A Class Solution to Hypo-Fractionated Radiotherapy in High-Risk Localised Prostate Cancer Using 3-D CRT: A Case Study for Parirenyatwa Radiotherapy Centre

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Abstract

Prostate cancer (PCa) is the fourth most common cancer in men worldwide. In Zimbabwe, it is the most prevalent cancer among men leading to high mortality and morbidity. At present, radiation therapy is restricted to external beam as there are no facilities that offer prostatic brachytherapy in the country. Conventional fractionation radiotherapy, where total doses of 78Gy are given in 39 fractions at 2Gy/fraction, five days per week, has been the treatment of choice for patients with localised disease. This regimen has been associated with problems such as long waiting periods as well as increased mortality and morbidity due to undoubtedly long treatment periods. Hypo-fractionation has been associated with better tumour control while offering convenience to patients. This option also increases community accessibility, especially for resource-constrained nations like Zimbabwe with only two public institutions offering radiotherapy. However, hypo-fractionation comes with the demand for greater conformity during treatment planning in order to reduce radiotherapy complications. The aim of the study was to come up with the most appropriate treatment plan that can be adopted when dose escalation is considered in high-risk localised PCa using 3-Dimensional Conformal Radiotherapy (3-D CRT). A quantitative retrospective observational study was done in a sample of ten (n=10) patients with localised high-risk prostate cancer T2b-T4N1M0. Previously acquired pelvic computed tomography (CT) images of patients treated at Parirenyatwa Group of Hospitals Radiotherapy and Oncology Department were used. Nine (9) treatment plans were generated for each patient with different selected gantry angles from a minimum of five fields to a maximum of nine fields. The plans were analysed quantitatively by using cumulative dose volume histograms (DVHs); and qualitatively through slice-by-slice view of the volume. The research revealed that the three best treatment plans that provided good planning target volume (PTV) coverage, organs at risk (OAR) sparing and were considered clinically feasible were, in order of priority, plan 3 (direct anterior, 2 laterals and 2 posterior obliques); plan 8 (direct anterior, 2 laterals and 2 pairs of opposing obliques); and

plan 6 (2 laterals, 2 anterior obliques and 2 posterior obliques). With the employment of the three treatment planning techniques, hypo-fractionation in prostate radiotherapy is a possibility. It was recommended that the findings of the study be used in research studies of biological models to approximate the therapeutic index of hypo-fractionated radiotherapy (HFRT) of PCa on the Zimbabwean population.

Keywords: prostate cancer, radiotherapy, planning target volume (PTV), organs at risk (OAR).

Introduction

The International Agency for Research on Cancer (2016) reported that prostate cancer (PCa) is the fourth most common cancer overall and the second most common cancer in men worldwide. Simeon (2021) and Globocan (2020) indicated that PCa is a leading cancer in terms of incidence and mortality among men of African origin. In Zimbabwe, like most African states, PCa is the third most common cancer after cervix and breast, and the most common cancer among men (Globocan, 2020; Chokunonga, 2013). Of special note is that, in these low and medium-income countries (LMICs) like Zimbabwe, only 5% of patients with PCa have metastatic disease at presentation implying many have localised disease (Yan, 2021). This makes most patients suitable candidates to receive radiation therapy which is considered an effective curative treatment.

Management of PCa in Zimbabwe using radiation is limited to external beam radiation therapy (EBRT) (Mangoni *et al.*, 2014). Like most LMICs, EBRT facilities in Zimbabwe are scarce (Yan, 2021). This is evidenced by the fact that there are only three radiotherapy centres nationwide with two in the public and one in the private sector. Most patients cannot afford private services and; consequently, placing substantial pressure on the scarce public facilities.

In order to achieve normal tissue sparing radiation therapy (RT) is given in fractions which is referred to as fractionated radiotherapy (IAEA, 2022). Conventional fractionation (1.8-2.0 Gy/fraction) is based on the alpha–beta ratio of 10Gy for malignant tumours and 3Gy for normal tissues (IAEA, 2022). However, for the most common PCa type, adenocarcinoma, the alpha-beta ratio is lower than 10Gy (~1.5Gy), making it relatively resistant to lower radiation doses (Runhan, 2008). Thus, greater fractional doses (above 2.0Gy per fraction), also known as hypo-fractionated radiotherapy (HFRT), were seen to offer better tumour control radio-biologically (Yan, 2021). In addition, there are markedly reduced doses and toxicity to OAR particularly the rectum and bladder, offering high conformal doses to the clinical target volume

(Pan, et *al.,* 2018; Zietman *et al.,* 2005; Zelefsky, 2012). With moderate HFRT, the joint guideline state that men with low-risk, intermediate-risk and high-risk PCa can be administered with fractionation schedules of 60-72 Gy over 4-6 weeks, with the bulk of current evidence supporting equivalent results with the use of 60Gy in 20 fractions over 4 weeks (Yan, 2021). The regimen of 60Gy in 20 fractions at 3Gy/fraction is also biologically equivalent to 78Gy given in 39 fractions at 2Gy/fraction which are currently used at the centre of interest.

The goal of hypo-fractionation is to reduce the overall treatment time without compromising the outcome. This has several advantages that include convenience for the patient, improved community accessibility and reduced healthcare costs (Hegemann *et al.,* 2014). HFRT has however been explored in centres with advanced treatment techniques like intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) while CFRT has remained the standard in LMICs like Zimbabwe where 3-D CRT is used (Michael, 2021). In addition, Michael (2021) argues that, with a strict margin of about 5-10mm, 3D conformal radiotherapy may be used in hypo-fractionated treatment regimens. Furthermore, Michael (2021) highlights that the bare minimum for HFRT delivery is a CT scanner and a linear accelerator with imaging capability, which is the case with Parirenyatwa radiotherapy centre (Zimfact, 2020).

The purpose of this study was to assess the possibility of adopting moderate HFRT in medium to high-risk PCa using the 3-D CRT technique by coming up with most clinically relevant plan.

Methods

Design

The study was a retrospective, quantitative observational study in which previously acquired CT images of the prostate were used to generate different plans. The scans were done at 5mm intervals as per the departmental pelvic scan protocols.

Study setting

The study was carried out at Parirenyatwa Group of Hospitals (PGH) radiotherapy centre. PGH is the largest and most sophisticated hospital complex in the country with a capacity of about one thousand eight hundred (1800) beds and a staff establishment of more than two thousand (About the Hospital, 2022). The hospital has a radiotherapy and oncology centre (RTC) which provides most of the cancer management services for the northern part of the country (Chokunonga *et al.,* 1999).

Study population
The study subjects were derived from histologically proven PCa patients treated with EBRT in the period January 2021 to February 2022 and logged in the treatment planning logbook at RTC.

Sample and sampling procedure
The researcher used purposive sampling to get a sample size of ten (n=10) patients which was equivalent to other previously reviewed studies (Runham *et al*., 2013; Shawata *et al.*, 2019). Purposive sampling allowed the researchers to get an in-depth focus on the small sample (Nikolopoulou, 2022). This was because there were multiple parameters to be assessed for each patient and each plan.

Inclusion criteria
A group of patients with intermediate and high-risk PCa clinical stage T2b-T4N1M0 (tumour extends into the seminal vesicles), or rectum or bladder, PSA>20, grade group 4/5 Gleason score 8-10, and pelvic nodes involvement. Their age groups ranged from seventy to seventy-five years which is the range associated with good radiotherapy response (Zaorsky, 2020).

Exclusion criteria
Excluded from the study were men who were treated with HFRT regimen for palliation. Patients were ineligible if they had prior radical prostatectomy, prior malignancy, or distant metastasis.

Data collection procedure
Previously acquired CT images of ten (n=10) patients with T2b-T4N1M0 carcinoma of the prostate who had been treated using the four-field (box) technique were used in the study as follows:

a) Treatment planning CT data was collected from ten simulations where a bladder filling and bowel voiding protocol was used and the scans were acquired at 5mm intervals with the patient in the supine position
b) The clinical target volume (CTV) and planning target volume (PTV) were defined according to departmental protocol as follows: The CTV included the prostate gland, pelvic nodes and the proximal 1cm seminal vesicles. The PTV was created by extending

the CTV by 1cm in all directions except posteriorly where 0.7cm was used to minimise dose to the rectum.

c) The OAR, namely the colorectal, urinary bladder and femoral heads were outlined by one oncologist in order to reduce inter-observer variation.
d) Nine treatment plans for each of the ten selected patients (a total of 90 plans) were generated using the Eclipse treatment planning system. This was a forward planning process where the AAA algorithm, 10MV photon beam energies on the Varian (true beam) linear accelerator were used.
e) All plans were shaped at the beam's eye view (BEV) to encompass the PTV using multi-leaf collimators (MLCs).
f) The reference normalisation point for all plans was the isocentre which was also the volumetric centre of the PTV.

Beam arrangements used were as shown in Table 1.

Table 1: Beam Arrangements for prostate irradiation

Plan number	**Number of fields**	**Description or technique**	**Gantry angles (°)**
1	5F	Open equi-spaced	0; 72; 144; 216; 288
2	5F sunrise	Sunrise	0; 45; 90;270,315
3	5F 3	Direct anterior, 2 laterals and 2 posterior obliques	0; 90; 120; 240; 270
4	6F	Open equi-spaced	0; 60; 120; 180; 240; 300
5	6F obliques	2 laterals and 2 directly opposing obliques (oblique 1)	45; 90; 135; 225; 270; 315
6	6F obliques 2	2 laterals, 2 anterior obliques and 2 posterior obliques (oblique 2)	30; 90; 120; 240; 270; 330
7.	7F	Open equi-spaced	0; 52; 104; 156; 208; 260; 312
8	7F2	Direct anterior, 2 laterals and 2 pairs of opposing obliques	0; 60; 90; 120; 220; 270; 300
9	9F	Open equi-spaced	0; 40; 80;120; 160; 200; 240; 280; 320

All plans were normalised to 100% at the isocentre. Of the published recommended moderate HFRT schedules, the researcher used 60Gy in 20 fractions at 3Gy/fraction, as this was the least fractionated schedule and may be considered safe for starters. All plans were then evaluated quantitatively and qualitatively using physical tools and dosimetric concepts. In physical and dosimetric analysis, the aim was to check on the target volume coverage and sparing of OAR

in different plans using DVH data and viewing slice-by-slice dose distribution using isodose curves.

Quantitative data analysis

The collected data were exported to Excel for quantitative analysis. For PTV, graphs of the average parameters of D_{min}, D_{max}, and D_{mean}, homogeneity index (HI) and conformity index (CI) were calculated for each set of beam arrangements using the ten patients. The same concept was also applied for OAR analysis considering the set dose constraints described above. Statistical analysis of dose constraints and PTV were further done for pairwise comparisons (t-test) with a significance level of $p<0.05$, using the Statistical Package for Social Sciences (SPSS).

Ethical considerations

Since the research involved use of patient data, the researchers sought approval from the Clinical Director, Radiotherapy Head of Department and Chief Physicist at PGH. No further ethical approval was sought as it was a virtual dosimetric study.

Results

Analysis of target volume coverage

Analysis of target volume coverage was done by analysing isodose distributions within the PTV, calculations of the homogeneity index as well as the conformity index. The best three plans were plan 8 (7F2), plan 6 (6F oblique 2), and plan 3 (5F3). Their averaged D_{min}, D_{max} and D_{mean}, in that order, were as follows: Plan 8: (95.8±1.08 %; 107.3±2.02%; 100.01±1.09%); Plan 6: (95.56±1.90%; 105.3±1.88%; 100.2±0.888); and plan number 3 (94.89± 1.04; 106.38± 0.886; 100.06±0.488).

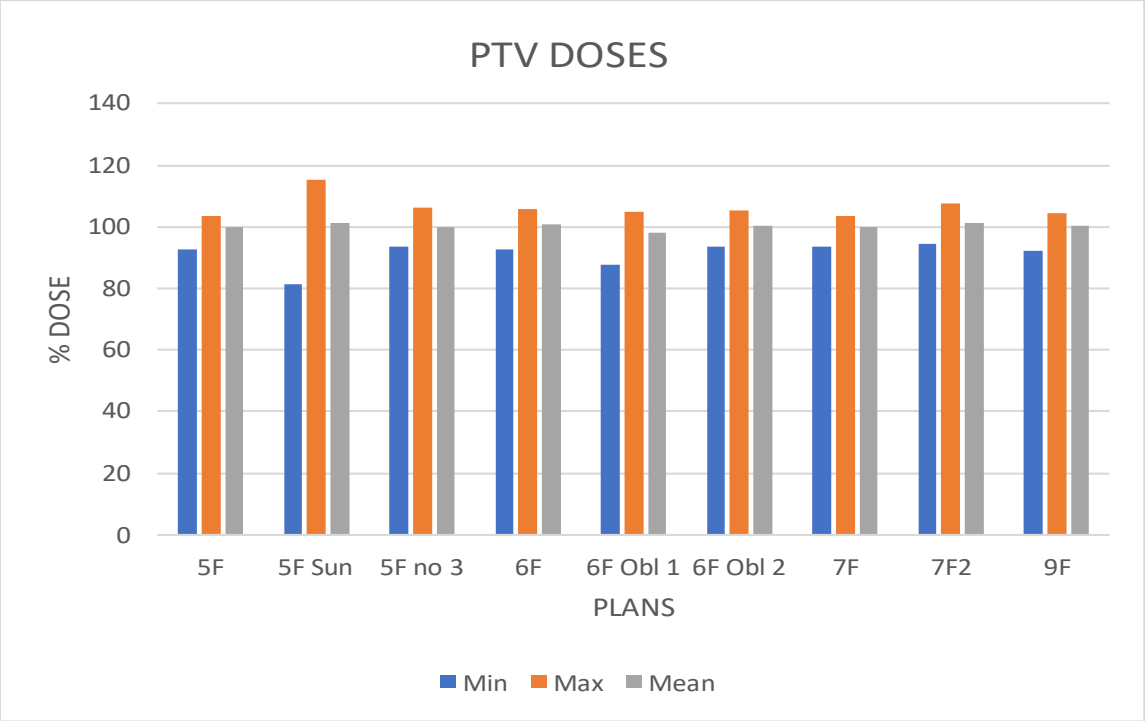

Figure 1*:* The averaged values of D_{min}, D_{max} and D_{mean} of PTV for the nine treatment plans

The worst plan was plan number 2 (5F sunrise) with the following average values D_{min} (82%±6.285), D_{max} (116% ± 2.67) and D_{mean} of 101.09% ± 2.90. The D_{min} and D_{max} were therefore 12% and 8% off the expected values, respectively. In qualitative analysis, it was observed that there was great heterogeneity in the PTV with the 95% isodose line not covering the posterior aspect of the tumour volume in 50% of the plans. This treatment plan was then excluded from further t-test analysis after bearing in mind that there are limited modifications that can be done to a plan to get it to the desired outcome. *T-tests* were done between the top three plans at 95% confidence interval. For plan 8 (7F2) and plan 6 (6F obl2), the significance level was 0.06, while for plan 8 and plan 3 it was 0.07, which were all statistically insignificant.

Tumour coverage was further evaluated using homogeneity index (H.I) and conformity index (CI). The HI was determined using two formulae $HI = \left[\frac{D_2 - D_{98}}{D_{50}}\right] \times 100\%$. Or $HI = \left[\frac{D_2 - D_{98}}{D_{pr}}\right] \times 100\%$, where: D2 – is the minimum dose to 2% of the target volume indicating the maximum dose, D98 - is the minimum dose to the 98% of the target volume, indicating the 'minimum dose', and D50 is the dose received by 50% of the target volume, indicating the 'mean' dose and D_{pr} is the prescribed dose.

In this regard, all the plans had HI values less than 0.1 except for plan 2. Plan 1 was the best followed by plan 7 (7F) and plan 3 (5F3). The HI values were 0.026±0.0013, 0.055± 0.0021 and 0.06±0.0018, respectively. There were no significant differences in HI (1) and HI (2) for all the plans confirming that the prescribed dose was equal to PTV D_{mean} as expected.

A CI value of 1 is ideal and the definition used was $CI = PTV/TV$ where PTV is the planning target volume and TV is the treated volume. Regarding CI, the top three plans were plan 9 (9F) with mean value of 1.9210 ± 0.002, followed by plan 4 (6F) 2.025± 0.0132, and plan 3 (5F3) 2.201±0.0439.

T-tests at 95% CI were done between plan 4 (6F) and plan 9 as well as between plan 6 and plan 3. A *P*-value of 0.131, which was not statistically significant, was obtained for the test between plan 4 and plan 9. For plans 6 and 3, a value 0.003 was calculated, which was statistically significant.

The dose constraints intervals for HFRT schedules of 3Gy/fraction for the rectum, bladder and femoral heads were used. The recommendations were as follows: rectum: V100%<3%, V41%<80%; bladder: V100%<5%, V68%<50%; femoral head V68%<50%.

Analysis of dose to the rectum

Values for averaged V41% and V100% rectum doses per treatment plan are shown in Figure 2 below.

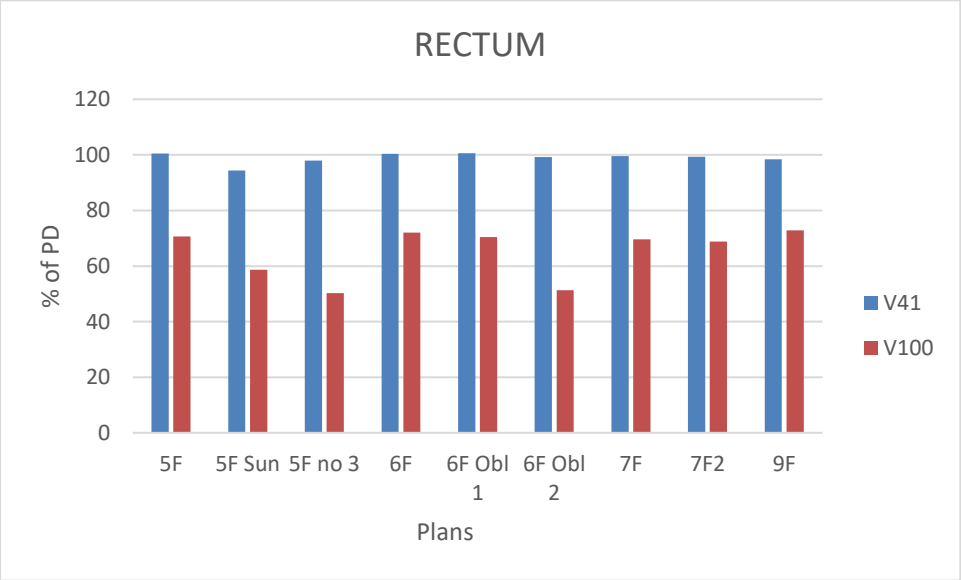

Figure 2: Rectum Dose constraints per treatment plan

There was generally no significant variation in the doses delivered to the rectum as far as V41% and V100% were concerned. However, the following three plans had notable reduced V41% mean values: plan 2 (5F sun): 94.358 ± 1.031%, followed by plan 3 (5F3) with 97.989 ± 0.768, plan 9 (9F) with 98.446± 1.005% and; lastly, plan 6 (6 field oblique 2) which had 99.235 ± 0.432 % of the prescribed dose.

In terms of V100%, the top four techniques were plan number 3 (5F3) with an averaged dose of 50.241±1.328%, plan 6 (6F oblique 2): 51.301± 1.011, plan 2 (5F sun) 58.022± 0.917 and; lastly, plan 8 (7F2) with 68.012 ± 1.002. A statistical analysis at the dose constraint intervals was done as a quantitative review using t-test pairwise comparisons with a significance level of $P<0.05$ considered to be significant.

Analysis of radiation dose to the bladder

Radiation dose to the bladder was also considered and values of dose constraints per treatment plan are shown in Figure 3.

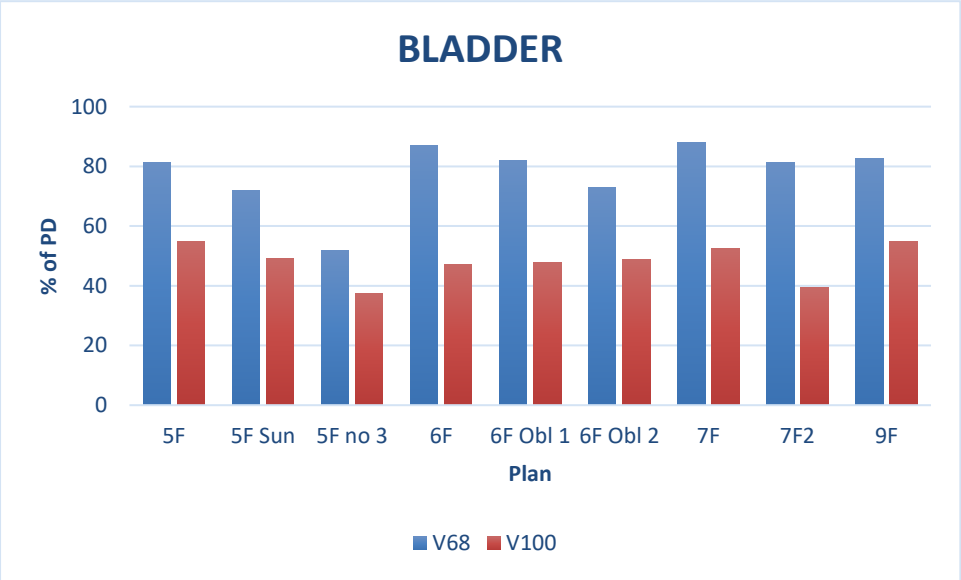

Figure 3: Urinary bladder dose constraints

With respect to V68% and V100%, the plans that gave the least doses were plan 3 (5F no. 3), plan 2 (5F sun), plan 8 and; lastly, plan 6 (6F oblique 2). The averaged values of V68% and V100% for the best plans were as follows: plan 3: (51.792±0.323; 37.447± 0.102), plan 2 (71.832±1.032; 49.034±0.917), plan 6 (72.103±0.052; 48,023±1.062).

Plan 7 (7F) and plan 4 (6F) had the highest doses to the bladder while the remaining four had comparable dose levels. V68% and V100 for plan 7 were 88.106±1.034%, and 52.468±2.013.

Analysis of radiation dose to femoral heads

Radiation dose to femoral heads was analysed and averaged values per treatment plan are shown in Figure 4 below.

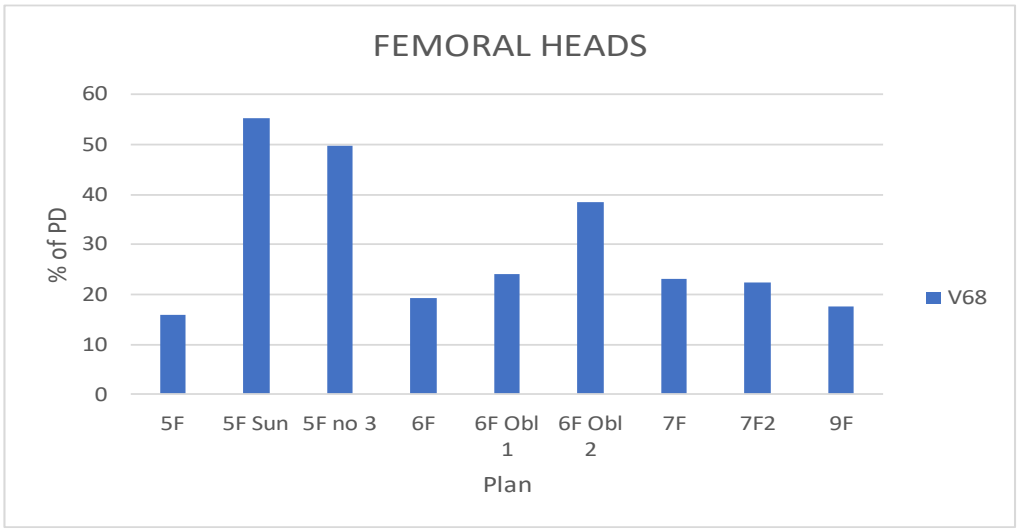

Figure 4: V68% Femoral head doses

The femoral dose was determined per patient by taking the highest V68% value on either side. In this regard, the best plans were 5F, 6F, 9F, 7F2 and 7F. Their averaged values were 15.234±2.001; 17.043±1.073; 17.239±1.025; 19.022±1.034; 22.011±1.224. In addition to the above mentioned, techniques 6F oblique 1, 6F oblique 2 and 5F number 3 also met the dose constraint requirement of V68%<50%.

To check the significance in the differences of doses to OAR, pairwise comparison was made for some chosen techniques that met most of the requirements using *t-tests*. For plan 3 and plan 6, while dose constraints for rectum at V41% and V100% the *P* values were all above 0.05, V68% of the bladder and femoral heads had p-values of 0.001 and 0.02, respectively; and these were statistically significant. However, between plan 8 and plan 6, all the p-values were above 0.05 and therefore insignificant.

Comparison of DVHs

In order to compare the different plans, DVHs of different beam arrangements were superimposed and analysed. One such comparison is shown in Figure 5 below.

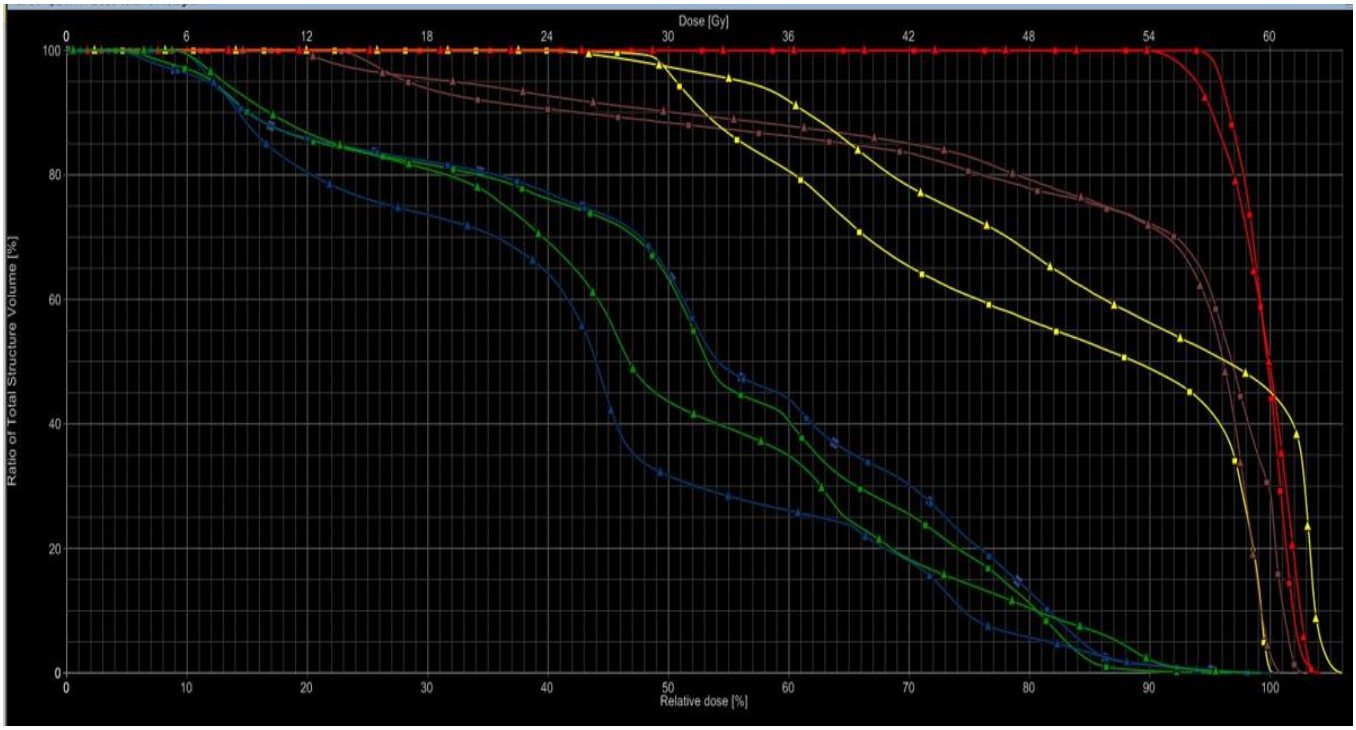

Figure 5: DVHs for PTV, rectum, bladder and femoral heads. (Boxes for 5F3 and triangles for 7F2)

From the DVHs, although the PTV maximum dose for 7F2 is slightly above that of 5F3, the beam arrangement was giving notably higher doses to the bladder (yellow). Otherwise, rectum and femoral doses were comparable for both plans. This observation led to the conclusion that plan 7F2 with gantry angles (0; 52; 104; 156; 208; 260; 312) and plan 3 (5F3) with beam arrangements direct anterior, two laterals and two posterior obliques (gantry angles in degrees: 0, 90, 120, 240 and 270), are equally suitable plans.

Discussion

Conformal treatment planning is a very subjective exercise with the end result depending on inter-observer variation, individual preference and patient anatomy. Despite this, for every parameter that was considered in the study, top three or four plans were identified. For PTV coverage the best plans were plan 8, plan 6 and plan 3. For HI, plan 1 was best followed by plan 7 (7F) and plan 3 (5F3). The HI values were 0.026±0.0013, 0.055± 0.0021 and 0.06±0.0018, respectively. Regarding CI, the top three plans were plan 9 (9F) with a mean value of 1.9210 ± 0.002 followed by plan 4 (6F) 2.025± 0.0132 and plan 3 (5F3) 2.201±0.0439. In terms of rectum sparing, the top four techniques were plan number 3 (5F3), plan 6 (6F oblique plan 2 (5F sun) and lastly plan 8 (7F2). With respect to bladder dose constraints V68% and V100%, plans that gave the least doses were plan 3 (5F no. 3), plan 2 (5F sun), plan 8 and;

lastly, plan 6 (6F oblique 2). The last OAR considered was the femoral head where V68% was used and best plans were plan 1, plan 4, plan 9 and plan 8. The DVH analysis summarised and revealed plan 8 and plan 3 to be comparatively competitive plans.

From statistical analysis, the best dose coverage regarding PTV D_{min} of 95% was for plan 8 (7F2) with the average dose of 95.7% (5730cGy) with the 95% isodose envelope covering the PTV in nine out of ten patients; plan 3 and plan 6 had almost similar results. *T-tests* done between plan 8 and plan 6 and between plan 3 and plan 8 showed statistically insignificant differences in D_{min} results. The worst plan that did not meet the D_{min} requirement was plan 2 (5F sun) with a D_{min} of 88%. With regards to D_{mean}, there were no notable differences in all the nine techniques with all values within 100% ± 0.53%; therefore, PTV D_{max} was considered. All plans met the condition of D_{max}<107% of the prescribed dose except for plan 2 where D_{max} was 115%. The top four plans in terms D_{min} and D_{max} and D_{mean} were plan 8 (7F2), plan 7 (7F), plan 3 (5F3) and plans 5 and 6 (6F and 6F oblique 2), respectively. The differences were also statistically insignificant as depicted by the *t-test* results in which all *p*-values were above 0.05.

However, in terms of homogeneity, plan 2 with five equispaced fields was the best although its dose was 99.67 ± 0.899% as opposed to the top four plans in which D_{mean} was at least 100%. The PTV coverage results were like those obtained by Shawata *et al.* (2019) who reported that the 7F technique (gantry angles 0; 60; 90; 120; 220; 270;300) provided the best PTV mean dose coverage while the 5F3 (gantry angles 0; 45; 90; 270; 315) had the least dose coverage with a mean dose of 99%. Some of their patients were treated with the five-field technique as it saved on therapy delivery time.

Unlike in the current study where 95% isodose envelope of plan 2 (5F sun (gantry angles: 0; 45; 90; 270; 315)) could not cover the posterior aspect of the PTV, Runham *et al.* (2008) managed to achieve it. This was mainly attributed to the study population which had prostate confined-disease (T1 -T2 N0M0), although 45° wedges were also utilised. Shawata *et al.* (2019) also managed to achieve the condition by using open fields using higher energy (15MV) photons unlike in the current study where the highest energy available was 10MV.

The most important limiting factor in radiotherapy dose delivery to the prostate is the rectum. Other OARs considered in the study were the urinary bladder and the femoral heads. The dose constraints for the OAR in the study were obtained based on the ASTRO, ASCO and AUA

recommended intervals for HFRT schedules of 3Gy/fraction for the rectum, bladder and femoral heads.

The dose to the rectum could not meet the set constraints mainly because, in this study, the rectum was part of the treatment volume as the pelvic lymph nodes were involved. This was different from the guidelines where pelvic nodes are not included in the PTV (Morgan, 2018). In an article comparing CFRT and HFRT of the prostate with nodal involvement, Vladimir *et al.* (2020) highlighted that the clinical trial and Italian trial carried by Arcangeli *et al.* (2017) were the only trials with published results on the subject. The rectum dose constraints used with IMRT technique were V50Gy<17%; V31Gy < 31% (Vladimir *et al.*, 2020).

The other OAR that was considered was the urinary bladder where dose constraints for V100% and V68% were analysed. Although all techniques did not ultimately satisfy the conditions of V68% <50% and V100< 5%, mainly due to the reasons indicated in the case of rectum doses, plan 3 could be modified to suit the required standard. The results seemed to agree with those obtained by Runham (2008), where 5F3 (gantry angles 0; 90; 120; 240; and 270) and 6F (gantry angles 30; 90; 120; 240; 270; 330) had statistically insignificant results at 95% CI. Although in Runham (2008) the 5F technique results absolutely agreed with those from Shawata *et al*., (2019). Unfortunately, Shawata *et al.* (2019) did not have the 5F3 technique in their studies. The 5F technique was the 5Fsun in this study, which was the second top plan in terms of bladder sparing.

Lastly, the study also considered femoral head doses where V68%<50% was used. All plans met this requirement except for the 5Fsun where the averaged doses were about 55%. However, the best three plans with remarkably low doses were the 5F equispaced with direct anterior, followed by the 9F (equispaced with a direct anterior) and 6F (equispaced and a direct anterior). The results were contrary to those found by Shawata *et al.* (2019), where plan 2 had the least doses to the femurs. This difference could be attributed to the higher photon energies that were used (15MV versus 10MV). From analysing PTV and OAR doses, the information was consolidated and other factors taken into consideration in order to come up with the best technique that could be adopted clinically.

Conclusion

The purpose of treatment planning is to achieve a reasonable therapeutic index where good tumour control and normal tissue sparing are simultaneously achieved. Analysing the PTV

coverage and OAR seeks to achieve this aim. In order to answer this objective, the researchers examined the DVHs for PTV and OAR, 95% isodose envelope, homogeneity index and potential treatment delivery time. Analysing the DVHs for the techniques 5F3, 6F oblique 2 and 7F2 one could pick very little variations. In fact, the t-test analysis of the 6F oblique 2 and 5F3 were not statistically significant.

In conclusion, plan 3 (5F3) is the best treatment plan if dose escalation is to be considered. Although this plan was not among the top ones in femoral head doses, it met the requirement of V68%<50%. The plan also has the advantage of saving on treatment time (few treatment fields) thus making it more clinically feasible. The other two plans that may be considered in order of priority are plan 6 (6F oblique 2) and plan 8 (7F2) to cater for differences in patient anatomy, inter observer variation and individual preferences. With flexible manoeuvring and optimisation provided by current treatment planning systems (TPSs), it is hoped that the techniques will produce quality dosimetry and; ultimately, a reasonably positive outcome for the patients.

Study limitations

HFRT in high-risk PCa disease with pelvic lymph node involvement is still a controversial topic where more evidence-based results are awaited (Vladimir, 2020). As a result, to the researcher's knowledge, there were no established standards regarding dose constraints, especially for the OAR. The established guidelines, for example, those by Swanson *et al.* (2020), aimed at encouraging implementation research of HFRT in PCa in Africa, and indicated only patients with T1-T2 tumours as eligible. However, in Zimbabwe, like in most LMICs, the majority of patients present with advanced localised disease (T3-T4) (Musarurwa *et al*., 2019). The problem is exacerbated by the fact that advanced techniques like IMRT are not available in these countries. To the researcher's knowledge, there were two established trials with pelvic nodes irradiation, namely the Vladimir *et al.* (2020) 10-year trial, which followed the Italian one of Arcangeli *et al.* (2017). While the Italian trial used 3D-CRT technique, there were no results on the OAR dose constraints used and thus insufficient to draw guidelines from. The limited literature on the subject was therefore a major limitation of the study.

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