Dosimetric Analysis of Patients Receiving Radiotherapy with VMAT Technique in Localized Prostate Cancer and Its Correlation with Side Effects

Sıtkı Utku Akay (✉ suakay91@hotmail.com)

Marmara Üniversitesi Tıp Fakültesi <https://orcid.org/0000-0001-8523-4858>

İlknur Alsan Çetin

Marmara Üniversitesi Tıp Fakültesi

Gülnoz Nural Bekiroğlu

Marmara Üniversitesi Tıp Fakültesi

Research

Keywords: Prostate cancer, side effect, radiotherapy

Posted Date: August 23rd, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-812311/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Aim: It is aimed whether there is a relationship between dosimetric data of localized prostate cancer patients who have been treated with curative radiotherapy and gastrointestinal (GIS), genitourinary (GUS), anal and sexual side effects and whether there is a difference between dosimetric data and clinical findings between risk groups.

Method : Eighty-seven patients who received curative radiotherapy for localized prostate cancer between 2014 - 2019 were included in the study. Dosimetrically; whether there was a relationship between V30, V40, V50, V60, V65, V70, V75 for rectum and bladder; D90 for the penile bulb, V72, V74, V76 for the bulbomembranous urethra, V30, V45, V53, Dmax for the anus and V45 (cc) for the intestine data and the side effects was analyzed. It was evaluated whether there was a relationship between testosterone values and sexual side effects. The Kolmogorov-Smirnov test, One Way ANOVA (F-test), and paired-sample T-test were used as statistical methods. For statistical significance, $p < 0.05$ was accepted.

Results : The mean age of the patients was 69 (50-86), the mean PSA (ng/dl) before RT was 25.1 (0.9-339), the median RT dose was 76 Gy (74-78 Gy), and the mean follow-up period was 38.2 months. PTVmax, PTVmean, PTVmin, bladder V40, bladder V50, rectum V30, rectum V40, rectum V50 and intestinal V45 (cc) were determined as dosimetric data showing differences between risk groups. A statistically significant relationship was found between rectum V30 ($p = 0.017$), V60 ($p = 0.019$), V65 ($p = 0.008$), V70 ($p = 0.007$) and V75 ($p = 0.034$) and chronic GIS side effects. G2 GIS side effects were observed in 4 patients (4.6%) in the entire patient group in the acute period. A statistically significant relationship was found between the patients receiving hormonotherapy ($p = 0.021$) and testosterone values at the last control ($p = < 0.001$) and chronic sexual side effects.

Conclusion: Attention should be paid to the rectum V30, V60, V65, V70, and V75 values to minimize the long-term GIS side effects of patients who have undergone RT. Testosterone level and HT status affect chronic sexual toxicity.

Introduction And Aim

Prostate cancer is one of the two most common cancers in men, and its incidence increases with advanced age (1, 2). In the treatment of localized prostate cancer, surgery, external radiotherapy (RT), hormonotherapy, brachytherapy can be applied alone or in combination according to the stage of the disease and the patient's preferences. Surgery and external radiotherapy are the most preferred treatment modalities in the definitive treatment of localized prostate cancer (2, 3). While urinary incontinence and erectile dysfunction (ED) are more common in radical prostatectomy than radiotherapy, intestinal side effects are more common in patients receiving radiotherapy; these data should be considered when deciding on the curative treatment modality (4–6). Treatment success and survival rates are high with curative radiotherapy in localized prostate cancer; therefore, monitoring long-term gastrointestinal (GIS), genitourinary (GUS), and sexual side effects is essential in determining patients' quality of life (7–9). In

prostate cancer radiotherapy, increased biochemical recurrence-free survival and progression-free survival have been detected with dose escalation; however, side effects related to radiotherapy may increase with dose escalation (9–11). Parallel to technological developments in external radiotherapy applications over time; it has become possible to protect normal tissues and organs better while dose escalation on the prostate (12, 13). In studies evaluating the side effects of localized prostate cancer patients after external radiotherapy; It has been found that there is a relationship between the doses received by the rectum and bladder and GIS, GUS symptoms, and anal sphincter dose and fecal incontinence (14–21). While the relationship between urethral dose and urinary symptoms has been detected for brachytherapy, the exact relationship has not been shown for external radiotherapy (22, 23). In studies evaluating ED after radiotherapy, it was found that there is a relationship between penile bulb dose and ED (24–27). This study aims to determine whether there is a relationship between dosimetric data and acute and chronic side effects in localized prostate cancer patients treated with image-guided radiotherapy (IGRT) and VMAT technique and to determine whether there is a difference between dosimetric data and clinical findings between risk groups.

Materials And Methods

The study is a single-center study. It was conducted retrospectively. Patients who received curative radiotherapy for localized prostate cancer in Marmara University Radiation Oncology Clinic between 2014–2019 and had a follow-up of at least six months after treatment were included in the study. Patients with lymph node positivity, distant metastasis, previous RT application, or surgery history due to prostate cancer were not included in the study.

Patients who underwent RT for localized prostate cancer in 2014 and later were divided into low, intermediate, and high-risk classes according to National Comprehensive Cancer Network (NCCN) risk classification. GIS and GUS side effects noted in the outpatient clinic follow-ups of the patients were graded according to the Radiation Therapy Oncology Group (RTOG) morbidity scale and sexual side effects according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 side effect scale. The side effects seen from the beginning of the treatment until three months after the end of the treatment were named acute, and the side effects seen six months and after the end of the treatment as chronic side effects. Differences between risk groups in terms of dosimetric data and acute and chronic side effects were analyzed.

Radiotherapy

Patients were simulated in the supine position, with an empty rectum and a full bladder. An intravenous contrast medium was administered in the high-risk patient group. A slice thickness of 3 mm was used for simulation CT scanning. CT was scanned to include the entire pelvis. Knee pads were used for immobilization in all patients.

Normal organs drawn in prostate cancer are the bladder, rectum, penile bulb, intestines, and femoral heads. In addition to these structures, the bulbomembranous urethra and anus were also contoured. All contours drawn were checked in sagittal and coronal sections, and necessary corrections were made. Dosimetric data of PTVmax, PTVmean, PTVmin, V30, V40, V50, V60, V65, V70, V75 for rectum; for bladder V40, V50, V65, V75; D90 for the penile bulb, V72, V74, V76 for the bulbomembranous urethra; V30, V45, V53, Dmax for the anal sphincter and V45 (cc) for the intestine were obtained. It was evaluated whether there was a significant difference in dosimetric parameters between the risk groups. Whether there is a relationship between dosimetric data of the bladder and urethra and GUS side effects, dosimetric data of the rectum and intestine with GIS side effects, dosimetric data of the anus and anal side effects, penile bulb dosimetric data, and testosterone values before and after RT and sexual side effects was evaluated.

In drawing the urethra, the study of Kataria on urethral contouring in patients undergoing prostate cancer radiotherapy was used. Contours were made by fusion with MRI, which are pelvic MR images. In patients without MRI images, the urethral contour was obtained by drawing the urethra in the prostatic and penile parts where the urethra could be detected, and then continuing this drawing towards the upper and lower sections, taking into account the urethral anatomy and the studies on the urethra. Then, dosimetric data of the contoured bulbomembranous urethra were obtained.

In target volume contouring, the prostate was contoured as GTV in the low-risk patient group. The prostate was contoured as GTV and the seminal vesicle as CTV-tumor in the intermediate-risk patient group. In the high-risk patient group, the prostate was contoured as GTV and the seminal vesicle as CTV-tumor. The lymph node regions of patients with a risk of lymph node involvement > 15% in the Roach formula were also included in the treatment area. Obturator, external iliac, internal iliac, presacral, and distal main iliac lymph node areas were contoured as CTV-lymph nodes in patients receiving treatment for the lymph node. PTV was created by giving a margin of 0.5 cm to the area adjacent to the rectum posterior to the GTV and CTV tumor structures and 1 cm in all other directions. In the high-risk patient group, a PTV-lymph node was created by giving a margin of 0.7 cm in all directions to the CTV-lymph node.

One of the dose schemes of 74 Gy / 37 fraction and 76 Gy / 38 fraction was administered to the low-risk group patients as the radiotherapy dose. Intermediate-risk patients were administered either a 76 Gy / 38 fraction or a 78 Gy / 39 fraction dose scheme. A dose of 54 Gy / 27 fraction was defined for the seminal vesicle. High-risk patients received 78 Gy / 37 fraction. A dose of 54 Gy / 28 fraction to the seminal vesicle and a 46 Gy / 28 fraction to the lymph node area was defined.

All patients were planned with the VMAT technique. Simultaneous integrated boost (SIB) technique was applied in the high-risk patient group. In the plan evaluation, attention was paid to the dose-volume data received by normal organs and the dose limits published by The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) group, which indicates the estimated risk of toxicity due to radiotherapy. All patients were treated with IGRT. For IGRT, daily cone-beam CT (CBCT) was used.

Follow-up

All patients were followed up at weekly controls during radiotherapy, side effects were noted during these controls, and necessary treatments were applied. Before and after the treatment, total PSA and total testosterone values of all patients were observed. Patients were invited to follow-up visits every three months until two years after the end of treatment, every six months for 2–5 years, and annual controls after five years. In the follow-up after RT, the side effects of the patients were noted, graded according to RTOG and CTCAE v2.0 scale, and total PSA and total testosterone examinations were observed.

Statistical Analysis

A normal distribution test of dosimetric data, which are continuous random variables, was performed with the Kolmogorov-Smirnov test as a statistical method. One-Way ANOVA (F-test) test was used in dosimetric measurement mean comparisons of risk groups and analyzing whether there was a relationship between dosimetric data and side effects. If statistical significance was obtained as a result of the F test, to determine which group mean was different from the other, Tukey HSD multiple comparison test was used when the variances of the risk groups were equal, and Tamhane's T2 multiple comparison test was used when the variances were not equal. The paired-sample t-test was used to determine whether there was a relationship between chronic sexual side effects and hormonotherapy, testosterone level, and comorbidity. A Chi-square test was used to compare acute and chronic side effects between groups. For statistical significance, $p < 0.05$ was accepted. Analyzes were performed with SPSS 22.0.

Results

A total of 87 patients, including 27 low-risk, 30 intermediate-risk, and 30 high-risk prostate cancer patients, were analyzed. The mean age of the patients was 69 (50–86), 67 in the low-risk group, 70 in the intermediate-risk group, and 71 in the high-risk group. ADT was applied to 5 patients (18.5%) in the low-risk group, and the duration of ADT was three months in all of these patients. In these patients, HT was applied neoadjuvant to reduce prostate volume before RT. ADT was applied to all patients in the intermediate and high-risk patient groups. It was applied as six months for the medium-risk patient group and a median of 43 months (15–72) for the high-risk patient group. The median RT dose was 76 Gy (74–78 Gy). The median RT dose was 76 Gy in the low and intermediate-risk group, while it was 78 Gy in the high-risk group. The mean follow-up period was 38.2 (6–66) months. Patient and treatment characteristics are shown in Table 1. The means of the measured dosimetric data in all patient groups and low, intermediate, and high-risk groups are shown in Table 2. It was found that the dosimetric data evaluated showed normal distribution. Dosimetric data showing significant differences between risk groups are shown in Table 3. It was analyzed whether there is a relationship between dosimetric data and acute and chronic side effects. As a result of the analysis, a significant relationship was found between rectum V30 ($p = 0.017$), V60 ($p = 0.019$), V65 ($p = 0.008$), V70 ($p = 0.007$) and V75 ($p = 0.034$) and chronic GIS side effects (Table 4).

Table 1
Patient and treatment characteristics

	All patients	Low risk	Intermediate risk	High risk
Number of patients	87	27	30	30
Follow-up	38,2 months (6–66)	31,7 months (6–63)	36 months (7–66)	46,2 months (14–62)
Age	69(50–86)	67(53–79)	70(58–77)	71(50–86)
PSA	25,1(0,9-339)	5,5(0,9–9,2)	10,7(3,4–18,4)	57,3(5-339)
Comorbidity is present	53(%60,9)	18(%66,7)	17(%56,7)	18(%60)
Duration of ADT	17,2 months (0–72)	0,5 months (0–3)	6 months	43,5 months (15–72)
RT (median)	76 Gy (74–78)	76 Gy (74–76)	76 Gy (76–78)	78 Gy

Table 2
Mean and standard deviation values of dosimetric data

		All patients	Low risk	Intermediate risk	High risk
PTV(Gy)	Dmean	78,9 ± 1,1	78,5 ± 0,7	78 ± 0,6	80,1 ± 0,4
	Dmax	82,7 ± 1,3	82,9 ± 0,7	81,4 ± 0,9	83,8 ± 0,9
	Dmin	67,2 ± 3,8	67,4 ± 3,5	65,6 ± 3,9	68,5 ± 3,5
Bladder (%)	V40	33,6 ± 12,7	24,2 ± 12	30,6 ± 8,4	45 ± 7,4
	V50	23,4 ± 9,1	18,9 ± 9,9	22,6 ± 6,8	28,2 ± 8,5
	V60	16,3 ± 7,2	14,6 ± 7,8	16,1 ± 5,9	18 ± 7,6
	V65	13,8 ± 6,3	12,8 ± 6,9	13,6 ± 5,2	14,7 ± 6,9
	V70	11,7 ± 5,5	11 ± 5,8	11,7 ± 4,6	12,3 ± 6,1
	V75	9,3 ± 4,5	8,8 ± 4,4	9,3 ± 3,9	9,8 ± 5,1
Rectum(%)	V30	50,6 ± 16	38,6 ± 11,4	47,1 ± 9,5	64,8 ± 14,1
	V40	36,9 ± 11,6	29,7 ± 9,2	34,4 ± 6,9	45,9 ± 11,8
	V50	25,3 ± 7,6	22,8 ± 7,7	24,9 ± 6,9	27,8 ± 7,8
	V60	17 ± 6,1	17,1 ± 6	17 ± 6,1	17 ± 6,3
	V65	13,8 ± 5,1	14,1 ± 4,4	13,9 ± 5,4	13,5 ± 5,5
	V70	10,8 ± 4,1	11,1 ± 3,3	10,9 ± 4,6	10,5 ± 4,4
	V75	7,4 ± 3,3	7,4 ± 2,8	7,4 ± 3,8	7,5 ± 3,4
Penile bulb(Gy)	D90	31,5 ± 18,1	28,1 ± 14,1	31,7 ± 20,7	34,5 ± 18,5
Urethra (%)	V72	56,1 ± 10,9	58,9 ± 9,7	54,3 ± 12,1	55,5 ± 10,3
	V74	53,3 ± 10,8	56,2 ± 9,8	51,2 ± 11,9	52,7 ± 10,2
	V76	49,5 ± 10,8	52,6 ± 9,6	46,9 ± 12,3	49,3 ± 10
Anus (%)	V30	5,4 ± 16,8	9,7 ± 24,2	3,9 ± 11,8	3,1 ± 12,4
	V45	1,4 ± 9,3	4,1 ± 16,4	0,4 ± 1,7	0,1 ± 0,5
	V53	0,9 ± 7,9	3,1 ± 14,2	0 ± 0,2	0 ± 0
	Dmax(Gy)	18,5 ± 16,7	21,1 ± 20,6	17,9 ± 16	16,8 ± 13,6
Intestine (cc)	V45	23,7 ± 44,7	1,7 ± 8,6	1,2 ± 4,2	65,9 ± 55

Table 3
Dosimetric data showing significant difference
between risk groups

Dosimetric data		p-value
PTVmean	Low-Medium	0,018
	Low-High	< 0,0001
	Medium-High	< 0,0001
PTVmin	Low-Medium	0,189
	Low-High	0,463
	Medium-High	0,009
PTVmax	Low-Medium	< 0,0001
	Low-High	0,001
	Medium-High	< 0,0001
Bladder V40	Low-Medium	0,033
	Low-High	< 0,0001
	Medium-High	< 0,0001
Bladder V50	Low-Medium	0,241
	Low-High	< 0,0001
	Medium-High	0,031
Rectum V30	Low-Medium	0,023
	Low-High	< 0,0001
	Medium-High	< 0,0001
Rectum V40	Low-Medium	0,159
	Low-High	< 0,0001
	Medium-High	< 0,0001
Rectum V50	Low-Medium	0,531
	Low-High	0,035
	Medium-High	0,301
Intestine V45	Low-Medium	0,998
	Low-High	< 0,0001

Dosimetric data	p-value
Medium-High	< 0,0001

Table 4
P-values of rectum V30, 60, 65, 70 and 75 and chronic GIS side effects relationship

Dosimetric data	p-value	Side effects grade	p-value
Rectum V30 (%)	0,017	G0-G1	0,019
		G0-G2	0,527
		G1-G2	0,195
Rectum V60 (%)	0,019	G0-G1	0,737
		G0-G2	0,021
		G1-G2	0,077
Rectum V65 (%)	0,008	G0-G1	0,487
		G0-G2	0,013
		G1-G2	0,026
Rectum V70 (%)	0,007	G0-G1	0,421
		G0-G2	0,012
		G1-G2	0,02
Rectum V75 (%)	0,34	G0-G1	0,564
		G0-G2	0,05
		G1-G2	0,71

It was observed that the most common acute and chronic side effects in patients were GUS side effects. While no G3 acute side effect was observed, a chronic G3 side effect was observed as a GUS side effect in only one patient. Percentages in all patient groups and risk groups according to the degrees of acute GIS, GUS, anal side effects are shown in Fig. 1, and the percentages in all patient groups and risk groups according to the degrees of chronic GIS, GUS, anal side effects are shown in Fig. 2.

Of the 87 patients evaluated, 28 (32.2%) had erectile dysfunction before RT. These patients were excluded while evaluating chronic side effects. Of the remaining 59 patients, 36 (61%) had no sexual side effects, eight patients (13.5%) had G1, and 15 patients (25.4%) had G2 sexual side effects. No G3 sexual side effects were observed. While a statistically significant relationship was found between chronic sexual side effects and the testosterone value ($p = < 0.001$) at the last control and whether patients took HT or

not ($p = 0.021$), there was no relationship between the presence of comorbidity and chronic sexual side effects.

There was no significant difference between the low and intermediate-risk groups in terms of side effects. A significant difference was found between acute GUS ($p = 0.016$) and chronic anal ($p = 0.002$) side effects between low and high-risk groups. A significant difference was found between the intermediate and high-risk groups in terms of chronic anal ($p = 0.01$) side effects (Table 5).

Table 5
Side effects showing significant differences between risk groups

		Side effects grade			
Side effects	Risk group	G0	G1	G2	p-value
Acute GUS side effect	Low	7	9	11	0,016
	High	5	21	4	
Chronic anal side effect	Low	27	0	0	0,002
	High	21	9	0	
Chronic anal side effect	Intermediate	28	1	1	0,015
	High	21	9	0	

Discussion

The median follow-up period is 60 months (36–135 months) in the meta-analysis conducted by Ohrid, which includes 11835 patients who received definitive radiotherapy for prostate cancer; G2 GIS side effect was found to be 15%, GUS side effect 17%; G3 GIS side effects 2%, and GUS side effect 3%. In this meta-analysis, the median RT dose was 72 Gy, and studies using different RT techniques such as IMRT, 3DRT, and proton therapy were included in this study (9). In the meta-analysis conducted by Viani, which evaluates dose escalation in prostate cancer radiotherapy, studies involving different RT techniques are discussed; and it was concluded that by using IMRT and IGRT, morbidity due to radiotherapy could be reduced (10). In the long-term results of the RTOG 9406 study of 1084 patients investigating the results of dose escalation in the radiotherapy of prostate cancer, for the PTV dose of 78 Gy; $\geq$ G3 GIS side effect was detected as 9%, and GUS side effect was detected as 12%; the median follow-up time in this study was 6.1 years, and 3DRT was used as the RT technique (28). In Zhong's study of 127 patients with localized prostate cancer treated using IMRT, the median follow-up period was 4.8 years, and a reduction in acute, chronic $\geq$ G2 GIS and GUS side effects was shown with the use of IGRT. Daily CBCT was used as the IGRT technique in this study (29). Compliance with QUANTEC dose constraints by the protocols of our clinic, the sensitivity shown in the patient setup, daily CBCT, and IGRT have been influential in determining the rates of side effects lower than the literature data.

In a study conducted by Peeters, which examined the relationship between dosimetric data after RT applied to prostate cancer and GIS side effects, in a median follow-up of 44 months, for the PTV dose of 78, chronic $\geq$ G2 GIS side effect was determined as 26%, $\geq$ G3 GIS side effect 4% and the rate of fecal incontinence as 10% (14). Rectal bleeding is associated with rectal wall V55-65; in particular, V65 is the most associated dosimetric parameter with rectal bleeding. Fecal incontinence was found to be associated with anal dosimetric data (especially Dmean > 33 Gy), and an increase in stool frequency ($\geq$ 6 times) was found to be associated with anorectal V40. In Heemsbergen's study, bleeding, which is one of the side effects of late GIS, develops depending on the doses received by the rectum and fecal incontinence due to the doses received by the anus (15). In our study, the rate of anal side effects was found to be very low. These anal side effects were anal pain and/or pain-bleeding complaints after difficulty in defecation.

In the study conducted by Jackson, 586 patients were included, rectal bleeding ($\geq$ G2 side effect) was associated with V71 in the PTV 70.2 Gy group and with V77 in the PTV 75.6 Gy group (16). In the study of Fiorino, PTV was applied in the range of 70–78 Gy, and chronic $\geq$ G2 rectal bleeding is associated with rectum V50, V60, and V70, and it has been recommended to keep V50 below 60–65%, V60 below 45–50%, and V70 below 25–30% to reduce the risk of rectal bleeding (17). In Huang's study of 163 patients, PTV 74–78 Gy was applied, and as a result of the median 5-year follow-up, $\geq$ G2 late GIS side effect was found to be associated with rectum V60, V70, V75.6, and V78 values (18). In Vargas's study, 331 patients were analyzed, doses ranging from 70.2 to 79.2 Gy were administered to PTV, and chronic $\geq$ G2 rectal side effects were associated with rectum V50, V66, V66.6, V70, V72 values (19). In a study of 301 patients in which Kuban investigated the dose escalation results in prostate cancer radiotherapy, $\geq$ G2 rectal side effects were associated with dosimetric values in the rectum V40-V78 range (20). As in the study of Vargas, it was suggested to keep the rectum V70 below 25% to avoid $\geq$ G2 rectal side effects. In the study conducted by Suzuki and planned using IMRT on 82 patients, $\geq$ G1 rectal bleeding was associated with rectum V30, V40, V50, and V60 (21). As a result of our analysis, it is understood that the dosimetric parameters of the rectum V30, V60, V65, V70, and V75, which are associated with chronic GIS side effects, are compatible with the literature data. Among these dosimetric data, particular attention should be paid to rectum V65 and V70 values, which differ in G1 and G2 chronic GIS side effects.

A significant side effect that can develop after curative treatments for localized prostate cancer is erectile dysfunction. In Macdonald's study on patients who underwent brachytherapy, no relationship was found between penile bulb dosimetry and erectile dysfunction (24). In Roach's study, penile bulb Dmedian to be $\geq$ 52.5 was associated with erectile dysfunction (25). In Wielen's meta-analysis, it has been determined that the penile bulb has a negligible effect on achieving an erection. It has been stated that structures that have a role in the erection process, such as the neurovascular bundle, corpus cavernosum, and internal pudendal artery, should also be taken into account to preserve erectile function (26). In the study conducted by Yıldırım, penile bulb dose and testosterone level were found to be associated with sexual side effects, while taking HT was not found to be associated with sexual side effects (30). As a result of our analysis, no relationship was found between penile bulb D90 and ED, but a relationship was found

between the testosterone level found at the last control and whether the patients took HT or not and sexual side effects.

Conclusion

Our study found a low percentage of acute and chronic side effects in definitive radiotherapy of localized prostate cancer patients. The applied planning technique and the use of daily IGRT were influential in the emergence of these results. V30, V60, V65, V70, and V75 values of the rectum were associated with chronic GIS side effects. Attention should be paid especially to the rectum V65, V70 data to avoid $\geq$ G2 chronic rectal side effects. Testosterone level and HT status affect chronic sexual toxicity.

Abbreviations

RT

Radiotherapy

ED

Erectile Dysfunction

GIS

Gastrointestinal

GÜS

Genitourinary

CT

Computerized Tomography

IMRT

Intensity Modulated Radiotherapy

VMAT

Volumetric Arc Therapy

IGRT

Image Guided Radiotherapy

PSA

Prostate Specific Antigen

ADT

Androgen Deprivation Therapy

NCCN

National Comprehensive Cancer Network

3DRT

Three Dimension Radiotherapy

GTV

Gross Tumor Volume

CTV

Clinical Target Volume

PTV

Planning Target Volume

RTOG

Radiation Therapy Oncology Group

CTCAE

Common Terminology Criteria for Adverse Events

SIB

Simultaneous Integrated Boost

QUANTEC

Quantitative Analyses of Normal Tissue Effects in the Clinic

CBCT

Cone Beam Computerized Tomography

Declarations

1.Ethical Approval and Consent to Participate

The manuscript was conducted retrospectively with the ethics committee approval with the protocol number 09.2018.584. We would like to submit our manuscript as a original article in BMC Radiation Oncology, named “Dosimetric Analysis of Patients Receiving Radiotherapy with VMAT Technique in Localized Prostate Cancer and Its Correlation with Side Effects”. The submitted manuscript (including the text, tables, figures, graphs, images, and any other related content) is original and has not been submitted to another journal for publication, has not been published before in whole or in part.

2.Consent for Publication

I give my consent for the manuscript to be published in BMC Radiation Oncology, RAON-D-21-00486. The authors guarantee that the article does not infringe any persona' or property right of others and accept the responsibility of the content of this manuscript and all other legal responsibilities related to the manuscript.

3.Availability of Supporting Data

I understand that the text and any pictures or videos published in the article will be freely available on the internet and may be seen by the general public. The pictures, videos and text may also appear on other websites or in print, may be translated into other languages or used for commercial purposes.

4.Competing Interests

There are no conflicts of interest in connection with this paper.

5.Funding

There is no funding source for this manuscript.

6. Authors' Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

7. Acknowledgements

Thanks my family for all their support.

Thank you for your time and assistance.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Nov;68(6):394–424.
2. Mottet N, Bellmunt J, Bolla M, Briers E, Cumberbatch MG, De Santis M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: Screening, diagnosis, and local treatment with curative intent. *Eur Urol*. 2017 Apr; 71(4): 618–629.
3. Alsan Çetin I. Current approach in radiation therapy for prostate cancer. 2019; *Bull Urooncol* 2020; 19: 49–55.
4. Shrader-Bogen CL, Kjellberg JL, McPherson CP, Murray CL. Quality of life and treatment outcomes. prostate carcinoma patients' perspectives after prostatectomy or radiation therapy. 1997 May; 79(10): 1977–1986.
5. Lee WR, Hall MC, McQuellon RP, Case DL, McCullough DL. A prospective quality-of-life study in men with clinically localized prostate carcinoma treated with radical prostatectomy, external beam radiotherapy, or interstitial brachytherapy. *Int J Radiat Oncol Biol Phys*. 2001 Nov 1; 51(3): 614–23.
6. Litwin MS, Flanders SC, Pasta DJ, Stoddard ML, Lubeck DP, Henning JM. Sexual function and bother after radical prostatectomy or radiation for prostate cancer: multivariate quality-of-life analysis from CaPSURE. *Cancer of the Prostate Strategic Urologic Research Endeavor Urology*. 1999 Sep;54(3):503–8.
7. Borghede G, Hedelin H. Radiotherapy of localised prostate cancer. Analysis of late treatment complications. A prospective study. *Radiother Oncol*. 1997 May;43(2):139–46.
8. Koper PC, Jansen P, van Putten W, van O Marjolein, Wijnmaalen AJ, Lebesque JV, et al. Gastro-intestinal and genito-urinary morbidity after 3D conformal radiotherapy of prostate cancer: observations of a randomized trial. *Radiother Oncol*. 2004 Oct;73(1):1–9.
9. Ohri N, Dicker AP, Showalter TN. Late toxicity rates following definitive radiotherapy for prostate cancer. *Can J Urol*. 2012 Aug;19(4):6373–80.

10. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys.* 2009 Aug 1; 74(5): 1405–18.
11. Beckendorf V, Guerif S, Pris EL, Cosset JM, Bougnoux A, Chauvet B, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys.* 2011 Jul 15; 80(4): 1056–63.
12. Oh CE, Antes K, Darby M, Song S, Starkschall G. Comparison of 2D conventional, 3D conformal, and intensity-modulated treatment planning techniques for patients with prostate cancer with regard to target-dose homogeneity and dose to critical, uninvolved structures. *Med Dosim Winter.* 1999;24(4):255–63.
13. Jerezek-Fossa BA, Vavassori A, Fodor C, Santoro L, Zerini D, Cattani F, et al. Dose escalation for prostate cancer using the three-dimensional conformal dynamic arc technique: analysis of 542 consecutive patients. *Int J Radiat Oncol Biol Phys.* 2008 Jul 1; 71(3): 784–94.
14. Peeters STH, Lebesque JV, Heemsbergen WD, van Putten WLJ, Slot A, Dielwart MFH, et al. Localized volume effects for late rectal and anal toxicity after radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2006 Mar 15;64(4): 1151–61.
15. Heemsbergen WD, Hoogeman MS, Hart GAM, Lebesque JV, Koper PCM. Gastrointestinal toxicity and its relation to dose distributions in the anorectal region of prostate cancer patients treated with radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005 Mar 15; 61(4): 1011–8.
16. Jackson A, Skwarchuk MW, Zelefsky MJ, Cowen DM, Venkatraman ES, Levegrun S, et al. Late rectal bleeding after conformal radiotherapy of prostate cancer. II. Volume effects and dose-volume histograms. *Int J Radiat Oncol Biol Phys.* 2001 Mar 1; 49(3): 685–98.
17. Fiorino C, Sanguineti G, Cozzarini C, Fellin G, Foppiano F, Menegotti L, et al. Rectal dose-volume constraints in high-dose radiotherapy of localized prostate cancer. *Int J Radiat Oncol Biol Phys.* 2003 Nov 15; 57(4): 953–62.
18. Huang EH, Pollack A, Levy L, Starkschall G, Dong L, Rosen I, et al. Late rectal toxicity: dose-volume effects of conformal radiotherapy for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2002 Dec 1;54(5):1314-21.
19. Vargas C, Martinez A, Kestin LL, Yan D, Grills I, Brabbins DS, et al. Dose-volume analysis of predictors for chronic rectal toxicity after treatment of prostate cancer with adaptive image-guided radiotherapy. *Int J Radiat Oncol Biol Phys.* 2005 Aug 1;62(5): 1297 – 308.
20. Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys.* 2008 Jan 1; 70(1): 67–74.
21. Suzuki RK, Omura M, Takano S, Matsui K, Hongo H, Yamakabe W, et al. Clinical and dosimetric predictors of late rectal bleeding of prostate cancer after TomoTherapy intensity modulated radiation therapy. *J Med Radiat Sci.* 2017 Sep;64(3):172–9.

22. Earley JJ, Abdelbaky AM, Cunningham MJ, Chadwick E, Langley SEM, Laing RW. Correlation between prostate brachytherapy-related urethral stricture and peri-apical urethral dosimetry: a matched case-control study. *Radiother Oncol.* 2012 Aug;104(2):187–91.
23. Thomas C, Keyes M, Liu M, Moravan V. Segmental urethral dosimetry and urinary toxicity in patients with no urinary symptoms before permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys.* 2008 Oct 1; 72(2): 447–55.
24. Macdonald AG, Keyes M, Kruk A, Duncan G, Moravan V, Morris WJ. Predictive factors for erectile dysfunction in men with prostate cancer after brachytherapy: is dose to the penile bulb important? *Int J Radiat Oncol Biol Phys.* 2005 Sep 1; 63(1): 155–63.
25. Roach M, Winter K, Michalski JM, Cox JD, Purdy JA, Bosch W, et al. Penile bulb dose and impotence after three-dimensional conformal radiotherapy for prostate cancer on RTOG 9406: findings from a prospective, multi-institutional, phase I/II dose-escalation study. *Int J Radiat Oncol Biol Phys.* 2004 Dec;1(5):1351–6. 60).
26. Van der Wielen GJ, Mulhall JP, Incrocci L. Erectile dysfunction after radiotherapy for prostate cancer and radiation dose to the penile structures: a critical review. *Radiother Oncol.* 2007 Aug;84(2):107–13.
27. Mangar SA, Sydes MR, Tucker HL, Coffey J, Sohaib SA, Gianolini S, et al. Evaluating the relationship between erectile dysfunction and dose received by the penile bulb: using data from a randomised controlled trial of conformal radiotherapy in prostate cancer (MRC RT01, ISRCTN47772397). *Radiother Oncol.* 2006 Sep;80(3):355–62.
28. Michalski JM, Bae K, Roach M, Markoe AM, Sandler HM, Ryu J, et al. Long-term toxicity following 3D conformal radiation therapy for prostate cancer from the RTOG 9406 phase I/II dose escalation study. *Int J Radiat Oncol Biol Phys.* 2010 Jan 1; 76(1): 14–22.
29. Zhong Q, Gao H, Li G, Xiu X, Wu Q, Li M, et al. Significance of image guidance to clinical outcomes for localized prostate cancer. *Biomed Res Int.* 2014; 2014: 860639.
30. Yildirim HC, Ergen SA, Sedef E, Sahin M, Cavdar Karacam S, Senocak MS, et al. Erectile dysfunction in prostate cancer patients treated with intensity-modulated radiation therapy. *Indian J Cancer Jan-Mar.* 2020;57(1):70–5.