Original Article

Dosimetric analysis of patients receiving radiotherapy with VMAT technique in localized prostate cancer and its correlation with side effects

ABSTRACT

Aim: The aim was to study the relationship between dosimetric data of localized prostate cancer patients who have been treated with curative radiotherapy (RT) and gastrointestinal (GIS), genitourinary (GUS), anal and sexual side effects, and whether there was a difference between dosimetric data and clinical findings between risk groups.

Methods: Eighty-seven patients who received curative radiotherapy for localized prostate cancer between 2014 and 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 were analyzed. It was evaluated whether there was a relationship between testosterone values and sexual side effects. The Kolmogorov–Smirnov test, one-way analysis of variance (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 Prostat specific antigen (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 four patients (4.6%) in the entire patient group during the acute period. A statistically significant relationship was found between the patients receiving hormonotherapy ($P = 0.021$) and testosterone values at the last control ($P \leq 0.001$) 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 in patients who have undergone RT. Testosterone level and ADT status affect chronic sexual toxicity.

KEY WORDS: External radiotherapy, normal tissue toxicity, prostate cancer

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INTRODUCTION AND AIM

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

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increase with dose escalation in patients undergoing prostate cancer RT, the side effects related to RT can also increase.[9-11] It is now possible to protect normal tissues and organs better while escalating the dose to the prostate.[12,13] Studies that evaluated the side effects after external RT for localized prostate cancer that the dose received by the rectum and bladder was related to GIS and GUS symptoms and anal sphincter and fecal incontinence.[14-20] The relationship between the urethral dose and urinary symptoms has been determined for brachytherapy, but that for external RT is not well understood.[21,22] A relationship between the penile bulb dose and ED was reported by studies evaluating ED after RT.[23-26] This study aimed to determine the potential relationships between dosimetric data and acute and chronic side effects in localized prostate cancer patients treated with image-guided radiotherapy (IGRT) and volumetric arc therapy (VMAT). We also determined whether there is a difference between the dosimetric data and clinical findings according to risk groups.

MATERIALS AND METHODS

This was a single-center retrospective study. Patients who received curative RT for localized prostate cancer at the Marmara University Radiation Oncology Clinic between 2014 and 2019 and were followed up for at least 6 months after treatment were included in the study. Patients with positive lymph nodes, distant metastasis, previous RT applications, or a surgical history due to prostate cancer were not included in the study. Ethics committee approval was obtained with the protocol number 09.2018.584. It was obtained on 7th September 2018.

Patients undergoing RT for localized prostate cancer in 2014 were later divided into low-, intermediate-, and high-risk classes according to the National Comprehensive Cancer Network risk classification. The GIS and GUS side effects of the patients noted in the outpatient clinical follow-ups were graded according to the Radiation Therapy Oncology Group morbidity scale, and sexual side effects were graded according to the Common Terminology Criteria for Adverse Events v5.0 side effects scale. The side effects seen from the beginning of the treatment until 3 months after the end of treatment were called acute, and the side effects seen at 6 months and the end of the treatment were defined as chronic side effects. Differences in the dosimetric data and acute and chronic side effects among the risk groups were analyzed.

Radiotherapy

Patients were situated in the supine position, with an empty rectum and a full bladder. An intravenous contrast medium was administered to the high-risk patient group. A slice thickness of 3 mm was used to simulate the computed tomography (CT) scan. The CT scan included the entire pelvis.

The organs affected by prostate cancer are the bladder, rectum, penile bulb, intestines, and femoral heads. In addition, the bulbomembranous urethra and anus were contoured. All contours drawn were checked in sagittal and coronal sections, and necessary corrections were made. The dosimetric data of PTVmax, PTVmean, PTVmin, V30, V40, V50, V60, V65, V70, and V75 for the rectum; V40, V50, V65, and V75 for the bladder; D90 for the penile bulb, V72, V74, and V76 for the bulbomembranous urethra; V30, V45, V53; Dmax for the anal sphincter; and V45 (cc) for the intestines were obtained. Significant differences in the dosimetric parameters among the risk groups were evaluated. The relationships of the bladder and urethra dosimetric data with GUS side effects, the rectal and intestinal dosimetric data with GIS side effects, the anal dosimetric data with anal side effects, penile bulb dosimetric data with the testosterone levels before and after RT and with sexual side effects were evaluated.

Urethral contours were made by fusion with pelvic magnetic resonance images (MRIs). The urethral contour was obtained in patients without MRI images by drawing the urethra in the prostatic and penile parts where the urethra was detectable, and then continuing this drawing toward the upper and lower sections, considering the urethral anatomy and studies on the urethra. Then, dosimetric data of the contoured bulbomembranous urethra were obtained.

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

The dose schemes of 74 Gy/37 fractions and 76 Gy/38 fractions were administered to the low-risk patients as the RT dose. Intermediate-risk patients were administered either a 76 Gy/38 fraction or 78 Gy/39 fraction dose scheme. A dose scheme of 54 Gy/27 fractions was applied to the seminal vesicle. High-risk patients received 78 Gy/37 fractions. Doses of 54 Gy/28 fractions to the seminal vesicle and 46 Gy/28 fractions to the lymph node area were used.

The double arc Volumetric arc therapy (VMAT) technique was used for planning in all patients. The simultaneous integrated boost technique was applied in the high-risk patient group. In the planning evaluation, attention was paid to the dose–

volume data received by the normal organs and the dose limits published by The Quantitative Analysis of Normal Tissue Effects in the Clinic group, which indicates the estimated risk of toxicity due to RT. All patients were treated with IGRT. Daily cone-beam CT (CBCT) was used for IGRT.

Follow-up

All patients were followed up weekly during RT. Side effects were noted during these visits, and the necessary treatments were applied. The total prostate-specific antigen and total testosterone levels were determined before and after treatment in all patients. The patients were invited to follow-up visits every 3 months for 2 years, every 6 months for 2–5 years, and annually after 5 years. The side effects of the patients were noted at the follow-up visits after RT and graded according to the RTOG and CTCAE v2.0 scales, and the total prostate-specific antigen and total testosterone levels were determined.

Statistical analysis

The normality of the distribution of the dosimetric data, which are continuous random variables, was evaluated using the Kolmogorov–Smirnov test. One-way analysis of variance (F-test) was used to compare the dosimetric means of the risk groups and determine the potential relationships between the dosimetric data and side effects. If a difference was detected by the F-test, Tukey's HSD multiple comparison test was used when the variances of the risk groups were equal and Tamhane's T2 multiple comparison tests when the variances were unequal. The paired-sample *t*-test was used to determine the potential relationships of the chronic sexual side effects with hormonotherapy, testosterone level, and comorbidities. The Chi-square test was used to compare acute and chronic side effects between the groups. A P value < 0.05 was considered significant. Analyses were performed using the SPSS 22.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 87 patients with prostate cancer, comprising 27 low-risk, 30 intermediate-risk, and 30 high-risk patients, were analyzed. The mean age was 69 (50–86) years in all patients, 67 years in the low-risk group, 70 years in the intermediate-risk group, and 71 years in the high-risk group. Androgen deprivation therapy (ADT) was applied to five patients (18.5%) in the low-risk group, for a duration of 3 months. In these patients, ADT was applied as neoadjuvant therapy to reduce the prostate volume before RT. ADT was applied to all patients in the intermediate risk patients for 6 months and in the high-risk patients with a median of 43 (15–72) months, respectively. None of the patients received chemotherapy for prostate cancer. The median RT dose was 76 (74–78) Gy in all patients, 76 Gy in the low- and intermediate-risk groups, and 78 Gy in the high-risk group. The mean follow-up period was 38.2 (6–66) months. The patient and treatment characteristics are shown in Table 1. The means of the dosimetric data in all patients and the low-, intermediate-, and high-risk groups are shown in Table 2. The dosimetric data were normally distributed. The dosimetric data with significant differences among the risk groups are shown in Table 3. The relationships of the dosimetric data with acute and chronic side effects were assessed. As a result, we detected significant relationships of the rectal V30 ($P = 0.017$), V60 ($P = 0.019$), V65 ($P = 0.008$), V70 ($P = 0.007$), and V75 ($P = 0.034$) with chronic GIS side effects [Table 4].

GUS side effects were the most common acute and chronic side effects. While no G3 acute side effects were observed, chronic G3 side effects were observed in one patient. The rates of acute GIS, GUS, and anal side effects according to severity in all patients and in each risk group are shown in Figure 1, and the respective chronic side effects are shown in Figure 2.

Of the 87 patients evaluated, 28 (32.2%) had ED before RT. These patients were excluded from the evaluation of chronic side effects. Of the remaining 59 patients, 36 (61%) had no sexual side effects, whereas eight (13.5%) had grade (G) 1 and 15 (25.4%) G2 sexual side effects. No G3 sexual side effects were observed. A significant relationship was detected between chronic sexual side effects and the testosterone level ($P < 0.001$) at the last control and whether patients took ADT or not ($P = 0.021$). No relationship was detected between comorbidities and chronic sexual side effects.

No significant difference in side effects was observed between the low- and intermediate-risk groups. Significant differences were found in acute GUS ($P = 0.016$) and chronic anal ($P = 0.002$) side effects between the low- and high-risk groups. A significant difference in chronic anal ($P = 0.01$) side effects was found between the intermediate- and high-risk groups [Table 5].

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*
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
	Medium-High	<0,0001

A second primary cancer was detected in five patients (6%). The median time until the development of the second cancer was 18 (12–27) months. Four patients developed non-pelvic cancer (non-small cell lung cancer, small cell lung cancer, uveal melanoma, or gastric cancer), and one developed pelvic cancer (sigmoid colon cancer).

DISCUSSION

In the meta-analysis conducted by Ohri *et al.*, which included 11,835 patients who received definitive RT for prostate cancer, the incidence rates of G2 GIS side effects, G2 GUS side effects, G3 GIS side effects, and G3 GUS side effects were 15%, 17%, 2%, and 3%, respectively.[9] In a meta-analysis of studies using different RT techniques conducted by Viani *et al.*,[10] it was concluded that morbidities due to RT could be reduced using intensity-modulated RT (IMRT) and IGRT. G3 GIS side effects were detected in 9% and GUS side effects in 12% of 1,084 patients at a PTV dose of 78 Gy in the long-term results of the RTOG 9406 study investigating dose escalation in RT for prostate cancer.[27] A reduction in acute and chronic ≥ G2 GIS and GUS side effects was detected with the use of IGRT in the study of *et al*. of 127 patients with localized prostate cancer treated with IMRT. Daily CBCT was used as the IGRT technique in that study.[28] In our study, chronic GIS and GUS side effects were detected in 8% of cases. As planning techniques, daily CBCT and IGRT have been influential in reducing side effects.

Rectal bleeding (≥ G2) was associated with V71 in the PTV 70.2 Gy group and with V77 in the PTV 75.6 Gy group in a study conducted by Jackson *et al.*[15] that included 586 patients. In a study by Fiorino *et al.*,[16] PTV was applied in the range of 70–78 Gy, and chronic ≥ G2 rectal bleeding was associated with rectal V50, V60, and V70. A dose of 74–78 Gy to the PTV was applied by Huang *et al.*[17] in 163 patients, and late ≥ G2 GIS side effects were associated with rectal V60, V70, V75.6, and V78 values at the median 5-year follow-up. Vargas *et al.*[18] analyzed 331 patients receiving doses of 70.2–79.2 Gy to the PTV, and chronic ≥ G2 rectal side effects were associated with the rectal V50, V66, V66.6, V70,

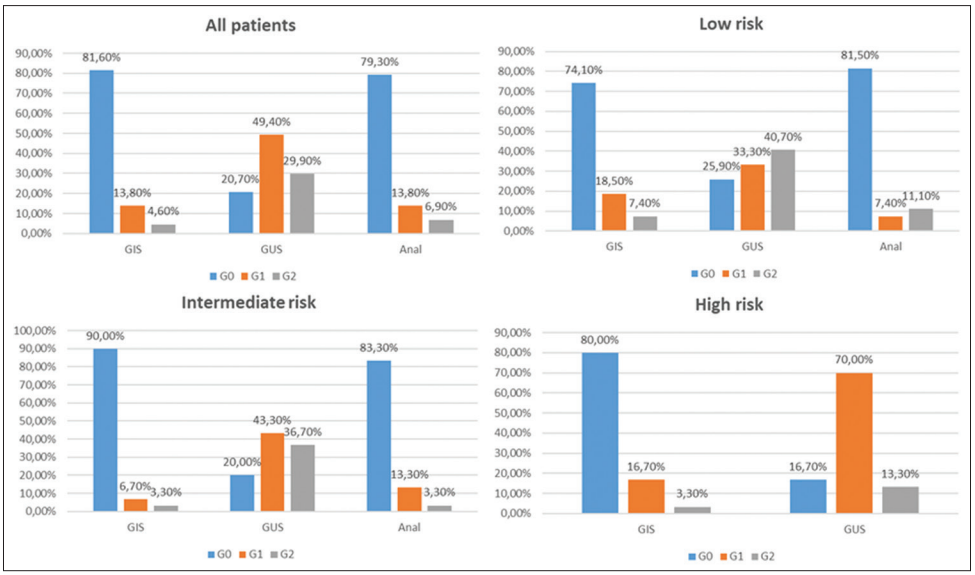

Figure 1: Percentages in all patient groups and risk groups according to the degrees of acute GIS, GUS, anal side effects

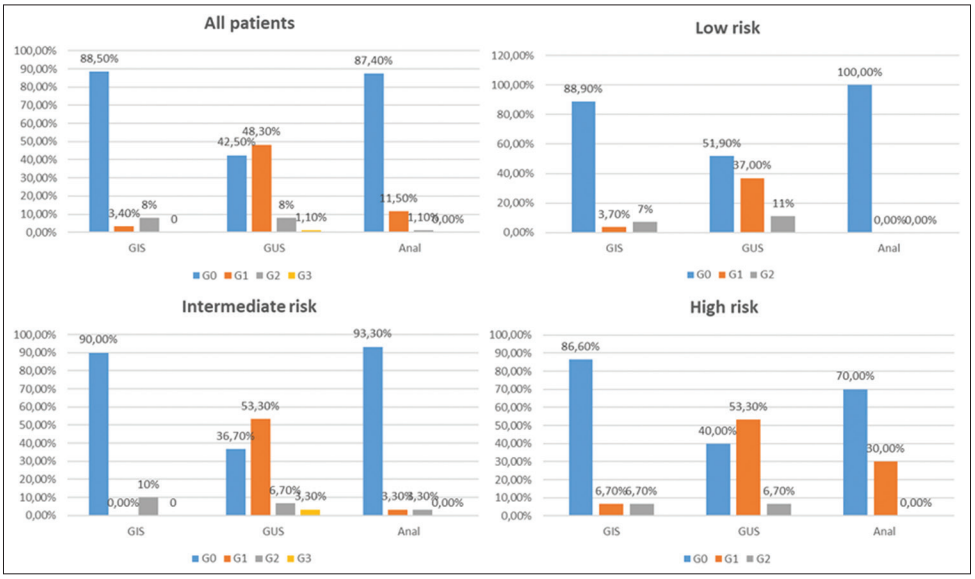

Figure 2: Percentages in all patient groups and risk groups according to the degrees of chronic GIS, GUS, anal side effects

Table 4: *P* values of rectum V30, 60, 65, 70, and 75 and chronic GIS side effect relationship

Dosimetric data	*P*	Side effects grade	*P*
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

and V72 values. Kuban *et al.*[19] investigated the RT dose escalation results in 301 prostate cancer patients, and the ≥ G2 rectal side effects were associated with the dosimetric values in the rectal V40–V78 range. As in the study of Vargas *et al.*, it was suggested to maintain the rectal V70 below 25% to avoid ≥ G2 rectal side effects. Suzuki *et al.*[20] used IMRT planning in 82 patients and found that ≥ G1 rectal bleeding was associated with the rectal V30, V40, V50, and V60 values. In our study, there were significant relationships of rectal V30 ($P = 0.017$), V60 ($P = 0.019$), V65 ($P = 0.008$), V70 ($P = 0.007$), and V75 ($P = 0.034$) with chronic GIS side effects. Close relationships were detected between rectal dosimetry and side effects.

ED is a significant side effect that can develop after curative treatment for localized prostate cancer. Macdonald *et al.*[23]

Table 5: Side effects showing significant differences between risk groups

Side effects	Risk group	Side effects grade			*P*
		G0	G1	G2	
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	

found no relationship between penile bulb dosimetry and ED among patients who underwent brachytherapy. Roach *et al*.[24] reported that a penile bulb Dmedian ≥52.5 was associated with ED. In a meta-analysis, Wielen *et al*.[25] reported that the penile bulb had a negligible effect on achieving an erection. It has been reported that the structures involved in the erection process, such as the neurovascular bundle, corpus cavernosum, and internal pudendal artery, should be considered to preserve erectile function. In a study by Yıldırım *et al*.,[29] the penile bulb dose and testosterone levels were associated with sexual side effects, whereas ADT was not. We found no relationship between the penile bulb D90 and ED, but a relationship was observed between the testosterone level at the last control and whether the patients took ADT or not, and sexual side effects.

According to the studies of Buwenge and Jahreiß,[30,31] VMAT and IMRT may increase the risk of secondary malignant neoplasms after RT for prostate cancer. In our study, secondary malignant neoplasms were detected in 6% of patients, but the number of patients and the follow-up period were insufficient to derive any conclusion. Bell *et al*.,[32]) showed that kv-CBCT had negligible effects on plan quality. In our study, kv-CBCT was used for IGRT.

CONCLUSION

We found a low rate of acute and chronic side effects during definitive RT for localized prostate cancer. The applied planning technique and the use of daily IGRT affected the results. The V30, V60, V65, V70, and V75 values of the rectum were associated with chronic GIS side effects. Attention should be paid to the rectal V65 and V70 values to avoid ≥ G2 chronic rectal side effects. The testosterone levels and ADT status affected chronic sexual side effects.

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Conflicts of interest
There are no conflicts of interest.

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;68:394-24.
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;71:618-29.
3. Alsan Çetin I. Current approach in radiation therapy for prostate cancer. 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. Cancer 1997;79:1977-86.
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;51:614-23.
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;54:503-8.
7. Borghede G, Hedelin H. Radiotherapy of localised prostate cancer. Analysis of late treatment complications. A prospective study. Radiother Oncol 1997;43:139-46.
8. Koper PC, Jansen P, van Putten W, van Os 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;73:1-9.
9. Ohri N, Dicker AP, Showalter TN. Late toxicity rates following definitive radiotherapy for prostate cancer. Can J Urol 2012;19:6373-80.
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;74:1405-18.
11. Beckendorf V, Guerif S, Prisé 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;80:1056-63.
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;24:255-63.
13. Jereczek-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;71:784-94.
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;64:1151-61.
15. 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;49:685-98.
16. 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;57:953-62.
17. 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;54:1314-21.
18. 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;62:1297-308.
19. 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;70:67-74.
20. 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;64:172-9.
21. 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;104:187-91.
22. 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;72:447-55.
23. 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;63:155-63.
24. 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;60:1351-6.
25. 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;84:107-13.
26. 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;80:355-62.
27. 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;76:14-22.
28. 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. doi: 10.1155/2014/860639.
29. 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 2020;57:70-5.
30. Buwenge M, Scirocco E, Deodato F, Macchia G, Ntreta M, Bisello S, *et al*. Radiotherapy of prostate cancer: Impact of treatment characteristics on the incidence of second tumors. BMC Cancer 2020;20:90.
31. Jahreiß MC, Aben KKH, Hoogeman MS, Dirkx MLP, de Vries KC, Incrocci L, *et al*. The risk of second primary cancers in prostate cancer survivors treated in the modern radiotherapy era. Front Oncol 2020;10:605119. doi: 10.3389/fonc. 2020.605119.
32. Bell K, Heitfeld M, Licht N, Rübe C, Dzierma Y. Influence of daily imaging on plan quality and normal tissue toxicity for prostate cancer radiotherapy. Radiat Oncol 2017;12:7.