Moderate versus extreme hypofractionated radiotherapy: a toxicity comparative analysis in low- and favorable intermediate-risk prostate cancer patients

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Abstract

Purpose External beam radiotherapy (EBRT) is an effective treatment option for low- and favorable intermediate-risk prostate cancer (PCa) and it is usually delivered in conventional fractionation or with moderate hypofractionation (hRT), with comparable results. In the last years, a new treatment approach with stereotactic body radiotherapy (SBRT) has shown promising results. The aim of the present study was to directly compare the toxicity and outcome between hRT and SBRT in low and favorable intermediate PCa patients.

Materials and methods The hRT schedules were: 71.4 Gy or 74.2 Gy in 28 fractions for low- or favorable intermediate-risk PCa, respectively, while the SBRT schedules were: 35 Gy or 37.5 Gy in five fractions, for low or favorable intermediate risk, respectively. Toxicity assessment was performed according to CTCAE v5.0 grading. The International Prostatic Symptoms Score (IPSS) was also recorded.

Results One hundred forty-nine patients were analyzed, overall 81 (54.36%) patients were low risk and 68 (45.64%) were favorable intermediate risk. Sixty-nine (46.3%) patients were treated with hypo-RT and 80 (53.7%) with SBRT. Median follow-up was 33 months (range 11–58 months). The actuarial survival rate was 98.66%. The 3-years BFS rates were 95.5% and 100% for hRT and SBRT, respectively ($p = 0.051$). One case (0.6%) of acute grade 3 urinary toxicity occurred in a patient with favorable intermediate risk treated with hRT. He initially suffered gross hematuria and acute urinary retention not treatable with urinary catheter, therefore a suprapubic catheter was placed and steroids were administered. No differences in acute, late or severe toxicity were detected.

Conclusion Stereotactic body radiotherapy reported a good clinical outcome and safe toxicity profile. Results are comparable to hRT, but a longer follow-up is needed to assess the late effectiveness and toxicity.

Keywords Prostate cancer · Low risk · Favorable intermediate risk · Hypofractionated radiotherapy · SBRT · Stereotactic body radiotherapy

Introduction

Prostate cancer (PCa) is the most common cancer in Europe among men over 70 years old (Torre et al. 2016). Approximately 80% of men with PCa diagnosis have an organ-confined disease. External beam radiation therapy (EBRT) is a common treatment option for localized prostate cancer, with results comparable to surgery (Hamdy et al. 2016). Typically, EBRT has been delivered in conventionally, 2 Gray (Gy), fractionated regimens, with total doses ranging from 74 to 80 Gy (assuming an α/β ratio ~ 10 as most malignant tumors). In the last two decades, there has been a great improvement in the radiobiological understanding

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of PCa, and the results of several studies calculated an α/β of 1.5–3 Gy (Fowler et al. 2001). The low α/β estimated for PCa suggests a greater sensitivity to increased fraction size (Fowler et al. 2001). Moreover, the fractionation sensitivity of PCa, relative to nearby normal tissues, could allow better local control without toxicity increase, using hypofractionation and create dose escalation opportunities (Brenner and Hall 1999). Starting from this background, several trials have demonstrated the efficacy and relatively low toxicity of hypofractionated radiotherapy (hRT) (Incrocci et al. 2016; Lee et al. 2016; Hoffman et al. 2014; Arcangeli et al. 2012; Pollack et al. 2013), as well as potential logistic and financial advantages (Zemplényi et al. 2018).

More recently, several extreme hypofractionation/stereotactic body radiotherapy (SBRT) schedules (dose/fraction 7–10 Gy) were introduced into clinical practice alongside moderate hypofractionation (dose/fraction 2.5–4 Gy). The effect of SBRT on tumor cells seems to differ from the effect of conventional or moderate hypofractionation, and is probably exerted through tumor microenvironment modification and vessel endothelial cell apoptosis (Kim et al. 2015; De Bari et al. 2016; Shibamoto et al. 2015). Prospective SBRT trial results in localized PCa showed biochemical-free survival (BFS) rates ranging from 93 to 100% and acute/late toxicity rates of < 1% and 3.6%, respectively (Alongi et al. 2013, 2019; Scorsetti et al. 2014; Pham et al. 2010; Katz et al. 2013; Kupelian et al. 2013; Mantz 2014; Hannan et al. 2016; Musunuru et al. 2016; Zimmermann et al. 2016; Kishan et al. 2019).

The aim of the present study was to compare SBRT and hRT outcomes in low and favorable intermediate-risk class PCa. Toxicity was the primary end-point; biochemical-free survival (BFS) and overall survival (OS) were also assessed.

Materials and methods

Between January 2014 and August 2018, 215 patients affected by low and favorable intermediate-risk PCa were treated. In order to evaluate local treatment effectiveness and to reduce possible confounding factors, 66 patients, treated with SBRT (16) and hRT (50) were excluded, due to concomitant administration of ADT. Therefore, a retrospective analysis was performed on 149 patients affected by low and favorable intermediate PCa. Patients treated with SBRT were enrolled in a phase II pilot feasibility study, approved by the internal ethical committee (No. Prot. SBRT PROG112CESC) (Alongi et al. 2019). Patients were included according to the following characteristics: age ≤ 85 years; WHO performance status ≤ 2; PSA < 20 ng/ml; histologically proven PCa at low or favorable intermediate favorable risk, for which ADT was not mandatory; T1–T2 stage; no pathologic lymph nodes on computed

tomography (CT) and magnetic resonance imaging (MRI); no distant metastases; no previous prostate surgery other than transurethral prostate resection (at least a 6-month interval before initiation of RT); no malignant tumors in the last 5 years. Exclusion criteria were: clinical positive nodes or a lymph node involvement risk > 15%; previous transurethral resection of the prostate (TURP) less than 6 months before RT; previous prostate surgery other than TURP; previous pelvic irradiation; previous ADT.

Treatment characteristics

Treatment characteristics were detailed in previous papers (Alongi et al. 2013, 2019; Scorsetti et al. 2014) and are summarized hereafter. All patients were simulated in the supine position using Combifix™ (CIVCO, Orange City, IA, USA). A noncontrast-enhanced CT scan was acquired in the treatment position (slice thickness of 3 mm). Patients were requested to follow a bladder filling protocol and to present themselves with the rectum empty at simulation (planning CT) as well as at treatment delivery. Treatment was performed using TrueBeam™ Linac (Varian Medical System, Palo Alto, CA, USA). Target definition was based on MRI T2-sequence acquired in treatment position to determine the position of the urethra, as well as to better define the anatomical relationships between the prostate and rectum, bladder, and penis bulb. The clinical target volume (CTV) was as follows: the prostate gland only in case of low-risk PCa, and the entirety of the seminal vesicles (SV) and prostate gland in case of favorable intermediate-risk PCa. The planning target volume (PTV) for SBRT consisted of clinical target volume (CTV) + 5 mm margin in each direction, except 3 mm posteriorly. The PTV for hRT consisted of CTV + 8 mm margin in each direction, except 6 mm posteriorly and cranially.

The SBRT schedules consisted of five fractions of 7 Gy (total dose of 35 Gy) for low-risk disease and five fractions of 7.5 Gy (total dose of 37.5 Gy) for favorable intermediate-risk, delivered on 5 consecutive or alternating days; these doses corresponded to normalized total doses (NTD) in 2 Gy per fraction (NTD2) between 70–75 and 85–90 Gy for an α/β estimated between 3 and 1.5 Gy for PCa. The hRT schedules consisted of 28 fractions of 2.55 Gy (total dose 71.4 Gy) for low-risk disease and 28 fractions of 2.65 Gy (total dose 74.2 Gy) for favorable intermediate-risk; these doses corresponded to NTD2 between 79.25–82.62 Gy and 83.85–87.98 Gy for an α/β estimated between 3 and 1.5 Gy for PCa. See treatment characteristics in Table 1. Couch repositioning was completed after automatic CBCT matching to the reference planning CT, followed by manual adjustments. Matching was performed on fiducial markers (when available); in selected cases in which markers were not implanted due to patients' comorbidity or for patients' refusal, intraprostatic calcifications were used as a surrogate

Table 1 Treatment characteristics ($n = 149$)

Hypofractionated schedule ($n = 69$)	
Median CTV volume cc (range)	65.8 (15.4–142.8)
Median PTV volume cc (range)	165.1 (61.8–299.8)
71.4 Gy/28 fractions	22 (14.8)
74.2 Gy/28 fractions	47 (31.5)
SBRT schedule ($n = 80$)	
Median CTV volume cc (range)	65 (35.4–161.1)
Median PTV volume cc (range)	124.6 (72.6–253.7)
35 Gy/5 fractions	59 (39.6)
37.5 Gy/5 fractions	21 (14.1)

CTV clinical target volume, *PTV* planning treatment volume, *SBRT* stereotactic body radiotherapy

(Zeng et al. 2008). Intrafraction motion monitoring was not evaluated, according to previous experiences with the same technology published in similar experiences (Scorsetti et al. 2014; Alongi et al. 2013). Alpha-blockers were routinely administered in patients with large volume prostate (> 80 cc) or in those presenting with urinary symptoms.

SBRT planning

Dose prescription for SBRT was as follows: for low-risk patients, the dose distribution was normalized to assure that at least 95% of the PTV received at least 95% of 35 Gy, while less than 2% of the PTV received 107% of 35 Gy. For favorable intermediate-risk patients, the dose was prescribed to at least 95% of PTV minus any overlap with the rectum, bladder, or urethral planning risk volume (PRV) (i.e., 3 mm isotropic expansion from the urethra), while assuring both 95% of the whole PTV received at least 95% of 35 Gy (i.e., 33.2 Gy), and less than 2% of the PTV received 107% of 37.5 Gy. Urethral sparing was performed in patients with favorable intermediate risk according to our previous experience (Ruggieri et al. 2015). OAR planning objectives were V18 Gy ≤ 35%, V28 Gy ≤ 10%, V32 Gy ≤ 5%, and Dmax ≤ 35 Gy for the rectum; Dmax ≤ 35 Gy for the bladder; and Dmax ≤ 35 Gy for the urethra. Dmax always referred to the hottest 1 cm3 of the conceived organ at risk (OAR). Beam energy was equal to 10 MV in flattening filter-free (FFF) mode.

Hypofractionated RT planning

The planning objective was to cover 95% of each PTV with at least 95% of the prescribed dose. Dmax < 107% was requested for PTV1 only. OAR planning objectives were V50 Gy < 45%, V60 Gy < 30%, V65 Gy < 20%, and Dmax < 70 Gy for the rectum; V60 Gy < 35% for the bladder; D1cm3 < 50 Gy for the femurs (in particular, femoral heads); and V20 Gy < 40%,

Dmean < 20 Gy, and Dmax < 48 Gy for the intestinal cavity (Fersino et al. 2017). Beam energy was equal to 6 MV.

Follow-up

Thereafter, physical examination, toxicity assessment, IPSS, and clinical response with PSA evaluation were performed after 45–60 days following treatment or before if clinically indicated. Subsequently, follow-up was performed according to internal guidelines: every 4 months for the first 2 years, and every 6 months for the 3 years thereafter. A benign PSA bounce was defined as a 0.2 ng/ml or greater rise in PSA that then returned to the previous nadir. Tumor response was evaluated according to the American Society for Radiation Oncology (ASTRO) definition of PSA relapse (nadir value of PSA + 2 ng/ml) (Roach et al. 2006). Toxicity was assessed during and after SBRT according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Acute toxicity was defined as an adverse event occurring within 90 days from the beginning of SBRT, whereas late toxicity occurring after 90 days.

Statistics

The primary end-point of the present study was treatment-related toxicity. Secondary end-points were BFS and OS. Descriptive statistics of all variables were performed. BFS and OS were estimated using the Kaplan–Meier method and calculated from the end of RT. BFS was defined as the time between end of treatment and increase of PSA value corresponding to the nadir + 2 ng/ml or last follow-up. OS was defined as death from any cause or the last follow-up. Patients alive without progressive disease at the time of data analysis were censored. Univariate analysis was performed with the log-rank test to correlate survivals with the following independent variables: treatment schedules, risk class, previous abdominal surgery, toxicity, and PSA bounce. A multivariate analysis was performed with the multiple logistic regression method and the log-rank test to identify predictive factors; we included all the clinically relevant variables in the analysis. Variables were included in the multivariate analysis according to the correlation from the univariate analysis (p value ≤ 0.2). Statistical analysis was performed using STATA statistical software version 15 (STATA Corp, College Station, TX). A p value ≤ 0.05 indicated a significant association.

Results

Patient characteristics

One hundred forty-nine patients affected by PCa were treated at our Institution. Eighty-one (54.3%) had low-risk PCa: 59

(39.6%) of them were treated with SBRT and 22 (14.8%) with hRT. Sixty-eight (45.7%) patients were affected by favorable intermediate-risk PCa: 21 (14.1%) of them were treated with SBRT and 47 (31.5%) with hRT. In the SBRT subgroup, 52 (65%) out of 80 patients were treated within the phase II SBRT trial with rigid inclusion criteria, including volume ≤ 80 cc (Alongi et al. 2019). Twenty-eight (35%) out of 80 SBRT patients were treated with the same schedule after the end of the prospective study, without specific cut-off regarding prostate dimensions, if OAR constraints during planning were achieved. Patient characteristics are reported in Table 2.

Biochemical control, survival and treatment of failure

Median follow-up was 33 months (range 11–58 months) for the entire cohort, 33 months (range 11–58 months) for SBRT group, and 31 months (range 12–50 months) for hRT group. Actuarial BFS was 96.2%. The 3-year BFS for the SBRT and hRT groups were 100% and 95.5%, respectively (Fig. 1; log-rank = 0.051). Patients experiencing a biochemical failure were treated with ADT. Median OS was not reached and the 3-year OS was 96.4% and 100% for the SBRT and hRT groups, respectively. Actuarial survival was 95.5% and two patients died of non-oncological, non-treatment related causes. No factors were correlated with BFS or OS at the multivariate analysis.

PSA kinetics

Median nadir PSA value for the entire population was 0.35 ng/ml (range 0.01–3.82 ng/ml). There were no statistically significant differences in median nadir value between SBRT and hRT (0.36 ng/ml versus 0.32 ng/ml). We observed a rapid decline in PSA values in the first year after treatment; median time to nadir was 24 and 21 months for SBRT and hRT, respectively ($p \geq 0.05$). We reported 16 (10.7%) cases of benign PSA bounce (range 1.06–8.4 ng/ml) and the median time to PSA bounce was 12 months (range 2–53 months). No statistically significant difference in PSA bounce regarding risk class and treatment schedule was identified. Figure 2 depicts the PSA kinetics of the two treatment schedules.

Toxicity

There was only 1 (0.7%) case of grade 3 genitourinary (GU) toxicity in the hRT group. From the univariate analysis, hRT patients reported a significant increase in grade 1 acute rectal toxicity ($p = 0.011$) and grade 1–2 acute GU toxicity ($p = 0.00$), as compared to SBRT. No statistically significant differences in late toxicity were detected. Patients

Table 2 Patient characteristics ($n = 149$)

Mean age (years)	74
Range (years)	45–84
Hypertension	
Yes	84 (56.38)
No	65 (43.62)
Diabetes	
Yes	17 (11.41)
No	132 (88.59)
Hypercholesterolemia	
Yes	36 (24.16)
No	113 (75.84)
Previous abdominal surgery	
Yes	39 (26.17)
No	110 (73.83)
Stage	
SBRT ($n = 80$)	
T1b	2 (2.5)
T1c	10 (12.5)
T2a	24 (30)
T2b	12 (15)
T2c	32 (40)
hRT ($n = 69$)	
T1b	6 (8.5)
T1c	7 (10)
T2a	21 (30.5)
T2b	11 (16)
T2c	24 (35)
Gleason	
6 (3 + 3)	87 (58.39)
7 (3 + 4)	62 (41.61)
Initial PSA	
Median value (ng/ml)	6.4
Range (ng/ml)	1.48–19
Risk class	
Low	81 (54.36)
Favorable intermediate	68 (45.64)
IPSS pre-RT	
Median score	4
Range	0–20
IPSS after RT	
Median score	6
Range	0–20
Marker	
SBRT ($n = 80$)	
Fiducials	15 (18.5)
Intraprostatic calcifications	42 (52.5)
None	23 (29)
hRT ($n = 69$)	
Fiducials	6 (8.6)
Intraprostatic calcifications	23 (33.3)
None	40 (57.9)

IPSS International Prostatic Symptom Score, *SBRT* stereotactic body radiotherapy, *hRT* hypofractionated radiotherapy
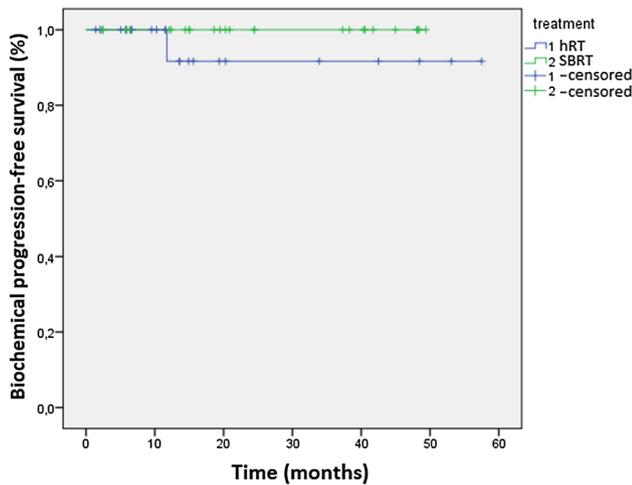
Fig. 1 Kaplan–Meier curve showing biochemical progression-free survival stratified according to treatment schedule (*hRT* hypofractionated radiotherapy, *SBRT* stereotactic body radiotherapy)
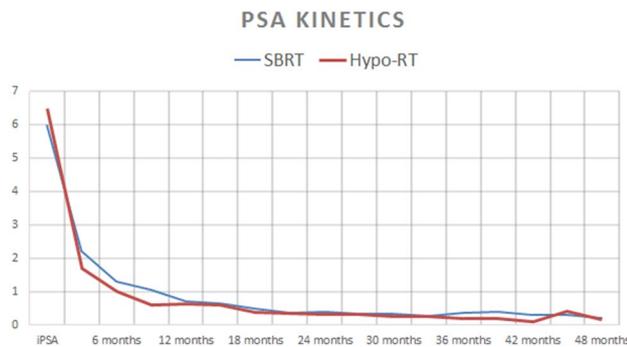

Fig. 2 PSA kinetics stratified according to treatment schedule

treated with SBRT could have received treatment alternating (22 patients) versus consecutive (58 patients) days, but there was no differences in rectal ($p = 0.18$) and GU ($p = 0.1$) acute toxicity. No differences in acute toxicity were detected between the two SBRT schedules. Median IPSS before RT was 4 (range 0–20) and median IPSS after RT was 6 (range 0–20). There were no differences in IPSS before and after

RT between hRT and SBRT. At the multivariate analysis, no factor was correlated to acute or late toxicity. Acute and late toxicities are reported in Table 3.

Discussion

The linear-quadratic model represents the basis for predicting the clinical effects of alternative fractionation schemes in RT. High fractionation-sensitivity seems to be an intrinsic property of PCa (Dasu and Toma-Dasu 2012). From a clinical point of view, the α/β ratio of PCa seems lower than that of the surrounding organs at risk (rectum, bladder), allowing for safe dose/fraction escalation and therapeutic ratio improvement (De Bari et al. 2016). Apart from the radiobiological basis, the interest in hypofractionated regimens is also based on the logistical aspects when short overall treatment time may reduce treatment costs and improve the patient's compliance (Collins et al. 1991). From a clinical point of view, several randomized trials (Incrocci et al. 2016; Dearnaley et al. 2016) employed moderate hypofractionation in daily clinical practice, showing results comparable to conventional fractionation. A step forward in the reduction of overall treatment time is possible through "extreme hypofractionation" schedules (usually from 4 to 8 fractions in 1/2 weeks), also called SBRT. Since 2014, the National Comprehensive Cancer Network (NCCN) Guidelines stated that, in departments with appropriate technology and staff expertise, an extreme hypofractionated treatment delivered by SBRT in PCa could be considered as an alternative to conventional fractionation.

So far, no randomized trial has compared moderate hypofractionation regimens versus extreme hypofractionated schedules in PCa. In a recent propensity score-based comparison (Franzese et al. 2019) between moderate hypofractionation and extreme hypofractionation, no difference in terms of disease control and survival were reported. The authors included patients who underwent hormonal therapy for both groups of the patients analyzed (i.e., 15.6% of moderate hypofractionated group and 21% of SBRT arm). Finally, another study compared moderate hypofractionation

Table 3 Acute and late toxicity ($n = 149$)

	Hypofractionation			SBRT		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Acute toxicity						
Genitourinary	29 (19.5%)	9 (6%)	1 (0.7%)	13 (8.7%)	4 (2.7%)	0
Rectal	20 (13.4%)	2 (1.3%)	0	8 (5.4%)	2 (1.3%)	0
Late toxicity						
Genitourinary	6 (4%)	2 (1.3%)	0	3 (2%)	2 (1.3%)	0
Rectal	4 (2.7%)	4 (2.7%)	0	8 (5.4%)	1 (0.7%)	0

SBRT stereotactic body radiotherapy

vs. SBRT in terms of side-effect profiles (Johnson et al. 2016). Based on these considerations, we analyzed herein findings of two patient cohorts affected by low- and favorable intermediate-risk prostate cancer who underwent two different RT hypofractionation schedules (i.e., more than 70 Gy in 28 fractions and 35/37.5 Gy in five fractions). The patients who underwent SBRT were enrolled in a prospective phase II pilot feasibility study, published recently (Alongi et al. 2019).

Concerning the study population analyzed here, the actuarial BFS was 96.2% at a median follow-up of 33 months (range 11–58 months). More specifically, the 3-year BFS for the SBRT and hRT groups were 100% and 95.5%, respectively (log-rank test = 0.051). At the time of the analysis, a single case of G3 toxicity was recorded in the hRT group. From the univariate analysis, hRT patients reported a significant increase in grade 1 acute rectal toxicity ($p = 0.011$) and grade 1–2 acute GU toxicity ($p = 0.00$) as compared to SBRT.

Oliai et al. (2016) treated 263 patients with SBRT and IMRT for localized PCa, using Cyberknife. The administered schedules were 35–37.5 Gy/5 fractions and 72–79.2 Gy/28 fractions. No grade > 3 genitourinary toxicity was reported, and grade 2 genitourinary toxicity occurred in 14% (SBRT group) and 12% of the patients (IMRT group). Gastrointestinal grade 2 toxicity occurred in 3% and 1% in the SBRT and IMRT groups, respectively.

PACE-B trial is a randomized trial which compared SBRT to conventionally and moderately hypofractionated RT (CFMHRT). The protocol toxicity analysis was recently presented showing no significant differences in ≥ grade 2 GU (23.2% versus 27.2%) and GI (10.1% versus 12.1%) for SBRT and CFMHRT, respectively (Van As et al. 2019). We reported a relative low rate of late toxicity, as compared to the 5-year 10–11.2% grade ≤ 2 GU and 4.5–7% grade ≤ 2 GI reported in other series (Katz et al. 2013; Kishan et al. 2019). Although these results are promising, the optimal tolerability in the late setting should be mitigated by the relative short follow-up, since some patients have < 24 months follow-up. Thus, a longer follow-up is needed to definitively assess long-term late toxicity.

It is recognized that PSA nadir and time to nadir were reported as significant predictors for disease-free survival and distant metastases-free survival (Ray et al. 2006). Previous studies reported a lower value of PSA nadir for SBRT and HDR brachytherapy as compared to IMRT, but without differences in time to PSA nadir and bounce (Kishan et al. 2016). In another study, the PSA kinetics of SBRT and conventionally fractionated radiotherapy were evaluated, reporting a median nadir value of 0.24 and 0.6 ng/ml (Anwar et al. 2014). Park et al. found a PSA nadir value after SBRT to the prostate of 0.12 ng/ml and a median time to nadir of 47.3 months (Park et al. 2018). The authors

described kinetics characterized by a rapid PSA decrease in the first year after treatment and a following slow decrease until nadir. In the present study, no differences in time to PSA nadir, PSA nadir value, and PSA bounce were detected between SBRT and hRT. The PSA kinetics showed characteristics similar to those previously reported. Moreover, we observed a rapid decline in PSA values in the first year after treatment; median time to nadir was 24 and 21 months for SBRT and hRT, respectively ($p > 0.05$).

Our study presents some intrinsic limitations: the retrospective nature, the relatively small sample size, the short follow-up, and the absence of quality of life assessment; moreover, the use of different PTV concepts and the absence of a planned early clinical visitation could have lead to a different toxicity incidence report. The strengths are the patient homogeneity, the exclusive use of RT that may have avoided possibly confounding concomitant ADT, the prescription homogeneity, and the short recruitment period.

In brief, the results of our study showed no differences in efficacy and tolerability between SBRT and hypofractionation in low- and favorable intermediate-risk prostate cancer patients. Nevertheless, a longer follow-up is needed to definitively assess long-term efficacy and toxicity.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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