Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Late toxicity for prostate cancer patients treated with hypofractionated helical tomotherapy

Elona Cekani[a,1], *José Luis López-Guerra*[b,*,1], *Rodrigo Barrientos*[a], *Patricia Tavera*[c], *Juan Manuel Praena-Fernandez*[d], *Eleonor Rivin del Campo*[e], *Ignacio Azinovic*[c], *Raul Matute*[f]

[a] *Máster Internacional en Aplicaciones Tecnológicas Avanzadas en Oncología Radioterápica de la Universidad de Murcia, GenesisCare Fundación, Madrid, Spain*
[b] *Department of Radiation Oncology, University Hospital Virgen del Rocio, Sevilla, Spain*
[c] *Department of Radiation Oncology, GenesisCare, Madrid, Spain*
[d] *Methodology Unit, University Hospital Virgen del Rocio, Spain*
[e] *Department of Radiation Oncology, Tenon University Hospital, Paris, France*
[f] *Department of Radiation Oncology, University Hospital La Paz, Madrid, Spain*

ARTICLE INFO

Article history:
Received 15 May 2018
Received in revised form
17 January 2019
Accepted 20 April 2019

Keywords:
Prostate cancer
Late toxicity
Helical tomotherapy
Radiation therapy
Hypofractionation

ABSTRACT

Aim: The purpose of this study is to evaluate the long term tolerability of hypofractionated helical tomotherapy (HT) in localized prostate cancer patients.
Background: Previous hypofractionated schedules with conventional RT were associated with excessive toxicity, likely due to inadequate sophistication of treatment delivery. There are few data about late toxicity after HT.
Materials and methods: We evaluated 38 patients with primary adenocarcinoma of the prostate. There were 9 (24%), 15 (39%), and 14 (37%) patients with high, intermediate, and low risk, respectively. Patients were treated with hypofractionated HT from May 2008 to February 2011. Hypofractionation regimens included: 68.04 Gy at 2.52 Gy/fraction ($N = 25$; 66%), 70 Gy at 2.5 Gy/fraction ($N = 4$; 11%) and 70.2 Gy at 2.6 Gy/fraction ($N = 9$; 23%). Late genitourinary (GU) and gastrointestinal (GI) toxicity was scored using the Radiation Therapy Oncology Group scoring system.
Results: Median age at diagnosis was 70 years (range 49–80) and median follow-up, 5.8 years. Late grade 1, 2 and 3 GI toxicity were 13%, 24%, and 2.6%, respectively. Late grade 1, 2, 3 GU toxicity were 29%, 21%, and 8%, respectively. Sexual toxicity was evaluated in 19 patients to be grade 1, 2 in 11% and grade 3 in 16%. Multivariate analysis showed that patients with higher values of rectum V50 associated with late GI toxicity ($P = 0.025$). Patients with PSA ≤ 8 ($P = 0.048$) or comorbidities ($P = 0.013$) at diagnosis were associated with higher late GU toxicity. Additionally, PSA ≤ 8 also associated with moderate (grade ≥ 2) late GU toxicity in the multivariate analysis ($P = 0.028$).

* *Corresponding author at*: Department of Radiation Oncology, Virgen del Rocío University Hospital, Manuel Siurot avenue, s/n. 41013, Seville Spain.
E-mail address: chanodetriana@yahoo.es (J.L. López-Guerra).
[1] These authors contributed equally to this work.
https://doi.org/10.1016/j.rpor.2019.04.001

Conclusions: Hypofractionated HT can be delivered safely with limited rates of moderate and severe late toxicity. The proportion of the rectum that receives a moderate and high dose, having comorbidities, and PSA at diagnosis seem to associate with long term toxicity.

1. Background

Prostate cancer is the most common cancer in men in the United States[1] and the second most common one in the European Union.[2] Although Phase III randomized trials have shown improved biochemical control rates in the treatment of localized prostate cancer with radiotherapy (RT) above 70 Gy, a significantly higher risk of late toxicity was observed for patients treated in the high-dose arms of these studies.[3–5] Consequently, several strategies have been proposed to limit the radiation-induced toxicity, such as the use of intensity-modulated RT (IMRT).

Sensitivity of prostate cancer cells is characterized by a low α/β ratio in the range of 0.8–2.2 Gy,[6] thus delivering treatment fractions higher than the standard 2 Gy/fraction may be radiobiologically effective. Furthermore, delivering a higher dose in a reduced number of fractions may be most convenient for patients and logistically advantageous for busy RT departments. The drawback of a hypofractionated schedule is the potential increase in toxicity. Previous hypofractionated schedules with conventional RT (i.e. three-dimensional conformal RT [3DCRT]) were associated with excessive toxicity, likely due to inadequate sophistication of treatment delivery plan design and targeting.

The advent of conformal techniques has enabled the delivery to be tailored to individual patient anatomy.[7] The sharp dose gradients created with helical tomotherapy (HT) can shape the high dose region to the planning target volume and limit the dose to the bladder, rectal wall, and femoral heads. Image guided RT (IGRT) for prostate cancer allows the adjustment and positional correction of the radiation beams based on daily imaging to account for the variability of the target position. IGRT potentially represents a more accurate form of dose delivery for patients receiving radiotherapy for prostate cancer. Given the more targeted nature of these treatments, margins routinely used around the clinical target volume to account for organ motion and variability of the target position can be further reduced if daily positional correction of the treatment target is performed.[8] Although evidence of dose-fraction sensitivity of the late responding normal tissues has continued to accumulate in RT for prostate cancer, the knowledge of how this relates to a hypofractionated treatment approach remains sparse.[9]

The purpose of this study was to evaluate the incidence and severity of late toxicity in patients with localized prostate cancer treated with hypofractionated HT as well as the assessment of potential risk factors, with the hypothesis that increasing the dose per fraction is possible without increasing the risk of late injury to the surrounding normal tissue.

2. Aim

The purpose of this study is to evaluate the long term tolerability of hypofractionated helical tomotherapy (HT) in localized prostate cancer patients.

3. Materials and methods

3.1. *Selection criteria*

The institutional review board approved a retrospective chart review, which was conducted for individuals with prostate cancer treated with hypofractionated HT from August 2008 through Feb 2011. Inclusion criteria were having a primary diagnosis of adenocarcinoma of the prostate (cT1-T3N0M0), no prior history of pelvic surgery or RT, and having a minimum follow-up of 3 years. We identified 38 patients (Table 1) who met such criteria. Patients were grouped according to the clinical TNM staging system[10] and D'Amico[11] risk classification score. Pretreatment evaluation consisted of documented history and physical examination, including performance status and digital rectal examination. Serum prostate-specific antigen (PSA) values and transrectal ultrasound-guided biopsy of the prostate were obtained before RT. Abdominal evaluation with computed tomography ± magnetic resonance imaging was also required before radiation treatment.

3.2. *Treatment*

Patient immobilization and treatment planning has been previously described.[12] Briefly, the planning tumor volume (PTV) was defined by a 5- to 9-mm margin around the prostate capsule (5 mm in the antero-posterior direction, 7 mm in the lateral direction, and 9 mm in the cranial caudal direction). Hypofractionation regimens included: 68.04 Gy at 2.52 Gy/fraction ($N = 25$; 66%), 70 Gy at 2.5 Gy/fraction ($N = 4$; 11%) and 70.2 Gy at 2.6 Gy/fraction ($N = 9$; 23%). Dosimetric parameters for radiation treatment planning are shown in Table 2. Median treatment duration was 40 days (range, 34 to 44). Concurrently, high-risk patients received a conventionally fractionated schedule of radiation to the pelvic lymph nodes (48.6 Gy at 1.8 Gy/fraction) and distal seminal vesicles (54 Gy at 2 Gy/fraction). Neoadjuvant androgen deprivation therapy (ADT) was given to intermediate ($N = 15$) and high-risk patients ($N = 9$). In addition, three low risk patients received neoadjuvant ADT due to a large prostate volume. Finally, high-risk patients also received adjuvant ADT.

Table 1 – Patient characteristics.

Characteristic	Num. of patients (%)
Median age in years (range)	69 (49–80)
Past medical history ($N = 27$)[a]	
Cardiovascular disease or risk factors[b]	19 (70)
Urinary symptoms	11 (40)
Gleason	
<7	22 (58)
7	15 (39)
>7	1 (3)
T stage	
T1	20 (53)
T2	16 (42)
T3	2 (5)
PSA (ng/mL)	
<10	25 (66)
10–19	7 (18)
>20	6 (16)
Risk	
Low	14 (37)
Intermediate	15 (39)
High	9 (24)
Androgen deprivation	
No	11 (29)
Yes	29 (71)
Fractionation (Gy)	
≤2.52	29 (76)
>2.52	9 (24)
Radiation dose (Gy)	
<70	25 (66)
≥70	13 (34)
PLNs irradiation	
No	31 (82)
Yes	7 (18)
Prostate PTV volume (cc)	
Median (range)	137 (73–397)

Abbreviations: Num., number; PSA, prostate specific antigen; PLNs, pelvic lymph nodes; PTV, planning tumor volume.

[a] Eleven patients did not report past experiences with illnesses, operations or injuries.

[b] Cardiovascular risk factors included: hypertension ($N = 6$), diabetes ($N = 6$) and dyslipidemia ($N = 8$).

3.3. *Patient follow-up*

During the course of radiotherapy, patients were seen at least weekly, and more often if needed, for clinical evaluation and disease management. They were evaluated at approximately 1–3 months after completion of therapy and then every 3 months. The follow-up evaluations consisted of a history and physical examination. PSA values were obtained every 3 months for the first year after treatment, every 6 months for 2 years, and annually thereafter during follow-up. Imaging and additional studies were obtained at the discretion of the treating physician.

3.4. *Statistical methods*

All data analyses were done using SPSS (version 19.0) statistical software. The primary endpoint was the occurrence of late GU and GI toxicity scored by the RTOG scoring system.[13] Cox proportional hazards analysis was performed to calculate odds ratios (ORs) and confidence intervals (CIs) to evaluate the influence of patient, tumor, and treatment characteristics on risk of late toxicity. Multivariate analyses were performed by using a logistic regression model, with a stepwise backward elimination procedure. A P value of less than 0.05 was considered statistically significant.

Table 2 – Dosimetric parameters for radiation treatment planning.

Dosimetric parameter	Median (range)
Bladder D_{max} (Gy)	71 (69–75)
Bladder D_{min} (Gy)	2 (0.7–24)
Bladder median dose (Gy)	36 (17–51)
Bladder V_5 (%)	100 (100)
Bladder V_{10} (%)	94 (41–100)
Bladder V_{60} (%)	17 (7–30)
Bladder V_{65} (%)	12 (3–26)
Bladder V_{70} (%)	3 (0–20)
Rectum D_{max} (Gy)	72 (69–74)
Rectum median dose (Gy)	35 (18–45)
Rectum V_5 (%)	100 (100)
Rectum V_{10} (%)	93 (52–100)
Rectum V_{50} (%)	24 (7–30)
Rectum V_{55} (%)	19 (7–30)
Rectum V_{60} (%)	14 (5–26)
Rectum V_{65} (%)	11 (3–21)
Rectum V_{70} (%)	2 (0–14)
Femoral head D_{max} (Gy)	34 (21–53)
Femoral head median dose (Gy)	19 (12–33)
Femoral head V_5 (%)	100 (88–100)
Femoral head V_{10} (%)	100 (75–100)
Femoral head V_{50} (%)	0 (0–0.3)
Small bowel[a] D_{max} (Gy)	33 (2–67)
Small bowel[a] median dose (Gy)	2 (1–25)
Small bowel[a] V_5 (%)	5 (0–100)
Small bowel[a] V_{10} (%)	2 (0–100)
Small bowel[a] V_{50} (%)	0 (0–3.38)
Penile bulb[b] D_{max} (Gy)	66 (49–73)
Penile bulb[b] median dose (Gy)	53 (34–68)
Penile bulb[b] V_5 (%)	100 (100)
Penile bulb[b] V_{10} (%)	100 (100)
Penile bulb[b] V_{50} (%)	72 (0–100)

Abbreviations: D_{max}, maximum radiation dose; D_{min}, minimum radiation dose; V_x, percentage of organ volume receiving ≥x radiation dose.

[a] Available in 19 patients.

[b] Available in 9 patients.

Table 3 – Late complications for all patients according to Radiation Therapy Oncology Group toxicity grading scale.

	Genitourinary toxicity Num. patients (%)	Gastrointestinal toxicity Num. patients (%)
Grade 1	11 (29)	5 (13)
Grade 2	8 (21)	9 (24)
Grade 3	3 (8)	1 (2.6)

4. Results

Median age at diagnosis was 70 years (range 49–80) and median follow-up, 6 years (range 3–8). Late grade 1, 2 and 3 gastrointestinal (GI) toxicity were 13% ($N = 5$), 24% ($N = 9$), and 2.6% ($N = 1$), respectively (Table 3). Late grade 1, 2 and 3

genitourinary (GU) toxicity were 29% ($N = 11$), 21% ($N = 8$), and 8% ($N = 3$), respectively. Patients with pelvic treatment did not experience any late grade ≥2 GU toxicity. Sexual toxicity was evaluated in 19 patients being to be 1, 2 in 11% and grade 3 in 16%. Five patients (13%) had biochemical recurrence. Additionally, two of these patients also had bone metastasis.

Univariate analysis (Table 4) showed that patients with higher values of rectum V50, V60, V65 and V70 associated with late grade ≥1 GI toxicity (OR: 5.15; CI: 1.23–21.5; $P = 0.025$) but only V50 retained significance after multivariate analysis (Fig. 1; late grade ≥1 GI toxicity: 21% vs. 58%; OR: 5.15; CI: 1.23–21.5; $P = 0.025$). Patients having diagnosis PSA >8 (median) or higher values (>5 Gy) of bladder minimum dose (OR: 0.15; CI: 0.03–0.65; $P = 0.012$) associated with lower late GU toxicity (Grade ≥ 1). In contrast, having comorbidities at diagnosis was associated with higher late GU toxicity (OR: 12.86; CI: 2.22–74.54; $P = 0.004$). Multivariate analysis showed that only PSA ≤8 (late grade ≥1 GU toxicity: 79% vs .37%; $P = 0.048$) or comorbidities at diagnosis (late grade ≥1 GI toxicity: 74% vs. 18%; $P = 0.013$) associated with higher late GU toxicity. Comorbidities associated with greater toxicity were mainly cardiac risk factors (hypertension [$N = 5$], dyslipidemia [$N = 4$], obesity [$N = 2$], diabetes [$N = 5$],) or heart diseases ($N = 4$), and history of inguinal hernia ($N = 7$) or genitourinary diseases (kidney stones [$N = 4$], benign prostatic hyperplasia [$N = 2$], and history of transurethral resection [$N = 3$]).

Patients with Intermediate/high risk prostate cancer had lower risk of having late grade ≥2 GU toxicity (OR: 0.2; CI: 0.04–0.89; $P = 0.035$). The use of androgen deprivation (OR: 0.09; CI: 0.02–0.5; $P = 0.005$) or PSA >8 (OR: 0.05; CI: 0.006–0.45; $P = 0.008$) was also associated with a lower risk of having late grade ≥2 GU toxicity. Finally, those cases with a past history of heart disease associated with a higher risk of having late grade ≥2 GU toxicity (OR: 7.65; CI: 1.37–42.71; $P = 0.02$). PSA >8 was the only parameter retaining significance in the multivariate analysis (late grade ≥2 GU toxicity: 40% vs. 8%; OR: 0.08; CI: 0.008–0.78; $P = 0.028$) while the use of androgen deprivation showed marginal significance ($P = 0.062$). We did not find any statistically significant association between having acute GU or GI toxicity and the development of late toxicity.

5. Discussion

Many studies have demonstrated that biochemical recurrence is reduced when performing dose escalation from 68–70 Gy to 76–79 Gy.[14] Several large scale trials[15,16] on moderate hypofractionation with doses from 2.4–3.4 have published their results with equivalent outcomes to conventional RT. A theoretical radiobiological rational[17] supports the use of hypofractionation, especially for men with favorable baseline bladder and bowel function. Our pertinent findings can be summarized as follows. First, we found that moderate late GI and GU toxicity is experienced by one out of four (~25%) and five (~20%) prostate cancer patients treated with hypofractionated HT, respectively. In addition, we found that the rate of grade ≥3 late toxicity was less than three and ten percent for GI and GU symptoms, respectively. Second, we found that patients with higher values of rectum V50 associated with late GI toxicity, increasing the risk of suffering this toxicity considerably (21% vs. 58%). Third, we found that patients with PSA ≤8 or comorbidities at diagnosis were associated with higher late GU toxicity. Finally, we found that PSA ≤8 also associated with moderate (grade ≥2) late GU toxicity. Our findings suggest that hypofractionated HT appears to be a safe therapeutic option in patients with prostate cancer.

Luka et al.,[18] reported the outcome of a randomized trial comparing two fractionation schedules for patients with localized prostate cancer. The hypofractionated arm included patients treated at 52.5 Gy in 20 fractions with late grade 3–4 GU and GI toxicity as low as 1.9% and 1.3%, respectively. The biologically equivalent dose (BED) calculated in 2-Gy was 119.6 Gy, which is 20% lower than ours. The CHHiP trial[15] assessed the efficacy and side-effects of two hypofractionated schedules (60 Gy in 20 fractions or 57 Gy in 19 fractions). The British trial reported grade 3–4 GU and GI late toxicity of 0% and 1.4%, respectively, in the 57 Gy group, and 2.2% and 3.6%, respectively, in the 60 Gy group. Although the BED was similar to ours, the GU toxicity rates reported were much lower than what we found. This divergence may be partially explained by the existence of different patient selection and treatment methods: the CHHIP trial did not allow comorbid conditions precluding radical radiotherapy and pelvic lymph nodes were not included in the target volumes. The phase III trial of Arcangeli et al.,[19] reported the toxicity of patients treated at 62 Gy in 3.1-Gy fractions. The 3-year incidence of late complications ≥grade 2 was 17% for GI and 16% for GU complications. A correlation of toxicity with dose–volume parameters was not found in that study.

Pollack et al.,[20] described the late side effects observed in patients treated with 70.2 Gy in 26 fractions at 2.7 Gy per fraction. The overall incidences of grade 1, 2, and 3 late GI reactions were 53.7%, 16.1%, and, 2.0%, respectively. In terms of GU toxicity, the overall (crude) incidences of grade 1, 2, and 3 late GU reactions were 51.7%, 40.9%, and 4.0%, respectively. The phase 3 trial of the MD Anderson Cancer Center[21] showed that a modest decrease from 42 to 30 (72 Gy/2.4 Gy) fractions appeared to yield a similar GU toxicity profile but a concerning increase in rectal toxicity, particularly in men receiving a large total dose to the rectum. The actuarial 5-year grade ≥2 GU toxicity was 15.8% and the grade ≥2 GI toxicity was 10.0%. Kupelian et al.,[22] reported the best outcome in terms of late toxicity. The experience of the Cleveland Clinic included patients with localized prostate cancer treated with hypofractionated IMRT at 70 Gy delivered at 2.5-Gy/fraction within 5 weeks. The actuarial late RTOG grade 2 or worse rectal toxicity rate at 5 years was 6% and the grade 3 or worse rectal toxicity rate at 5 years was 2%. The actuarial late RTOG grade 2 or worse urinary toxicity rate at 5 years was 7% and only one grade 3 late urinary toxicity developed. The series of patients were all treated with transabdominal ultrasonography as daily image guidance system.

We found that patients with higher rectum V50 associated with an increase of late GI toxicity. Pollack et al.,[20] examined baseline factors for association with onset of late toxicity. The trial identified in the univariate analyses that organ volumes above the high-constraint dose marker (V50 >25%) for the bladder and low-dose marker (V31 >35%) for the rectum as significant. However, none of the factors examined were significant in the multivariate analysis. In agreement with our study, the MD Anderson Cancer Center[21] found that

Table 4 – Univariate analysis of factors associated with late genitourinary (GU) and gastrointestinal (GI) toxicity.

Variable	Late GU toxicity ≥1		Late GU toxicity ≥2		Late GI toxicity ≥1		Late GI toxicity ≥2	
	OR	*P* value	OR	*P* value	OR	*P* value	OR	*P* value
Age (years)								
≤Median	1.00		1.00		1.00		1.00	
>Median	1.54	0.51	1.29	0.72	1.24	0.74	1.00	1.00
Comorbidities at diagnosis								
No	1.00		1.00		1.00		1.00	
Yes	12.86	**0.004**	5.88	0.11	2.13	0.33	1.89	0.47
Heart disease								
No	1.00		1.00		1.00		1.00	
Yes	3.85	0.05	7.65	**0.020**	0.51	0.32	0.57	0.46
PSA								
≤Median	1.00		1.00		1.00		1.00	
>Median	0.15	**0.012**	0.05	**0.008**	0.80	0.74	0.58	0.46
Risk								
Low	1.00		1.00		1.00		1.00	
Intermediate/high	0.12	**0.014**	0.20	**0.035**	1.28	0.71	1.51	0.60
Androgen deprivation								
No	1.00		1.00		1.00		1.00	
Yes	0.00	0.99	0.09	**0.005**	0.71	0.66	0.93	0.93
Fractionation (Gy)								
≤2.52	1.00		1.00		1.00		1.00	
>2.52	3.26	0.18	4.79	0.05	2.37	0.27	3.06	1.17
Radiation dose (Gy)								
>70	1.00		1.00		1.00		1.00	
≥70	0.77	0.71	1.97	0.35	1.52	0.54	2.50	0.23
Prostate PTV (cc)								
≤Median	1.00		1.00		1.00		1.00	
>Median	0.64	0.51	0.77	0.72	1.24	0.74	0.57	0.46
PLNs treatment								
No	1.00							
Yes	0.22	0.09		NA		NA		NA
Bladder D_{max} (Gy)								
≤Median	1.00		1.00					
>Median	0.64	0.51	1.79	0.72		NA		NA
Bladder D_{min} (Gy)								
≤Median	1.00		1.00					
>Median	0.15	**0.012**	0.25	0.08		NA		NA
Bladder median dose (Gy)								
≤Median	1.00		1.00					
>Median	0.26	0.05	0.77	0.72		NA		NA
Bladder V_5 (%)								
≤Median	1.00		1.00					
>Median	0.19	**0.023**	0.39	0.21		NA		NA
Bladder V_{10} (%)								
≤Median	1.00		1.00					
>Median	0.26	0.05	0.25	0.08		NA		NA
Bladder V_{50} (%)								
≤Median	1.00		1.00					
>Median	0.26	0.05	0.77	0.72		NA		NA
Bladder V_{55} (%)								
≤Median	1.00		1.00					
>Median	0.41	0.19	1.29	0.72		NA		NA
Bladder V_{60} (%)								
≤Median	1.00		1.00					
>Median	0.50	0.30	1.11	0.88		NA		NA
Bladder V_{65} (%)								
≤Median	1.00		1.00					
>Median	0.41	0.19	0.77	0.72		NA		NA
Bladder V_{70} (%)								
≤Median	1.00	0.51	1.00					
>Median	0.64	NA	3.87	0.08		NA		NA
Rectum D_{max} (Gy)								
≤Median					1.00		1.00	
>Median		NA		NA	1.95	0.32	1.73	0.46

– Table 4 (*Continued*)

Variable	Late GU toxicity ≥1		Late GU toxicity ≥2		Late GI toxicity ≥1		Late GI toxicity ≥2	
	OR	*P* value	OR	*P* value	OR	*P* value	OR	*P* value
Rectum median dose (Gy)								
≤Median					1.00		1.00	
>Median		NA		NA	3.11	NA	3.11	0.15
Rectum V_5 (%)								
≤Median					1.00		1.00	
>Median		NA		NA	0.87	0.84	0.75	0.68
Rectum V_{10} (%)								
≤Median					1.00		1.00	
>Median		NA		NA	1.24	0.74	1.00	1.00
Rectum V_{50} (%)								
≤Median					1.00		1.00	
>Median		NA		NA	5.15	**0.025**	1.73	0.46
Rectum V_{55} (%)								
≤Median					1.00		1.00	
>Median		NA		NA	3.11	0.10	1.73	0.46
Rectum V_{60} (%)								
≤Median					1.00		1.00	
>Median		NA		NA	5.15	**0.025**	3.11	0.15
Rectum V_{65}								
≤Median					1.00		1.00	
>Median		NA		NA	5.15	**0.025**	3.11	0.15
Rectum V_{70}								
≤Median					1.00		1.00	
>Median		NA		NA	5.15	**0.025**	3.11	0.15
Acute GU toxicity (grade ≥2)								
No	1.00		1.00		1.00			
Yes	1.40	0.64	0.89	0.88	3.33	NA		NA
Acute GI toxicity (grade ≥2)								
No							1.00	
Yes		NA		NA		0.14	1.97	0.42

Abbreviations: PSA, Prostate-specific antigen; PTV, planning tumor volume; PLNs, pelvic lymph nodes treatment; D_{max}, maximum dose; D_{min}, minimum dose; Vx, percentage of organ volume receiving ≥x radiation dose; GU, genitourinary; GI, gastrointestinal; NA, not applicable (Bladder dosimetric parameters were not assed for GI toxicity and rectum dosimetric parameters were not assed for GU toxicity; those variables with low number of events in subgroups were not analyzed).

minimizing the proportion of the rectum that receives moderate and high dose decreases the risk of late rectal toxicity. The proportion of rectum receiving 36.9 Gy, 46.2 Gy, 64.6 Gy, and 73.9 Gy was associated with the development of late GI toxicity. Kupelian et al.,[22] identified the volume of the rectum receiving the prescription dose of 70 Gy on the pretreatment plan as a significant predictor of rectal bleeding, advising to reduce it to the minimum possible. A phase II dose escalation study[23] analyzed factors predictive of chronic rectal toxicity treating localized prostate cancer with image-guided off-line correction with adaptive high-dose radiotherapy. Dose–volume histogram predicted for chronic toxicity: Rectal wall absolute and relative V50, V60, V66.6, V70, and V72 were significantly associated with chronic grade >2 rectal toxicity. The chronic rectal toxicity grade >2 risk was 9%, 18%, and 25% for the rectal wall relative V70 <15%, 25%–40%, and >40%, respectively. However, unlike us, they found that patients experiencing acute rectal toxicity were more likely to experience chronic toxicity. An Australian trial[24] also revealed that rectal pain of a moderate or severe grade during RT was the best predictor of the subsequent development of late toxicity, with a hazard ratio of 3.44. Only a small proportion of patients were treated by hypofractionation in both of the aforementioned studies,[23,24] which could explain the discrepancy with our findings.

We did not find a significant association between the pelvic treatment and any late grade ≥2 toxicity, which is in agreement with some reports from different authors[25] who found that pelvic irradiation with a hypofractionated regimen is well tolerated, with low rates of grade 3 or greater acute and late toxicity. Patients in our series had a median age of 70 years and many had comorbidities that worsened their baseline sexual function (i.e. hypertension, diabetes, dyslipidemia). Thus, 42.3% of patients already started the treatment with partial or complete erectile dysfunction. These findings are similar to those reported by Yeoh et al. and Deanerley et al. who identified erectile dysfunction in 36% and 43.6% of patients, respectively.[15,26]

Patients having comorbidities at diagnosis were found to associate with higher late GU toxicity. There are different authors[27,28] who have described the association between comorbidities and late toxicity, especially for rectal impairment. For example, the University of Michigan Medical Center[28] observed that a history of either myocardial infarction or congestive heart failure predicted grade ≥3 rectal toxicity, with lesser correlation with grade ≥2 toxicity. An age comorbidity model to predict rectal toxicity was developed and correlated with late rectal toxicity on multivariate analysis.

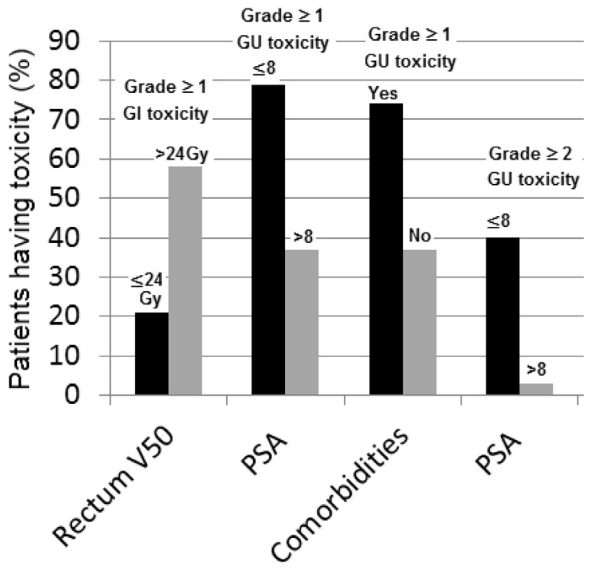

Fig. 1 – Proportion of patients having late genitourinary (GU) and gastrointestinal (GI) toxicity according those parameters that showed significance in the multivariate analysis.

Patients with PSA ≤8 at diagnosis were associated with higher late GU toxicity. These patients (PSA ≤8) had higher bladder volume (195cc vs. 184cc) and higher rate of acute GU toxicity (55% vs. 45%). In addition, the vast majority of patients with lower PSA at diagnosis received higher dose per fraction. Seven out of nine patients (78%) who underwent 2.6 Gy/fraction had lower PSA. It is previously reported[12] that patients treated at 2.6 Gy/fraction associated with higher rates of acute GU toxicity. The relatively high daily dose (2.6 Gy) seems to be a limiting factor with respect to potentially increased GU toxicity.

There are various techniques available for delivering hypofractionation regimens. Volumetric-modulated arc therapy (VMAT) has been shown to need lower monitor units (MUs) as well as shorter treatment time compared with HT.[29] For instance, Tsai et al.,[29] reported that significantly lower MUs were needed for VMAT (309.7 ± 35.4) than for HT (3368 ± 638.7; $P < 0.001$). The treatment time (minutes) was significantly shorter for VMAT (2.6 ± 0.5) than HT (3.8 ± 0.6; $P < 0.001$). The dosimetric impact of intrafraction prostate motion has been investigated for HT treatments and has been found to be small for the majority of fractions.[30] However, whether these divergences among techniques have a clinical impact is still unclear.

We acknowledge that there are limitations to our study. First, comparison of our results with reported results from clinical trials can be complex, due to heterogeneity regarding treatment volumes, fractionations, equivalent doses, dose constraints, different radiation techniques, etc. Second, the GI and GU score criteria may also differ. Finally, symptoms can be related to other causes and can be confusing. For instance, GI symptoms may be related to hemorrhoid bleeding instead of radiation rectorrhagia.

In one of the longest published follow-up series of prostate cancer patients treated with hypofractionated HT, we conclude that this technique can be delivered safely with limited rates of moderate and severe late toxicity. The proportion of the rectum receiving a moderate and high dose, comorbidities, and PSA at diagnosis seem to associate with long term toxicity. Our findings reflect that these parameters may be necessary to more accurately predict risks for late toxicity following hypofractionated HT.

Conflict of interest

None declared.

Financial disclosure

None declared.

REFERENCES

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. *CA Cancer J Clin* 2008;**58**:71–96.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013;**49**:1374–403.
3. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007;**8**:475–87.
4. Sathya JR, Davis IR, Julian JA, et al. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;**23**:1192–9.
5. Zietman AL, DeSilvio ML, Slater JD, et al. Comparison of conventional-dose vs. high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005;**294**:1233–9.
6. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: alpha/beta = 1.4 (0.9–2.2) Gy. *Int J Radiat Oncol Biol Phys* 2012;**82**:e17–24.
7. Junius S, Haustermans K, Bussels B, et al. Hypofractionated intensity modulated irradiation for localized prostate cancer, results from a phase I/II feasibility study. *Radiat Oncol* 2007;**2**:29.
8. Zelefsky MJ, Kollmeier M, Cox B, et al. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;**84**:125–9.
9. Hall EJ. A soft answer turneth away wrath. *Proverbs* 2009;**15**:1. International journal of radiation oncology, biology, physics, 74, 1333–4.
10. Zaorsky NG, Li T, Devarajan K, Horwitz EM, Buyyounouski MK. Assessment of the American Joint Committee on Cancer staging (sixth and seventh editions) for clinically localized prostate cancer treated with external beam radiotherapy and comparison with the National Comprehensive Cancer Network risk-stratification method. *Cancer* 2012;**118**:5535–43.
11. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;**280**:969–74.

12. Lopez Guerra JL, Isa N, Matute R, et al. Hypofractionated helical tomotherapy using 2.5–2.6 Gy daily fractions for localized prostate cancer. *Clin Transl Oncol* 2013;**15**: 271–7.
13. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;**31**:1341–6.
14. Zaorsky NG, Ohri N, Showalter TN, Dicker AP, Den RB. Systematic review of hypofractionated radiation therapy for prostate cancer. *Cancer Treat Rev* 2013;**39**:728–36.
15. Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. *Lancet Oncol* 2016;**17**:1047–60.
16. Incrocci L, Wortel RC, Alemayehu WG, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. *Lancet Oncol* 2016;**17**:1061–9.
17. Hausterman K, Fowler JF. A comment on proliferation rates in human prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;**48**:303.
18. Lukka H, Hayter C, Julian JA, et al. Randomized trial comparing two fractionation schedules for patients with localized prostate cancer. *J Clin Oncol* 2005;**23**:6132–8.
19. Arcangeli G, Saracino B, Gomellini S, et al. A prospective phase III randomized trial of hypofractionation versus conventional fractionation in patients with high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2010;**78**:11–8.
20. Pollack A, Walker G, Horwitz EM, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol* 2013;**31**:3860–8.
21. Hoffman KE, Voong KR, Pugh TJ, et al. Risk of late toxicity in men receiving dose-escalated hypofractionated intensity modulated prostate radiation therapy: results from a randomized trial. *Int J Radiat Oncol Biol Phys* 2014;**88**:1074–84.
22. Kupelian PA, Willoughby TR, Reddy CA, Klein EA, Mahadevan A. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys* 2007;**68**:1424–30.
23. Vargas C, Martinez A, Kestin LL, 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.
24. O'Brien PC, Franklin CI, Poulsen MG, Joseph DJ, Spry NS, Denham JW. Acute symptoms, not rectally administered sucralfate, predict for late radiation proctitis: longer term follow-up of a phase III trial—Trans-Tasman Radiation Oncology Group. *Int J Radiat Oncol Biol Phys* 2002;**54**:442–9.
25. McCammon R, Rusthoven KE, Kavanagh B, Newell S, Newman F, Raben D. Toxicity assessment of pelvic intensity-modulated radiotherapy with hypofractionated simultaneous integrated boost to prostate for intermediate- and high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2009;**75**:413–20.
26. Yeoh EE, Holloway RH, Fraser RJ, et al. Hypofractionated versus conventionally fractionated radiation therapy for prostate carcinoma: updated results of a phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2006;**66**:1072–83.
27. Choe KS, Jani AB, Liauw SL. External beam radiotherapy for prostate cancer patients on anticoagulation therapy: how significant is the bleeding toxicity? *Int J Radiat Oncol Biol Phys* 2010;**76**:755–60.
28. Hamstra DA, Stenmark MH, Ritter T, et al. Age and comorbid illness are associated with late rectal toxicity following dose-escalated radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2013;**85**:1246–53.
29. Tsai CL, Wu JK, Chao HL, Tsai YC, Cheng JC. Treatment and dosimetric advantages between VMAT, IMRT, and helical tomotherapy in prostate cancer. *Med Dosim* 2011;**36**:264–71.
30. Langen KM, Lu W, Ngwa W, et al. Correlation between dosimetric effect and intrafraction motion during prostate treatments delivered with helical tomotherapy. *Phys Med Biol* 2008;**53**:7073–86.