

Evaluating a hypofractionated radiotherapy schedule for prostate cancer at an institution in South Africa



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Background: Hypofractionated radiotherapy (HFRT) in the treatment of prostate cancer (PCa) has logistical and cost advantages, especially in a resource constrained setting. Studies have demonstrated equivalent efficacy with HFRT schedules using Intensity Modulated Radiation Therapy (IMRT) as treatment modality. However, higher rates of acute and late gastrointestinal (GI) and genitourinary (GU) toxicity have been reported when compared to conventionally fractionated radiotherapy (CFRT). In this study, we evaluate the efficacy and toxicity rates of a HFRT schedule using 3D conformal radiotherapy (RT) as treatment modality.

Aim: With this study, we aim to describe the safety and outcomes of a definitive HFRT schedule used for localised PCa. We hypothesise that there is no difference in the biochemical relapse rate and incidence rates of normal tissue toxicities between patients receiving CFRT and HFRT schedules.

Setting: This RT schedule was used at Tygerberg Academic Hospital in South Africa for the treatment of localised prostate cancer.

Methods: This is a retrospective study in which the records of patients diagnosed with localised PCa were reviewed. Patients were treated with either CFRT regimen to a total of 74Gy in 37 daily fractions for 5 days a week or a HFRT regimen to a total of 65Gy in 26 daily fractions for 4 days per week.

Results: In all, 116 patients were included in the study with a median follow-up of 57.2 months from the start of RT. No statistically significant differences in overall survival (OS) and biochemical relapse-free survival were found between the two schedules. A significant difference in acute GI toxicity was observed, with a higher incidence noted in the HFRT schedule. No significant differences were observed in late GI toxicity or in early and late GU toxicities.

Conclusion: This study observes a hypofractionated regimen using three-dimensional conformal radiation therapy (3DCRT) with similar efficacy and RT-related toxicities to CFRT.

Contribution: The HFRT schedule used in this study could be useful in hospitals with limited access to resources.

Keywords: gastrointestinal toxicity; genitourinary toxicity; limited resources; hypofractionated schedule; low- to middle income countries.

Introduction

Prostate cancer (PCa) is the second most diagnosed cancer and the sixth leading cause of cancer death in men worldwide. In 2018, an estimation of 1 276 000 new cases and 359 000 deaths occurred.¹ In low- to middle-income countries, the incidence of PCa is escalating with higher mortality rates than those seen in developed countries.^{2,3}

There are few cancer centres in sub-Saharan Africa. This results in patients travelling long distances to diagnostic and treatment centres. This leads to significant financial and logistic challenges to obtain treatment.⁴ Because of limitations in cancer prevention strategies, most cancers are diagnosed at an advanced stage.⁵ Additional factors contributing to the higher mortality rates in Africa include lack of radiotherapy (RT) access and insufficient human resources because of a critical shortage in skilled staff. The International Atomic Energy Agency (IAEA) recommends that one RT machine be available for a population size of 250 000; however, in Africa, there is one RT machine available for every population of 3.56 million.⁶ In March 2020, 430 RT machines were installed in Africa, of which 119 are available in South Africa and 97 in Egypt.⁷

Prostate cancer is the leading cancer diagnosis in men in Africa. The mortality rates are higher because of the late presentation of the disease, resulting in reduced availability of treatment options.³ The incidence of PCa is higher in South Africa compared to the rest of Africa, and despite a higher level of infrastructure and development in South Africa, the mortality rates are high as well.² According to GLOBOCAN 2020 data, the incidence rate of PCa in South Africa is 65.9/100 000, which is similar to those of North America (73.0/100 000), Western Europe (77.6/100 000) and Australia (75.8/100 000), but the mortality rates fall within the range of other sub-Saharan African countries. Middle and Western African mortality rates are 24.8 and 20.2/100 000. South Africa is reported to have mortality rates of 22.0/100 000. Several factors contributing to late presentation of disease and management challenges could be the reason for the increased mortality rates.²

Religious and cultural beliefs, and stigma regarding cancer diagnosis play a significant role in the advanced stage seen at diagnosis of disease.⁸ Because of resource constraints, a national screening policy does not exist in South Africa, resulting in a lack of prostate-specific antigen (PSA) screening implementation at primary health care facilities.⁹ This may additionally contribute to advanced presentation of PCa at our institution.

Prostate cancer has a significant impact on the burden of non-communicable disease in the public health sector globally.³ The management of PCa in low- and middle-income countries faces challenges with both patient and clinician factors. Access to healthcare, healthcare funding, limited RT treatment facilities, and limited access to hormonal, cytotoxic, and targeted therapies are among those challenging factors.¹⁰

The World Bank classifies South Africa as an upper-middle-income country,¹¹ and yet the country faces many challenges concerning access to healthcare, especially in the rural parts of the country where the vast majority of the population live in extreme poverty.¹²

It has been suggested that the use of hypofractionated radiotherapy (HFRT) schedules at cancer treatment facilities in Africa, as well as in other developing countries, can address some of these challenges, provided it is safe, and can maintain similar outcomes to conventional RT schedules.^{3,5} The use of 3D conformal RT with higher energies is a reasonable option provided set up verification with daily online electronic portal imaging with bony landmarks is available. This is suitable for fractionation schedules of 19–20 fractions.⁵

Hypofractionated RT in PCa has become an increasingly viable treatment option in recent years. Reports comparing moderate hypofractionation, which is larger radiation doses of 2.1–3.5Gy given daily over a shorter overall time, with conventional fractionation in PCa supports the use of

moderate hypofractionation.¹³ Conventional fractionation (1.8–2Gy per fraction daily) is based on the premise that tumour cells are less responsive to daily fraction size than normal tissue cells. The alpha-beta (α/β) ratio of a specific type is a measure of its response to RT fractionation, with low ratios associated with late-responding normal tissue, and high ratios with early-responding tissues and rapidly dividing tumours like squamous cell carcinoma.¹⁴

Prostate adenocarcinomas are considered to have a low α/β ratio and therefore considered to be sensitive to higher dose per fraction with reports of values ranging from 1 to 1.8Gy for PCa, which would favour the use of hypofractionation.^{15,16} A standard α/β value of 1.5Gy for PCa is used in the linear quadratic model to biologically equate HFRT regimens.¹⁵ However, there is a significant concern for increased incidence of early and late radiation toxicity, especially in the ano-rectum, bladder and urethra.¹⁷

In locally advanced PCa, conventional schedules for RT using 3D-conformal techniques use a daily dose of 1.8 to 2Gy for 38 to 45 fractions, with a total dose of ≥ 74 Gy.^{16,18,19} In Africa, the use of HFRT will assist with reduction in costs to facilities providing care, improves treatment waiting times because of limited RT machines available, as well as daily travelling costs and convenience to the patient.⁵ There are multiple clinical trials with evidence that supports the use of HFRT in PCa.¹⁷

According to the CHHip trial by Dearnaley et al., a hypofractionated schedule of 60Gy in 20 fractions over 4 weeks demonstrated non-inferiority to 74Gy in 37 fractions treated over 7–8 weeks with regards to biochemical or clinical failure rates at the 5-year interval. All RT was delivered using Intensity Modulated Radiation Therapy (IMRT) techniques. This hypofractionated dose was used based on an estimated α/β ratio of 1.8Gy for tumour. There were no significant differences in the proportion or cumulative incidences of radiation toxicities. A subgroups analysis by age showed that men older than 69 years had an improved biochemical or clinical failure rate with 60Gy compared to 74Gy, whereas younger men under the age of 69 years showed no differences.¹⁹

A Dutch non-inferiority trial (HYPRO) compared a hypofractionated schedule of 19 fractions of 3.4Gy, given three times per week, to conventional RT of 39 fractions of 2Gy, given 5 days per week. Intensity Modulated Radiation Therapy modality was used in 95% of patients in this study. Non-inferiority with regards to 5-year relapse-free survival was successfully demonstrated.²⁰ No difference in acute genitourinary (GU) toxicity was seen, the cumulative incidence of acute Grade 2 or worse gastrointestinal (GI) toxicity was however significantly higher in the hypofractionated arm (42.0% vs 31.2%).²¹ Non-inferiority for cumulative late Grade 2 or worse GU and GI toxicity could not be shown and notably, cumulative late Grade 3 GU toxicity was significantly higher in the hypofractionated arm. The HYPRO trial has shown that associated risk of acute GI

toxicity is higher, should the dose per fraction be $\geq 3\text{Gy/day}$.²¹ Baseline GU symptoms were significantly associated with incidence of both acute and late GU toxicities. Men older than 70 years and those on Androgen Deprivation Therapy (ADT) also demonstrated increased incidence of late GU toxicity.²² Baseline GU symptoms before the commencement of HFRT have shown to be a significant predictor as to the risk of acute radiation toxicity experienced during treatment,²³ and should be assessed carefully prior to the commencement of treatment.

This retrospective study aims to evaluate the safety and efficacy of a HFRT schedule for the definitive treatment of men with localised PCa at Tygerberg Hospital over a 3.5-year period. The study compares the characteristics and outcomes of patients treated with two different RT schedules, one hypofractionated and one using conventional fractionation, for this indication at Tygerberg Hospital from February 2015 to July 2018.

Methods

Study design

This is a single institution, retrospective, observational study in which clinical records of patients diagnosed with localised PCa who were treated with definitive RT between 01 February 2015 and 31 July 2018 at the Division of Radiation Oncology, Tygerberg Academic Hospital (TAH), Cape Town, were reviewed for RT toxicity and cancer outcomes. This study includes a subset of patients who received standard fractionation schedule of 74Gy/37# 5 days a week over a period of 7.4 weeks and a subset of patients who received a total of 65Gy in 2.5Gy fractions daily and were treated 4 days per week over a period of 6.5 weeks. The hypofractionated schedule was implemented in the division in 2017 as a pragmatic solution to an increasing patient load and diminishing staff numbers. The hypofractionation schedule selected was adapted from published hypofractionation studies showing equivalent outcomes to standard fractionation with IMRT. Using the data of the PROFIT,²⁴ CHHIP¹⁹ and RTOG 0415²⁵ trials and not having IMRT available in the division during the study period, the regimen we used was therefore calculated considering both the bioequivalence to conventional fractionation as well as the possibility of significant acute and late GU and GI toxicity using 3D-CRT as there are no available data from large clinical trials using 3D-CRT with HFRT regimens.

The EQD2 for this regimen equates to 74.29Gy using an α/β value of 1.5Gy. Patients were given two fractions, followed by a day of rest and the additional fractions thereafter, to consider repair of normal tissue and concern for toxicity.

Volume specification included visible prostate with extracapsular extension if MRI was available, or prostate and seminal vesicles (SV) depending on the risk stratification in the clinical target volume (CTV). The planning target volume (PTV) was the CTV with the expansion of 10 mm in all directions except the posterior margin of which a 7 mm

expansion was included in the PTV. The standard plan was given in two phases for both arms. The first phase for the conventionally fractionated radiotherapy (CFRT) arm included the prostate and SV and was planned to 50Gy/25#. The second phase was planned to 24Gy/12# to the prostate only. The first phase for the HFRT arm was planned to 50Gy/20# to the prostate and SV. The second phase included the prostate only and the patients received an additional 15Gy/6# in the HFRT arm. Planning included three fields: one anterior field and two posterior oblique fields with use of wedges and Multileaf collimators (MLCs) using 6MV – 18MV photons. The recommendations made by International Commission on Radiation Units and Measurements (ICRU) were followed for the absorbed dose prescription. QUANTEC dose constraints were used for the rectum, bladder and femur heads. Patient positioning and verification were done with Image Guidance using electronic portal imaging. This was reviewed on Days 1–3 and weekly thereafter with an acceptable tolerance of 5 mm using bony landmarks. Fiducial markers were not used for image verification. All patients were reviewed weekly during RT for signs and symptoms of toxicity and were recorded. Prophylactic RT to pelvic nodes was not routinely used in the division during the study period. Our primary endpoints were to assess the incidence and grading of acute and late RT related toxicities and biochemical free survival. Our secondary endpoints were to determine if there are significant associations between specific demographic, disease or treatment factors, and biochemical relapse-free survival (bRFS) in the cohort.

Study setting

Tygerberg Academic Hospital is a training hospital affiliated with a University in the Western Cape province in South Africa. It is one of the hospitals offering specialist oncology services, including chemotherapy and RT services, as well as palliative care and supportive services. The clinical oncology division provides outpatient clinic services and has a 40-bed in-patient facility. At the time of the study, the division had three linear accelerators, and a high-dose-rate brachytherapy unit. Furthermore, 3DCRT and gynaecological brachytherapy treatments were also offered. The division services about 2200 new oncology patients per year. Approximately 50 patients with PCa receive RT with radical intent as part of their treatment annually.

Study sample

Patients included in the study were required to have a histologically confirmed diagnosis of adenocarcinoma of the prostate, be over the age of 18 years, and received definitive external beam RT to the prostate during the study period. Patients were excluded if they had any of the following characteristics: clinical evidence of distant metastatic adenocarcinoma of the prostate, prostatectomy prior to RT, or a previous invasive malignancy that was actively treated in the 5 years before enrolment. Patients previously diagnosed with primarily resectable localised basal cell carcinoma (BCC) or squamous cell carcinoma (SCC) of the

skin and non-muscle invasive bladder cancer were included in the study. Two fractionation schedules were utilised in the division during the study period. During the first 2 years of the study period, patients were treated with 74Gy/37# daily for 5 days per week, with total treatment time of 7.4 weeks (conventional schedule). During the latter part of the study period, the divisional schedule was changed to 65Gy/26# 4 days a week (hypofractionated schedule).

Data collection

Participants for inclusion in the cohort were identified from the divisional RT management system list of all patients with PCa who received definitive RT from 01 February 2015 until 31 July 2018.

Clinical information was extracted from individual patient records as well as from patient databases such as the Tygerberg Electronic Content Management (ECM) system, National Health Laboratory System (NHLS) and the Picture Archiving and Communication System (PACS) with the permission from these departments.

Categorical variables collected in this study included ethnicity, clinical T stage, Gleason grade and pathological grade group, PCa risk group, and worst grade of early and late toxicities (graded according to RTOG Cooperative Group Common Toxicity Criteria).

Continuous data variables included were the age of patients and PSA values that were measured 6 weeks after completion of external beam radiation therapy (EBRT) and then at 3-monthly intervals.

The data were recorded in an Excel spreadsheet. A unique study code was linked to each patient's folder number in order to protect the patient's identity. A separate list identifying all folder numbers with its unique study code was kept by the principal investigator. This list is secured in a password-protected document on a password-protected computer.

Data analysis

The sample size was 116 patients in total. A total of 48 patients were included in the CFRT group, and a total of 68 patients were included in the HFRT group. The primary endpoint is to compare the prevalence of early and late RT-related toxicity between the two fractionation schedules. Data on toxicity to the GU and GI systems were found to be most complete. Acute toxicity was defined as any grade toxicity deemed related to treatment that occurred during or within 12 weeks after completion of RT. Late toxicity was defined as any grade toxicity persisting after 6 months following RT. As per previous larger trials,^{17,19,21} the rate of Grade 2 or more RT toxicity was used to compare RT schedules. Another primary endpoint is 5-year bRFS. Biochemical relapse is defined as a PSA concentration greater than the nadir plus 2 ng/mL⁻¹ (Phoenix definition).²⁶ Secondary outcomes were to evaluate

significant associations between specific demographic, disease or treatment factors and bRFS and overall survival (OS) in the cohort. Pearson's chi-squared test was used to assess correlation between the cohort demographics and fractionated schedules. Fisher's exact test was used to calculate the significance of the deviation from the null hypothesis.

Survival analyses were estimated using the Kaplan-Meier method, and survival comparisons between study arms were performed using the log rank test. Survival was calculated in months from the date of RT start to the date of first event, biochemical relapse for bRFS, and death or OS. In the absence of any event, OS follow-up of the patients that were alive was censored on 31 December 2021. Biochemical relapse-free survival was calculated as the time in months between date of RT start to date of PSA failure as determined by the Phoenix definition, or censoring. Patients who had not relapsed at the time of last PSA reading, were censored on the date of their last PSA. This was done because many patients did not fully adhere to the PSA monitoring schedule for the full study period.

Statistical significance was defined as $p < 0.05$. IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows (version 29.0.0.0 IBM Corp, NY) was used to conduct all statistical analysis.

Ethical considerations

Ethical approval was obtained from the Health Research Ethics Committee affiliated with the University (reference number S20/04/096). A waiver of individual informed consent was granted because of the nature of the study. This is a retrospective study based on clinical documentation. The use of data did not alter any clinical decision-making with respect to the patient. The patient was not required to actively participate in the study, and there were no contact between the study team and the patients related to the conduct of this study. All data were anonymised to ensure privacy and confidentiality of participants' personal information, with each participant assigned a unique study code that is password protected.

Results

Demographic and treatment characteristics

Between February 2015 and July 2018, 126 patients received definitive EBRT for PCa at our institution. Of these 126 patients, 116 were eligible for the study. Ten participants were excluded from the study – eight patients had concurrent or prior malignancies not accepted in our inclusion criteria, one patient was treated with IMRT, and one patient demised from abdominal aortic aneurysm (AAA) repair 6 weeks after completion of his RT with no follow-up details available. Table 1 shows patient and disease characteristics in the two arms. The median age was 65 years and the median time interval from histological diagnosis to RT start was 5.5 months.

TABLE 1: Patient and disease characteristics ($N = 116$).

Characteristics	Number of patients				<i>p</i>
	HFRT ($N = 68$)		CFRT ($N = 48$)		
	<i>n</i>	%	<i>n</i>	%	
Race	-	-	-	-	0.916
Black people	10	14.7	6	12.5	-
Mixed people	40	58.8	28	58.3	-
White people	18	26.5	14	29.2	-
 Gleason score	-	-	-	-	0.041
6	19	28.0	5	10.4	-
7	29	42.6	25	52.1	-
8	16	23.5	10	20.8	-
9	3	4.4	8	16.7	-
10	1	1.5	0	0.0	-
Grade group	-	-	-	-	0.065
1	19	27.9	5	10.4	-
2	20	29.4	20	41.7	-
3	9	13.2	5	10.4	-
4	16	23.5	10	20.8	-
5	4	5.9	8	16.7	-
T stage	-	-	-	-	0.641
T1	19	27.9	11	23.0	-
T2	39	57.4	29	60.4	-
T3	9	13.2	7	14.6	-
T4	1	1.5	0	0.0	-
N stage	-	-	-	-	0.076
N0	63	92.6	48	100	-
N1	5	7.4	0	0.0	-
Risk groups	-	-	-	-	0.070
Low risk	10	14.7	1	2.1	-
Favourable intermediate	16	23.5	18	37.5	-
Unfavourable intermediate	10	14.7	5	10.4	-
High risk	32	47.1	24	50.0	-
Age groups (years)	-	-	-	-	0.578
40–49	1	1.5	0	0.0	-
50–59	11	16.2	9	18.8	-
60–69	44	64.7	34	70.8	-
70–79	12	17.6	5	10.4	-
Age at RT start > 65 years	-	-	-	-	0.451
Yes	36	52.9	22	45.8	-
No	32	47.1	26	54.2	-
TURP	-	-	-	-	0.907
Yes	9	13.2	6	12.5	-
No	59	86.8	42	87.5	-
Active surveillance	-	-	-	-	0.836
Yes	9	13.2	7	14.6	-
No	59	86.8	41	85.4	-
Pre-RT ADT	-	-	-	-	0.775
Yes	35	51.5	26	54.2	-
No	33	48.5	22	45.8	-

Note: HFRT median age = 65 years and age range = 51 years – 73 years; CFRT: median age = 66 years and age range = 49 years – 73 years; *p*-value (age) = 0.681.

HFRT, Hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; RT, radiotherapy; TURP, Transurethral resection of the prostate; ADT, Androgen deprivation therapy.

Acute toxicity outcomes

Two patients in the CFRT group and one patient that received HFRT experienced Grade 3 acute GU toxicity. There were no Grade 3 acute GI toxicities reported. When considering individual grades of acute toxicity, there was no statistically significant difference in incidence between the two fractionation groups. A statistically significant difference was seen between the two fractionation schedules in acute GI toxicity when comparing acute GI grade < 2 with

grades ≥ 2 ($p = 0.041$) (Table 2). Less Grade 2 or more acute GI toxicity was seen in the CFRT group. No difference in acute GU toxicity for grade ≥ 2 versus grade < 2 was seen.

The incidence of toxicity was also reviewed for patients ≥ 65 years. A statistically significant difference in acute GI toxicity was observed between the two fractionation schedules in patients aged ≥ 65 years, favouring the use of CFRT in this age group. Grade ≥ 2 acute GI toxicity was only observed in the hypofractionated schedule (Figure 1). No patients over the age of 65 years developed Grade ≥ 2 acute GI toxicity in the CFRT schedule in this cohort. There were no statistically significant differences observed in the acute GU toxicities in patients ≥ 65 years in the different schedules.

Late toxicity outcomes

There were no statistically significant differences between the fractionation schedules with incidence of late GU toxicity when considering all grades of toxicity ($p = 0.087$). One patient in the CFRT group experienced Grade 3 late GU toxicity. There was no statistically significant difference with late GI toxicity incidence between the two schedules. There was also no difference with the cumulative incidence of Grade 2 or higher in both late GU and late GI toxicity (Table 2). No statistically significant difference in late GU toxicity incidence was observed in men ≥ 65 years, and no late GI toxicities were reported in men ≥ 65 years.

Survival outcomes

The median follow-up in our study cohort at the time of data censoring was 57.2 months. The median follow-up for the CFRT group was 71.5 months (range 10.9 m – 81.9 m) and 49.7 months (range 3.6 m – 80.6 m) in the HFRT group.

The 5-year bRFS by PCa risk group for the entire cohort was 100% for low-risk, 87% for intermediate risk, and 85.4% for high-risk.

The 5-year OS by PCa risk group for the entire cohort was 90.9% for low-risk, 79.9% for intermediate risk, and 80.3% for high-risk.

When comparing the two fractionation schedules, biochemical relapse occurred in 7 out of the 48 (14.6%) patients in the conventional fractionated group and 4 out of the 68 (5.9%) patients in the hypofractionated group. The 5-year bRFS was 86.5% in the CFRT group and 91% in HFRT group. There was no statistically significant difference in bRFS between the two fractionation schedules (p -value 0.843) (Figure 2).

The 5-year OS in the conventional RT group was 81.2%. The estimated 5-year OS in the HFRT group was 84.5%. There was no statistically significant difference between OS when comparing the fractionation schedule groups (p -value 0.927) (Figure 3).

TABLE 2: Grade of toxicity grouped by Grade < 2 and Grade ≥ 2 (N = 116).

Toxicity	Number of patients				p*
	HFRT (N = 68)		CFRT (N = 48)		
	n	%	n	%	
Acute GU	-	-	-	-	0.530
Grade < 2	44	64.7	36	75.0	-
Grade ≥ 2	20	29.4	12	25.0	-
Unknown	4	5.9	0	0.0	-
Late GU toxicity	-	-	-	-	0.691
Grade < 2	55	80.9	45	93.8	-
Grade ≥ 2	4	5.9	2	4.2	-
Unknown	9	13.2	1	2.1	-
Acute GI toxicity	-	-	-	-	0.041
Grade < 2	54	79.4	47	97.9	-
Grade ≥ 2	9	13.2	1	2.1	-
Unknown	5	7.4	0	0.0	-
Late GI toxicity	-	-	-	-	0.431
Grade < 2	62	91.1	46	95.8	-
Grade ≥ 2	0	0.0	1	2.1	-
Unknown	6	8.9	1	2.1	-

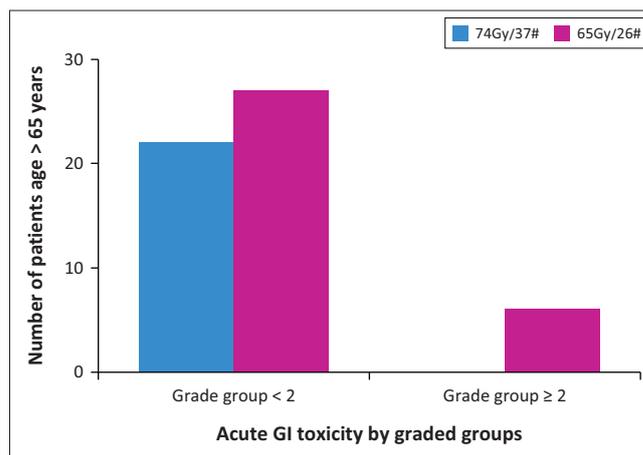
HFRT, Hypofractionated radiotherapy; CFRT, conventionally fractionated radiotherapy; GU, genitourinary; GI, gastrointestinal.

*, p-values do not include patients where the grade value was unknown.

There was a significant association with PSA nadir and bRFS ($p = < 0.001$; HR 5.75; 95% CI 2.26–14.65). Prostate-specific antigen at 3 months was not associated with OS; however, there was a significant association between PSA at 3 months and bRFS ($p = 0.03$; HR = 1.22; 95% CI 1.07–1.38). Secondary endpoints such as an association between race, histological grade group, risk grouping, T-stage, and N-stage and PSA at the start of treatment were analysed, and there was no association with bRFS. None of the patients with confirmed nodal disease on MRI developed biochemical relapse during the study period, and two out of the five patients with confirmed nodal disease died from non-PCa-related diseases. The use of ADT did not show any significant differences in OS or bRFS between the two schedules in this study.

A Gleason score of 9 demonstrated a significant association with OS ($p = 0.036$). A subset analysis comparing OS in males ≥ 65 years by fractionation schedules demonstrated no statistically significant difference ($p = 0.848$). Prostate-specific antigen nadir was significantly associated with OS ($p < 0.001$; HR = 2.38; 95% CI 1.47–3.85). A nadir with the value of >1 was associated with an increased risk of death. One patient with a PSA nadir > 3 ng/mL reached the endpoint of death; however, it was noted that the patient developed bladder cancer after his treatment of PCa and died from progressive bladder cancer.

There was no statistically significant difference when comparing all risk groups by fractionation schedules ($p = 0.525$). A subset analysis for high-risk PCa individuals was evaluated and did not show a statistically significant difference between the fractionation schedules for bRFS ($p = 0.803$) (Figure 4). For OS, high-risk group individuals did not show a significant difference when comparing the two schedules ($p = 0.830$) (Figure 5).



*, p-value = 0.038; Fisher's Exact test of proportion.

GI, gastrointestinal toxicity; 74Gy/37#, 74Gy in 37 daily fractions for 5 days a week; 65Gy/26#, 65Gy in 26 daily fractions for 4 days per week.

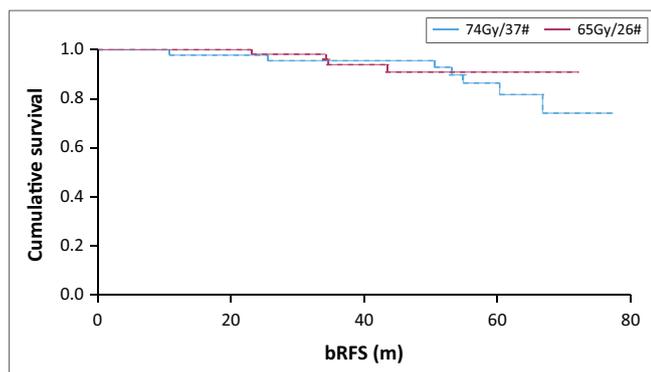
FIGURE 1: Acute GI toxicity grade groups in patients ≥ 65 years.

Discussion

In this retrospective study, we demonstrated that the use of an adapted hypofractionated schedule of 65Gy/26# and a conventional fractionated schedule of 74Gy/37# using 3D-CRT are both well tolerated regimens, with an increased risk of acute GI toxicity with the HFRT schedule. Acute GU and late GU and GI toxicities, however, did not demonstrate any significant differences over a follow-up period of nearly five years. In this cohort, we could also not show a difference between the bRFS and OS outcomes between the two RT fractionation groups.

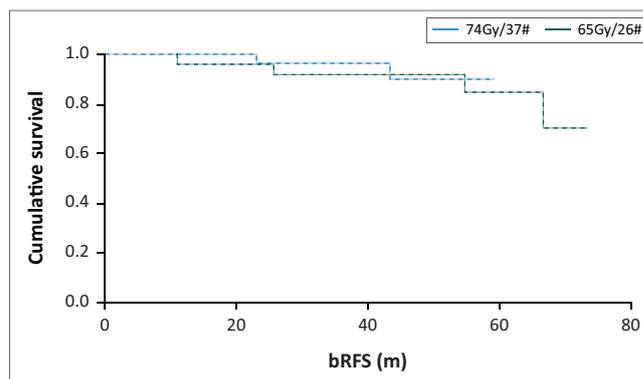
There are several large Phase III trials that looked at HFRT schedules for PCa. The CHHip trial by Dearnaly et al.¹⁹ demonstrated non-inferiority of a HFRT schedule of 60Gy in 20 fractions over 4 weeks to a CFRT schedule of 74Gy/37# over 7–8 weeks. There were no significant differences in radiation toxicities reported.¹⁹ A similar study was conducted by the Ontario Group of Oncology (PROFIT trial) in which a HFRT regimen of 60Gy in 20 fractions over 4 weeks demonstrated non-inferiority to a CFRT schedule of 76Gy in 38 fractions with no differences in late toxicities.^{19,27} The RTOG 0415 trial with a 70.2Gy in 36 fractions in four compared to CFRT regimen of 76Gy in 38 fractions showed significant Grade 2 and Grade 3 GI toxicity in the HFRT arm.^{19,28}

A Cochrane review by Hickey et al., which included 10 studies comparing hypofractionation with conventional RT found, with high certainty, evidence that the OS in men with PCa treated with hypofractionation is similar to conventional RT. There was no difference in acute GI toxicities among the comparative regimens.²⁹ Several other meta-analyses by Datta et al., Carvalho et al., Guo et al., and Royce et al., all suggest that efficacy of hypofractionation is comparable to conventional RT in treating intermediate to high-risk PCa. However, in these meta-analyses, hypofractionated regimens have been associated with an increased risk of GI toxicities.^{27,28,30,31}



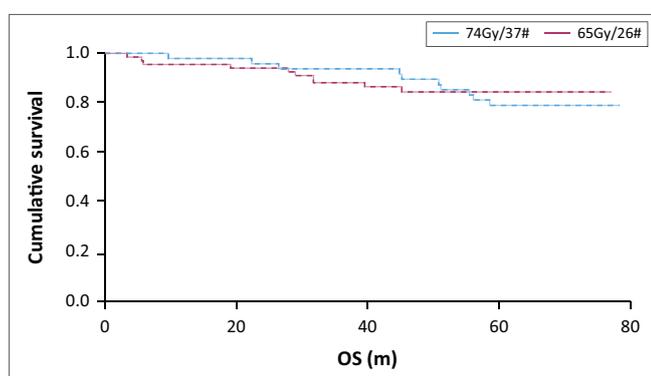
bRFS, biochemical relapse-free survival; 74Gy/37#, 74Gy in 37 daily fractions for 5 days a week; 65Gy/26#, 65Gy in 26 daily fractions for 4 days per week.

FIGURE 2: Biochemical relapse-free survival between radiotherapy fractionation groups: Survival functions.



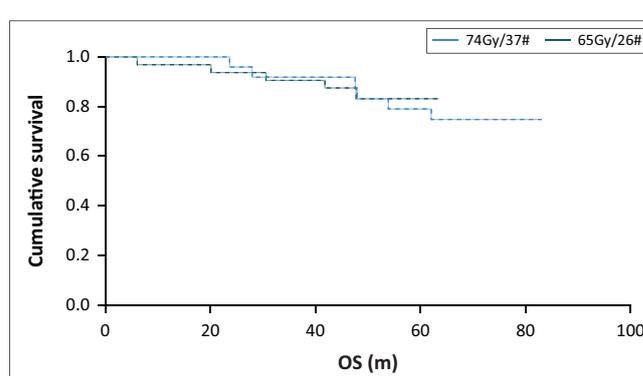
bRFS, Biochemical relapse-free survival; 74Gy/37#, 74Gy in 37 daily fractions for 5 days a week; 65Gy/26#, 65Gy in 26 daily fractions for 4 days per week.

FIGURE 4: Biochemical relapse-free survival high risk prostate cancer by radiotherapy fractionation schedule: Survival functions.



OS, Overall survival; 74Gy/37#, 74Gy in 37 daily fractions for 5 days a week; 65Gy/26#, 65Gy in 26 daily fractions for 4 days per week.

FIGURE 3: Overall survival between radiotherapy fractionation groups: Survival functions.



OS, Overall survival; 74Gy/37#, 74Gy in 37 daily fractions for 5 days a week; 65Gy/26#, 65Gy in 26 daily fractions for 4 days per week.

FIGURE 5: Overall survival high risk prostate cancer by radiotherapy fractionation schedule: Survival functions.

The large trials discussed here delivered hypofractionated regimens using IMRT. In our study, we used 3DCRT without prophylactic nodal RT. We demonstrated a significant increase in acute grade ≥ 2 GI toxicity with HFRT with Grade 2 GI toxicity being the worse toxicity reported. This risk remained increased for patients over 65 years of age. However, no difference in late GI toxicity and acute or late GU toxicity was found.

A randomised Phase III trial by Murthy et al. (POP-RT)³² demonstrated a 5-year bRFS and disease-free survival (DFS) benefit when including prophylactic pelvic nodal irradiation using a hypofractionated regimen at a single institution. A meta-analysis by Viani et al.³³ including 18 studies and a total of 1745 patients, reviewed moderate hypofractionated schedules between 2.4Gy and 3.4Gy daily, including prophylactic pelvic nodal irradiation, and demonstrated satisfactory tumour control rates and acceptable toxicity with use of IMRT or Volumetric Modulated Arc Therapy (VMAT). The benefit of prophylactic pelvic nodal irradiation is still a matter of controversy, and more data demonstrate a survival benefit in high-risk patients is eagerly awaited. In this study, high risk patients did not receive any pelvic nodal irradiation as IMRT and VMAT modalities were not available, and the safety using 3DCRT had not been established. Despite not treating pelvic nodes prophylactically, there was no associated risk of increased biochemical failure in the high-risk group of patients in our study.

The combination of EBRT and ADT leads to long-term survival in most patients. However, there remains a subset of individuals with a high risk of developing recurrence and death.³⁴ Because of resource constraints, a subset of individuals, which included all high-risk patients, were started on Goserelin at least 8 weeks prior to the start of RT at our institution. The data of ADT use were included in the study but did not demonstrate any significant findings.

The use of PSA measurements has been shown in previous studies to be a potential prognostic indicator. A study by Bryant et al.³⁴ demonstrated that a PSA of > 0.50 ng/mL at 3 months post-EBRT was associated with poor survival, especially in high-risk patients. This study demonstrated significant association with PSA at 3 months and bRFS. This study has also demonstrated PSA-nadir to be a possible useful prognostic indicator during follow-up for both bRFS and OS; however, larger prospective trials are required to demonstrate its significance.

Limitations in this study include the retrospective design and inclusion of a single institution with a limited number of patients. Retrospective cohort matching was not done between the fractionation groups which may have influenced outcomes. This fractionated schedule has not previously been studied using 3DCRT in PCa. A larger prospective study in a limited resource setting could explore this schedule further.

Conclusion

In this retrospective study, we demonstrate the use of a well-tolerated, safe and effective HFRT schedule using 3DCRT. Older patients should be carefully selected when using this HFRT schedule as higher incidence rates of GI toxicity may be seen. The HFRT schedule used could assist in reducing overall treatment time and reduce travel expenses in an institution with limited resources in low-income countries in Africa.

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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.

Authors' contributions

F.H. contributed to protocol, project development, data collection or management, data analysis, manuscript writing and editing. H.B. was involved in protocol, project development, data collection or management, supervision, writing, review and editing. P.S. was responsible for supervision, writing, review and editing.

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Data availability

The data that support the findings of this study are available from the corresponding author, F.H., upon reasonable request.

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