Medical Oncology (2019) 36:9
https://doi.org/10.1007/s12032-018-1233-1

ORIGINAL PAPER

Impact of image guidance on toxicity and tumour outcome in moderately hypofractionated external-beam radiotherapy for prostate cancer

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Received: 2 October 2018 / Accepted: 22 November 2018 / Published online: 27 November 2018

Abstract

To report toxicity and efficacy outcome of moderately hypofractionated image-guided external-beam radiotherapy in a large series of patients treated for prostate cancer (PCa). Between 10/2006 and 12/2015, 572 T1-T3N0M0 PCa patients received 70.2 Gy in 26 fractions at 2.7 Gy/fraction: 344 patients (60%) with three-dimensional conformal radiotherapy (3D-CRT) and 228 (40%) with intensity-modulated radiotherapy (IMRT). Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria and Houston definition (nadir + 2) were used for toxicity and biochemical failure evaluation, respectively. Median age was 74 years (interquartile range 69–77). Compared with 3D-CRT, in IMRT group more high-risk patients (29% vs 18%; $P = 0.002$) and more high-volume target (75% vs 60%; $P < 0.001$) were included. Acute gastro-intestinal (GI) toxicity $G > 1$ were registered in 8% and in 11% IMRT and 3D-CRT patients, respectively, whereas late GI $G > 1$ were observed in 2% and 16% IMRT and 3D-CRT patients, respectively. Acute genito-urinary (GU) toxicity $G > 1$ were registered in 26% and 40% IMRT and 3D-CRT patients, respectively, whereas late GU $G > 1$ occurred in 5% IMRT and 15% 3D-CRT patients. Multivariate proportional hazard Cox models confirmed significantly greater risk of late toxicity with 3D-CRT compared to IMRT for GU > 1 ($P = 0.004$) and for GI > 1 ($P < 0.001$). With a median 4-year follow-up, overall survival (OS), clinical progression-free survival (cPFS) and biochemical PFS (bPFS) for the whole series were 91%, 92% and 91%, respectively. cPFS and bPFS were significantly different by risk groups. Multivariate Cox models for bPFS and cPFS showed no difference between irradiation techniques and a significant impact of risk group and initial PSA. Moderately hypofractionated radiotherapy is a viable treatment option for localized PCa with excellent tumour control and satisfactory toxicity profile. IMRT seems associated with a reduction in toxicity, whereas tumour control was equal between IMRT and 3D-CRT patients and depended mainly on the risk category.

Keywords Prostate cancer · Image-guided radiotherapy · Hypofractionation · Dose escalation

Introduction

Prostate cancer (PCa) is the second most prevalent solid tumour diagnosed in men of the United States and Europe [1]. The standard non-surgical approach for localized PCa is radiation therapy (RT), conventionally given in 1.8/2-Gy per fraction, in combination with androgen deprivation therapy if needed. There is now convincing evidence that biochemical control is improved with dose escalation to the prostate [2]. One of the limitations of high-dose RT is the potential increase in both acute and late toxicity [3]. The technological improvements of the last decades, from three-dimensional

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conformal RT (3D-CRT) to intensity-modulated RT (IMRT) allowed to reduce the amount of potentially toxic high doses to rectum and urinary bladder [4]. At present time, several moderate hypofractionated trials have been carried out and information regarding the efficacy and safety of this approach is emerging [5, 6]. Data from institutional series and randomized trials suggest that the irradiation of prostate using a moderate hypofractionated regimen does not increase physician-assessed maximum urinary and intestinal toxicity compared to conventionally fractionated RT (CFRT) [7–9].

One of the first moderately hypofractionated schedule started at the Fox Chase Cancer Center (Philadelphia, PA, USA) in 2006 and was based on the daily dose of 2.7 Gy up to the total dose of 70.2 Gy in 26 fractions. Biologically, this schedule is equivalent to 84.4 Gy given in 2-Gy fractions, assuming α/β ratio for PCa of 1.5 Gy [10]. The preliminary report of the phase III randomized trial reported that hypofractionated RT results in less bowel symptoms than CFRT, with no increased burden of intestinal or urinary symptoms [11]. In addition, a recent study by Hoffman et al. confirmed the safety of this approach showing a comparable impact with conventional regimen on local toxicity [12].

The aim of this study is to assess the moderately hypofractionated image-guided RT (IGRT) using the Fox Chase Cancer Center's schedule in a single-institution series of patients with localized PCa, in terms of acute and late toxicity (primary endpoint). Additional outcomes were biochemical progression-free survival (bPFS), clinical progression-free survival (cPFS), prostate cancer-specific survival (PCSS) and overall survival (OS). Secondary outcome was the comparison of image-guided 3D-CRT versus IMRT.

Materials and methods

This retrospective study was performed within the notification presented to the Ethics Committee of IRCCS Istituto Europeo di Oncologia and Centro Cardiologico Monzino (via Ripamonti 435, 20141 Milano, Italy) regarding clinical and dosimetric aspects of hypofractionated IGRT for PCa (CE Notification No. 79).

Patients

Between October 2006 and December 2015, 572 T1-T3N0M0 PCa patients were treated at the Division of Radiotherapy of the Istituto Europeo di Oncologia with 3D-CRT and IMRT, receiving 70.2 Gy in 26 fractions at 2.7 Gy per fraction (equivalent to 84 Gy in 42 fractions, considering α/β of 1.5 Gy). Androgen deprivation therapy was added to RT in 217 patients (38%) and the median duration of assumption was 7 months (range 0.5–150).

Inclusion criteria

The inclusion criteria for moderate hypofractionated RT were as follows:

- Non-metastatic PCa (T1-T3N0M0);
- No concomitant inflammatory bowel disease;
- Non-significant severe comorbidity;
- Limited volume of the prostate and seminal vesicles (namely, clinical target volume (CTV) < 100 cm^3);
- Normal urodynamic study (no urinary obstruction, i.e. maximum urinary flow rate > 10 mL/s).

Patients were stratified into low-, intermediate- and high-risk groups, according to the National Comprehensive Cancer Network (NCCN) criteria [13]. Androgen deprivation was permitted for intermediate- and high-risk patients.

Treatment planning

Patients were asked to have full bladder and empty rectum before the acquisition of the planning computed tomography (CT) and each treatment session, as previously described in Jereczek-Fossa et al. [14].

As concerning 3D-CRT, two dynamic lateral 3D conformal 100° arcs were used, as described in [14]. The dose was prescribed in the International Commission of Radiation Units (ICRU) point [15]. Daily target localization has been previously described [14, 16], the choice being at discretion of the radiation oncologist and according to patient anatomy, imaging feasibility, etc.

In 2010, image-guided IMRT was implemented at our institution with Rapidarc™ (Varian Medical System, Palo Alto, CA). The delivered treatment consisted of one or two coplanar arcs, as described in Cambria et al. [17]. The patient set-up was checked by means of a cone-beam CT acquired by Varian OBI before each treatment fraction.

In 2012, Vero System (BrainLab AG, Feldkirchen, Germany and Mitsubishi Heavy Industries, Tokyo, Japan) was commissioned in our Institution. Moderately hypofractionated prostate IG-IMRT with this device was performed by means of 7 coplanar fixed fields.

CTV included the prostate in low-risk patients and the prostate and seminal vesicles (at least the proximal 10 mm) in the intermediate- or high-risk patients. The planning target volume (PTV) was obtained by adding a 7-mm margin to CTV in all directions, except posteriorly where a 3-mm margin was added. For 3D-CRT, an additional 5-mm margin was added in all directions beyond the PTV to account for the beam penumbra [18]. Dose-volume

histograms (DVH) for CTV, PTV, rectum, urinary bladder, and femoral heads were computed. DVH constraints have been established for conventional 3D-CRT based on Institutional clinical routine and scientific literature analysis [19]. For moderate hypofractionation, the constraints were recalculated using normalized total dose with α/β of 3 and 5 Gy for late responding tissues (rectum, urinary bladder, femoral heads). Based on this calculation, less than 30% of the rectal volume may receive a dose equal or greater than 61 Gy (86% of the total dose), and less than 60% of the rectal volume may receive a dose equal or greater than 35 Gy (50% of the total dose). Less than 50% of the urinary bladder volume may receive a dose equal or greater than 61 Gy (86% of the total dose) and less than 50% of femoral heads may receive a dose equal or greater than 43 Gy (61% of the total dose).

Follow-up procedure

RTOG/EORTC criteria were used to evaluate treatment toxicity [20]. Late toxicity was evaluated in patients with more than 3-month follow-up and within 4 years.

Biochemical progression-free survival (bPFS) was calculated from the date of end of RT to the date of first biochemical failure or last visit. Clinical progression-free survival (cPFS) was calculated from the date of end of RT to the date of first clinical progression or the date of last clinical assessment. Overall survival (OS) was calculated from the date of end of RT to the date of death or last contact with the patient. For patients lost to follow-up, information on vital status was obtained through municipal vital statistics offices. Houston criteria were used to define the biochemical failure (absolute nadir + 2 ng/mL at call) [21].

Statistical analysis

We used the Chi-squared test, the Mantel–Haenszel test for trend and the Student T-test to assess differences in the distribution of categorical, ordinal and continuous variables across groups of patients, respectively. Survival probabilities over time, as well as actuarial likelihood of late toxicity, were estimated by the Kaplan–Meier method [22], and differences over univariate subset of patients were evaluated by the log-rank test [23]. To calculate the impact of various patient, tumour, and treatment-related factors on tumour outcome and time to first late toxicity $G > 1$, multivariate proportional hazard Cox regression models were performed [24].

Statistical analyses were performed using the SAS statistical software (version 9.02 for Windows).

In order to compare the two cohorts of patients treated with image-guided 3D-CRT versus IMRT that had different median follow-ups, we carried out the analyses considering the first 48 months of both cohorts.

Results

Patient, tumour and treatment characteristics

The characteristics of the 572-patient cohort are summarized in Table 1. Mean age was 72.6 years (6.5 standard deviation). The majority had tumour stage T1 (61%). Gleason score was ≤ 7 in 82% of patients and concomitant diseases were reported in 89% patients. All patients completed radiotherapy: 344 patients (60%) were treated with image-guided 3D-CRT and 228 (40%) with IMRT, in particular 102 with Rapidarc™ and 126 with Vero System. Median duration of RT was 37 days (IQR: 36–41). Thirty-eight percent of patients received hormonal treatment.

Compared with 3D-CRT, in the IMRT group, we found significantly more high-risk patients (29% vs 18% respectively; $P = 0.002$), therefore more often received RT to prostate and seminal vesicles (75% vs 60%; $P < 0.001$) and more concomitant diseases (93% vs 85%; $P = 0.005$).

Treatment-related toxicity

Overall patient evaluation

Acute G1-G4 gastro-intestinal (GI) toxicity was registered for 79 patients (35%) with IMRT and 151 (44%) with 3D-CRT. Acute G1-G4 genito-urinary (GU) toxicity was observed in 159 patients (70%) with IMRT and 264 (77%) with 3D-CRT. Late GI toxicity was present in 21 patients (9%) with IMRT and 73 (21%) with 3D-CRT. Late GU toxicity was registered in 42 patients (19%) with IMRT and 89 (26%) with 3D-CRT (Table 2).

At 3 years, 91% of patients were free from late $G > 1$ GI and GU toxicity (Fig. 1). Concomitant diseases were not found to be associated with toxicity.

3D-CRT versus IMRT

Statistically significant more frequent acute and late $G > 1$ GI toxicity were found in 3D-CRT than IMRT (11% vs. 9%, $P = 0.035$ for acute and 16% vs 2%, $P < 0.001$ for late, respectively; Table 2; Fig. 2).

Statistically significant more frequent acute and late $G > 1$ GU toxicity were found in 3D-CRT than IMRT (40% vs 26%, $P = 0.014$, for acute and 15% vs 5%, $P = 0.002$, for late, respectively; Table 2; Fig. 2).

Multivariate Cox models for late $G > 1$ toxicity (Table 3) showed statistically significant increased risk of events in

Table 1 Patients and tumour characteristics and treatments

	Total	3D-CRT	IMRT	*P* value
	572	344	228	
T				
T1	348 (61)	209 (61)	139 (61)	0.407
T2	216 (38)	132 (38)	84 (37)	
T3	8 (1)	3 (1)	5 (2)	
Gleason score				
≤6	250 (44)	163 (47)	87 (38)	0.081
7	215 (38)	123 (36)	92 (40)	
8	72 (13)	39 (11)	33 (15)	
≥9	30 (5)	14 (4)	16 (7)	
Missing	5			
Age				
Median (IQR)	74 (69–77)	74 (69–77)	75 (69–77)	0.271
<60	28 (5)	20 (6)	8 (4)	0.376
60–64	51 (9)	28 (8)	23 (10)	
65–69	87 (15)	56 (16)	31 (14)	
70–74	161 (28)	100 (29)	61 (27)	
75–79	205 (36)	115 (33)	90 (40)	
80+	40 (7)	25 (7)	15 (6)	
Risk group				
Low	188 (33)	128 (37)	60 (26)	0.002
Intermediate	254 (44)	152 (44)	102 (44)	
High	127 (22)	61 (18)	66 (29)	
Missing	3			
iPSA				
7 (5; 11)	7 (5; 10)	8 (5; 11)	7 (5; 11)	0.071
<7	278 (49)	175 (51)	103 (45)	0.182
7 or more	294 (51)	169 (49)	125 (55)	
Indication RT				
Prostate	196 (34)	138 (40)	58 (25)	0.0003
Prostate + sv	376 (66)	206 (60)	170 (75)	
ADT				
No	355 (62)	213 (62)	142 (62)	0.930
Yes	217 (38)	131 (38)	86 (38)	
Concomitant diseases				
No	63 (11)	48 (14)	15 (7)	0.005
Yes	506 (89)	293 (85)	213 (93)	
Missing	3			
Diabetes	81 (14)	41 (12)	40 (18)	0.056
Cardiopathy	106 (19)	64 (19)	42 (19)	0.975
Hypertension	235 (41)	133 (39)	102 (45)	0.136
Vasculopathy	42 (7)	22 (6)	20 (9)	0.279
Connective tissue dis	2 (0.35)	0 (0)	2 (0.88)	0.0812
Diverticulosis	37 (6)	16 (5)	21 (9)	0.0289
Hip prosthesis	15 (3)	6 (2)	9 (4)	0.1045
Other cancer	54 (9)	25 (7)	29 (13)	0.0277
Polyposis	10 (2)	3 (1)	7 (3)	0.0486

P values are obtained with Chi-square or Fisher's exact tests for categorical variables; Mantel–Haenszel test for ordinal variables (trend); Wilcoxon rank test for continuous variables. Risk groups are defined according to the National Comprehensive cancer Network (NCCN) criteria

3D-CRT three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy, *T* tumour stage, *IQR* interquartile range, *iPSA* initial prostate-specific antigen, *RT* radiation therapy, *sv* seminal vesicles, *ADT* androgen deprivation therapy

3D-CRT compared to IMRT for both GU ($P=0.004$) and GI ($P<0.001$) adjusting for age and indication.

Oncological outcome measures

Overall patient evaluation

The actuarial 3-year bPFS, cPFS and OS were 94% (Fig. 1).

At univariate analysis, age, risk group, initial PSA, Gleason score, hormonal treatment and RT to the prostate and seminal vesicles (performed in intermediate- and high-risk cases) were found to be significantly associated with biochemical progression. Similar trends were found for clinical progression. In particular, statistically significant more frequent biochemical relapse at 3 years (5% vs 17%; Log-rank test $P<0.001$) and clinical relapse (5% vs 14%; Log-rank test $P<0.001$) were found in high-risk patients compared to low- and intermediate-risk patients (Fig. 2). Deaths were similar in the high-risk patients compared to low and intermediate risk (7.7% vs 8.6%; Log-rank test $P=0.52$).

In low- and intermediate-risk patients, we found a statistically significant better outcome with indication for RT to prostate-only vs RT to prostate and seminal vesicle (intermediate risk) and in the high-risk patients a significant association with initial PSA. Similar trends were observed for OS.

3D-CRT versus IMRT

Since high-risk patients were more frequently treated with IMRT than 3D-CRT, multivariate analyses for tumour outcome were stratified by risk groups. Multivariate Cox regression models for bPFS and cPFS showed no statistically significant difference between irradiation techniques in terms of tumour outcome, adjusting for age, indication to RT and initial PSA (Table 4). OS was also similar for patients treated with 3D-CRT and IMRT.

Discussion

The present study including 572 PCa patients showed a satisfactory toxicity profile and tumour outcome of moderate hypofractionated RT. IMRT was correlated with significant reduction in both acute and late GU and GI toxicity, whereas tumour control was comparable between IMRT and 3D-CRT patients and depended mainly on the risk category. To address the issue of prolonged treatment duration (with extended access to RT facilities and additional burden on

Table 2 Acute and late toxicity by grade and treatment modality

Type of toxicity	Type of RT	Tot	G1	G2	G3	G4	*P* value
Acute							
Genito-urinary, *n* (%)	IMRT	159 (70)	101 (45)	49 (22)	7 (3)	2 (1)	0.014
	3D-CRT	264 (77)	128 (37)	116 (34)	16 (5)	4 (1)	
Gastro-intestinal, *n* (%)	IMRT	79 (35)	59 (26)	19 (8)	0 (0)	1 (0)	0.035
	3D-CRT	151 (44)	112 (33)	35 (10)	4 (1)	0 (0)	
Late							
Genito-urinary, *n* (%)	IMRT	42 (19)	31 (14)	11 (5)	0 (0)	0 (0)	0.002
	3D-CRT	89 (26)	38 (11)	47 (14)	4 (1)	0 (0)	
Gastro-intestinal, *n* (%)	IMRT	21 (9)	14 (6)	5 (2)	1 (0)	1 (0)	< 0.001
	3D-CRT	73 (21)	19 (6)	34 (10)	19 (6)	1 (0)	

Acute toxicity is evaluated within 3 months. Late toxicity is evaluated for more than 3 months and within 48 months from radiotherapy

RT radiation therapy, *3D-CRT* three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy, *n* number, *G* grade

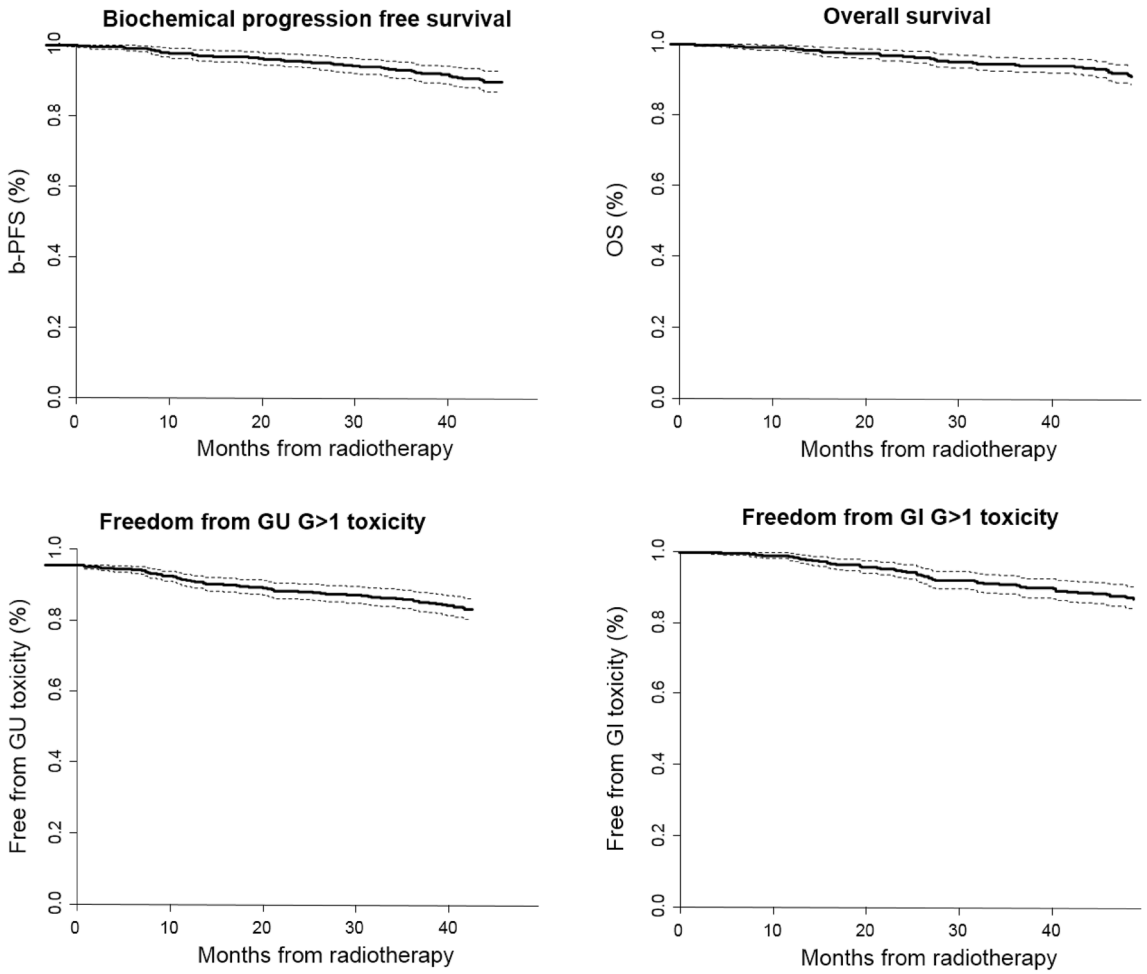

Fig. 1 Outcome and toxicity over time for overall population. Kaplan–Meier curves presenting biochemical progression-free survival, overall survival and freedom from genito-urinary and gastro-intestinal grade > 1 toxicity for overall patient population. *b-PFS* biochemical progression-free survival, *OS* overall survival, *G* grade, *GU* genito-urinary, *GI* gastro-intestinal

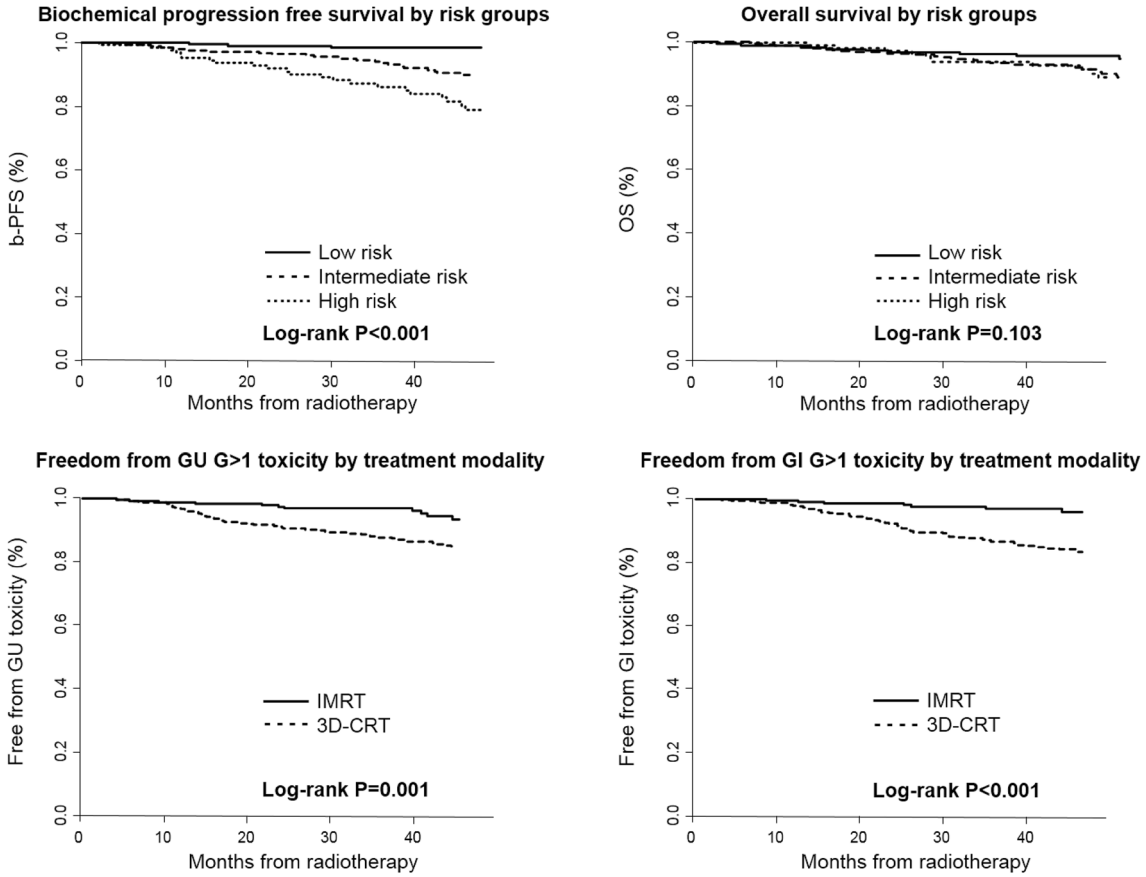

Fig. 2 Outcome and toxicity over time by groups. Kaplan–Meier curves presenting biochemical progression-free survival, overall survival and freedom from genito-urinary and gastro-intestinal grade > 1 toxicity by risk groups, defined according to NCCN classification, and by treatment modality. *b-PFS* biochemical progression-free survival, *OS* overall survival, *G* grade, *GU* genito-urinary, *GI* gastro-intestinal, *IMRT* intensity-modulated radiation therapy, *3D-CRT* three-dimensional conformal radiation therapy

both patients and staff) while maintaining equivalent PFS, an increasing number of studies have pursued the role of hypofractionated RT with higher daily doses delivered in a shorter amount of time. With longer-term and randomized hypofractionated RT data now reported in the literature, it seems appropriate to argue whether the time has come to make hypofractionation the new standard.

To the best of our knowledge, this is the largest published series treated with the Fox Chase moderate hypofractionation schedule. The original randomized Fox Chase study included 303 patients and 151 of them received hypofractionated radiotherapy [8, 25].

Pollack et al. planned a randomized controlled trial using data from a large retrospective database available at Fox Chase Cancer Center, including patients with intermediate- or high-risk PCa receiving 76 Gy in 2-Gy fractions or 70.2 Gy in 2.7-Gy fractions with or without concomitant androgen deprivation therapy. The hypofractionation regimen did not result in a significant reduction of tumour outcome: the 5-year rates of biochemical and/or clinical recurrence rate were 21.4% (95% CI 14.8–28.7%) for the conventional arm and 23.3% (95% CI 16.4–31.0%) for the hypofractionation arm (P value = 0.745). No statistically significant differences in late toxicity between two arms were observed, though men with compromised urinary function before treatment may not be ideal candidates for this approach [8]. Further multi-institutional, randomized, non-inferiority trials, including the Conventional or Hypofractionated High-dose Intensity-modulated RT for Prostate cancer (CHHiP) trial [26], the Dutch Hypofractionated Irradiation for Prostate cancer (HYPRO) trial [27], the RTOG 0415 trial [28] and the Prostate Fractionated Irradiation (PROFIT) trial [29] provide a conclusive answer about non-inferiority of moderate hypofractionation with respect to conventional fractionation and are likely to lead to the widespread adoption of the hypofractionation regimen [30]. With the exception of the HYPRO trial, available clinical evidence supported the idea that the short-term safety and efficacy of these experimental regimens are comparable to that of standard fractionation [31, 32].

Our results are confident with these findings, showing that hypofractionation for PCa is feasible and very

Table 3 Multivariate models for acute and late toxicity of grade ≥ 1

		OR (95%CI)	*P* value
Acute toxicity			
GU	IMRT vs. 3D-CRT	0.71 (0.48; 1.03)	0.071
	Age	1.00 (0.97; 1.03)	0.767
	Hormonal treatment	1.39 (0.94; 2.05)	0.096
GI	IMRT vs. 3D-CRT	0.66 (0.47; 0.94)	**0.022**
	Age	1.03 (1.00; 1.06)	0.039
	Hormonal treatment	1.82 (1.27; 2.62)	0.001
		HR (95%CI)	*P* value
Late toxicity			
GU	IMRT vs. 3D-CRT	0.38 (0.20, 0.74)	**0.004**
	Age	1.03 (0.99, 1.07)	0.160
	Indication to RT	1.91 (1.15, 3.16)	0.013
GI	IMRT vs. 3D-CRT	0.21 (0.10, 0.47)	**< 0.001**
	Age	1.03 (0.98, 1.07)	0.217
	Indication to RT	0.86 (0.50, 1.48)	0.597

Significant values ($P \leq 0.05$) are given in bold

Indication to RT indicates 'prostate vs. prostate and seminal vesicles'

3D-CRT three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy, *OR* odds ratio, *CI* confidence interval, *HR* Hazard ratio

well tolerated, with the vast majority of patients free from late side effects. Moreover, the use of different modalities (IMRT vs 3D-CRT) did not affect oncological outcomes.

The advantages of IMRT over 3D-CRT in terms of induced toxicity have been studied in several studies, demonstrating that IMRT usually reduces GI toxicity, with no significant differences in GU toxicity [33–35]. A recent meta-analysis from Yu et al. [33] showed a lower incidence of GI toxicity and a slightly higher incidence of GU toxicity in IMRT. As reported by several dosimetric studies, rectal sparing is increased by using IMRT with respect to 3D-CRT, whereas bladder sparing may not be significant [36, 37]. Our study confirms the results related to the reduction in GI toxicity with IMRT, whereas we found a decrease also in GU toxicity. This benefit could be potentially explained by the strict treatment protocol, requiring a filling bladder volume of at least 200 cm^3 before each treatment session. Moreover, the used image-guidance protocols contributed to increase the precision of dose delivery, with reduction of the dose to organs at risk (urinary bladder, rectum and bowel) as a consequence of increased positioning accuracy and reduction in planning safety margins. It is worthwhile to note that our population included patients treated for prostate-only or prostate and seminal vesicles, excluding high-volume patients treating pelvis, which may contribute to the observed decreased in both GI and GU toxicity. On the other hand, despite in IMRT group there was a higher incidence of bigger volumes (prostate and seminal vesicles) with respect to 3D-CRT group, this technique resulted in significant reduction of induced toxicity.

The strength of our study included a consistent use of modern highly conformed technique in all patients, the use of the

Table 4 Cox models for oncological outcome

Outcome	Risk groups		HR (95%CI)	*P* value
Biochemical	Low-intermediate	IMRT vs. 3D-CRT	1.72 (0.78, 3.78)	0.181
		Age	1.07 (0.99, 1.15)	0.077
		Indication to RT	0.12 (0.03, 0.49)	0.003
	High	IMRT vs. 3D-CRT	1.99 (0.83, 4.76)	0.121
		Age	1.02 (0.94, 1.10)	0.707
		iPSA	1.01 (1.00, 1.02)	0.012
Clinical	Low-intermediate	IMRT vs. 3D-CRT	1.82 (0.79, 4.23)	0.161
		Age	1.05 (0.97, 1.13)	0.215
		Indication to RT	0.13 (0.03, 0.56)	0.006
	High	IMRT vs. 3D-CRT	1.65 (0.64, 4.26)	0.303
		Age	1.00 (0.92, 1.09)	0.971
		iPSA	1.01 (1.00, 1.02)	0.011
Overall survival	Low-intermediate	IMRT vs. 3D-CRT	0.52 (0.23, 1.21)	0.128
		Age	1.04 (0.98, 1.10)	0.178
		Indication to RT	0.50 (0.24, 1.05)	0.068
	High	IMRT vs. 3D-CRT	0.52 (0.14, 1.98)	0.335
		Age	0.97 (0.88, 1.06)	0.473
		iPSA	1.01 (1.00, 1.02)	0.094

Indication stands for "prostate vs. prostate and seminal vesicles"

3D-CRT three-dimensional conformal radiation therapy, *IMRT* intensity-modulated radiation therapy, *iPSA* initial prostate-specific antigen, *HR* Hazard ratio, *CI* confidence interval

Houston definition and the employment of the clinical endpoint (cPFS and OS) [22, 23], differently from the majority of dose escalation studies which consider only biochemical control, although it is not a true surrogate outcome for PCa-specific survival [24]. Although our study showed very favourable results in terms of outcome and late toxicity, it has some limitations: this is a retrospective study with 4-year follow-up and we did not evaluate the baseline urinary function and quality of life of the patients treated with different modalities. For the clear-cut assessment of long-term complications and the clinical outcome, a follow-up time exceeding 10 years is required. Also the comparison between IMRT and 3D-CRT comes not from a randomized study but from two cohorts of patients treated in different time periods. Moreover, a dosimetric comparison of two radiotherapy techniques (3D-CRT and IMRT) is missing. However, the large number of "real-world" patients treated at one academic center and followed for a long period of time after radiotherapy constitute a next piece of the growing body of literature suggesting that hypofractionation may be an excellent treatment modality in non-metastatic prostate cancer.

Conclusion

The presented results confirm that image-guided moderately hypofractionated RT is a viable treatment option for localized PCa in terms of toxicity and clinical outcome. IMRT allowed a significant reduction of RT acute and late toxicity when compared to 3D-CRT. Further investigation is warranted in order to exclude the bias due to the non-randomized character of the study.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethical approval In this research, no animals were involved. All patients signed a written informed consent for radiation therapy and written informed consent for the use of the anonymized data for research or educational purpose. The study was performed within the Institutional Ethics Committee notification regarding clinical and dosimetric aspects of hypofractionated image-guided RT (IGRT) for PCa (CE Notification No. 79).

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