INCIDENCE OF SEVERE LATE TOXICITIES AND QUALITY OF LIFE IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER TREATED WITH CONCURRENT CHEMORADIOTHERAPY AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL SOUTH AFRICA, 2014-2017

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Declaration

I, Prinitha Pillay, declare that this research report is my own work. It has not been submitted before for any degree or examination at this or any other University.

Signed at: Johannesburg, South Africa on the 27th April 2020

Signed: *Prinitha Pillay*

Dedication

To Jens and our patients, sans you this means nothing.

Abstract

Purpose

The purpose of this study was to determine the incidence of bladder and gastrointestinal (GIT) complications in patients with severe-late cervical cancer (≥Grade 3 and >90 days after treatment completion) bladder and gastrointestinal complications; and to describe both the complication--related and sexual-health related quality of life experienced by these patients treated with chemoradiation for locally advanced cervical cancer.

Methods

This is a retrospective analysis of prospectively collected study data from a Phase III randomised controlled trial (RCT). This RCT investigated the benefits of combining hyperthermia with chemoradiation in 76 patients with FIGO Stage IIB and III cervical cancer whom were selected from the control arm. The Kaplan Meier time-to-event analysis was used to determine actuarial probability of complications, while clinician reported morbidity was recorded using Radiation Therapy Oncology Group (RTOG) criteria and patient reported outcomes (PRO) were recorded using EORTC QLQ - CX24 quality of life (QoL) questionnaires. These criteria were assessed at baseline, and then every three months post-treatment during the first year and every six months post-treatment in the second year.

Results

The mean age of the patients was 50 years (SD±10.6.). 50% were HIV positive with a mean age of 45.2 years (SD±9.3) and a median CD4 count of 518 (range 374-626). All patients completed the entire course of concurrent Cisplatin based chemotherapy and chemoradiation (CCRT) within 56 days. GIT complications were largely obstructive and appeared predominantly in the second year, and the risk of was similar independent of the presence of disease. Local rectal fistulas were more common in patients who ultimately died from disease progression. The predominant bladder complications were fistulas, where the highest risk of developing a fistula was in the first year and half as likely to develop in those with no evidence of disease (NED). In those with NED, 5.3% developed ≥Grade 3 bladder complications (Grade 3 n=1, Grade 4 n=2, Grade 5 fatality n=1) with an actuarial probability of 3.3% and

12.5% in the first and second year respectively. 3.5% of patients with NED developed ≥Grade 3 GIT complications (Grade 3 n=2, Grade 4 n=0, Grade 5 fatality n=2) with 0% in the first year and 23.1% actuarial risk during the second year. The probability of being alive with or without severe complications was not statistically different (Chi-Square 0.788 p=0.375 Log Rank: Mantel-Cox). It was noted that those without complications lived longer and the median survival had not been yet reached. Further to this, patients with complications reported more severe symptoms than those without complications (bladder 20% vs. 5% and GIT 21% vs. 8%), which tended to be complication specific symptoms e.g. incontinence in fistulas or related obstructive symptoms.

There was a large discordancy between clinician graded severe toxicity and PRO of toxicity in the GIT (7.9% vs.10%) and slightly different with bladder toxicity (9.2% vs. 7%). Clinician's grading using the worst toxicity underestimated the duration and quality of life that patients endured with Grade 3/4 symptoms before a Grade 5 fatality.

Sexual worry and poor body image, were present in 60% of patients at baseline and this remained constant for the first year post-treatment but decreased in those who survived beyond a year to 35-40%. 11% of patients reported being sexually active at baseline but this doubled by six months post–treatment and plateaued to 30% of patients after nine months post-treatment. 21% of women under 30 years, 22% of those aged 31-50 years and 10% of patients over 50 years of age reported having sex in the previous four weeks. Out of the 72 reports of sexual activity, pain during intercourse was reported in 65% of patients while 77% found intercourse enjoyable and 51% of the patients found it both enjoyable and painful. 26% of patients reported enjoying intercourse without pain and 14% who did not enjoy intercourse reported pain.

The main vaginal symptom was discharge, which was almost twice as prevalent as vaginal discomfort throughout the first two years post-treatment (71% vs. 43% at baseline; 40% vs. 27% at 6 months; 23% vs. 14% at 18 months). However, there was a clear and noteworthy improvement over time.

Conclusion

There is a high risk of developing severe complications in patients who survive the first year; and their quality of life outlook is significantly worse than those without complications. Monitoring patterns of tell-tale symptoms and their intensities reported by patients is, currently, the best ‘early-warning system’ to detect severe late complications. In light of the high fatality rate, a comprehensive multidisciplinary approach is needed for patients reporting the severest symptoms in order to rapidly avert complications and to support those who suffer the harrowing effects once they have developed complications. Providing care on a daily basis, but without the in-depth understanding of what is most meaningful to patients, only widens the gap in the care of patients. These findings can help health professionals to shape patient expectations by paying closer attention to concerns about their bodies and sexual function, and to reassure patients that there are improvements over time.

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Presentations

- South African Society of Medical Oncology Congress Durban 2018
- South African Congress of Oncology Cape Town 2019
- University of Witwatersrand School of Clinical Medicine Reseach Day 2019

Clinician and Patient Reported Outcomes for Severe Late Bladder and Gastrointestinal Toxicity in Locally Advanced Cervical Cancer Patients Treated with Chemoradiation.

Sexual Quality Of Life In Locally Advanced Cervical Cancer Patients Treated With Definitive Concurrent Chemoradiation.

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List of Abbreviations

2D	Two-Dimensional
3D	Three-Dimensional
ART	Antiretroviral treatment
BC	Bladder Complications
BED	Biologically Effective Dose
CCRT	Concurrent Cisplatin Chemotherapy and Radiation
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CTCAE	Common Terminology Criteria for Adverse Events
DVH	Dose-Volume Histogram
EBRT	External Beam Radiation Therapy
EORTC	European Organisation for Research and Treatment of Cancer -
FIGO	International Federation of Gynecology and Obstetrics
GIC	Gastrointestinal Complications
GYN	Gynaecological
HDR	High Dose Rate
HPV	Human Papillomavirus
ICRU	International Commission on Radiation Units and Measurements
IGBT	Image-Guided Brachytherappy
LDR	Low Dose Rate
MDT	Multi-disciplinary Team
NED	No Evidence of Disease
OAR	Organs at Risk
PRO	Patient Reported Outcomes
QoL	Quality of Life
RCT	Randomised Controlled Trial
RTOG	Radiation Therapy Ocology Group
RVF	Rectovaginal Fistula
SD	Standard Deviation
VVF	Vesicovaginal Fistula
Gy	Unit of absorbed ionizing radiation dose
$EQD2_3$	Equivalent Dose
BED_3	Biologically Effective Dose

Chapter 1 Introduction

Radiation therapy forms a critical part of the treatment process of cervical cancer. Radiation in the treatment of cervical cancer offers many benefits for cervical cancer patients in the form of tumour control and improved cervical cancer survival rates. However, the side effect profile of radiation therapy can have a significant impact on the quality of life (QoL) of cancer patients.

1.1 Background

1.1.1 Epidemiology of cervical cancer

The number of cervical cancer cases for all women are estimated to be between 5785, as per the South African National Cancer Registry Data from 2012 (1) and 7735 as documented in a 2016 report by Bruni et al (2). Countrywide data shows that an average 54.5% (3) of South African women are accessing screening services. However, these services are performed predominantly on an opportunistic basis and it is further estimated that the screening could be as low as 12% (4) of women in rural areas. Olorunfemi (5) in 2017 showed, in a study period from 1994-2012, that there were a total of 75 099 cervical cancer incident cases in South Africa and 25 101 mortalities (33%) - with women below 50 years of age accounting for 43% of the cases and 36% of deaths.

There are some recent advances that offer hope in terms of prevention and treatment of cervical cancer. Over the past 50 years there have been major developments in the management of cervical cancer with, namely, a) the development of the pap smear as a tool for screening for cervical cancer, b) the recognition that human papillomavirus (HPV) causes cervical cancer, c) the development of an effective routine HPV vaccination (now recommended for both young boys and girls) (6), d) HPV subtype testing, which enables improved forecasting of the risk of disease through early detection (7), and lastly, e) concurrent cisplatin chemotherapy and radiation (CCRT), which has been shown to improve outcomes of locally advanced cancer and, consequently, continues to be the definitive standard of care treatment for cervical cancer patients (8).

1.1.2 Determination of the extent of the disease

The staging system used to describe the extent of cervical cancer that is recommended by the World Health Organisation (WHO) is the system developed by the International Federation of Gynecology and Obstetrics (FIGO) (Appendix 2) (9). This system categorizes patients only in terms of the extent of clinically detectable local disease. The FIGO system specifically prohibits the use of surgical staging in the categorization of patients - making it accessible to patients and health service providers in resource limited settings.

According to the FIGO staging, each stage represents an anatomical distortion produced by lesions caused by the cervical cancer which have consequences for the determination of the optimal sequence of therapy. Forms of such anatomical distortion may include the tumour spreading beyond the cervix. In the case of direct extension, the tumour may expand directly to involve the vagina, uterus, paracervical tissues and, infrequently, the bladder or rectum- where tumour invasion of the periureteral tissues can cause ureteral obstruction and hydronephrosis. By contrast, indirect or discontinuous involvement of the tumour occurs by lymphatic metastasis to the lymphatics of the broad ligament.

For women who develop locally advanced disease (FIGO stage IIB-IVA), the 5-year survival rate for patients with stage IB2 (confined to the cervix) is 80%, with stages IIB, IIIB, and IVA is approximately 58%, 32%, and 16% respectively and is only 7% for IVB with distant metastasis (10).

1.1.3 Treatment of cervical cancer

The aim of cervical cancer treatment is to gain the maximum therapeutic effect in arresting the cancer growth at the site of origin (local control), while inducing the least side effects and physical complications.

Treatment strategies include external beam radiation therapy (EBRT) and brachytherapy (the word ‘brachy’ is Greek for ‘short distance’). Brachytherapy involves the precise placement of short-range radiation sources inside a hollow organ (intracavity) which are then used to deliver a high dose of radiation. Brachytherapy takes advantage of the inverse-square law, whereby the radiation dose quantity or intensity is inversely proportional to the square of the distance from the source,

resulting in the relative sparing of the surrounding normal structures. With this in mind, in order to maintain the dose of least harm to bladder and rectum, the placement of the applicators inside the pelvis is critical. In order to reduce damage from the radiation to the rectum or bladder, the vagina is packed to displace the rectum and bladder away from the intravaginal sources.

The Manchester System is a system of positioning of brachytherapy applicators according to anatomical landmarks. These 'landmarks' include: Point A corresponds to the paracervical triangle is a reference point located two centimetres lateral to, and two centimetres superior to the external cervical os in the plane of the intrauterine tandem. Point A anatomically represents the point where ureter passes under the uterine vessels (11), but bears no consistent relation to tumour volume (11). The location of 'Point B' of the Manchester System is usually three centimetres lateral to Point A, however, its location in the pelvis varies considerably according to the position of the intracavity system (11). Treatment from Point B takes into account the dose to lateral and more distant pelvic structures.

This technique not only plays an important role in the more specific delivery of radiation but also in averting complications, through lower collateral organ damage. This is due to the decreased intensity of radiation on surrounding organs and reduced exposure time through a reduced overall treatment time. The entire course of treatment should be completed in less than 56 days, which is important as excessive protraction of the overall treatment time compromises its effectiveness (12).

1.1.4 Radiotherapy- induced side effects

The process of acute radiation damage begins immediately after exposure (13). Exposure to radiation therapy causes cell death. This may be caused by either unrepaired or mis-repaired DNA damage. It also may occur through apoptosis or through the activation of various cellular signaling cytokines leading to an inflammatory response (14). The acute effects are the most pronounced in tissues where there is a high cell turnover such as the cells outlining the gastrointestinal tract and the skin. These acute effects of radiation develop when the rate of cell death exceeds that of cell replication and thus the necrotic cells can no longer be replaced. These effects develop during the course of the treatment or shortly afterwards and

remain for a maximum of three months and then begin to subside. Symptoms present at three months after completed treatment are considered to be late side effects. The degree and extent of radiotherapy-induced toxicity depends on many factors (Table 1.1)

Table 1.1 Radiotherapy-induced toxicity considerations

Radiation treatment related factors	**Tumour related factors and factors involving irradiated normal tissue**	**Patient related factors**	**Other treatments administered in sequence or concomitantly**
▪ Modality ▪ Total radiation dose ▪ Dose per fraction ▪ Overall treatment time ▪ Schedule ▪ Volume	▪ Size ▪ Grade ▪ Stage ▪ Histology ▪ Location ▪ Functional reserve in irradiated organ ▪ Structural organization of irradiated organ	▪ Age ▪ Smoking ▪ Diabetes mellitus ▪ Cardiovascular disease ▪ Inflammatory bowel disease ▪ Connective tissue disorder ▪ Injuries affecting pelvic floor ▪ Other co-morbidities ▪ Genetic susceptibility towards radiation induced injury	▪ Surgery ▪ Chemotherapy ▪ Biological treatment

1.1.5 Late morbidity after pelvic radiotherapy

Organs at risk of damage due to pelvic radiation include (i) the gastrointestinal tract (small bowel, colon, rectum and anus), (ii) bone and bone marrow, (iii) urinary tract (bladder, urethra and ureter), (iv) the sexual organs (vulva, vagina, uterus, ovaries) and (v) the skin.

The gastrointestinal tract

The predominant clinical features of injury in the gastrointestinal tract due to radiation therapy include (i) altered intestinal transit, (ii) nutrient malabsorption, and (iii) gut dysmotility (15). As the injury to bowel may occur in multiple sites, the range of symptoms patients can present with is vast and often have multiple aetiologies (16). Radiation exposure may cause progressive intestinal wall fibrosis resulting in strictures and obstruction with localized areas of ischaemic necrosis. This ultimately may give rise to fistulas or bowel perforation (17), having symptoms that clinically

manifest as rectal pain, bleeding, tenesmus and faecal urgency. The management of late radiation injury to the bowel remains challenging, with surgery indicated only in severe cases with complications (13).

The urinary tract

Post radiation exposure, late sequelae of the urinary tract are common. Morphologically, the initial phase of urinary tract toxicity is characterized by progressive mucosal breakdown. This ranges from superficial denudation to ulceration to, ultimately, secondary fibrosis of the bladder wall or the urethral sphincters (14). Urinary symptoms might be due to “global” injuries, such as radiation-induced cystitis (bladder infection and inflammation), or focal injuries in more severe conditions, such as fistula (abnormal opening in bladder wall), necrosis, ulceration, etc. However, because disease progression itself might involve bladder infiltration, separating radiation effects from the disease may be difficult.

Gonads and sexual function

Radiation-induced ovarian failure is inevitable as ovaries are within the target treatment field and permanent menopause is usually seen after a total exposure of 4-7Gy (18). Other sequalae of pelvic radiation include sexual dysfunction, vaginal fibrosis and atrophy (which may cause stenosis), or more serious complications like necrosis and fistula formation (13).

1.1.6 Health-related quality of life

Health-related quality of life is defined as a multidimensional measure, comprising physical, mental and social elements, as well as symptoms related to the disease and it is considered a subjective measure and is, consequently, most reliable when reported from the patients themselves (19). The assessment of patient-related outcomes, and not just clinician-based outcomes, has become a more essential part of the evaluation in gynecological oncology. To assist with this evaluation, the European Organization for Research in the Treatment of Cancer has developed the EORTC QLQ-30/CXCR24, which measures physical, emotional and social functioning, disease-specific symptoms, economic impact and global QoL (20).

1.2 Literature review

1.2.1 The incidence of severe late toxicity

The incidence of severe late toxicity was reported in early studies (1983-2000) to have actuarial five-year severe bowel and bladder complication rates in the order of 8 – 10% (21, 22). Following this, Rose et al. (23) in 2007 reported long term randomized control trial (RCT) results with CCRT in 526 patients, with a median follow-up of 106 months. In these patients there was an incidence of severe late bladder and gastrointestinal toxicity of 1% and 2% respectively, which occurred at 1.7 years (range, 0.2 to 7.9 years). Toxicities recorded in later trials are in the range of 1-3% (24).

More recent studies (in the last five years), however, show higher percentages of patients and more significant GIT complications. These range from 3% - 8% in patients who received postoperative treatment to the pelvis and as high as 20% in those with advanced disease (25,26).

Upon inclusion of CCRT in later RCTs (27), it was found that complications in the bladder (using the Common Terminology Criteria for Adverse Events [CTCAE]) of ≥Grade 3 were 1-14% and that GIT complications of ≥Grade 3 were 1-5%. Further to this, when studies included image based brachytherapy, Grade 4 bladder complications were recorded to be 1-4%; and GIT complications which of ≥Grade 3 were 2-4%; and lastly, late gynecological toxicity of ≥Grades 3 was 3% (27).

There have been numerous systematic reviews and meta-analyses regarding the incidence of severe late toxicity in radiation therapy for cervical cancer. However, they are plagued by issues such as (i) no long term outcome reporting, (ii) multiple fractionation schedules, (iii) different chemotherapy agents at different doses, (iv) low and high dose rate brachytherapy and (v) different reporting endpoints (27). Illustratively, the latest 2017 review found only four single agent cisplatin based CCRT studies (as used at CMJAH) (28).

Further to this, all of the above studies represent historical cancer controls in HIV negative populations. In these studies, the incidence of acute bladder (≥Grade 3 toxicity) of 0.8% (29) is much lower than the values presented in the systemic review

by Ntekin et al. which estimates that for HIV positive patients the incidence of acute bladder toxicity is around 4%, but then with similar rectal events of 10% vs. 9% respectively (30). It must be noted that these are for acute effects in HIV patients and that there is no data on HIV patients who experience late effects. This highlights the critical need to describe the incidence of severe late toxicity in settings with a high prevalence of HIV.

Furthermore, there is the influence of the introduction of high dose rate (HDR) brachytherapy on toxicity. Despite its practical advantages, there were concerns regarding its efficacy and safety compared to low dose rate (LDR) brachytherapy (31). Tumour control response is dose-dependent but so too is the risk of damage to normal tissues. This controversy has led to studies that showed, as per a recent 2014 Cochrane systematic review (32) in 1265 patients, that the risk of small bowel complications was higher RR=3.37 (95% CI 1.06 to 10.72) with HDR Brachytherapy (p= 0.04). However, when HDR brachytherapy was included as a part of CCRT, the results show no significant increases in late complications in bladder or rectal toxicity (33–36).

Some studies (34,36) did however find high rates of 7%, as in a German phase II study, which described the development of serious late toxicities (36). Additionally, 10 institutions from eight Asian countries participated in a study that reported high five-year actuarial rates in the rectum (7.9%), while there being favourable outcomes in bladder (0%) and small bowel 0% (37). The studies above have thus reassured us that HDR does not increase the risk of toxicity, although, further understanding of the dosimetric (the calculation of absorbed dose and optimization of dose delivery) contribution to toxicity was required.

When CT 3D image guided brachytherapy was introduced (from 2009), the comparison of the techniques dose-toxicity relationship revealed that the difference in dose to the rectal and bladder wall was significantly underestimated using the International Commission of Radiation Units and Measurements (ICRU) No. 38 reporting with 2D X-ray calculations (38–41).

One of the seminal studies to compare 2D versus 3D planning was the French STIC study (42) which treated patients with CCRT and brachytherapy. At 24 months, the

local relapse-free survival was 74% and 79% for 2D and 3D patients respectively. Of importance, though, were the Grade 3–4 toxicity rates, where there is a significant divergence: 23% toxicity for the 2D group and only 3% toxicity in the 3D groups. This was equally demonstrated in a 2017 systematic review (27), in which nine studies using 3D brachytherapy reported very low late severe bladder toxicity of 1-4%; GIT toxicity to be 2-4% and GYN complications at 3%. Despite a significant body of evidence over the last 30 years to substantiate the relationship between the ICRU point dose and the probability of late complications to the bladder and rectum (22,43–47), new evidence emerged of the correlations between dose-volume parameters instead. Thus 3D treatment has had far-reaching consequences over 2D based practices that long have been used, and which continue as standard practice, in resource limited settings.

In 2014, a RCT specifically designed to address the outcomes of patients (n=147) with locally advanced stage IIIB cervical cancer receiving CCRT versus radiation alone, with a median follow-up of 43.2 months, was conducted in a low-middle income country (Brazil). This study found toxicity profiles were comparable and not statistically significant (48). Overall all organ (≥Grade 3 toxicities) were 9.7% with CCRT versus 4% without chemotherapy. Individually, GIT organs accounted for the majority of the late toxicities (Table 1.2) (48).

Table 1.2 Late toxicity per organ in Brazilian trial by Zuliani et al. (48)

	CRT ITT n=72 Number of patients	**%**	**RT ITT n=75 Number of patients**		**Total n=149**	**%**
GI	21	58.3	22	68.8	43	28.8
Bladder	9	25.0.	7	21.9	16	10.7
Vagina	6	16.7	3	9.4	9	6.04

Studies regarding toxicity have to be carefully selected so reasonable baseline data can be used for any meaningful comparison- this can be complicated for the following reasons: firstly, as Kirwan et al. (49) indicate, the incidence of late toxicity may be underestimated as data is sparse and it depends on the length of follow-up and, importantly, is not always reported as actuarial rates. Reporting in actuarial rates allows for the adjustment of the number of cases under observation at the time when

late effects clinically start to manifest, providing a more accurate determination of the prevalence of late effects in long-term survivors. Secondly, the stage of cervical cancer is a significant factor in response to treatment and studies with patients with advanced stages IIB-IVA have to be carefully selected for comparison. And lastly, many studies, particularly when comparing the introduction of a chemotherapy agent, often have a propensity to rather report acute toxicity and not long-term late toxicity effects. In the South African context, all data has thus far been reported on acute toxicity (50–52).

Further to this, there have been even fewer reports on toxicity conducted in a randomized trial setting on advanced stage disease with no surgical interventions and using 2D planned HDR brachytherapy (as is standard of care in CMJAH) - other than the RCT done by Zuliani et al in Brazil 2014 as described above (48). This germane RCT in a LMIC indicated that Grade 3-4 toxicities are close to 10%, in keeping with historical data. The benchmark, however, should be the more sophisticated IGBT rates which are typically low and are now single digit figures reported at around 8% by Banerjee and Kamrava (2014) (53).

This review of the literature aims to provide an outline of the evolution of treatment of cervical cancer and how it has impacted treatment outcomes, side effects and complications. This is especially true where the conclusions derived about the actual incidences fail to reflect the severest and most feared outcomes, inhibiting the ability of practitioners to equip themselves with adequately tested information to be successful in limiting toxicity.

1.2.2 Health-related quality of life

Quality of life (QoL) is commonly compromised for patients with cervical cancer treated by radiotherapy. The majority report a reduction in physical, emotional, social, and economic support (54). This decrease in QoL is especially associated with radiotherapy more than surgery or chemotherapy due to the risk that these patients bare in the long-term from clinical and psychosocial consequences (55–57).

In this vein, the PORTEC randomised control trials have made an invaluable contribution to understanding of the effect of radiotherapy toxicity and QoL by providing data for different modalities including pelvic radiation compared with

vaginal brachytherapy and CCRT. In PORTEC-2, in 427 patients with endometrial cancer, who had surgery and then were randomly assigned to receive EBRT (n = 214) or vaginal brachytherapy (n = 213); the longitudinal long term QoL analysis showed persistently higher rates of bowel symptoms with EBRT (58). At 7 years, clinically relevant fecal leakage and limitations due to bowel symptoms were vastly different at 10.6% in the EBRT group versus only 1.8% for brachytherapy; and 39.3% of EBRT patients vs. 25.5% for urinary urgency.

QoL studies in African women are sparse. A review in 2016 found that out of a total of 380 research articles or reports only 4.1% assessed aspects of QoL among African women living with cervical cancer (59) and even fewer purposefully included women with locally advanced stage disease (60), thus these patients may be under-represented. In terms of QoL and cervical cancer in patients with HIV, Du Toit G and Kidd M (61) have shown that HIV positive women with cervical cancer in South Africa had no improvement in insomnia, appetite loss, nausea, vomiting, diarrhoea, social role or any of the sexual domains. By contrast, HIV-negative women did experience an improvement in these areas affecting QoL. Albeit a small sample, the QoL improvement experienced by HIV-negative women was statistically significantly greater than their HIV-positive counterparts. Whether or not this outcome is related to the consequences of the AIDS related background is unclear. Interestingly, the same author in the same study location in 16 patients and found that the presence of HIV/AIDS itself did not influence their quality of life but advanced-stage cancer did (62).

In a recent 2017 qualitative investigation into the QoL of 24 cancer patients (not pelvic specific) at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) poverty was the main issue that influenced physical aspects highlighting the complexity of QoL (63). Likewise another qualitative study at CMJAH explored the experiences of 16 women with advanced disease who described the harrowing effect on their lives below (64)

“After a year, eeee I found out that the poo (stool) comes out through the vagina…it wasn’t painful but disgusting, cause you can’t just walk freely because anytime it comes out a lot so that poo I had to go for this colostomy…then after that I was okey

but now I have got a problem of urine….it's like I can't hold urine… I have to go to the toilet now…that's my problem…"

A comprehensive overview done by Mirabeau-Beale et al. (65) which evaluated, in detail, both specific clinical physical effects and QoL results from various studies. This study highlighted the discordance between how readily physicians score a treatment toxicity compared to patients and suggested that a similar disconnect may exist between the domains of QoL that physicians prioritize compared to their patients. As one participant in the CMJAH study (64) described

"…it's just pain here, and when I come to tell the doctors I have pain here and here [pointing arms and joints] the doctors said no, am working here for the cancer not for the pain here and here, I also have got the problem but I can't tell them…"

1.2.3 Sexual QoL

Quality of life (QoL) is often compromised in patients treated by radiotherapy. The critical and illuminating finding by Burns et al. (55) was that gynaecological cancer survivors who experienced, in particular, late bowel and/or bladder dysfunction, bladder infections and incontinence due to treatment, had a significantly negative impact on their sexuality. Many studies show significant sexual dysfunction, sexual worry and body image concerns (104–112)

Despite these studies bringing attention to these hidden issues, a review of the literature reveals a few notable blind spots of experiences in 1) African women 2) those with locally advanced cancer and 3) HIV populations. A review of literature in 2018 of research in Africa found that out of a total of 380 research articles/reports only 4.1% assessed aspects of QoL among African women living with cervical cancer (59).

A qualitative study done at CMJAH exploring the experiences of women with cervical cancer and long-term effects of treatment (n=16) described the harrowing effect on their sex lives and relationships (64).

"Heish it's too much, my husband nay, he is not feeling alright with me, he has changed…he is saying am sick…it's not okey, he doesn't want to have sex because I feel tired, he just complains."

While the length of cervical cancer survivorship extends, this review highlights that patient's QoL is, to a large degree, invisible and the impact thereof might be grossly underestimated with numerous gaps still existing in our knowledge base.

1.3 Motivation and purpose of this study

In 2017, approximately 1200 new cases of cervical cancer were referred to CMJAH from lower–tier hospitals. This accounts for more than a quarter of all cancers at this institution (hospital records). A significant proportion of these cases (approximately 60%) presented at a late stage with locally advanced disease (Kotzen J, personal communication, 2017).

Toxicities from radiotherapy for cervical cancer have been extensively studied in the last decades and have generated a considerable body of research. Yet the paucity of data where the greatest burden of cervical cancer resides- in low- and middle-income countries (LMIC)- is particularly telling (66) and warrants further examination. Although CCRT has been the standard of care at CMJAH, particularly the late (> 90 days onwards) side effect profile has not been thoroughly documented compared to acute toxicities.

Thus, the primary objectives of this study are:

1. To determine the incidence of severe late gastrointestinal and bladder toxicities in women with locally advanced cervical cancer (LACC) 90 days after completing CCRT and onwards

2. To describe quality of life related to sexual function for patients with LACC treated with CCRT

The secondary objectives are:

1. To calculate doses delivered to rectum and bladder during high dose rate brachytherapy for those patients who developed severe grade 3 and 4 late rectal and bladder toxicities 90 days after completing CCRT and onwards

2. To describe patient reported rectal and bladder symptoms at each follow up visit for those patients who developed severe grade 3 and 4 late rectal and bladder toxicities 90 days after completing CCRT and onwards.

Chapter 2 Methods

2.1 Study Description

2.1.1 Study location

The Radiation Oncology Department of the University of the Witwatersrand, South Africa based at CMJAH, is a center for training specialists, with an outpatient and inpatient facility with 24 beds, and 4 LINACSs, 1Cobalt machine and 2 HDR (Ir192) remote after loading units. The waiting time is kept to start treatment within 40 days based on a prospective study on the impact of waiting times at this hospital (67).

2.1.2 Study design

This is a retrospective analysis of prospectively collected study data from the control arm of a Phase III randomized controlled trial investigating the benefits of the addition of hyperthermia to chemoradiation (Appendix 1).

2.1.3 Sample size

The control arm had 87 patients in total. 11 patients were excluded with 76 patients fulfilling the inclusion criteria and exclusion criteria below.

2.1.4 Study period

The study period for this research was 1 January 2014 to 30 June 2017. This period consisted of enrollment, treatment, follow up consultations and monitoring of each patient over a two-year period. Follow-up consisted of a physical examination; Quality of Life survey; routine blood investigations (full blood count with differential, creatinine clearance and electrolytes, CD4+ T-cell count and HIV viral load in HIV positive patients), a PAP smear and PET/CT scan at six months (Appendix 6).

2.1.5 Inclusion criteria

This study included all non-pregnant females between ages of 18-70 years with locally advanced cervical cancer (Stage IIB –IIIB) from only the control arm of the hyperthermia trial. Patients enrolled between 1 January 2014 and 30 June 2017 who completed treatment, and had at least 90 days of follow up.

2.1.6 Exclusion criteria

Patients who did not complete treatment. Completion of treatment, as per this study, is defined as 75Gy to Point A and pelvic sidewall more than 40Gy.

2.1.7 Treatment protocol

All patients with cervical carcinoma confined to the pelvis (Stages IIB to III) were prescribed to receive:

1. External beam pelvic radiation: a dose of 50Gy over five weeks was administered to the pelvis with a conventional fractionation consisting of 2Gy fraction per day, a total of five fractions per week [monday- friday]. For EBRT, 4 fields; AP/PA and laterals were used, however, blocks were not routinely used.
2. HDR brachytherapy with a total dose 24Gy was administered in 8Gy per dose to Point A. Orthogonal films were performed for each implant during intra-cavity treatment delivered by tandem or ring applicators. If institutional point ratio of 0.8 was violated, the subsequent insertions had to ensure it was below this threshold, but doses were not adjusted.
3. Chemotherapy using Cisplatin administered as three doses of 80 mg/m², 21 days apart on days 1, 21 and 42 of EBRT.

2.2 Methods

2.2.1 Study variables

The following data were collected for all patients records reviewed:

- Age
- BMI
- HIV status – if the patient was positive, the CD4 count was recorded whether the patient was on ARVs (it must be noted that all patients in the hyperthermia trial were required to be on ARVs)
- ECOG/Performance status
- FIGO Stage
- Number of chemotherapy cycles received
- Brachytherapy doses and cumulative Biological Effective Dose (BED)
- Number of HDR brachytherapy fractions received

2.2.2 Study data collection

Patients to be included in the study were identified through the records of the trial database. Once identified, patients' hospital numbers were used to trace patients files. Those records were then reviewed and the data extracted and transcribed into this study database along with the trial records. Study data was collected in a password protected Microsoft Excel data sheet (Appendix 4). The identified data was used for the study analysis. A Microsoft Excel tool developed by the American Brachytherapy Society was used to calculate the 2Gy equivalent dose for reporting the different fractionation schemes for EBRT and HDR using the EQD2 formula. On AP/PA and laterals 2D radiographs showing applicators, radio-opaque packing was used in the vagina with a contrast filled Foley catheter, allowing for the ICRU 38 bladder and rectal reference points to be determined independently.

2.2.3 Data Quality Assurance

Data quality assurance was ensured through the (i) design of the data abstraction structured checklist and (ii) complete verification of trial database using actual patient file information.

2.2.4 Data analysis

Data was transferred to and analysed using the statistical software package IBM SPSS version 24. Descriptive statistics were used to characterise the study sample. A check for normality was done and, when relevant, mean with standard deviations were reported. In circumstances where data were not normally distributed, medians with inter-quartile ranges were reported. A p-value threshold of 0.05 was used to identify statistically significant correlations between data. Statistical analysis pertinent to each objective is described below.

Incidence of complications

GIT and bladder toxicities were defined per clinical toxicity grades, as per RTOG criteria (Appendix 3). The recorded adverse events are the maximum grade of toxicity observed per patient while participating in the study. Analysis time for adverse events is the time between last treatment and occurrence of the event. The incidences of GIT and bladder toxicities were determined during the follow up of the patients. The follow up of a given patient was defined as the time elapsed between the administration of treatment and a follow-up or the development of the occurence

of an event. The median follow up was defined as the median time between a specific event and when the data on outcomes were gathered. Cumulative frequencies were calculated and the Kaplan-Meier time-to-event analysis was used to determine the actuarial probability of complications arising in patients.

Additionally, survival difference between those with and those without complications was determined using the Kaplan-Meier analysis and the Log Rank (Mantel-Cox) test was used to detect differences in the survival outcomes between the groups.

Brachytherapy doses

Brachytherapy dose analyses were calculated as per ICRU Report No. 38 for reporting techniques for cervical brachytherapy for the bladder and rectal point. Doses were converted to the biologically equivalent dose in 2Gy/fraction ($EQD2/_3$) for an alpha/beta (α/β) of 3 representing the organs at risk (OAR) and was cumulated as Biologically Effective Dose (BED) and EQD_2 as a function of brachytherapy and EBRT. The Wilcoxon sum rank test was used, as the doses was not normally distributed, to check if there was a statistically significant difference between the doses prescribed and ICRU tolerance doses of the organ at risk.

Patient reported outcomes

QoL was prospectively assessed using European Organization for Research and Treatment of Cancer Quality of Life cervical cancer module 24 (CX24) questionnaires, conducted at baseline, then every three months during the first year, and every six months post-treatment in the second year.

The health-related quality of life analyses were done according to the EORTC Quality of Life Group guidelines (46). Incidence and frequencies of each response (‘none at all, a little, quite a bit or very much’) are reported as percentages. For the comparison with clinician graded severe >Grade 3 toxicity, the frequency of patients reporting severe symptoms i.e ‘quite a bit’ and ‘very much’ scores were combined.

The CX24 questionnaire Q31-33 were used to assess GIT related symptoms, Q34-37 for bladder toxicity related symptoms and Q45-54, related to overall sexual functioning.

Vaginal symptoms corresponded to QLQ-CX24 questions Q41-43, body image Q45-47, sexual worry Q48, sexual activity Q49, and in those sexually active: Q50-53, for sexual function and Q54 for sexual enjoyment (Appendix 5).

2.2.5 Ethics

Ethics clearence was obtained from the University of Witwatersrand Human research Ethics Committee (HREC), ethics clearence number M170694 (Appendix 8). Permission was obtained from the CEO of CMJAH to conduct this study (Appendix 9)

Chapter 3 Results

A total of 87 patients from the contral arm were identified from the trial database, of which 76 were eligible for inclusion. Seven of the 76 patients with ≥Grade 3 bladder complications as per RTOG classification were identified. Four of these seven patients had no evidence of disease (NED) whereas the remaining three had disease progression but no conclusive evidence as to whether the complication was radiation related. A total of six patients were found to have a GIC. Of these patients, four had no evidence of disease (NED) during follow up. In the other two patients, with disease progression, it could not be conclusively ascribed to either purely disease or radiation. Three patients developed both BC and GIC and one of which had NED.

3.1 Patient Characteristics

The overall study population's mean age was 50 years ± 10.6 (n=76). With regard to HIV status, 50% (38/76) of the patients were HIV positive, with a mean age of 45.2 years ± 9.3 and a median CD4 count of 518 (range: 374-626). The mean body mass index (BMI) for 76 patients was 26.62 (± 6.5). Of these 76 patients, 11% were underweight and a significant proportion (25%) were overweight, 35% of which were considered obese. For those patients who experienced a severe late toxicity event, the mean age was 52.7 ±6.7 for those with BC and 46.5 ±7.0 for those with GIC, yet the mean BMI for these patients was the same as patients who did not experience any severe late toxicity event.

Concerning the FIGO staging of the population for this study, the sample consisted of 64% (n=49) FIGO IIIB of which 18 patients had hydronephrosis. Four of these 49 stage IIIB patients developed bladder complications, while 6 of the 7 with BC were stage IIIB. All patients with GIC were Stage IIIB. Regarding treatment, 89% of all patients received at least one dose of cisplatin. All patients completed an entire course of 50Gy in 25 fractions of EBRT and three doses of 8Gy brachytherapy fractions within 56 days.

Table 3.1 is a summary of the patients characteristics.

Table 3.1 Patients Characteristics

Variables	**Total SAMPLE N=76**		**BC and NED N=4**	**BC N=7**		**GIC and NED N=4**	**GIC TOXICITY N=6**	
	No	% Or Mean (SD) or Median (IQR)	No	No	% Or Mean (SD) or Median (IQR)%	No	No	% Or Mean (SD) or Median (IQR)
Age at enrolment	76	50.07± 10.6		7	52.7±6.7		6	46.5 ±7.0
Age Categorical								
20-39	16	21%		0	0%	1	1	
40-49	18	24%	1	2	29%	2	3	
50-59	26	34%	2	4	57%	1	2	
60-69	14	18%	1	1	14%			
70+	2	3 %		0	0%			
BMI kg/m2	73	26.62± 6.5			26.1 ±9.6			26.1±8.2
BMI Categorical								
Underweight <18.5	8	11%		2	29%		0	
Normal weight 18.5-25	21	29%		1	13%		3	
Overweight 25-30	18	25%		2	29%		2	
Obese >30	26	35%		2	29%		1	
HIV status								
Negative	38	50%	1	2	29%	0	1	
Positive	38	50%	3	5	71%	4	5	
CD4 Count	35	510 (374-626)		5	391 [360-455]		5	424 (413-639)
Stage of Cancer								
2B	27	36%	1	1	14%	0	0	
3B	49	64%	3	6	86%	4	6	
Hydronephrosis								
No	58	76%	4	6	86%	4	6	
Yes	18	24%	0	1	14%	0	0	
Cisplatin doses								
None	8	11%		0		0	0	
1 dose	32	42%	2	5	71%	3	5	
2 doses	36	47%	2	2	29%	1	1	

Months since completion of treatment at last follow-up								
3 months	1	1.3%		0			0	
6 months	12	15.7%	1	1			0	
9 months	13	17.1%					0	
12 months	16	21.1%	1	2		2	3	
18 months	17	22.4%	1	2			0	
24 months	17	22.4%	1	2		2	3	
Time interval between completion of treatment and death (months)								
3 months	0	0%	-	-			0	
6 months	8	10.5%	1	1			0	
9 months	3	4%	-	-			0	
12 months	5	6.6%	-	-			2	
18 months	7	9.2%	1	2		2	1	
24 months	3	4%	-	1			1	
≥ Grade 3 complications								
Bladder complications	7	9.2%	4	7				
GIT complications	6	7.9%						
Both bladder and GIT	3	3.9%	1	2				
Grade of max BC or GIC toxicity								
3	2	2.6%	1	2		2	2	
4	5	6.6%	2	4			2	
5	3	3.9%	1	1		2	2	
Status at 6 months								
Alive	67	88%	3	7		4	6	
Dead	6	8%	1	0		4	0	
Unknown	3	4%					0	
Deaths						2	4	
Total number of deaths end of study period	26	34%	2	4		2	4	
Deaths within the first year	15	20%	1	1		0	0	
Follow-up						2	4	
Less than 12 months	29	38%	1	2		2	3	
12-24 months.	34	45%	2	3			1	
More than 24 months	13	17%	1	2		2	2	

3.2 Bladder Complications

Table 3.2 Details of patients with severe bladder complications

	ID	Age	Stage	HIV	Cisplatin Doses	Grade	Detected at follow up visit (months)	Date last follow up visit (months)	Death at month	Total Bladder BED3/ EQD2_3	Details of complication and cause of death if applicable
BC with NED	29	54	2B	+	2	5	5.7	12.3	16.5	118/ 70.8	NED Biopsy of VVF confirmed radiatiom related at 6 months. COD: post-surgery for urinary diversion with renal failure at 16.5 months
	90	60	3B	-	1	4	8	18	-	*	NED VVF biopsy proven to be radiation related.
	161	52	3B	+	1	5	6	6	6	136/ 81.6	NED Widespread metastasis on 6 months f/u PET scan however no local disease at the time of death so considered NED. Renal failure and bladder obstruction.
	30	42	3B	+	2	3	18.5	24.5	-	131.6/ 78.9	NED Biopsy proven radiation related cystitis, had a urological intervention with CT IVP and stent urine obstruction. Both BC and GIC
BC with GIC	84	44	3B	+	1	3	9.6	18.2	19.5	120.6/ 72.4	Severe cystitis needing surgical intervention at 10months. COD: PD at 20months. Both BC and GIC
	75	56	3B	-	1	4	12	11.2	16	148.7/ 89.2	RVF and VVF no biopsy. COD: PD Both BC and GIC
	57	57	3B	+	1	4	18.5	26.8	-	134.7/ 80.8	VVF onset at 18.5 months and biopsy showing residual disease at 27months

*BC: bladder complication, GIC: gastrointestinal complication, NED: no evidence of local disease, f/u: follow up * missing data COD: cause of death PD: progression of disease VVF: vesico-vaginal fistula RVF: recto-vaginal fistula*

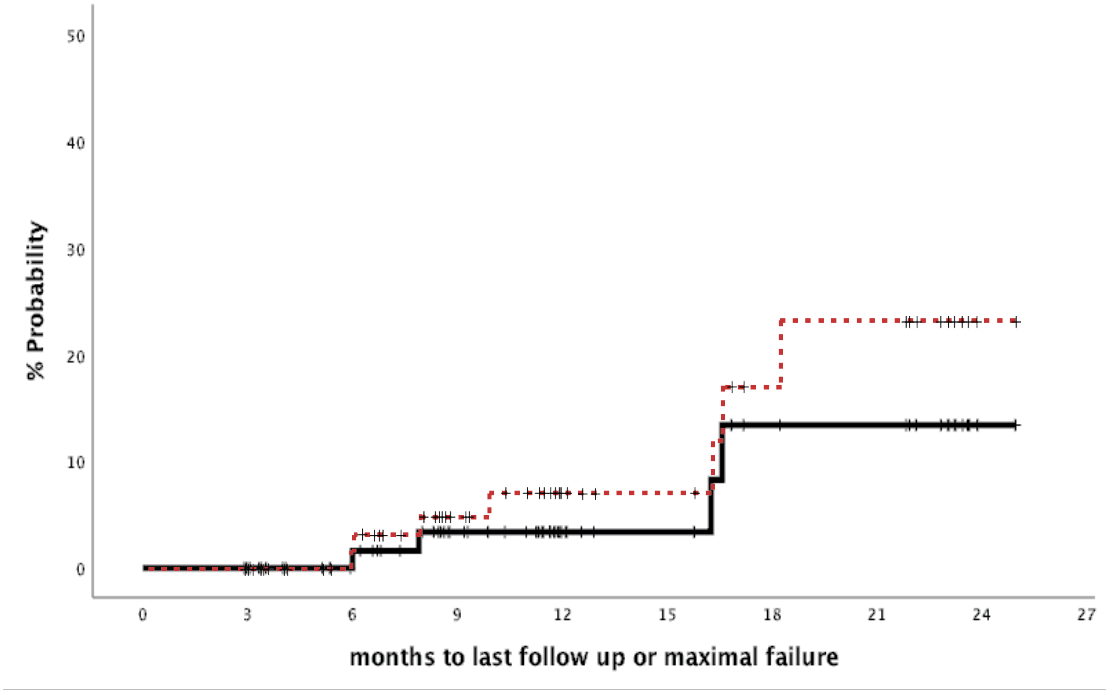


Figure 3-1 Kaplan Meier actuarial probability of developing a severe bladder complication for all patients (dashed line) compared to those with no evidence of disease (solid line). (QoL-axis scale to 50%)

3.2.1 Incidence of bladder complications

The median time of follow up was 11.7 months (IQR 8.1-17.3 months; range 3 - 25.4 months) where 62% of patients had at least 12 months of follow-up, of which there were 13 patients (17%) who had at least 24 months of follow-up. However, during the study period a total of 34% of the overall sample (n=26) patients had died.

Bladder complications had an incidence of 9.2% of the total sample (seven patients in the sample of 76), which translates to 8.7% incidence rate per year and an actuarial probability of 6.9% and 20.7% at 1 and 2 years respectively. Consequently, it was determined that the median time to develop complications was 11.9 months (range 6 - 18.6 months).

Patients with bladder complications but had NED made up 5.3% of the total sample (n=4) and developed complications with an actuarial probability of 3.3% and 12.5% at 1 and 2 years respectively.

In terms of the grading of the bladder complications:

- Two of the seven patients with bladder complications had Grade 3 urinary obstruction, which necessitated a urological intervention.
- Four of the seven developed an initial Grade 4 vesicovaginal fistula (VVF), with one of them further classified by maximal damage i.e. a Grade 5 fatality.
- Four of the seven patients required surgical intervention excluding biopsies; and
- Of the four patients with NED, there was one with a Grade 3 complication, one with Grade 4 complication and the remaining two had fatal complications.

In total, four fatalities occurred, two of which are considered to be related to disease progression and two related to radiation. One of the radiation related fatalities was initially a Grade 4 event, which was detected at 5.7 months, however the patient died at 16.5 months. The other fatality developed bladder complication at 6 months and died immediately from bladder outlet obstruction. The majority of patients died much later than the onset of the toxicity – illustrating that they lived for an extended period with the complications.

Analyses showed that stage of disease was not statistically significant between those who developed the complication and those without (OR 1.33 (0.3-5.2) p=0.7 chi 0.15 =-0.7).

Further to this, multiple organ- bladder and GIT complications- occurred in three patients; with concurrent vesicovaginal fistula (VVF) and recto-vaginal fistula (RVF) developing in two of these three patients. With regard to the two patients that died, one developed RVF at 6 months and a VVF at 9.6 months but lived for 13.5 months after treatment. The other developed RVF at 9 months and bladder complications at 12 months and died within seven months, both patients died from disease progression. The third patient is still alive and is considered disease free.

Regarding frequencies of complications - when calculated, frequencies versus the actuarial estimates of complications were different. The cumulative frequencies of complications after the first year was 5.26% and another 5% in the next year, indicating that just as many events occurred within the first year as in the second

year. By contrast, the actuarial risk is significantly higher at two years at 20.7%. For those patients with NED, the cumulative frequency was 2.6% at after the first year and 2.8% in the second year, versus a 3.3% and 12.5% actuarial probability at 1 and 2 years.

The probability of being alive with or without severe complications was not statistically different (Chi-Square 0.788 p=0.375 Log Rank (Mantel-Cox). However, those without complications lived longer and the median survival was not yet reached.

3.2.2 Brachytherapy doses

One of the seven patients had missing data. Four of six patients exceeded $EQD2_3$ of >75Gy. All patients had at least one fraction that exceeded a point ratio relative to Point A of 80%.

The median $EQD2/_3$ was 79.9Gy (range 70.8-89.2Gy) did not significantly exceed the threshold of 75Gy and was not different to the threshold 80Gy (Wilcoxon signed rank test for equality of medians to the threshold 75Gy p=0.173 and 80Gy p=0.834).

The median BED_3= 133.6Gy (range 118-148.7Gy). The Grade 5 fatalities doses to the bladder were BED3 =118Gy and 136Gy and $EQD2/_3$ of 70.8Gy and 81.6Gy respectively. Patients with VVF all exceeded 80Gy (range 81-89Gy).

3.2.3 Patient reported outcomes

Concerning patient reported outcomes, overall there was a 77% response to the questionnaire. Overall bladder morbidity i.e. frequency, dysuria and leaking urine was reported over the study period with a frequency of 32% of those with bladder complications which was three times higher (11%) than those without complications. The overall bladder morbidity remained high and matched the baseline prevalence of 20% through 6 - 18 months, with a temporary respite at the 12-month mark (Figure 3-2).

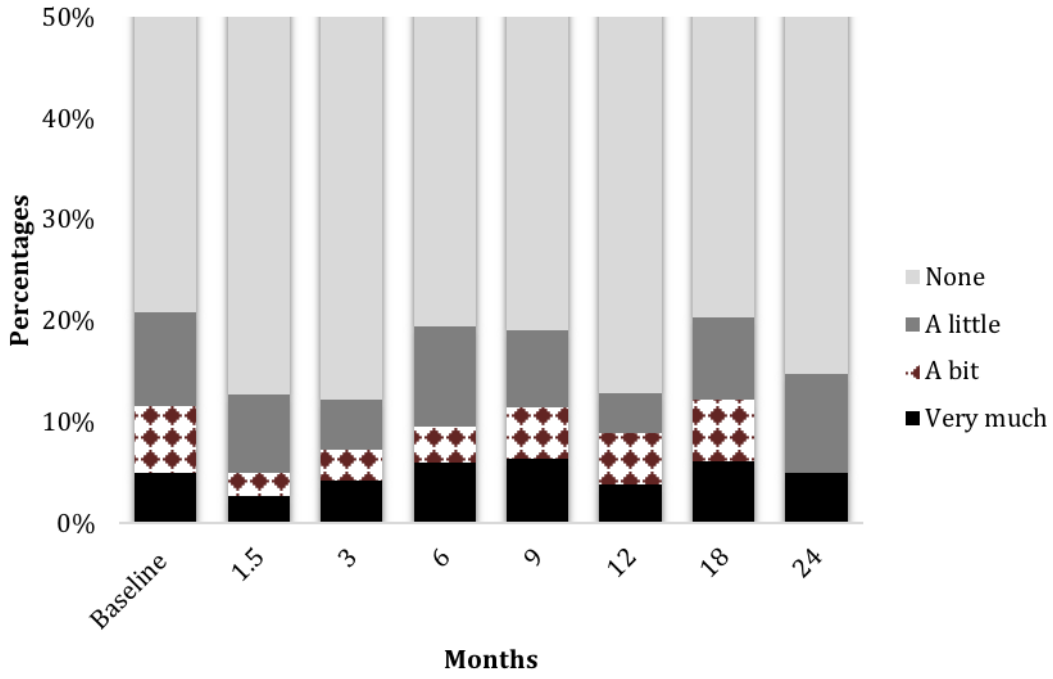


Figure 3-2 Overall bladder morbidity over time

In terms of symptoms, Figure 3-3 highlights that leaking urine is a very specific symptom that was reported by patients with fistulas throughout the course of follow-up. Very few patients reported difficulty to empty their bladder with only seven patients at baseline and two patients reporting symptoms at three and six month follow-up visits. However, it was these two patients who developed obstructive complications. By contrast, dysuria is the most frequent and constantly elevated complaint with a significant number of patients reporting this symptom.

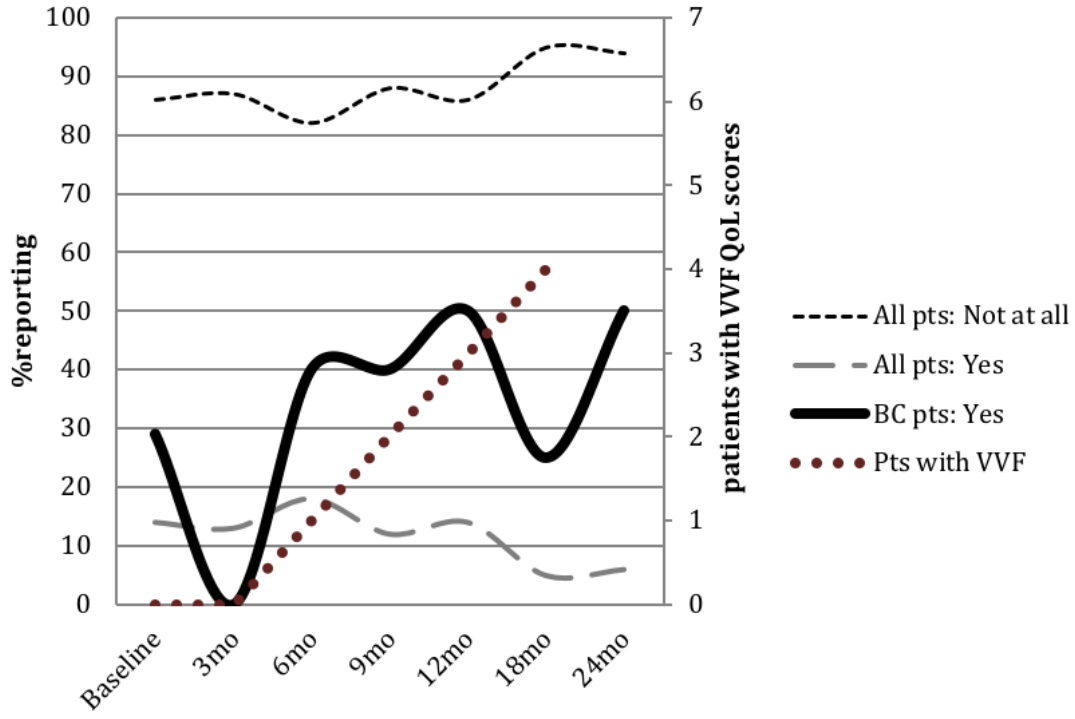


Figure 3-3 Comparing PRO leaking urine for all patients and those with bladder complications (BC). Cumulative frequencies of patients with fistulas are shown.

3.2.4 Clinician vs. Patient reported severe toxicity

Clinician graded bladder toxicity was found in 9.2% of patients while the frequency of patients reporting severe (‘quite a bit’ and ‘very much’) urinary symptoms was, on average, 7%. It was noted to be 5% in those without complications, but four times higher (21%) in those with complications. This shows that the frequency of “severe urinary symptoms” patient reported outcomes (PRO) slightly correlates with the clinicians. Nonetheless, those with bladder complications reported significantly more severe urinary symptoms overall.

3.3 Gastrointestinal Complications

Table 3.3 Details of patients with severe gastrointestinal complications

	ID	Age	Stage	HIV	Cisplatin Doses	Grade	Detected at follow up visit (months)	Date last follow up visit (months)	Death at month	Total Rectal BED3/ EQD2_3	Details of complication and cause of death if applicable
BOTH BC and GIC	75	56	3B	-	1	4	10	11.3	16	116.4/ 69.8	Both Grade 4 VVF & RVF COD: PD
	84	44	3B	+	1	4	6	18	19.5	119.7/ 71.8	Both Grade 3 BC and Grade 4 RVF COD: PD
GIC with NED	30	42	3B	+	2	3	18.5	24.5	-	115/ 69	NED Biopsy proven radiation related cystitis, had urological intervention with CT IVP and stent for urine obstruction. Bowel obstruction. Both BC and GIC detected at 18 months
	82	45	3B	+	1	3	25	25	-	126.5/ 75.9	NED Biopsy proven severe proctitis with significant bowel related symptoms.
	86	37	3B	+	1	5	11.6	11.6	13	120.4/ 72.3	NED Bowel obstruction due to radiation, confirmed on biopsy
	87	52	3B	+	1	5	10.8	10.8	12	125.5/ 75.3	NED COD: complications from radiation, with more bowel than rectal symptoms

*BC: bladder complication, GIC: gastrointestinal complication, NED: no evidence of local disease, f/u: follow up * missing data COD: cause of death PD: progression of disease VVF: vesico-vaginal fistula RVF: recto-vaginal fistula*

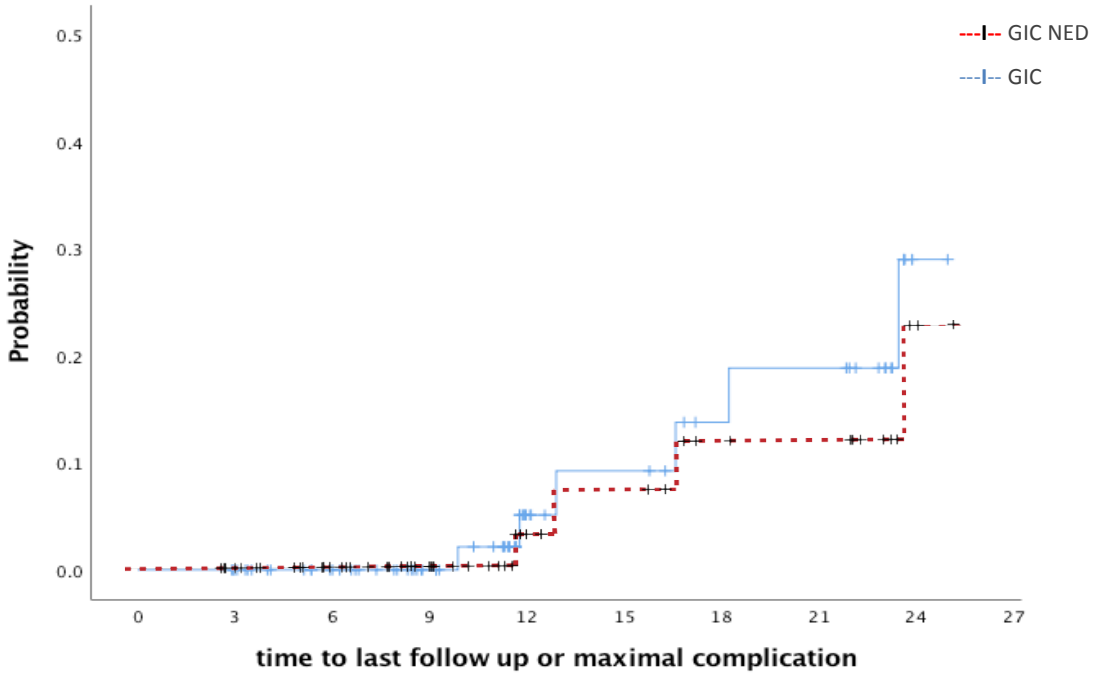


Figure 3-4 Kaplan Meier acturial probability of developing a severe GIC (solid line) and GIC with no evidence of disease (dashed line)

3.3.1 Incidence of GIC

With regard to patient follow-up, the median time of follow up, to event was 11.9 months (IQR 8 - 18.5 mo.; range 6 - 18.5 mo). In the case of GIT complications, the incidence was 7.9% ≥ Grade 3 GI toxicity. It was found that there was an equal frequency of 2.6% for Grade 3, 4 and 5; with a 7.6% incidence rate per year and an actuarial probability of 3.7% and 25.8% at 1 and 2 years respectively, and finally, in those with NED it was 0% and 23.1% respectively (Figure 3-4).

In terms of the grading of the GIT complications, of the six patients with GIT complications, two patients had a Grade 3 event and the remaining four had an initial Grade 4 event. Ultimately, two of these patients died, which was then recorded as the maximal (Grade 5) radiation related toxicity. Only two of the six patients had a fistula complication and both patients had disease progression. Those with NED had bowel related symptoms and complications.

Fatalities were noted in four patients, where two were considered strictly radiation related.

For the patients with GIC, the duration of the median time-to-event for Grade 3 was 17 months, versus 10 months for Grade 4 and 12 months for the one with Grade 5 complication. All patients with NED, onset occurred after one year.

With regard to the impact of the stage of the disease on the development of GIC, it was determined that the stage of disease did not play a role as there was no significant difference between actuarial probabilities of late complications in relation to stage.

Additionally, looking at the cumulated frequencies (4.6% and 12% per year) and actuarial estimates of complications (3.7% and 25.8%) - both increased over time, as expected, with late complications however, notably, the cumulated frequencies underestimated the risk to patients in the second year.

Finally, with regard to the survival for those with and without complications- there was no statistical difference noted (Chi-Square 0.788 p=0.375 Log Rank (Mantel-Cox). However, it was noted that those without complications lived longer (Figure 3-5)

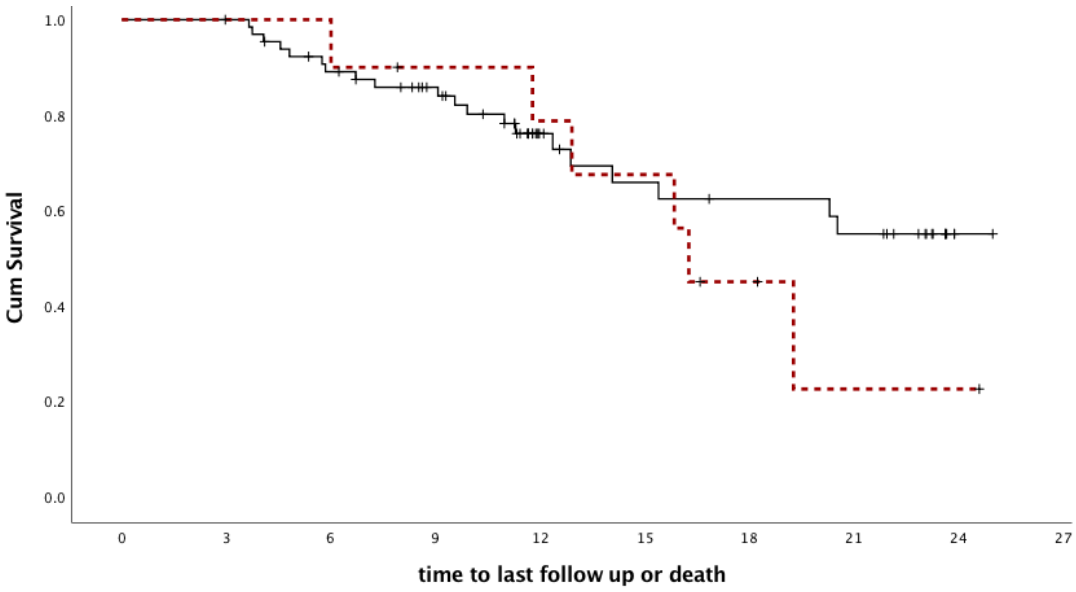


Figure 3-5 Survival for those with complications (dashed line) compared to those without complications (solid line)

3.3.2 Brachytherapy doses

The median EQD2/$_3$ was 72.1Gy (range 69-75.9Gy) which was not different from the threshold of 70Gy or 75Gy (Wilcoxon signed rank test for equality of medians to the threshold p=0.116). Only in two patients was the maximum 75Gy reached, but all patients' dosage exceeded 70Gy. The median cumulative BED$_3$ =120.1Gy (range 115-126.5Gy).

3.3.3 Patient reported outcomes [PRO]

Concerning PRO, there was a 77% response to the QoL questionnaire, showed an overall bowel morbidity (combined QLQ-CX24 questions 31-33) in a consistent amount of patients (20-25%) whose symptomatology persisted throughout the entire follow up period. This showed little differentiation over time when compared to their baseline report as shown in Figure 3-6.

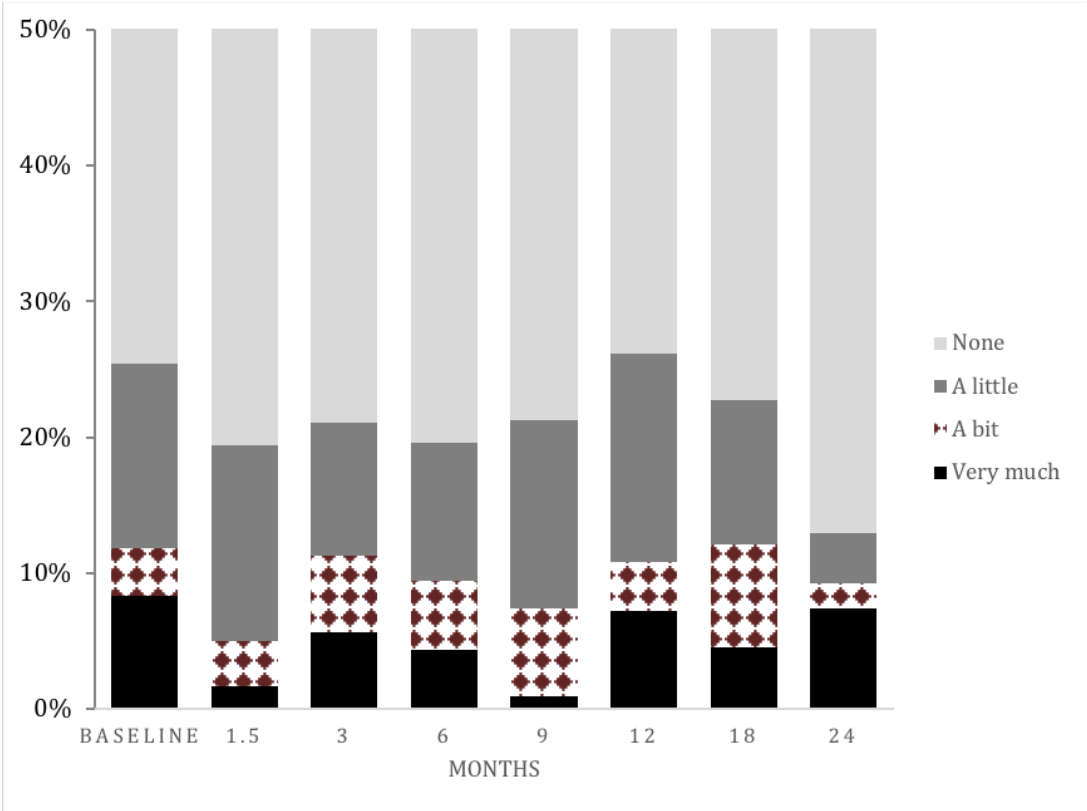


Figure 3-6 Overall bowel morbidity (abdominal cramps, difficulty controlling bowel and blood in stools) in all patients

Abdominal cramps were a common symptom expressed and were determined, upon further individual symptom analysis, to be the predominant symptom with the highest incidence and most persistent over 2 years. The cumulative prevalence was 46%, where 63% of patients reported abdominal cramps at baseline with only half as many (n=26) going on to report it in the subsequent follow-ups. There were 3 patients who had bowel obstruction and who reported severe abdominal cramps at *all* follow up visits preceding the event. The second most prevalent reported symptom was blood in the stool at 14%, compared to the 45% of patients experiencing abdominal cramps. Figure 3.7 show the relationship between obstruction symptoms in this patient with obstructive complications.

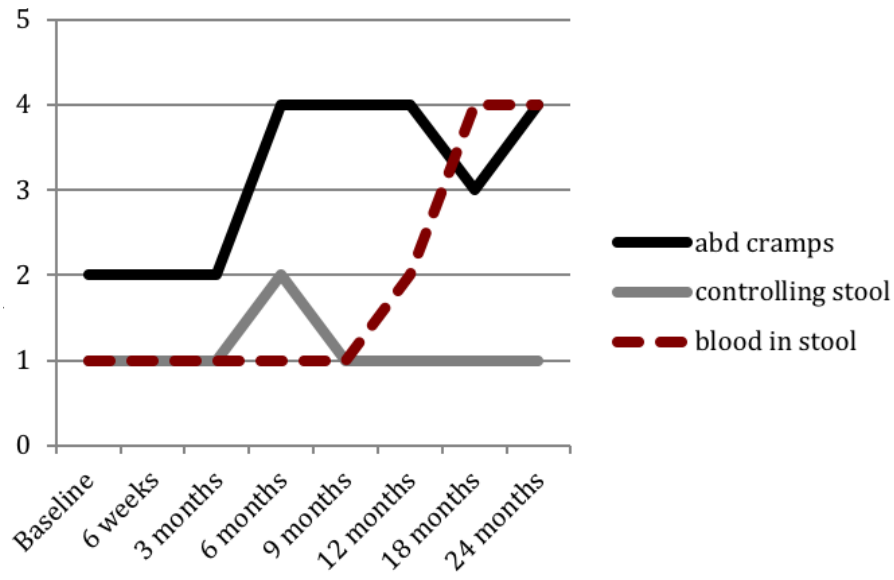


Figure 3-7 Obstructive symptoms predomiinate in patients with bowel obstruction

3.3.4 Clinician vs. Patient reported severe toxicity

The overall frequency of reporting the clinical equivalents of severe such as ‘quite a bit’ and ‘very much’ in patients with GIT complications was 35% (Table 3-4). The clinician RTOG scoring ≥ Grade 3 toxicity incidence was 7.9%, much lower than the 10% patients who reported in the ‘clinically equivalent proxy’ i.e. ‘quite a bit’ and ‘very much’. The incidence of severe symptoms was twice as much in those with GIC (21%) than those without (Table 3.4). Notably, the frequency of severe symptoms of those with GIC was significantly larger than those without.

Table 3.4 Overall bowel morbidity comparing clinician graded and patient graded complications

Overall Bowel Morbidity PRO (%) vs. Clinician RTOG grading						
	All N=76	Without GIC N=70	≥Grade 3 GIC n=6	Grade 3 N=2	Grade 4 N=2	Grade 5 N=2
Very much	5	4	13	11	11	12
Quite a bit	5	4	9	6	17	9
A little	12	12	11	17	3	12
None at all	78	80	67	66	69	67
Frequency of PRO symptoms (%)						
Abdominal cramps						
Any	46	46	46	50	50	50
Severe	21	19	34	25	42	40
Incontinence						
Any	5	4	15	6	25	20
Severe	3	2	6	0	25	10
Blood in stools						
Any	14	12	35	44	25	30
Severe	6	4	24	25	25	20

3.4 Overall quality of life

The global symptomatic burden of bowel, urinary, general, gynaecological and sex related symptoms (EORTC QLQ-CX24 questions Q31-54) were significantly higher in those with versus those without complications (60% vs. 25%) as seen in . Those who died (32%) had faced a higher burden than those that remained alive (25%), yet it's recognized that all patients still experienced significant symptoms.

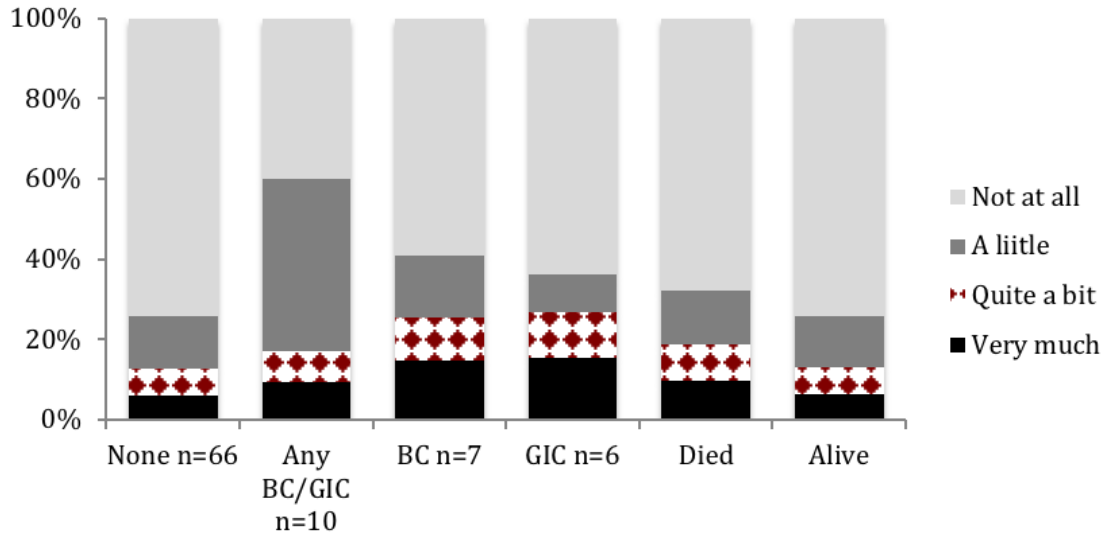


Figure 3-8 Global symptomatic burden (bladder, bowel, vaginal, and general symptoms and sexual function EORTC QLQ/CX24 questions 31-54) of patients with and without complications and those alive and who died

3.5 Sexual Function

Sexual worry characterized by the worry that sex would be painful was prevalent in half of all patients. At baseline, almost 60% of patients at baseline expressed this concern and this remained constant for the first year but decreased over time to 35-40% in those who had survived beyond a year.

Looking at the trend in this reporting, there was a dip at the six week visit where, perhaps, sex is not a priority for patients - whereas later it was seen that this worry increased from 6-9months when the patients were, potentially, feeling better clinically and having sex became more of a concern. This corresponds to the increase in sexual activity at the same time period in Figure 3-9. However, the majority of patients (84%) reported not being sexually active at all. Only 11% of patients (n=8) reported being sexually active at baseline and this doubled by six months (n=17) and plateaued to 30% of patients after nine months. Overall, 10% of patients over 50 years of age reported having sex which is half that of younger women (Appendix 7).

Unexpectedly, a vast number of patients (75%) who are sexually active found it enjoyable (ranging from 36% ‘a little’ to 42% ‘very much’) while just as many (60-70%) reported it being painful, with half of these patients experienced severe pain. Out of the 72 reports of sexual activity, pain during intercourse was reported in 65% of patients while 77% found intercourse enjoyable. However 51% enjoyed sex while

still experiencing pain and 26% enjoyed sex without pain and 14% who did not enjoy intercourse reported pain.

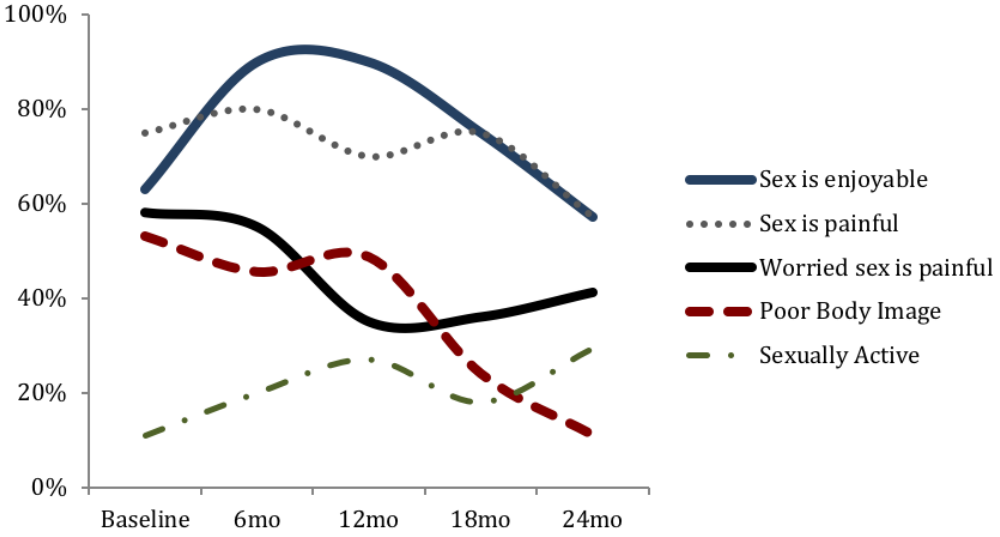
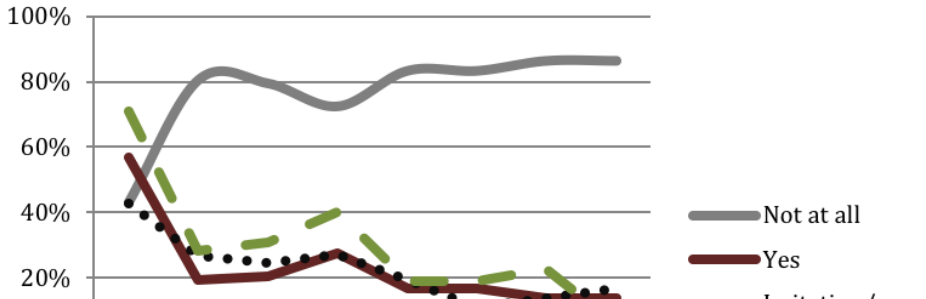


Figure 3-9 Comparison of responses to Sexual Quality of Life questions



	BL	6wks	3mo	6mo	9mo	12mo	18mo	24mo
Not at all	43%	81%	79%	73%	83%	83%	86%	86%
Yes	57%	19%	21%	27%	17%	17%	14%	14%
Irritation/sore	43%	27%	25%	27%	19%	11%	14%	17%
Discharge	71%	28%	31%	40%	19%	19%	23%	6%

Figure 3-10 Vaginal symptoms

With regard to complaints of vaginal symptoms, the highest proportion of patients reported complaints of discharge instead, with 71% at baseline and 40% at six months, this, was much higher than reports of vaginal soreness and/or irritation, which was reported at only 43% and 27% respectively, as illustrated in Figure 3-10.

With regard to poor body image- this was delineated as feeling less attractive, feminine and dissatisfied with your body and was reported in half of all patients at baseline and remained constant concern for half of all patients up to a year post treatment as seen in Figure 3.9. Overall, all age groups had similar poor body image concern, however this was more prevalent in younger patients, 40% of whom, when asked if they felt less attractive, feminine or satisfied, reported the higher scale item of ‘very much’ - indicating a the intense importance of this aspect of understanding post-treatment experiences of patient.

Differences by age in this study are shown in Appendix 7. Sexual worry was the most discordant between post and pre-menopausal groups with 40% of women older than 50 years compared to 60% and 86% of 31-50 years and under 30 years old women respectively.

Chapter 4 Discussion

The present study sought to determine the incidence of severe late bladder and GIT complications and describe the quality of life of these patients with locally advanced cervical cancer treated with CCRT. The main finding of this research is that there remains a very high morbidity and mortality risk, with an undeniable impact on patient's QoL.

4.1 Demographics

We know from the study by Olorunfemi (5) in 2017 that in HIV positive patients, the peak for developing cervical cancer was 40-49 years (24.9% of n= 18717). This age group is closely followed by those who are 50-59 years (23.0% of n=17264) where the mean age at cervical cancer diagnosis was 52.3 (SD 13.7) years and almost half (43.1%) of the cases were of reproductive age (15-49 years) (5).

In this study the mean age at enrollment was 50 years, with HIV positive patients averaging at 45.2 ± 9.3 years. This is in keeping with the Olorunfemi study. The preceding suggests that cervical cancer rates are likely to increase among older PLWHA (and indeed in the general population) as access to ART and screening increases. This is reflected in this sample. Those who had any severe complication showed no difference in age compared to the overall study population.

In this study, 21% of HIV positive patients developed a severe bladder complication and 71% of patients with any complications were HIV positive. Although this is a high prevalence, there was no statistically significant relationship found between HIV and severe toxicity. Clinically, however, it could be considered significant in that it can limit treatment. This is an important finding because, to date, there is little data on late effects in HIV positive patients. In the data that exists from higher income countries, with good screening programmes, most refer to early stage cases and only a few HIV patients that were enrolled in trials. Historically, HIV patients were also excluded from receiving chemotherapy.

4.2 Bladder Complications

4.2.1 Incidence and temporal nature of complications

This study found an incidence of 9.2% but an actuarial risk of 6.9% and 20.7% at 1 and 2 years respectively which is significantly higher than our contemporary comparator Zuiliani et al. who reported a 5-year actuarial rate of 9.7% with a virtually identical treatment protocol (48). These results are especially high considering the short median follow up and that the 3-4 years actuarial rates reported during the 1980-1990s was7-15% (22,68)- even after doses to the central pelvis were limited to less than 50Gy (69).

Additionally, early 1-year actuarial estimates compared to the 2-year risk are significantly different and overall much higher than expected. It was found that cumulated frequencies and actuarial estimates of complications do not correlate and can be misleading. The cumulated frequencies were found to increase as expected with late onset events; however, we see that just as many events occurred within the first year as within the next. This could be explained by the high early mortality rate. It is, therefore, clinically significant that proportionally 5% of patients who do survive a year, develop complications, however an actuarial probability of 20.7% gives an accurate sense of the real risk to surviving patients. Cumulated frequencies can therefore misjudge the risk especially in advanced disease as these patients often die of their disease ahead of the period of the greatest risk for complications.

The separation of risk by grade showed that Grade 4 VVFs occurred earlier within the first year whilst the later milder Grade 3 events occurred later with almost 6-month difference in the median time to event. One possibility is that it is hard to differentiate between a malignant or treatment induced fistula. However, it seems that in this study, the early VVFs were more radiation related as the two patients who developed VVFs at 6 and 8 months had confirmed radiation changes on biopsy and the patient who had both a RVF and VVF, who ultimately died from disease progression, also had the highest brachytherapy bladder point dose (89.2Gy).

This is important as it gives us confidence in ascribing the development of early VVFs to radiation but the early onset of VVF is concerning and needs to be further

characterized. In addition, the time at which they appear may help in alerting the clinician that follow up visits should be geared toward this pattern.

In patients who have an advanced form of disease - their first year remains precarious, both for the risk of bladder complications and risk of death. Illustratively, three patients, accounting for 4% of this cohort of 76, suffered complications affecting both the bladder and rectum - two of whom eventually died.

Advanced disease plays an important role in the development of complications, as shown by Lanciano et al. 'Pattern of Care' Study, where the 5-year actuarial major complication rates were 16% and 20% for advanced Stage II and Stage III patients, respectively (70). The difference between actuarial probabilities over time is consistent with a more aggressive therapy approach and with higher total doses of radiotherapy in patients with the most locally advanced tumours (69–71) and the relatively poor prognosis of patients with cervical cancers - which was equally observed in this study.

Although there were no statistically significant associations in this study with advanced stage of disease and those who developed complications (with or without evidence of disease), this study's high mortality rate was consistent with the high tumour burden and advanced disease. Of the 26 patients who died, the median time to death was 10.5 months (range 3.7-20.9 months) alarmingly, with 60% having died before one year.

4.2.2 Brachytherapy doses

This study did not seek to make any definitive conclusions or correlate HDR doses with outcome. In this institution (CMJAH), the protocol is to ensure that the bladder does not recives more than 80% relative to Point A, and if it is that future isnertions should ensure doses less than the threshold but there is no rule that there will be a dose adjutment.. This study found the median doses exceeded the standard thresholds and almost all patients had at least one fraction that violated the insitiuitonal 'rule' of a point ratio of 0.8. The high doses exceeding recommended thresholds could be one explanation for the high morbidity rates (72) as studies have found a correlation with Point A doses greater than 80Gy and severe bladder complications (44,73) and in advanced disease. The 'Patterns of Care' study found

that in advanced disease there is a significant relationship between Point A dose and complications >85Gy (72).

By contrast, it could be considered that in locally advanced disease the dose to Point A should be sufficiently high to deliver at least 85Gy to the tumour and, by default, implies that the high dose to organs at risk (OAR) is an accepted trade off. It can be argued that if one does not treat to such high doses that proximate the OAR tolerance doses, the tumour may not be receiving the adequate dose. Most recently Manea et al. in 2018, found a cumulative incidence at three years of 2.7%, and when correlating the ICRU dose to the bladder, the incidence ≥ Grade 3 complications were higher (35.6% vs. 21.6%) when the dose exceeded a much lower threshold of 65Gy (HR 13.5 p=0.018) (74). The authors recommend that dose should be kept less than 70-75Gy (74).

In our institutional treatment planning protocols, a clinical markup for conventional 2D planning is used as opposed to the more conformal 3D planning which also could account for the high morbidity rates. Our results are broadly still consistent with rates from studies using CCRT and 2D techniques as seen in the seminal French STIC trial whose urinary ≥ Grade 3 toxicity rate was 9.2% (75). However, the STIC trial median follow up was 24 months while our study was 12 months. The high complication rates seen in our study, when compared to more IGBT techniques which range between 1- 4% for both GI and bladder toxicity, falls significantly short of saving patients at this institution from major morbidity (53,76).

Using IGBT compared to 2D BT has caused a threefold decrease in the rate of global (urinary, bowel, gynaecological) serious side effects, as noted from the French STIC trial 22.7% to 2.6% (75); 21% vs. 7% in the Vienna study by Potter et al (77); and in the recent retrospective analysis from Leiden (78) and Aarhus (79) universities, a decline from 15% to 8% and 10% to 3% respectively was shown. In 2008, an international study on MRI-guided brachytherapy in locally advanced stage cervical cancer (EMBRACE) started and the data most recently published in 2018 in fact demonstrated an astonishingly low 1% VVF in their cohort (80). Further, in this study there was an actuarial 3-year incidence of Grade 3–4 urinary morbidity of 5.3% with most events being urinary frequency, incontinence and ureteral strictures, while Grade 3–4 fistula and bleeding were <1.0% at 3/5-years and without a Grade 5

fatality (80). The benefits of IGBT, as recently shown by Ren et al. in 2016 (81) where 2D planned DVHs were found to deliver significantly less dose to the tumour and more to OARs (especially in eccentric tumours) than 3D planned DVHs. This could be an explanation for high local recurrence rates and disease related mortality -- suggesting that this unit at CMJAH might not be achieving local control.

Cost-effectiveness in LMIC setting could be a barrier to introducing IGBT, however, one of the first studies to evaluate 3D IGBT compared with conventional (2D) brachytherapy for locally advanced cervical cancer from Kim et al (82) shows that it is economically feasible. An inexpensive trans-rectal ultrasound, for example, has been found to be superior to CT, with reasonable image quality (83).

4.2.3 Patient reported outcomes

The study aimed to provide a description of the prospectively collected patient reported symptoms in those who experienced severe late complications. Dysuria was the most frequent complaint and was a commonly reported symptom even beyond the first year with up to a third of the study sample, at any one point in time, still suffering pain when urinating.

Studying the individual urinary symptom levels provides a better understanding than looking at overall aggregated bladder PRO. Patients have very specific symptoms for example; patients with urinary obstruction have difficulty emptying the bladder, while those with fistulas reported, rather, that consistently leaking urine was a major symptom that they experienced. The latter, though, should not to be confused with frequently passing urine, which is a more generalised symptom that is shown to improve for the majority of patients.

In 2017 a RCT proved that a web-based PRO, compared to the usual in-clinic care, for metastatic patients receiving chemotherapy improved the median survival dramatically by 5 months (84). This reveals how patients involved in their care can actually impact on what matters most – their survival. Importantly, it resulted in less hospitalisation, which has a major implication in LMIC settings, such as South Africa, thus PRO may be of use as a prognostic factor for clinical outcomes in patients (85).

Reassuringly, the frequency of severe urinary PRO was found to correlate with the frequency of clinician ≥ Grade 3 complications. The significance of these findings is that specificity of symptoms can alert a clinician to those at risk of developing severe PRO. This data can help guide communication prior to treatment, which will shape expectations and quality of life during recovery and assist in drawing greater attention to patient reported concerns about the impact of the disease and treatment.

Further to this, strategies need to be put in place to negotiate health service obstacles such as interacting with different doctors per each follow-up, inconsistent reporting by junior doctors, language and communication nuances, navigating embarrassment around ask questions about symptoms and the actual reporting of symptoms.

4.3 Gastrointestinal Complications

The study reports on findings in a cohort from prospectively collected information from follow-up visit clinician toxicity assessments as well as concurrent patient reported symptoms in patients with locally advanced cervical cancer.

4.3.1 Incidence and temporal nature of complications

Overall 7.9% of patients developed a severe complication. It was 5.3% in patients with no evidence of local disease, but who had more bowel than rectal related complications, the majority of which necessitated surgery and half of which died. In patients who died from progression of disease, it could not be conclusively excluded as a complication due to radiation independent of disease or whether it was purely due to disease progression, notably these were the only patients who developed a rectal-vaginal fistula.

There was a much higher risk of developing GIT complications beyond the first year, Incidence of proctitis PRO emerges much later with increasing intensity. Notably, there is no visible effect on fecal leakage, with only 5% of patients reporting this symptom and, expectedly, this was specific to those with fistulas. This is in contrast to the EMBRACE trial finding with diarrhea and incontinence being the most frequent PRO (86). It is unclear if using IGBT plays a role in this stark difference.

The high incidence overall though is in keeping with the comparator Brazilian trial which found the highest morbidity related to GIT organs, which was 2-3 times higher than bladder complications. Recent studies in the last five years though show higher and significant gastrointestinal symptoms can be found in up to 20% of patients with locally advanced and unresectable tumours who require EBRT and brachytherapy (25,26). The findings of this study are echoed when Ushijima and colleagues (87), who found with a similar treatment protocol – that of 51 patients; seven patients (13.7%), developed late GIT toxicities between 6 -114 months post treatment. Of the seven cases, four required surgery for life threatening intestinal perforation. By contrast, 10 institutions from eight countries participated in a study which reported the 5-year actuarial rates of major complications in the rectum to be 7.9%, the bladder to be 0% and small bowel 0%, which illustrates a favourable outlook on small bowel but high rectal complication rates (37).

4.3.2 Patient reported outcomes and quality of life

It was noted that there was a much higher risk of developing GIT complications beyond the first year, where the predominant symptom reported was abdominal cramps. The vast amount of patients reported this symptom as severe, however - for those with bowel obstruction- abdominal cramps were constantly reported and always reported at its severest intensity. Those with fistulas were the only patients reporting the very telling symptom of not being able to control their bowel. Across the study there was discordancy with patient's assessment of toxicity severity being greater than that found by clinicians.

This study has shown that severe morbidity is most pronounced when patients report a symptom that eventually is related to the specific complication they developed as is the case with both urine and bowel obstructive morbidity Figure 3-3 and Figure 3-7.

Strikingly, a fifth of patients at some point complained of the severest ('very much') cramps and majority of these reported on more than one occasion. Of these patients there were three patients who complained consistently of severe cramps in the abdomen at each visit, and all of which developed Grade 4 complications, which occurred at 12 months - with two patients dying approximately one month after the bowel complication was detected. The complexity of such a pervasive severe symptom patient especially one as seemingly "benign" as cramps can be easily missed or even dismissed, as it is so common. Yet this study highlights that patients do and can alert the physician to severe toxicity related symptoms, however for bowel symptoms it is key to track the intensity over time, therein lays the potential signal of severe toxicity.

Patients treated with pelvic radiation have been found to have a high frequency of bowel complication symptoms which are clinically relevant (12,23,40,43,44,48,73,87–89,86,90–92), as well having the associated limitations in daily activities, for example, needing to remain in close proximity to a toilet at any given point in the day, as well as having a lower social functioning many years after treatment (58,65,93).

In this study, what marks a difference from other studies, is that the patients baseline quality of life are marked by a high burden of symptoms. What is reassuring, however, is that there was an improvement by 9 months post treatment, with less

than half of patients reporting abdominal cramps. However, the first year is marked by predominance of cramps and this symptomatic burden is then replaced by severe proctitis in the second year. The overall morbidity as shown in Figure 3-6, demonstrates that in some patients the most severe symptoms did not abate and were indicative of severe toxicity.

4.3.3 Brachytherapy doses

The dosimetric analysis found that all patients with GIT complications were within the range of acceptable rectum thresholds and no individual patients exceeded a point ratio of 80%. This 'negative' finding led to the 'uncovering' of the effect of the subjective nature of the rectal point determination, and by implication that there is a false reassurance that only a breach of the threshold will cause toxicity in the patient.

Several authors have pointed out that the ICRU reference points do not generally represent the maximum dose to the rectum (42) (94) (95). Fellner et al. (94) found that the maximum dose to the rectum can be up to 1.5 times higher than the dose at the ICRU reference point and the dose to these points is supposed to be of clinical relevance, however, only some studies confirmed this correlation (44,46,96,97) while other publications failed to highlight this relationship (98,99). Even so, the studies that do find a correlation are often not consistent with regard to what threshold to recommend. In most cases, and as at this institution (CMJAH), these are based on the American Brachytherapy Society older recommendations, that a point ratio of 80% and rectal doses should be below 75Gy (100).

In terms of EQD2, Perez et al. (44) found an increase in >80Gy while Sakata et al. (101) found a steep rise with a 5% and 50% rectal complication rate at 64Gy and 79Gy respectively. Further to this, Roeske et al. (88) found an even lower threshold with a clear increase in GI toxicity over 60Gy. The TBED/3 was correlated by Perez and colleagues (44) in 1211 patients of > Grade 3 rectal complications with more than $TBED_3$ of 120Gy, while Clark et al (46) (in 43 patients) correlated that BED > 125Gy to the rectal point.

Subsequently, Kuku et al. (102) found in their studies that there were complications rates of 0%, 14%, 44%, 72% in $TBED_3$ to the rectal point in patients receiving doses less than 100Gy, 100-120Gy, 120-140Gy and more than 140Gy respectively. It must

be noted, though, that these maximum doses come with the provison that the technical parameters are adequate and, if so, then 100Gy can be recognized as the maximum dose to result in an acceptable incidence of morbidity in patients.

Problems arise with this threshold calculation in practice, as how the calculation is acquired can lead to false conclusions. During the calculations of the ICRU point doses it was noticed that the line drawn that was meant to represent the posterior vaginal wall, as approximated by vaginal packing, was inconsistent. Inadequate vaginal packing may be affected by many factors such as (i) pain tolerance for those given sedation as opposed to general anesthetic; (ii) poor identification of the radiopaque gauze and (iii) vaginal wall or poor x-ray quality. This observation led to further investigations and discussions with registrars, and it was found that some had been mistakenly drawing the vaginal wall 0.5 cm further from the packing. Thus, the calculations by the physicists who add a further (relative to magnification) 0.5 cm as the rectal point would clearly result in lower doses. Resultantly, the ICRU rectal doses in this study should be interpreted with caution, as it is the most subjective, clinician and training dependent. The practical implication of this finding is that training for junior doctors must be a priority.

Considering all of the above, the difficulty is then how to stay below a TEQD2/$_3$ of 75Gy to the rectum. There are some indications that a 20Gy dose may be the upper limit for the dose to be delivered each week to avoid severe rectal complications (103). However, in order to achieve this, without compromising local control in this trial protocol - using 50Gy in 25 fractions EBRT and 24Gy in 3 fraction of BT, during the week that BT is administered, will result in a cumulative TEQD2/$_3$ of 20.8Gy, which is achieved if the point ratio of 75% instead of the current 80% and drops to 19.6Gy at 70% of point A per 8Gy fraction. This is in keeping with recommendation by Clark et al. (43) that for a higher dose per fraction of 8-10Gy the dose to the rectum should be less than 76Gy which corresponds to 75% of this protocol's total EQD2.

Even though there is still doubt if the contribution of even one fraction is equally important despite an overall cumulative dose being less than the threshold, it would then be advisable to aim for less than 75Gy but move towards a lower 75%-point ratio.

Ultimately, the high incidence and increased risk of severe GIT complications of a more bowel obstruction nature beyond the first year of treatment should be investigated further as it may have major implications for the dosing and administration of therapy.

4.4 Reporting of Toxicity

4.4.1 Implications of reporting the maximal damage alone

The median time to develop the initial Grade 3 or 4 event was 9.6 months, yet increased to almost 12 months, when taking the fatal Grade 5 maximal damage as the defining event. The patient who developed a Grade 4 VVF at six months, died more than a year later. Recording of maximal damage means that the information about less severe complications will easily be lost, however, during this time the patient endures increasingly severe complications and a decreasing quality of life, this experience is not captured by the statistics. This is important for understanding the complications associated with the course and progression of the disease. In addition, death cannot be considered the same as, for example, severe haematuria that is reversible. The need to report grade separately and the time of occurrence of each complication grade is critical.

4.4.2 The relationship between cure and complications

The results from different treatment modalities are usually reported as probabilities of cure. However, the probability of being free of complications and cured is actually the goal of treatment.

In this study, the 1 and 2-year probability of being alive for those with and without severe complications () was not statistically different but its clinically important. Those without complications have a better probability of being alive at 2 years overall. What is noteworthy is that the median survival for these patients without complication was not yet reached compared to 21 months for the whole cohort and 13 months for those with complications (Table 4-1). We can see that those without complications do have a small but better outlook and a better QoL.

Table 4.1 Comparing survival

	1-year OS	**2-year OS**	**Median survival**
All patients	76%	48%	21 mo
No complications	71%	60%	Not yet reached
Bladder or GIT	57%	34%	13 mo

**OS- overall survival*

4.5 Sexual Function and Quality of Life

Vaginal discharge presenting as the major complaint is an important observation as many studies found vaginal discomfort as the main vaginal symptoms that was reported while this study found that irritation and soreness is not; and this is one of the first studies to report vaginal discharge as the main symptom. This might well be imitating a partial response to treatment with residual disease manifesting as discharge or recurrence- especially in light of the high mortality rate in the first year in this study. Notably, 50% of younger patients (<50 years) reported more discharge than the 11% of older patients. However, there is a clear and significant improvement of vaginal symptoms over time.

Additionally, an important study by Mantegna et al. (116) looked specifically at those who were disease free, whereas many studies do censor those who were confirmed at a time point to have disease progression (56,120). However, this study did not look at disease free individuals and so the effect of disease related symptoms on sexual QoL cannot be separated purely from the effect of treatment, nor the effect of disease cure worry on sexual QoL. The high mortality rate in this sample would make any observations on pure radiation impact on QoL difficult.

It must be considered that other physical symptoms can play a role in body image and sexual QoL such as diarrhoea, dysuria, having a colostomy, mood changes etc. (117) (118). This includes, fatigue itself, which was noted up to two years later (119). There, too, can be no real distinction of 'worry' being solely related to one cause. A recent 2017 qualitative investigation into the QoL of 24 cancer patients (not pelvic specific) at CMJAH highlighted that the main issue that influenced physical aspects for patients was poverty (63). Worry about cure from disease might, in and of itself override a woman's sexual function and might well be one aspect of life she would compromise on as the disease itself is so tightly associated with sexual activity. This study however did not explore these correlations.

The discordance between how readily physicians score a treatment toxicity compared to patients has been shown (65) and physicians may prioritise different domains in their patients, to those that their patients prioritise.

In addition, the reluctance of healthcare professional to discuss sexuality (121–124) and the reluctance for patients to report results on sexual QoL has resulted in an unmet need of patients. This is shown by the notable discrepancy found by Vistad et al. (119) where 58% of PRO of vaginal discomfort were reported, whilst the clinician actuarial incidence rate was only 23%.

This study did not specifically look at comparing patient's reports and clinicians reports with regard to sexual issues because current follow up in our hospital setting does not ask about sexual issues at all. Contributing factors in this setting to the lack of reporting of sexual QoL complaints can relate to the long wait for a follow up visit where many patients wait 6 months or up to a year for a follow up; as well as doctors having limited time in overwhelmed clinics with human resource shortages. It would prudent to ask for example:

1. *Are you sexually active?*
2. *Do you want to be?*
3. *What do you attribute your worry to?*
4. *Is there anything I can do to help?*

Thus, to best serve these patients providing care on a daily basis without the in-depth understanding of what is most meaningful to our patients only widens the gap in the care of patients. Open communication is needed prior to treatments so as to help shape expectations and to pay attention to their concerns about their bodies and sexual function and to help reassure patients that there are improvements over time.

One of the key findings is the overwhelming worry that so many of the patients have over the entire two years that sex would be painful, and correspondingly finding that a small number of patients are sexually active.

Unexpectedly, with the majority (75%) who are sexually active found it enjoyable, yet half of patients found sex both enjoyable and painful, In the few patients who were sexually active, >60% reported a short and tight vagina and severe dyspareunia. This was similar across all age groups. This echo's Jensen et al earlier study where 54% of those sexually active had vaginal dryness, however the reports of pain in the patients in this study were considerably higher (42%) (113) - a 'frozen' pelvis could explain as to why sexual activity would be painful. As dryness was not reported as a

main concern, it is possible that this could be due to the use of artificial lubricant, this and the improvement in body image overall could intersect to ensure sex can still be enjoyable.

However, this is appreciating that painful sex does not necessarily have to mean that one cannot still enjoy it. Further to this, worry by itself should not prohibit patients from trying to have sex but it is necessary in consultation to focus on how to tackle that expectation and then to navigate the reality that it can indeed be painful. Although only a small number of patients were sexually active, it is reassuring that it does increase over time.

Sexuality has been found to be significantly related with age and with pretreatment levels of sexual interest in one QoL series of 229 women with cervical cancer treated between 1998 and 2008 in the Netherlands (109). In this study, a significant number of older women had sexual concerns. This is particularly important as the likelihood of diagnosing cervical cancer in women older than 50 years as compared to women of the reproductive age (15 – 49 years) has increased during the anti-retroviral treatment (ART) era as compared to the pre-ART era (5).

Initially the motivation for this study was based on the observation that our patients are young, and decades of treatments advances have extended their lifespan and thus there is a major need to understand how they spend future decades dealing with the fallout of this treatment. This study findings challenged this, the first being that older women have just as much of a sexual identity as younger women, that needs to be supported and appreciated. Secondly, in this setting the first year is clearly the most fragile and ‘consequential’. Lastly, that despite the startlingly high mortality in advanced disease there are many who do survive, but their real risk of morbid long term effects are significant.

Until now, research in this area of radiotherapy has primarily focused on symptoms related to nearby organs at risk, such as the bladder, bowel and rectum however the vagina is both the target and an OAR. While it is of great importance to understand the clinically relevant patient health outcomes, what matters to the patient should not be forgotten. This study has allowed patients to report their own experiences and hopefully help clinician’s move to a more mutual and holistic assessment of “toxicity”.

Chapter 5 Strengths and Limitations

A number of limitations and shortcomings need to be considered. First, fatality ascribed to radiation treatment is a serious assertion and are in the best trial-controlled settings still difficult to be completely conclusive. In the setting of this hospital - it is hard to confirm and report with confidence as death certificates are not available and post mortems are not done. If the patient passed away at another hospital, reliance is then on the testimony from family or contacting the treating doctor.

A limitation of this study is the short follow up time and that the data needs to mature. However, the majority of patients did have either a follow-up or had died by 12 months. It has been noted that all investigations and treatments for those with adverse events were not standardized at this hospital.

Bias could have been introduced by patients who are less well and thus, may be more likely to return for follow-up appointments than patients who are doing very well and not experiencing significant side-effects from their treatment. Equally, those who are unwell might not come as they may be too sick to travel or take transport. However, the principal investigator did call all patients to complete the questionnaire if they did not necessarily come to clinic and the high response rates helps to reduce this bias.

Another caveat is that patients over time become more likely to delineate their individual symptoms more precisely because they have been doing the questionnaire over time. This, however, is a potential benefit because as it is an indication that the patients are becoming more informed and involved in their care and are mindful to its treatment, thereby preventing potential worse outcomes.

Looking at the strengths of the study, this trial had rigorous follow-up that was ensured between completion of treatment and 24 months. This was done through telephonic reminders, and in the case a visit missed the PI followed up the patient. All mortality data in these circumstances were verified and supported by PET-CT scans when done. The integrity of the information collected is considered reliable, and I verified all information independently of the trial database.

A direct comparison of our results with those reported in randomised studies can be limited by the heterogeneity of the various other chemoradiotherapy trials in terms of patient population and methods of reporting their analyses. This study, however, was homogenous in singly representing patients with locally advanced stage IIB and IIIB disease and with all patients completing concurrent chemoradiation within 56 days. Although this study was conducted in one centre in South Africa, the results should be generalizable to other regions especially Sub-Saharan Africa and resource limited settings, which use 2D dosimetric evaluation of brachytherapy doses delivered and work under difficult circumstance with majority patients presenting with advanced disease.

This study's added value is that it provides data for both those with no evidence of disease and those where disease progression occurred. It highlights the difference between understanding symptoms and the patients experience beyond a technical physical RTOG grading system, the intersection and validation of which was further supported in this study as the clinician and patient reported symptoms were done at the same intervals and at the same visit.

Chapter 6 Conclusion and Recommendations

In spite of advances made to treat and cure locally advanced cervical cancer and efforts to comply with the recommended dose schedules and constraints for an organ at risk, undesired severe toxicity is still occurring. The motivation for this study was to investigate this, as well as to complement it with the patients' own experience.

This study has found a distinct difference in the risk and configuration of severe complications.

In the case of bladder complications – the most prominent severe complications are fistulas, which are highest in the first year and half as likely in those without evidence of local disease. This compared to the appearance, in the second year, of the predominant obstructive bowel (and not rectal) complications with a similar risk irrespective of disease presence. Local rectal fistulas were more common in patients who died from disease. The high mortality from complications is concerning and these unexpected findings warrant further investigation and strategies to reduce bowel complications. However, it is reassuring that only a small number of patients who developed severe bladder (3.9%) and GIT (5.3%) complications were patients with no evidence of disease.

To minimise the underestimation of morbidity, complications reported as actuarial estimates and not just frequencies has been shown to provide a more accurate, higher risk to those who survive beyond the first year. This study showed that earlier rates before one year in advanced disease should be reported more deliberately. This is because patients with advanced disease experience both high coexisting radiation toxicity and disease recurrence with devastating quality of life effects.

Further, the difference between risk of complication in those with no evidence of disease (almost half with bladder complications) reveals the superimposition of toxicity related symptoms and disease and needs to be further interrogated in this setting so that the real picture of radiotherapeutic complications in advanced disease can be illuminated and understood.

The worse the grade toxicity after radiotherapy is important for clinicians, however this study has highlighted that it is just as important to monitor how long lesser troublesome complications precede it. Fundamentally, it speaks to the endurance of the suffering that patients experience due to our treatment. Although not statistically significant, it is clinically significant that they patients without complications have a worse outlook and survival compared to those without complications.

This study reports, for the first time, the long-term, prospective, longitudinal evaluation of the quality of life in a large series of women with locally advanced cervical cancer on the African continent. Through this, it was noted that patients with complications have the greatest global symptomatic burden among all patients and across all pelvic organs. These patients are significantly more likely to suffer severe symptoms and tend to have complication specific symptoms, for example - incontinence in fistulas or related obstructive symptoms. Additionally, these patients experience a substantial burden of vaginal discharge. The QoL questionnaire has shown that essentially listening to and monitoring the patients who show a pattern and intensity of symptoms over time that are organ specific, potentionally serves as the best early warning system.

Regarding sexual QoL in women, this study has shown that women should not be defined solely by their disease, symptoms or menopausal status, and should not preclude a good and happy sexual life. What is of note in this study is that many more women are able to become sexually active over time, and despite pain they are still able to enjoy sex. This is important to convey to patients that are overwhelmed by the constant worry that sex will be painful. It is recognized, however, that a very small portion of patients reported to be sexually active.

Following this, sexual QoL is also linked to body image concerns. This study showed that the first year for patients is marked by a lack of feeling attractive and feminine, which does not improve from baseline until the second year. Body image anxieties are similarly high in all age groups and signals that one should not cloud age with how women feel about their bodies, nor how they link it to sex and their experience of it.

There are shortcomings of the QoL questionnaire. An example of this are that vaginal shortness and pain is only asked of those sexually active, effectively underestimating the prevalence of this in patients who are much less sexually active. If one could account for those who are inactive it could help to understand whether these are the very reasons for inactivity. It fails also to differentiate or quantify the impact of advanced disease on QoL, as these patients might be the most vulnerable and affected. Additionally, what the questionnaire fails to ascertain is whether it is the anxiety of the disease recurrence itself, that preoccupies patients, could be attributed to treatment effect on QoL. Another limitation is that it is European derived and validated in the northern hemisphere and might not be cross-culturally cognisant in the African context where sexual worry might not just be limited to it being painful.

This study also discussed improving brachytherapy dose delivery by a revision to more conservative point dose thresholds in keeping with the recent 2018 ABS for recommendation for resource limited settings of a threshold of 75Gy for both bladder and rectum; and supports using a more conservative point dose ratio of 75%. Considering the misrepresentation of the rectal dose from inter-observer variability and poor verification of posterior vaginal wall – more attention should be paid to accurately and reproducibly locating the rectal point on orthogonal films. Great note should be taken of this, especially in resource-limited settings that will continue to rely on 2D ICRU 38 based point dose guidance, and especially when carried out by junior staff in training - where there is no dose determination or imaging that guides applicator positioning.

Further to this, transitioning from 2D to 3D BT in very carefully selected clinical cases should be prioritized. Although there is a higher cost and time consumption associated with the nature of the imaging and the 3D treatment planning process, these should be counterbalanced by the improvement in treatment outcome. These will result in a lower overall cost of care, less hospitalisation, less surgical interventions and loss of life.

However, this not negate implementation of simpler interventions e.g. a full bladder protocol to displace bowel out of the treatment field.

Equally, the findings would support that a comprehensive MDT approach is needed e.g. surgeons, stoma care nurses, nutritionists, counselors as well as radiation oncologists, to catch those who report the severest intensity symptoms so as to avert serious complications and support those who do develop complications.

This study has uniquely shown that the risk of developing severe complications is lower in those patients with no evidence of disease than those who experience disease progression but that the impact of complications on QOL are not dissimilar. However, the lived experience of these patients and overall outlook is extremely different and far worse than those without complications. Accompanying this, is the unusual and stark radiation related bowel and bladder treatment complication pattern in this setting, with clear and indicative symptomatic warning signs. The patient's experience of the illness needs to be more effectively extracted (with better questionnaires, etc.) so that clinicians can prioritise and address major clinical and sexual problems that are causing symptoms and related anxieties.

This study ultimately highlights that even though individuals are traditionally categorised as alive or dead, side effect or not; we fail to appreciate the contours of their experience.

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Appendices

1. **Description of hyperthermia trial**
2. **Revised FIGO staging for Cervical Cancer, ECOG Performance status**
3. **RTOG toxicity scale**
4. **Data collection sheet for this study**
5. **Quality of Life Questionnaires EORTC CX24**
6. **Follow-up collection sheet used in the hyperthermia trial**
7. **Ethics Clearance**
8. **Letter of Permission from CEO**
9. **Plagiarism report**

Appendix 1: Description of the hyperthermia trial

The aim of the study is to investigate the clinical and radiosensitising effects of the addition of hyperthermia to standard treatment protocols for locally advanced cervical cancer patients.

Objectives:

Primary

- Determine PFS in all registered patients, regardless of completion (Intent to Treat-ITT).
- Determine PFS in the subset of patients who complete the prescribed chemo-radiotherapy.
- Determine the overall survival at two years.

Secondary

- To evaluate the adverse effects associated with hyperthermia.
- To evaluate the effect of hyperthermia on chemotherapy and RT toxicity.
- To describe the quality of life of enrolled patients via assessments before, immediately after, and at 3, 6, 9, 12, 18 and 24 months after completion of therapy using a Quality of Life (QoL) questionnaire (see Appendix 5).
- To evaluate economic viability of the addition of hyperthermia to standard treatment protocols.
- To evaluate the effect, if any, of hyperthermia treatments on the HIV disease status of HIV-positive patients, assessed by CD4 counts, viral load and presence of AIDS defining illnesses before and after treatment.
- To describe and compare cervical cancer recurrence patterns in all patients.

Study design:

Randomised Phase III Clinical Trial

Methodology:

All patients will receive the standard treatment for cervical cancer. This includes three doses of chemotherapy (cisplatin), six weeks of radiation therapy and three brachytherapy treatments – subject to dose modification rules. This will be

administered three weeks apart during the radiation therapy. All the patients in this study will receive two modulated electro-hyperthermia treatments per week added to their radiation treatment, using the Oncotherm technology. Statistical analysis will be used to compare outcomes in the two groups.

Population:

HIV-negative and HIV-positive women with locally advanced cancer of the cervix, Stages IIB to III.

Sampling size:

The study will consist of 236 patients randomly divided into a control group (N=118) and a study group (N=118).

Duration:

48 months (24 months of recruitment and 24 months of follow-up).

Outcomes:

Local disease control, quality of life, the acute toxicity and HIV status will be assessed and recorded immediately after treatment and at 3 and 6 months after completion of the treatment protocols. The effect of the addition of hyperthermia on late toxicity, survival rates and cost to the state will be reported and analysed.

Appendix 2: Revised FIGO staging for Cervical Cancer (ECOG Performance)

Carcinoma of the Cervix

IA1	Confined to the cervix, diagnosed only by microscopy with invasion of < 3 mm in depth and lateral spread < 7 mm
IA2	Confined to the cervix, diagnosed with microscopy with invasion of > 3 mm and < 5 mm with lateral spread < 7mm
IB1	Clinically visible lesion or greater than A2, < 4 cm in greatest dimension
IB2	Clinically visible lesion, > 4 cm in greatest dimension
IIA1	Involvement of the upper two-thirds of the vagina, without parametrial invasion, < 4 cm in greatest dimension
IIA2	> 4 cm in greatest dimension
IIB	With parametrial involvement
IIIA/B	Unchanged
IVA/B	Unchanged

Pecorelli S. (2009) **Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium**. *International Journal of Gynaecology and Obstetrics* Vol. 105, No. 2, pp:103-4

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, ambulatory, able to carry out LIGHT work (eg office work)
2	Ambulatory, capable of selfcare, unable to carry out work activities. Up/about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix 3: RTOG toxicity scale

Late Toxicity (RTOG) – Mark the applicable box, if any

		Gr 1	Gr 2	Gr 3	Gr 4
Bone	None	Asymptomatic Reduced bone density	Moderate pain or tenderness Growth retardation Irregular bone sclerosis	Severe pain or tenderness Complete arrest of bone growth Dense bone sclerosis	Necrosis/ Spontaneous fracture
Kidney	None	Transient albuminuria No hypertension No related anaemia Mild impairment of renal function Urea 25-35 mg% Cr 1.5-2.0 mg% CCr >75%	Moderate albuminuria 2+ Mild hypertension No related anaemia Moderate renal function impairment Urea>36-60 mg% CCr (50-74%)	Severe albuminuria Severe hypertension Anaemia (<10g%) Severe renal failure Urea >60 mg% Cr >4.0 mg% CCr <50%	Malignant hypertension Uremic coma Urea >100%
Bladder	None	Slight epithelial atrophy Minor telangiectasia (microscopic haematuria)	Moderate frequency Generalized telangiectasia Intermittent macroscopic haematuria	Severe frequency Severe telangiectasia Frequent haematuria Severe dysuria ↓bladder capacity <150 cc	Necrosis Capacity < 100 cc Severe haemorrhagic cystitis
Skin	None	Slight atrophy Pigmentation change Some hair loss	Patch atrophy Moderate telangiectasia Total hair loss	Marked atrophy Gross telangiectasia	Ulceration
Subcutan-eous tissue	None	Slight induration (fibrosia) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic Slight field contracture <10% linear reduction	Severe induration Loss of subcut. tissue Field contracture >10% linear measurement	Necrosis
Mucous Membrane	None	Slight atrophy and dryness	Moderate atrophy and telangiectasia Little mucous	Marked atrophy with complete dryness Severe telangiectasia	Ulceration
GI	None	Mild diarrhoea Mild cramping Bowel movement 5 times daily Slight rectal discharge or bleeding	Moderate diarrheal Moderate colic Bowel movement >5 times daily Excessive rectal mucus or intermittent bleeding	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula

Details:

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Dr's Name: _____ Signature: _____

Appendix 4: Data Collection Sheet

RETROSPECTIVE REVIEW OF LATE TOXICITIES AND QoL OF PATIENTS WITH LACC CERVICAL CANCER 2014-2017

Patient ID		**Start Date**	
DXT No.		**Last #**	
		Last follow up	
		Deceased	
Demographics			**General notes**
Age			
Weight			
Height			
BMI			
HIV	☐		
HAART	☐		
CD4			
ECOG			
Stage	☐ **IIB** ☐ **III**		
Hydronephrosis	☐		
PET OAR involved			
Pre Rx	☐ **Bladder**	☐ **Rectal**	
Post Rx	☐ **Bladder**	☐ **Rectal**	

Toxicity G1-4	**Urinary**	**Notes**	**Bowel**	**Notes**
6 wks.				
3 mo.				
6 mo.				
9 mo.				
12 mo.				
18 mo.				
24 mo.				
Chemo cycles	☐ **0**	☐ **1**	☐ **2**	☐ **3**
HDR				
Applicator				
Fractions	☐ **0**	☐ **1**	☐ **2**	☐ **3**
Bladder %				
Rectal %				
Dose Point A				
Dose Point B				
Total Dose point A				
Total Dose point B				

Appendix 5: Quality of Life Questionnaire

ENGLISH

EORTC QLQ – CX24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems, please answer by circling the number that best applies to you.

During the past week:		**Not at all**	**A little**	**Quite a bit**	**Very much**
31.	Have you had cramps in your abdomen?	1	2	3	4
32.	Have you had difficulty in controlling your bowels?	1	2	3	4
33.	Have you had blood in your stools (motions)?	1	2	3	4
34.	Did you pass water/urine frequently?	1	2	3	4
35.	Have you had pain or a burning feeling when passing water/urinating?	1	2	3	4
36.	Have you had leaking of urine?	1	2	3	4
37.	Have you had difficulty emptying your bladder?	1	2	3	4
38.	Have you had swelling in one or both legs?	1	2	3	4
39.	Have you had pain in your lower back?	1	2	3	4
40.	Have you had tingling or numbness in your hands or feet?	1	2	3	4
41.	Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42.	Have you had discharge from your vagina?	1	2	3	4
43.	Have you had abnormal bleeding from your vagina?	1	2	3	4
44.	Have you had hot flushes and/or sweats?	1	2	3	4
45.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46.	Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
47.	Have you felt dissatisfied with your body?	1	2	3	4

Please go on to the next page

During the past 4 weeks:	Not at all	A little	Quite a bit	Very much
48. Have you worried that sex would be painful?	1	2	3	4
49. Have you been sexually active?	1	2	3	4

Answer these questions only if you have been sexually active during the past 4 weeks:	Not at all	A little	Quite a bit	Very much
50. Has your vagina felt dry during sexual activity?	1	2	3	4
51. Has your vagina felt short?	1	2	3	4
52. Has your vagina felt tight?	1	2	3	4
53. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4

Appendix 6: Follow-up collection sheet used in the hyperthermia trial

J. Follow up Name: _____

Date: _____ Study No: _____GT No: _____

Days since completion of treatment: _____ Follow up no: ____of 6 Dx/Stage: _____

HIV status/CD4/ART: _____

Treatment received: _____

Complications: _____

Exam:

General Condition: _____

Weight: _____ ECOG: _____

Colour: _____ Hydration: _____

Lymph nodes: sc/axillary/inguinal/other: _____

Thyroid: _____ Breasts: _____ Calves: _____

Abdomen: _____ _____

Vaginal Exam: _____

Rectal Exam/bimanual palpation: _____

Speculum (if required): _____ Pap: _____

Impression: _____

		Describe / Grade
PV bleeding	□ Yes □ No	
PV discharge	□ Yes □ No	
Urinary symptoms	□ BOM □ Haematuria □ FOM □ Dysuria □ Incontinence □ None	
Stool symptoms	□ PR bleeding □ Diarrhoea □ Incontinence □ Constipation □ Tenesmus □ None	
Constitutional symptoms	□ Anorexia □ LOW □ Fatigue □ None	
Other		

_____
_____
_____
_____

Appendix 7: Gynaecological QoL parameters by age

	All patients	<30 years	31-50 years	>50 years
Have you had irritation or soreness in your vagina or vulva?				
No	72%	71%	67%	75%
A little	16%	8%	20%	13%
Severe	12%	21%	13%	12%
Have you had discharge from your vagina?				
No	63%	43%	56%	71%
A little	21%	21%	22%	18%
Severe	16%	36%	22%	11%
Have you had any abnormal bleeding from your vagina?				
No	77%	71%	74%	79%
A little	14%	8%	15%	15%
Severe	9%	21%	11%	6%
Have you had hot flushes and/or sweats?				
No	59%	57%	61%	58%
A little	22%	21%	18%	25%
Severe	19%	22%	21%	17%
Have you felt physically less attractive as a result of your disease or treatment?				
No	62%	57%	59%	66%
A little	12%	7%	8%	14%
Severe	26%	36%	33%	20%
Have you felt less feminine as a result of your disease or treatment?				
No	63%	64%	59%	67%
A little	11%	15%	8%	13%
Severe	26%	21%	33%	20%
During the past 4 weeks have you worried that sex would be painful?				
No	51%	14%	41%	61%
A little	7%	15%	9%	6%
Severe	42%	71%	50%	33%
During the past 4 weeks have you been sexually active?				
No	84%	79%	79%	90%
A little	12%	14%	15%	8%
Severe	4%	7%	6%	2%
Has your vagina felt dry during sexual activity?				
No	47%	100%	47%	44%
A little	23%	0%	23%	25%
Severe	30%	0%	30%	31%
Has your vagina felt short?				
No	41%	33%	44%	36%
A little	30%	33%	27%	36%
Severe	29%	34%	29%	28%
Has your vagina felt tight?				
No	41%	33%	46%	34%
A little	30%	33%	27%	34%
Severe	29%	34%	27%	32%
Have you had pain during sexual intercourse or other sexual activity?				
No	39%	100%	40%	31%
A little	29%	0%	25%	40%
Severe	32%	0%	35%	29%
Was sexual activity enjoyable for you?				
No	22%	33%	18%	29%
A little	36%	67%	34%	37%
Severe	42%	0%	48%	34%

Appendix 8: Ethics Clearance

R14/49 Dr Prinitha Pillay

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M170694

NAME: (Principal Investigator)	Dr Prinitha Pillay
DEPARTMENT:	Radiation Oncology Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	Incidence of Severe Late Toxicities and Quality of Life of Patients with Locally Advanced Cervical Cancer Treated with Concurrent Chemoradiotherapy at Charlotte Maxeke Johannesburg Academic Hospital South Africa, 2014-2017
DATE CONSIDERED:	30/06/2017
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr J. Kotzen
APPROVED BY:	CB Penny Professor CB. Penny Co-Chairperson, HREC (Medical)
DATE OF APPROVAL:	19/09/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/3rd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially review June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 20.9.17

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 9: Letter of Permission CEO

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL

Enquiries:
Mr. Johannes Maepa
Office of the Clinical Director
Tell: (011) 488-3365
Email:johannes.maepa@gauteng.gov.za
05 September 2017

Ref:

Dr. Prinitha Pillay

STUDY TITLE: Incidence of Severe Late Toxicities and Quality of Life in Patients with Locally Advanced Cervical Cancer Treated with Concurrent Chemoradiotherapy at Charlotte Maxeke Johannesburg Academic Hospital South Africa, 2014-2017

Permission to conduct the above mentioned study is provisionally approved. Your study can only commence once Ethics approval is obtained. Please forward a copy of your ethics clearance as soon as the study is approved by the Ethics committee for the CEO's to give you the final approval to conduct the study.

Supported / ~~not supported~~

Dr. M.I. Mofokeng
Clinical Director
DATE: 6/9/2017

Approved/~~not approved~~

Ms G. Bogoshi
Chief Executive Officer
Date: 07/09/2017

Appendix 10: Plagiarism Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I PRINITHA PILLAY (Student number: 9202883V) am a student registered for the degree of MMED in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

- I have followed the required conventions in referencing the thoughts and ideas of others.

- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 8 November 2019

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