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DOSIMETRIC COMPARISON STUDY OF THREE DIMENSIONAL CONFORMAL RADIOTHERAPY (3DCRT) VERSUS DIFFERENT INTENSITY MODULATED RADIOTHERAPY (IMRT) TECHNIQUES IN PROSTATE CANCER TREATMENT

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ABSTRACT

IMRT is a well-known and widely used treatment technique for carcinoma of the prostate (PCa) because it permits dose escalation to the tumour while sparing normal tissues. In Sri Lanka, along with IMRT, the 3DCRT technique is also used in the treatment of PCa. This study was carried out to compare 3DCRT treatment against Simultaneous-Integrated Boost Intensity Modulated Radiation Therapy (SIB-IMRT), Sequential IMRT, and Standard IMRT using dosimetric parameters such as Planning Target Volume (PTV) coverage by prescribed dose, Conformity Index (CI), Homogeneity Index (HI), percentage of maximum, minimum and mean dose to PTV and dose to 50% volume (D50) of the rectum, bladder, and femoral heads. Thirty-one PCa patients' treatment plans were included in the study. For evaluation purposes, the Dose-volume Histograms (DVHs) were compared in all techniques. The D50 to femoral heads showed a significant difference ($p < 0.05$) in the 3DCRT technique against all IMRT techniques as the dose to femoral heads was significantly greater in 3DCRT therapy in many patients. SIB-IMRT showed a significantly higher PTV coverage and dose conformity in PTV than 3DCRT while the Sequential IMRT technique showed a greater homogeneity in PTV and critical organ sparing to 3DCRT technique. However, when considering other dosimetric parameters, there was no significant difference between 3DCRT and IMRT.

KEYWORDS: *Dosimetric, 3DCRT, IMRT, SIB-IMRT, Sequential IMRT, Prostate Cancer*

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1. INTRODUCTION

According to the national cancer registry data, the incidence of prostate cancer reported in Sri Lanka is rising and majority of cases have metastatic spread at the time of diagnosis (Abeygunasekera *et.al,* 2015). 3D conformal radiation therapy (3DCRT) and Intensity Modulated Radiotherapy (IMRT) is the main radiotherapy techniques used to treat PCa. The use of these advanced techniques allows better sparing of more normal tissue high doses than with the conventional two dimensional (2D) radiotherapy. During 2D radiotherapy, a large volume is treated to high doses to ensure proper coverage of the PTV due to difficulties in localization of the tumour (Spiess, 2011). Therefore, surrounding normal tissues were incorporated in the treated volume. As a result, the prescribed dose was limited by the tolerance of organs at risk such as rectum and bladder, to a dose of 60-65Gy (Choe & Liauw, 2010). With 3DCRT, it has been possible to deliver a higher dose with more conformity using standard dose fractions (2 Gy per fraction). Previous studies have shown improved prostate-specific antigen (PSA) control with dose escalation, at the cost of increasing probability surrounding tissue toxicity (Zelefsky et. al., 2008). There is a study confirming the significant increase in late rectal complications in the delivery of 70 Gy or more on 25% of the rectum volume (Webb & Naham, 1993). A study by Zelefsky et.al., (2008) has reported that the dose levels beyond 75.6 Gy with 3DCRT increased risks of Grade 2 rectal and bladder-related late toxicities.

At present, IMRT is a commonly used treatment technique in developing countries like Sri Lanka as it helps to reduce the volume of the rectum and bladder being exposed to higher doses in clinically localized PCa. The volume of the rectum and bladder receiving more than 40 Gy is reduced by 20% in conformal 3DCRT radiotherapy and it is further reduced by 45% in IMRT (Taylor & Powell, 2004). In contrast to 3DCRT, IMRT can deliver a dose up to 81 Gy with 99% conformity to the clinical target volume (CTV) and limiting the doses carried to the rectal wall in between 50 and 77 Gy and the bladder wall between 55 and 85 Gy, and the femoral heads between 25 and 60 Gy (Zelefsky et. al., 2000).

With the increasing use of the simultaneous integrated boost intensity-modulated radiotherapy (SIB-IMRT), it has been possible to deliver a simultaneously escalated per fraction dose to different tissues (PTVs) in a single treatment session resulting in an increased therapeutic ratio and shortening of overall treatment time (Mohan et. al., 2000 and Orlandi et. al., 2010). The previous treatments used dose escalation with daily doses of about 2 Gy per fraction up to a total dose higher than 80 Gy for treatment where the treatment times were prolonged for more than eight weeks.

In Sri Lanka, 3DCRT is commonly used in most cancer treatment centres due to the lack of advanced treatment facilities such as IMRT. Moreover, the cancer treatment centres equipped with IMRT treatment facility is continuously using 3DCRT technique to manage the workload and patients' waiting list. The main purpose of this study is to evaluate 3DCRT against IMRT based on the dosimetric parameters such as PTV coverage by prescribed dose, dose conformity in the target volume (CI), dose homogeneity in the target volume (HI), percentage of maximum, minimum and mean dose to PTV and D50 of organs at risk (OAR) (such as bladder, rectum and femoral heads).

2. METHODOLOGY

2.1. Patient Selection

This study was a retrospective cohort study conducted at National Cancer Institute Maharagama, Sri Lanka between the years 2016-2018. Treatment plans for patients with localized prostate cancer and with or without lymph nodes (LN) metastasis treated with standard IMRT, SIB-IMRT and Sequential IMRT were included in the study. Eleven patients have had prostate cancer confined to the prostate gland and had been treated using standard IMRT and twenty patients' prostate cancer had spread beyond the prostate gland and had been treated using

sequential IMRT and SIB-IMRT techniques. 3DCRT plans were generated for each IMRT plan of patients. The ethical clearance for the study was obtained from the Institution of Biology Sri Lanka.

2.2. Target volume delineation

In a low risk patient, the gross tumor volume (GTV) was equal to CTV1, which in turn was equal to the total prostate gland. In Intermediate risk patients, CTV1 included prostate gland and seminal vesicles, and CTV2 included prostate gland only. In high-risk patients CTV1 included regional pelvic lymph nodes, seminal vesicles and prostate, and CTV2 included prostate gland and seminal vesicles, whereas CTV3 included prostate only.

2.3. Treatment planning

A 6 MV clinical linear accelerator with 80 pairs of the dynamic multi-leaf collimator (MLC) has been used in the generation of IMRT treatment plans, and static MLC has been used in 3DCRT treatment plans. The prescribed dose used in both IMRT and 3DCRT treatment plans was 56-76 Gy to the PTV. The treatments have been planned to deliver 95% -107% of the prescribed dose to the isocenter. All plans have been generated using the Eclipse (version 8.6) treatment planning software, and plans have been optimized using direct parameter machine optimization. The parameters for optimization used are the specified dose to the PTV, the dose limits for each of the critical structures, and the respective penalties for deviation from these criteria. According to the Radiation Therapy Oncology Group (RTOG) protocol, dose-volume constraints for 3%, 15%, 30%, 50% and 60% of rectum volume were 74Gy, 70Gy, 65Gy, 60Gy, and 50Gy respectively. Dose-volume constraints for 5%, 25%, and 50% volume of the bladder were 74Gy, 60Gy, and 50Gy respectively. The dose-volume constraint for 50% volume of the femoral head was 50Gy.

2.4 Dose prescriptions

The low-risk group (T1-T2a and Gleason Score (GS) ≤6 and PSA≤10 ng/ml) or the intermediate-risk group (T2b and/or GS = 7 and/or PSA > 10-20 ng/ml) has been treated with a standard dose of 66 Gy -76 Gy over 33 to 38 fractions (2Gy/F). The two techniques, i.e. Sequential IMRT technique and SIB-IMRT were used to treat high-risk patients (T2c or PSA > 20 ng/ml or GS > 8-10). In Sequential IMRT, treatment radiation has been delivered in two to three phases within 6 to 7 weeks. In each phase, the same dose of 2 Gy/fraction has been delivered to pelvic nodes, seminal vesicles and the prostate using a dynamic multi-leaf collimator. In the first-phase, for all the cases equally spaced, non-opposed 8-coplanar beams have been used and for the boost phases, different IMRT beam arrangements have been used in the plans. In the first-phase, the dose for the CTV1 (pelvic lymph nodes, seminal vesicles and prostate) has been 54 Gy (27 fractions, 2 Gy/fraction), in the second phase, the dose to the CTV2 (prostate and seminal vesicles) has been 12 Gy (6 fractions, 2 Gy/fraction) and in the third phase, the dose to the CTV3 (prostate) has been 8 Gy (4 fractions, 2 Gy/fraction). The total physical dose for pelvic nodes was 54 Gy, for seminal vesicles it was 66 Gy and for prostate it was 74 Gy.

In SIB-IMRT treatment, the radiotherapy has been given as a single phase, using a dynamic multi-leaf collimator. In all SIB-IMRT plans equally spaced, non-opposed 8- coplanar beams have been used. Respectively 54 Gy, 66 Gy and 74 Gy doses have been delivered to pelvic lymph nodes, seminal vesicles and prostate in 30 fractions at a 1.8 Gy/fraction, 2.2 Gy/fraction and 2.5 Gy/fraction within 6 weeks.

In the 3D-CRT method, 4 beams; anterior posterior (AP) and posterior anterior (PA) and 2 lateral beams were used in treatment plans. The Low-risk or intermediate-risk group's patients were treated with a standard dose (66 Gy -76 Gy over 33 to 38 fractions (2Gy/Fraction)). For the high-risk group, radiation was delivered in three phases using a static multi-leaf collimator, reducing the field size of the target volume. In the first phase, the dose for CTV1 (pelvic lymph nodes, seminal vesicles and prostate) was 54 Gy (27 fractions, 2 Gy/fraction), in the second phase, the dose to the CTV2 (prostate and seminal vesicles)

was 12 Gy (6 fractions, 2 Gy/fraction) and in the third phase, the dose to the CTV3 (prostate) was 8 Gy (4 fraction, 2 Gy/fraction). The total physical doses were 54 Gy for pelvic nodes, 66 Gy for seminal vesicles and 74 Gy for prostate.

2.5. Method of assessment and comparison of 3DCRT and IMRT plans

To compare the 3DCRT and IMRT techniques dose volume histograms (DVHs) of the PTV and the OAR (rectum, bladder and femoral heads) were used. The dose to every delineated structure in the PTV was obtained using these DVHs. To compare treatment modalities, the dosimetric parameters analyzed were the percentage of prescribed dose to 100% PTV, percentage of maximum, minimum and mean dose to PTV, Homogeneity Index (HI), Conformal Index (CI) and D_{50} of rectum, bladder and femoral heads. D_{50} of rectum, bladder and femoral heads were assessed to see whether doses are at or above dose constraint values of RTOG protocol. The Dose volume constraints as per RTOG protocols for D_{50} of Rectum, Bladder and Femoral heads are 60Gy, 50Gy and 50Gy respectively. HI index and CI index were calculated using equations 1 and 2.

$$HI = \frac{D_5}{D_{95}} \qquad (1)$$

$$CI = \frac{PTV_{95\%PD}}{V_{PTV}} \qquad (2)$$

Where, D5 and D95 are the doses delivered to 5% and 95% of the PTV respectively. HI value approximate to 1 indicates the homogenous dose distribution in the PTV. CI value approaching 1 indicates a higher degree of conformity. The results obtained under each group were presented as mean with standard deviation. The Wilcoxon signed rank test is used to compare the dosimeteric parameters of the treatment strategies. The probability value (p value) < 0.05 was considered as statistically significant.

3. RESULTS

3.1. Comparison and assessment of 3DCRT against standard IMRT

The results obtained for the comparison of 3DCRT against standard IMRT treatment are discussed in this section.

Table 1: The percentage of maximum, minimum and mean dose to PTV and percentage of prescribed dose to PTV in the standard IMRT against 3DCRT.

	Maximum dose (%)		Minimum dose (%)		Mean Dose (%)		%Prescribe dose to 100% PTV volume	
Patients no	IMRT	3DCRT	IMRT	3DCRT	IMRT	3DCRT	IMRT	3DCRT
1	105.4	104.0	75.3	85.6	96.2	99.1	88.0	83.0
2	104.9	103.7	79.0	88.9	100.6	98.9	92.0	92.0
3	105.2	102.1	83.0	76.1	100.1	98.3	87.6	86.5
4	107.5 *	104.1	80.6	85.2	102.0	100.0	91.3	86.5
5	106.2	102.6	82.7	87.2	100.0	97.3	87.9	90.0
6	108.0 *	102.5	89.0	78.6	104.4	99.2	94.0	93.0
7	107.3 *	104.3	79.6	92.1	97.3	99.8	86.0	94.0
8	107.4 *	106.9	79.5	79.8	102.8	99.5	88.0	86.0
9	103.0	103.1	79.1	80.7	97.3	73.4	96.0	90.0
10	100.4	104.3	84.2	90.1	97.2	100.1	90.0	93.0
11	105.6	105.3	71.5	87.9	100.0	99.0	86.0	92.0
Mean (SD)	105.5 (2.2)	103.9 (1.4)	80.3 (4.6)	84.7 (5.2)	99.8 (2.6)	96.8 (7.8)	89.7 (3.3)	89.6 (3.6)
Z value	-1.956 0.050		-1.600 0.110		-1.156 0.246		0.000 1.000	

Table 1 summarizes the percentage of maximum, minimum and mean dose to PTV and percentage of prescribed dose to 100% PTV. The maximum doses (D_{max}) to PTV in standard IMRT is significantly higher than the 3DCRT except the patient number 10 (see figure 1(a)). However, there was no statistically

significant difference in D_{max} values between two treatment methods (p=0.050). The minimum doses (D_{min}) in standard IMRT method are inferior to the 3DCRT method except the patient number 3 and 6 (see figure 1(b)). There is no statistical significance between D_{min} values in the two treatment methods (P=0.110).

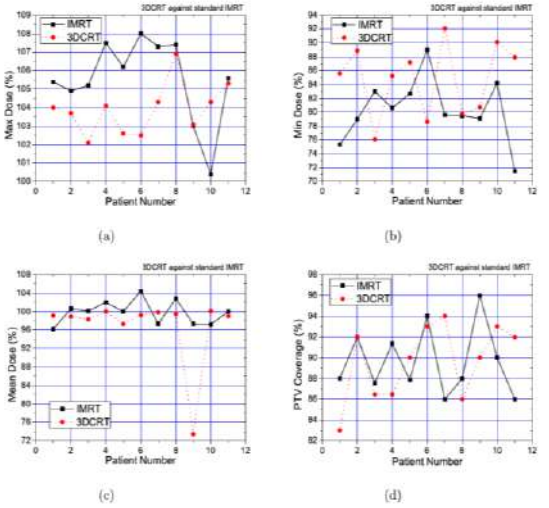

Figure 1: Comparison of 3DCRT against standard IMRT (a) maximum dose (b) minimum dose (c) mean dose and (d) PTV coverage

The mean doses (D_{mean}) are comparable and within the acceptable limit except the patient number 9 where the mean dose is very low (73.4%) in 3DCRT plan (see figure 1(c)). Further, there is no statistical significance between mean dose (D_{mean}) values in two treatment methods (P=0.246). The PTV coverage is also comparable in the two methods (see figure 1(d)). Some 3DCRT plans (patient no. 5,7,10 and 11) show better tumour coverage than IMRT techniques. However, there is no statistical significance between mean PTV coverage in the two techniques (P = 1.000).

Table 2 and figure 2(a) reveal that both Standard IMRT and 3DCRT have a uniform distribution of dose in the PTV as mean HI values calculated for both methods are comparable and approximating to 1. Therefore, there is no statistical significance in the homogeneity of dose in the two methods (p=0.610). CI values show a variation between the two methods. For instance, plans of 1, 6 and 10 provide high conformity in IMRT than that in 3DCRT. In contrast, 3DCRT plans of patients 5, 7 and 11 shows high conformity to the target volume compared to IMRT. The rest of the CI values are comparable in one method against the other. Overall, CI values showed no statistical significance between the two methods (p=0.285).

Table 2: Comparison of HI values and CI values in the standard IMRT against 3DCRT

Patient no.	HI value		CI value	
	IMRT	3DCRT	IMRT	3DCRT
1	1.13	1.05	0.95	0.70
2	1.07	1.07	1.00	0.95
3	1.08	1.08	0.97	0.95
4	1.10	1.08	0.99	0.95
5	1.03	1.01	0.89	0.92
6	1.02	1.09	1.00	0.85
7	1.13	1.07	0.80	1.00
8	1.10	1.11	0.96	0.92
9	1.04	1.07	0.98	1.00
10	1.06	1.06	0.98	0.85
11	1.09	1.08	0.90	0.95
Mean (SD)	1.08(0.04)	1.07(0.03)	0.95(0.06)	0.91(0.09)
Z value	-0.5096		-1.0669	
P value	0.610		0.285	

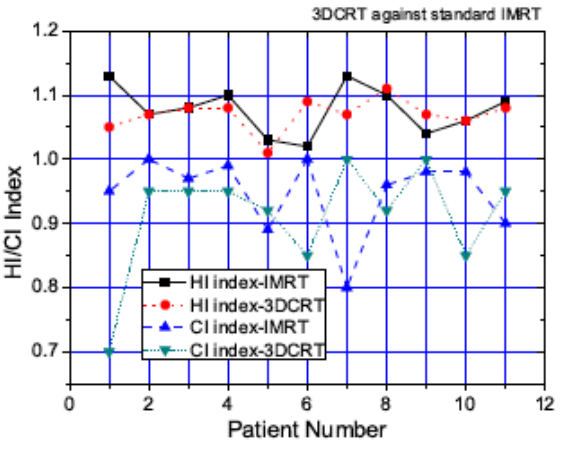

Figure 2a: HI and CI Index

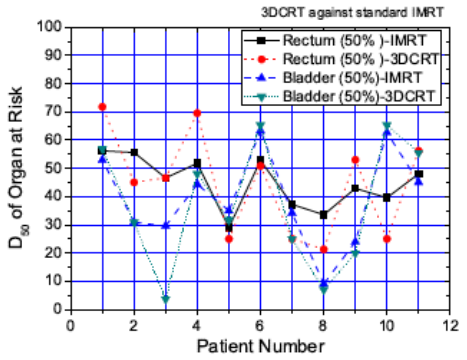

Figure 2 b: D_{50} Rectum and Bladder

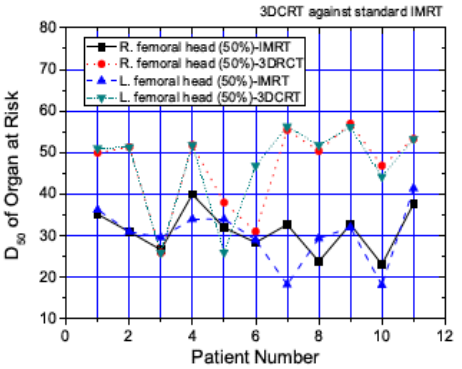

Figure 2 C: D_{50} Femoral heads

Table 3 summarizes dose to 50% volumes (D_{50}) of organs at risk. In the comparison of D_{50} of the rectal wall there is no statistical significance found between the two methods (p=0.881). Further evaluation revealed that in 3DCRT method, the patient numbers 1 and 4 have received an obvious higher D_{50} rectal dose, which exceeds the dose constraint. While in IMRT method, all eleven patients have received a dose under the dose constraint (see figure 2(b)).

In the comparison of D_{50} of bladder, D_{50} of bladder of patient plans 1, 6 and 10 exceeded the dose constraint in both methods and overdoses are greater in 3DCRT method than in IMRT. In the patient 8 plan, it is noted that bladder gets under dose in both methods. Additionally, in the patient plan 3, bladder gets a very lower dose in both methods. In the patient plan 11, bladder gets a greater dose in 3DCRT plan than in IMRT. However, there is no significant difference between the two methods (p=0.803).

In the comparison of D_{50} to right and left femoral heads the two methods are statistically significant (p=0.0044, p = 0.007). It is clearly observed that overdose to femoral heads are seen in 3DCRT method in many patients 'plans while all IMRT plans have delivered a dose below the doses constrain (see table 3). Overdose in 3DCRT was particularly seen in plans where dose is at or above the 74Gy.

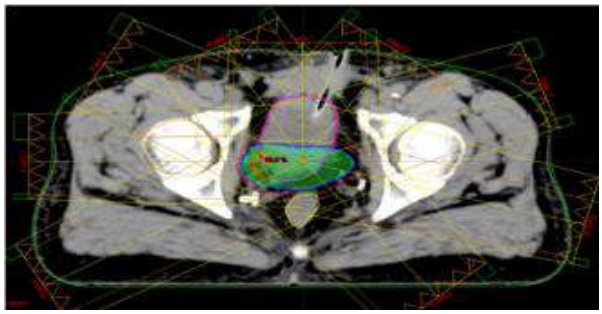

Figure 3: IMRT plan of the patient 10 shows a part of the bladder volume ink out line structure) is included within the PTV (Red out lined)

Table 3: The Comparison of the D50 Rectum, D 50 Bladder and D50 Femoral heads in the Standard IMRT against 3DCRT

	Rectum D_{50} (Gy)		**Bladder D_{50} (Gy)**		**D_{50} Right femoral head (Gy)**		**D_{50} Left femoral head (Gy)**	
Patient no	**IMRT**	**3DCRT**	**IMRT**	**3DCRT**	**IMRT**	**3DCRT**	**IMRT**	**3DCRT**
1	56.2	71.8*	53.0*	57.0*	35.2	50.0	36.3	51.1*
2	55.6	45.1	31.0	31.0	31.0	51.3*	31.0	51.3*
3	46.6	46.6	29.6	3.7*	26.6	25.9	29.6	25.9
4	51.8	69.6*	44.4	48.1	40.0	51.8	34.0	51.8*
5	29.0	25.1	35.0	31.7	32.0	38.0	34.0	26
6	52.8	50.8	63.4*	65.3*	28.4	31.0	29.0	46.9
7	37.2	25.1	34.2	25.1	32.7	55.5*	18.2	56.2*
8	33.6	21.4	9.1*	7.0*	23.8	50.4	29.4	51.8*
9	42.9	53.0	24.0	20.0	32.8	56.9*	32.0	56.2*
10	39.6	25.1	62.7*	65.3*	23.1	46.9	18.2	44.2
11	48.1	56.2	45.1	55.5	37.7	53.3	41.4	53.3*
Mean (SD)	44.9 (9.2)	44.5 (18.2)	39.2 (16.5)	37.2 (22.3)	31.2 (5.4)	46.4 (10.2)	30.3 (7.0)	46.8 (10.9)
Z value	-0.1529		-0.255		-2.845		-2.667	
P value	0.88076		0.803		0.0044		0.00758	

Table 4: The percentage of Maximum, Minimum and Mean dose to PTV and percentage of prescribed dose to PTV in the SIB-IMRT against 3DCRT.

	Max Dose (%)		Min Dose (%)		Mean Dose (%)		PTV Coverage (%)	
Patient No	SIB-IMRT	3DCRT	SIB-IMRT	3DCRT	SIB-IMRT	3DCRT	SIB-IMRT	3DCRT
12	105.5	105.3	89.3	76.7	102.5	98.6	94.0	84.0
13	98.9	105.7	85.3	82.2	96.3	98.2	90.5	85.0
14	109.0*	102.7	92.6	58.4	105.3	77.7	97.0	88.5
15	105.8	103.5	78.7	77.1	96.8	98.9	94.4	90.9
16	104.4	105.0	71.5	64.5	95.2	97.4	90.2	96.5
17	107.8*	106.0	85.4	76.5	102.5	99.9	92.5	85.7
18	104.0	102.0	62.4	65.0	85.7	82.2	94.0	86.0
19	104.2	107.4*	82.0	89.0	97.0	102.0	86.0	92.0
20	104.0	99.4	79.2	92.5	100.0	101.3	88.0	76.6
21	106.0	104.0	90.5	72.6	102.0	98.7	94.0	85.0
Mean SD	105.0 (2.7)	104.1 (2.3)	81.7 (9.3)	75.5 (10.8)	98.3 (5.6)	95.5 (8.4)	92.1 (3,3)	87.0 (5.4)
P value	0.3843		0.1676		0.384		0.037	

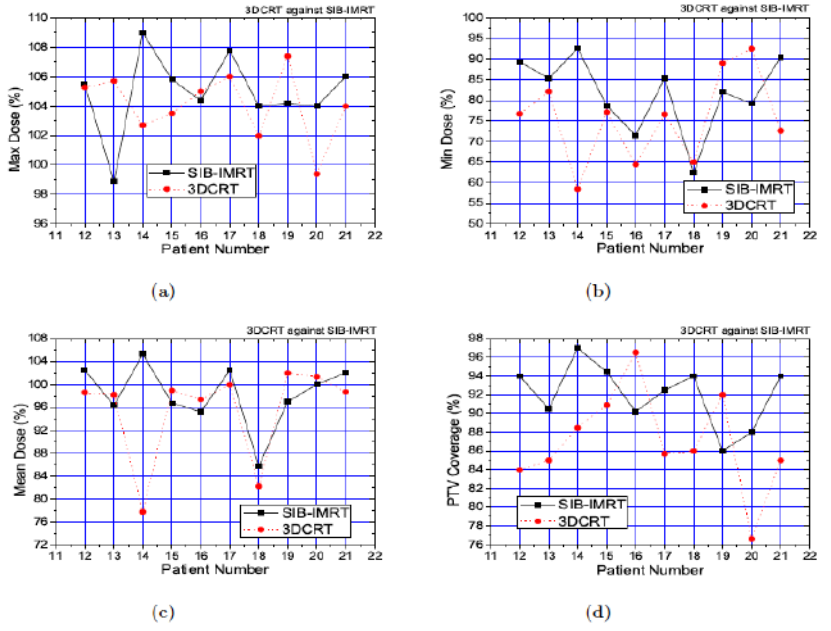

Figure 4: Comparison of 3DCRT against SIB-IMRT (a) maximum dose (b) minimum dose (c) mean dose and (d) PTV coverage

3.2 Comparison and assessment of 3DCRT against SIB-IMRT

Results of maximum PTV dose (D_{max}), minimum PTV dose (D_{min}), mean PTV dose (D_{mean}) and percentage of prescribed dose to 100% PTV volume (DV 100%) obtained for the comparisons of 3DCRT against SIB-IMRT treatment are summarized in tables 4 and analyzed graphically in figure 4. Except for the PTV coverage (p= 0.037), other parameters showed no statistical significance between the two methods. SIB-IMRT plans show a better PTV coverage than the 3DCRT plans (see table 4).

Figure 5(a) and table 5 disclose that SIB-IMRT and 3DCRT have achieved the uniform homogeneity in the PTV. But mean HI value in SIB-IMRT is more approximate to 1, which indicates that the dose distribution is more uniform with SIB-IMRT. Conversely there is no statistical significance (p=0.152) in homogeneity in 3DCRT against SIB-IMRT. The conformity index (CI) is statistically superior in SIB-IMRT plans (p=0.037). However, both HI and CI values are comparable between the methods in the patient plans 16, 17, 18 and 19 (See table 5).

In the comparison of D_{50} of the rectum in 3DCRT against SIB-IMRT, all the patients have received a dose less than the dose constraint (60Gy) to 50% of the rectum wall in both methods. So both methods have been successful in Preventing rectum being overdosed (see Table 6 and figure 5(b)). There is no statistical significance in D50 rectum in SIB-IMRT against 3D-CRT (p=0.168). In the comparison of D_{50} the bladder walls are under the dose constraint in both methods except in the patients 14, 16 and 18 where the dose has exceeded by 8 Gy, 10 Gy and 4 Gy respectively in 3DCRT plans. In patients 15 and 21, both techniques have overdosed bladder by 2.5 Gy to 8 Gy respectively (See table 6). However, there is no statistical significance between the D_{50} of bladder in two methods (p=0.263).

Table 5: Comparison of HI values and CI values in the SIB-IMRT against 3DCRT

	HI value		CI value	
Patient no	**SIB-IMRT**	**3DCRT**	**SIB-IMRT**	**3DCRT**
12	1.06	1.12	0.99	0.9
13	1.04	1.1	0.92	0.9
14	1.07	1.2	1.0	0.97
15	1.02	1.13	1.0	0.97
16	1.08	1.05	0.95	1.0
17	1.08	1.08	0.99	0.95
18	1.04	1.06	1.0	0.95
19	1.09	0.96	0.95	0.95
20	1.09	1.18	0.95	0.84
Mean	1.06	1.10	0.97	0.94
SD	0.02	0.07	0.03	0.05
P value	0.152		0.037	

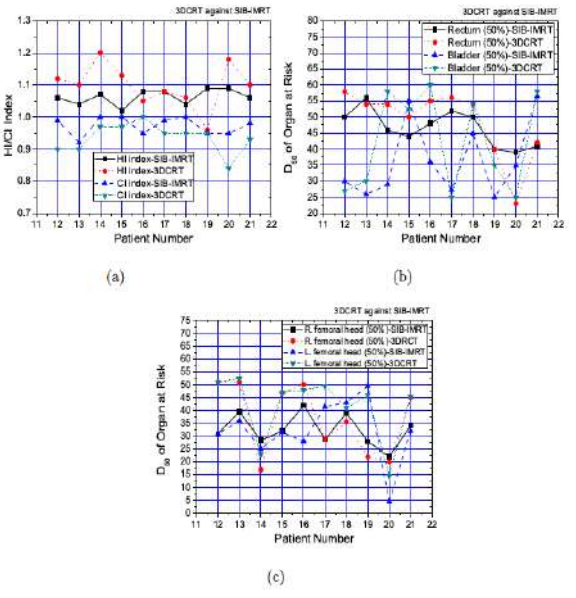

Figure 5: Comparison of 3DCRT against SIB-IMRT (a) HI and CI Index (b) D_{50} Rectum and Bladder (c) D_{50} Femoral heads.

In the study, D_{50} dose to femoral heads in all patients in both methods were below dose constraint (see figure 5(c)). But D_{50} to left femoral heads were noticeably greater in 3DCRT plans (See table 6) than in SIB-IMRT plans and this difference was statistically significant (p=0.0285). Even though D_{50} to right femoral heads were also higher in 3DCRT plans over SIB-IMRT plans, this difference was not statistically significant (p=0.308).

Table 6: The Comparison of the D_{50} Rectum, D $_{50}$ Bladder and D_{50} Femoral heads in the SIB- IMRT against 3DCRT

Patient No	D50 Rectum		D 50 Bladder		D 50 Right Femoral head		D50 Left. Femoral head	
	SIBIMRT	3DCRT	SIB-IMRT	3DCRT	SIB-IMRT	3DCRT	SIB-IMRT	3DCRT
12	50	58	30	27	31	51	31	51
13	56	54	26	30	39.5	51	36	52.5
14	46	54	29	58*	28.5	17	25	23
15	44	50	55*	52.5	32	47	31.5	47
16	48	55	36	60	42	50	28	48
17	51.9	56	27.4	25	28.8	28.8	41.5	49.5
18	50	54	45	54*	39	35.5	43	41
19	40	40	25	35	28	22	49.5	46
20	39	23	35	25	22	20	4.5	14.5
21	41	42	56.5*	58*	34	45	32	45.5
Mean	46.59	48.6	36.49	42.45	32.48	36.73	32.2	41.8
SD	5.6	10.8	11.7	15.2	6.2	13.8	12.3	12.7
P value	0.168		0.263		0.308		0.0285	

3.3. Comparison and assessment of 3DCRT against sequential IMRT

The results obtained for the comparison of 3DCRT against Sequential (phase) IMRT treatment plans are summarized in table 7. The D_{max} values in PTV in the sequential IMRT is slightly greater than that in 3DCRT except in the case of patient numbers 28, 30 and 31 (see figure 6(a)). However there is no significant difference in the D_{max} values in the two methods (p=0.093). D_{min} is almost comparable in the two methods and there is no significant difference in the D_{min} in the two methods (p=0.447). Conversely, there is a significant difference in D_{mean} (p=0.037) between two methods.

Table 7: The percentage of Maximum, Minimum and Mean dose to PTV and percentage of prescribed dose to PTV in the standard Sequential IMRT against 3DCRT

Patient no	Max Dose (%)		Min Dose (%)		Mean Dose (%)		PTV Coverage (%)	
	Sequential IMRT	3DCRT	Sequential IMRT	3DCRT	Sequential IMRT	3DCRT	Sequential IMRT	3DCRT
22	106.4	101.26	67	29.12	95.5	90.4	70.8	85
23	100.2	97.77	87.46	72.05	96.56	85.2	89.2	74.32
24	103.19	101.63	60.3	69.99	82.9	80.01	91.6	66.6
25	107.13	101.2	81.1	66.58	100.15	81.8	92.3	106.1
26	107.5	103.3	78.94	60.38	99.33	84.12	90.27	93
27	105.1	103.3	84.9	91.26	100.35	99.38	89.7	95
28	102.5	105.3	75.7	82.22	94.9	100.1	85.1	91.2
29	106.6	103.94	75.2	87.3	100.12	98.9	87.8	91.2
30	104.6	105.28	83.93	87.03	100.28	99.44	92.3	92.94
31	103.8	105.38	86.6	86.58	100.24	98.96	98.21	89.28
Mean	104.7	102.8	78.1	73.3	97.0	91.8	88.7	88.5
SD	2.2	2.3	8.4	17.7	5.1	7.9	6.8	10.5
P value	0.093		0.447		0.037		0.803	

The mean PTV coverage with prescribed dose is more or less similar in both sequential IMRT and 3DCRT. Except in the patient 23 and 24, the sequential IMRT shows a better PTV coverage than that in the 3DCRT (see figure 6(d)). However, there is no significant difference in the PTV coverage in the two methods (p>0.803).

Table 8 reveals that sequential IMRT and 3DCRT homogeneity in the PTV is statistically significant (p=0.0226). But CI values in the two methods are comparable and there is no statistical significance between the two methods (p =0.638).

Table 9 compares Dose to 50% volume of rectum, bladder and femoral heads in 3DCRT and sequential IMRT. In the comparison of D_{50} to rectum all the patients have received a dose less than dose constraint (60Gy) in both sequential IMRT and 3DCRT methods (see figure 7(a)). Therefore, there was no statistical significance in the D_{50} to rectum in the two methods (p=0.13)

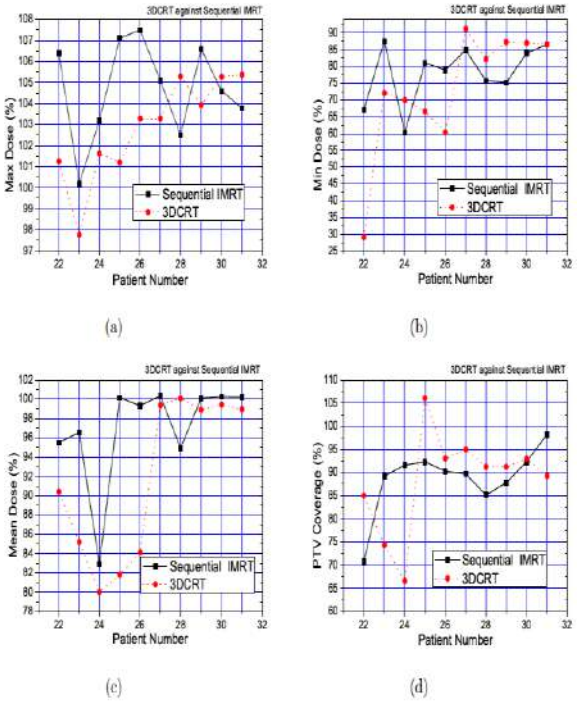

Figure 6: Comparison of 3DCRT against Sequential IMRT (a) maximum dose (b) minimum dose (c) mean dose and (d) PTV Coverage

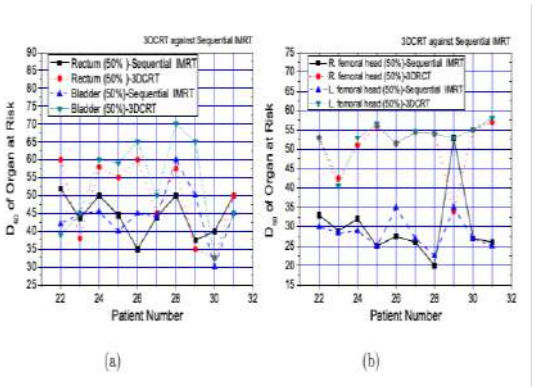

Figure 7: Comparison of 3DCRT against Sequential IMRT (a) D_{50} Rectum and Bladder (b) D_{50} Femoral heads

Table 8: Comparison of HI values and CI values in the Sequential IMRT against 3DCRT

		HI value		CI value	
Patient no		**SequentialIMRT**	**3DCRT**	**Sequential IMRT**	**3DCRT**
22	PTV1	1.11	1.15	0.92	0.92
	PTV2	1.4	1.15	0.86	0.95
	PTV3	1.24	1.06	0.73	0.73
23	PTV1	1.06	1.2	1	0.95
	PTV2	1.11	1.2	1	1
	PTV3	1.12	1.04	0.85	0.1
24	PTV1	1.08	1.18	0.97	0.97
	PTV2	1.1	1.21	1	1
	PTV3	1.08	1.2	1	1
25	PTV1	1.12	1.14	0.95	1
	PTV2	1.17	1.7	1	1
26	PTV1	1.09	1.4	1	1
	PTV2	1.13	1.19	1	1.0
27	PTV1	1.41	1.43	0.99	0.98
	PTV2	1.07	1.05	0.95	1
28	PTV1	1.15	1.15	1	1
	PTV2	1.09	1.09	0.7	0.98
29	PTV1	1.3	1.4	1	0.97
	PTV2	1.1	1.14	0.95	0.93
30	PTV1	1.4	1.57	0.98	0.98
	PTV2	1.07	1.1	0.98	0.95
31	PTV1	1.2	1.35	1	0.98
	PTV2	1.1	1.09	0.95	0.95
Mean		1.16	1.23	0.95	0.92
SD		0.11	0.17	0.08	0.19
P value		.0226		0.638	

In the patients 24,25,26 and 29 of 3DCRT plans, D_{50} dose to bladder were above the dose constraint (see table 8 and figure 7(a)), and there is statistical significance between the D50 of bladder in the two methods (p=0.03).

The comparison of sequential IMRT with D_{50} of femoral heads (left and right) showed statistical significance as the mean dose to D_{50} femoral heads are 20 Gy higher in 3DCRT. However, the doses to femoral heads in both methods were below the dose constraint value (see figure 7(b).

Table 9: The Comparison of the D_{50} Rectum, D_{50} Bladder and D_{50} Femoral heads in the Sequential IMRT against 3DCRT

	D_{50} Rectum		D_{50} Bladder		D_{50} Right femoral head		D_{50} Left femoral head	
	Sequential IMRT	3DCRT	Sequential IMRT	3DCRT	Sequential IMRT	3DCRT	Sequential IMRT	3DCRT
22	52	60	42	39	33	53	30	53
23	43.5	38	45	45	29	42.5	28.5	40.5
24	50	58	45.5	60*	32	51	29	53
25	44.5	55	40	59*	25	56	25	56.5
26	35	60	45	65*	27.5	51.5	35	51.5
27	44	45	44	50	26	54.5	27	54.5
28	50	57.5	60*	70*	20	54	22.5	54
29	37.5	35	50	65*	53	34	35	53
30	40	32.5	30	32.5	27	55	27	55
31	50	50	45	45	26	57	25	58
Mean	44.65	49.1	44.65	53.05	29.85	50.85	28.4	52.9
SD	5.85	10.74	7.52	12.54	8.91	7.18	4.11	4.75
P value	0.13		0.03		0.005		0.005	

4. DISCUSSION

In the Standard IMRT plan (Figure 1) and SIB-IMRT plan (Table 4) there were regions where the maximum dose is greater than 107% of the prescribed dose which were to be assumed as hot spots. These hot spots should be taken into account as they can affect toxicity and tumor control probability (Arno *et. al.,* 2005). According to the International Commission on Radiation Units and measurements, a "Hot spot" is an area outside PTV but within the GTV, which receives a higher dose than the prescribed dose (> 100 % of the prescribed dose). Hot spots are considered significant if the minimum diameter exceeds 15 mm. It is noted that areas in the standard and SIB-IMRT plans with the maximum dose which is greater than 105% of the prescribed dose but as the area of such overdose was significantly negligible (minimum diameter of area < 1 mm) they were not considered as a hot spot and identified as pin point.

The minimum doses in most patients in Standard IMRT, Sequential IMRT, SIB –IMRT and corresponding 3DCRT were less than 93% of the prescribed dose (Table 1,4 and 8). A cold spot is an area which receives a lower dose than the prescribed dose (< 93 % of prescribed dose). The total volume of any cold spot should be <1 % of the PTV (Arno *et. al.,* 2005). It is noted that this was, as doses were not normalized to 107% but to 100%. Anyhow this had no effect on the patient's treatment. There were no significant differences between the minimum doses to PTV in any IMRT and corresponding 3DCRT treatment plans.

Comparison of 3DCRT against standard IMRT; the over dose to the rectum in patient 1 and 4 in 3DCRT plan (see table 3) is due to the large PTV margin including part of the rectal wall in the prostate PTV. But in IMRT, due to the ability to modulate beam intensity and curve iso-dose lines to the shape of the tumour volume spared the rectal wall being overdosed. Overdose to bladder in patient plans 1,6 and 10 in both techniques (see table 3) is due to the portion of bladder volume being included within the PTV (see figure 3). Though patients were advised to follow bladder protocol before radiotherapy scanning, bladder may not have been fully filled or the size of the prostate may have been large. It was also found that the bladder volume of patient 6 was anatomically smaller in size (39 cm^2) and 66% of bladder volume was overdosed. In the patient 10, the bladder was overdosed by both methods as about 48% bladder volume was included within the PTV and 52% of total bladder volume was overdosed. However, in both treatments plans, D_{50} bladder outside PTV and volume of bladder outside PTV were in acceptable range. (D_{50} bladder dose outside PTV was 43 Gy and 35Gy respectively in IMRT and 3DCRT plans). In the patient plan 3, the bladder gets very lower dose in both methods as PTV enclosed only prostate, and the rectum, bladder and femoral heads are lined outside the PTV. In the patient plan 11, the bladder gets a greater dose in 3DCRT plan due to optimization limitations in 3DCRT technique, and thus the plan cannot be improved further, as resultant would under dose PTV. Overdose to femoral heads in 3DCRT plans above 74 Gy is mainly due to use of opposed beams (AP/PA and Lateral beams) and inability to shape the beam according to the geometry of the tumor. It has been

confirmed in previous studies that four-field technique is suitable for prescribed dose of up to 74 Gy and further dose escalation delivers a dose above 50Gy to femoral necks, which is above RTOG dose constraint protocols (Hardcastle *et. al.,* 2010). In the use of 4 fields opposed beams technique, the two lateral incidence beams and transmitting beams of opposite lateral fields pass through the femoral heads. The 3DCRT techniques is safe to use in patient treatments when the prescribed dose to PTV is below 74Gy. However, if 3DCRT is used for the treatment with a dose above 74Gy, overdosing of femoral heads can be reduced with less weight to lateral fields or with more beams incorporated into the treatment plan.

The PTV coverage was found to be statistically high in SIB-IMRT plans compared to corresponding 3DCRT plans (Table 4, Figure 4). This may be due to the ability of the SIB-IMRT technique to deliver an escalated hypo-fractionated dose to planning target volume (i.e. 1.8 Gy, 2.2Gy and 2.5 Gy) in a single phase yielding a high conformity and a better PTV coverage. The previous studies also have confirmed that the SIB-IMRT technique is more conformal to the target and revenues a better coverage (Orlandi *et. al.,* 2010, Bansal *et. al.,* 2012 and Hernandez *et. al.,* 2013). 3DCRT delivers the same per fraction dose in 2-3 phases to planning target volume which requires optimization of several plans and therefore the dose is less conformal to the target.

The conformity index (CI) too is statistically superior in SIB-IMRT plans (Table 4). This may be due to capability of SIB-IMRT in delivering a conformal dose to target through escalated hypo-fractionated dose. It is confirmed in past studies, that SIB-IMRT has a higher dose conformity and homogeneity in the target volume (Khayaiwong, 2012). Mohan *et. al.,* (2000) has stated in his studies that when the majority of dose has already been delivered, it is difficult to achieve a high level of dose conformation with remaining fractions in the boost plans due to non-homogenous dose distribution. This can be the reason for 3DCRT technique showing a less dose conformity.

In the patient plans 14 and 18, there were overdoses to bladder in 3DCRT plans due to the pelvic lymph nodes been included in the treatment PTV (see figure 6). As the 3DCRT has its limitation in beam shaping, the bladder has received an overdose. It was also noted that in-patient 16 the bladder is overdosed in 3DCRT plan due to an anterior field being passed through the bladder. In the patient 15 and 21 the bladder is overdosed in both plans due to PTV including part of the bladder. D_{50} of the bladder outside PTV volume is 31 Gy and the volume of bladder overdose is about 2% of the total bladder volume, and as the dose and the volume (dose < 50 Gy and volume < 50 cm^3) were in the acceptance limit both treatment plans were approved for treatment. In the patient plan 21 about 22.2% of the total bladder volume was included as a part of PTV.

In the comparison of sequential IMRT and 3DCRT, the patient number 22 (see table 7) shows a very lower value for the D_{min} in 3DCRT plan. This is not considered as a cold spot as the volume is less than 1 mm. D_{mean} is statistically significant (p=0.037) in the two methods. This may be because many patient plans of the sequential-IMRT show better D_{mean} values compared to 3DCRT plans (see figure 6(c)).

The Homogeneity Index (HI) was statistically improved in sequential IMRT because optimization of several plans in sequential IMRT is more feasible than optimization of several plans in 3DCRT. 3DCRT has its limitations in controlling beam intensity modulation and shaping, whereas in IMRT, beam intensity can be modulated and diverse intensity doses can be delivered to the complex target volume to gain a uniform dose distribution (Shimizuguchi et al (2017)). However, HI values are comparable in the patient plan 27-31(see table 8).

In the patients 24,25,26 and 29 of 3DCRT plans, D_{50} doses to bladder was above the dose constraint (see table 8 and figure 7(a)). This is because the pelvic lymph nodes of the patient were involved in the PTV. In the patient 28, both methods have overdosed the bladder, as the bladder was included in the PTV due to Bladder metastasis.

As in 3DCRT method, the mean D_{50} to right and left femoral heads are approximately 20Gy higher than sequential IMRT and there is a statistically significant ($p=0.005$) in the D_{50} to femoral heads (see table 8) in the two methods. Higher dose in 3DCRT is due to lateral incidence beams and opposing lateral transmitting beams are passing through the femoral heads in 3DCRT plans.

5. CONCLUSIONS

Results of the study demonstrated that SIB- IMRT showed foremost PTV coverage by prescribed dose, dose conformity and dose homogeneity compared to 3DCRT, and it may be due to the ability to deliver increasing per fraction doses to booster volumes in a single treatment session. With the Sequential IMRT, better critical organ sparing was noted compared to 3DCRT. This may be due to a low dose per fraction to critical organs along with low per fraction (<2Gy) dose to target volume. Furthermore, the study also provides a proof-of-principle that 3DCRT is also reasonably good enough to use in treatment for low and intermediate risk groups of prostate cancer as PTV coverage is above 85% of prescribed dose and also as critical organ sparing was not inferior to standard IMRT at prescribed dose below 74Gy.

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7. REFERENCES

Abeygunesekera, A.M., Wijayarathna, S.N., Desilva, K., Upayasearum, G., Suvendran, S., & Weerasinge, S. (2015). Clinicopatholoical characteristics and primary treatment of prostate cancer in urology unit of Sri Lanka. *Cancer research and therapeutics.* 11(4), pp. 780-785.

Arno, J. M., and John, C. R. (2005). Intensity Modulated Radiation Therapy: A Clinical Perspective John Scott Company; ISBN-10:1550092464

Arsenijevic, T, Stankovic, K.D., Acimovic, M., & Jelic, L.R., (2011). Radiotherapy in Prostate Cancer, Prostate Cancer – Diagnostic and Therapeutic Advances *IntechOpen*, pp.169-194.

Bansal, A, Kapoor, A, Singh, S.K., Kumar, N, Oinam A.S, & Sharma C.S. (2012). Dosimetric comparison ofstandard three-dimensional conformal radiotherapy followed by intensity-modulated radiotherapy boost schedule (sequential IMRT plan) with simultaneous integrated boost {IMRT (SIB IMRT) treatment plan in patients with localized carcinoma prostate. *Indian Journal of Urology*, 28(3), pp. 300-306.

Bauman, G. (2008). Prostate Cancer Genitourinary Practice Guideline London: London health science center, p. 22.

Brenner, D.J. (2000). Toward optimal external-beam fractionation for prostate cancer, *International Journal of Radiation Oncology Biology Physics*.48, pp. 315-316.

Chung, H. Polf, J., Badiyan, S., & Biagioli, M. (2017). Rectal dose to prostate cancer patients treated with proton therapy with or without rectal spacer. *Journal of Applied Clinical Medical Physics*, 18, pp. 32-39.

Cliford, C.K.S. (2005). Practical Essentials of Intensity Modulated Radiation Therapy (2nd Ed.). Philadelphia, Pa; London: Lippincott Williams Wilkins.

Edge, S, Byrd, D.R, Compton, C.C., Fritz, A.G., Greene, F., & Rotti, A. (2010). American Joint Committee on Cancer Staging Manual (7th Ed.). New York: Springer; pp. 457-464.

Greene, D.E., Mayadev, J.S., & Valicenti, R.K. (2012). Radiation treatment for patients with intermediate-risk prostate cancer, *Therapeutic Advances in Urology*, 4(3), pp. 113-124.

Hardcastle, N., Davies, A., Foo, K., Miller, A., & Metcalfe, P.E. (2010). Rectal dose reduction with IMRT for prostate radiotherapy. *Journal of Medical Imaging and Radiation Oncology.* 54, pp. 235-248.

Heidenreich, A., Bellmunt, J., Bolla, M., Joniau, S., Mason, M., Matveev, V., Mottet, N., Schmid, H.P., Vander, K., Wast, T., Wiegel, T., & Zattoni, F. (2011). EAU guidelines on prostate cancer. Part 1: screening, diagnosis and treatment of clinically localized prostate cancer. *European Urology*, 59, pp. 61-71.

Hernfandez, T.G, Gonzfalez, A.V., Peidro, J.P., Ferrando, J.V., Gonzfalez, L.B., Caba~nero, D.G., & Torrecilla, J.L. (2013). Radiobiological comparison of two radiotherapy treatment techniques for high-risk prostate cancer. *Reports of practical oncology and Radiotherapy*.18(5), pp. 265-271.

Ishikawa, Y., Kadoya, N., Matsushita, H., Sugawara, T., Kubozono., M. Umezawa,R., Ymamoto,T., Kozumi, M., Takeda, K., & Jingu, K. (2014). DoseVolume Constraints in Rectum in Patients with Prostate Cancer after 74-Gy in 3-Dimensional. Conformal Radiotherapy, *Journal of Radiology and Radiation Therapy*.2(2), pp. 1032.

Jackson, A., Skwarchuk, M.W., Zelefsky, M.J., Cowen, D.M., Venkatraman, E.S., Levegrun, S., Burman, C.M.,Kutcher, G.J., Fuks, Z., Liebel, S.A., & Ling, C.C. (2001). Late rectal bleeding after conformal radiotherapy of prostate cancer (II): Volume effects and dose-volume histograms. *Journal of Radiation Oncology, Biology, Physics.* 49, pp. 685-98.

Khan, F.M. (2003). The physics of radiation therapy (3rd Ed.). Philadelphia: Lippincott Williams and Wilkins.

Khan, F.M., & Potish, R.A. (1998). Treatment planning in radiation oncology. Baltimore: Williams and Wilkins; 435, p. 7.

Khayaiwong, P., Tungboonduangjit, P., Sivalee, S., Vipa, B., Sornjarod, O., Taweap, S., Puntiwa, O. (2012). Dosimetric Comparison between Simultaneous Integrated Boost and Sequential Intensity-Modulated Radiotherapy Techniques in Nasopharyngeal Carcinoma Thai Medical Physicist Society, Faculty of Allied Health Sciences Naresuan University, Bangkok (Thailand) 6, 77, 80, 122.

Mattes, M.D.,Lee, J.C., Elnaiem, S., Guirguis, A., Ikoro, N.C., & Ashamalla, H.(2014). A predictive model to guide management of the overlap region between target volume and organs at risk in prostate cancer volumetric modulated arc therapy. *Journal of Radiation Oncology.* 32(1), pp. 23-30.

Matthias, G., Jurgen, M., Kurt, B., Dirk, V., & Michael, F. (2006). Distinct effects of rectum delineation methods in 3D-conformal vs. IMRT treatment planning of prostate cancer. *The journal of Radiation Oncology*.1, p. 34.

Mundt, A.J., & Roeske, J.C. (2013). Intensity Modulated Radiation Therapy: A Clinical Perspective Reportof practical oncology and radiotherapy. 18(5), pp. 298-303.

Nichol, A.M., Warde, P., & Bristow, R.G. (2005). Optimal Treatment of Intermediate-Risk Prostate Carcinoma with Radiotherapy: *Clinical and translational issues Cancer.* 104(5). pp. 891-905.

Orlandi, E., Palazzi, M., Pignoli, E., Fallai, C., Giostra, A. & Olmi, P. (2010). Radiobiological basis and clinical results of the simultaneous integrated boost (SIB) in intensity modulated radiotherapy (IMRT) for head and neck cancer. *Critical Reviews in Oncology/Hematolology*. 73(2), 111, p. 25.

Palma, D., Vollans, E., James, K., Nakano, S., Moiseenko, V., Shafer, R., McKenzie, M., Morris, J., & Otto,K. (2008). Volumeteric modulated arc therapy for delivery of prostate radiotherapy: comparisonwith intensity modulated radiotherapy and three dimensional conformal radiotherapy. *International journal of Radiation Oncology Biology and Physics.* 72(4), pp. 996-1001.

Raspall, R.F., Inoriza, J.M., Serrano, A.R, Sanz, C.A., et.al (2013). Late rectal and bladder toxicity following radiation therapy for prostate cancer: Predictive factors and treatment results Report of practical oncology and radiotherapy. 18(5), pp. 298,303.

Salimi, M., TakAbi, K.S., Nedaie, H.A. (2017). Assessment and Comparison of Homogeneity and Conformity Indexes in Step-and-Shoot and Compensator-Based Intensity Modulated Radiation Therapy (IMRT) and Three-Dimensional Conformal Radiation Therapy (3D CRT) in Prostate Cancer. *Journal of Medical Signals and Sensors*. 7(2), pp. 102-107.

Serrano, N.A, Kalman, N.S., Anscher, M.S. (2017). Reducing rectal injury in men receiving prostate cancerradiation therapy current perspectives. 9, 339-p. 350.

Sharyan, H.A., Allehyani, S.H., Tolba, A.R. (2015). Dosimetric Comparison of 3DCRT Versus Rapid Arc in Terms of Iso-dose Distribution, Dose Volume Histogram (DVH) and Dosimetric Results for the PTV and Critical Organs for Glioblastoma (GBM). *American Journal of Medicine and Medical Sciences*. 5(5), 208-219.

Shimizuguchi, T., Nihei, K., Okano, T., Machitori, Y., Ito, K., & Karasawa, K. (2017). A comparison of clinical outcomes between three dimensional conformal radiotherapy and intensity modulated radiotherapy for prostate cancer. *International Journal of clinical Oncology*. 22(2), pp. 373-379.

Storey, M., Pollack, A., Zagars, G., Smith, L., Antolak, J., & Rosen, I. (2000). Complications from radiotherapy dose escalation in prostate cancer: Preliminary results of a randomized trial. *Journal of Radiation Oncology, Biology, Physics.* 48, pp. 635-642.

Taylor, A. & Powell, M. E. B. (2004). Intensity-modulated radiotherapy| what is it?. *The journal of Cancer Imaging*.4(2), pp. 68-73.

Webb, S., & Nahum, A.E. (1993). A model for calculating tumour control probability in radiotherapy including the effects of inhomogeneous distributions of dose and clonogenic cell density. *Physics in Medicine and Biology. 38*, pp. 653-566.

Zelefsky, M.J., Chan, H., Hunt, M. et al (2006). Long-Term Outcome of High Dose Intensity Modulated Radiation Therapy for Patients with Clinically Localized Prostate Cancer. *The journal of urology.*176, pp. 1415-1419.

Zelefsky, M.J., Fuks, Z., Happersett, L., Lee, H.J., Ling, C.C., Burman, C.M., Hunt, M., Wolfe, T., Venkatraman, E.S., Jackson, A., Skwarchuk, M., & Leibel, S,A. (2000). Clinical experience with intensity modulated radiation therapy (IMRT) in prostate cancer. *Journal of Radiology and Radiation therapy.* 55,pp. 241-249.

Zelefsky, M.J., Fuks, Z., Hunt, M., Lee, H.J., Lombardi, D., Ling, C.C., Reuter, V.E., Venkatraman, E.S. & Leibel,S.A. (2001). High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer. *The journal of urology*. 166, pp. 876-881.

Zelefsky, M.J., Levin, E.J., Hunt, M., Yamada, Y., Shippy, A.M., Jackson, A. & Amols, H.I. (2008). Incidence of late rectal and urinary toxicities after three dimensional conformal radiotherapy and intensity modulated radiotherapy for localized prostate cancer. *International Journal of Radiation Oncology, Biology, Physics*. 70(4), pp. 1124-1129

Zhu, S.Y., Mizowaki, T., Nagata, Y., & Takayama, K. (2005). Comparison of three-radiotherapy treatment planning protocols of definitive external-beam radiation for localized prostate cancer, *International Journal Clinical Oncology*. 10, pp. 398-404.