e-ISSN 2083–4640
ISSN 1507–1367

RESEARCH PAPER

Reports of Practical Oncology and Radiotherapy
2022, Volume 27, Number 1, pages: 142–151
DOI: 10.5603/RPOR.a2022.0012
Submitted: 09.11.2021
Accepted: 21.01.2022

Tomotherapy-based moderate hypofractionation for localized prostate cancer: a mono-institutional analysis

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ABSTRACT

Background: To date, few studies have been published on image-guided helical tomotherapy (HT) in a moderate hypofractionation of localized PCa. We report outcome and toxicity of localized PCa patients treated with HT-based moderate hypofractionated radiotherapy.

Materials and methods: 76 patients were retrospectively analyzed. A total dose of 60 Gy (20 × 3 Gy) or 67.5 Gy (25 × 2.7 Gy) was prescribed. The χ^2 test was used to analyze associations between toxicity and dosimetric and clinical parameters. The Cox proportional hazard regression model was used for multivariate analysis. Kaplan-Meier method was used for survival analysis.

Results: median follow-up was 42.26 months [interquartile (IQR), 23–76). At 4-year, overall survival (OS) and metastasis-free survival (MFS) were 91% and 89%, respectively. At multivariate analysis, smoking habitude was associated with MFS [hazard ratio (HR) 7.32, 95% CI: 1.57–34.16, p = 0.011]. Acute and late grade ≥ 2 gastro-intestinal (GI) toxicity was observed in 6.5% and 2.6% of patients, respectively. Acute and late grade ≥ 2 genito-urinary (GU) toxicity were 31.5% and 3.9%. Four-year late GI and GU grade ≥ 2 toxicity were 3% and 7%, respectively. Acute GI toxicity was associated with statins medication (p = 0.04) and androgen deprivation therapy (p = 0.013). Acute GU toxicity was associated with the use of anticoagulants (p = 0.029) and antiaggregants (p = 0.013).

Conclusions: HT-based moderate hypofractionation shows very low rates of toxicity. Smoking habitude is associated with the risk of developing metastases after radical treatment for localized PCa.

Key words: localized prostate cancer; helical-tomotherapy; image-guided radiotherapy; toxicity; outcome

Rep Pract Oncol Radiother 2022;27(1):142–151

Introduction

External beam radiotherapy (EBRT) is a treatment option in the cure of localized prostate cancer (PCa) [1]. Recently, several retrospective and large randomized phase III trials have demonstrated that hypofractionated radiotherapy (2.4–4.0 Gy per fraction) is non-inferior to conventional fractionation (1.8–2.0 Gy per fraction). More specifically, some moderate hypofractionation schedules (60–70.2 Gy in daily fractions of 2.7–3.1 Gy) have been widely investigated and long-term follow-up is

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available [2–5]. Based on the results of these trials, moderately hypofractionated radiotherapy using cutting-edge techniques (i.e., intensity-modulated radiation therapy (IMRT) and image-guidance) is now considered an alternative to conventionally fractionated radiotherapy for localized PCa [6, 7]. The use of advanced EBRT techniques, such as IMRT, improve target dose distribution and normal tissues sparing, and image guided radiotherapy (IGRT) allows checking the daily treatment reproducibility. Helical tomotherapy (HT) delivers IMRT using a 6-MV linear accelerator mounted on a slip-ring CT gantry, performing volumetric megavoltage CT (MVCT) image guidance. To date, few reports have been published on HT-based hypofractionated radiotherapy for patients affected by localized PCa [8–10]. In this retrospective study, we report outcome and toxicity of 76 patients affected by localized prostate cancer treated with HT moderate hypofractionated radiotherapy.

Materials and methods

Patients and treatment features

Seventy-six patients affected by localized prostate cancer underwent helical tomotherapy-based hypofractionated radiotherapy between August 2013 and March 2019 in our Department. All patients provided informed consent. Median age at diagnosis of localized PCa was 76 years [interquartile (IQR), 73–78). Median prostate-specific antigen (PSA) level was 6.5 ng/mL (IQR, 4.8-9.2). All patients had pathologically confirmed prostate cancer. Pre-treatment evaluation consisted of physical examination and data collection about co-morbidities (diabetes, colitis, previous abdominal/pelvic surgery), about the use of medications (antihypertensive, antiaggregants, and anticoagulants, statins), and smoking habitude during radiotherapy (Tab. 1). We evaluated baseline urinary function by uroflowmetry. Patients were stratified according to D'Amico classification: 16 (21%) patients were in the low-risk group, 34 (44.5%) in the favorable intermediate, 8 (10.5%) in the unfavorable intermediate-risk group and 18 (24%) in the high-risk group. Eventually, based on the International Society of Urological Pathology (ISUP) grading, 34 patients were in grade group 1, 19 in grade 2, 10 in grade 3, and 9 and 4 in grade group 4 and 5, respectively [11]. Androgen deprivation therapy (LHRH analogues) at the time of radiotherapy was prescribed in 43 cases. Regarding radiotherapy, all patients underwent planning CT (2.5 mm slice thickness) with empty rectum and comfortably full bladder in a supine position using a knee fix and foot fix (Combifix®, CIVCO Medical Solutions, Orange City, IA, USA) for immobilization [12]. CT images were transferred to a treatment planning system (Pinnacle®; Philips, Fitchburg, WI, USA) to delineate the clinical target volume (CTV) that included the prostate in the low-risk group, and the prostate plus 2/3 of the seminal vesicles in the intermediate and high-risk groups. PTV was obtained by anisotropic expansion of CTV (5 mm in the posterior direction, 6 mm in all the others). The rectum and the bladder were contoured as solid organs [12]. Other organs at risks (OARs) were the femoral heads, penile bulb, bladder trigone and urethra. More specifically, the trigone was defined as a triangle-shaped structure located in the base of the bladder starting from the level where the ureters reach the bladder wall to the transition of the urethra, and the urethra (not visible at CT imaging) was defined as a cylindrical structure (8 mm in diameter) at the center of the CTV [13]. We respected the following dose-constraints: for the rectum, $V_{58} \leq 15\%$, $V_{50} \leq 30\%$, $V_{30} \leq 50\%$; for the bladder, $V_{60} \leq 5\%$, $V_{58} \leq 15\%$, $V_{50} \leq 30\%$, $V_{40} \leq 50\%$. Moreover, the urethra and trigone had to receive a dose < 105%. Treatment plans were delivered by HT (helical slice 6 MV photon beam), with a field width of 1 or 2.5 cm, a pitch value of 0.287 and a modulation factor ranging from 1.8 to 3. A total dose of 60 Gy (20 × 3 Gy) or 67.5 Gy (25 × 2.7 Gy) was prescribed to the PTV. A criterion of 95% of the target volume receiving the 95% of prescribed dose was satisfied for all plans. Daily image-guidance was performed by Megavoltage CT to correct patient setup (according to bone and soft tissue anatomy) and to take into account inter-fraction variability.

Follow-up and statistics

Patients were evaluated every 3 months for one year, then every 6 months for the next years. Clinical end-points were overall survival (OS), metastasis-free survival (MFS), and biochemical relapse-free survival (b-RFS). Toxicity was registered according to the Common Terminology

Table 1. Patient characteristics (76 patients)

	Mean	Median	IQR	N. of patients (%)
Age [years]	75	76	73–78	
PSA [ng/mL] at diagnosis	7.6	6.5	4.8–9.2	
Clinical stage				
T1c				7 (9.25)
T2a				16 (21)
T2b				13 (17)
T2c				33 (43.5)
T3a				4 (5.25)
T3b				3 (4)
Gleason score				
6				34 (44.5)
7				29 (38)
8				9 (12)
9				3 (4)
10				1 (1.5)
Risk class				
Low				16 (21)
Interm. favor				34 (44.5)
Interm. unfavor				8 (10.5)
High				18 (24)
Uroflowmetry				
Q_{max} [mL/s]	17.5	18	13–21	
Q_{ave} [mL/s]	8.4	8	6–10	
BMI	27.2	27	24.7–29	
Diabetes				
Yes				6 (8)
No				70 (92)
Smoking habitude				
Yes				9 (12)
No				67 (88)
Abdominal surgery				
Yes				55 (72.5)
No				21 (27.5)
Antihypertensive medication				
Yes				49 (64.5)
No				27 (35.5)
Antiaggregants				
Yes				22 (29)
No				54 (74)
Anticoagulants				
Yes				7 (9.25)
No				69 (90.75)
Statins				
Yes				26 (34)
No				50 (66)
ADT				
Yes				43 (56.5)
No				33 (43.5)

PSA — prostate-specific antigen; BMI — body mass index; ADT — androgen deprivation therapy; Q_{max} — maximum flow rate; Q_{ave} — average flow rate

Criteria for Adverse Events (CTCAE) v5.0. Acute (within 90 days from the start of radiotherapy) and late (> 90 days from the start of radiotherapy) genito-urinary (GU) and gastro-intestinal (GI) toxicities were analyzed, and grade ≥ 2 toxicity was correlated with clinical and dosimetric parameters. Dose-Volume-Histograms (DVHs) were used to provide a quantitative analysis. The maximum dose (D_{max}), and a set of appropriate Vx (percent of OAR volume receiving at least the × dose) were evaluated for the rectum and bladder. For statistical analysis, dosimetric parameters in the high-dose range defined by 5 Gy intervals (e.g. D_{max}, V50, V55, V60) and continuous clinical variables (e.g. body mass index, baseline PSA, CTV volume, uroflowmetry peak flow rate) were dichotomized by the median value. Concerning clinical variables, the assumption of antihypertensive medication and/or anticoagulants, antiaggregants, statins, androgen deprivation therapy (ADT), the smoking habit during radiotherapy, a positive history for diabetes, and previous abdominal surgery were analyzed.

Statistical Package for the Social Sciences (IBM-SPSS® version 25.0 IBM Corp., Armonk, NY, USA, 2017) was used for statistical analysis. The $\chi 2$ test with Yates' continuity correction or Fisher's exact test were performed to analyze categorical variables, Mann-Whitney test was used to analyze continuous or discrete variables. Survival curves were calculated using the Kaplan-Meier product-limit method, followed by log-rank test to evaluate differences in expected event probability between groups; 95% confidence intervals (95% CI) were reported. The Cox proportional hazard regression model was used for multivariate analysis. Statistical significance was set at $p \leq 0.05$.

Results

With a median follow-up of 42.26 months (IQR, 23–76), no patient died from PCa. At 2- and 4-year, OS was 100% (95% CI: 95.8–100) and 91% (95% CI: 83–99.7) (Fig. 1A), respectively, whereas b-RFS was 90% (95% CI: 82–96.9) and 79% (95% CI: 71.4–92.7) (Fig. 1B). Eight patients developed metastatic disease, with a 4-year MFS of 89% (95% CI: 80–98.6) (Fig. 1C). At log-rank test, high-risk disease (low-risk 90.9%, 95% CI: 73.9–100 *vs.* favorable-risk 100%, 95% CI not calculable *vs.* unfavorable-risk 87.5%, 95% CI: 64.6–100 *vs.* high-risk 81.5%, 95% CI: 58.1–100; p = 0.01) and ISUP class 4–5 (ISUP 1–2 100%, 95% CI not calculable *vs.* ISUP 3 90%, 95% CI: 71.4–100 *vs.* ISUP 4–5 85.7%, 95% CI: 59.8–100; p = 0.03) were associated with a worse MFS (Tab. 2). Eventually, smoking habitude negatively affected MFS (smokers 68.6%, 95% CI: 32.1–100 *vs.* non-smokers 95.3%, 95% CI: 88.8–100; p = 0.001). At bivariate Cox-analysis, smoking habitude (HR: 8.32, 95% CI: 1.93–35.75, p = 0.004), high-risk class (HR: 2.57, 95% CI: 1.21–5.45, p = 0.014) and ISUP class 4–5 (HR: 2.79, 95% CI: 1.20–6.49, p = 0.017) were all confirmed as significant variables for MFS. In a multivariate model, built on significant variables at bivariate analysis, only smoking habitude emerged as an independent and significant variable (HR: 7.32, 95% CI: 1.57–34.16, p = 0.011).

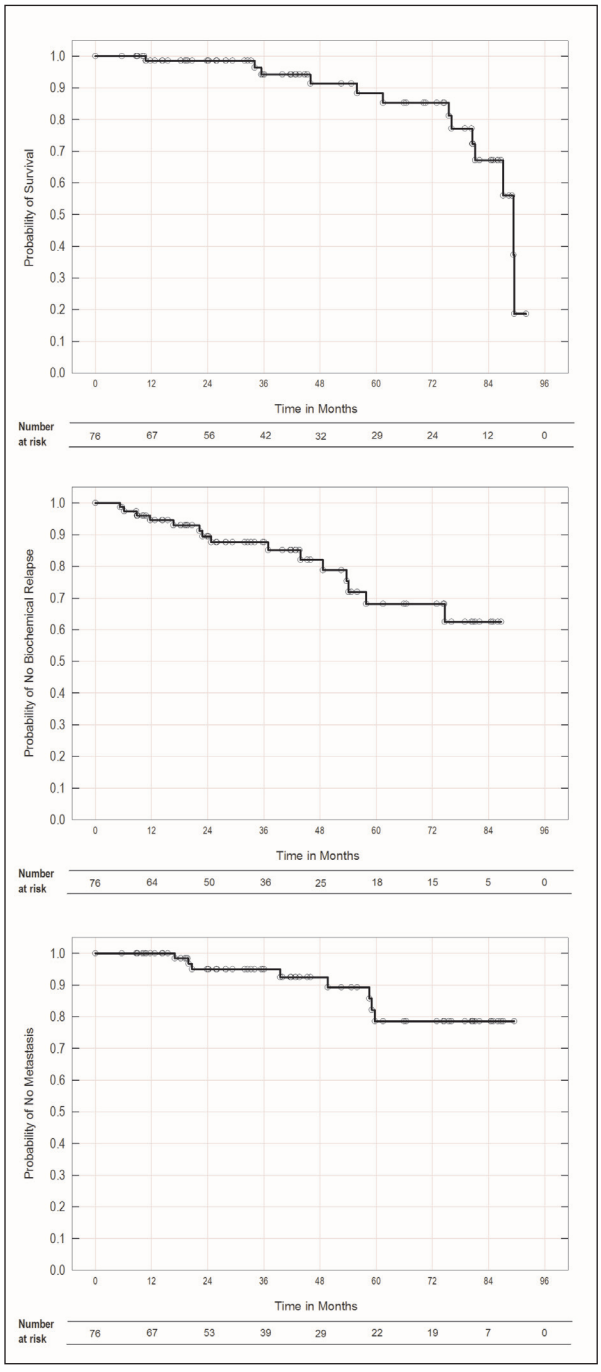

Figure 1. A. Overall survival; B. Biochemical relapse-free survival (b-RFS); C. Metastasis-free survival (MFS)

About gastro-intestinal toxicity (Tab. 3), acute G2 toxicity was observed in 6.5% of cases, late G2 was 2.6% (2 patients), and no acute or late G3 toxicity was registered. Four-year late GI toxicity of grade ≥ 2 was 3% (Fig. 2A). Acute GU grade ≥ 2 toxicity was reported in 31.5% of patients (Tab. 3), no patient had late G2 toxicity while 3 (3.9%) patients developed a grade 3 toxicity (stenosis of the urethra). Four-year late GU toxicity of grade ≥ 2 was 7% (Fig. 2B).

At χ^2 test for the associations between acute toxicity of grade ≥ 2 and clinical and dosimetric variables (Tab. 4), we found that statins medication (p = 0.04) and ADT (p = 0.013) are associated with a significant reduction of acute GI grade ≥ 2 toxicity, whereas acute GU grade ≥ 2 toxicity was significantly associated with the use of anticoagulants (p = 0.029) and antiaggregants (p = 0.013). We found no association between late toxicity and independent variables (data not shown) because of the small number of events (2 cases of late GI grade ≥ 2 toxicity and 3 of GU toxicity).

Discussion

The strengths of this study are the homogeneity of patients' population and treatment modality, which is based on cutting-edge techniques (helical

Table 2. Fisher's exact test and log–rank test for biochemical–free and metastasis–free survival

	Biochemical recurrence				Metastasis onset			
	No	Yes	p-value Fisher's exact test	p-value log-rank test	No	Yes	p-value Fisher's exact test	p-value log-rank test
BMI								
< 27	27	8			–	–		
≥ 27	34	7	0.57		–	–	–	
Smoking habitude								
No	55	12			62	5		
Yes	6	3	0.36		6	3	0.048*	0.001*
Baseline PSA [ng/mL]								
< 6.5	30	7			34	3		
≥ 6.5	31	8	0.54		34	5	0.72	0.37
D'Amico risk class								
Low	14	2			15	1		
Favorable	29	5			33	1		
Unfavorable	4	4			6	2		
High	17	4	0.22		14	4	0.03*	0.01*
ISUP grading								
1–2	45	8			50	3		
3	6	4			8	2		
4–5	10	3	0.28		10	3	0.04*	0.03*
ADT								
No	32	1			32	1		
Yes	29	14	0.01*	0.002*	36	7	0.12	0.09
CTV [cm^3]								
≤ 45	31	8			–	–		
> 45	30	7	0.54		–	–	–	

BMI — body mass index; PSA — prostate-specific antigen; ISUP — International Society of Urological Pathology; ADT — androgen deprivation therapy; CTV — clinical target volume

Table 3. Common Terminology Criteria for Adverse Events (CTCAE v5.0) toxicity scale (76 patients)

	G1	G2	G3
Gastro-intestinal			
Acute	27.6% (21/76)	6.5% (5/76)	0% (0/76)
Late	6.5% (5/76)	2.6% (2/76)	0% (0/76)
Genito-urinary			
Acute	31.5% (24/76)	28.9% (22/76)	2.6% (2/76)
Late	11.8% (9/76)	0% (0/76)	3.9% (3/76)

tomotherapy with daily volumetric image-guidance). Limitations are the retrospective analysis and the absence of patient self-assessed toxicity. We had a very low cumulative incidence of late toxicity compared with data of other studies [4, 5]. In the CHHiP trial, 5-year late GI grade ≥ 2 toxicity was 11.9% [4] whereas we had a 4-year cumulative incidence of 3%. With a median follow-up of 6 years, in the PROFIT trial (60 Gy, 20 × 3 Gy) the rate of late GI grade ≥ 2 toxicity was 8.9% [5]. Differences between results in terms of late toxicity might be due to differences in CTV to PTV margins and treatment techniques. In our series, we planned 6 mm expansion in all directions, except in the posterior where

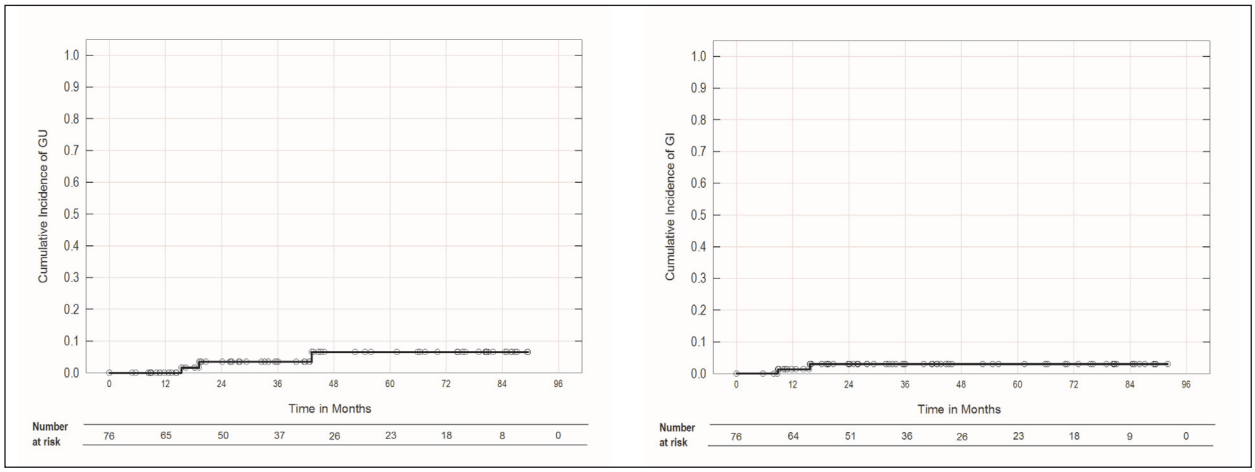

Figure 2. Actuarial late grade ≥ 2 toxicity. **A.** Genito-urinary. **B.** Gastro-intestinal

Table 4. χ^2 test for the association between acute toxicity and clinical and dosimetric variables

	Acute GI toxicity			Acute GU toxicity		
	< 2	≥ 2	p-value	< 2	≥ 2	p-value
BMI						
< 27	31	4		25	10	
≥ 27	40	1	0.17	27	14	0.63
Smoking habitude						
No	63	4		45	22	
Yes	8	1	0.47	7	2	0.71
Abdominal surgery						
No	20	1		15	6	
Yes	51	4	0.57	37	18	0.78
Diabetes						
No	66	4		48	22	
Yes	5	1	0.34	4	2	0.62
Antihypertensive medication						
No	24	3		18	9	
Yes	47	2	0.34	34	15	0.80
Antiaggregants						
No	52	2		42	12	
Yes	19	3	0.14	10	12	0.013*
Anticoagulants						
No	64	5		50	19	
Yes	7	0	0.60	2	5	0.029*
Statins						
No	49	4		37	13	
Yes	22	1	0.04*	15	11	0.19
Uroflowmetry Qmax [mL/s]						
≤ 18	–	–		21	15	
> 18	–	–	–	31	9	0.08

Table 4. χ^2 test for the association between acute toxicity and clinical and dosimetric variables

	Acute GI toxicity			Acute GU toxicity		
	< 2	≥ 2	p-value	< 2	≥ 2	p-value
ADT						
No	28	5		24	9	
Yes	43	0	0.013*	28	15	0.62
CTV [cm^3]						
≤ 45	38	1		30	9	
> 45	33	4	0.19	22	15	0.13
Rectal volume [cm^3]						
≤ 60	37	2		–	–	
> 60	34	3	0.67	–	–	–
Rectum D_{max} [Gy]						
< 67	33	3		–	–	
≥ 67	38	2	0.66	–	–	–
Rectum D_{mean} [Gy]						
< 20	33	4		–	–	
≥ 20	38	1	0.19	–	–	–
Rectum V50 (%)						
< 9	32	4		–	–	
≥ 9	39	1	0.18	–	–	–
Rectum V55 (%)						
< 6	32	4		–	–	
≥ 6	39	1	0.18	–	–	–
Rectum V60 (%)						
< 3	31	2		–	–	
≥ 3	40	3	0.62	–	–	–
Bladder volume [cm^3]						
< 215	–	–		23	13	
≥ 215	–	–	–	29	11	0.46
Bladder D_{max} [Gy]						
< 66	–	–		16	11	
≥ 66	–	–	–	36	13	030
Bladder V55 (%)						
< 7	–	–		23	11	
≥ 7	–	–	–	29	13	0.54
Bladder V60 (%)						
< 4	–	–		18	10	
≥ 4	–	–	–	34	14	0.61

GI — gastrointestinal; GU — genito-urinary; BMI — body mass index; ADT — androgen deprivation therapy; CTV — clinical target volume; Qmax — peak flow rate

5 mm was applied. For instance, in the CHHiP study a 10 mm per protocol isotropic expansion and no image-guidance in 53% of the patients led to an intrinsic increased exposure of OARs to irradiation. In a randomized phase 2 substudy of the latter trial testing the impact of IGRT on acute and late GI and GU side effects, patients who underwent image-guided radiotherapy with reduced margins (IGRT-R) had a 2-year late GI grade ≥ 2 toxicity of 5.8% [14], which are similar to our result. We regis-

tered acute and late GU grade ≥ 2 toxicity (Tab. 3) in 31.5% and 3.9% of the patients, respectively, in line with data of the patients treated with IGRT-R in the CHHiP substudy [14] who had acute and late GU grade ≥ 2 toxicity in 24% and 3.9% of cases, respectively. Recently, 10-year updated results of a Phase II trial on 96 patients treated with intensity modulated image-guided moderate hypofractionated radiotherapy showed low 8-year cumulative incidence of grade ≥ 2 late gastro-intestinal (4%) and genito-urinary (12%) toxicity in the 60 Gy cohort [15]. Compared with conformal radiotherapy without image-guidance, cutting-edge technologies in treatment planning and delivery have progressively been used in clinical practice increasing the safety and, therefore, minimizing the risk of toxicity [16]. In our analysis, we found that statins and ADT were associated with a lower incidence of acute GI toxicity. Statins might act as anti-thrombotic and anti-inflammatory agents inhibiting pro-fibrotic and pro-inflammatory cytokines, thus leading to the remodeling of the microenvironment of the irradiated tissue, eventually reducing the burden of radiation injury [17–19]. Recently, Palumbo et al. [20] reported that statins were an independent factor associated with the reduction of acute GI toxicity in 195 patients treated with IMRT for localized PCa. The protective effect of ADT on the intestinal tissue, which has been demonstrated in animal models [21] as well as in clinical studies [22–24], could depend on the reduction of radiation-induced cytokines and pro-inflammatory molecules (i.e., IL-6, NFkB, TGFβ) [21] within the irradiated rectal wall in patients under androgen deprivation. We identified anticoagulants and antiaggregants as clinical variables associated with acute GU toxicity, but we have to consider that anticoagulant therapy itself is a risk factor for urinary complaints and hematuria. In a French retrospective study [25], these agents significantly affected late GU toxicity in 965 patients treated with EBRT for localized PCa. Even though the relationship between radiation-induced toxicity and anticoagulants is not clear, some reports showed that their use could be associated not only with GU but also with rectal toxicity [22, 24, 26] in patients undergoing radiotherapy for localized PCa. About oncologic outcomes, in our analysis clinical prognostic factors (D'Amico risk class and ISUP grade) are important tools in detecting the risk of disease progression in localized PCa patients. Furthermore, we found a strong correlation between smoking habitude and the risk of developing metastases (HR: 8.32, 95% CI: 1.93–35.75, p = 0.004). In fact, several authors demonstrated a significant cancer specific survival decrease in tobacco smokers affected by solid tumor [27–29]. Nonetheless, it seems that non-smoking and ex-smoker cancer patients have a better prognosis compared with smoking patients [30, 31]. Regarding PCa patients, Steinberger et al. [28] found a statistically significant correlation between the 10-year likelihood of MFS and smoking activity (rates of 72.2%, 85.8%, and 87.3% for smokers, former smokers and non-smokers, respectively, p < 0.001). Kenfield et al. [32] reported a worse prognosis in smokers affected by PCa compared with non-smokers. Mechanisms by which tobacco smoking contributes to widespread progression of solid tumors include activation of angiogenesis and proliferation pathways increasing tumor growth and the ability of tumor cells to metastasize, epigenetic effects including DNA methylation selecting aggressive tumor clones, interference with cell-mediated antitumor immune response [28–32]. Eventually, cigarette smoking leads to high blood levels of free and total testosterone contributing to progression in PCa patients [28, 30, 32].

Our study adds information about the safety and efficacy of cutting-edge techniques in the treatment of localized PCa with moderate hypofractionation. The main difference between the present and the few other experiences published in literature about tomotherapy-based moderate hypofractionation is that the majority of them are based on simultaneous integrated boost (SIB) modality in order to include pelvic lymph nodes in the target volume [8–10].

Conclusions

Localized PCa patients treated with tomotherapy-based moderate hypofractionation and with volumetric image-guidance show very low rates of acute and late toxicity. Respecting planning dose-constraints, it seems that baseline clinical features and individual factors such as co-morbidities and lifestyle choices have an impact on radiation-induced toxicity and on the risk of disease progression.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

None declared.

Ethics approval

Ethical approval was waived by the local Ethics Committee of the University of Perugia in view of the retrospective nature of the study and all the procedures being performed were part of routine care. The study was performed according to the Declaration of Helsinki and written informed consent was obtained for all patients.

Consent to participate

All patients provided informed consent for this retrospective analysis.

Consent for publication

All patients provided informed consent for publication, and no identifying information is included in this article.

Availability of data

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Code availability

The software application for data storage is Excel and the software application for data analysis is SPSS.

Acknowledgments

None declared.

Authors' contribution

All authors have made a substantial contribution to research design, or the acquisition, analysis or interpretation of data. All authors have drafted the paper and revised it critically and have approved the submitted final version. Study concept and design: G.I., M.V.T., C.M. Acquisition of data: R.B., M.V.T., C.M., E.A., C.Z. Analysis and interpretation of data: V.B., R.B., G.I., M.V.T., C.Z. Drafting of the manuscript: M.V.T., G.I., C.A., E.A. Critical revision of the manuscript for important intellectual content: C.A., G.I. Statistical analysis: V.B., R.B., C.M., C.Z. Supervision: G.I., R.B., C.A.

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