UNIVERSITY OF CAPE TOWN

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MMed Part III (minor dissertation)

VOLUMETRIC MODULATED ARC THERAPY VERSUS 3D CONFORMAL RADIOTHERAPY IN THE TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER. A SINGLE INSTITUTION, COMPARATIVE DOSIMETRIC STUDY.

By

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ABBREVIATIONS

3D-CRT - 3Dimensional Conformal Radiotherapy
ASIR - Age Specific Incidence Rate
CI - Conformity Index
CT - Computed Tomography
CTV - Clinical Target Volume
EBRT - External Beam Radiotherapy
ECOG - Eastern Cooperative Oncology Group
EPIC - Expanded Prostate Cancer Index Composite
ESMO - European Society of Medical Oncologists
FIGO - International Federation of Gynaecology and Obstetrics
GOG - Gynaecology Oncology Group
GSH - Groote Schuur Hospital
GTV - Gross Tumour Volume
GU - Genitourinary
HI - Homogeneity Index
ICRU - The International Commission on Radiation Units and Measurements
IMRT - Intensity-Modulated Radiation Therapy
IV - Irradiated Volume
LACC - Locally Advanced Cervical Cancer
MRI - Magnetic resonance imaging
MU - Monitor Units
OAR - Organs at Risk
PTV - Planned Target Volume
QUANTEC - Quantitative Analyses of Normal Tissue Effect in the Clinic
RTOG - Radiation Therapy Oncology Group
TV - Treated Volume
VMAT - Volumetric Modulated Arc Therapy

DECLARATION:

I, Dr. Visham Bhagaloo, declare that the work presented in this dissertation is my own. Where information, ideas or words derived from others have been included, I have adequately cited and referenced the original source.

This is an unsponsored study and was done for educational purposes only; as a MMED for a postgraduate degree from the University of Cape Town. I therefore declare that neither the whole work nor any part of it has been, is being or is to be submitted for another degree to any other university. I also state that this work has not been reported or published prior to registration for the abovementioned degree.

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ABSTRACT:

Background: External Beam Radiotherapy is essential in the management of locally advanced cervical cancer (LACC). Generally, VMAT is thought to achieve higher conformity to the Planned Target Volume (PTV) and better sparing of organs at risk (OAR) when compared to 3D-CRT. This study focused on these principles as it applied to treatment and potential toxicity in the management of LACC.

Aim: To compare dosimetric parameters between VMAT and 3D-CRT in the management of LACC.

Setting: The study analysed patients treated at Groote Schuur Hospital between May and December 2017.

Method: A non-randomized comparative retrospective study. EBRT plans for 3D-CRT and VMAT were generated and data on treatment parameters for PTV $D_{50\%}$, D_{max}, D_{mean}, Conformity Index (CI), Homogeneity Index, Treated Volume (TV), Irradiated Volume (IV) and OAR constraints; femoral heads, bladder, bowel bag, rectum and bone marrow were collected.

Results: Of the 45 patients assessed, VMAT showed significantly lower treatment parameter values for CI (1.09 vs 1.49; p<.001) and TV (1613.1 cm^3 vs 2230.3 cm^3; p< .001) whereas, 3D-CRT showed lower D_{max} (48.1Gy vs 49.2Gy; p<.001) and IV (10652.2 cm^3 vs 14618.1 cm^3; p<.001). OAR doses revealed a decreased maximum dose with VMAT to both femoral heads, a lower V_{45} for bowel bag (182.3 cm^3 vs 411.3 cm^3; p<.001) and a lower V_{40} for bone marrow (19.1% vs 38.7%; p< .001) and rectum (88.5% vs 96%). A reduced 3D-CRT dose was noted for bladder D_{max} (47.4Gy vs 48.3Gy; p< .001).

Conclusion: VMAT offered a superior dosimetric option, with better OAR dose sparing and optimal tumour dosimetry.

Keywords: Cervical cancer, VMAT, 3D-CRT, radiation therapy, dosimetry

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STUDY PROTOCOL:

Introduction

The global, yearly incidence of cervical cancer in 2012 was 528,000 with an annual death rate of 266,000[1]. It is the fourth most common cancer in women worldwide[2,3] with 85% occurring in developing countries, and the leading cause of death[1,4]. In South Africa cervical cancer remains the third most common cancer diagnosed with an estimated 7735 new cases in 2012 and 4,248 deaths[5]. In developing countries, patients usually present with locally advanced stage disease and are treated with concurrent chemotherapy and external beam radiotherapy (EBRT) followed by brachytherapy. This study seeks to compare dosimetric values for Volumetric Modulated Arc Therapy (VMAT) to 3-D Conformal Radiotherapy (3D-CRT), both external beam radiotherapy options in the management of locally advanced cervical cancer (Stage 1B2- IVA) at Groote Schuur Hospital.

Purpose of the study

The primary objective:

- To determine whether VMAT is dosimetrically superior to 3D-CRT in the treatment of locally advanced cervical cancer at Groote Schuur Hospital.

Primary Research Hypothesis:

- VMAT is dosimetrically superior to 3D-CRT.

  (a) D_{max} to organs in series is reduced in VMAT compared to 3D-CRT.

  (b) VMAT improves Conformity Index (CI) and Homogeneity Index (HI) to the Planned Treatment Volume (PTV) when compared to 3D-CRT.

  (c) D_{mean} to organs in parallel are reduced in VMAT when compared to 3D-CRT.

  (d) Irradiated volume (IV) is increased in VMAT when compared to 3D-CRT.

  (e) Treated volumes (TV) are reduced in VMAT compared to 3D-CRT.

Background

Cervical cancer remains one of the most concerning cancers for women in developing countries as it represents the leading cause of death by a malignant condition. In May 2017 VMAT was added as a treatment option for locally advanced cervical cancer (LACC) at Groote Schuur Hospital. Multiple studies on Intensity Modulated Radiotherapy (IMRT) have suggested a decrease in gastrointestinal and haematological toxicities with preliminary outcomes suggesting similar tumour control and survival [6-8]. To date, there have been no studies to investigate the change from 3D-CRT to VMAT at our institution or similar low-middle income centres. This study seeks to provide dosimetric data comparing EBRT options; 3D-CRT and VMAT in the treatment of LACC.

Methodology

This is a non-randomized comparative retrospective study. The patients who presented to Groote Schuur Hospital with LACC as staged using FIGO 2009 between May 2017 to December 2017 and completed treatment will form the study population. The patients selected would have completed treatment using VMAT and concurrent chemotherapy followed by brachytherapy. The selected patients who meet the inclusion criteria will have a second radiotherapy plan generated using 3D-CRT by an experienced radiotherapy planner. The plans generated will be evaluated by two Radiation Oncologist and accepted or rejected based on plan evaluation criteria. Plans are deemed acceptable when the PTV is covered between 95-107% of the dose, OAR are within tolerance as compared to QUANTEC guidelines and no hotspots (volume outside PTV >100% PTV dose + 15mm size). Rejected plans will be re-planned and analysed again. The 3D-CRT plans will be used for study analysis only, as these patients have all completed treatment. The plans will be compared with special emphasis on $D_{2\%}$, $D_{98\%}$, $D_{50\%}$, D_{max}, D_{mean}, CI, HI, separation, TV and IV. The data will be collected on REDCap database with de-identification of patient information. The results will guide as to dosimetric superiority (Minimized OAR toxicity and superior PTV coverage) between 3D-CRT and VMAT at Groote Schuur Hospital for the management of LACC.

Characteristics of the study population

The study population will include all patients with locally advanced cervical cancer who received definitive chemotherapy and radiotherapy followed by brachytherapy at Groote Schuur Hospital between May 2017 to December 2017.

Inclusion Criteria:

- Minimum age of 18 years.
- Advanced staged disease (FIGO 2009).
- Performance Status (ECOG)- 0-2.
- Received treatment between May 2017 to December 2017.
- HIV positive and negative disease.

Exclusion Criteria:

- Connective tissue disorders.
- Previous pelvic radiotherapy.
- Performance status (ECOG) 3-4.
- Post-op early stage cervical cancer who qualify for RT

Recruitment and enrolment

The patient population was selected from those confirmed with locally advanced cervical cancer at Groote Schuur Hospital and received treatment between May 2017 to December 2017. Once the inclusion criteria were met the patient was included in the study. Information regarding dosages will be retrieved from the planning system and all other data from medical records. This information will be used to substantiate the dosimetrically superior option.

Research procedures and data collection methods

A data collection form (Appendix iii) will be generated using the REDCap database including general demographics and de-identified to maintain privacy. The dosimetric values identified will be collected from the planning system for 3D-CRT and VMAT. Statistical analysis will follow to determine the significance of the data gathered.

Data analysis

The dosimetric values gathered will be analysed using a Shapiro-Wilk test to determine if the data is normally distributed. The result then determines if a simple paired T-test or a two tailed Wilcoxon Signed Rank Test will be used to determine the statistical significance of the data collected. Statistical significance was accepted when $P<0.05$.

Description of Risks and Benefits

Potential Risks and Discomforts:

This is a retrospective dosimetric comparative study with patients who have completed treatment with VMAT for locally advanced cervical cancer and will now have a simulated 3D-CRT plan. The plans will be compared with the parameters outlined above. There will be no direct patient interaction and treatment has been completed in all participants, as such there is minimal risk.

Potential Benefits:

The study will provide evidence on the dosimetrically superior option for the treatment of locally advanced cervical cancer at Groote Schuur.

Informed Consent:

Consent will not be obtained as this is a retrospective study and does not directly affect care.

Privacy and Confidentiality:

The data collected will be stored on the REDCap database under password protection with access granted to the principal investigators. The data stored will be de-identified to ensure privacy and confidentiality.

Reimbursement for Participation:

There will be no reimbursement for participation as the study has no direct interaction with patients.

What happens at the end of the study?

It is the hope that the data analysed will be statistically significant and as such provide evidence to the dosimetrically superior option for the treatment of locally advanced cervical cancer at Groote Schuur Hospital.

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Lastly, I would like to acknowledge the patients without whom this study would not have been possible.

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CHAPTER 1: INTRODUCTION & LITERATURE REVIEW

OBJECTIVES:

The literature review was undertaken to provide a background on locally advanced cervical cancer (LACC), while proving data on its management with special emphasis on external beam radiotherapy. The data analysed will hopefully afford a history of the advancements in radiotherapy while assessing its dosimetric and clinical effect. Furthermore, comparisons between 3Dimensional-Conformal Radiotherapy and Volumetric Modulated Radiotherapy will be highlighted, focusing on pros and cons. It is hoped that the review will outline the limited information available to date, including data from lower and middle-income countries, and the discrepancies associated in the field.

LITERATURE SEARCH STRATEGY:

To retrieve the widest variety of information and published articles we used Google Scholar, Pub Med, Journal articles, Web sites, and Google. Search words utilised included; Locally Advanced Cervical Cancer (LACC), 3Dimensional- Conformal Radiotherapy (3D-CRT), Volumetric Modulated Arc Therapy (VMAT), dosimetric benefit of VMAT vs 3D-CRT in LACC, side effects of VMAT vs 3D-CRT, Intensity Modulated Radiotherapy (IMRT), Lower and Middle Income Countries (LMIC).

The articles generated were reviewed for applicability and relevance to the given topic. Additionally, the limited data found suggested a definite need for further studies with the greatest issue arising from small study populations. Meta-analyses and some retrospective studies supplied the foundation of the information, but less robust observational studies were considered once their analysis suggested credible, accurate and most importantly, reproducible information.

DATA:

In 2018, the World Health Organisation (WHO) published statistics stating that cervical cancer was the fourth most frequent cancer in women globally, representing 6.6% (570,00 cases) for that year, of which 90% of deaths occurred in low- and middle-income countries (LMIC).[1] Professor Denny et al., when reviewing cervical cancer in Africa, stated that 267.9 million women aged 15 years and older are at risk of developing cervical cancer. Of these, 80,000 are diagnosed with cervical cancer yearly, and more than 60,000 die from the disease.[2] The highest rates of cervical cancer in Africa, based on the Age Standardized Incidence Rate (ASIR > 40/100,000), are found in Eastern and Southern Africa. In Southern Africa, the highest percentages were found in Lesotho and Swaziland followed by South Africa mainly as a result of inadequate screening programmes.[2] The National Cancer Registry of South Africa suggested that cervical cancer is the 3rd most common cancer among South African women with a 1 in 42 lifetime risk of cervical cancer.[3] In 2014, South Africa registered 5735 new cases of cervical cancer representing 15.17% of all female cancers.[3] Over 60% of the patients diagnosed with cervical cancer ranged within the 35 to 60 age group, undoubtedly affecting the female work force in South Africa. As such, appropriate, standardised and effective treatment with minimal toxicity is imperative in the management of early and locally advanced cervical cancer (LACC).

The European Society of Medical Oncologist (ESMO) describe locally advanced cervical cancer as those Staged between IB2 and IVA using the 2009 International Federation of Gynaecology and Obstetrics (FIGO) classification.(Appendix iv) To date, there is limited data on stage of diagnosis in South Africa as updated staging registries are lacking. From our experience at Groote Schuur Hospital (GSH), observational estimates suggest a higher percentage of patients present with locally advanced disease. This is in direct contrast to international publications in which patients present with earlier stage disease, mainly due to robust screening programmes.[4] In 1997 Landoni et al compared surgery vs radiotherapy in the treatment of FIGO Stage IB (most <4cm) or IIA cervical cancers.[5] The study population showed equal efficacy of treatment with External Beam Radiotherapy (EBRT) or surgery with the radiotherapy group having far less toxicity. On further analysis the study was heavily dominated by resectable early stage disease and it is believed that in more advanced disease a

definitive benefit would have been revealed for EBRT over surgery. Within 2 years following Landoni's et al. study , 3 randomised studies were published showing the benefit of combining chemotherapy with radiotherapy in the management of LACC .[6-8] In the analysis done by Rose et al for the Gynaecology Oncology Group (GOG), 526 women were randomly assigned to receive cisplatin-based chemotherapy or hydroxyurea. The combination of cisplatin-based chemotherapy led to an improvement in survival and progression free survival when compared to hydroxyurea. Today, LACC is managed definitively with EBRT and concurrent chemotherapy followed by brachytherapy.[9] EBRT is indicated in approximately 60% of patients with cervical cancer treated with curative intent as seen in the article comparing VMAT to 3D-CRT by Delaney et al .[10] Surgical intervention is limited to early stage disease in modern practice, mainly Stage 1A and 1B1.

External Beam Radiotherapy has evolved over time in the management of cancer with greater emphasis placed on improving the therapeutic index. The therapeutic index is defined as a relationship of tumour control probability and normal tissue complication probability at unique doses of radiation.[11] Initially, LACC was treated with conventional radiotherapy, utilising bony structures as landmarks. However, this has been replaced with more conformal radiotherapy using CT based images. 3D-CRT emerged as the EBRT treatment of choice for LACC in the late 1990's offering better target coverage and reduced bladder radiation. This was shown in the study of 20 patients with Stage IIB and IIIB comparing beams eye view planning to four field box by Gerstner et al.[12] While noted to have a small patient population, the study showed a 20% geographical miss when using conventional treatment with an increased volume of bladder and bowel bag in the treated volume. In 2013, a small dosimetric study done by Goswami et al. and published in the South Asian Journal of Oncology compared conventional radiotherapy to conformal radiotherapy. In the study, Goswami et al. suggested that 3D-CRT gives better coverage improving local control and survival at the expense of larger fields and similar dose homogeneities.[13] 3D-CRT is the most widely used method of EBRT[14] but has been associated with increased toxicity including genitourinary symptoms, gastrointestinal symptoms and bone marrow suppression particularly when combined with concurrent chemotherapy.[15] At GSH all patients treated with curative intent receive concurrent chemotherapy, increasing possible toxicities. It is with this concern in mind that

Volumetric Modulated Arc Therapy (VMAT), a type of Intensity Modulated Radiotherapy (IMRT), was considered to improve dosimetric optimisation and minimise toxicities for patients treated with EBRT for LACC.

In 2003, S. Webb from the Royal Marsden NHS, London described IMRT as “a form of inverse planning that delivers radiation to the patient via fields that have non-uniform radiation fluence”.[16] The University of California, San Francisco Department of Radiation Oncology defines inverse planning “as a method of radiation treatment planning where one starts with the desired dose distribution, or clinical objectives, and then determines the treatment parameters that will achieve it.” VMAT is a form of IMRT combining variable dose rates and gantry speeds, a single gantry motion and dynamic multi-leaf collimation.[17] Numerous studies across different primary cancer sites suggest that VMAT may potentially offer a more conformal dose around tumour, improve avoidance of organs at risk, minimise toxicity and when necessary, allow for dose escalation.[18-20] Taking into account these principles, studies have been designed to compare the dosimetric and clinical benefit of VMAT to 3D-CRT in the management of LACC.

Appropriate tumour coverage is imperative in mitigating the possibility of residual disease post treatment and reducing the possibility of local recurrence. This will undoubtedly result in improved overall survival. Mundt et al. studied whole pelvic radiotherapy with IMRT in 40 patients with gynaecological cancers and found that IMRT offered excellent Planned Target Volume (PTV) coverage. They showed that on average 98.1% of the PTV received the prescription dose. Additionally, the average percentage of the PTV receiving 110% and 115% of the prescription dose was 9.8% and 0.2% respectively. [21] The study, while under powered with a small population size, did not directly compare 3D-CRT to IMRT. As such, the findings can only be used as stand-alone data, and not a direct comparison of tumour control dosimetric superiority. In 2008, Taylor et al. examined the dosimetric differences among conventional radiotherapy, 3D-CRT and VMAT for 40 women. The study showed optimal tumour dosimetry with IMRT and allowed dose painting and dose escalation when compared to 3D-CRT. OAR toxicity was also reduced as VMAT allowed sparing of the rectum and bladder. [22] Chen et al. in 2007 compared 4 field box conventional radiotherapy to IMRT in patients with cervical cancer post hysterectomy. 68 patients

with similar pathological findings were assigned to either IMRT or 4 field box and followed up for 4 years to assess toxicity and tumour control. The results suggested that IMRT offered similar locoregional control while allowing greater tolerance to chemoradiotherapy. Another study done by Lukovic et al. showed that despite treating a larger volume, 4 field box technique is less homogenous and provides inferior coverage of the PTV compared to VMAT.[23] It is noted that both studies previously mentioned, examined the effect of radiotherapy in post-operative patients and not LACC. However, both authors are of the belief that the effect of radiotherapy in LACC, while not exact, will have many similarities to the patients in their study groups. Kam et al. showed that with increasing conformity, dose escalation was now safe and feasible, maximising tumour dose and allowing for selective dose escalation.[24]These studies suggest the prospect of offering improved coverage with the possibility of localised dose escalation may further enhance the therapeutic effect of VMAT when compared to 3D-CRT.

The incidence and severity of radiation toxicity to OAR are multifactorial. These factors include the volume of tissue treated, dose received and the technique for delivery of radiation therapy. IMRT, with theoretical benefit for improving OAR sparing, was then examined in numerous trials to minimise the most common toxicities associated with LACC radiotherapy; Genitourinary (GU), Gastrointestinal (GU) and Haematological.[25, 26] Mell et al reviewed 83 patients with LACC between 2011 to 2015 to determine if IMRT reduced haematological and GI toxicity when given with concurrent chemotherapy. The phase 2 study revealed a clinical benefit for both acute GI and haematological toxicities with promising therapeutic outcomes when the radiation dose was lowered. This phase 2 multicentre study analysed a diverse population but was limited by patient numbers and included both post resection and radical patients. Additionally, the data compared Image guided IMRT vs IMRT and comparison with conventional RT was based on recorded data.[27] Hasselle et al. reviewed 111 patients who were treated with IMRT and showed low toxicity and favourable outcomes, supporting its safety and efficacy in the treatment of cervical cancer.[25]This article had a larger study population improving its statistical strength. However, there was no direct comparison to 3D-CRT and as such the result must be analysed with this fact in mind. Radiation Therapy Oncology Group (RTOG) 1203 compared IMRT to 3D-CRT radiotherapy in cervical cancer and the results showed significantly lower scores for

gastrointestinal and urinary toxicity when using IMRT.[28] The study utilised the Expanded Prostate Cancer Index Composite (EPIC) to compare toxicities. EPIC is a questionnaire filled by patients on completion of treatment and subsequent follow ups to determine the clinical effect of treatment on their quality of life. The mean EPIC bowel score declined 23.6 points in the 3D-CRT group and 18.6 points in the IMRT group while the urinary score declined 10.4 points in the standard RT group and 5.6 points in the IMRT group. A larger decline from baseline suggested a poorer tolerance to treatment.

Multiple studies have also evaluated GI and GU toxicity, suggesting an improvement in both acute and chronic toxicities when IMRT was compared to 3D-CRT. [25, 29, 30] Gandhi et al. reviewed 44 women between 2010 and 2012 who received 50.4Gy in 28 fractions with either whole pelvic IMRT or conventional radiotherapy. For an average 22 months, the patients were followed up and the results revealed comparable clinical outcomes with significantly less toxicity using IMRT when compared to 3D-CRT.[29] A retrospective study done in 2011 assessed 109 patients with LACC to determine the toxicity and tumour control associated with IMRT treatment. They were followed up for a median of 32.5 months and the results suggested the treatment regimen were well tolerated with favourable acute and late toxicity.[30] Naik et al. also examined 40 patients equally distributed into two arms, comparing 3D-CRT to VMAT in the management of LACC. The results showed better conformity with reduction in dose to D_{35} and D_{50} for the bladder and rectum respectively, as well as a reduction in V_{45} for small bowel and V_{20} for bone marrow. This dosimetric benefit translated into a reduction in toxicity for both GI and GU systems, with no clinical difference found with bone marrow dose. The final analysis suggested IMRT plans were superior to the 3D-CRT in reducing the volume receiving high doses in the bladder, rectum and bowel.[31] Further OAR sparing was noted in RTOG 418, a phase II study that looked at 83 patients with cervical and endometrial cancer treated with IMRT alone. IMRT was associated with lower rates of haematological toxicities with a lower V_{40} volume and higher rates of cisplatin use when compared to 3D-CRT.[32] Additionally, the study by Brixey et al compared women receiving EBRT, either 3D-CRT or IMRT between 2000 to 2001 to determine the haematological effect. 36 patients treated with IMRT were compared to 88 patients receiving 3D-CRT with similar volume delineation, dose

prescriptions and chemotherapy. The final results showed that IMRT lowered haematological toxicities and offered improved sparing when used, compared to 3D-CRT, to treat gynaecological malignancies.[26] Treatment which offers greater OAR sparing and minimises clinical toxicities are likely to improve compliance which affects tumour control and outcome. [33]

While the studies listed above have suggested IMRT to be a superior dosimetric and clinical option, others have not shown this superiority and questioned its benefit. Yang et al. systematic review of gynaecological cancers in 2012, suggested that IMRT did not differentially affect the average percent volumes receiving a set dose to the bone marrow or bladder.[34] Also, a retrospective multi-centre study done in 2014 by Erpolat et al. proposed that while IMRT offers a dose reduced bone marrow volume, the clinical benefit was not found to be significant. The patient population follow up showed no difference between the two techniques, VMAT versus 3D-CRT, for acute or chronic haematological toxicity.[35]

With the advent of VMAT additional issues regarding target definition, patient and target immobilisation, tissue deformation and reproducibility remain to be validated. [35-37] Lim et al. published a phase 2 article with expert opinion on CTV definition and contouring for patients being treated with IMRT for cervical cancer. 19 experts in the field agreed on guidelines which would hopefully synchronise contouring volumes while taking into consideration the specialised nature of IMRT contouring.[36]

Although minimising the treated volume limits OAR toxicity, this may also increase the possibility of geographical miss, as inter and intra fraction organ motion may not be fully encompassed. Jadon et al. reported a systemic review in which this motion was examined and showed the greatest variability of the uterus ranging from 5 mm to 40mm.[38] This variation in motion was not covered in IMRT [36] contouring guidelines as suggested and poses a serious issue when considering tumour control. However, with improved imaging localisation, such as daily kilovoltage cone beam CT as compared to megavoltage orthogonal images, tumour localisation, deformation and reproducibility may be minimised. The study done by Ahmad et al. in 2012 posited that pelvic rotations are large and should not be ignored. As a result, corrections with 6D

positioning devices is imperative in reducing CTV to PTV expansion and avoiding geographical miss.[39]

CONCLUSION:

Studies comparing conventional techniques to Volumetric Modulated Arc Therapy in the management of locally advanced cervical cancer (LACC) are scarce, outdated and patient populations are small. To the best of our knowledge, there are no published articles in South Africa comparing these two modalities in the management of LACC. This study aims to provide local data that will hopefully clarify the dosimetrically superior option between these two approaches and support the switch to VMAT at our institution. We also hope to compare our data to international studies to determine if our results are comparable and if further optimisation of our techniques may be needed to provide the best care to our patients.

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CHAPTER 2:
PUBLICATION - READY MANUSCRIPT

VOLUMETRIC MODULATED ARC THERAPY (VMAT) VERSUS 3D CONFORMAL RADIOTHERAPY (3D-CRT) IN THE TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER. A SINGLE INSTITUTION, COMPARATIVE DOSIMETRIC STUDY.

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ABSTRACT:

Background: External Beam Radiotherapy is essential in the management of locally advanced cervical cancer (LACC). Generally, VMAT is thought to achieve higher conformity to the planned target volume (PTV) and better sparing of organs at risk (OAR) when compared to 3D-CRT. This study focused on these principles as it applied to treatment and potential toxicity in the management of LACC.

Aim: To compare dosimetric parameters between VMAT and 3D-CRT in the management of LACC.

Setting: The study analysed patients treated at Groote Schuur Hospital between May and December 2017.

Method: A non-randomized comparative retrospective study. EBRT plans for 3D-CRT and VMAT were generated and data on treatment parameters for PTV $D_{50\%}$, D_{max}, D_{mean}, conformity index (CI), homogeneity index, treated volume (TV), irradiated volume (IV) and OAR constraints; femoral heads, bladder, bowel bag, rectum and bone marrow were collected.

Results: Of the 45 patients assessed, VMAT showed significantly lower treatment parameter values for CI (1.09 vs 1.49; p<.001) and TV (1613.1 cm^3 vs 2230.3 cm^3; p< .001) whereas, 3D-CRT showed lower D_{max} (48.1Gy vs 49.2Gy; p<.001) and IV (10652.2 cm^3 vs 14618.1 cm^3; p<.001). OAR doses revealed a decreased maximum dose with VMAT to both femoral heads, a lower V_{45} for bowel bag (182.3 cm^3 vs 411.3 cm^3; p<.001), and a lower V_{40} for bone marrow (19.1% vs 38.7%; p< .001) and rectum (88.5% vs 96%). A reduced 3D-CRT dose was noted for bladder D_{max} (47.4Gy vs 48.3Gy; p< .001).

Conclusion: VMAT offered a superior dosimetric option, with better OAR dose sparing and optimal tumour dosimetry.

Keywords: Cervical cancer, VMAT, 3D-CRT, radiation therapy, dosimetry

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INTRODUCTION

Globally, cervical cancer is the fourth most frequent cancer in women, representing 6.6% (570,00 cases) in 2018, of which 90% of deaths occur in low- and middle-income countries.[1] In 2014, South Africa registered 5735 new cases of cervical cancer, representing 15.17% of all female cancers, and the third most common cancer in women.[2] In South Africa, data is limited regarding stage of presentation, however at Groote Schuur Hospital (GSH) a higher percentage of the patients treated for cervical cancer, present with locally advanced disease. Locally advanced cervical cancer (LACC) (Stage 1B2- IVA (FIGO 2009)) is associated with a poorer prognosis with 5-year survival rates of 58% in Stage IIB, 30% in Stage III and 16% in Stage IVA.[3] Cervical cancer continues to affect middle age females and has been associated with numerous socioeconomic factors especially in lower middle-income countries.[4] Considering these factors, appropriate, beneficial, minimally toxic and proven efficacious treatment is imperative.

LACC is managed definitively with External Beam Radiotherapy (EBRT) and concurrent chemotherapy followed by brachytherapy.[5] EBRT is indicated in approximately 60% of patients with cervical cancer treated with curative intent [6] as surgical intervention is limited to early stage disease, mainly Stage 1A and 1B1. 3D Conformal Radiation (3D-CRT) is the most widely used method of EBRT [7] but has been associated with significant toxicity including genitourinary symptoms, gastrointestinal symptoms and bone marrow suppression, particularly when combined with concurrent chemotherapy. [8] At GSH, all LACC patients treated radically with curative intent, receive concurrent chemotherapy, with radiotherapy increasing possible toxicities. It is with this concern in mind that Volumetric Modulated Arc Therapy (VMAT) was considered to improve dosimetric optimisation and potentially minimise toxicity for patients treated with EBRT for LACC.

VMAT is a form of intensity-modulated radiation therapy (IMRT) linking together variable dose rates and gantry speeds, a single gantry motion and dynamic multi-leaf collimation.[9] Patients with cervical cancer who were treated with IMRT have reported improved target volume coverage which also allowed for dose escalation while reducing the radiation dose to organ at risk (OAR).[10] Additional studies have shown

contradictory information suggesting no dosmietric or clinical benefit with selected OAR sparing when IMRT was used.[11, 12]The ability to offer improved coverage while sparing OAR may allow for a superior therapeutic effect of VMAT when compared to 3D-CRT. Taking this into consideration and the contrasting published results, this study may help to determine the better dosimetric option at our institution.

The incidence and severity of radiation toxicity are multifactorial. These factors include the volume of tissue treated, dose received (D_{max} and D_{mean}), and the technique for delivery of radiation therapy (3D-CRT versus IMRT) administered. Radiation Therapy Oncology Group (RTOG) 1203 compared IMRT to 3D-CRT radiotherapy in cervical cancer. The results showed significantly lower scores for gastrointestinal and urinary toxicity when using IMRT.[13] The study utilised the Expanded Prostate Cancer Index Composite (EPIC) to compare toxicities. EPIC is a questionnaire used to assess function and toxicity post-treatment. The mean EPIC bowel score declined 23.6 points in the 3D-CRT group and 18.6 points in the IMRT group. The mean urinary score declined 10.4 points in the standard RT group and 5.6 points in the IMRT group. A larger decline from baseline suggested a poorer tolerance to treatment. RTOG 418 further suggested that IMRT was associated with lower rates of haematological toxicities with a lower V_{40} volume and higher rates of cisplatin use when compared to 3D-CRT.[14]

With the advent of VMAT, issues regarding target definition, patient and target immobilisation, tissue deformation and reproducibility remain to be validated as additional factors that limit the OAR toxicity and treatment profiles.[12, 15, 16] To minimise the effects listed, specialised contouring guidelines for cervical cancer VMAT treatments have been published and implemented.[17] Additionally, with improved imaging localisation such as daily kilovoltage cone beam CT as compared to megavoltage orthogonal images, tumour localisation, deformation and reproducibility may be minimised.[18]

Studies comparing conventional techniques to VMAT in the management of LACC are scarce and patient populations are small.[9] To date, there are no published articles in South Africa comparing 3D-CRT and VMAT. At GSH, VMAT, the accepted standard

of treatment internationally, [7,8,9] was added as a treatment option in May 2017. This study aims to provide clarity on the dosimetrically superior option between these two modalities.

METHODS

Study aims and objectives:

The aim of the study was to determine if VMAT is dosimetrically superior to 3D-CRT in the treatment of patients with LACC staged with the 2009 FIGO system (Appendix iv). The study included patients who were treated with VMAT for LACC at GSH between the period of May to December 2017.

Study population:

Formal sample size calculations were not performed. The number of patients was based on the feasibility of data collection and processing. The patients included were those treated radically for LACC with VMAT and concurrent chemotherapy, had a minimum age of 18 years and an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Patients not meeting these criteria were excluded from the study. Further exclusion criteria were connective tissue disease, poor performance status, previous pelvic radiotherapy, previous surgery and metastatic disease on imaging.

Scientific Design:

Methods and Materials:

This is a non-randomized comparative retrospective study. The medical records of all patients treated for LACC between the period of May to December 2017, meeting the inclusion criteria were reviewed. Data relating to age, stage and histological type were recorded. The patients' VMAT radiation therapy plans were reviewed and the following information extracted: PTV $D_{50\%}$, D_{max}, D_{mean}, conformity index (CI), homogeneity index(HI), treated volume (TV) , irradiated volume (IV) and OAR constraints; right and left femoral heads, bladder, bowel bag, rectum and bone marrow . For the purpose of

this study, clinically acceptable 3D-CRT plans were generated and used solely for dosimetrc comparison.

Treatment

All patients were discussed at the combined Gynaecology clinic for decision making on treatment approach and patients suitable for concurrent chemotherapy and radiotherapy identified. These patients were prescribed a bowel prep with Senna/Docusate (stimulant/ laxative) and lactulose for two weeks prior to CT scan simulation and continued throughout treatment to aid with rectal emptying and reproducibility.

On the day of treatment, a bladder protocol was followed: patients were asked to empty their bladders then drink 250cc of water, followed by a thirty-minute waiting period before the CT simulation scan was performed. This bladder protocol was repeated daily while on treatment to further improve bladder reproducibility. At GSH an inferior tumour limit is determined clinically, and the corresponding CT location marked to aid with lower limit delineation of tumours as MRI imaging is not routinely available for all patients. Patients were aligned using triangulation technique and scanned with intravenous and oral contrast in the supine position with knee rest and ankle stocks using 5 mm slices from T12 vertebral body to mid femur. On the scan date, tattooing of the skin with three-point pelvic markings were done to improve setup and minimise rotational errors during treatment. The final CT images were imported and contoured using the ECLIPSE planning system.

The contouring guidelines[17, 19, 20] utilised at GSH generated a Clinical Target Volume (CTV). The CTV tumour comprised of the Gross Tumour Volume (GTV), cervix, uterus, parametrium and vagina. GTV delineation without MRI imaging was exceptionally difficult. As a result, it was assumed, once the cervix was contoured the disease was encompassed. Vaginal contouring was dependent on the extent of the disease. For minimal or no vaginal involvement, the upper half of the vagina was contoured. If the

upper half of vagina was involved with tumour, the upper two thirds was contoured and for extensive disease the entire vagina was contoured. Additionally, the mesorectum was included for Stage III B or extensive nodal involvement. The CTV nodes were generated using a 7-millimetre margin around the common, internal and external iliac vessels while using a 10-millimetre strip anterior to the sacrum. The obturator nodes were contoured with a 10-millimetre strip which connected the external and internal iliac vessels. Inguinal nodes with a seven mm expansion were contoured when there was round ligament and lower third of vagina involvement. The PTV tumour was created with a 1.5 cm expansion superior, anterior and posterior with 1 cm in all other directions and PTV node was generated with a symmetric 7 mm expansion circumferentially. The OAR's: right femoral head, left femoral head, bladder, bowel bag, bone marrow [23] and rectum, were also delineated using RTOG guidelines for the female pelvis.[20] The patient's final plans were prescribed to a dose of 46.0 Gy to the mean volume in 23 fractions.

EBRT plans were generated using the ECLIPSE system and optimisation criteria for VMAT technique. The plans were evaluated by the attending radiation oncologist based on the following criteria: PTV coverage (ensuring the volume was adequately covered by the 95% isodose line), Dose Maximum (highest doses within the PTV which should be less than 107% for D_{max} & $D_{2\%}$), Hot Spots (a significant dose and corresponding volume (typically < $2cm^3$ & >107% dose) outside of the PTV), Monitor Units (MU) (accepted as less than 300MU per Gy for VMAT), Homogeneity Index, Conformity Index and OAR toxicities as defined by Quantec.[21] The plans were approved once all criteria were assessed and found to be within acceptable limits. The approved plans were then assessed by the Medical Physics department using quality assurance protocols. The Gamma Index was then evaluated before the plan was finally approved and treatment began. At GSH, a difference of 3% dose and a 3mm geometrical location between the planned dosimetric value and the generated doses on the treatment machines, are accepted. All patients with LACC, treated radically, also received concurrent weekly cisplatin at a dose of 40 mg/m^2. Chemotherapy should ideally be commenced on Mondays to ensure a synergistic effect with chemotherapy and radiotherapy. However, due to logistical issues, chemotherapy is given on a Thursday at GSH. Daily set up and verification was confirmed using offline

EPID verification. Additionally, brachytherapy commenced within the last week of EBRT using a 2D system prescribed to a Manchester point system.

The patients selected for this study, who met the inclusion criteria, had a second plan generated using 3D-CRT technique for similar target volumes contoured for prior VMAT planning. Senior radiographers, with experience in 3D-CRT cervical cancer, were used and blinded to previous radiotherapy plans with VMAT to reduce any possible bias. The plans were generated with mix energy beams, 18 MV and 6 MV photon energy, and no restrictions were placed on the number of fields or use of beam modifiers. At GSH, a four-field box was used for pelvic PTV structures with varying energies to ensure appropriate coverage and minimal toxicity to OAR. The final assessment and approval followed the criteria previously mentioned. Nine (20%) of the 3D-CRT plans were rejected as the criteria was not met. These included poor superior PTV coverage, OAR exceeded constraint and unacceptable hot spots. The plans were eventually accepted after suggested corrections were made. All 45 plans were again reviewed by an independent oncologist and once agreed, forwarded for Quality Assurance. External plan validation was also completed with the Im Sure^{TM} system which utilises an independent planning system to verify dose prescribed was the dose given.

Dosimetric Data.

Post plan assessment for both VMAT and 3D-CRT focused on recording PTV $D_{2\%}$, PTV $D_{98\%}$, PTV $D_{50\%}$, D_{max}, D_{mean}, conformity index (CI), homogeneity index (HI), treated volume (TV), irradiated volume (IV) and patient separation, to fully assess treatment parameters.

Treated Volume: The volume enclosed by an isodose surface, selected and specified by the radiation oncologist as being appropriate to achieve the purpose of treatment[22]. At GSH the 95% isodose line was used.

Irradiated Volume: The volume of tissue that receives a dose that is considered significant in relation to normal tissue tolerance[22]. At GSH the 20% isodose was used.

Homogeneity Index: $\frac{PTV\ D_{2\%} - PTV\ D_{98\%}}{PTV\ D_{50\%}}$ [23]

Conformity Index: $\frac{Treated\ Volume}{PTV\ Volume}$ [23]

Patients' OAR doses were recorded based on Quantec constraints; right and left femoral head maximum dose (D_{max}<52 Gy)[24], bladder maximum dose (D_{max}< 65Gy)[24], small bowel (bowel bag) absolute volume (V_{45}< 195cc)[24], bone marrow relative volume (V_{40} < 40%)[23] and rectum relative volume (V_{40}< 100%)[13] were assessed.

Statistical Consideration

Statistical analysis was done using SPSS Version 25. Comparison of dosimetric values for 3D-CRT to VMAT was done using Wilcoxon Signed rank test as the initial Shapiro-Wilk test showed that the data was not normally distributed. Additionally, Mann Whitney U tests were used when comparing cervical cancer by stage. A *p* value < .05 was deemed statistically significant.

Ethical Considerations:

Throughout the study patient privacy and confidentiality were strictly maintained. Anonymity was upheld by deidentifying the patients, the data collected was stored on the REDCap system under password protection and limited access. Ethical approval for the study was granted by the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town. Reference Number – HREC REF: 625/2018. (Appendix ii)

RESULTS

Patient Characteristics:

The mean age of the 45 patients was 52.8 ± 10.8 years.

The most common stage of disease identified was Stage IIB (n= 22) followed by Stage IIIB (n= 25). The other stages are illustrated in Figure 1

The most common histology was Squamous Cell Carcinoma (n= 38) as seen in Figure 1 with adenocarcinomas representing 7 patients.

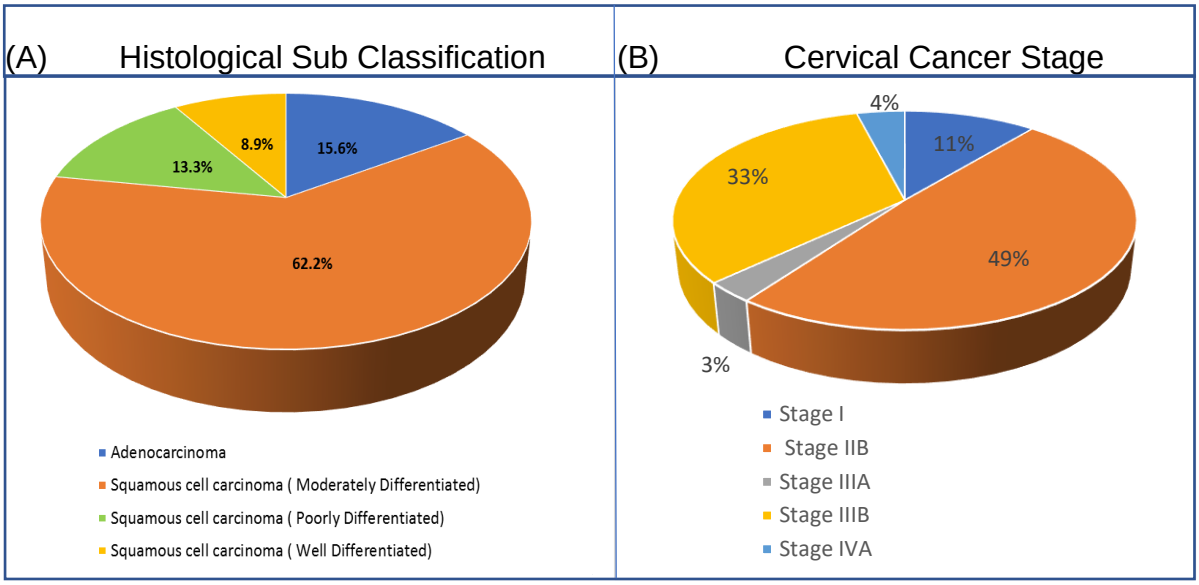

Figure 1: (A) Percentage distribution by Histological Type.
(B) Percentage distribution by Stages of disease.

Tumour Control:

Table 1: Tumour Dosimetric Parameters for VMAT and 3D-CRT

	VMAT		3D-CRT		*z*	*p*
	Median	IQR	Median	IQR		
PTV $D_{2\%}$ (Gy)	47.8	47.5 – 48.0	47.7	47.4 – 48.3	-0.70	.483
PTV $D_{98\%}$ (Gy)	44.1	43.8 – 44.4	44.4	44.2 – 44.6	-2.97	.003
PTV $D_{50\%}$ (Gy)	46.0	46.0 – 46.1	46.6	46.1 – 46.9	-5.45	<.001
Homogeneity Index	0.08	0.07 – 0.09	0.07	0.06 – 0.08	-1.47	.142
D_{max} (Gy)	49.2	48.9 – 49.5	48.1	47.7 – 48.6	-5.37	<.001
D_{mean} (Gy)	46.0	46.0 – 46.0	46.5	46.1 – 46.7	-5.17	<.001
Treated Volume 95 Isodose (cm^3)	1613.1	1471.4 – 1776.4	2230.3	1960.3 – 2457.9	-5.84	<.001
PTV Volume (cm^3)	1443.9	1331.8 - 1661.2	1443.9	1331.8 – 1661.2	-0.37	.715
Conformity Index	1.09	1.06 – 1.12	1.49	1.44 – 1.59	-5.84	<.001
Irradiated Volume 20 Isodose(cm^3)	14618.1	12844 – 17943.2	11910.4	10652.2 – 14272.9	-5.77	<.001

Table 1 examined the dosimetric values recorded for both treatment planning options. The median PTV volume for the patients treated was 1450 cm^3 with D_{mean} favouring VMAT and a D_{max} value favouring 3D-CRT. Additionally, PTV $D_{2\%}$ was reviewed, which is considered a volume assigned to a maximum dose rather than a point dose, no statistical difference was found between 3D-CRT and VMAT.

The conformity index for VMAT showed a lower median value when compared to 3D-CRT while the improved homogeneity index associated with 3D-CRT was deemed statistically insignificant. Dosimetric assessment also showed approximately a 600 cm^3 smaller median TV and a 2700 cm^3 larger IV for VMAT when compared to 3D-CRT.

Organs at risk:

VMAT displayed lower median doses when compared to 3D-CRT for both the right and left femoral head (Table 2). Figure 2 compared the relative volume of bone marrow receiving 40 Gy, showing a 2 times larger volume affected with 3D-CRT as compared to VMAT. Figure 3 compared the volume of bowel receiving a dose of 45 Gy and showed a median volume 200 cm^3 greater with 3D-CRT than that recorded for VMAT. Additional dosimetric parameters for bone marrow and bowel bad are found in Table 2.

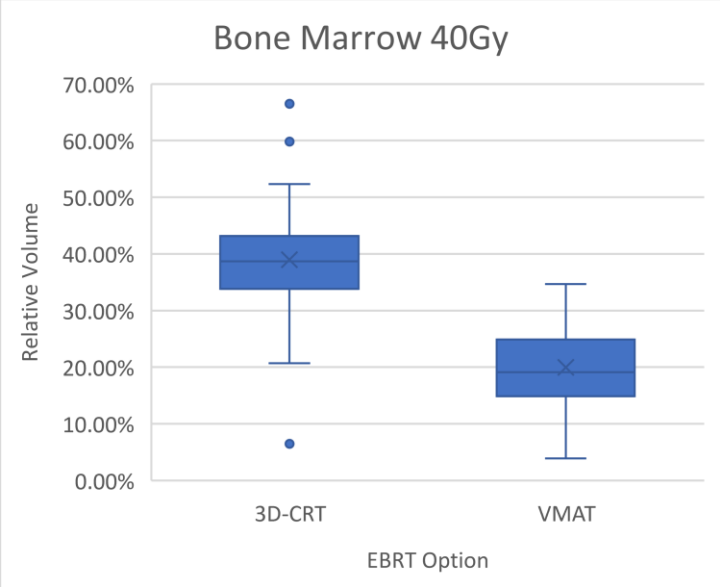

Figure 2: Box and Whisker plot comparing Bone Marrow relative volume at 40Gy.

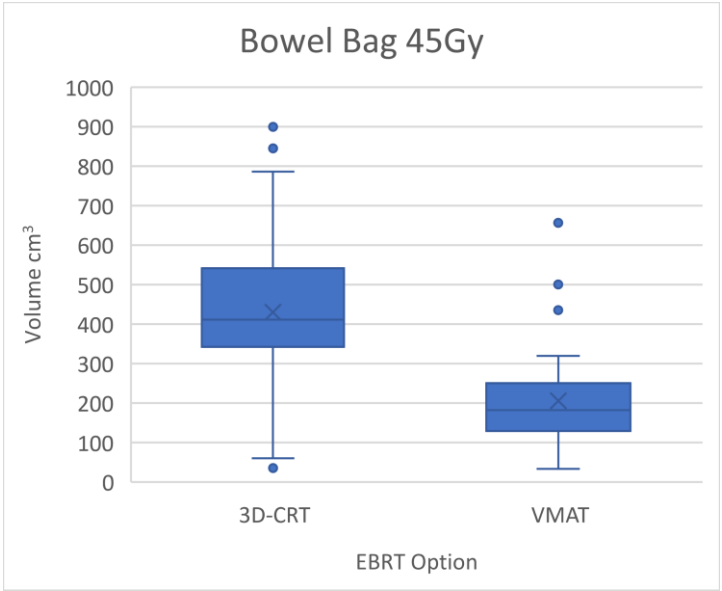

Figure 3: Box and Whisker plot comparing Bowel Bag absolute volume at 45 Gy.

Median bladder D_{max} was lower for 3D-CRT when compared to VMAT (Table 2). All OAR dosimetric values are seen in Table 2.

Rectum, V_{50}< 50 as per Quantec was 0 as the maximum dose on both plan groups were less than 50Gy. As such, comparitive statistical analysis was done using V_{40}< 100% as seen in RTOG 1203.[13]

Table 2: VMAT vs 3D-CRT Organ at Risk dosimetry.

Organ	*VMAT*			3D-CRT		*p*
	Median	*IQR*		*Median*	*IQR*	
Right Femoral Head (D_{max})	45.6	44.8- 46.8		46.6	46.1- 47.3	<.001
Left Femoral Head (D_{max})	45.4	44.0- 46.2		46.8	45.7 - 47.4	<.001
Bladder (D_{max})	48.3	47.9- 48.7		47.4	47.0 - 47.9	<.001
Bowel Bag (Vol cm^3)	182.3	129.3- 250.2		411.3	342.1 - 541.4	<.001
Bone Marrow (Vol %)	19.1	14.9- 24.9		38.7	33.9 - 43.2	<.001
Rectum (Vol %)	88.5	83.3- 96.0		96.0	90.0- 99.8	<.001

Sub Group Analysis

When comparing Stage IIB to IIIB cancer groups, statistically signifcant differences were only found for VMAT Treated Volume 95 Isodose (U = 83, p = .010), 3D-CRT Treated Volume 95 Isodose (U = 70, p = .003) and PTV Volume (U = 83, p = .010). Table 3. No difference was noted for OAR dosimetry.

Table 3: Comparison of statistically significant volumes between 3D-CRT and VMAT between Stage IIB and Stage IIIB.

	Stage IIB		**Stage IIIB**		*p*
	Median	IQR	Median	IQR	
VMAT Treated Volume	*1558.5*	1461.23-1693.83	*1754.70*	1571.50-1993.30	.01
3D Treated Volume	*2188.6*	1940.5-2340.03	*2473.00*	2309.90-2616.70	.003
PTV Volume	*1429.10*	1295.10-1579.25	*1658.10*	1439.2-1862.7	.01

DISCUSSION:

The aim of this study focused on determining the dosimetrically superior EBRT option in the management of LACC at Groote Schuur Hospital, South Africa. To date, no similar studies have been done in South Africa comparing 3D-CRT to VMAT in the management of LACC. Most institutions with the capability to offer IMRT have done so with little local evidence or dosimetric proof of superiority. 3D-CRT remains the preferred treatment reference, to which all inverse planning options are compared when managing LACC.[25, 26] This study examined dosimetric values for OAR and assessed tumour dosimetry between 3D-CRT and VMAT to determine the superior option.

Both 3D-CRT and VMAT showed appropriate dose coverage of the PTV. This coverage was deemed appropriate once the 95% isodose line encompassed the PTV. Additionally, the PTV D_{max} and D_{mean} were found to be within an acceptable range as outlined in ICRU guidelines. [18] Further quantitative analysis of the plans showed VMAT having a superior, statistically significant conformity index compared to 3D-CRT (Table 1). Similar results were presented in the study done by Guy JB et al. in 2016 comparing the dosimetrically superior option in LACC [9]. Conformity index values closer to one suggests a more conformal distribution of higher doses as represented by TV. As radiotherapy moves toward greater precision, improved conformity is essential in tumour dose escalation[27] and minimizing high dose exposure to OAR.

One of the major goals of radiotherapy is to deliver the maximum prescribed dose to a selected target volume uniformly, thus increasing the likelihood of tumour control. The homogeneity index, defined as the uniformity of dose distribution in the target volume, gives a numerical representation of this distribution. The homogeneity index between both methods of treatment were numerically different, indicating a small benefit towards 3D-CRT (Table 1). However, the value was not deemed statistically significant. At GSH, a homogeneity index less than 0.1 is accepted, which was achieved in both EBRT options.

It has been suggested that IMRT offers superior OAR sparing in gynaecological malignancies.[28] Similar findings in this study have supported this. OAR toxicity may

be affected by maximum dose as seen with the right femoral head, left femoral head and bladder, while volume dependant doses may affect organs such as bowel bag and bone marrow. Small bowel toxicity, as determined for bowel bag contours suggest a < 10 % Grade 3 toxicity for late effects and acute effects when V45Gy< 195 cm^3.[17] The 3D-CRT median dose from this study revealed a value of 411.3 cm^3 receiving 45Gy while 182.3 cm^3 for VMAT (Table 2 and Figure 3). Mell et al suggested a correlation between this dosimetric value and clinical symptoms tending to less acute and chronic symptoms when smaller volumes are exposed to similar doses.[29] Rectal dose comparisons also showed a more favourable dosimetric value for VMAT and as seen in RTOG 1203 a possible decrease in clinical toxicity.[30]

Bone marrow contouring guidelines and dose constraints[31] have been well documented in cervical cancer patients. Clinical toxicity, secondary to bone marrow suppression, with EBRT appears to have a greater clinical impact when combined with concurrent chemotherapy as opposed to EBRT alone.[6] At GSH, this was noted in previous observational studies which altered the timely delivery of EBRT, especially in patients receiving concurrent chemotherapy. In the study population, the 3D-CRT patients' median absolute volume receiving 40 Gy was twice that of VMAT (Table 2 and Figure 2), considerably increasing the risk of Grade 2 and greater bone marrow toxicity. Bone marrow toxicity secondary to EBRT may result in delayed treatments which are in turn associated with poorer outcomes. In a study done by Girinsky et al. in 1993 the results showed when treatment exceeded 52 days, loss of local control and overall survival, was approximately 1% per day. [32]

While VMAT was superior in limiting OAR dose constraints to most organs contoured, 3D-CRT offered a reduced maximum dose to the bladder (Table 2). This result is contradictory to similar studies including Lin. Y et al. whose research documented lower bladder doses in a meta-analysis of cervical cancer treatment with IMRT.[33] It has been postulated that limited prioritisation for the bladder contoured in the optimisation software used by staff at GSH may be the reason for the difference in values. Both VMAT and 3D-CRT bladder max doses were within Quantec [17] constraints and it was difficult to determine the extent of clinical impact of these differences.

VMAT can reduce the TV by improving the conformity index. It also limits the OAR toxicity by allowing multiple beam entry points as it rotates around a patient avoiding OAR contours. This sparing effect has led to an increase in lower doses from multiple small fields. The IV, represents that volume of tissue irradiated by a dose that is clinically significant. This study revealed a significantly larger IV with VMAT, when compared to 3D-CRT (Table 1). Concern regarding secondary malignancies with increased integral dose as represented by IV has been studied extensively and most studies suggest integral dose is not a good estimator of quantifying cancer induction.[34]

Lastly, sub-group analysis (Table 3) also revealed no statistically significant increase in OAR dosimetric values in Stage IIB vs IIIB cervical cancer when treated with either 3D-CRT or VMAT. The significant volume differences are based on unique guidelines used for Stage IIIB which includes contouring of the mesorectum and vagina depending on degree of involvement. This data suggests that while Stage IIIB does result in larger contoured PTV tumour volumes, the OAR dosimetric values were comparable to Stage IIB.

LIMITATIONS:

This study is subject to limitations, including the retrospective nature and small sample size. Additionally, the dosimetric data gathered represent numerical values, which were compared against Quantec[17] guidelines to determine the possibility of clinical complications. These guidelines, while not extensively validated for VMAT, have been the backbone to which dosimetric values are compared to minimise clinical OAR toxicity.

CONCLUSION

Minimising toxicities while optimising tumour treatment is essential in the successful management of LACC. The data analysed for the investigated study population showed dosimetric benefit of VMAT over 3D-CRT in the management of LACC with improved OAR sparing. Improved OAR sparing with lower doses to the femoral heads, bowel bag and bone marrow, as seen with VMAT planning, will possibly reduce both early and late toxicities. VMAT also offered comparable tumour coverage and dosimetry, equally homogenous dose distribution, with the added benefit of improved conformity and possible dose escalation. Maintaining and improving tumour dosimetry with a reduction in toxicity, allows for better compliance with treatment which is integral in improving outcomes. It is the hope of the authors that this study will provide support towards VMAT as a treatment option for LACC at GSH while remaining vigilant of new uncertainties.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Author's contributions

Data collection, analysis and manuscript composition was done by V.B. Senior review, expert consultation and final documentation approval was done by N.F. and A.H. The authors alone are responsible for the content and writing of this article.

Disclaimer

The views and opinions expressed in this article are those of the authors and not an official position of the University of Cape Town or Groote Schuur Hospital.

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APPENDECIES

Appendix i: Instructions to Authors

Submission Guidelines for the South African Journal of Oncology

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings, clearly present the overall results and any meta-analysis.

Word limit	3500-4000 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Original Research Article full structure

Title:

- Full title: Specific, descriptive, concise, and comprehensible to readers outside the field. Max 95 characters (including spaces).
- Tweet for the journal Twitter profile: This sentence/statement will be used on the journal Twitter profile to promote your published article. Max 101 characters (including spaces). If you have a Twitter profile, please provide us your Twitter @ name. We will tag you to the Tweet.

Abstract: The Abstract should provide the context or background for the study and should state the study's purpose, basic procedures (selection of study participants, settings, measurements, analytical methods), main findings (giving specific effect sizes and their statistical and clinical significance, if possible), and principal conclusions. The Abstract should not exceed 250 words. Please minimize the use of abbreviations and do not cite references in the abstract. Refer to the relevant article type's guideline you are submitting for the abstract sections.

Introduction: The Introduction should put the focus of the manuscript into a broader context and explain its social and scientific value. Address this to readers who are not experts in this field and include a brief review of the key literature. If there are relevant controversies or disagreements in the field, they should be mentioned. Conclude with a brief statement of the overall aim of the experiments and a comment about whether that aim was achieved. Cite only directly pertinent references, and do not include data or conclusions from the work being reported.

Methods: The Methods section should provide clarity about how and why a study was done in a particular way. It should provide enough detail for reproduction of the findings. Protocols for new methods should be included, but well-established methodological procedures may simply be referenced. A full description of the methods should be included in the manuscript itself rather than in a supplemental file. Only information that was available at the time the plan or protocol for the study was being written must be included; all information obtained during the study belongs in the Results section. If an organization was paid or otherwise contracted to help conduct the research (examples include data collection and management), then this should be detailed in the methods.
The methods section should include:

- The selection and description of participants or description of materials.
- The aim, design and setting of the study.
- The description of the processes, interventions and comparisons. Generic drug names should generally be used. When proprietary brands are used in research, include the brand names in parentheses.
- The type of statistical analysis used, including a power calculation if appropriate.

The Methods section should include a statement indicating that the research was approved or exempted from the need for review by the responsible review committee (institutional or national). If no formal ethics committee is available, a statement indicating that the research was conducted according to the principles of the Declaration of Helsinki should be included.

Results: Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical significance attached to them, if any. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.” Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

Conclusion: It is useful to begin the discussion by briefly summarizing the main findings and explore possible mechanisms or explanations for these findings. Emphasize the new and important aspects of your study and put your findings in the context of the totality of the relevant evidence. State the limitations of your study and explore the implications of your findings for future research and for clinical practice or policy. Discuss the influence or association of variables, such as sex and/or gender, on your findings, where appropriate, and the limitations of the data. Do not repeat in detail data or other information given in other parts of the manuscript, such as in the Introduction or the Results section. Link the conclusions with the goals of the study

but avoid unqualified statements and conclusions not adequately supported by the data. In particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analyses. Avoid claiming priority or alluding to work that has not been completed. State new hypotheses, when warranted and label them clearly.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named.
Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

The above manuscript section guidelines are adapted from the recommendations from the International Committee of Medical Journal Editors: preparing for submission, available from http://www.icmje.org/recommendations/browse/manuscript-preparation/preparing-for-submission.html on April, 24, 2017.

Appendix ii: Official Ethical Approval Letters

Radiation Oncology

Professor Jeannette Parkes
Head of Division

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19 May 2018

Dear Dr Visham Bhagaloo

Permission is hereby granted to Dr Visham Bhagaloo for the following research study to be conducted in the department of Radiation Oncology:

MMed Title: Volumetric Modulated Arc Therapy versus 3D- Conformal Radiotherapy in the treatment of locally advanced cervical cancer. A single institution, comparative dosimetric study.

Please note that permission is also required from Dr Eick through Lionel Naidoo's institutional research committee, and from Ethics committee before commencing the research study.

Kind regards

Signature Removed

Professor Jeannette Parkes
Head of Division
Radiation Oncology

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

28 September 2018

HREC REF: 625/2018

Dr Nazia Fakie
Radiation Oncology
LE33

Dear Dr Nazia

PROJECT TITLE: VOLUMETRIC MODULATED ARC THERAPY (VMAT) VERSUS 3D CONFORMAL RADIOTHERAPY (3D-CRT) IN THE TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER. A SINGLE INSTITUTION, COMPARATIVE DOSIMETRIC STUDY. (Masters Candidate - Dr V. Bhagaloo)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 September 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Visham Bhagaloo will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.

HREC 625/2018

Western Cape Government
Health

GROOTE SCHUUR HOSPITAL

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Dr N. Fakie
RADIATION ONCOLOGY

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Dear Dr Fakie,

RESEARCH PROJECT: Volumetric Modulated ARC Therapy (VMAT) Versus 3D Conformal Radiotherapy (3D-CRT) in the Treatment of Locally Advanced Cervical Cancer. A Single Institution, Comparative Dosimetric Study (Master's Candidate Dr Visham Bhagaloo)

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 September 2019.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) No additional costs to the hospital should be incurred i.e. Lab, consumables or stationary.
d) **No patient folders may be removed from the premises or be inaccessible.**
e) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
f) Confidentiality must be maintained at all times.
g) Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) Kindly submit a copy of the publication or report to this office on completion of the research.

I would like to wish you every success with the project.

Yours sincerely

Signature Removed

DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 29 January 2019

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UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	28.2.2021
☐ Not approved	See attached comments		
Signature Chairperson of the HREC	Signature Removed	Date Signed	13/02/2020

Comments to PI from the HREC
Thank you for the study donation form.

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	5th February 2020		
HREC REF Number	625/2018	Current Ethics Approval was granted until	30th Sept 2019
Protocol title	Volumetric Modulated Arc Therapy (VMAT) versus 3D Conformal Radiotherapy (3D-CRT) in the treatment of locally advanced cervical cancer. A single institution comparative dosimetric study.		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.			
Principal Investigator	Dr. Nazia Fakie		
Department / Office Internal Mail Address	LE33, Radiation Oncology Department, Groote Schuur Hospital		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

Appendix iii: Data Collection Form

Confidential

My First Instrument

Record ID	_____
Radiotherapy Number	_____
Radiotherapy Type	◯ 3D-CRT ◯ VMAT
Age	_____
Stage	◯ Stage I ◯ Stage IIa ◯ Stage IIb ◯ Stage IIIa ◯ Stage IIIb ◯ Stage IVa
Histology	◯ Adenocarcinoma ◯ Squamous cell carcinoma (Well Differentiated) ◯ Squamous cell carcinoma (Moderately Differentiated) ◯ Squamous cell carcinoma (Poorly Differentiated)
Separation	_____
PTV D 2%	_____
PTV D 98%	_____
PTV D 50%	_____
Homogenity Index	_____
D max	_____
D mean	_____
Treated Volume 95% Isodose	_____
PTV Volume	_____

Conformity Index	_____
Irradiated Volume 20% Isodose	_____
Right Femoral Head D max	_____
Left Femoral Head D Max	_____
Bladder Dmax	_____
Rectum	_____
Bowel Bag	_____
Bone Marrow	_____

Appendix iv: FIGO 2009 Cervical Cancer Staging

TNM clinical classification

TNM categories	FIGO stages	Definition
T – Primary Tumour		
TX		Primary tumour cannot be assessed
T0		No evidence of primary tumour
Tis		Carcinoma *in situ* (preinvasive carcinoma)
T1	I	Tumour confined to the cervix[a]
T1a[b,c]	IA	Invasive carcinoma diagnosed only by microscopy. Stromal invasion with a maximal depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less[d]
T1a1	IA1	Measured stromal invasion 3.0 mm or less in depth and 7.0 mm or less in horizontal spread
T1a2	IA2	Measured stromal invasion more than 3.0 mm and not more than 5.0 mm with a horizontal spread of 7.0 mm or less[d]
T1b	IB	Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a/IA2
T1b1	IB1	Clinically visible lesion 4.0 cm or less in greatest dimension
T1b2	IB2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2	II	Tumour invades beyond uterus but not to pelvic wall or to lower third of vagina
T2a	IIA	Tumour without parametrial invasion
T2a1	IIA1	Clinically visible lesion 4.0 cm or less in greatest dimension
T2a2	IIA2	Clinically visible lesion more than 4.0 cm in greatest dimension
T2b	IIB	Tumour with parametrial invasion
T3	III	Tumour involves lower third of vagina, or extends to pelvic wall, or causes hydronephrosis or non-functioning kidney
T3a	IIIA	Tumour involves lower third of vagina
T3b	IIIB	Tumour extends to pelvic wall, or causes hydronephrosis or non-functioning kidney
T4	IVA	Tumour invades mucosa of the bladder or rectum, or extends beyond true pelvis[e]
N – Regional Lymph Nodes[f]		
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node metastasis
M – Distant Metastasis[f]		
M0		No distant metastasis
M1		Distant metastasis (includes inguinal lymph nodes and intraperitoneal disease). It excludes metastasis to vagina, pelvic serosa, and adnexa

[a]Extension to corpus uteri should be disregarded.

[b]The depth of invasion should be taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumour from the epithelial–stromal junction of the adjacent most superficial papillae to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.

[c]All macroscopically visible lesions even with superficial invasion are T1b/IB.

[d]Vascular space involvement, venous or lymphatic, does not affect classification.

[e]Bullous oedema is not sufficient to classify a tumour as T4.

[f]No FIGO equivalent.

TNM, tumour, node and metastasis.

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