A retrospective study to evaluate local control and freedom from biochemical failure in Prostate cancer treated with Hypo-fractionated split course 3D conformal radiotherapy at Universitas Academic Hospital, Bloemfontein, South Africa.

Researcher
Dr Joseph M. Mthombeni
Registrar in Radiation Oncology
Department of Oncology, University of the Free State, Bloemfontein, South Africa
Contact Details: +27 72 7495 788
Email address: joeymthombeni@gmail.com

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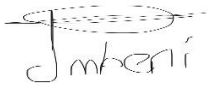
Research Supervisor
Dr Karin Vorster
Senior Specialist Radiation Oncologist
Department of Oncology, University of Free State, Bloemfontein, South Africa
Contact details: +2772 376 6677
Email address: VorsterK@ufs.ac.za

DECLARATION

I, Joseph M. Mthombeni declare that the course work Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification: Mmed in Radiation Oncology at the University of the Free State is my independent work, and that I have not previously submitted it for a qualification at another institution of higher education.



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Dr J.M Mthombeni Date

ABSTRACT

A retrospective study to evaluate local control and freedom from biochemical failure in Prostate cancer treated with Hypo-fractionated split course 3D conformal radiotherapy at Universitas Academic Hospital, Bloemfontein, South Africa.

J Mthombeni[1] K Vorster[2]

Background: Prostate cancer is the most common malignancy in men and the second most common cause of death for men in South Africa and universally. Three-dimensional conformal radiotherapy (3DCRT) is a safe and efficacious method to deliver radiation for prostate malignancy patients in all risk groups with acceptable toxicity rates and adequate biochemical control.

AIM: To describe local control and freedom from biochemical failure in Prostate cancer patients treated with Hypo-fractionated split course external beam radiotherapy in a specified population for a given period.

Methods: A retrospective descriptive cohort was conducted. Files of 142 patients with locally confined prostate adenocarcinoma who was treated at the Universitas Annex Hospital between 2003-2013 were reviewed. Data collected included demographics, risk factors, recurrence risk stratification, Gleason score, TNM staging, and PSA levels.

Results: The prevalence of disease control was 108/142=76.1% at the end of the study period (60 months). The median age of the study participants was 68 years. Of the study participants, 40.14 % were white, 54.23% were black, and 5.63% were other races. At a median follow up of 5 years, all low-risk patients that participated in this study had disease control (local and biochemical), intermediate and high-risk patients with disease control were 12.68% and 59.15% respectively. The 34(23.9%) patients that had progression of the disease, 2.11% (3) and 21.83% (31) were intermediate and high risk, respectively.

Conclusion: Hypo-fractionated split course 3DCRT in patients with localized prostate cancer has a significant locoregional disease control and freedom from biochemical failure.

Keywords: Prostate cancer; locally confined; radiotherapy; hypofractionation; biochemical failure; split course; 3DCRT.

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LIST OF ABBREVIATIONS

NCR	National Cancer Registry
3DCRT	Three-Dimensional Conformal Radiotherapy
PSA	Prostate Specific Antigen
DRE	Digital Rectal Examination
CT	Computer Tomography
MRI	Magnetic Resonance Imaging
PET	Positron Emission Tomography
AJCC	American Joint Committee on Cancer
TNM	Tumour Node Metastases
DVH	Dose Volume Histogram
XRT	Radiotherapy
SEER	Surveillance, Epidemiology and End Results
SV	Seminal vesicles
EBRT	External Beam Radiotherapy
ECOG PS	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
RTOG	Radiation Therapy Oncology Group
NCCN	National Comprehensive Cancer Network
P	Prostate
ICRU	International Commission on Radiation Units

CHAPTER 1

CHAPTER 1

1.1 Introduction

1.1.1 Background

Prostate cancer is the most common malignancy in men and the second most common cause of death for men in South Africa and globally. According to the pathology-based National Cancer Registry (NCR) 2006 data, there were 4631 new cases of prostate cancer that were reported in 2006 only, and 63 886 cases reported over the 20 years, 1986 to 2006. As per the World Health Organization, the numbers are expected to double by 2030 on account of the ageing population. [1]

Of the known or suspected risk factors for prostate malignancy, the most significant is age. The median age at diagnosis is 68 years, and the disease incidence increases rapidly with advancing age. Although the risk for development of histologically proven prostate cancer is constant across countries and races, there is considerable inconsistency in the incidence of clinically evident disease and mortality among different populations worldwide and the United States. [2]

For instance, for the 2331 deaths from prostate malignancy announced by the national cancer registry in 2009, 971 (42%) were black, 529(23%) were from an unknown population, 546 (22%) were colored, 251 (11%) were white, and 34 (2%) were Asian/ Indian. In the United States of America, the rate and mortality associated with prostate malignancy are higher among African Americans. There is a reported 30 to 50-fold difference in risk between African-American men at the extreme end of the spectrum and native Japanese at the lower end.
One can, therefore, deduce that prostate cancer is a global problem, and its incidence and mortality vary with race, age and geographic populations.
Treatment modalities available for locally confined prostate cancer comprises of radiotherapy with radiation techniques such as external beam radiation therapy (3D conformal/Intensity-modulated radiotherapy), Brachytherapy and Proton radiation; Radical prostatectomy, active surveillance and/or observation are available used options.

This descriptive cohort focused on the efficacy of split course External beam hypo-fractionated Three-dimensional conformal radiotherapy (3DCRT) in the treatment of prostate cancer. There is proof proposing that prostate cancer growth has a low α/ß level much lower than that of organs, for example, the urinary bladder, rectum and small bowel. This legitimizes a therapeutic rationale for hypofractionation with the possible result of superior tumor control at a lower toxicity rate. Three-dimensional conformal hypo-fractionated radiotherapy is a safe and effective method to deliver therapeutic radiation for prostate cancer patients in all risk groups with acceptable toxicity rates and adequate biochemical control and can be used as a standard of care.

However, there is no evidence from South African patients describing locoregional control and freedom from biochemical failure in hypo-fractionated regimes. The guidelines followed at our institution are extrapolated from international data. The biochemical and locoregional control in patients treated with split course radiotherapy is also unknown in South Africa and globally.

1.1.1 Study Objectives

This study aimed to describe the locoregional control and freedom from biochemical failure in patients with locally confined prostate cancer, treated with hypo-fractionated split course 3DCRT at Universitas Annex from 2003-2013. With this data, we anticipate evaluating the current standard of care in the treatment of localized prostate cancer in our institution. We also hope to contribute to treatment guidelines for locally confined prostate cancer in South Africa, and other developing countries.

1.2 Literature review

1.2.1 Diagnosis and Workup

a) Prostate-Specific Antigen test:

Prostate-specific antigen (PSA)- is a glycoprotein produced by prostate epithelial cells. Its production is increased in prostate cancer. Studies have demonstrated that rising PSA can precede clinical disease by 5-10 years or longer [3]. The upper limit of normal PSA is 4.0 ng/mL, with a sensitivity of 21-51% depending on the grade of the tumor. The specificity is 91%. In addition to prostate malignancy, there is a variety of benign conditions that can elevate PSA levels. The most common conditions are prostatitis and benign prostatic hyperplasia. There is no evidence showing that these benign conditions lead to prostate cancer, however, it is possible that a patient may have one or both conditions and develop prostate malignancy as well. [4]

b) Digital Rectal Examination

Digital rectal examination (DRE) is an important element in the screening and assigning clinical stage; however, only 25%-50% of men with an abnormal digital rectal examination have cancer on biopsy. [5]

c) Histology and the Gleason Grading System

A transrectal or trans-perineal biopsy cores are obtained from the prostate, on designated anatomical sites. Transrectal ultrasound guided systematic biopsy is regarded as a standard diagnostic test of prostate cancer compared to digitally directed biopsy. This was proven in a landmark trial by Hodge et al published by the journal of urology in 1989[18]. Adenocarcinoma is the most common histological type arising from the peripheral acinar glands of the prostate. In the Gleason grading system, the cells are scored on a scale of 1 to 5 based on their differentiation. Those nearest to 1 are considered as low-grade tumor cells and will in general resemble normal cells. Cells nearest to 5 are viewed as high grade and scarcely resemble normal cells. The entirety of the two most prevalent Gleason patterns i.e Primary and Secondary patterns is then determined, giving a Gleason Score ranging from 2-10. [6]

d) Imaging

Imaging strategies are essential for staging and for detecting metastases and tumor recurrence. Anatomic imaging methods include sonar, radiographs, Computer Tomography (CT) and Magnetic Resonance Imaging (MRI). Functional imaging techniques include radionuclide bone scan and PET/CT. Pelvic CT/MRI is recommended in patients with longer life expectancy and intermediate to high-risk disease to exclude nodal involvement. Technitium bone scintigraphy is recommended in patients with T2 local disease and PSA >10 ng/ml. It remains standard of care in detection of bone metastasis in high risk prostate cancer. [7]

1.2.2 Staging and Risk stratification

The staging of prostate cancer is according to the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control. The 8th edition released in 2017, combines information about the primary tumour (T), lymph node(N) involvement, and presence or absence of distant metastases(M). The serum PSA level and the histologic grade based on the Gleason score of the primary tumor are also incorporated. All these parameters classify men into prognostic stage groups according to their risk of recurrence. These systems are useful to stratify disease-free survival, compare treatment results, and provide a means to appropriately recommend treatment options [8]. Please refer to *table 1* below.

Table 1:NCCN risk stratification

Risk Profile	**Criteria**
Very Low Risk	-T1c - Gleason score 6 -PSA< 10ng/ml -Fewer than 3 biopsy cores positive, ≤50% cancer in any core -PSA Density <0,15ng/ml/cc
Low Risk	-T1-T2a -Gleason score 6 -PSA<10ng/ml
Intermediate Risk -Favorable	-T2b-T2c or -Gleason score 3+4=7/ISUP group 2 or -PSA 10-20ng/ml And, Percentage of positive biopsy cores < 50%
Intermediate Risk -Unfavorable	-T2b-T2c Or -Gleason score 3+4=7/ISUP group 2 or Gleason score 4+3=7/ISUP group 3 OR -PSA10-20ng/mL
High Risk	-T3a or -Gleason score 8-10 -PSA>20ng/ml

Very High Risk	-T3b-T4 -Primary Gleason pattern 5 -2 or 3 high risk features ->4 cores with Grade Group 4 or 5

Majority of patients we see at our facility have high-risk disease. This could be attributed to a variety of factors affecting our population of patients. These factors include lack of patient education about prostate cancer screening, limited access to primary health care facilities for early detection, and barriers limiting early access to the Oncology department including prolonged waiting times and transport challenges.

1.2.3 General Management trends

The optimal management of clinically localized confined prostate cancer remains a controversy and is often a source of great frustration and nervousness for many patients who are compelled to decide regarding a treatment intervention for their disease.

The treating Oncologist or Urologist must be aware that the natural history of this disease is variable and determined by a variety of prognostic factors. The different forms of therapy for prostate cancer can negatively affect the sexual function and quality of life of the patient. While counselling and discussing treatment options, it is essential to avail all information regarding the natural history of this disease, its prognosis, the potential benefit of the different treatment modalities, and all acute and late complications of the treatment. Life expectancy and quality of life considerations should be carefully discussed with the patient and their family.

External beam radiotherapy confers long term disease control outcomes in men with localized prostate cancer, these outcomes are similar or equal to that of radical prostatectomy [19]. The developments in computing and imaging over the past 20 years led to various technological advances in treatment planning and delivery of EBRT to the prostate [20]. These advances include the utilization of cross-sectional imaging for radiation treatment planning, and developments in treatment delivery such as IMRT and daily image guidance. These innovations allow escalated doses of radiation to be delivered to the prostate precisely and conformally improving the therapeutic ratio. *Lukka et al* and *Yeoh et al* demonstrated the lack of evidence in efficacy and safety of hypo-fractionated regimes in prostate cancer without the use image guided radiotherapy (IGRT). When using IGRT as recommended, it is important to note the different modalities used to evaluate the position of the prostate, the modalities include sonar guidance, placement of fiducial markers, cone beam computed tomography and tracking of the position of prostate using 4D techniques. Each of these systems has pros and cons such as costs and accuracy. There is limited evidence to evaluate quality of life, toxicity and local prostate cancer control with the use of non-modulated 3DCRT treatment techniques in patients treated with EBRT moderate fractionation schedules. The studies that showed non-inferior biochemical control without significant toxicity in moderate hypo-fractionated schedules compared with conventional fractionation used IMRT or other modulated techniques. One randomized control trial conducted in Brazil compared EBRT 3DCRT with IMRT and delivering a total dose of 70Gy in 25 fractions of 2.8Gy per fraction. A total of 215 men were enrolled in this study, evenly divided between 3DCRT and IMRT. At a median follow up of 56 months, the rate of GI toxicity was 24% in the 3DCRT arm and 7% in the IMRT arm. The five -year rate of biochemical control was 94.3% in the 3DCRT arm and 95.4% in the IMRT arm proving IMRT to be safer than 3D-CRT techniques. [22]

External beam 3DCRT utilizes a computer programming system to coordinate computed tomography (CT) images of the patients' anatomy in the treatment position. According to a study that compared 2D and 3D conformal radiation, 3D modality allows higher cumulative doses of radiation to be delivered with negligible adverse effects to bladder and rectum [9]. Hypo-fractionated regimes i.e giving 2.4-5Gy per fraction over 4-6 weeks have been evaluated in randomized trials, and their efficacy has been proven to be

equal or non-inferior to conventionally fractionated radiotherapy (1.8-2Gy per fraction). There is not enough South African data reflecting the actual statistics of patients that achieve local control and freedom from biochemical failure. Hence it is essential to run this study so that accurate statistics based on local patients are known.

A variety of radiation fractionation schedules have been conducted and tested in clinical trials. The Conventional or Hypo-fractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHip) trial randomly selected 3216 patients with intermediate or high-risk prostate adenocarcinoma to conventional treatment of 74Gy in 37 fractions or into two hypofractionation schedules of 57Gy in 19 fractions or 60Gy in 20 fractions, using intensity modulated external beam radiotherapy technique. The hypo-fractionated schedule using 60Gy in 20 fractions was proven to be non-inferior to conventional fractionation with 5-year recurrence-free survival rates of 88% for conventional treatment and 91% for hypo-fractionated treatment. The 57Gy schedule was found to be inferior.

The Dutch HYPRO trial randomized 820 intermediate- to high-risk patients to 39 fractions (5 fractions per week) of 2 Gy or 19 fractions of 3.4 Gy (5 fractions per week). The purpose of this study was to evaluate whether an increased dose of 12.4 Gy (In 2Gy fractions) using hypo-fractionated external beam radiation would achieve a significant increase in relapse-free survival (RFS) of 10% as compared with conventional fractionation. At a median follow-up of 60 months, there was no significant differences in RFS. The RFS was 80% and 77% after hypofractionation and conventional fractionation, respectively. There was more acute grade ≥ 2 small bowel toxicity during treatment in the CHHiP and the HYPRO trial; however, the acute toxicity between the treatment arms disappeared after completion of treatment. In terms of late toxicity, the CHHip trial did not show any difference in late toxicity between conventional and hypofractionation. [10,17]

The RTOG 0415 study was directed to evaluate the distinctions in post-treatment quality of life between hypo-fractionated and conventional fractionation external beam radiation treatment in men with low risk prostate carcinoma, and it likewise indicated non-inferiority of hypo-fractionated external beam radiotherapy of 70Gy in 28 fractions versus 73.8Gy in 41 fractions in low risk prostate cancer patients. This investigation affirmed that there is no clinically significant difference in toxicity between the two treatment arms. In addition, this study demonstrated an increased late toxicity in small bowel and bladder with hypo-fractionated external beam radiotherapy as compared to conventional treatment. [11]

The Prostate Fractionated Irradiation Trial (PROFIT) by *Catton et al* assigned a total of 1.206 patients with intermediate risk prostate cancer to 60Gy in 300cGy fractions (Moderate hypofractionation) or 78Gy in 200cGy fractions (conventional fractionation) using IMRT. The primary end point was to determine biochemical failure as per ASTRO criteria. The secondary end points included biochemical clinical failure (BCF), toxicity, quality of life and mortality from prostate cancer. At a median follow up of 5 years, there was no difference in biochemical failure in both arms. The overall rates of toxicity were equivalent although a significant increase in GI toxicity ($\geq$ grade 2) in the hypofractionation arm and late GI toxicity in the conventional treatment arm were observed. The PROFIT trial is different from the CHHip and RTOG 0415 trials as it compared modern hypofractionation to a modern conventional escalated dose of 78Gy.

Another Mono- institutional phase II study that included 97 patients with locally confined prostate cancer, independent of their risk class was performed. This study aimed to evaluate the feasibility of a hypo-fractionated plan delivered by 3D conformal radiation technique to prostate and seminal vesicles in combination with hormonal treatment. The patients were appointed to a schedule of 62Gy (3.1Gy per day, 4 times a week) in 20 fractions over 5 weeks. After a median follow up of 39 months, the biochemical control was 83% for all the patients that participated in this study. [12]

A phase III randomized trial compared hypo-fractionated (62Gy in 20 fractions in 5 weeks) with conventional treatment (80Gy in 40 fractions in 8 weeks) delivered to prostate and seminal vesicles. The primary aim of the investigation was to measure late toxicity, and additional aims were freedom from biochemical failure, Prostate cancer-specific survival, and overall survival. At a median follow up of 9 years, no differences were observed in genitourinary and gastrointestinal toxicity of grade 2 or greater between the two treatment arms. The 10-year freedom from biochemical failure was 72% in the hypofractionation group and 65% in the conventional group. The 10-year overall survival rates were 75% in the hypofractionation group and 64% in the conventional group, the 10-year Prostate cancer-specific survival was 95% and 88%, respectively. [13]

During volume delineation and treatment planning, it is recommended to use normal tissue and dose volume constraints that are similar or directly adapted from one these randomized control trials. One should be cautious if normal tissue volumes and dose constraints other than those used in these published studies are used. There is a variety in heterogeneity among the Gross tumor volume (GTV), Clinical target volume (CTV) and Planning target volume (PTV) in published literature. In patients receiving moderate hypofractionation, the target includes the prostate with or without a portion of the seminal vesicles and inclusion of pelvic lymph nodes based on disease risk stratification. For instance, the CHHip, RTOG 0415 and PROFIT trials did not use PTV expansions exceeding 10mm. The PTV margin expansion posteriorly (i.e rectal interface) did not exceed 4mm. In addition to the differences in target volume definition, these trials varied substantially in prescribed total radiation dose, use of concurrent androgen deprivation therapy, dose volume constraints used in treatment planning and radiation techniques i.e 3DCRT and IMRT. Therefore, these described differences in treatment outcomes may not be explained by the variability in target volume definition alone.

From these studies, one can confirm that Hypo-fractionated 3DCRT is a safe and effective method to deliver therapeutic radiation for prostate cancer patients in all risk classes with acceptable toxicity rates and adequate biochemical control. Also, because of the number of treatment days, hypo-fractionated regimes offer economic and logistic advantages of reducing the burden of limited radiotherapy resources in previously disadvantaged countries. It is also convenient for patients.

In conclusion, these trials have been representative of the prostate cancer patient population and it does not appear to be a constant impact of the patient's age, anatomy or comorbidities on the efficacy of hypo-fractionated regimes that would preclude its use. However, given the limited published findings of these randomized control trials beyond 5-years, additional follow-up and analyses will add more value to these studies.

1.2.4 Post-treatment Surveillance

Following the completion of treatment, patients should undergo ongoing assessments for treatment-related side effects, as well as preventive and general health. History and physical examination are important components during post-treatment surveillance. However, following radical prostatectomy or radiotherapy recurrent localized prostate cancer is seldom symptomatic, and it often manifests by rising PSA only. The role of the digital rectal examination is unclear [14]. Thus, serum PSA is the mainstay of surveillance testing for patients who have undergone localized treatment. The interpretation of changes in serum PSA after radiotherapy can be difficult since normal prostatic glandular tissue is present. Thus, serum PSA levels are probably not going fall to undetectable levels following the course of radiotherapy.

The American Society for Radiation Oncology (ASTRO) established the PHOENIX Criteria which describes a PSA rise of ≥2 ng/mL above the nadir as a biochemical failure, in a patient previously treated with definitive radiotherapy, with or without androgen deprivation therapy. Therefore, all patients with

rising PSA values of ≥2ng/mL above nadir following definitive local radiotherapy are regarded to have a biochemical failure. And the local or distant progression of the disease will have to be investigated. [15]

1.2.5 Rationale for hypofractionation

In localized prostate cancer, radical or curative conventional external beam radiotherapy has always been used as standard of care. Conventional treatment is defined as delivery of a daily dose of 1.8Gy-2Gy over 7-8 weeks, to a total dose of 74 to 79.4Gy. The fractional doses in conventional treatment stems from the presumed relative sensitivity of cancerous and normal tissue. The response of normal and malignant tissues to the fractional and total doses of conventional treatment has been an area of great research in the past 30 years. The research led to the development of the Linear quadratic formula.

The linear Quadratic Model with its alpha/beta value depicts the curvature of cell killing both for tumor control and normal tissue sequelae in relation to the of radiotherapy dose administered. The alpha/beta ratio represents the dose where the linear and quadratic component cause similar amount of cell killing. Generally, the higher the alpha/beta ratio is, the more linear the cell survival curve will be. Whereas a lower alpha/beta ratio (high beta relative to alpha) will result in a curved cell survival shoulder.
This is important to note, as tissues with low alpha/beta are relatively resistant to low doses of radiotherapy in comparison to tissues with a higher alpha/beta. Given this, radiosensitive tissues or high proliferative tumours have a high α/ß ratio of more than 10Gy and radioresistant tissues or slowly dividing tumours have a low α/ß ratio of about 3-5Gy.

Hypofractionation is classified into “moderate hypofractionation” and “ultra-hypofractionation’. Moderate hypofractionation is regarded as a fraction size ranging from 2.4Gy and 3.40Gy whereas ultra-hypo-fraction is defined as a fraction size of 5Gy or more. The upper limit of 5Gy per fraction reflects the findings from body of literature suggesting a threshold beyond which the linear-quadratic formula is invalid. [21]

Most tumours have a high α/ß ratio and can, therefore, be treated with conventionally fractionated radiotherapy (using single doses of 1.8-2.0Gy). But some tumors, i.e prostate cancer, sarcomas, and melanoma have a low α/ß ratio and therefore higher fractional doses can be delivered with the aim of achieving better tumor control with approximately equal side effects. Furthermore, the rationale of fractionation in radiotherapy is additionally based upon the higher self-repair potential of normal tissue compared to tumor cells, this facilitates an immediate repair of most radiation-induced sub-lethal DNA damage in normal tissues between the fractions and thus permitting a relative tumor-specific therapeutic effect. [16]

1.3 Conclusion

Men diagnosed with locally confined prostate cancer may have more than one therapy options. The treating oncologist and urologist have an important duty of assisting patients to understand the facts needed to make this decision.
The hypo-fractionated radiotherapy schedules in the treatment of locally confined prostate cancer have been thoroughly studied in multiple clinical trials, and it has been unequivocally established to be standard of care. There is no evidence in South Africa, or globally describing locoregional control and freedom from biochemical failure specifically in patients with locally confined prostate adenocarcinoma treated with split course hypo-fractionated 3DCRT, contrary to the continuous hypo-fractionated regimens studied. All patients who are candidates for EBRT must be offered moderate hypofractionation regardless of patients age, anatomy, comorbidity or urinary function. However, the treating radiation

oncologist must discuss the limited follow up beyond five years for most of the fore mentioned randomized control trials and the limited data comparing 3DCRT with IMRT.

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CHAPTER 2

A retrospective study to evaluate local control and freedom from biochemical failure in Prostate cancer treated with Hypo-fractionated split course 3D conformal radiotherapy at Universitas Academic Hospital, Bloemfontein.

J Mthombeni[1] K Vorster[2]

1. MBChB, Registrar Radiation Oncology, Universitas Hospital, University of the Free State, Bloemfontein, South Africa.
   Email: joeymthombeni@gmail.com
2. MBChB, Mmed (Radiation Oncology), Senior Specialist Radiation Oncologist, Universitas Hospital, University of the Free State, Bloemfontein, South Africa.
   Email: VorsterK@ufs.ac.za

2.1 Introduction

In our facility, prostate cancer is the most common malignancy in elderly men. The majority of our patients present with high-risk disease, this occurs due to a variety of factors. As mentioned in literature review 1.2.3, the factors commonly include lack of patient education about prostate cancer screening, limited access to primary health care facilities for early detection, and barriers limiting early access to the Oncology department including prolonged waiting times and transport challenges.

After clinical, biochemical and radiologic evaluation all our patients are discussed in a Urology-Oncology combined clinic, and a combined decision is made to offer the best treatment option based on ECOG status, histological findings, PSA value, radiologic and radioisotopes imaging. We offer radical radiotherapy to all our patients with low to high risk locally confined prostate cancer. The radiotherapy is either delivered in 3DCRT technique, which this cohort looked at, or IMRT which our department adopted in 2011. Patients with the low and intermediate-risk disease are typically offered radical prostatectomy if they do not have any contraindications to surgery.

Our radical 3DCRT approach involves delivering radiotherapy with a linear accelerator using pelvic opposing and planned fields. The prescribed schedule is 60Gy in 3Gy fractions given Monday to Friday for 2 weeks, with a 2 weeks break, followed by another 2 weeks of radiotherapy to a total of 6 weeks. The 2 weeks rest in between radiotherapy treatment was adopted in our facility to allow patients to recover from acute side effects of radiation, and due to a backlog in our linear accelerators. It is our clinical impression that our patients tolerate the split course schedule radiotherapy better and tend to complete treatment with manageable radiation side effects.
All our patients with Intermediate to high-risk disease are offered adjuvant LHRH analogue for 2-3 years. Neo-adjuvant LHRH analogues are mostly prescribed to patients with a large prostate to shrink it before radiotherapy, as well as patients who await their radiotherapy dates to prevent progression of the disease.

Prostate cancer remains a common malignancy in our facility. As much as the department has adopted IMRT since 2011, we still offer 3DCRT to a great number of our prostate cancer patients who are not for IMRT for various reasons (e.g. Body habitus, inability to immobilize patient for IMRT, MRI breakdown).

2.2 Ethical considerations

This study was approved by the Health Sciences Research Ethics Committee of the University of the Free State. Approval number: UFS-HSD2019/0497/2708. The necessary permission was requested and obtained from the Oncology and Free State Department of Health heads of department. Informed consent was not required as this was a retrospective study, and all patient data was held confidential.

2.3 Study setting

The study consisted of patients treated at the Department of Oncology, Universitas Annex Hospital, Bloemfontein, Free State, South Africa.

The radiation protocol of locally confined prostate cancer at our facility:
A. Procedures before simulation of patient
1. All patients are discussed at Urology-Oncology multidisciplinary meeting to confirm staging and risk stratification.
-Bowel preparation is prescribed for all patients. Patients are advised that Glycerine suppositories must be inserted per rectum 30minutes before planning CT and daily before radiation to ensure an empty rectum.
-If the patient gives a history of constipation, he will have to be optimized into a good bowel routine before starting the process.
-The patient needs to have an empty bladder before CT simulation and at each treatment, for reproducibility of bladder position.
-Informed Consent is obtained from the patient.

B. Simulation
a) Patient positioning:
- The patient is set up in pro-step immobilization apparatus with U-pillow under his head and arms crossed over his chest.
-The pro-step index bars are customary set at 5 and 11.
-On the pro-step, the feet position and feet angling must be chosen to have the patient immobile and comfortable.
Measurements: - Lateral tattoo height
- Separation on anterior tattoo
- Anterior tattoo to the base of the penis.

b) CT Simulation
The patient is Scanned from the superior border of L3 Vertebra to 5cm below pubic rami with 2-3mm slices.
Once the scans have been completed, a day is allowed for contouring, planning and Quality assurance. All the information recorded must be indicated on the scanner information sheet.

C. Contouring
The clinician contours the volumes as per RTOG contouring guidelines:
a) Organs at risk (OAR):
I) Bladder - Contour on the outer bladder wall and delineating the prostate base from the bladder.
ii) Rectum - Include the rectal wall in the volume. As per EORTC, 1-2cm above and below the plane of the PTV.
iii) Small bowel - Contour the peritoneal surface of the pelvis and abdomen up to the level of L5/S1.
iv) Femoral heads – Contoured proximal up to the lesser trochanter

b) Target volume:
i) GTV (Prostate) - Apex 1-1.5cm above penile bulb
ii) Seminal vesicles
iii) Lymph nodes: Right and Left - Contour Obturator, Internal and External iliac nodes up to the level of true pelvis S2/S3.
iv) CTV1: Prostate(P) + proximal Seminal Vesicle (SV).
v) CTV2: For Intermediate and high-risk patients CTV1 +Lymph Nodes
Contouring as per risk Stratification:

High risk: All patients - PTV45
T3b: PTV60 - P + Seminal Vesicles
T3a: PTV60 - P + 50% Seminal Vesicles
T1 and T2: PTV60 - Prostate
Intermediate PSA 10-20, Gleason 3+4
All patients - PTV45
PTV60: Prostate
Low risk
Only PTV60 – Prostate

E. Dose prescription and delivery
- ≥ 98% of PTV should receive at least 95% of the prescribed dose. According to the ICRU prescription the dose range for the PTV should be between 95-107% of the prescribed dose.
-Opposing radiation field borders: Superior- True pelvis, Inferior-1cm under the obturator foramen, Lateral-1cm lateral of pelvic walls. In the first course of treatment, 300cGy central dose daily X7(Opposing fields) is given followed by 300cGy X3 (Planned fields). The planned fields cover the contoured PTV with a 3- 5mm margin.

The patient rests for 2 weeks without treatment. And in the second course of the treatment we give 300cGY central dose daily X7(Planned fields) followed by 300cGy central dose daily x3 (Small field boost). The small field boost covers the contoured prostate and seminal vesicles (If involved) with a 1cm margin.

-The dose-limiting constraints to the OAR are based on hypo-fractionated 3Gy per fraction doses as converted from 2Gy per fraction by the EQD2 formula.
Limitations for the OAR: (QUANTEC data is used) in standard fractionation.
*Rectum:50% of volume maximum 50Gy
20% of volume maximum 70Gy
15% of volume maximum 75Gy
*Bladder: 50% of volume maximum 65Gy
35% of volume maximum 70Gy
15% of volume maximum 80Gy.
*Small bowel: Volume <195cc 43.5Gy
*Femoral heads: Maximum doses ≤45Gy
F. Approval:
The specialist evaluates the total volume on the Dose Volume Histogram (DVH)

-OAR: Within tolerances as indicated.
The specialist Oncologist signs off the plan and DVH on the Monaco planning system and Mosaiq, and then approve the prescription.
As mentioned previously, following completion of treatment, patients undergo ongoing assessments for treatment-related side effects and monitoring to exclude recurrence of the disease. History and physical examination are an important component during post-treatment surveillance. We review them at one

month after radiation at our follow up or outreach clinics, then on three monthly intervals for two years, followed by six monthly intervals up to 5 years, then annually. In all these follow up appointments, the serum PSA is taken to monitor disease response, control and exclude recurrence. If we find an elevated PSA as per Phoenix criteria or clinical suspicion of local or distant recurrence, we would further investigate with imaging.

2.4 Methods

2.4.1 Study design

This was a cohort descriptive study.

2.4.2 Data collection

Data collected consisted of patients with locally confined prostate cancer patients treated from 2003 to 2013 at Universitas Annex Hospital, Department of Oncology, Bloemfontein, South Africa. The patients were identified using the departmental database. During the 10 years, a total of 3984 were seen with prostate cancer of all stages, this is according to our database statistics. During data collection, we screened a total of 3400 files, and 142 patients met our inclusion criteria. As previously elaborated, most of our patients present with advanced disease and were treated palliatively.

Inclusion criteria included:
-Male patients with histologically proven adenocarcinoma of the prostate.
-Patients with the locally confined disease after full staging.
-Patients with Low to high-risk disease (based on Gleason score, PSA and TNM staging).
-Patients who received neoadjuvant or adjuvant LHRH analogue/ or Neither.
-Patients treated with definitive hypo-fractionated 3D Conformal radiotherapy and completed treatment course.
-Residents of the Free State Province
-Patients without metastatic disease on skeletal scintigram

Exclusion Criteria included:
-Histological subtypes other than Adenocarcinoma
-Prior surgery (Radical Prostatectomy)
-Patients treated with other radiation modalities e.g IMRT/ Brachytherapy
-Patients from Lesotho and other provinces. These patients are excluded because they do not follow up at our facility after treatment, we do not have their records post-radiotherapy.
-Patients who did not complete the course of treatment.

2.4.3 Measurements

A datasheet was designed by the researcher to record the variables of interest. The variables recorded include age, race, family history, tumor local stage(T1a-T4b), Gleason score, risk stratification, date of completion of radiation, pretreatment PSA, first PSA post-radiotherapy (XRT), nadir PSA, and PSA at the progression of the disease or last follow up at 60 months post treatment. Other variables recorded included whether patients received neo-adjuvant and or adjuvant LHRH analogue.

The aim of the study was to evaluate and describe biochemical and locoregional control of the disease at a median 60 months follow up period. To determine biochemical control, we relied upon the Phoenix

criteria definition of biochemical recurrence, defined as a Nadir PSA value increasing above 2ng/ml. Therefore, all patients that had a PSA below 2ng/ml at 60 months follow up were regarded to have biochemical control.

Local recurrence was defined as the presence of prostate tumor felt on digital rectal examination, and ultimately confirmed on MRI or repeat biopsy. Therefore, to determine local control, we relied upon a normal digital rectal examination and absence of distant metastasis on nuclear and radiological imaging. Absence of local recurrence and distant metastasis i.e normal digital examination and absence of distance metastasis at 60 months follow up was regarded as local control. We defined distant metastases as the evidence of macroscopic disease in sites other than the prostate gland, confirmed on Nuclear medicine or radiological imaging.

We defined disease control as presence of local and biochemical control after radiotherapy at the end of the 60 months follow up period. The following variables were measured to determine disease control:
I.) Date of disease progression i.e date of first PSA recorded to be 2ng/ml above nadir or first diagnosis of metastatic disease.
II) Site of disease progression i.e None, local, distant metastasis or local +distant metastasis
III) Ultimately, using variables I and II above, disease control was documented as no response, stable or disease progression. No response was defined as a persistently elevated PSA post XRT, stable disease as PSA value remaining at nadir without diagnosis of metastatic disease or local recurrence in the 60 months follow up window. Lastly, disease progression was determined by detection of PSA elevation by 2ng/ml above nadir or diagnosis of local recurrence or metastatic disease at any point during the 60 months follow up window.

2.4.4 Data analysis

The data was analyzed with the help of Ms. Riette Nel from the Department of Biostatistics, University of the Free state. Descriptive statistics, namely; frequencies, percentages for categorical data, medians and percentiles for numerical data were calculated.

2.5 Results

142 patients met our inclusion criteria.

2.5.1 Age

Number of participants	Median age	Lower quartile 25^{th} percentile	Upper quartile 25^{th} percentile	Minimum age	Maximum age
142	68	63	72	46	83

Table 2

2.5.2 Race

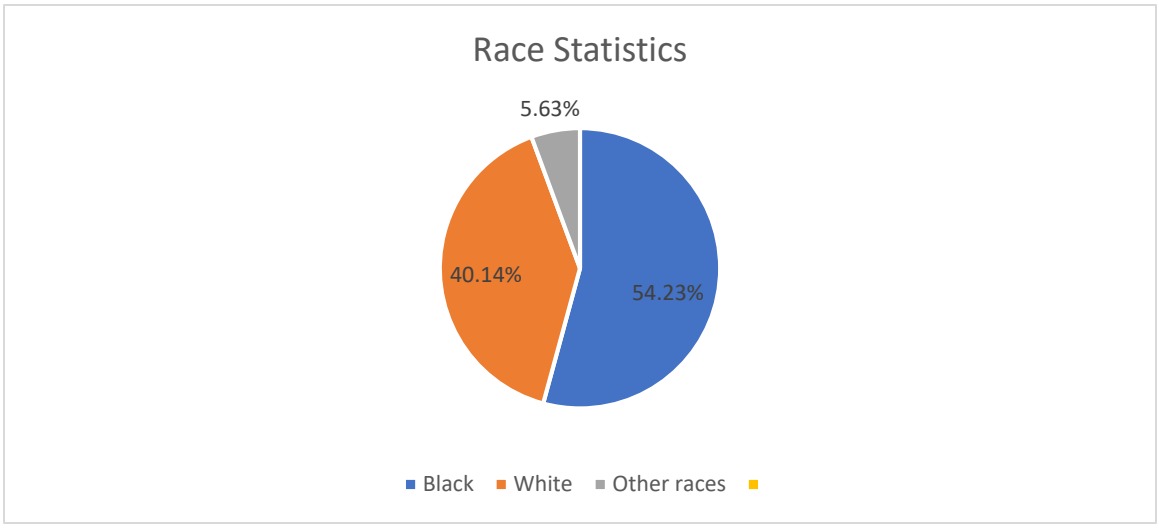


Figure 1

2.5.3 Family history

From our cohort, 99(69.72%) of the patients had no documented family history of prostate cancer, 12 (8.45%) had a documented family history and 31(21.83%) a family history of cancer was unknown. Documented family history was defined as, patients with a first degree relative with prostate cancer.

2.5.4 LHRH analogue

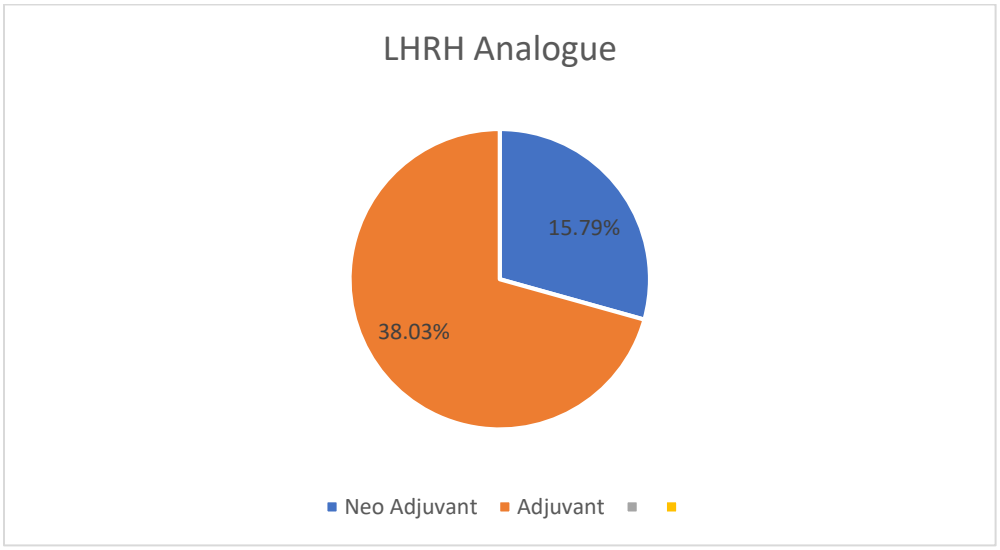


Figure 2

2.5.5 Disease profile

2.5.5.1 TNM classification

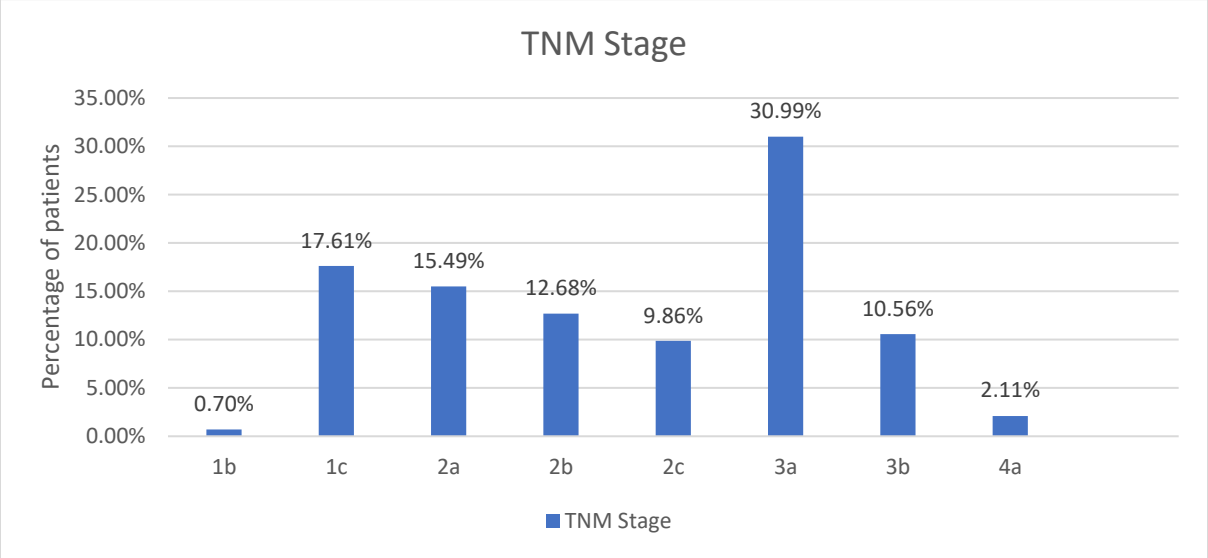


Figure 3

2.5.5.2 Gleason Score

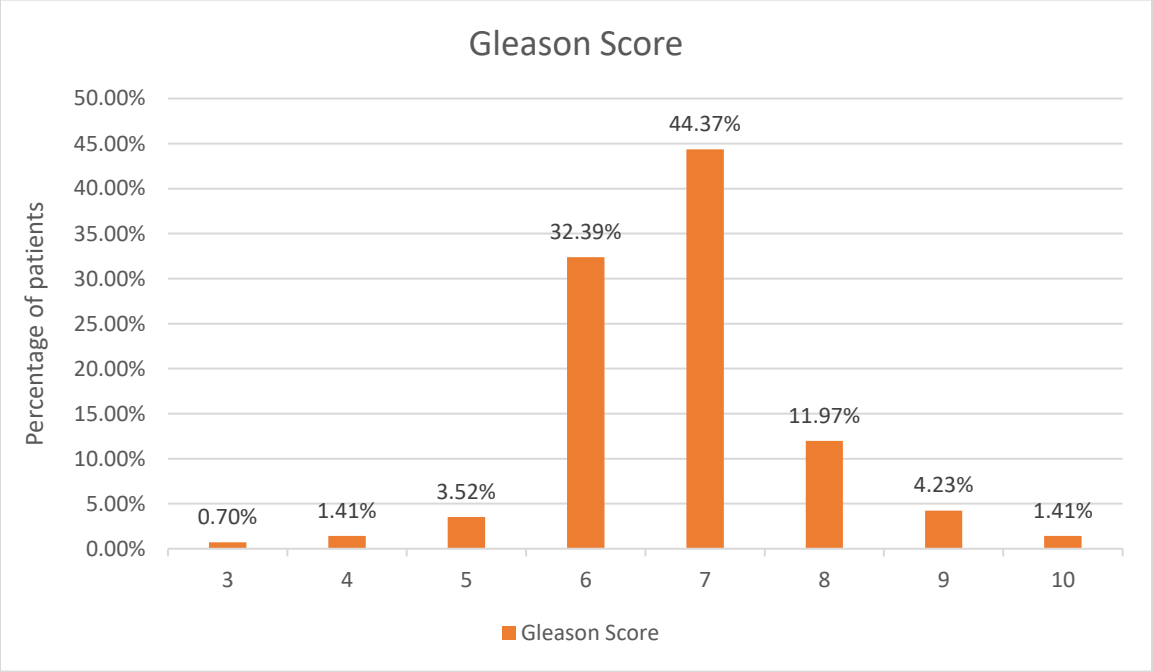


Figure 4

2.5.5.3 PSA

PSA	Number of patients(N)	Median	Lower Quartile 25th percentile	Upper Quartile 75th percentile	Minimum	Maximum
Pretreatment	142	24.315	14.0	52.0	2.35	254.1
First After radiation	142	2.7	0.5	8.1	0.03	45.0
Nadir	142	0.115	0.1	0.5	0	44.3
Last, follow up	108	0.3	0.1	0.6	0	2.1
At progression of the disease	34	10.65	4.7	35.8	2.0	272.9

Table 3

2.5.5.4 Risk stratification

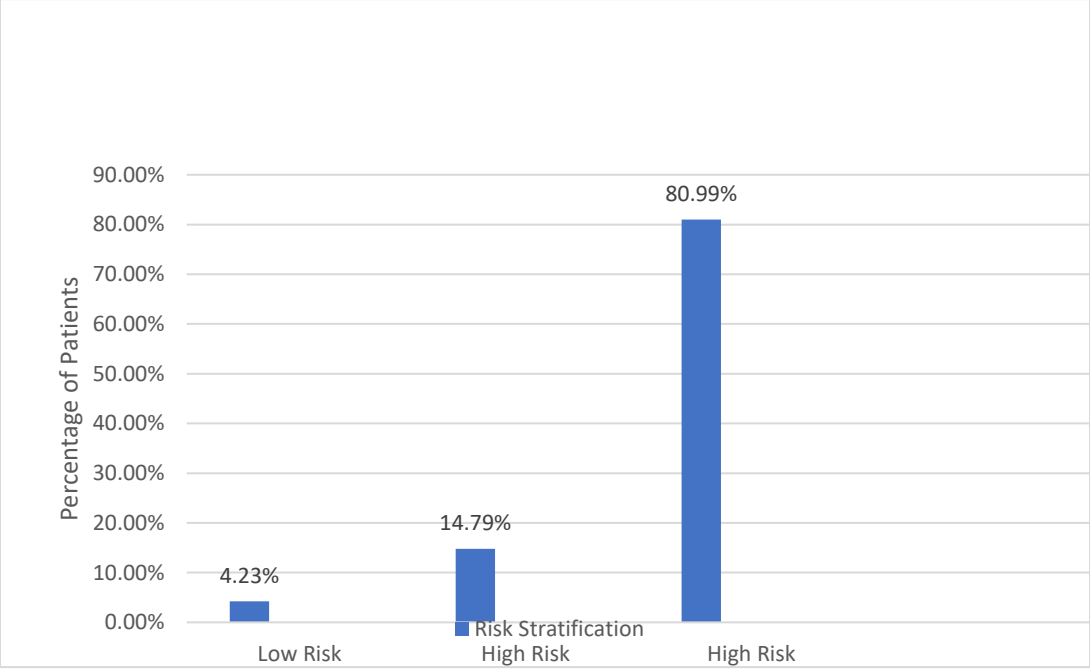
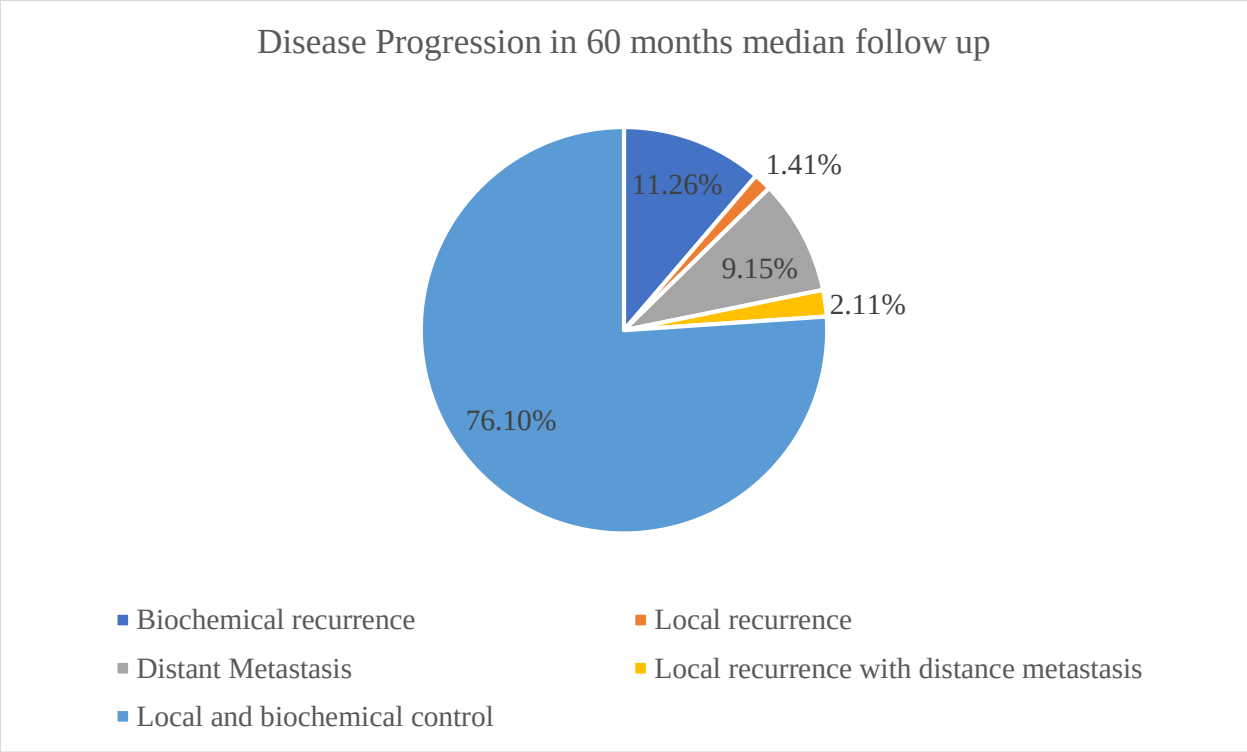


Figure 5

2.5.6 Site of progression of the disease

From the 34 patients that had progression of the disease, 16 (11.26%) only had a biochemical recurrence, without any measurable disease. Two patients (1.41%) had local recurrence, 13(9.15%) had distant metastases, and 3 patients (2.11%) had local recurrence and distant metastases. The reflected percentages were calculated using the total number of the patients (142) included in this study. Please refer to **figure 6** below for graphic representation.

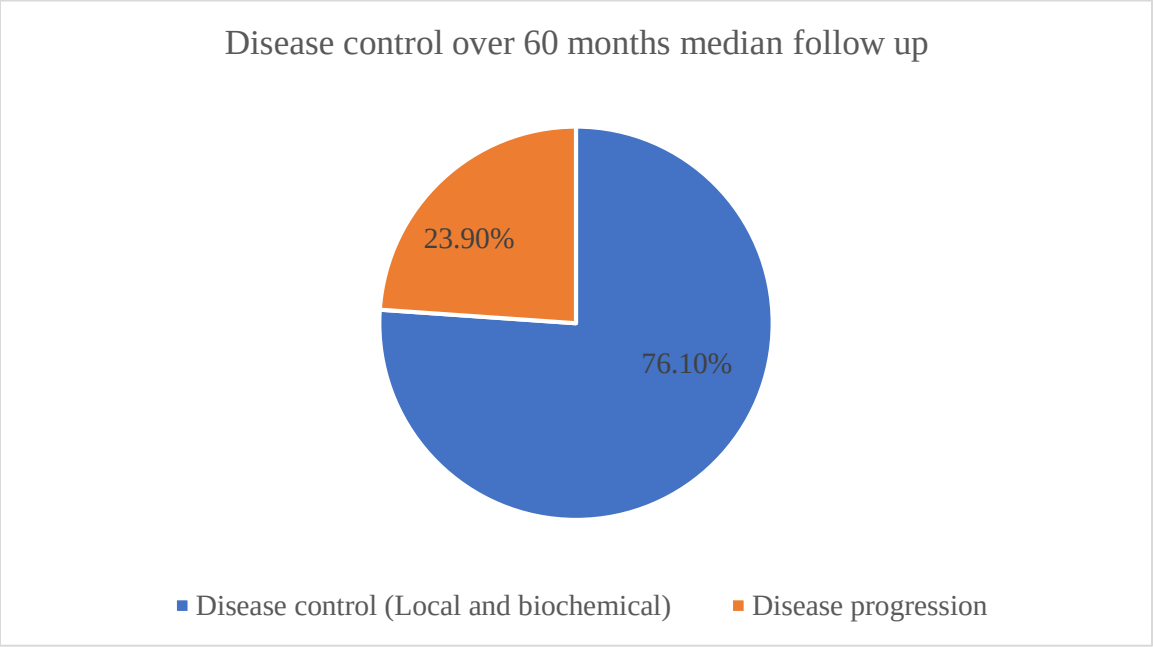
Figure 6: Disease progression in 60 months median follow up.



2.5.7 Disease control (Local and Freedom from Biochemical failure)

The prevalence of disease control in this cohort was (108/142)76.1% at the end of the study period (60 months). Therefore, 76.1% of the study patients at the end of the study period (60 months) had local control and freedom from biochemical failure.
All low-risk patients had stable disease, intermediate and high-risk patients with stable disease were 12.68% and 59.15% respectively. As previously mentioned in section 2.4.3, stable disease was defined as PSA value remaining at nadir without diagnosis of metastatic disease or locoregional recurrence in the 60 months follow up window. The 34 patients that had progression of the disease, 2.11%(3) and 21.83%(31) were intermediate and high risk, respectively.

Figure 7: Disease control over 60 months median follow up.



2.6 Discussion

The age distribution of our patients ranged between 46 and 83 years. The data was distributed skew therefore the median and percentiles were used as a summary statistic. The median age of our study participants was 68, 63 was the age at the lower quartile 25th percentile, whereas, 72 was at the upper quartile 75th percentile. This is following the data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. The data confirmed that prostate cancer rarely occurs before the age of 40, but the incidence rises sharply after the age of 40 years, peaking between the ages of 65 and 74. The percentages of new cases of prostate cancer for men 35 to 44, 45 to 54, 55 to 64, 65 to 74, 75 to 84, and 85 between 2011 and 2015 were 0.5, 9.0, 32.7, 38.8,15.1, and 3.9 per cent, respectively. [17]

The age distribution of patients in our study correlates with global statistics, and the median age of our patients is in keeping with the findings from the SEER database, where a majority of prostate cancer patients ranges from age 65-74 years.

The patients were routinely stratified according to ethnicity i.e white, black or other races. This was done because it was found that prostate cancer is most common in black than white or Hispanic men (Refer to 1.1.1 paragraph 4). According to findings from the SEER database, screening in the 1980s led to a progressive rise in the incidence of disease, with the rate being higher in blacks [18]. Our findings were that 40.14 % of the treated patients were white, 54.23% were black, and 5.63% were other races. These findings are in keeping with global statistics. However, the number of treated black patients was expected to be higher given that the majority of our patients are black. This cohort also showed that 12% of the patients had a family history of prostate cancer, whereas 40.14% had no history, and 21.83% had an unknown history of prostate cancer.

All our patients were risk-stratified according to the National Cancer Comprehensive Network Guidelines. The staging is based on pretreatment PSA, Gleason score and tumor size based on findings from digital rectal examination or biopsy findings. The data of the pretreatment PSA was distributed skew therefore the median and percentiles were used as a summary statistic. The median pretreatment PSA Was 24.3ng/L, with 14ng/L at the lower quartile and 52 at upper quartile. The patients with the lowest and highest PSA levels in the study population were 2.35ng/L and 254.1ng/l respectively. The latter patient with the highest PSA value had no documented metastatic disease on a skeletal scintigram.

In the Chhip trial as previously reported, the rate of biochemical control was 90.9% for the group that received 60Gy. The analysis of results from Mono-institutional phase two study revealed a biochemical control rate of 83%. The RTOG 0415 shows a biochemical free rate of 72%. Our rate of biochemical control is 76.1%. When comparing our results with these studies, one needs to be cognizant of the disadvantages of a retrospective study as we conducted. Our study, given its retrospective nature, it is prone to misclassification bias and subject confounding. The studies reported above are prospective, and therefore have a superior level of evidence compared to retrospective studies. The good prevalence (76%) of biochemical and local control revealed by our study may be used as a generated hypothesis to be studied further by larger and more reliable prospective studies.

There is no published South African or international data describing the side effect profile in patients treated with split course hypo-fractionated radiotherapy.
The aim of our study was to determine local control and freedom from biochemical failure, the side effect profile of our study population was therefore not documented.

2.7 Conclusion

In our retrospective review, we found that hypo-fractionated split course, 3DCRT is a valid treatment option for locally confined Prostate cancer with good locoregional and biochemical control. The split course treatment does not negatively affect local and biochemical control. The clinical benefits of hypo-fractionated approach used in this study should not be withheld from patients with locally confined prostate cancer treated in facilities where 3D conformal radiotherapy technology is accessible.

2.8 Acknowledgements

The authors acknowledge Ms Riette Nel from the Department of Biostatistics, the University of the Free State for statistical analysis of the data and methodological and writing input.

2.9 Declaration of conflict of interest

The authors declared no conflicts of interests concerning the research, authorship and publication of this article.

2.10 Authors contribution

Dr Joseph M. Mthombeni was the principal investigator for this study. The study was done in partial fulfilment of the degree Mmed in Radiation Oncology. Dr Karin Vorster was the supervisor of this study.

2.11 Disclaimer

The views expressed in this submitted publication are of the author, and it does not reflect the official position of the institution.

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LIST OF APPENDICES