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ORIGINAL ARTICLE

Image-guided radiation therapy produces lower acute and chronic gastrointestinal and genitourinary toxicity in prostate cancer patients

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Summary

Purpose: *This paper compares individual radiation therapy techniques used for prostate cancer and their benefits in clinical practice.*

Methods: *We retrospectively analyzed 921 patients with localized prostate tumors treated between 1997 and 2012. We divided the patients into four groups according to the selected treatment technique (conformal radiation therapy [3DCRT], intensity-modulated radiation therapy [IMRT], image-guided radiation therapy [IGRT], and volumetric-modulated arc therapy [VMAT]) and evaluated the incidence of acute and chronic gastrointestinal (GI) and genitourinary (GU) toxicity.*

Results: *The incidence of grade 2 or greater acute GU and GI toxicity was significantly higher among techniques other than IGRT (p<0.001). We found the same results in the case of grade 3 or greater acute GU toxicity (p<0.001). Grade 3 or higher acute GI toxicity occurred only in one patient treated by 3DCRT. Cumulative late GI toxicity of grade 2 or higher and grade 3 or higher was recorded over 3 years significantly more frequently among non-IGRT techniques as compared to IGRT (p<0.001). As regards GU toxicity, we found significantly higher incidence only for grade 2 or higher (p<0.001), not for grade 3 or higher. No occurrence of grade 4 toxicity was recorded. The greatest incidence of patients without acute and chronic GI/GU toxicity was recorded in connection with VMAT.*

Conclusions: *IGRT demonstrated a pronounced reduction in acute and chronic GU and GI toxicity as compared to non-IGRT techniques in the treatment of localized prostate cancer.*

Key words: *3DCRT, IGRT, IMRT, prostate, toxicity, VMAT*

Introduction

The introduction of computed tomography and the possibility to calculate spatial dosage have allowed the development of 3D conformal radiation therapy (3DCRT). With additional technological advancement, more state-of-the-art methods, such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) and volumetric-modulated arc therapy (VMAT), were gradually introduced into practice. The fundamental aim of this development was to increase the dose in the target volumes and at the same time minimize doses in organs at risk. In randomized studies, such increased dose has shown better clinical results; at the same time, however, it brings greater risk of toxicity in patients treated for prostate cancer [1-10].

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An alternative to these techniques is stereotactic radiation therapy using extreme hypofractionation, proton therapy and brachytherapy. Stereotactic radiation therapy is associated with higher urological toxicity as compared to IMRT but equivalent gastrointestinal morbidity [11]. In comparison with IMRT, proton therapy reduces the risk of urinary toxicity and erectile dysfunction. On the other hand, it increases the risk of hemorrhage and proctitis and may have higher treatment costs [12-15]. Brachytherapy, either in isolation or in combination with external beam radiation, offers a highly conformal technique with the possibility to escalate the dose. Dosimetric studies have demonstrated better preservation of healthy tissues in comparison with VMAT [16,17]. Disadvantages of this technique include its invasiveness, technical equipment demands, and steep learning curve [18,19].

The aim of this retrospective analysis was to compare the incidences of acute and chronic gastrointestinal (GI) and genitourinary (GU) toxicity when using 3DCRT, IMRT, IGRT and VMAT techniques.

Methods

We conducted a retrospective analysis of 921 patients treated between 1997 and 2012 by means of curative radiation therapy for localized prostate cancer. Of those, 522 patients were treated with hormonal therapy and 187 patients underwent transurethral resection of the prostate/transvesical prostatectomy (TURP/TVPE). The patients were divided into four groups according to the chosen radiation technique: 305 were treated by 3DCRT, 274 by IMRT, 195 by IGRT, and 147 by VMAT.

During treatment the patient lays on his back, with the upper limbs placed on the chest and the lower limbs immobilized using a cushion placed under the knees and lower legs (VacLock/Dual Leg Positioner Cushion, MEDTEC).

In all groups, the clinical target volume covered the prostate and base of the seminal vesicles. In case of impairment of the seminal vesicles, the volume was extended to cover them fully. The planning target volume (PTV) encompassed the clinical target volume (CTV) + a 10 mm isotropic margin in the 3DCRT and IMRT groups, 6-8 mm margin in the IGRT group, and 6 mm margin in the VMAT group. The contouring of organs at risk was identical for all patients. The urinary bladder was delineated in optimally filled, the rectum was contoured 10 mm above and below the PTV, and the heads of both hip joints were also delineated. Planning for 3DCRT radiation therapy was executed in a 3D planning system (CadPlan 2.7.9., Varian) using four coplanar fields (30°, 90°, 270°, 330°) with photon energy of 6 MeV (Clinac 600 C, Varian). The prescribed dose was 70-74 Gy, with 2 Gy per fraction. The patient's positioning was verified once per week using electronic portal imaging (PortalVision 3.8, Varian).

Planning for IMRT used the inverse planning method (CadPlan R.3.6.3. with module Helios/Eclipse 7.3, Varian) with five coplanar fields (45°, 100°, 180°, 260°, 315°). Radiation beams were modulated using a multileaf collimator (MLC) by the sliding window method with a photon energy of 6 or 18 MeV. The prescribed dose was 74-82 Gy (82 Gy in the case of simultaneous integrated boost on the gross tumor volume), with 2 Gy per fraction. The patient's positioning was verified by the same method as for the 3DCRT group.

IGRT planning for the first 200 patients treated followed an adaptive protocol similar to that for IMRT, except CTV-PTV margin. The margin used was de¬scribed earlier and Figure 1 shows the adaptive protocol [20]. For the remaining 74 patients, the margin was set concentrically at 6 mm, and the position was verified and corrected online on a daily basis by means of CBCT. The prescribe dose for IGRT was 78 Gy, with 2 Gy per fraction.

Planning for VMAT was done following the inverse planning method using RapidArc technology with 2-3 rotations at photon energy of 6 or 18 MeV (Clinac 2100,

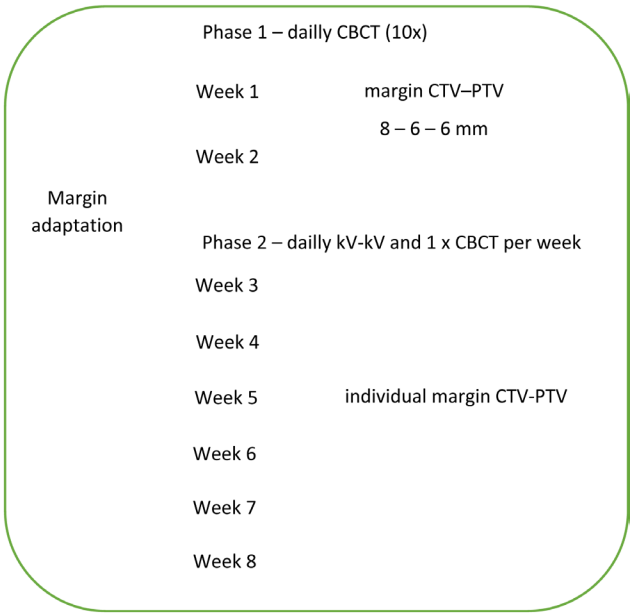

Figure 1. Adaptive protocol. In the first phase of therapy, the margin was set at 8 mm, 6 mm and 6 mm along the anteroposterior, craniocaudal and laterolateral axes, respectively. After two weeks of treatment with online setting using cone beam computed tomography (CBCT) and with monitoring of the prostate position in relation to the skeleton, the first 10 fractions were evaluated and the average position of the isocenter in relation to the pelvis (systematic error Σ) and the measurement distribution around the average position (random error σ) were determined. The radiation plan for the second phase of radiation therapy was adjusted, on the one hand, by shifting the isocenter to its average position and, on the other, by setting the CTV-PTV margin according to the size of the random error. The settings were verified in the second treatment phase on a daily basis using the kV-kV method of registering the pelvis, with a weekly check by CBCT.

Varian). The prescribed dose was 78-84.8 Gy (84.8 Gy in the case of simultaneous integrated boost on the gross tumor volume), with 2-2.12 Gy per fraction. The patient's positioning was verified and subsequently corrected each day online using CBCT (OBI 1.3, Varian Medical Systems).

Table 1 presents the dose constraints for the target volumes and organs at risk.

We evaluated the incidence of acute and chronic GI and GU toxicity. Acute toxicity was assessed once per week during radiation treatment and 3 months after completing therapy. Chronic toxicity was assessed 6 months after completing therapy and every 6 months thereafter. We employed the EORTC/RTOG scoring system to evaluate acute toxicity and the Fox Chase (FC) modification of RTOG and the Late Effects Normal Tissue Task Force (LENT) scoring system to evaluate chronic toxicity. The median monitoring period was 48.1 months (6.5-87.8) for 3DCRT, 60 months (7.7-110) for IMRT, 31.7 months (7.1-49.7) for IGRT, and 30.1 months (10.6-45.8) for VMAT.

Statistics

Standard descriptive statistics were used to describe the data: median with 5th and 95th percentile range or arithmetic mean with 95% confidence interval for continuous variables and relative and absolute frequencies for categorical variables. Given the non-normal data distribution, the nonparametric Kruskal-Wallis ANOVA test for comparing multiple groups was selected to test the hypothesis. The ML chi-square test was used to evaluate individual groups. In this case, normal distribution was verified by the Shapiro-Wilcox test and histogram. Based

Table 1. Dose constraints for the target volumes and organs at risk

	IMRT	*IGRT*	*VMAT*
PTV	95% of the prescribed dose must cover at least 95% of the PTV	95% of the prescribed dose must cover at least 95% of the PTV	95% of the prescribed dose must cover at least 95% of the PTV
Bladder	70 Gy - ≤ 30% of the bladder	75 Gy - ≤ 10 cm^3	75 Gy - ≤ 10 cm^3
		70 Gy - ≤ 20 cm^3	70 Gy - ≤ 20 cm^3
		50 Gy - ≤ 35 cm^3	50 Gy - ≤ 35 cm^3
Rectum	75 Gy - ≤ 15% rectum volume (or 15 cm^3)	75 Gy - ≤ 5%	75 Gy - ≤ 5%
	70 Gy - ≤ 25% rectum volume	70 Gy - ≤ 20 %	70 Gy - ≤ 20 %
		50 Gy - ≤ 50 %	50 Gy - ≤ 50 %

Table 2. Basic description of sample data set: dose

	3DCRT[1] (N=305)	*IMRT[1] (N=274)*	*IGRT[1] (N=195)*	*VMAT[1] (N=147)*
Age (years)	70.0	71.0	69.6	70.0
	(58.0; 77.0)	(57.4; 77.6)	(59.1; 78.5)	(59.5; 79.1)
Hormone therapy, n (%)				
Neoadjuvant	97 (31.8)	128 (46.7)	99 (50.8)	90 (61.2)
Adjuvant	26 (8.5)	17 (6.2)	45 (23.1)	20 (13.6)
None	182 (59.7)	129 (47.1)	51 (26.1)	37 (25.2)
TURP/TVPE, n (%)				
No	211 (69.2)	227 (82.8)	173 (87.4)	138 (86.8)
Yes	94 (30.8)	47 (17.2)	25 (12.6)	21 (13.2)
Dose (Gy) , n (%)				
66	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.6)
70	217 (71.1)	0 (0.0)	4 (2.0)	2 (1.3)
72	0 (0.0)	4 (1.5)	0 (0.0)	0 (0.0)
73	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
74	88 (28.9)	89 (32.5)	6 (3.0)	13 (8.1)
76	0 (0.0)	0 (0.0)	14 (7.1)	11 (6.9)
78	0 (0.0)	127 (46.4)	173 (87.4)	122 (76.3)
82	0 (0.0)	53 (19.3)	0 (0.0)	0 (0.0)
84.6-84.8	0 (0.0)	0 (0.0)	0 (0.0)	11 (6.9)
Follow-up	48.1	60	31.7	30.1
(median, months)	(6.5; 87.8)	(7.7; 110)	(7.1; 49.7)	(10.6; 45.8)

[1]Median shown with 5th and 95th percentile range (in parentheses) for continuous variables. Absolute and relative frequencies of categories for categorical variables.

on the verified normality, the data was tested for the presence of deviations. Boxplots were used to identify outliers, which were then removed. A logistic regression test was used to compare the differences of tests against the norm.

A 2-sided p value <0.05 was considered statistically significant.

Results

The analyzed sample contained a total of 921 patients with localized prostate cancer treated with primary radiation therapy. Table 2 presents a breakdown of patients according to radiation therapy technique, age, bladder and rectum volumes, applied dose, and median monitoring period.

Acute GI toxicity

Grade 2 or higher acute GI toxicity occurred in 32.1% (98/305) of patients treated with 3DCRT, 23.4% (64/274) of those treated with IMRT, 7.7% (15/195) of patients treated with IGRT, and 4.1% (6/147) of those treated with VMAT (p≤0.001). Only one patient exhibited G3 toxicity (from the 3DCRT group). We observed the most marked difference in grade 1 acute GI toxicity between the groups treated with 3DCRT and IMRT (41.6% [127/305] and 33.2% [91/274], respectively) and between those treated with IGRT and VMAT (9.2% [18/195] and 4.1% [6/147], respectively) (p≤0.001). Absolutely no trace of acute GI toxicity was found in 26.2%, 43.4%, 83.2% and 91.8% of patients, respectively (p≤0.001).

Table 3. Toxicity after radiation therapy in general description

	3DCRT[1] (N=305)	*IMRT[1] (N=274)*	*IGRT[1] (N=195)*	*VMAT[1] (N=147)*	*p[2]*
Acute GI toxicity, n (%)					
0	80 (26.2)	119 (43.4)	162 (83.1)	135 (91.8)	**<0.001**
1	127 (41.6)	91 (33.2)	18 (9.2)	6 (4.1)	
2+3	98 (32.1)	64 (23.4)	15 (7.7)	6 (4.1)	
1+	225 (73.8)	155 (56.6)	33 (16.9)	12 (8.2)	**<0.001**
2+	98 (32.1)	64 (23.4)	15 (7.7)	6 (4.1)	**<0.001**
3+	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0.529
Acute GU toxicity, n (%)					
0	97 (31.8)	91 (33.2)	110 (56.4)	109 (74.1)	**<0.001**
1	113 (37.0)	85 (31.0)	48 (24.6)	16 (10.9)	
2	69 (22.6)	65 (23.7)	30 (15.4)	21 (14.3)	
3+4	26 (8.5)	33 (12.0)	7 (3.6)	1 (0.7)	
1+	208 (68.2)	183 (66.8)	85 (43.6)	38 (25.9)	**<0.001**
2+	95 (31.1)	98 (35.8)	37 (19.0)	22 (15.0)	**<0.001**
3+	26 (8.5)	33 (12.0)	7 (3.6)	1 (0.7)	**<0.001**
	3DCRT[3] (N=301)	*IMRT[3] (N=265)*	*IGRT[3] (N=177)*	*VMAT[3] (N=126)*	*p[2]*
Chronic GI toxicity, n (%)					
0	149 (49.5)	190 (71.7)	144 (81.4)	112 (88.9)	**<0.001**
1	86 (28.6)	50 (18.9)	27 (15.3)	9 (7.1)	
2	46 (15.3)	18 (6.8)	5 (2.8)	3 (2.4)	
3	20 (6.6)	7 (2.6)	1 (0.6)	2 (1.6)	
1+	152 (54.1)	75 (29.1)	33 (18.8)	14 (11.3)	**<0.001**
2+	66 (23.5)	25 (9.7)	6 (3.4)	5 (4.0)	**<0.001**
3+	20 (7.1)	7 (2.7)	1 (0.6)	2 (1.6)	**0.001**
Chronic GU toxicity, n (%)					
0	144 (47.8)	176 (66.4)	150 (84.7)	110 (87.3)	**<0.001**
1	76 (25.2)	69 (26.0)	19 (10.7)	7 (5.6)	
2	29 (9.6)	9 (3.4)	4 (2.3)	4 (3.2)	
3+4	52 (17.3)	11 (4.2)	4 (2.3)	5 (4.0)	
1+	157 (52.2)	89 (33.6)	27 (15.3)	16 (12.7)	**<0.001**
2+	81 (26.9)	20 (7.5)	8 (4.5)	9 (7.1)	**<0.001**
3+	52 (17.3)	11 (4.2)	4 (2.3%)	5 (4.0)	**<0.001**

[1]Absolute and relative frequencies of categories. [2]Statistical significance tested using ML chi-square test. Statistically significant values are in bold font. [3]Patients with data for both acute and chronic toxicity.

Acute GU toxicity

Grade 2 or higher acute GU toxicity was recorded in 31.1% (95/305) and 35.8% (98/274) of patients treated with 3DCRT and IMRT, respectively, versus only 19% (37/195) and 15% (22/147) of those treated with IGRT and VMAT, respectively (p<0.001). Grade 3 or higher acute GU toxicity occurred in 8.5% (26/305) and 12% (33/274) vs. 3.6% (7/195) and 0.7% (1/147) of cases for the respective techniques (p<0.001). Absolutely no trace of acute GU toxicity was recorded in 31.8% (97/305) of patients treated with 3DCRT, 33.2% (91/274) of those treated with IMRT, 56.4% (110/195) of patients treated with IGRT, and 74.1% (109/147) of those treated with VMAT (p<0.001).

Of the 921 patients analyzed, 869 exhibited cumulative late toxicity, while 52 patients (4 from the 3DCRT group, 9 from IMRT, 18 from IGRT, and 21 from VMAT) could not be objectively evaluated because they were lost to follow-up.

Late GI toxicity

The 3-year cumulative incidence of grade 2 or higher late GI toxicity was 23.5% (66/301) for

Table 4. Radiation therapy techniques and risk of toxicity

	IMRT (reference: 3DCRT)		*IGRT (reference: 3DCRT)*		*VMAT (reference: 3DCRT)*	
	(95% CI)[1]	*p*	*(95% CI)[1]*	*p*	*(95% CI)[1]*	*p*
Acute GI toxicity						
1+	0.463 (0.327; 0.657)	**<0.001**	0.072 (0.046; 0.114)	**<0.001**	0.032 (0.017; 0.060)	**<0.001**
2+	0.644 (0.445; 0.931)	**0.019**	0.176 (0.099; 0.314)	**<0.001**	0.090 (0.038; 0.211)	**<0.001**
3+	-	-	-	-	-	-
Acute GU toxicity						
1+	0.938 (0.662; 1.328)	0.718	0.360 (0.248; 0.523)	**<0.001**	0.163 (0.105; 0.253)	**<0.001**
2+	1.231 (0.871; 1.740)	0.239	0.518 (0.336; 0.798)	**0.003**	0.389 (0.233; 0.650)	**<0.001**
3+	1.469 (0.854; 2.527)	0.164	0.400 (0.170; 0.939)	**0.035**	0.073 (0.010; 0.547)	**0.011**
Chronic GI toxicity						
1+	0.387 (0.273; 0.549)	**<0.001**	0.225 (0.145; 0.349)	**<0.001**	0.123 (0.067; 0.223)	**<0.001**
2+	0.371 (0.226; 0.608)	**<0.001**	0.125 (0.053; 0.295)	**<0.001**	0.147 (0.058; 0.375)	**<0.001**
3+	0.381 (0.159; 0.916)	**0.031**	0.080 (0.011; 0.600)	**0.014**	0.227 (0.052; 0.984)	**0.044**
Chronic GU toxicity						
1+	0.464 (0.330; 0.652)	**<0.001**	0.165 (0.103; 0.264)	**<0.001**	0.133 (0.075; 0.236)	**<0.001**
2+	0.222 (0.132; 0.374)	**<0.001**	0.129 (0.061; 0.273)	**<0.001**	0.209 (0.101; 0.431)	**<0.001**
3+	0.207 (0.106; 0.407)	**<0.001**	0.111 (0.039; 0.312)	**<0.001**	0.198 (0.077; 0.508)	**<0.001**
	IGRT (reference: IMRT)		*VMAT (reference: IMRT)*		*VMAT (reference: IGRT)*	
	(95% CI)[1]	*p*	*(95% CI)[1]*	*p*	*(95% CI)[1]*	*p*
Acute GI toxicity						
1+	0.156 (0.100; 0.244)	**<0.001**	0.068 (0.036; 0.129)	**<0.001**	0.436 (0.217; 0.878)	**0.020**
2+	0.273 (0.151; 0.496)	**<0.001**	0.140 (0.059; 0.331)	**<0.001**	0.511 (0.193; 1.350)	0.175
3+	-	**-**	-	**-**	-	-
Acute GU toxicity						
1+	0.384 (0.263; 0.561)	**<0.001**	0.173 (0.111; 0.271)	**<0.001**	0.451 (0.283; 0.718)	**<0.001**
2+	0.421 (0.272; 0.650)	**<0.001**	0.316 (0.189; 0.530)	**<0.001**	0.752 (0.422; 1.339)	0.332
3+	0.272 (0.118; 0.628)	**0.002**	0.050 (0.007; 0.370)	**0.003**	0.184 (0.022; 1.512)	0.115
Chronic GI toxicity						
1+	0.581 (0.365; 0.923)	**0.021**	0.317 (0.171; 0.587)	**< 0.001**	0.545 (0.179; 0.964)	**0.027**
2+	0.337 (0.135; 0.839)	**0.019**	0.397 (0.148; 1.062)	0.066	1.178 (0.351; 3.947)	0.791
3+	0.209 (0.026; 1.717)	0.145	0.594 (0.122; 2.903)	0.520	2.839 (0.255; 31.651)	0.396
Chronic GU toxicity						
1+	0.356 (0.220; 0.577)	**<0.001**	0.288 (0.161; 0.515)	**<0.001**	0.808 (0.415; 1.572)	0.530
2+	0.580 (0.250; 1.347)	0.205	0.942 (0.416; 2.133)	0.887	1.625 (0.609; 4.335)	0.332
3+	0.534 (0.167; 1.704)	0.289	0.954 (0.324; 2.807)	0.932	1.787 (0.470; 6.792)	0.394

[1]Based on logistic regression. p - Statistically significant p-values are shown in bold font.

3DCRT, 9.7% (25/265) for IMRT, 3.4% (6/177) for IGRT, and 4.0% (5/126) for VMAT (p<0.001). In the case of grade 3 or higher toxicity, the risk of incidence was 7.1% (20/301), 2.7% (7/265), 0.6% (1/177), and 1.6% (2/126), respectively (p=0.001). No cases of grade 4 toxicity were recorded in the entire research sample. Absolutely no trace of toxicity was found in 49.5% (149/301) of 3DCRT cases, 71.7% (190/265) of IMRT cases, 81.4% (144/177) of IGRT cases, and 88.9% (112/126) of VMAT cases (p≤0.001).

Late GU toxicity

The 3-year cumulative incidence of grade 2 or higher late GU toxicity was 26.9% (81/301) for 3DCRT, 7.5% (20/265) for IMRT, 4.5% (8/177) for IGRT, and 7.1% (9/126) for VMAT (p≤0.001). Grade 3 or higher toxicity occurred in 17.3% (52/301), 4.2% (11/265), 2.3% (4/177), and 4.0% (5/126) of cases, respectively. As with GI toxicity, no cases of grade 4 toxicity were recorded. At 87.3% (110/126), VMAT showed the highest rate of patients manifesting no signs of toxicity, followed by IGRT at 84.7% (150/177), IMRT at 66.4% (176/265), and 3DCRT at 47.8% (144/301) (p≤0.001).

Table 3 presents the relationship between individual techniques and risks of acute or chronic toxicity.

Patients treated with 3DCRT exhibited a statistically significant higher risk of late GU and GI toxicity at grade 2 or higher and at grade 3 or higher as compared to patients treated with IMRT, IGRT and VMAT. We obtained similar results in the case of grade 2 or higher acute GI toxicity. In the case of acute GU toxicity at grade 2 or higher and at grade 3 or higher, we found a statistically significant higher risk in the case of 3DCRT as compared to IGRT and VMAT, though not compared to IMRT.

Patients treated with IMRT showed a higher risk of acute GI and GU toxicity at grade 2 or higher and at grade 3 or higher as compared with IGRT and VMAT. Comparing IMRT with IGRT, we observed a significantly higher risk only in the case of grade 2 or higher late GI toxicity, while in the case of grade 3 or higher there was a visible but not significant trend. In the case of late GU toxicity, we recorded no significantly higher risk at either grade. VMAT did not demonstrate a significantly lower risk of late GU or GI toxicity at either grade as compared with IMRT. In comparing IGRT and VMAT, no statistically significant difference was observed regarding the risk of late GI or GU toxicity at grade 2 or higher or at grade 3 or higher. Table 4 presents comparisons of the individual techniques.

Discussion

Modern radiation therapy methods have introduced many possibilities for reducing treatment-related toxicity [6-8,21]. Our study found more-frequent incidence of grade 2 or higher acute GI toxicity in the cases of 3DCRT and IMRT (32.1% and 23.4% of patients, respectively) than in the cases of IGRT and VMAT (7.7% and 4.1% of patients, respectively) (p≤0.001). Grade 3 or higher acute GI toxicity was found in only one patient (from the 3DCRT group). Patients treated with VMAT exhibited the lowest rate of acute GI toxicity (with 91.8% showing no signs). Our results concur with those found in the literature. The incidence of grade 2 or higher acute GI toxicity has been reported in the range of 28-57% of patients treated with 3DCRT, 15-30% of those treated with IMRT, and 3-30% of patients treated with IGRT [9,21-31]. Grade 3 acute GI toxicity has been observed in as many as 6% of the cases.

Our sample also showed similar results in the case of grade 2 or higher GU toxicity as for acute GI toxicity (31.1% for 3DCRT and 35.8% for IMRT vs. 19% for IGRT and 15% for VMAT; p≤0.001). Grade 3 acute GU toxicity occurred more frequently in patients treated with 3DCRT (8.5%) and IMRT (12%) than in those treated with IGRT (3.6%) or VMAT (0.7%) (p≤0.001). Patients treated with VMAT showed the lowest incidence of acute GU toxicity (with 74.1% showing no signs). Again, comparing our results with those of other individual studies, we find that they also correspond in the case of grade 2 acute GU toxicity (24-49% for 3CDRT, up to 36% for IMRT, and 33-54% for IGRT) [21-31]. Grade 3 acute GU toxicity occurred in up to 13% of cases applying non-image-guided radiotherapy methods and up to 6% of cases applying IGRT methods (IGRT and VMAT). Comparing incidences of acute toxicity between individual studies is highly problematic, however, since not only are different techniques used but also different CTV-PTV margins and doses.

Among our sample, patients treated with 3DCRT exhibited the most frequent incidence of grade 2 or higher cumulative chronic toxicity (23.5% for GI toxicity and 26.9% for GU toxicity). In comparing the four studied techniques (3DCRT, IMRT, IGRT and VMAT), there is a clear decreasing trend in chronic GI toxicity of grade 2 (15.3%, 6.8%, 2.8% and 2.4%, respectively) (p≤0.001) and grade 3 (7.1%, 2.6%, 0.6% and 1.6%, respectively) (p≤0.001). Chronic GU toxicity shows a similar trend. Three-year cumulative incidence of grade 2 toxicity was recorded in 9.6%, 3.4%, 2.3% and 3.2% of patients, respectively (p≤0.001), while grade 3 toxicity was

observed in 17.3%, 4.2%, 2.3% and 4.0% of patients, respectively (p≤0.001).

The incidence of late GI toxicity in our sample was comparable to that reported by Zelefsky et al [32], who compared toxicity in 1,571 patients treated with 3DCRT and IMRT and found the incidence of grade 2 or higher GI toxicity to be 13% for 3DCRT patients and 5% for IMRT patients. On the other hand, the incidence of grade 2 or higher late GU toxicity was 20% for patients treated with IMRT and 8% for those treated with 3DCRT. Unlike our patients, however, their IMRT patients were treated with a dose of 81 Gy and their 3DCRT patients with a dose of 66-81 Gy.

IGRT methods offer the possibility to correct interfraction movements and reduce the safety margins and thus to diminish toxicity risk [21]. Zelefsky et al evaluated toxicity in 186 patients treated with IGRT and non-IGRT techniques [7]. All patients were treated with the same dose and had the same safety margin (PTV). In the IGRT group, the incidences of grade 2 or higher 3-year late GU and GI toxicity were 10.4% and 1.0%, respectively. In another study, Sveistrup et al reported an incidence of grade 2 or higher chronic GI toxicity of 57.3% for 3DCRT vs. 5.8% for IGRT and an incidence of grade 2 or higher GU toxicity of 41.8% for 3DCRT vs. 29.7% for IGRT [33], thus, as in the comparison of studies concerning acute toxicities, we see the same limitations in cases of chronic toxicities. Here as well, different treatment protocols, methods, scoring systems and radiation therapy techniques were used.

The comparison of individual radiation therapy modalities revealed that patients treated with IGRT techniques show a significantly lower risk of grade 2 or higher acute and chronic toxicity (GI and GU) compared to patients treated with 3DCRT. Comparing IGRT techniques with IMRT, we see significantly lower risks of grade 2 or higher acute toxicity (both GI and GU) and grade 2 or higher late toxicity (GI only). In other cases, though we find no significant results, we do observe a clear trend favoring IGRT methods. A likely reason could be the different proportion of patients receiving doses of 74/78 Gy in the IMRT group (32.5%/46.4%) versus the IGRT group (3%/87.4%) and VMAT group (8.1%/76.3%) as well as the different CTV-PTV margins for individual techniques. Comparing static and dynamic techniques using IGRT, we found no benefit as measured by the incidence of either acute or chronic toxicity of grade 2 or higher. On the other hand, the highest number of patients exhibiting no acute or chronic toxicity was recorded among those treated with the dynamic VMAT technique.

Although in our study the dynamic VMAT technique showed no marked benefit as regards the incidence of acute and chronic toxicity, as compared to the static technique it does generally offer certain advantages (e.g. reduction of treatment time and intrafraction movements, improvement of dose distribution, reduction number of monitor units) [34-36].

One limitation of our study is that it constitutes a single institution's retrospective analysis. We did not stratify the patients according to T stage, Gleason score, PSA or comorbidity. The results also may have been influenced by possible hormone therapy. High-risk patients treated with IMRT techniques also underwent hormone therapy, while among the 3DCRT group those with stage T3 cancer received the treatment. A certain bias also may have resulted from the different treatment protocols for the individual groups as relates to dose, CTV-PTV margin, and, in the case of 3DCRT, the definition of contouring for organs at risk. On the other hand, this study benefits from the continuity of the treatment process, contouring, verification and evaluation within a single institution. The sample of patients was uniform as regards ethnicity, and stratification was done in the case of TURP or TVPE. Furthermore, despite the aforementioned limitations, we believe the consistent method of contouring, dose specification, and application of identical constraints in planning across individual techniques, as well as the use of identical toxicity evaluation scales for late toxicity classification, mean that this sample was relatively consistent.

Conclusions

Our study has shown that the IGRT technique markedly reduces toxicity. In combination with the RapidArc method, it also shortens the radiation time and thereby reduces the risk of intrafraction movements. Technological advances will certainly lead to further individualization of care, for example in the form of online adaptive radiation therapy

Conflict of interests

The authors declare no conflict of interests.

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