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Evaluation of target motion and determination of optimal treatment margins for prostate cancer treated with external beam radiotherapy on the Halcyon™

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I, Marion Algar, was the main author of this manuscript. My contributions were conceptualising the topic, gathering of data, analysis of data and write-up of the manuscript.

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FORMAT

This minor dissertation is being submitted as a publication-ready manuscript according to the South African Journal of Oncology (SAJO) submission guidelines. This article has not been submitted for publication.

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LIST OF ABBREVIATIONS AND SYMBOLS

3D-CRT	Three-Dimensional Conformal Radiotherapy
3-DOF	3-Degrees of Freedom
ADT	Androgen Deprivation Therapy
AP	Antero-Posterior
CBCT	Cone-Beam Computed Tomography
CT	Computed Tomography
CTV	Clinical Target Volume
EBRT	External Beam Radiotherapy
ESTRO-ACROP	European Society for Radiotherapy and Oncology-Advisory Committee for Radiation Oncology Practice
FDK-CBCT	Feldkamp-Davis-Kress Cone-Beam Computed Tomography
FFF	Flattening Filter-Free
iCBCT	Iterative Cone-Beam Computed Tomography
IGRT	Image-Guided Radiotherapy
IMRT	Intensity-Modulated Radiotherapy
ML	Medio-Lateral
MLC	Multi-Leaf Collimator
MRI	Magnetic Resonance Imaging
PTV	Planning Target Volume
RMS	Root Mean Square
SI	Supero-Inferior
SIB	Simultaneous Integrated Boost
STD	Standard Deviation
VMAT	Volumetric Modulated Arc Therapy
Σ	Systematic Error
σ	Random Error
#	Fraction

Evaluation of target motion and determination of optimal treatment margins for prostate cancer treated with external beam radiotherapy on the Halcyon™

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ABSTRACT

Background

External beam radiotherapy (EBRT) is an important part of the treatment for prostate cancer. To account for organ motion and set-up error, margins are used in radiotherapy planning. These are essential for the delivery of safe and effective treatment.

Aim and Setting

To measure prostate motion during the course of EBRT on the Halcyon™ at Groote Schuur Hospital. Using published margin recipes, the minimum clinical target volume (CTV)-planning target volume (PTV) expansion margin was calculated.

Patients and Methods

Prostate motion was evaluated by comparing prostate position on the planning CT to cone-beam CT (CBCT) scans. Prostate position error in the medio-lateral (ML), antero-posterior (AP) and supero-inferior (SI) directions was measured for each CBCT. The systematic (Σ) and random (σ) error of prostate motion was calculated. The minimum CTV-PTV margin was determined.

Results

The mean position error of the prostate was -0.04mm (95% CI -0.14, 0.10), -0.30mm (95% CI -0.70, 0.15) and -0.40mm (95% CI -0.89, 0.00) in the ML, AP and SI directions, respectively. Using Van Herk's margin formula (2.5Σ +0.7σ), the following minimum CTV-PTV margins for the ML, AP and SI directions were calculated: 1.9mm, 6.9mm and 7.8mm, respectively. Using Stroom's margin formula (2Σ +0.7σ), the following minimum CTV-PTV margins for the ML, AP and SI directions were calculated: 1.6mm, 5.8mm and 6.6mm, respectively.

Conclusion

Based on prostate motion, our institution's current margins are sufficient. However, further studies are necessary to measure other factors that influence the CTV-PTV margin before considering reducing this margin.

INTRODUCTION

Prostate cancer is the second most common cancer diagnosis and the fifth leading cause of cancer-related death amongst men, worldwide.[1] By 2030, the global burden of prostate cancer is predicted to rise to 1.7 million new cases and 499,000 new deaths as a result of growth and aging of the world's population.[2] In South Africa, prostate cancer has the highest incidence and accounts for 25% of cancers diagnosed in men.[3]

There are different curative treatment options for localised prostate cancer. These include surgery and/or radiotherapy. Androgen deprivation therapy (ADT) may also be combined with radiotherapy.[4] Types of radiotherapy include external beam radiotherapy (EBRT) and brachytherapy. Advanced EBRT techniques such as intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) are able to achieve highly conformal dose distributions compared to three-dimensional conformal radiotherapy (3D-CRT).[4] This allows for a sharp dose gradient around the target and reduction of dose to surrounding normal tissues.[5]

In transitioning to these advanced, highly conformal radiotherapy techniques, there is increased risk of geographical miss. Adequate margins applied to the target volumes are essential to avoid geographical miss.[4] Geographical miss not only leads to under-dosing of the tumour (thus compromising control of the tumour) but may result in increased dose to normal tissues (causing increased early and late side effects).

The prostate is a mobile structure. Its attached seminal vesicles are even more mobile.[6] The position of the prostate is influenced by rectal and bladder filling as well as breathing. Increased prostate motion during radiotherapy has been associated with increased biochemical failure, reduced local control and increased normal tissue toxicity.[7] Inter-fraction motion may occur between treatment fractions and intra-fraction motion may occur whilst treatment is being delivered.[8]

When preparing for the radiotherapy planning CT scan, patients are asked to empty their bowels and comfortably fill their bladders. This is done in a standard way to minimise fluctuations in bladder and rectal volume. These instructions are followed prior to each fraction of radiotherapy in order to best simulate the patient's anatomy at the time of the planning CT scan. Patients are positioned supine and immobilised with a Combifix™ (a pelvis and lower limb immobilisation device) to improve set-up reproducibility.

After the planning CT is transferred to the treatment planning system, contouring of volumes begins. The first target volume contoured is the clinical target volume (CTV). This includes the entire prostate and may include some or all of the seminal vesicles as well as regional lymph nodes (depending on the risk stratification).[9] The CTV incorporates the gross tumour as well as possible

areas of microscopic spread whilst respecting anatomical boundaries.[10] The internal target volume (ITV) is defined by an internal margin. This margin accounts for physiological movement resulting in changes in the shape, size and position of the target.[11] The planning target volume (PTV) is a geometric concept that incorporates the internal margin as well as a set up margin. The set-up margin accounts for beam and patient set-up inaccuracies. The CTV-PTV margin ensures adequate daily coverage of the CTV in order to achieve the goal of treatment (in this case, cure).[11] At our institution, the current CTV-PTV margin is an anisotropic margin of 10mm (except 7mm posteriorly).

Errors in target delineation have a direct impact on treatment outcomes.[9] In the setting of advanced radiotherapy techniques (such as IMRT and VMAT) with sharp dose gradients, errors in delineation may result in under-dosing of the tumour.[9] Thus it is essential to follow guidelines and ideally peer review delineated target volumes. At our institution, the ESTRO-ACROP consensus guideline is followed for target volume delineation.[9] To further improve target volume delineation, magnetic resonance imaging (MRI) can be fused to the planning CT. MRI has superior soft-tissue contrast which allows for more detailed visualisation of the prostate and surrounding structures.[9] The use of MRI is not always possible in resource-constrained environments.

Image-guided radiotherapy (IGRT) is an essential part of geometric verification in radiotherapy. It is used to reduce errors arising from differences in patient and tumour position from the intended treatment.[8] There are a variety of techniques used for IGRT such as portal imaging, ultrasound, cone-beam CT (CBCT), MRI and electromagnetic transponders.[4] Implanted fiducial markers may also be used in conjunction with portal imaging or CBCT.

In 2019, our institution acquired a new linear accelerator called the Halcyon™ (Varian Medical Systems, Palo Alto, CA, USA). The Halcyon™ is a ring-based linear accelerator with a 6MV flattening filter-free (FFF) beam and double-stacked multi-leaf collimators (MLCs). This machine has on-board CBCT which allows for bone and soft tissue visualisation. Standard treatment verification techniques usually use registration of bony anatomy alone. The use of CBCT provides significant additional information such as target visualisation, avoidance of critical organs and treatment response assessment.[12] Bone and soft tissue imaging is superior compared to bone imaging alone as the position of the prostate rarely correlates with bone or surface anatomy.[13]

High quality images, taken prior to each treatment, are essential to provide accurate and precise radiotherapy. The Halcyon™ has advantages in terms of IGRT as it utilises kV-iCBCT (iterative CBCT). iCBCT uses software (Acuros® CTS) which allows for fast and accurate calculation of image scatter.[14] It also uses a statistical (iterative) reconstruction algorithm compared to standard kernel-based correction used in Feldkamp-Davis-Kress (FDK)-CBCT.[14] This combination results in advanced image

quality compared to the conventional FDK-CBCT.[14] It allows for improved accuracy of soft-tissue-based IGRT. It also means that iCBCT can be used for contouring and dose calculation in the setting of online adaptive radiotherapy.[14]

Errors that result in geometric uncertainty are divided into systematic and random errors.[4] Systematic error is often referred to as "treatment preparation error".[4] Introduction of systematic error occurs in the treatment planning process and is related to patient set-up, target delineation, or changes in target position and shape between delineation and treatment.[4] These errors occur daily throughout treatment in the same direction and are of similar magnitude.[8] Systematic error results in a shift of the aggregated dose distribution away from the CTV. Random error is often referred to as "treatment execution" error. It may occur at any stage of treatment and is related to patient set-up, and change in target position or shape between and during treatment fractions. It varies in direction and magnitude for each fraction of treatment. Random error results in blurring of the dose distribution around the CTV.[4]

There are a variety of margin recipes that can be used to calculate the required CTV-PTV margin. These include Van Herk's $(2.5\Sigma + 0.7\sigma)$[15] and Stroom's $(2\Sigma + 0.7\sigma)$[16] margin recipes. The symbol Σ denotes systematic error and the symbol σ denotes random error. These margin recipes incorporate both systematic and random error. Van Herk's recipe ensures that the CTV will receive at least 95% of the prescribed dose in 90% of the patients.[15] Stroom's recipe ensures that 99% of the CTV will receive at least 95% of the prescribed dose.[16]

After the acquisition of the Halcyon™, soft tissue visualisation during set-up verification was possible for the first time at our institution. This study was aimed at measuring prostate motion during the course of radiotherapy for patients with prostate cancer treated on the Halcyon™. The systematic and random prostate position errors were calculated. Van Herk's and Stroom's margin recipes were used to determine the minimum CTV-PTV margin.

METHODS

Study Aims and Objectives

The aim of this study was to quantify inter-fraction prostate motion during the course of radiotherapy. The primary objective was to determine the systematic and random error of prostate motion relative to bony anatomy. The secondary objective was to assess if the current CTV-PTV margins, used at our institution, are adequate.

Study Population

The patient population included 20 patients with prostate cancer who were treated with definitive radiotherapy in 2019-2021. All patients were treated on the Halcyon™ and underwent online image-guidance with daily CBCT imaging.

Study Design

This was a retrospective observational study. Prostate motion on 10 CBCTs (done at fractions 1, 2, 3, 6, 11, 12, 16, 21, 22 and 26) was evaluated for 20 patients treated on the Halcyon™. The prostate was contoured on each planning CT and 10 subsequent CBCTs per patient by a single senior radiation oncology registrar using the ESTRO-ACROP guideline. This standardised guideline was used to control intra-observer variability. The seminal vesicles were not contoured. Using the automatic match algorithm, each CBCT was rigidly registered to the corresponding planning CT on bone settings. The registration allowed for translations but not rotations in order to simulate the use of the Halcyon's™ 3-degrees of freedom (3-DOF) couch. This match was reviewed and adjusted manually if indicated. The centre of mass shift of the contoured prostates on the CBCTs was compared to that of the prostate contoured on the planning CT for each patient. This was measured in the medio-lateral (ML), antero-posterior (AP) and supero-inferior (SI) directions. This was the prostate position error. Using these error values, the following were calculated:

1. The individual mean prostate position error per patient in all 3 directions. The standard deviation of these means was calculated. This represented the systematic error (Σ).[17]
2. The individual standard deviations of prostate position error per patient in all 3 directions. The root mean square of the standard deviations of all patients was calculated. This represented the random error (σ).[17]
3. Using Van Herk's (2.5Σ + 0.7σ) and Stroom's (2Σ + 0.7σ) margin recipes, the minimum CTV-PTV margin was determined in all 3 directions.[15,16]

Radiotherapy Technique

At CT simulation, all patients were scanned in the supine position. They were immobilised using a Combifix™. After voiding their bladders, bladder preparation was done by providing patients with 750ml of water to drink 40 minutes before the planning CT. Prior to the planning CT scan, patients were advised to empty their bowels. A mini-scan was performed first to confirm that the bladder was adequately filled and the rectal AP-diameter was acceptable. Oral and IV contrast was given. Patients were scanned from the level of T12 to mid-femur using 3mm slices. These images were then transferred to the Eclipse™ (Varian Medical Systems, Palo Alto, CA, USA) treatment planning system.

For contouring, the CTV included the prostate and, in most cases, the seminal vesicles with a second CTV dose level defining the lymph nodes. An anisotropic margin of 10mm (except 7mm posteriorly) was added to the CTV prostate and seminal vesicles to create PTV67.5Gy. An isotropic margin of 5mm was added to the CTV nodes to create PTV48.6Gy. Organs at risk were also contoured. These included the bladder, rectum, small bowel, large bowel, femoral heads and penile bulb.

Treatment was delivered using the Halcyon™. The technique used was VMAT. Radiotherapy was given as a simultaneous integrated boost (SIB). Treatment was given daily, Monday to Friday, for 27 fractions over 5.5 weeks. The dose per fraction (#) was 2.5Gy/# for PTV67.5Gy and 1.8Gy/# for PTV48.6Gy. Daily, online CBCTs were done for set-up verification and evaluation of rectal size and bladder filling.

Image Analysis

Prior to analysis, the prostate on each planning CT and the prostate on 10 subsequent CBCTs, done during the course of EBRT, were contoured for each patient by a single senior radiation oncology registrar. 200 CBCTs were compared to 20 planning CTs for the 20 patients. A total of 220 prostates were contoured. Half of the contours were independently reviewed by a single qualified radiation oncologist. Each CBCT was rigidly, automatically registered to the planning CT using bone settings. This registration was done for the vertical, longitudinal and lateral directions only. This simulated the registration that was performed online prior to treatment at the machine with a 3-DOF couch. All registrations were reviewed and adjusted manually if indicated.

Data Analysis

Following image registration, prostate motion was measured by comparing the centre of mass shift of the prostate contoured on the planning CT and that of the prostate contoured on each CBCT, in all 3 directions. For each patient, the mean position error of the prostate across the 10 CBCTs was calculated for each direction. The standard deviation of all the calculated means, for each direction, represented the systematic position error (Σ).[13] The standard deviations of the translations for each patient across the CBCTs were also calculated. The root mean square of these values was calculated in order to determine the random position error (σ).[13] Van Herk's (2.5Σ +0.7σ) and Stroom's (2Σ +0.7σ) margin recipes were used to calculate the CTV-PTV margin using the systematic and random error values.

Ethical Considerations

The Human Research Ethics Committee of the University of Cape Town approved the proposed study (HREC 256/2022). Informed consent was not required as this was a retrospective review of imaging records only. All data that was collected was stored on a password protected laptop.

RESULTS

Translation Displacements

The largest variation in prostate position was in the AP and SI directions. The smallest variation in prostate position was in the ML direction. Figures 1, 2 and 3 demonstrate the distribution of the prostate position errors in the ML, AP and SI directions, respectively. The prostate position errors were normally distributed in the ML, AP and SI directions (skewness ≤ 2 × standard error of skewness). More than 95% of the prostate position errors were within 5mm.

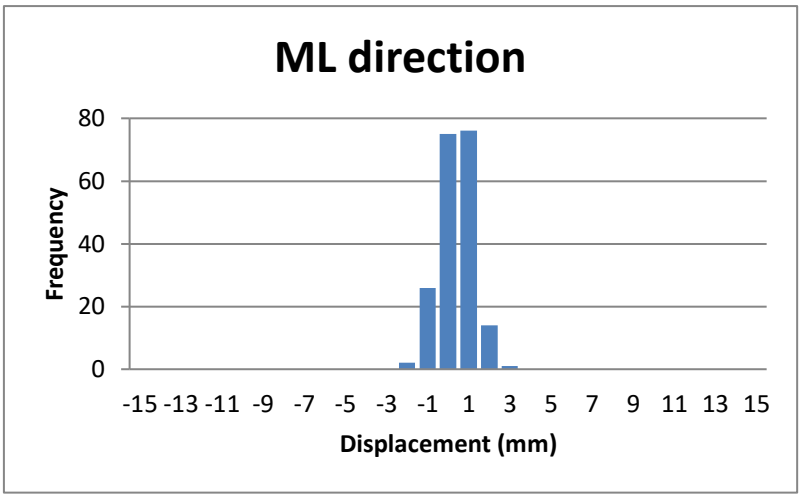

Figure 1: Distribution of the prostate position errors in the medio-lateral direction.

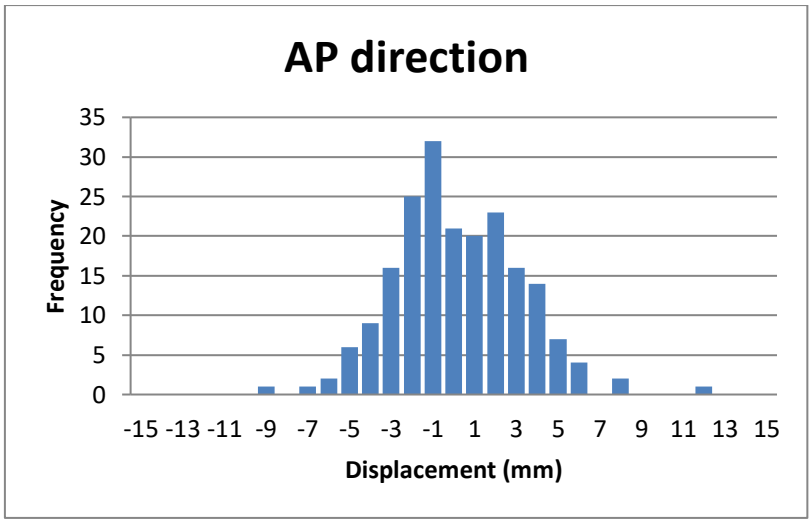

Figure 2: Distribution of the prostate position errors in the antero-posterior direction.

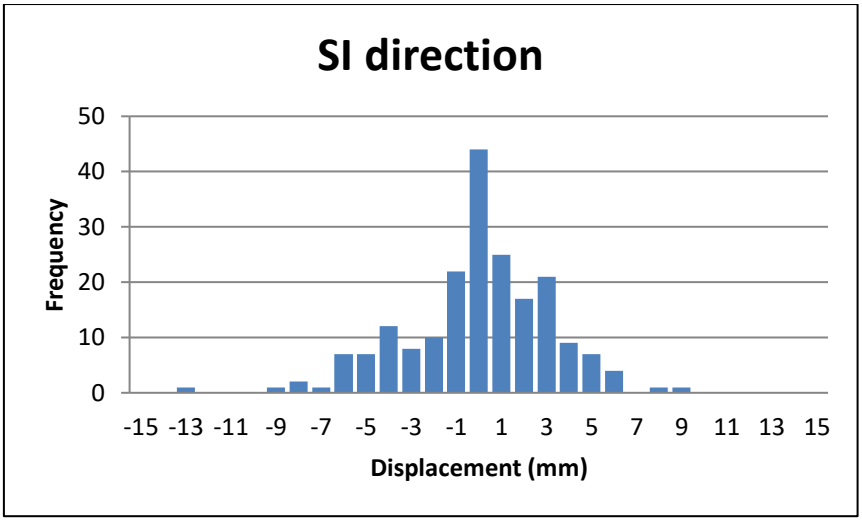

Figure 3: Distribution of the prostate position errors in the supero-inferior direction.

Figures 4 – 6 show the daily individual prostate position errors for each patient for all 3 directions during the course of EBRT.

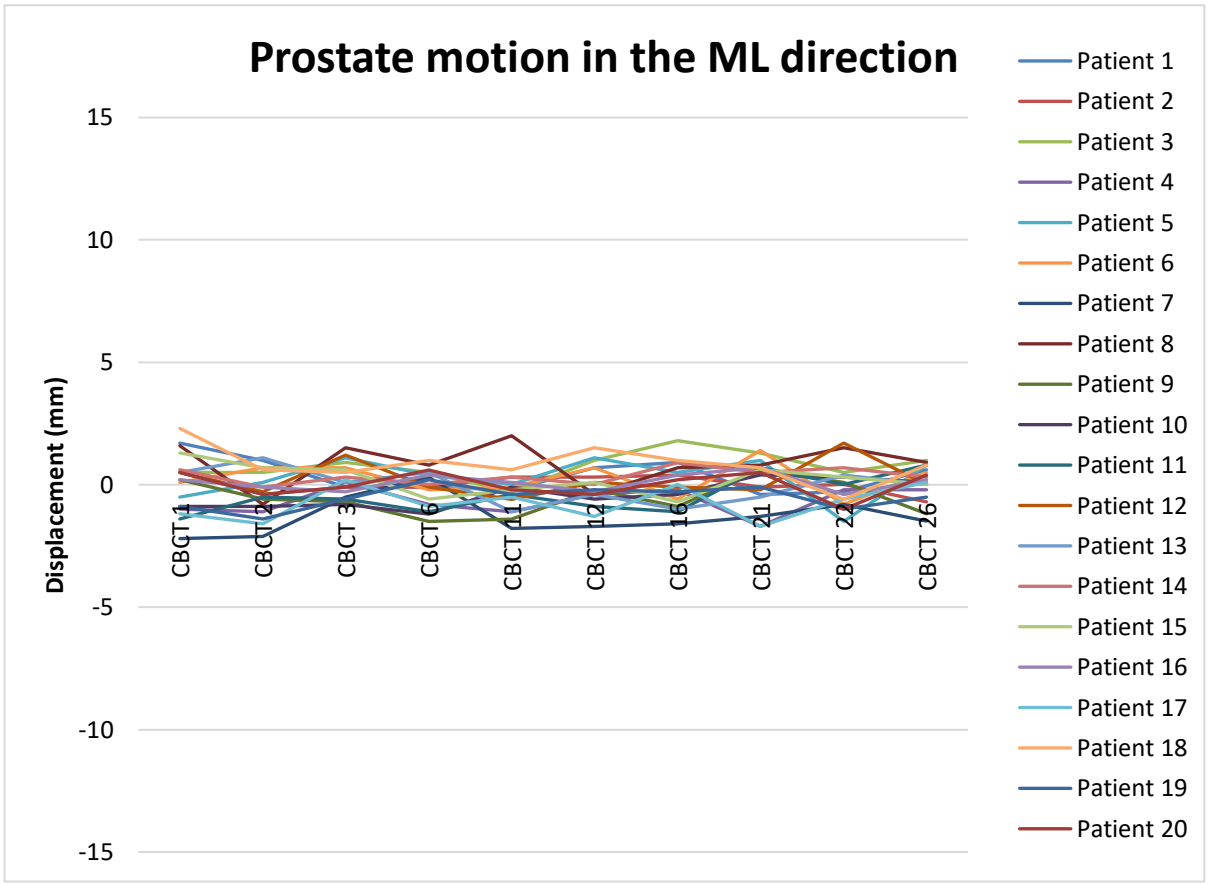

Figure 4: Daily individual prostate motion errors for each patient in the medio-lateral (ML) direction.

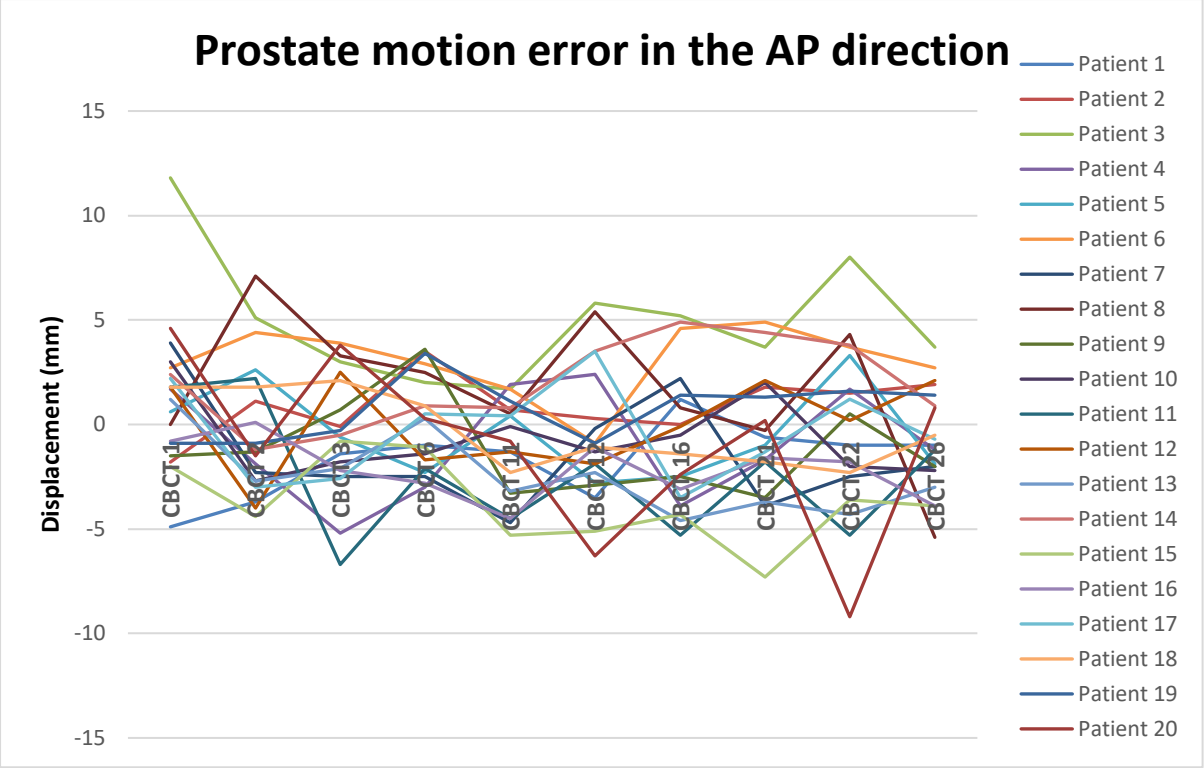

Figure 5: Daily individual prostate motion errors for each patient in the antero-posterior (AP) direction.

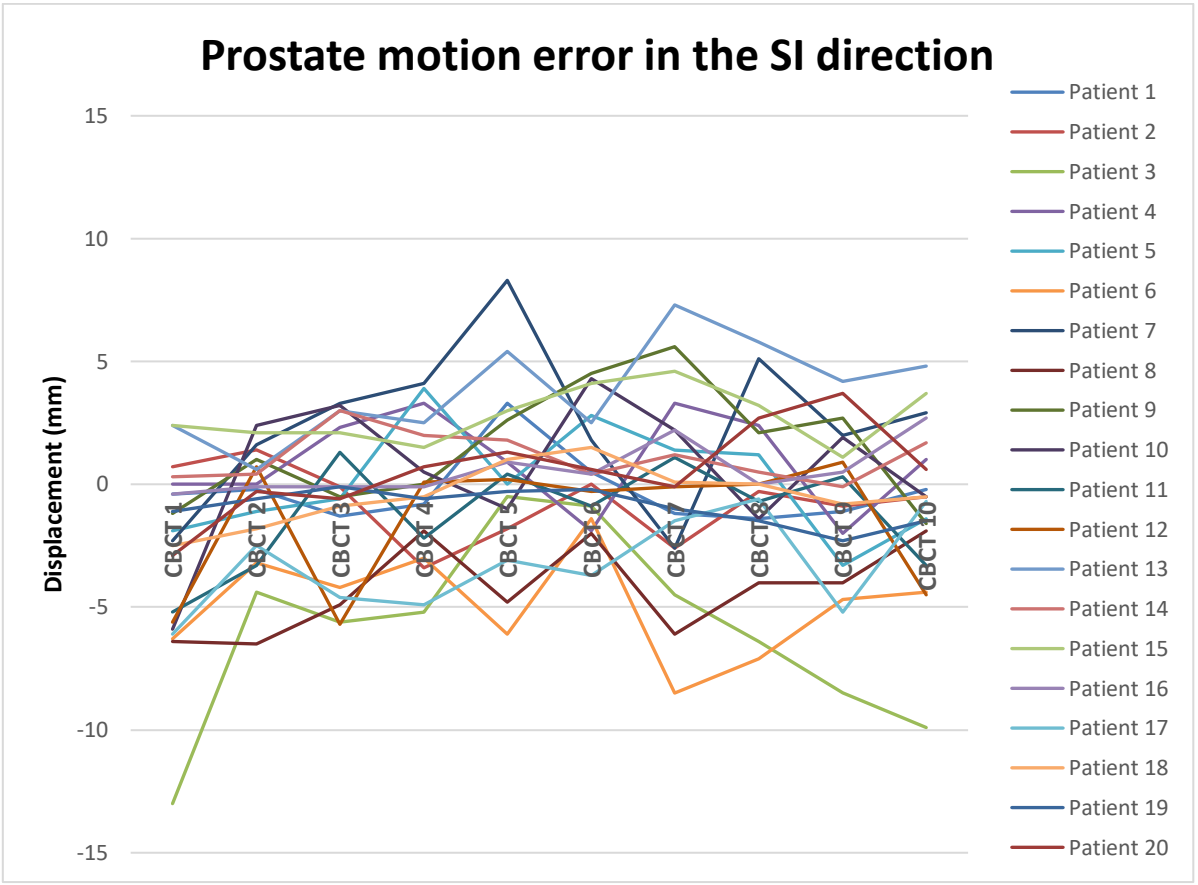

Figure 6: Daily individual prostate motion errors for each patient in the supero-inferior (SI) direction.

Systematic and Random Errors

As Table 1 illustrates below, the mean position error of the prostate in the ML, AP and SI directions was -0.04mm (95% CI -0.14, 0.10), -0.30mm (95% CI -0.70, 0.15) and -0.40mm (95% CI -0.89, 0.00), respectively. The systematic position errors ranged from 0.57mm to 2.54mm and the random position errors ranged from 0.65mm to 2.38mm. The largest position errors occurred in the AP and SI directions and the smallest position errors occurred in the ML direction.

Function	ML	AP	SI
M	-0.02mm	-0.30mm	-0.40mm
Σ	0.57mm	2.08mm	2.54mm
σ	0.65mm	2.38mm	2.10mm

Table 1: The mean (M), systematic (Σ) and random (σ) position errors calculated in the medio-lateral (ML), antero-posterior (AP) and supero-inferior (SI) directions.

Margin Calculation

Using Van Herk's and Stroom's margin recipes, the minimum CTV-PTV margins in the ML, AP and SI directions were calculated (see Table 2 below for results).

	ML	AP	SI
Van Herk (2.5Σ +0.7σ)	1.9mm	6.9mm	7.8mm
Stroom (2Σ +0.7σ)	1.6mm	5.8mm	6.6mm

Table 2: The CTV-PTV margin calculated using different margin recipes.

DISCUSSION

This study was the first in our institution to evaluate prostate motion during the course of EBRT. The aim of this study was to calculate the necessary CTV-PTV margins for the prostate accounting for inter-fraction motion only. The largest prostate position error was found in the AP and SI directions and the smallest error was in the ML direction. This is most likely due to fluctuations in bladder filling and rectal distension. Although not a measured outcome in this study, the CBCTs with the highest prostate position error had large variations in the bladder and rectal volumes. See figures 7-9 below.

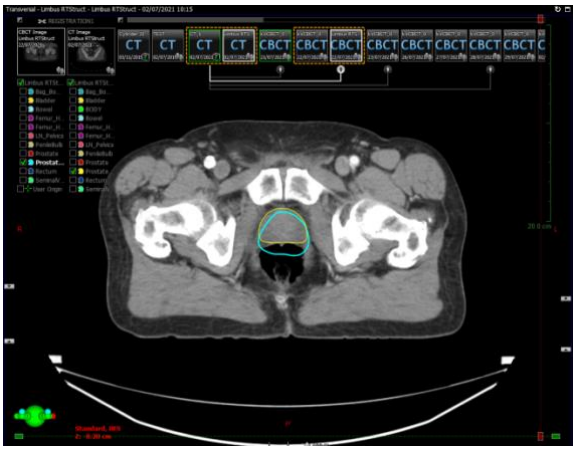

Figure 7: Axial slice of planning CT. Note distended rectum. Prostate contoured on planning CT in *yellow*. Prostate contoured on CBCT in *turquoise.*

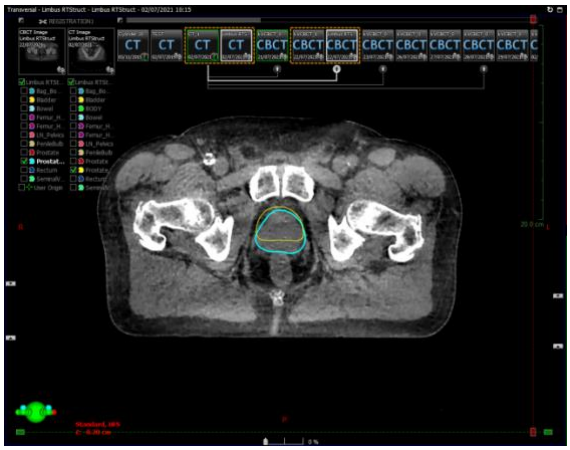

Figure 8: Axial slice of CBCT. Note less distended rectum. Prostate contoured on planning CT in *yellow*. Prostate contoured on CBCT in *turquoise.*

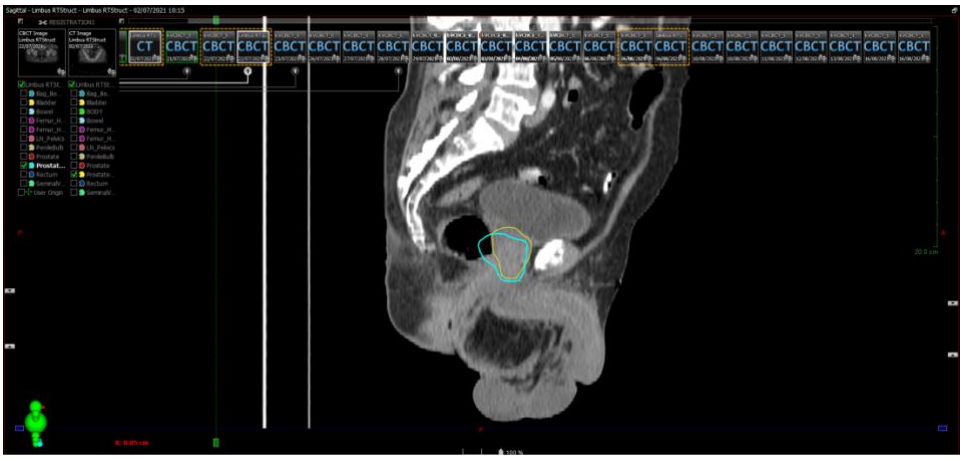

Figure 9: Sagittal slice of planning CT. Note distended rectum with resultant anterior displacement of prostate. Prostate contoured on planning CT in *yellow*. Prostate contoured on CBCT in *turquoise.*

Previous work by Kershaw et al[17] quantified motion of the prostate, seminal vesicles and lymph nodes. Using a 3-DOF couch and bone registration, the recommended CTV-PTV margins for the prostate alone in the ML, AP and SI directions were 2mm, 8mm and 6mm, respectively.[17] These margins are similar to those calculated from this study. Of note, the study by Kershaw et al used repeat CT scans instead of CBCTs to evaluate organ motion. This was based on the availability of CT, improved image quality and the larger field of view required to observe the superior nodal regions.[17] At our institution, iCBCT is used. As mentioned previously, iCBCT has superior image quality compared to FDK-CBCT. For our study, CBCT was chosen due to availability and good image quality.

In a study by Marnouche et al[18], prostate displacement was measured using CBCTs and bone registration. The systematic and random errors were calculated. The CTV-PTV margin was determined using Van Herk's margin recipe. This margin was 5.42mm, 8.03mm and 8,73mm in the

ML, AP and SI directions. This study included fewer patients (15) and fewer CBCTs (6.3 per patient on average). The calculated margin was slightly larger than in our study. Similarly to our study, the largest margin was in the SI direction followed by the AP and ML directions.

A large study by Mesías et al[19] evaluated inter-fraction set-up errors for a variety of sites, including the prostate, using CBCT. For the prostate, 63 patients were included and 1615 CBCTs were analysed. Using Van Herk's margin recipe, the CTV-PTV margin for the prostate was 9.2mm, 10mm and 8.4mm in the ML, AP and SI directions. These margins are slightly larger than those calculated in our study.

Using Van Herk's and Stroom's margin recipes, the calculated CTV-PTV margins are within the current CTV-PTV margin used at our institution. However, this margin accounts for inter-fraction prostate motion and set up error only. There are additional components that contribute to the combined systematic error and combined random error. For the combined systematic error, these components include target delineation, intra-fraction motion, IGRT accuracy and machine accuracy.[6] For the combined random error, these components include IGRT accuracy (system and observer-related) and intra-fraction motion.[6] The recommended CTV-PTV margins from this study are a minimum margin. Further studies would need to be done to quantify all components that contribute to systematic and random error. Only then could true recommendations for CTV-PTV margins be provided.

As mentioned above, target delineation error contributes to systematic error. Following contouring guidelines may reduce this error. In addition to following contouring guidelines, an MRI may be fused to the planning CT to improve target delineation. MRI provides high soft-tissue contrast which allows for more detailed visualisation of the prostate and its surrounding structures.[9] CT scans overestimate prostate size by 35% compared to MRI.[20] Thus CT-based prostate delineation is larger in comparison to CT-MRI fusion-based delineation. This increases the volume of irradiated surrounding normal tissues. By performing CT-MRI fusion-based radiotherapy, normal tissue toxicity may be reduced through smaller, more precise target volume delineation. Additionally, intra- and inter-observer variability during contouring may contribute to target delineation error. This is a potential limitation in this study as a single observer contoured the prostates with half of these contours assessed by a radiation oncologist.

This study quantified motion of the prostate alone. However the seminal vesicles are frequently included in the CTV for definitive EBRT. The seminal vesicles are known to be more mobile than the prostate.[21] A recent review showed that the systematic and random errors of seminal vesicle motion range from 1-7mm and 1-5mm, respectively.[22] The majority of studies reported a CTV-PTV margin of

8mm for the seminal vesicles.[22] These errors were mostly uncorrelated to prostate motion.[22] Motion of the seminal vesicles would need to be measured in order to ascertain the optimal CTV-PTV margins for the high dose CTV.

This study included 20 patients and 10 CBCTs per patient. If more patients and more CBCTs per patient were included, this may have decreased the uncertainty in the prostate position error measurements. Although half of the contoured prostates were reviewed by a radiation oncologist, this did not fully eliminate potential target delineation errors. As mentioned previously, target delineation is a known component of combined systematic error.[6]

Additional aspects to IGRT may improve imaging accuracy and treatment margins. Implanted fiducials in combination with portal imaging or CBCTs improve prostate localisation in treatment verification.[12] Combining fiducial markers with CBCT may allow for a further CTV-PTV margin reduction. This margin reduction would in turn reduce normal tissue toxicity. It is important to note the disadvantages of fiducial marker implantation. It is an invasive procedure which may result in discomfort, bleeding and infection.[12] It also comes with additional cost.

Future studies assessing not only prostate motion but also seminal vesicle and pelvic node motion are needed at our institution. In addition to inter-fraction target motion assessment, errors related to target delineation, intra-fraction target motion, IGRT accuracy and machine accuracy, need to be quantified. It is important that margins take into account all elements of treatment uncertainties. Caution needs to be applied before implementing margin reductions in the clinical setting. If a margin reduction is introduced, monitoring of treatment outcomes is needed.

CONCLUSION

Prostate motion varies the most in the SI and AP directions. Based on prostate motion, in conjunction with daily online IGRT, our institution's current CTV-PTV margin is sufficient. However it is important to note that a CTV-PTV margin not only takes into account inter-fraction target motion. It also includes intra-fraction motion, target delineation errors, observer variations when executing IGRT, and technical accuracy limitations of equipment. Thus further investigation is required to quantify these errors in order to determine optimal CTV-PTV margins which allow for improved tumour control without increasing normal tissue toxicity.

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Competing Interests

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in the writing of this article.

Author Contributions

MA developed and wrote the manuscript. LP supervised this work. All authors discussed the results and contributed to the final manuscript.

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Data Availability

The authors confirm that the data supporting the findings of this study are available within the article and/or supplementary material.

Disclaimer

The views expressed in this article are those of the author and co-authors. These views are not an official position of the institution.

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DATA COLLECTION INSTRUMENT

Patient Number	Centre of Mass Shift ML Direction [mm]	Centre of Mass Shift AP Direction [mm]	Centre of Mass Shift SI Direction [mm]
Planning CT	-	-	-
CBCT 1			
CBCT 2			
CBCT 3			
CBCT 6			
CBCT 11			
CBCT 12			
CBCT 16			
CBCT 21			
CBCT 22			
CBCT 26			
Individual mean error			
Standard deviation (STD)			

	ML	AP	SI
Mean 1			
Mean 2			
Mean 3			
Mean 4			
Mean 5			
Mean 6			
Mean 7			
Mean 8			
Mean 9			
Mean 10			
Mean 11			
Mean 12			
Mean 13			
Mean 14			
Mean 15			
Mean 16			
Mean 17			
Mean 18			
Mean 19			
Mean 20			
MEAN POP			
STD (Σ)			

	ML	STD^2 (for ML)	AP	STD^2 (for AP)	SI	STD^2 (for SI)
STD 1						
STD 2						
STD 3						
STD 4						
STD 5						
STD 6						
STD 7						
STD 8						
STD 9						
STD 10						
STD 11						
STD 12						
STD 13						
STD 14						
STD 15						
STD 16						
STD 17						
STD 18						
STD 19						
STD 20						
MEAN	-		-		-	
RMS (σ)	-		-		-	

ETHICAL APPROVAL

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

Room 45 E-52-E-Floor- Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6492
Email: hrec-submissions@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

05 May 2022

HREC REF: 256/2022

Dr L Punt
Department of Radiation Oncology
GSH
Email: Lydia.punt@uct.ac.za
Student: marion_algar@hotmail.com

Dear Dr Punt

PROJECT TITLE : EVALUATION OF TARGET MOVEMENT AND DETERMINATION OF OPTIMAL TREATMENT MARGINS FOR PROSTATE CANCER TREATED WITH EXTERNAL BEAM RADIOTHERAPY ON THE HALCYON™ AT GROOTE SCHUUR HOSPITAL (MMED CANDIDATE-DR MARION ALGAR)

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

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

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19. Please refer to guidance letter dated 02 February 2022 on our website:
http://www.health.uct.ac.za/fhs/research/humanethics/forms

Approval is granted for one year until the 30 May 2023.

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)

The HREC acknowledge that the student: Dr Marion Algar will also be involved in this study

Please quote the HREC REF 256/2022 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.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637. Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

INSTITUTIONAL APPROVAL

Western Cape Government

GROOTE SCHUUR HOSPITAL

Enquiries: Dr Bernadette Eick
E-mail: *GSHResearch.Request@westerncape.gov.za*

Dr Lydia Punt
Radiation Oncology

Email: Lydia.Punt@uct.ac.za

Dear Dr Punt,

RESEARCH PROJECT: **EVALUATION OF TARGET MOVEMENT AND DETERMINATION OF OPTIMAL TREATMENT MARGINS FOR PROSTATE CANCER TREATED WITH EXTERNAL BEAM RADIOTHERAPY ON THE HALYCON AT GROOTE SCHUUR HOSPITAL**

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 May 2024.**

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 as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
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 always be maintained.
g) Once the research is complete, please submit a copy of the publication or report.
h) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**
i) **All Clinical Trials to be registered on Clinicom with Michelle Riley or Rowan James, michelle.riley@westerncape.gov.za / rowan.james@westerncape.gov.za**

G46 Management Suite, Old Main Building, Private Bag X,

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

Yours sincerely

pp:
DR BERNADETTE EICK
CHIEF OPERATIONAL OFFICER
Date: 29 June 2023

C.C. Prof Parkes, Dr Aziz, Mr Mohamed

DEPARTMENTAL APPROVAL

Radiation Oncology

Professor Jeannette Parkes
Head of Division

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07 March 2023

Dr L Punt

Dear Punt

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

Project Title: Evaluation of target movement and determination of optimal treatment margins for prostate cancer treated with external beam radiotherapy on the Halcyon at Groote Schuur Hospital (MMED candidate – Dr Marion Algar)

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

Kind regards

Prof Jeannette Parkes
Radiation Oncology Department

SOUTH AFRICAN JOURNAL OF ONCOLOGY (SAJO) CRITERIA FOR SUBMISSION

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