Received:
02 January 2019

Revised:
15 February 2019

Accepted:
08 March 2019

<https://doi.org/10.1259/bjr.20190021>

Cite this article as:

Franzese C, D'agostino G, Di Brina L, Navarria P, De Rose F, Comito T, et al. Linac-based stereotactic body radiation therapy vs moderate hypofractionated radiotherapy in prostate cancer: propensity-score based comparison of outcome and toxicity. *Br J Radiol* 2019; **92**: 20190021.

FULL PAPER

Linac-based stereotactic body radiation therapy vs moderate hypofractionated radiotherapy in prostate cancer: propensity-score based comparison of outcome and toxicity

¹CIRO FRANZESE, ¹GIUSEPPE D'AGOSTINO, ¹LUCIA DI BRINA, ¹PIERINA NAVARRIA, ¹FIorenza DE ROSE, ¹TIZIANA COMITO, ¹DAVIDE FRANCESCHINI, ¹PIETRO MANCOSU, ¹STEFANO TOMATIS and ^{1,2}MARTA SCORSETTI

¹Radiotherapy and Radiosurgery, Humanitas Clinical and Research Center - IRCCS, Rozzano, Via Manzoni 56, Italy

²Department of Biomedical Sciences, Humanitas University, Via Manzoni, Italy

Address correspondence to: Dr. Ciro Franzese
E-mail: ciro.franzese@humanitas.it

Objective: Prostate cancer represents the second most common malignancy in the world and majority of patients have diagnosis of localized disease. The aim of the present study was to compare two cohorts of patients treated with moderate hypofractionation (MHRT) or stereotactic body radiation therapy (SBRT).

Methods: We included patients treated between 2010 and 2015. Inclusion criteria were: adenocarcinoma of the prostate; class risks low or intermediate; WHO performance status 0–2. We evaluated rectal, gastrointestinal toxicity and genitourinary. Measures of outcome were biochemical disease-free survival and overall survival. Propensity score was used to approximate the balance in covariates.

Results: 209 patients were included, treated with MHRT ($n = 109$) or SBRT ($n = 100$). Median follow-up time was 37.4 months. Rates of biochemical disease-free survival at 1- and 3 years were 100 and 95%, respectively. There was no significant difference between the two groups

($p = 0.868$). Rates of overall survival at 1- and 3 years were 100 and 97.1%, respectively with no differences between the two groups ($p = 0.312$). After propensity scoring matching, no differences were observed in terms of acute and late rectal and gastrointestinal toxicity. While mild genitourinary side-effects were more common in SBRT group (45.5% vs 19.5%), Grade 2 and 3 toxicity was increased after MHRT (11.7% vs 2.6%; $p = 0.029$).

Conclusions: Moderate hypofractionation and SBRT are two effective and safe options for the treatment of low- and intermediate-risk prostate cancer. The analysis showed no difference in terms of disease's control and survival but increased moderate and severe toxicity after MHRT.

Advances in knowledge: Moderate hypofractionation and SBRT are comparable in terms of efficacy while moderate and severe toxicity is more common in the first one.

INTRODUCTION

Prostate cancer (PC) represents the second most common malignancy in the world and the majority of PC patients have diagnosis of localized disease.¹ The treatment of PC with conventional radiotherapy (RT) encompassed the use of 74–80 Gy delivered 37–40 fractions of 1.8–2 Gy each.² In the last two decades, studies showed that PC may benefit from hypofractionated RT, due to the low α/β of 1.5 Gy.^{3,4} This hypothesis opened to the possibility of dose escalation in the treatment of PC, with the use of large dose per fractions. According to the fraction's size, hypofractionation is considered “moderate” if the dose is comprised between 2.4 and 4 Gy and “extreme” if the dose is higher than 4

Gy. Different trials compared in the recent years moderate hypofractionation radiation therapy (MHRT) with conventional fractionation radiation therapy (CRT). Three large randomized studies have been published, with dose per fraction of 2.5–3.4 Gy, and demonstrated that MHRT can be considered safe and effective as CRT.^{5–7} With the advancement of RT technique, stereotactic body radiation therapy (SBRT) has been implemented in different setting, including PC. Chen et al.⁸ treated 100 PC patients with 36.25 Gy in five fractions (7.25 Gy per fraction) with a median follow-up of 27 months. Biochemical disease-free survival (BDFS) was 99%, and no acute $\geq$ Grade three gastrointestinal (GI) or genitourinary (GU) toxicity was recorded.

King et al⁹ performed a pooled analysis of 1100 patients, all treated with SBRT. After a median follow-up of 36 months, the 5 year BDFS for low-, intermediate- and high-risk disease was 95%, 84%, and 81%, respectively. On-going trials are randomizing patients to SBRT vs CRT or MHRT (NCT01584258).

The aim of the present study was to compare pattern of toxicity and outcome of two cohorts of patients treated with MHRT or linac-based SBRT in a single institution, with the application of propensity score matching to reduce selection bias.

PATIENTS AND METHODS

Study design and participants

We conducted a retrospective comparative analysis of patients affected by PC treated with RT at our institution (Humanitas Clinical and Research Center). We extracted demographic and clinical data of patients treated between 2010 and 2015 from a prospectively maintained registry database. Inclusion criteria were: (1) histologically proven adenocarcinoma of the prostate; (2) National Comprehensive Cancer Network (NCCN) class risks low or intermediate; (3) World Health Organization (WHO)

performance status 0–2. Class risks were defined according to NCCN v1.2018: low risk if clinical stage T1–T2a, Gleason scores ≤ 6 , prostate-specific antigen (PSA) <10 ; intermediate risk if clinical stage T2b–c, Gleason score 7, PSA 10–20.

INTERVENTION

Patients were treated with two schedules of RT, MHRT or SBRT. Both the treatments were delivered with volumetric modulated arc therapy (VMAT) in its RapidArc form with the use of flattening filter free beams. A contrast-free CT scan was acquired for the simulation of all patients. The gross tumour volume (GTV) encompassed the prostate or the prostate plus seminal vesicles according to NCCN class risk. Proximal 1/3 of seminal vesicles were included in the CTV only for intermediate risk PC patients. The clinical target volume (CTV) was equal to GTV. Planning target volume (PTV) was generated by the expansion of GTV (1) for MHRT by 7 mm in all directions, except posteriorly where expansion was 5 mm; (2) for SBRT by 5 mm in all directions, except posteriorly where expansion was 3 mm. The dose schedules were as follows: (1) MHRT group: 74.2–71.4 Gy (65.5–61.6 Gy on seminal vesicles if intermediate risk) delivered in 28 consecutive fractions; (2)

Table 1. Patients and disease characteristics before and after PSM

	Before PSM			After PSM		
	Moderate hypofractionation	SBRT	<i>p</i> -value	Moderate Hypofractionation	SBRT	<i>p</i> -value
Number patients	109	100		77	77	
Age y, median (95% CI)	73.7 (47–83)	72 (48–82)		72.7 (47.3–82)	72 (48–82)	0.621
Age ≤75 >75	65 (59.6%) 44 (40.4%)	77 (77%) 23 (23%)	0.013	58 (75.3%) 19 (24.7%)	58 (75.3%) 19 (24.7%)	1.000
PS 0 1 2	68 (62.4%) 29 (26.6%) 12 (11%)	81 (81%) 17 (17%) 2 (2%)	0.011	59 (76.6%) 16 (20.8%) 2 (2.6%)	59 (76.6%) 16 (20.8%) 2 (2.6%)	1.000
Previous abdominal surgery No Yes	72 (66.1%) 37 (33.9%)	66 (66%) 34 (34%)	0.993	55 (71.4%) 22 (28.6%)	48 (62.3%) 29 (37.6%)	0.231
Hypertension No Yes	53 (48.6%) 56 (51.4%)	47 (47%) 53 (53%)	0.814	37 (48%) 40 (52%)	35 (45%) 42 (55%)	0.747
Diabetes mellitus No Yes	91 (83.5%) 18 (16.5%)	91 (91%) 9 (9%)	0.106	67 (87%) 10 (13%)	68 (88.3%) 9 (11.7%)	0.806
Initial PSA	7.7 (1.50–19)	7.31 (2.2–17)	0.400	6.61 (2.03–19)	7.49 (2.2–17)	0.619
Gleason Score 3 + 3 3 + 4 4 + 3	54 (49.5%) 37 (33.9%) 18 (16.5%)	66 (66%) 23 (23%) 11 (11%)	0.056	45 (58.4%) 25 (33.5%) 7 (9.1%)	45 (55.8%) 23 (29%) 11 (14.3%)	0.6193
NCCN class risk Low Intermediate	42 (38.5%) 67 (61.5%)	57 (57%) 43 (43%)	0.008	34 (44.2%) 43 (55.8%)	34 (44.2%) 43 (55.8%)	1.000
ADT No Yes	92 (84.4%) 17 (15.6%)	79 (79%) 21 (21%)	0.312	62 (80.5%) 15 (19.5%)	58 (75.3%) 19 (24.7%)	0.437

ADT, androgen deprivation therapy; CI, confidence interval; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen; PSM, propensity scoring matching; SBRT, stereotactic body radiation therapy.

Figure 1. Biochemical disease free survival (BDFS) according to the treatment before propensity score matching. MHRT, moderate hypofractionated radiotherapy group; SBRT, stereotactic body radiation therapy group.

SBRT group: 35 Gy delivered in five fractions on alternate days. No patients received prophylactic lymph node irradiation. Daily cone beam CT (CBCT) and online shift with action level of 1 mm was performed for all patients in both arms. All treatments were performed with full bladder and empty rectum.

Androgen deprivation therapy (ADT) was administered in intermediate risk patients treated with MHRT. The ADT was in the form of antiandrogen or gonadotropin-releasing hormone agonist (LHRH analogue). Treatments with ADT were started with the RT and continue up to 6 months.

OUTCOME MEASURES

Patients were evaluated every 3 months for the first year and every 6 months from 2 to 5 years. Clinical examination and PSA value

were recorded for all the evaluations. Radiological and nuclear medicine examinations were planned according to the physician choice.

Toxicity was recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 criteria. The limit of 6 months from the first day of treatment was used to distinguish acute from late toxicity. We evaluated GU, rectal and GI toxicity (for toxicity related to upper or lower bowel tracts, respectively).

STATISTICAL ANALYSIS

The distribution of clinical characteristics was analyzed using percentiles for continuous variables, and percentages and frequencies for categorical variables. The time to biochemical failure (BDFS) was defined as the time between the first day of RT treatment and the date of the PSA failure. Overall survival (OS) was defined as the time between the first day of RT and death or last follow-up. We used Kaplan–Meier method to assess survival and log-rank statistic was used to test for differences between the patient's and treatment's characteristics. All of the analyses were performed using STATA V13 software (STATA Corp, College Station, TX).

Propensity scoring matching (PSM) is a balancing approach whereby a numerical value is assigned for the probability of an intervention. The aim is to approximate the balance in measured covariates. In our investigation, we aimed to standardize the groups based on propensity to receive one RT treatment schedule over another. The following variables were selected: age at time of diagnosis, Performance status (PS), NCCN class risk. To minimize selection bias inherent in treatment group allocation, propensity score modeling was used to match the two groups using a logistic regression approach.¹⁰ An absolute standard bias measure <0.20 is considered small, and sufficient overlap is required for the propensity scores.¹¹

Table 2. Cox regression analysis of biochemical disease free survival (BDFS) and overall survival (OS) before and after propensity score matching (PSM)

	Biochemical disease free survival						Overall survival					
	Before PSM			After PSM			Before PSM			After PSM		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Age >75	0.29	0.03–2.37	0.253	4.08	0–1	1.000	1.54	0.62–3.85	0.348	1.46	0.42–5.05	0.549
PS	1.26	0.49–3.20	0.624	1.09	0.26–4.44	0.903	1.93	1.08–3.42	0.025	0.35	0.05–2.55	0.306
Previous abdominal surgery	1.68	0.45–6.28	0.436	1.58	0.35–7.09	0.545	1.27	0.50–3.24	0.612	1.25	0.36–4.29	0.719
Hypertension	1.45	0.36–5.83	0.593	1.08	0.24–4.87	0.911	1.20	0.48–3.00	0.687	0.77	0.23–2.53	0.670
Diabetes mellitus	4.94	0–1	1	5.00	0–1	1.000	2.84	1.02–7.93	0.045	0.77	0.09–6.07	0.809
Initial PSA	1.10	0.96–1.27	0.155	1.13	0.97–1.33	0.111	1.04	0.93–1.16	0.414	1.05	0.91–1.21	0.481
Gleason Score	1.32	0.35–4.95	0.678	1.96	0.43–8.77	0.379	1.58	0.64–3.91	0.315	0.72	0.21–2.47	0.606
NCCN class	1.33	0.35–4.96	0.671	2.22	0.43–11.49	0.338	1.63	0.64–4.16	0.300	0.94	0.28–3.09	0.925
ADT	1.01	0.21–4.90	0.982	1.20	0.23–6.18	0.828	1.48	0.53–4.12	0.448	2.04	0.59–6.99	0.254
RT treatment	1.11	0.29–4.22	0.868	0.92	0.20–4.14	0.920	0.60	0.22–1.61	0.312	1.28	0.36–4.53	0.698

Figure 2. BDFS according to the treatment after propensity score matching. BDFS, biochemical disease-free survival; MHRT, moderate hypofractionated radiotherapy group; SBRT, stereotactic body radiation therapy group.

RESULTS

Patient characteristics are reported in Table 1. A total of 209 patients were included in the analysis, treated with MHRT ($n = 109$) or SBRT ($n = 100$). Median age was 73.7 years for MHRT group and 72 years for SBRT group. PS was 0 in 62.4 and 81% for MHRT and SBRT groups, respectively. Previous abdominal surgery, hypertension and diabetes mellitus were equally distributed between the two groups. Median initial PSA (iPSA) was 7.7 ng ml^{-1} in MHRT group and 7.3 ng ml^{-1} in SBRT group. Gleason Score was classified as 4 + 3 in 16.5 and 11% of MHRT and SBRT groups, respectively. Hormonal therapy was used only in 15.6% of MHRT group and 21% of SBRT group. After 1:1 matching, there were 77 patients in each group, respectively. Distribution of covariates was adequately balanced in the matched data set, as shown in Table 1.

Median follow-up time was 37.4 months (4.4–77.7). Median follow-up for MHRT group was 40.5 months (4.1–77.7) and for SBRT group was 32.6 months (4.4–57.5). Patients were treated with a shift over time. Moderate hypofractionation was applied from 2010 to 2015 while SBRT from 2012 to 2015.

Among all patients, nine had biochemical relapse during follow-up (five in the MHRT group and four in the SBRT group). The rates of BDFS at 1- and 3 years were 100 and 95% (95%CI 89.8–97.6%), respectively. Median BDFS was not reached. There was no significant difference in terms of BDFS between the two groups ($p = 0.868$). Figure 1 illustrates BDFS according to the treatment. There was no impact of the analyzed risk factors on BDFS as shown in Table 2.

After PSM, there were no difference [hazard ratio (HR) 0.92; 95% confidence interval (CI) (0.20–4.14); $p = 0.920$] in terms of BDFS between the two groups with 1- and 3 years rates of 100%, 93.7% [95% CI (84.1–97.6%)], for MHRT, and 100 and 96.2% [95%CI (85.7–99%)], for SBRT (Figure 2).

Median OS was not reached. Rates of OS at 1- and 3 years were 100 and 97.1% [(95% CI (93.7–98.7%))], respectively. No differences were observed in terms of OS between the two groups ($p = 0.312$), with 1- and 3 years rates of 100 and 95.4% [95% CI (89.3–98%)] for MHRT group, and 100 and 99% [95% CI (93.1–99.8%)] for SBRT group, respectively. After PSM, no difference was obtained in terms of OS between the two groups [HR 1.28; 95% CI (0.36–4.53); $p = 0.698$]. At analysis of correlation between risk factors and survival, low PS [HR 1.93, 95% CI (1.08–3.42); 0.025] and presence of diabetes mellitus [HR 2.84, 95% CI (1.02–7.93); 0.045] were correlated with worse outcome.

Patterns of toxicity are detailed in Table 3 and Figures 3–4. Before matching, acute rectal toxicity of moderate–severe grade is reported more commonly in the MHRT group (13.8% vs 6% of SBRT group) even if not statistically significant ($p = 0.062$). No differences were observed between the two groups in terms of acute GI toxicity. Grade 2–3 GI toxicity was reported by 1 (0.9%) patient and 2 (2%) patients of MHRT and SBRT groups, respectively ($p = 0.511$). Acute GU toxicity of grades 2 and 3 was more common in SBRT group (31%) compared to MHRT group (18.3%, $p = 0.033$). Regarding the late setting, rectal toxicity was more common in the MHRT in group as grades 2 and 3 (4.6% and 3.7% for MHRT, vs 1% and 0 for SBRT; $p = 0.019$). Mild and comparable was the late GI toxicity between the two treatments ($p = 0.272$). While GU side-effect of Grade 1 was more common after SBRT (44% vs 19.3%), grades 2 and 3 toxicity was increased after MHRT (9.2 and 2.8 vs 2% and 0; $p = 0.000$). In detail, for MHRT group Grade 3 side-effects were represented by acute severe rectal bleeding (one patient), acute gross hematuria (one patient), acute urinary retention (three patients), late severe rectal bleeding (four patients), late urethral stenosis (three patients), while Grade 3 toxicity for SBRT group was represented by bowel subocclusion (one patient).

After PSM, both acute and late GU toxicity continued to be significantly worse in MHRT group for Grade 2 ($p = 0.023$) and Grade 2–3 (0.002), respectively. No other differences for the remaining domains were observed.

DISCUSSION

In this study we compared the toxicity and outcome of two sample of patients treated with MHRT or SBRT for low and intermediate risk PC.

After PSM we didn't find any statistical difference in acute rectal and GI toxicity between MHRT and SBRT patients. A difference was observed for acute GU toxicity, with an increased rate of Grade 2 side-effects in SBRT group (29.9% vs 15.6%) but an increased rate of Grade 3 for MHRT patients (2.6% vs 0%). Yu et al¹² conducted a retrospective comparison of costs and toxicity in national sample of Medicare beneficiaries treated with SBRT or CRT in the form of IMRT. A total of 1335 SBRT patients and 2670 IMRT patients were analyzed and in the 6 months after RT 15.6% of SBRT vs 12.6% of IMRT patients had GU toxicity [odds ratio 1.29; 95% CI (1.05–1.53); $p = 0.009$]. Such study is, however, limited by several issues, including the lack of RT details (e.g. delivered dose and dose constraints) and also grade

Table 3. Pattern of toxicity before and after PSM

	Before PSM			After PSM		
	Moderate hypofractionation	SBRT	<i>p</i> -value	Moderate hypofractionation	SBRT	<i>p</i> -value
Acute rectal toxicity						
1	13 (11.9%)	15 (15%)	0.263	12 (5.6%)	8 (10.4%)	0.305
2	14 (12.8%)	6 (6%)		9 (11.7%)	5 (6.5%)	
3	1 (0.9%)	0		1 (1.3%)	0	
0–1	94 (86.2%)	94 (94%)	0.062	67 (87%)	72 (93.5%)	0.174
2–3	15 (13.8%)	6 (6%)		10 (13%)	5 (6.5%)	
Acute GI toxicity						
1	6 (5.5%)	6 (6%)	0.770	3 (94.8%)	5 (6.5%)	0.668
2	1 (0.9%)	1 (1%)		1 (1.3%)	1 (1.3%)	
3	0	1 (1%)		0	1 (1.3%)	
0–1	108 (99.1%)	98 (98%)	0.511	76 (98.7%)	75 (97.4%)	0.560
2–3	1 (0.9%)	2 (2%)		1 (1.3%)	2 (2.6%)	
Acute GU toxicity						
1	31 (28.4%)	32 (32%)	0.010	22 (28.6%)	28 (36.4%)	0.023
2	17 (15.6%)	31 (31%)		12 (15.6%)	23 (29.9%)	
3	3 (2.8%)	0		2 (2.6%)	0	
0–1	89 (81.7%)	69 (69%)	0.033	63 (81.8%)	54 (70.1%)	0.090
2–3	20 (18.3%)	31 (31%)		14 (18.2%)	23 (29.9%)	
Late rectal toxicity						
1	6 (5.5%)	14 (14%)	0.019	5 (6.5%)	11 (14.3%)	0.109
2	5 (4.6%)	1 (1%)		4 (5.2%)	1 (1.3%)	
3	4 (3.7%)	0		2 (2.6%)	0	
0–1	100 (91.7%)	99 (99%)	0.014	71 (92.2%)	76 (98.7%)	0.053
2–3	9 (8.3%)	1 (1%)		6 (7.8%)	1 (1.3%)	
Late GI toxicity						
1	1 (0.9%)	3 (3%)	0.272	1 (1.3%)	2 (2.6%)	0.560
Late GU toxicity						
1	21 (19.3%)	44 (44%)	0.000	15 (19.5%)	35 (45.5%)	0.002
2	10 (9.2%)	2 (2%)		6 (7.8%)	2 (2.6%)	
3	3 (2.8%)	0		3 (3.9%)	0	
0–1	96 (88.1%)	98 (98%)	0.005	68 (88.3%)	75 (97.4%)	0.029
2–3	13 (11.9%)	2 (2%)		9 (11.7%)	2 (2.6%)	

GI, gastrointestinal; GU, genitourinary; PSM, propensity scoring matching; SBRT, stereotactic body radiation therapy.

of toxicity and score used for assessment. The whole cohort of our patients was treated in a single institution with gantry-based RT technique, in the form of VMAT—Rapidarc. The outcome of 90 patients treated with SBRT was reported in other study.¹³ The most represented acute toxicity included urinary symptoms of urgency, increase of urinary frequency, nocturia. Both Grade 1 and Grade 2 urinary toxicity were observed in 32.2 and 32.2% of patients. The logistic regression showed a significant correlation between urinary toxicity of grade >1 and dimensions of CTV. A large multiinstitutional study¹⁴ published in 2015 included 803 patients treated with CRT, SBRT or brachytherapy and quality of life was investigated through EPIC-26 questionnaires.

Regarding late setting, we didn't observe any grade ≥3 toxicity in the SBRT group. However Grade 3 rectal and GU side-effects were reported in the MHRT group by 2 (2.6%) and 3 (3.9%) patients, respectively. These results are in line with the majority

of trials. Among the linac-based SBRT trials, only Kim et al¹⁵ reported the highest incidence of grade ≥3 GU toxicity with 4.9% in their dose-escalation trial published in 2014. Loblaw et al¹⁶ reported 1% of genitourinary toxicity with the dose of 35 Gy in five fractions.

In our study, SBRT was provided with the dose of 35 Gy in five fractions, corresponding to the low end of the most commonly reported dose range (32.5–40 Gy). Theoretically, this lower dose could justify a mild pattern of toxicity compared to higher doses. However, a recent published trial was published on this subject by Zelefsky et al.¹⁷ 36 patients were enrolled in a dose escalation SBRT Phase I study. The initial dose level was 32.5 Gy in five fractions, and doses were then escalated to 35, 37.5 and 40 Gy. The study showed no significant differences in rates of acute ($p = 0.16$ – 0.43) or late toxicities ($p = 0.36$ – 0.88) between the different dose groups. The only differences were observed in the patterns

Figure 3. Bar graph showing pattern of toxicity in the acute and late setting for MHRT (black bars) and SBRT (grey bars). From left to right: rectal toxicity, GI toxicity and GU toxicity. GI, gastrointestinal; GU, genitourinary; MHRT, moderate hypofractionation radiation therapy; SBRT, stereotactic body radiation therapy.

of urinary symptoms and the time to symptom resolution. Ricco *et al*¹⁸ performed a comparison between SBRT and conventional intensity modulated radiotherapy (IMRT) for localized PC in 270 patients. There was no significant difference in disease control between SBRT vs IMRT ($p = 0.46$) with 6 year rates of 91.9% for SBRT and 88.9% for IMRT. Regarding toxicity, there were no Grade 3 GI or GU toxicities for either SBRT or IMRT at last follow-up.

Robotic SBRT was compared to conventional IMRT by propensity score in the study of Oliai *et al*.¹⁹ Here, 263 patients with low to high risk PC were treated with 35–37.5 Gy in 5 fx with Cyberknife or 75.6 Gy in 42 fractions. Both modalities were well tolerated, with acute and late GU not exceeding Grade 3 and GI toxicity Grade 2. Grade 2 GU toxicity was observed in 12 and 14% of IMRT and SBRT groups, respectively, and Grade 2 GI toxicity in 1 and 3% respectively. Main advantage of our study was the homogeneity of the sample, including patients treated in the same period, from 2010 to 2015, with the same RT technique (VMAT in its Rapidarc form) and comparable image guidance radiation therapy (IGRT—use of daily verification with CBCT

for all the included patients). In this way, we could potentially correlate the differences in toxicity to the different fractions used, rather than the RT technique, however taking into account the retrospective nature of the study.

While considering the short follow-up for PC, our analysis didn't demonstrate any difference in outcome, both in terms of biochemical recurrence and in survival. After the application of PSM, rates of BDFS at 1- and 3 years were 100 and 93.7% for MHRT patients and 100 and 96.2% for SBRT groups ($p = 0.920$). So far no prospective trials have been published comparing moderate with extreme hypofractionation. Kuban *et al*²⁰ conducted a randomized trials comparing moderate hypofractionation with CRT and after 5 years no statistically significant difference was observed. Pollack *et al*²¹ compared 76 Gy in 38 fractions vs 70.2 Gy in 26 fractions and the 5-year disease failure were 21.4% for CRT and 23.3% for MHRT ($p = 0.745$). More recently, a randomized, Phase 3, non-inferiority trial was conducted with assignment to conventional (74 Gy delivered in 37 fractions) or hypofractionated schedules (60 Gy in 20 fractions or 57 Gy in 19 fractions).²² A total of 3216 males were

Figure 4. Bar graph showing pattern of toxicity in the acute and late setting after propensity score matching for MHRT (black bars) and SBRT (grey bars). From left to right: rectal toxicity, GI toxicity and GU toxicity. GI, gastrointestinal; GU, genitourinary; MHRT, moderate hypofractionation radiation therapy; SBRT, stereotactic body radiation therapy.

enrolled in 71 centers and 60 Gy resulted to be non-inferior to 74 Gy (HR 0.84, pNI = 0.0018). The authors concluded that MHRT with 60 Gy in 20 fractions is recommended as a new standard of care for external-beam RT of localized prostate cancer. Di Muzio et al²³ published the results of a Phase I–II trial evaluating the dose of 74.2 Gy in 28 fractions over 211 patients enrolled. After a follow-up of 5 years, BDFS was 93.7% (low risk: 94.6%; intermediate risk: 96.2%) and OS were 88.6% (low risk: 90.5%; intermediate risk: 87.4%). Regarding SBRT, several trials demonstrated the efficacy of this treatment with the use of 6.7–10 Gy per fractions. King et al²⁴ reported 4-year actuarial BDFS was 94% for 67 patients with low-risk PC treated with 36.25 Gy in five fractions. Katz et al²⁵ published a large trial including 515 patients with low-risk ($n = 324$), intermediate-risk ($n = 153$) or high risk ($n = 38$) disease. At a median follow-up of 72 months, the 7-year BDFS was 95.8 and 89.3% for the low and intermediate-risk, respectively. No difference was observed between the two schedules of doses. King et al⁹ published in 2013 a pooled analysis that included 1100 patients treated with SBRT on PC (58% with low risk and 30% with intermediate-risk). At a median follow-up of 36 months, the 5-y BDFS was 93% overall, and 95 and 84% for patients with low and intermediate risk, respectively.

This study is limited by several issues, including the retrospective nature of the analysis and the limited number of patients. The short follow-up of 37 months limits the possibility to really compare both the long-term outcomes in PC and also definitive late toxicities. Moreover, the absence of quality of life evaluation doesn't allow comparing the two fractionations in terms of impact of the main symptom-specific bother items. Finally, the intrinsic limits of the propensity score method are not negligible; indeed propensity score can balance variables identified and added in the analysis, but it does nothing to balance unmeasured characteristics and confounders.

CONCLUSION

Moderate hypofractionation and SBRT can be considered two viable and effective options for the treatment of low- and intermediate-risk PC. In the absence of randomized trials, the present study confirms the comparability of the two treatment schedules in terms of efficacy. While extreme hypofractionation was associated with an increased mild GU toxicity, moderate and severe side-effects were more common in the MHRT group. Prospective trials are necessary, including evaluation of impact on quality of life.

REFERENCES

- Schröder FH, Hugosson J, Roobol MJ, Tammela TLJ, Ciatto S, Nelen V, et al. Screening and prostate-cancer mortality in a randomized European study. *N Engl J Med* 2009; **360**: 1320–8. doi: <https://doi.org/10.1056/NEJMoa0810084>
- Benjamin LC, Tree AC, Dearnaley DP. The role of Hypofractionated radiotherapy in prostate cancer. *Curr Oncol Rep* 2017; **19**: 30. doi: <https://doi.org/10.1007/s11912-017-0584-7>
- Brenner DJ, Hall EJ. Fractionation and protraction for radiotherapy of prostate carcinoma. *Int J Radiat Oncol Biol Phys* 1999; **43**: 1095–101. doi: [https://doi.org/10.1016/S0360-3016\(98\)00438-6](https://doi.org/10.1016/S0360-3016(98)00438-6)
- Fowler J, Chappell R, Ritter M. Is α/β for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 2001; **50**: 1021–31. doi: [https://doi.org/10.1016/S0360-3016\(01\)01607-8](https://doi.org/10.1016/S0360-3016(01)01607-8)
- Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. *Lancet Oncol* 2012; **13**: 43–54. doi: [https://doi.org/10.1016/S1470-2045\(11\)70293-5](https://doi.org/10.1016/S1470-2045(11)70293-5)
- Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, et al. Randomized phase III Noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. *J Clin Oncol* 2016; **34**: 2325–32. doi: <https://doi.org/10.1200/JCO.2016.67.0448>
- Catton CN, Lukka H, Gu C-S, Martin JM, Supiot S, Chung PWM, et al. Randomized trial of a Hypofractionated radiation regimen for the treatment of localized prostate cancer. *J Clin Oncol* 2017; **35**: 1884–90. doi: <https://doi.org/10.1200/JCO.2016.71.7397>
- Chen LN, Suy S, Uhm S, Oermann EK, Ju AW, Chen V, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. *Radiat Oncol* 2013; **8**: 58. doi: <https://doi.org/10.1186/1748-717X-8-58>
- King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. *Radiat Oncol* 2013; **109**: 217–21. doi: <https://doi.org/10.1016/j.radonc.2013.08.030>
- Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011; **46**: 399–424. doi: <https://doi.org/10.1080/00273171.2011.568786>
- Cohen J. Statistical power analysis for the behavioral. *Hillsdale* 1988; **474**.
- JB Y, Cramer LD, Herrin J, Soulos PR, Potosky AL, Gross CP. Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer : Comparison of Toxicity. *J Clin Oncol* 2014; **32**: 1–11.
- D'Agostino G, Franzese C, De Rose F, et al. High-quality Linac-based stereotactic body radiation therapy with flattening filter free beams and volumetric modulated Arc therapy for Low-Intermediate risk prostate cancer: a mono-institutional experience with 90 patients. *Clin Oncol* 2016; **28**.
- Evans JR, Zhao S, Daignault S, Sanda MG, Michalski J, Sandler HM, et al. Patient-reported quality of life after stereotactic body radiotherapy (SBRT), intensity modulated radiotherapy (IMRT), and brachytherapy. *Radiat Oncol* 2015; **116**: 179–84. doi: <https://doi.org/10.1016/j.radonc.2015.07.016>
- Kim DWN, Cho LC, Straka C, Christie A, Lotan Y, Pistenmaa D, et al. Predictors of rectal tolerance observed in a dose-escalated phase 1-2 trial of stereotactic body radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2014; **89**: 509–17. doi: <https://doi.org/10.1016/j.ijrobp.2014.03.012>
- Loblaw A, Cheung P, D'Alimonte L, Deabreu A, Mamedov A, Zhang L, et al. Prostate stereotactic ablative body radiotherapy using a standard linear accelerator: toxicity, biochemical, and pathological outcomes. *Radiat Oncol*

- 2013; **107**: 153–8. doi: <https://doi.org/10.1016/j.radonc.2013.03.022>
17. Zelefsky MJ, Kollmeier M, McBride S, Varghese M, Mychalczak B, Gewanter R, et al. 5-Year Outcomes of a phase I dose escalation study using stereotactic body radiosurgery for patients with low and intermediate risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2019;03 Jan 2019. doi: <https://doi.org/10.1016/j.ijrobp.2018.12.045>
 18. Ricco A, Manahan G, Lanciano R, Hanlon A, Yang J, Arrigo S, et al. The comparison of stereotactic body radiation therapy and intensity-modulated radiation therapy for prostate cancer by NCCN risk groups. *Front Oncol* 2016; **6**: 184. doi: <https://doi.org/10.3389/fonc.2016.00184>
 19. Oliai C, Bernetich M, Brady L, Yang J, Hanlon A, Lamond J, et al. Propensity score matched comparison of SBRT versus IMRT for the treatment of localized prostate cancer. *J Radiat Oncol* 2016; **5**: 187–95. doi: <https://doi.org/10.1007/s13566-015-0237-0>
 20. Kuban DA, Nogueras-Gonzalez GM, Hamblin L, Lee AK, Choi S, Frank SJ, et al. Preliminary report of a randomized dose escalation trial for prostate cancer using Hypofractionation. *International Journal of Radiation Oncology*Biophysics* 2010; **78**: S58–S59. doi: <https://doi.org/10.1016/j.ijrobp.2010.07.170>
 21. Pollack A, Walker G, Horwitz EM, Price R, Feigenberg S, Konski AA, et al. Randomized trial of hypofractionated external-beam radiotherapy for prostate cancer. *J Clin Oncol* 2013; **31**: 3860–8. doi: <https://doi.org/10.1200/JCO.2013.51.1972>
 22. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year Outcomes of the randomised, non-inferiority. *Lancet* 2016;.
 23. Di Muzio NG, Fodor A, Noris Chiorda B, et al. Moderate Hypofractionation with simultaneous integrated boost in prostate cancer: long-term results of a phase I-II study. *Clin Oncol* 2015;.
 24. King CR, Brooks JD, Gill H, Presti JC. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2012; **82**: 877–82. doi: <https://doi.org/10.1016/j.ijrobp.2010.11.054>
 25. Katz AJ, Kang J. Quality of life and toxicity after SBRT for organ-confined prostate cancer, a 7-year study. *Front Oncol* 2014; **4**: 301. doi: <https://doi.org/10.3389/fonc.2014.00301>