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Extreme hypofractionated stereotactic radiotherapy for localized prostate Cancer: Efficacy and late urinary toxicity according to transurethral resection of the prostate history

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ABSTRACT

Background and purpose: Extreme hypofractionated stereotactic body radiotherapy (SBRT) is a therapeutic alternative for localized low- or intermediate-risk prostate cancer. Despite the availability of several studies, the toxicity profile of SBRT has not been comprehensively described. This real-world evidence study assessed the efficacy and toxicities associated with this regimen, and potential prognosis factors for genitourinary toxicities.
Materials and methods: This retrospective study included 141 consecutive patients with localized prostatic adenocarcinoma treated with CyberKnife™ SBRT, as primary irradiation, at the Oscar Lambret Center between 2010 and 2020. The prescribed dose was 36.25 Gy in 5 fractions. Acute and late toxicities were graded according to the CTCAE (version 5.0). Biochemical recurrence-free survival (bRFS) and overall survival (OS) were estimated using the Kaplan–Meier method. The cumulative incidence of biochemical recurrence (cBR) was estimated using the Kalbfleisch–Prentice method.
Results: Among the included patients, 13.5 % had a history of transurethral resection of the prostate (TURP). The median follow-up was 48 months. At 5 years, bRFS, cBR, and OS were 72 % (95 %CI: 61–81), 7 % (95 %CI: 3–14), and 82 % (95 %CI: 73–89), respectively. Twenty-nine patients experienced at least one late toxicity of grade ≥ 2; genitourinary ($N = 29$), including 3 cases of chronic hematuria, and/or gastrointestinal ($N = 1$). The cumulative incidence of late urinary toxicity of grade ≥ 2 was 20.6 % at 5 years (95 %CI: 13.9–28.1). Multivariate analysis revealed that a history of TURP was significantly associated with late urinary toxicity of grade ≥ 2, after adjusting for clinical target volume (Odds Ratio = 3.06; 95%CI: 1.05–8.86; $P = 0.04$).
Conclusion: Extreme hypofractionated SBRT is effective for localized prostate cancer with a low risk of late toxicity. A history of TURP is associated with a higher risk of late urinary toxicity. These findings may contribute to the optimal management of patients treated with this regimen, particularly those with a history of TURP.

Introduction

Globally, prostate cancer is the second most common cancer and fifth leading cause of cancer-related mortality in men, with 1.41 million cases and 375 thousand deaths, respectively, per year [1,2].

The management of localized prostate cancer includes various options, including radical prostatectomy, external beam radiotherapy with or without hormone therapy, brachytherapy, and active surveillance

Abbreviations: ADT, Androgen deprivation therapy; bRFS, Biochemical recurrence-free survival; CTV, Clinical target volume; cBR, Cumulative incidence of biochemical recurrence; OR, Odds ratio; PSA, Prostate-specific antigen; PTV, Planning target volume; SBRT, Stereotactic body radiation therapy; OS, Overall survival; RFS, Recurrence-free survival; TURP, Transurethral prostate resection; TURB, Transurethral bladder resection; UIR, Unfavorable intermediate risk.

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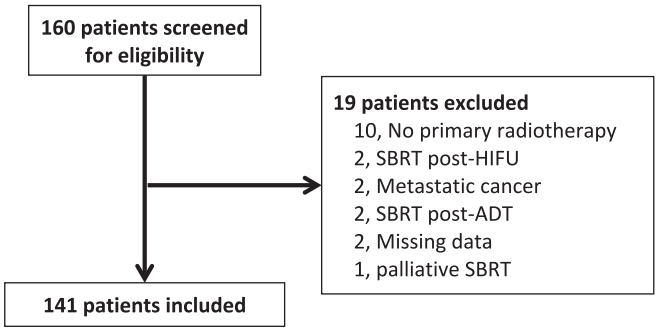

Fig. 1. Patient enrollment flow chart. SBRT, stereotactic body radiotherapy; HIFU, high-intensity focused ultrasound; ADT; androgen deprivation therapy.

Table 1
Patient characteristics.

Patient characteristics	N = 141	
Age at end of RT		
Median – (Range)	73	(54–91)
Mean – SD	73	6.7
Watchful waiting output		
No	120	85.10 %
Yes	21	14.90 %
Previous TURB		
No	138	97.90 %
Yes	3	2.10 %
Previous TURP		
No	122	86.50 %
Yes	19	13.50 %
Previous erectile dysfunction (MD = 29)		
No	57	50.90 %
Yes	55	49.10 %
Inflammatory bowel disease		
No	140	99.30 %
Yes	1	0.70 %
Anticoagulant therapy (MD = 1)		
No	124	88.60 %
Yes	16	11.40 %
Antiplatelet therapy		
No	81	57.40 %
Yes	60	42.60 %
α-blocker therapy		
No	106	75.20 %
Yes	35	24.80 %
Smoking history (MD = 42)		
Non-smoker	42	42.40 %
Former smoker	45	45.50 %
Current smoker	12	12.10 %
Cumulative smoking pack-years		
Median (range)		
Former smoker (MD = 31)	33.5	(3–80)
Current smoker (MD = 5)	38.8	(13–80)
WHO performance status score (MD = 1)		
Fully active	99	70.70 %
Restricted in physically strenuous activity	40	28.60 %
Ambulatory and capable of all self-care	1	0.70 %

Table 2
Disease characteristics.

Disease characteristics	N = 141	
Baseline PSA (ng/ml)		
Median – (Range)	7.7	(2.2–24)
Mean – SD	8.4	3.7
ISUP grade		
1	64	45.40 %
2	61	43.30 %
3	13	9.20 %
4	1	0.70 %
5	2	1.40 %
Number of positive biopsies (MD = 9)		
Median – (Range)	4	(1–12)
Mean – SD	4.1	2.3
Number of biopsies (MD = 12)		
Median – (Range)	12	(4–24)
Mean – SD	13	2.2
% of positive biopsies (MD = 12)		
Median – (Range)	31.3	(7.1–100)
Mean – SD	31.9	18.7
Clinical T stage		
T1c	84	59.60 %
T2a	38	27.00 %
T2b	14	9.90 %
T2c	3	2.10 %
T3b	2	1.40 %
M Stage		
M0	83	58.90 %
Mx	58	41.10 %
D'Amico risk classification		
Low	45	31.90 %
Favorable intermediate	47	33.30 %
Unfavorable intermediate	42	29.80 %
High	7	5.00 %

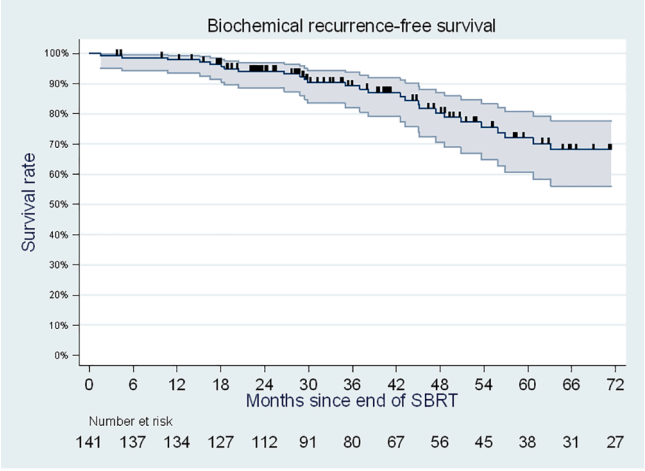

Fig. 2. Biochemical recurrence-free survival SBRT, stereotactic body radiotherapy.

[3,4]. Sophisticated technological advances have facilitated the rise of stereotactic body radiotherapy (SBRT), allowing the delivery of high doses per fraction, accounting for inter- and intra-fractional movements, depending on the equipment. These advances have enabled dose escalation, justified in the prostatic context owing to a low α/β ratio, suggesting high radiosensitivity to high doses per fraction [5,6]. Nevertheless, concerns regarding the potentially increased risk of late toxicities following this treatment, especially genitourinary toxicities, have garnered attention [7–9].

Recent studies on extreme hypofractionation, with or without SBRT, have provided additional insights. A phase III study, the HYPO-RT-PC, demonstrated that for intermediate-risk cancers, a scheme of 42.7 Gy in 7 fractions was non-inferior in terms of RFS compared with normofractionated SBRT of 78 Gy in 39 fractions; a slight increase in acute toxicities of grade ≥ 2, though similar late toxicities were observed [10]. Another phase III study, the PACE-B, comparing a standard regimen (normo- or moderate hypofractionated) to a regimen of 36.25 Gy in 5 fractions, found that the risk of late toxicity with ultra-hypofractionation is low and similar to longer schedules; however, a flare of toxicity was observed 1 year post-SBRT. At 2 years, cumulative incidence rates of RTOG grade 2 or worse genitourinary toxicity were 10.6 % (95 % CI 8·0–14·0) for standard regiment and 18.3 % (14·9–22·4) for SBRT (HR 1·80 [95 % CI 1·25–2·61]; log-rank p = 0·0015) [11,12].

Kishan et al.'s study demonstrated excellent local control at 7 years post-SBRT, coupled with a low risk of late complications [13].

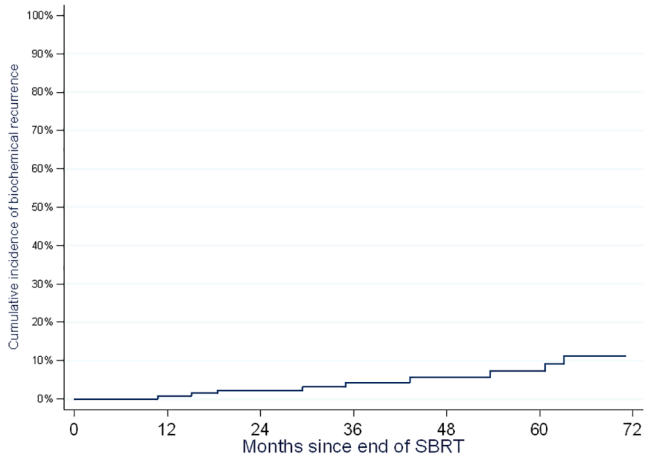

Fig. 3. Cumulative incidence of biochemical recurrence. SBRT, stereotactic body radiotherapy.

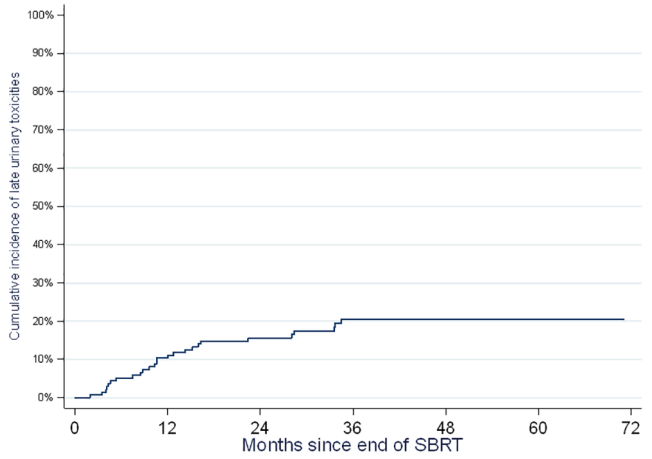

Fig. 4. Cumulative incidence of late urinary toxicity. SBRT, stereotactic body radiotherapy.

Moreover, in the long term, hypofractionation could offer economic advantages [14] and better adherence/applicability. Nevertheless, despite promising results of these studies, the efficacy and toxicity profile of SBRT for patients with localized prostate cancer, in particular those with a history of transurethral resection of the prostate (TURP), is not well-documented. Our study aimed to analyze the biochemical recurrence-free survival and overall survival rates associated with this therapeutic regimen and its toxicity profile.

Materials and methods

Study design and patient enrollment

This retrospective study conducted at the Oscar Lambret Center, Lille, France. Patients meeting eligibility criteria were consecutively enrolled. Inclusion criteria were as follows: age $\geq$ 18 years; a histopathological diagnosis of localized prostatic adenocarcinoma; and treatment with SBRT as primary irradiation at the Oscar Lambret Center from 2010 to 2020. Exclusion criteria included patient refusal for the use of their clinical data for research purposes.

Treatment characteristics

All patients underwent pre-treatment intraprostatic fiducial marker placement and planning MRI. Rectum and bladder preparation preceded the centering CT scan and each session. A fiducial-based CT-MRI image fusion was performed before defining the clinical target volume (CTV). Urethra delineation was optional.

The RayStation TPS (RaySearch Laboratories AB, Stockholm, Sweden) was used for treatment planning. The prescribed dose was 36.25 Gy in 5 fractions, every other day. The planning target volume (PTV) was 3 mm posteriorly (toward the rectum) and 5 mm in other directions, similar to the PACE B protocol. Dose constraints from this protocol were applied to organs at risk. Dosimetric data were reported according to the International Commission on Radiation Units and Measurements report 91 guidelines. Dosimetry was performed using Precision™, and the final dose calculation was performed via a Ray Tracing algorithm. The CyberKnife™ System (Accuray™ Inc., Sunnyvale, CA, USA) was used for SBRT.

Patients were classified into different risk groups according to the D'Amico classification. The intermediate-risk group was subdivided into favorable intermediate-risk or unfavorable intermediate-risk (UIR) groups according to the Zumsteg criteria [15].

Table A1
Treatment characteristics.

Treatment characteristics	N = 141	
Stereotactic body radiotherapy		
Radiotherapy duration		
Median – (Range)	12	(9–41)
Mean – SD	12.8	3.7
Total dose delivered (Gy)		
Median – (Range)	36.3	(34.6–36.5)
Mean – SD	36.2	0.3
Prescription isodose (%) (MD = 4)		
Median – (Range)	81	(73–90)
Mean – SD	81.8	3.5
Radiotherapy fractions received (Gy)		
Median – (Range)	7.3	(6.9–7.3)
Mean – SD	7.2	0.1
Hormone therapy		
Received hormone therapy		
Yes	19	13.50 %
Hormone therapy type (MD = 2)		
LHRH agonist	13	76.40 %
LHRH antagonist	2	11.80 %
Other	2	11.80 %
Hormone therapy delivered (MD = 5)		
Median – (Range)	10.9	(2.144.1)
Mean – SD	15.2	14.4

MD, missing data; LHRH, luteinizing hormone-releasing hormone.

Study objectives

The primary objective was to assess biochemical recurrence, defined according to the Phoenix criteria as serum prostate-specific antigen (PSA) level exceeding nadir + 2 ng/mL, confirmed by another rising measurement, with nadir being the lowest value observed after local treatment.

Secondary objectives were to estimate RFS, overall survival (OS), evaluate and classify toxicities, identify prognostic factors associated with late toxicity, and study PSA evolution. Secondary endpoints included local recurrence, all-cause mortality, and toxicity grades according to the Common Terminology Criteria for Adverse Events version 5.0, and distinguishing acute (<3 months post-radiotherapy) and chronic (>3 months post-radiotherapy) toxicities. Adverse effects were recorded until the date of the latest information.

Statistical analyses

All collected data were analyzed using standard descriptive

Table A2
Stereotactic body radiation therapy dosimetric parameters.

Stereotactic body radiation therapy	N = 141	
CTV		
Clinical target volume (MD = 3)		
Median − (Range)	53.4	(20.3–182.8)
Mean − SD	58.7	23.7
D98% (MD = 3)		
Median − (Range)	37.4	(32.7–40.6)
Mean − SD	37.7	1.5
D95% (>40) (MD = 3)		
Median − (Range)	38	(35.3–41.2)
Mean − SD	38.2	1.5
D50% (MD = 3)		
Median − (Range)	40.8	(36.4–44.6)
Mean − SD	40.9	1.8
D2% (MD = 3)		
Median − (Range)	43.3	(38.8–48.2)
Mean − SD	43.3	2
PTV		
D98% (MD = 3)		
Median − (Range)	35.6	(26.9–36.9)
Mean − SD	35.3	1.4
D95% (>36.25) (MD = 3)		
Median − (Range)	36.3	(31.3–40)
Mean − SD	36.1	1
D50% (MD = 3)		
Median − (Range)	39.9	(36.8–42.3)
Mean − SD	39.9	1.3
D2% (MD = 3)		
Median − (Range)	43.3	(38.8–47.9)
Mean − SD	43.2	1.9
Bladder		
Dmin 98 % (MD = 3)		
Median − (Range)	2.1	(0.3–11.3)
Mean − SD	3	2.4
D50% (MD = 3)		
Median − (Range)	10.9	(1.2–20.3)
Mean − SD	10.9	4
Dmax 2 % (MD = 3)		
Median − (Range)	35.9	(26.7–41.6)
Mean − SD	35.4	2.6
V37 Gy (<5–10 cc) (MD = 4)		
Median − (Range)	1.9	(0–25.3)
Mean − SD	2.5	3
V18.1 Gy (<40 %) (MD = 4)		
Median − (Range)	23.5	(3.8–62)
Mean − SD	25	11.9
Rectum		
Dmin 98 % (MD = 3)		
Median − (Range)	3.2	(0.6–15)
Mean − SD	3.6	2.3
D50% (MD = 3)		
Median − (Range)	12.5	(5.6–21.4)
Mean − SD	12.6	3.5
Dmax 2 % (MD = 3)		
Median − (Range)	35.5	(29.4–38.3)
Mean − SD	35.1	1.4
V36 Gy (<1–2 cc) (MD = 4)		
Median − (Range)	0.7	(0–9)
Mean − SD	0.8	1
V29 Gy (<20 %) (MD = 4)		
Median − (Range)	11.6	(2.1–30.6)
Mean − SD	11.7	4.4
V18.1 Gy (<50 %) (MD = 4)		
Median − (Range)	32.3	(7.4–73.5)
Mean − SD	32.2	11.4
Urethra		
Contoured urethra (MD = 3)	37	26.80 %
Yes		
V42 Gy (<50 %)		
Median − (Range)	35.9	(0–88.7)
Mean − SD	30.3	23.1
D50%		
Median − (Range)	41.2	(33.1–44.7)
Mean – SD	40.6	2.1
D0.035 cc		
Median − (Range)	43.9	(37.3–49)
Mean – SD	43.4	2.4
Dvol − 0.035 cc		
Median − (Range)	36.6	(3.5–40.8)
Mean – SD	31.5	10.7
Penile bulb		
Contoured penile bulb (MD = 3)		
Yes	61	44.20 %
V29.5 Gy (<50 %)		
Median − (Range)	0	(0–61.5)
Mean − SD	5.7	11.8
Femoral head		
Contoured femoral head (MD = 3)		
Yes	133	96.40 %
Right V14.5 Gy (<5%) (MD = 1)		
Median − (Range)	0	(0–2.6)
Mean − SD	1.2	2.5
Left V14.5 Gy (<5%)		
Median − (Range)	0.1	(0–52.5)
Mean − SD	2.1	5.8
Intestine		
Bowel bag (MD = 3)		
Yes	110	79.70 %
V30 Gy (<1cc) (MD = 31)		
Median − (Range)	0	(0–2.8)
Mean − SD	0	0.3
V18.1 Gy (<5cc) (MD = 31)		
Median − (Range)	0	(0–23.3)
Mean − SD	0.7	2.6

CTV, clinical target volume; PTV, planning target volume; MD, missing data.

statistical methods. Categorical variables were presented as frequency and percentage and continuous variables as median with range or interquartile range and mean with standard deviation. The number of missing data was specified for each variable.

Median follow-up was estimated by from the end date of radiotherapy to the date of the last follow-up for all living patients (clinical or biological).

Biochemical recurrence-free survival (bRFS), defined as the time from the end of radiotherapy to biochemical recurrence or all-cause mortality, was estimated using the Kaplan–Meier method. Events (biochemical recurrence and/or death) were considered as those that occurred during the "documented" medical follow-up, i.e., before the last available date indicating medical follow-up.

The cumulative incidence of biochemical recurrence (cBR) was estimated using the Kalbfleisch–Prentice method, considering deaths without prior biochemical recurrence as competing events.

Overall survival, defined as the time from the end of radiotherapy to all-cause mortality, was estimated using the Kaplan–Meier method. Observations of living patients were censored at the date of the latest information.

The cumulative incidence of local recurrence was estimated by the Kalbfleisch–Prentice method, considering regional or metastatic recurrences without associated local relapse as a competing event, and deaths without prior local relapse.

Prognostic factors associated with late toxicity were determined

Table A3
Toxicities.

Characteristics (N = 141)	Grade 1		Grade 2		Grade 3		All grades	
At least one event, n (%)	56	39.70 %	66	46.80 %	4	2.80 %	126	89.40 %
Acute toxicities								
At least one event, n (%)	51	22.70 %	56	36.20 %	2	1.40 %	109	77.30 %
Acute urinary disorders	49	28.40 %	52	36.90 %	0		101	71.60 %
Acute proctitis	26	18.40 %	10	7.10 %	2	1.40 %	38	27.00 %
Acute burning micturition	NA		NA		NA		50	35.50 %
Late toxicities								
At least one event, n (%)	65	46.10 %	27	19.20 %	2	1.40 %	94	68.60 %
Chronic urinary disorders (MD = 4)	56	40.90 %	25	18.30 %	1	0.70 %	82	59.90 %
Chronic hematuria (MD = 6)	9	6.70 %	2	1.50 %	1	0.70 %	12	8.90 %
Chronic proctitis (MD = 6)	15	11.10 %	1	0.70 %	0		16	11.90 %
Late hemorrhagic proctitis (MD = 6)	13	9.60 %	1	0.70 %	0		14	10.40 %
Late burning micturition (MD = 6)	NA		NA		NA		20	14.80 %
Erectile dysfunction N = 57 (MD = 11)	NA		NA		NA		22	38.60 %

MD, missing data.

Table A4
Prognostic factors – Late urinary toxicities of grade ≥ 2.

	Late urinary toxicities – grade ≥ 2						
		Univariate analysis			Multivariate analysis		
	Events/N	Odds Ratio	95 % CI	*P* value	Odds Ratio	95 % CI	*P* value
Age in years							
≤70	7/40	1	(1.51–3.61)	0.42			
71–79	17/76	1.36	(0.09–2.64)				
≥80	2/21	0.50					
Previous TURB							
No	25/134						
Yes	1/3						
Previous TURP				0.04			0.04
No	19/118	1			1		
Yes	7/19	3.04	(1.06–8.72)		3.06	(1.05–8.86)	
Anticoagulant therapy (N = 136)				0.48			
No	24/120	1					
Yes	2/16	0.57	(0.12–2.69)				
α-blocker therapy				0.88			
No	18/104	1	(0.59–3.93)				
Yes	8/33	1.53					
Hormone therapy				0.13			
No	25/118	1					
Yes	1/19	0.21					
CTV (N = 134)			(0.03–1.62)				
OR/10 cm^3	29/108	0.91	(0.74–1.12)	0.37	0.92	(0.74–1.13)	0.43
Bladder Dmin 98 % (N = 134)	25/134	0.92	(0.75–1.11)	0.38			
Bladder D50% (N = 134)	25/134	0.94	(0.84–1.04)	0.24			
Bladder Dmax 2 % (N = 134)	25/134	1.07	(0.89–1.28)	0.45			
Bladder V37 Gy (N = 134)	25/134	1.07	(0.94–1.22)	0.29			
Bladder V18.1 Gy (N = 134)	25/134	0.98	(0.94–1.01)	0.22			
Contoured urethra (N = 134)				0.53			
No	19/99	1					
Yes	6/35	0.87	(0.32–2.39)				

TURP, transurethral resection of the prostate; TURB, transurethral resection of the bladder; CTV, clinical target volume.

using univariate and subsequently, multivariate logistic regression models to estimate the odds ratio (OR). Studied variables included anticoagulant treatment, history of transurethral resection of the prostate (TURP) and bladder (TURB), age, androgen deprivation therapy (ADT), use of α-blockers, CTV (prostate), and dosimetric factors. All variables were tested in univariate models. Significant variables ($P < 0.20$) were subsequently included in an initial multivariate model. Variables included in the final model were those significantly explaining the risk of late toxicity ($P < 0.05$).

The cumulative incidence of toxicity was estimated using the Kalbfleisch–Prentice method. Cumulative incidence of late toxicity was estimated considering deaths without prior urinary toxicity as a competing event. Estimates were accompanied by their 95 % CIs. The significance level was set at $P < 0.05$. The Stata v17.0 software (StataCorp. 2017; Stata Statistical Software: Release 17. StataCorp LLC, College Station, TX, USA) was used for statistical analysis.

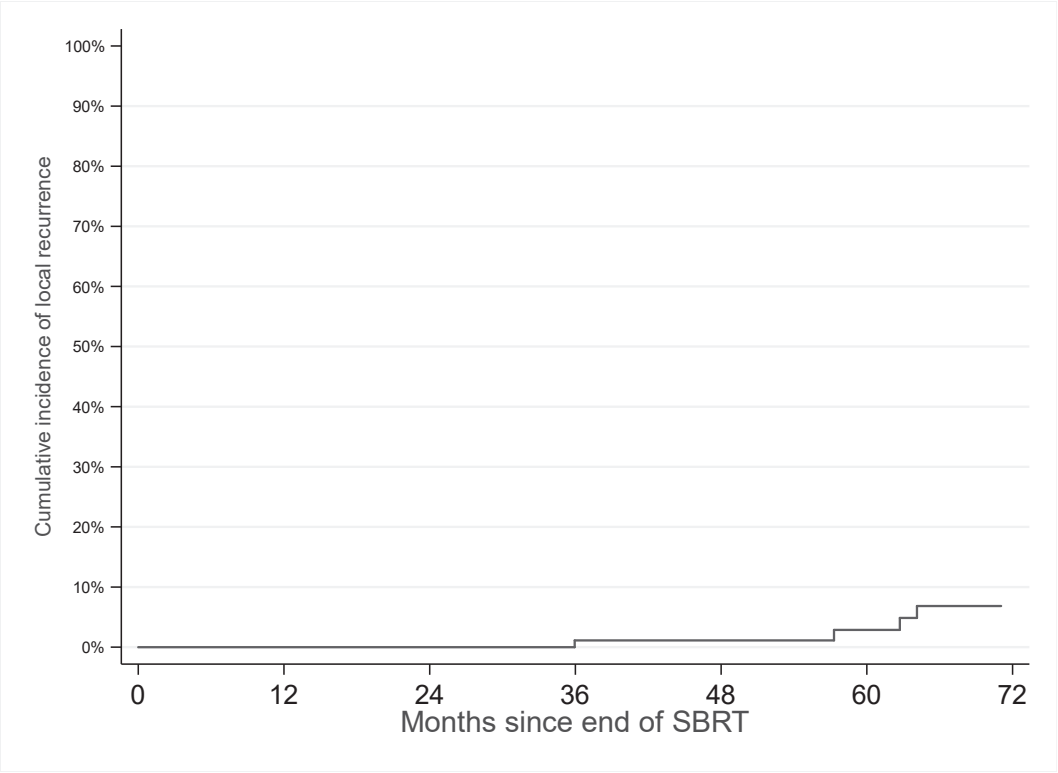

Fig. A1. Cumulative incidence of local recurrence. SBRT, stereotactic body radiotherapy.

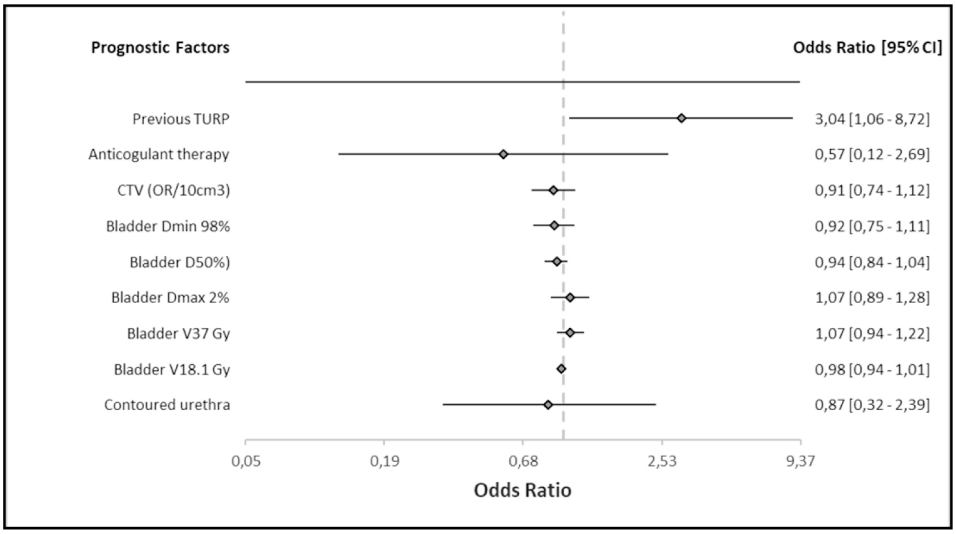

Fig. A2. Forest plot (Univariate analysis of late urinary toxicity). CTV, clinical target volume; TURP, transurethral resection of the prostate.

Ethical considerations

The study complied with the MR 004 reference methodology adopted by the French Data Protection Authority. All participants provided consent for the use of their clinical data for research purposes. The study was approved by the institutional ethics review board (CEC-2022–020).

Results

Among a total of 160 eligible patients, 141 were included in the analyses. (Fig. 1).

The median age at diagnosis was 73 years (range, 54–91). Approximately 99.3 % of the patients had a WHO performance status score of 0 or 1; 49.1 % had pre-treatment erectile dysfunction, and 13.5 % and 2.1 % had a history of TURP and TURB, respectively. The interval between TURP and SBRT was superior to 6 months in all patients except one (3.9 months).While 24.8 % of the patients were on α-blockers, 11.4 % and 42.6 % were on curative anticoagulation or antiplatelet therapy, respectively. Approximately 12.1 % and 45.5 % of the patients were active or former smokers, respectively (Table 1).

RT, radiotherapy; TURP, transurethral resection of the prostate; TURB, transurethral resection of the bladder; MD, missing data.

Mild and moderate urinary symptoms were found in 68.8 % (IPSS inferior to 7) and 31.2 % (IPSS from 8 to 19) of patients, respectively.

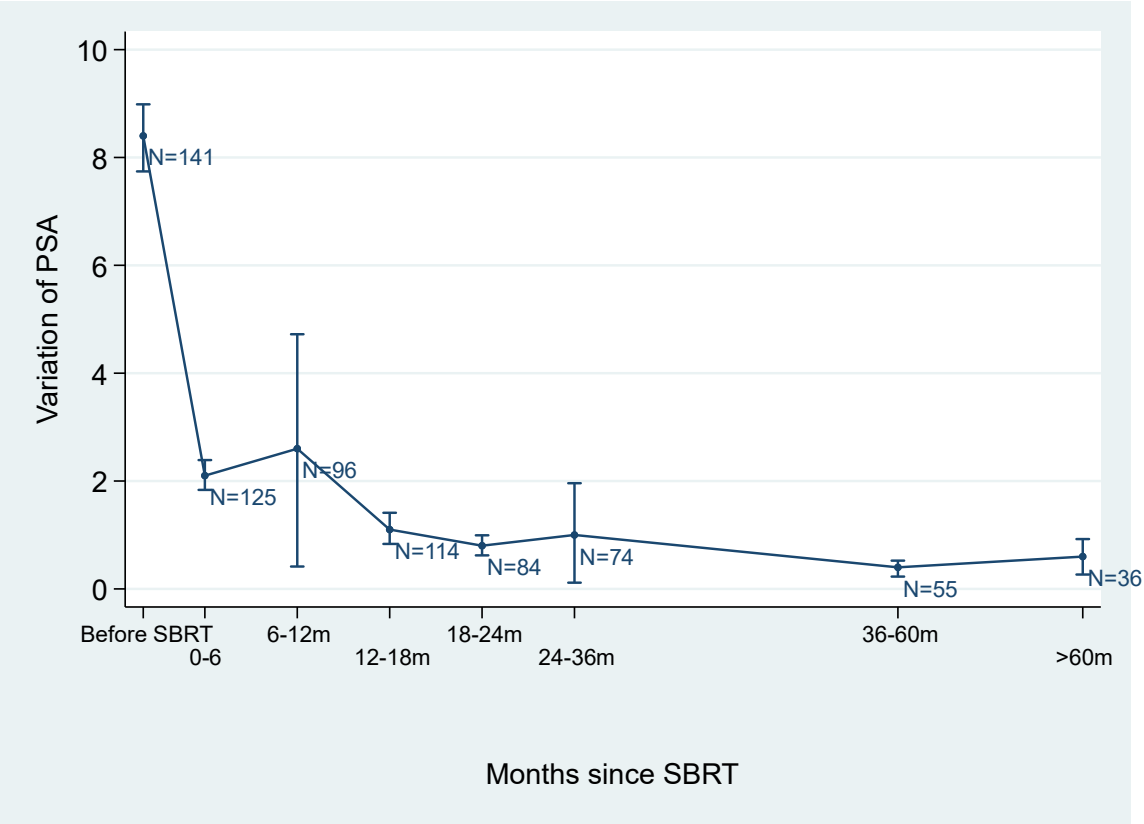

Fig. A3. Variation in prostate-specific antigen. PSA, prostate-specific antigen; SBRT, stereotactic body radiotherapy.

The median pre-treatment PSA was 7.7 ng/ml. Regarding risk classification, 32 %, 33 %, 30 %, and 5 % of the patients had low-, favorable intermediate-, unfavorable intermediate, and high-risk cancer, respectively (Table 2).

PSA, prostate-specific antigen; MD, missing data; ISUP, International Society of Urological Pathology.

The average irradiation duration was 12 days, with a prescribed dose of 36.25 Gy in 5 fractions and a median prescription isodose of 81 %. Concurrent ADT was prescribed for 13.5 % of the patients for an average duration of 15.2 months.

The median (IQR) D98%, D50%, and D2% of the CTV were 37.4 Gy (32.7–40.6), 40.8 Gy (36.4–44.6), and 43.3 Gy (38.8–48.2), respectively. The median (IQR) D98%, D50%, and D2% of the PTV were 35.6 Gy (26.9–36.9), 39.9 Gy (36.8–42.3), and 43.3 Gy (38.8–47.9), respectively.

The median CTV was 53.4 cc (20.3–182.8). The median dose received by 50 % of the bladder and rectum were 10.9 Gy (1.2, 20.3) and 12.5 Gy (5.6, 21.4), respectively. The median volume of the bladder receiving 37 Gy was 1.9 cc (0–25.3), that of the rectum receiving 36 Gy was 0.7 cc (0–9), that of the urethra receiving 42 Gy was 35.9 % (0–88.7), and that of the penile bulb receiving 29.5 Gy was 5.7 %. Tables A1 and A2 list the treatment data.

The median follow-up for patients, estimated using the Schemper method, was 47.7 months (range in living patients, 3.4–144.9). During analysis, 32 events, including 22 deaths and 10 biochemical recurrences (8 clinical recurrences, including 3 local, 1 locoregional, 1 regional, 1 locoregional and metastatic, and 1 regional and metastatic) were reported. All patients with biochemical recurrences were alive as of the latest update.

While bRFS at 2 and 5 years was 94.1 % (95 % CI: 88.5–97) and 72.1 % (95 % CI: 61–81), respectively (Fig. 2), cBR was 2.2 % (95 % CI: 0.6–5.9) and 7.3 % (95 % CI: 3–14), respectively (Fig. 3).

The cumulative incidence of local recurrence was 2.9 % at 5 years (Fig. A1). Overall survival was 82.3 % (95 % CI: 73–89) and 71.5 % (95 % CI: 60.7–79.8) at 5 and 8 years, respectively.

Occurrence of post-SBRT erectile dysfunction was reported in only the 57 patients who did not have prior erectile dysfunction. Among these, 22 experienced post-SBRT erectile dysfunction, 24 did not have post-SBRT erectile dysfunction, and post-SBRT information data was missing for 11 patients.

Acute genitourinary and gastrointestinal toxicities of grade ≥ 2 were reported in 52 (36.9 %) and 12 (8.5 %) patients, respectively. Late genitourinary toxicity of grade ≥ 2 was reported in 29 (20.6 %) patients, including 3 cases of chronic hematuria. Late gastrointestinal toxicity of grade ≥ 2 (rectal bleeding) was reported in only 1 (0.7 %) patient. No grade 3 gastrointestinal toxicity was reported (Table A3).

Late urinary toxicity data were collected for 137 patients, among whom 26 experienced late urinary toxicity of grade ≥ 2. The cumulative incidence of late urinary toxicity of grade ≥ 2 was 10 %, 15.6 %, and 20.6 % at 1 (95 % CI: 5.9–16.1), 2 (95 % CI: 10–22.2), and 5 (95 % CI: 13.9–28.1) years, respectively. The 14 competing events included all-cause mortalities. A plateau was observed at 3 years with no new events, even beyond 72 months (Fig. 4).

In the univariate analysis using the Cox model, 2 variables were found to be significantly associated ($P < 0.20$) with late urinary toxicity of grade ≥ 2: a history of TURP ($P = 0.04$) and ADT ($P = 0.13$) (Fig. A2).

In the multivariate analysis, only a history of TURP was significantly associated with late urinary toxicity of grade ≥ 2, after adjusting for CTV volume with an OR of 3.06 (95 % CI: 1.05–8.86, $P = 0.04$) (Table A4).

Discussion

In this study, we have highlighted the efficacy and low risk of late toxicity of extreme hypofractionated SBRT for localized prostate cancer

using real-world data. To the best of our knowledge, this is the largest cohort of French patients treated with SBRT for localized prostate cancer, with a significant median follow-up of 4 years.

In our study, the 5-year bRFS of 72.1 % was primarily dominated by non-cancer-related deaths, while cBR remained excellent (7.3 % at 5 years). This bRFS is slightly lower than that reported in the literature, probably due to the inclusion of 35 % of patients with UIR and high-risk cancers. These risk groups are under- or unrepresented in studies on SBRT [11,16,17].

Severe toxicities were rare in both acute and late phases. Acute genitourinary and gastrointestinal toxicities of grade $\geq$ 2 observed in our study were similar to those in previously studies. Late toxicities of grade $\geq$ 2 are mainly urinary, such as pollakiuria and dysuria, requiring treatment with α-blockers. In our study, a cumulative incidence of late genitourinary toxicity of grade $\geq$ 2 of 15.6 % and 20.6 % at 2 and 5 years, respectively, which plateaued at 3 years with no further new events, were observed. Only few cases of hematuria and rectal toxicity (grade $\geq$ 2; 2.2 % and 0.7 %, respectively) were observed, comparable to those observed in previous studies [11,13,14,17–19]. In our series the median CTV volume was 53.4 cc (20.3–182.8). Some patients presented with volume superior to 150 cc, nevertheless, we did not find a significant association in our study.

Multivariate analysis revealed a significant association between a history of TURP and an increased risk of GU toxicities of grade $\geq$ 2 (OR = 3.06), while significant association was observed with the median dose received by the bladder, CTV, or age, similar to those observed in other studies [19–21]. Several studies, including Murthy et al.'s study, which used a propensity score, found no significant difference between increased late toxicities and a history of TURP [22,23]. However, Ishiyama et al.'s systematic review of external beam radiotherapy and brachytherapy [24], and Huck et al.'s study [25] on SBRT, with a similar fractionation scheme as in our study, revealed a significant association between a history of TURP and genitourinary toxicities. In Pepin et al., late grade 2 and grade 3 urinary toxicity occurred in 23 (48.9 %) and 3 (6.4 %) patients treated with SBRT after TURP, respectively [26]. Gurka et al. reported a significant increase in post-SBRT hematuria and suggested a waiting-period of 6 months between TURP and SBRT initiation might reduce the associated toxicities [27]. SBRT is not contraindicated after a TURP if a minimum interval of 3 months is respected in GETUG recommendations [28]. Nevertheless the level of evidence of this recommendation is low.

Huck et al.'s recent study, which reviewed available data on urinary morbidity in patients with prostate cancer treated with post-TURP SBRT, suggested that the use of cavity-sparing techniques via adaptive MRI-guided SBRT may prove beneficial in this patient population and that this approach required further research [29]. Leeman et al. reported a significant association between the maximum dose received by the urethra and late urinary toxicities of grade $\geq$ 2; with a dose < 107 % of the prescribed dose, the expected rate of late urinary toxicities of grade $\geq$ 2 was 5.2 % [30]. Zilli et al. investigated urethra-sparing in SBRT and reported a good toxicity and efficacy profile [31]. Salembier et al. propose specific contouring and dose volume parameters regarding prostate brachytherapy in a post TURP setting and a similar work for SBRT would be of interest [32].

The promising potential of extreme hypofractionated regimens in patients with UIR and high-risk cancers is under research. Available data from the SHARP consortium, which included 7 phase II trials and prospective registries comprising 344 patients, indicated an effective and well-tolerated SBRT profile, with a median follow-up of nearly 50 months. Notably, 19 % of patients received nodal irradiation, and the estimated 4-year bRFS rate was 81.7 %. The cumulative incidence of late urinary and gastrointestinal toxicities of grade $\geq$ 3 was 2.3 % and 0.9 %, respectively [33].

Glicksman et al.'s phase II study, reported data on nodal irradiation of 25 Gy in 5 fractions for 165 patients, of whom 85 % received hormonal therapy, with a median follow-up of 38 months. The cumulative incidence of late genitourinary and gastrointestinal toxicities of grade $\geq$ 2 at 3 years was 58 % and 11.3 %, respectively, while that of grade $\geq$ 3 toxicities was 1 % and 0 %, respectively. The 3-year bRFS was 98 % [34].

Phase III studies are ongoing to confirm the good efficacy and safety profile of SBRT. While PACE-NODES compares nodal irradiation in 5 fractions with prostate-only irradiation [35], the PACE-C trial is investigating SBRT in patients with UIR and high-risk cancers receiving concurrent hormone therapy and on a larger CTV.

Our study has some limitations. The first is its retrospective design, and the second is the analysis of urethral dosimetric data because of the number of patients in whom the urethra was delineated. In order to achieve a higher level of evidence, it would be advantageous to conduct additional prospective studies with mandatory delineation of ureters in patient with a history of TURP.

Conclusions

This study has highlighted the favorable safety and efficacy profile of SBRT and the significant association between a history of TURP and late genitourinary toxicity of grade $\geq$ 2. These findings may contribute to the optimal management of patients treated with this regimen, especially those with a history of TURP.

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Maxime Galienne: Conceptualization, Methodology, Investigation, Data curation, Writing – review & editing. **Séverine Risbourg:** Software, Formal analysis, Data curation. **Thomas Lacornerie:** Resources. **Alexandre Taillez:** Resources. **Eric Lartigau:** Resources. **Maël Barthoulot:** Conceptualization, Methodology, Software, Formal analysis, Data curation. **David Pasquier:** Conceptualization, Methodology, Validation, Resources, Project administration, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A

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