasion
T3	III	Cervical carcinoma extends to the pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctioning kidney
T3a	IIIA	Tumor involves lower third of the vagina, with no extension to pelvic wall
T3b	IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
T4[a]	IVA	Tumor invades mucosa of the bladder or rectum and/or extends beyond the true pelvis
Regional lymph nodes (N)		
Regional lymph nodes include paracervical, parametrial, hypogastric (obturator), common, internal and external iliac, presacral, and sacral.		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
Distant metastasis (M)		
MX		Presence of distant metastasis cannot be assessed
M0		No distant metastasis
M1	IVB	Distant metastasis

AJCC, American Joint Committee on Cancer; FIGO, International Federation of Gynecologists and Oncologists.
[a]*Note:* Presence of bullous edema is not sufficient evidence to classify a tumor as T4.
Modified from Fleming ID, Cooper JS, Henson DE, et al. eds. *AJCC cancer staging manual,* 5th ed. Philadelphia: Lippincott-Raven, 1997:173–174.

Appendix C – Abbreviations

ABBREVIATIONS

ABS	American Brachytherapy Society
AP	Anterior-posterior
ASIR	Age-Specific Incidence Rates
BED	Biologically effective dose
CRE	Cumulative Radiation Effect
EBRT	External beam radiotherapy
EORTC	European Organization for Research and of Cancer Treatment
FIGO	International Federation of Gynecologists and Obstetricians
HDR	High dose-rate
IAEA	International Atomic Energy Agency
ICBT	Intracavitary brachytherapy
ICRU	International Commission on Radiation Units and Measurements
LAT	Lateral
LDR	Low dose-rate
LQ model	Linear Quadratic model
NCR	National Cancer Registry
NSD	Nominal Standard Dose
RTOG	Radiation Therapy Oncology Group
TDF	Time Dose Factors
WHO	World Health Organization
α/β	Alpha/Beta ratio

Appendix D –
Certificate of language editing

RUTH ULLYATT: ENGLISH LANGUAGE EDITING AND TRANSLATION

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This is to certify that I, Dr Ruth Carol Ullyatt, have edited and proof-read the language of the Master's thesis of Deidre Long entitled *An analysis of dose-effectiveness and incidence of late rectal complications of high dose-rate brachytherapy in the radical treatment of cervical cancer.* I have also collated the text on computer and printed it out.

DR RUTH ULLYATT
BA; BA Hons (Classics); BA Hons (English); MA (English); Ph. D (English); UED.