Salvage Stereotactic Reirradiation for Local Recurrence in the Prostatic Bed After Prostatectomy: A Retrospective Multicenter Study

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Article info

Abstract

Background: Management of local recurrence of prostate cancer (PCa) in the prostatic bed after radical prostatectomy (RP) and radiotherapy remains challenging.

Objective: To assess the efficacy and safety of salvage stereotactic body radiotherapy (SBRT) reirradiation in this setting and evaluate prognostic factors.

Design, setting, and participants: We conducted a large multicenter retrospective series that included 117 patients who were treated with salvage SBRT for local recurrence in the prostatic bed after RP and radiotherapy in 11 centers across three countries.

Outcome measurements and statistical analysis: Progression-free survival (PFS; biochemical, clinical, or both) was estimated using the Kaplan-Meier method. Biochemical recurrence was defined as prostate-specific antigen nadir +0.2 ng/ml, confirmed by a second increasing measure. The cumulative incidence of late toxicities was estimated using the Kalbfleisch-Prentice method by considering recurrence or death as a competing event.

Results and limitations: The median follow-up was 19.5 mo. The median SBRT dose was 35 Gy. The median PFS was 23.5 mo (95% confidence interval [95% CI], 17.6–33.2). In the multivariable models, the volume of the recurrence and its contact with the urethrovesical anastomosis were significantly associated with PFS (hazard ratio [HR]/10 cm³ = 1.46;

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95% CI, 1.08–1.96; p = 0.01 and HR = 3.35; 95% CI, 1.38–8.16; p = 0.008, respectively). The 3-yr cumulative incidence of grade ≥ 2 late GU or GI toxicity was 18% (95% CI, 10–26). In the multivariable analysis, a recurrence in contact with the urethrovesical anastomosis and D2% of the bladder were significantly associated with late toxicities of any grade (HR = 3.65; 95% CI, 1.61–8.24; p = 0.002 and HR/10 Gy = 1.88; 95% CI, 1.12–3.16; p = 0.02, respectively).

Conclusions: Salvage SBRT for local recurrence in the prostate bed may offer encouraging control and acceptable toxicity. Therefore, further prospective studies are warranted.

Patient summary: We found that salvage stereotactic body radiotherapy after surgery and radiotherapy allows for encouraging control and acceptable toxicity in locally relapsed prostate cancer.

1. Introduction

Prostate cancer (PCa) is the second most common cancer and fifth most common cancer in terms of mortality in men worldwide [1]. Radical prostatectomy (RP), with or without adjuvant or salvage external beam radiation therapy (EBRT) in cases of biochemical recurrence (BCR), remains one of the standards of care for curative strategies [2,3]. Unfortunately, between 0% and 50% of men treated with salvage EBRT after RP present with disease progression at 5 yr [4,5].

The development of multiparametric magnetic resonance imaging (mpMRI), choline, and prostate-specific membrane antigen (PSMA) positron emission tomography/-computed tomography (PET-CT) allows the identification and localization of local recurrence with higher sensitivity and specificity [6–11]. Image-guided local therapies for recurrent PCa after RP and EBRT can delay or avoid the use of systemic therapies.

Salvage stereotactic body radiation therapy (SBRT) allows for encouraging disease control and acceptable toxicity in patients with a local failure previously treated with definitive radiotherapy [12–14].

Local failure after RP and salvage or adjuvant EBRT is often managed with observation or long-term androgen deprivation therapy (ADT); however, the benefit of salvage local treatment by stereotactic reirradiation is unknown. Some retrospective studies have evaluated the use of SBRT in this context with limited sample sizes [15–21]. No prospective study evaluating the efficacy and safety of reirradiation in this setting has been published to date.

We report the largest multicenter retrospective series of salvage reirradiation in the prostatic bed for local recurrence of PCa previously treated with RP and postoperative EBRT. The aim of this study is to evaluate the efficacy and toxicity of SBRT in this setting and identify factors associated with the risk of recurrence and late toxicity.

2. Materials and methods

2.1. Inclusion/exclusion criteria

All consecutive patients who met the eligibility criteria in the participating centers were retrospectively included in the study. The inclusion criteria were as follows: men aged ≥ 18 yr who were initially treated for PCa histologically proven with RP and EBRT (with or without ADT) as adjuvant or salvage treatment with three-dimensional conformal radiation therapy or intensity-modulated radiotherapy. These patients presented a biochemical relapse (defined by a prostate-specific antigen [PSA] at a rate of ≥ 0.2 ng/ml above the nadir confirmed by a second increasing measure [22]) and a recurrence within the prostatic bed diagnosed on choline PET-CT, PSMA PET-CT, and/or pelvic mpMRI. Biopsy was not mandatory if all diagnostic elements were univocal. Recurrence was treated using SBRT (with or without ADT).

The exclusion criteria included patients with lymph node involvement or distant metastasis identified on choline PET-CT, PSMA PET-CT, and/or magnetic resonance imaging (MRI), CT scan, or bone scan. Our population has 23 patients in common with the study by Perennec et al [21].

2.2. Treatment

As the study was retrospective, there was no common treatment protocol. However, dosimetric data were reported according to the International Commission on Radiation Units and Measurements (ICRU) 91 report, allowing a detailed description of delivered treatment.

The biologically effective dose (BED) delivered to the target volumes was calculated using an alpha/beta ratio of 2 Gy for PCa cells, as well as the BED associated with the GTV50% and PTV50%.

2.3. Endpoints

The primary objective was to evaluate the efficacy of SBRT in this setting in terms of disease control. Recurrence included biochemical and clinical factors. BCR was defined as a PSA rate of ≥ 0.2 ng/ml above the nadir confirmed by a second increasing measure. For patients treated with ADT and salvage SBRT, the PSA value before the start of ADT was considered the pre-SBRT PSA level. Progression-free survival (PFS) after SBRT was defined as the time interval from the date of the start of SBRT to the date of BCR and/or clinical recurrence or to the date of death from any cause. Data were censored at the date of the last news for patients who were still alive and did not relapse. Overall survival

(OS) was defined as the time from SBRT to death from any cause, and data were censored at the date of the last news for patients still alive.

The secondary objectives were to describe acute and late gastrointestinal (GI) and genitourinary (GU) toxicities of SBRT according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [23]. Adverse events (AEs) were reported until the last follow-up, with grade ≥2 events considered clinically meaningful. AEs likely related to or increased by SBRT were defined as "toxicity" events. Acute toxicity was defined as quick recovery (within 6 mo after SBRT), and late toxicity was defined as occurrence or persistence after 6 mo.

2.4. Statistical analysis

PFS and OS were estimated using the Kaplan-Meier method from the start date of SBRT. The prognostic factors for PFS were evaluated using multivariable Cox models to estimate the hazard ratios (HRs), considering the following factors: D'Amico risk group at initial diagnosis, time interval between the end of EBRT and start of SBRT, location of recurrence (recurrence in contact with the urethrovesical anastomosis, yes or no), PSA before SBRT (ng/ml), ADT with or before SBRT for recurrence, gross tumor volume (GTV), and BED (≤120 vs >120 Gy).

Toxicity was described according to the timing (early vs late), type (GI vs GU), and grade. The cumulative incidence of late toxicity was estimated overall and by type of toxicity by considering the time interval from the start of SBRT to the date of late toxicity using the Kalbfleisch-Prentice method [24], which considers recurrence or death without prior toxicity as a competing event. Factors associated with an increased risk of late toxicity (considering any grade as a primary analysis and grade ≥2 as a secondary analysis) were studied using multivariable cause-specific Cox models. The considered factors were time interval between the end of EBRT and start of SBRT; location of recurrence (recurrence in contact with the urethrovesical anastomosis, yes or no); GU or GI residual toxicities of grade 1, 2, or 3 before SBRT treatment; and D2% of the bladder (Gy).

The median follow-up was estimated using the inverse Kaplan-Meier method (Schemper) from the start of SBRT to the date of the last follow-up.

In the multivariable models, all tests were performed with a two-sided alpha level of 0.05. Estimates are provided with their 95% confidence intervals (95% CIs). Analyses were performed using STATA software (version 15.0; StataCorp. LLC, College Station, TX, USA).

2.5. Data collection and regulatory aspects

The study complies with the "reference methodology" MR004 adopted by the French Data Protection Authority (CNIL), and every participating center was responsible for checking that patients did not object to the use of their clinical data for research purposes. The study database was developed using the Ennov-Clinical software.

3. Results

3.1. Population

We included 117 patients from 11 centers who underwent salvage reirradiation in the prostatic bed for isolated local recurrence of PCa between July 2011 and November 2020, with 50% of patients treated after October 2017. The primary tumor characteristics are shown in Table 1. Using the D'Amico classification system, approximately 46% of the patients were classified to have an intermediate risk and 37% were classified to have a high risk. Patients underwent salvage or adjuvant EBRT with a median interval since prostatectomy of 19 mo (interquartile range [IQR], 5–47 mo). The median PSA value before EBRT was 0.5 ng/ml (IQR, 0.3–1 ng/ml), and the median PSA nadir after EBRT was 0.1 ng/ml (IQR, 0.02–0.12 ng/ml). EBRT was used as a salvage treatment in the majority of patients (76%). The median total dose of radiotherapy delivered was 66 Gy (IQR, 66–70 Gy; Supplementary Table 1). Twenty-six patients (25%) received concomitant ADT for a median duration of 12 mo (IQR, 6–24 mo). After the first radiotherapy treatment, 69 patients out of the 116 informative patients experienced residual toxicities (Supplementary Table 2). Forty-six patients experienced residual GU toxicities (34 grade 1, 11 grade 2, and one grade 3), and six patients experienced GI residual toxicities (all grade 1).

3.2. Recurrence

All patients presented with recurrence within the prostatic bed, diagnosed on imaging. The characteristics of disease recurrence are listed in Table 1. A combination of MRI and PET-CT was the most common imaging modality used to confirm relapse (66% with choline PET-CT). Nearly a third were diagnosed using PET-CT alone (30% with choline PET-CT), and MRI was performed alone in few patients (4%). The median time interval from the start of the first radiotherapy treatment to the recurrence was 57.9 mo (IQR, 31.7–98.0 mo). The median PSA value at diagnosis of recurrence or before the start of SBRT was 0.8 ng/ml (IQR, 0.4–2.0 ng/ml). Twenty-three patients underwent biopsy of the prostatic bed (20%). For five patients, the biopsies were negative, and recurrence was confirmed through a double imaging examination with positive MRI and choline PET-CT. Most of the patients had their relapse posterior to the bladder (46%) and/or at the urethrovesical anastomosis (46%). Relapse in the seminal vesicle remnant was found in 33% of the patients, and lateropelvic recurrence was found in 15%. Combining the different reported locations, a total of 25 patients (23%) had a recurrence limited to the urethrovesical anastomosis.

3.3. Stereotactic reirradiation

The median interval between the end of the first radiotherapy treatment and start of SBRT was 79.8 mo (IQR, 55.4–116.7 mo). The median total dose of SBRT was 35 Gy (IQR, 30–36 Gy), with a median of 6 Gy (IQR, 4–6 Gy) per fraction, with no significant difference in the total dose (p = 0.6),

Table 1 – Characteristics of the primary tumor and disease recurrence in the prostatic bed

Characteristics	Total N = 117	
Primary tumor		
PSA at initial diagnosis (ng/ml), MD = 4		
Median (IQR)	8.1	(5.6–11.5)
D'Amico NCCN classification at initial diagnosis, MD = 19		
Low	17	17%
Intermediate	45	46%
High	36	37%
Postoperative PSA (ng/ml), MD = 13		
Median (IQR)	0.03	(0.01–0.15)
ISUP group at prostatectomy, MD = 8		
ISUP 1	14	13%
ISUP 2	46	42%
ISUP 3	27	25%
ISUP 4	12	11%
ISUP 5	10	9.2%
Tumor stage at prostatectomy [a], MD = 4		
pT2	55	49%
pT3	7	6.2%
pT3a	29	26%
pT3b	22	20%
Nodal stage on prostatectomy [a], MD = 4		
pN0	68	60%
pN1	15	13%
pNx	30	27%
Margin status at prostatectomy, MD = 9		
R0	57	53%
R1	50	46%
R2	1	0.9%
Disease recurrence in the prostatic bed		
Interval between first radiotherapy and recurrence (mo), MD = 4		
Median (IQR)	57.9	(31.7–98.0)
PSA at diagnosis of recurrence (ng/ml), MD = 2		
Median (IQR)	0.8	(0.4–2.0)
PSA doubling time (mo), MD = 72		
Median (IQR)	12	(7–18)
Biopsy of the prostatic bed		
Yes	23	20%
ISUP group of prostatic bed recurrence, MD = 8	N = 15	
ISUP 2	4	27%
ISUP 3	2	13%
ISUP 4–5	9	60%
Type of imaging confirming relapse: MRI		
MRI not done [b]	35	30%
MRI performed and positive	80	68%
MRI performed and negative	2	1.7%
Size of the recurrence on MRI if positive (mm), MD = 17	N = 63	
Median (IQR)	13.0	(10.0–16.0)
Type of imaging confirming relapse: choline PET-CT		
Choline PET-CT not done	22	19%
Choline PET-CT performed and positive	86	74%
Choline PET-CT performed and negative	9	7.7%
Type of imaging confirming relapse: PSMA PET-CT		
PSMA PET-CT not done	87	74%
PSMA PET-CT performed and positive	25	21%
PSMA PET-CT performed and negative	5	4.3%
Location of recurrence (several locations per patient possible, proportions are given per category)		

Table 1 (continued)

Characteristics	Total N = 117	
Seminal vesicle remnant, MD = 7	36	33%
Posterior to the bladder, MD = 7	51	46%
Lateropelvic, MD = 7	16	15%
Contact with urethrovesical anastomosis, MD = 8	50	46%
Location of recurrence, MD = 8		
UV anastomosis only	25	23%
Other [c]	84	77%

AJCC = American Joint Committee on Cancer; IQR = interquartile range; ISUP = International Society of Urological Pathology; MD = number of patients with missing data; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PET-CT = positron emission tomography/computed tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; UV = urethrovesical.
[a] AJCC eighth classification.
[b] Data were missing for one patient and considered as MRI not done; their diagnosis was confirmed using choline PET-CT.
[c] Among the 84 patients with recurrence locations classified as "other," 25 had a recurrence in contact with the urethrovesical anastomosis combined with another site (seminal vesicle remnant, posterior to bladder, or at a lateropelvic location).

D98% (p = 0.5 and p = 0.2 in GTV and planning target volume [PTV], respectively), and D50% (p = 0.9 and p = 0.7 in GTV and PTV, respectively) distributions between patients with a recurrence in contact with the urethrovesical anastomosis and other patients (Supplementary Table 3). Fiducial markers were used most frequently (58%), and Cyberknife was the most used type of accelerator (59%). ADT was used before or concomitantly with SBRT in 48/117 (41%) of the patients, with a median duration of 1 mo (IQR, 1–6 mo) and with the first-generation ADT performed most frequently (96%). The dosimetric values of SBRT are listed in Table 2. The median PTV was 14.1 cm^3 (IQR, 7.1–23.7 cm^3; Supplementary Fig. 1).

3.4. Oncological outcomes

The median follow-up was 19.5 mo (IQR, 10.2–40.3 mo). At the time of the analysis, a recurrence was reported after SBRT in 54 patients out of the 115 informative patients: 16 had BCR only, four had clinical relapse only, and 34 had both biochemical and clinical relapses. The clinical relapses occurred on the prostatic bed or on the treated lesion, or were metastatic in 39%, 33%, and 47% of cases, respectively. Imaging was performed at relapse in 43 patients (80%). Choline PET-CT was performed in 34 patients, the results of which were always positive; mpMRI was performed in 11 patients, with positive results observed for eight of them (73%); and PSMA PET-CT was performed in nine patients, with positive results observed for eight of them (89%). In addition, three deaths with no prior recurrence were reported out of a total of nine deaths.

The median PFS was 23.5 mo (95% CI, 17.6–33.2). The PFS at 1 yr was 74% (95% CI, 64–81), 48% at 2 yr (95% CI, 36–59), and 27% at 3 yr (95% CI, 15–41; Fig. 1).

In the multivariable Cox model, a recurrence in contact with the urethrovesical anastomosis and GTV were significantly associated with poorer PFS (HR = 3.35; 95% CI, 1.38–8.16; p = 0.008, and HR associated with an increase of 10 cm^3, HR/10 cm^3 = 1.46; 95% CI, 1.08–1.96; p = 0.01).

Table 2 – Characteristics and dosimetric values of SBRT

Characteristics of the SBRT interventions	Total N = 117	
SBRT duration (d)		
Median (IQR)	10	(9–13)
Schedule		
Daily	N = 15	13%
One other day	N = 102	87%
Total dose of SBRT (Gy)		
Median (IQR)	35	(30–36)
Number of fractions		
5	77	66%
6	40	34%
BEDtotal		
Median (IQR)	144	(120–144)
Scheme		
20 Gy/5 fractions (BEDtotal = 60)	1	0.9%
25 Gy/5 fractions (BEDtotal = 87.5)	6	5.1%
30 Gy/5 fractions (BEDtotal = 120)	44	38%
32.5 Gy/5 fractions (BEDtotal = 138)	7	6%
35 Gy/5 fractions (BEDtotal = 158)	19	16%
36 Gy/6 fractions (BEDtotal = 144)	40	34%
Dose per fraction (Gy)		
Median (IQR)	6.0	(6.0–6.0)
SBRT type of accelerator, MD = 4		
Cyberknife	67	59%
Vero	21	19%
Other	25	22%
Use of interfraction image-guided radiation therapy	114	97%
Use of intrafraction image-guided radiation therapy	68	58%
Use of fiducial markers	68	58%
Dosimetric values of the target volumes		

	GTV		PTV	
Volume (cm³)	N = 112	MD = 5	N = 108	MD = 9
Median (IQR)	4.0	(1.9–8.3)	14.1	(7.1–23.7)
D98% (Gy)	N = 108	MD = 9	N = 108	MD = 9
Median (IQR)	32.6	(30.3–36.7)	30.4	(28.9–34.2)
D50% (Gy)	N = 108	MD = 9	N = 108	MD = 9
Median (IQR)	35.4	(32.5–40.8)	34.1	(32.1–39.3)
D2% (Gy)	N = 104	MD = 13	N = 103	MD = 14
Median (IQR)	37.1	(32.9–42.5)	36.9	(32.6–42.5)
BEDGTV50%/PTV50% (Gy)	BEDGTV50% (N = 108)		BEDPTV50% (N = 108)	
Median - (IQR)	145.7	(131.7–165.4)	142.2	(129.9–160.6)
Dosimetric values of the organs at risk				

	Rectum		Bladder	
D2% (Gy)	N = 108	MD = 9	N = 107	MD = 10
Median (IQR)	24.3	(17.1–28.3)	25.5	(18.7–30.7)

BED = biologically effective dose; GTV = gross tumor volume; IQR = interquartile range; MD = number of patients with missing data; PTV = planning target volume; SBRT = salvage stereotactic body radiotherapy.
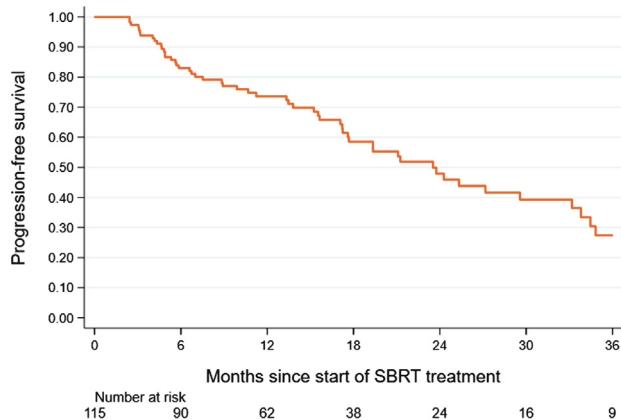

Fig. 1 – Progression-free survival since SBRT treatment in months. SBRT = stereotactic body radiotherapy.

The D'Amico risk group at initial diagnosis, time interval between the end of EBRT and the start of SBRT, PSA level before SBRT, use of ADT with or before SBRT for the current recurrence, and BED were not significantly associated with PFS in the multivariable analysis (Table 3). We also observed a significant association between PSA doubling time and risk of progression in the univariate analysis (HR = 0.91; 95% CI, 0.84–1.00; p = 0.04); we did not include this variable in the multivariable model because of the high number of patients with missing data.

Overall, death was reported in nine patients at the last follow-up. The OS rates at 1, 3, and 5 yr were 99% (95% CI, 94–100), 89% (95% CI, 75–95), and 85% (95% CI, 70–93), respectively (Supplementary Fig. 5).

3.5. Safety

Fifty-two patients experienced at least one GU or GI toxicity: 19 had an early toxicity, a late toxicity occurred in 13 patients who had no early toxicity, and 20 patients had an

Table 3 – Value of prognostic factors on PFS: multivariable Cox models (N = 86)

Characteristics	Adjusted HR (95% CI)	p value
D'Amico risk group at initial diagnosis (MD = 18)		0.09
Low	1.91 (0.74–4.95)	
Intermediate	1 (ref)	
High	2.44 (1.09–5.49)	
Time interval between end of EBRT and start of SBRT		0.6
HR/1 mo	0.99 (0.98–1.01)	
Recurrence location (MD = 8)		0.008
UV anastomosis unrelated to another location	3.35 (1.38–8.16)	
Other	1 (ref)	
PSA before SBRT (MD = 2)		0.8
HR/1 ng/ml	1.02 (0.86–1.20)	
Use of ADT with or before SBRT for the current recurrence		0.5
No	1 (ref)	
Yes	0.75 (0.34–1.64)	
Gross tumor volume (MD = 5)		0.01
HR/10 cm^3	1.46 (1.08–1.96)	
Biologically effective dose (Gy)		0.9
≤120	1 (ref)	
>120	0.94 (0.40–2.25)	

Adjusted HR = hazard ratio estimated in the multivariable model including all variables listed in the table; ADT = androgen deprivation therapy; 95% CI = 95% confidence interval; EBRT = external beam radiation therapy; MD = number of patients with missing data; PFS = progression-free survival; PSA = prostate-specific antigen; ref = reference; SBRT = salvage stereotactic body radiotherapy.

early toxicity and a late toxicity or an early event persisting 6 mo after the start of SBRT, leading to a total of 33 patients experiencing at least one late toxicity (Supplementary Fig. 2–4).

Late GU toxicities affected 30 patients: 16 patients had grade 1, nine had grade 2, and five had grade 3 toxicities.
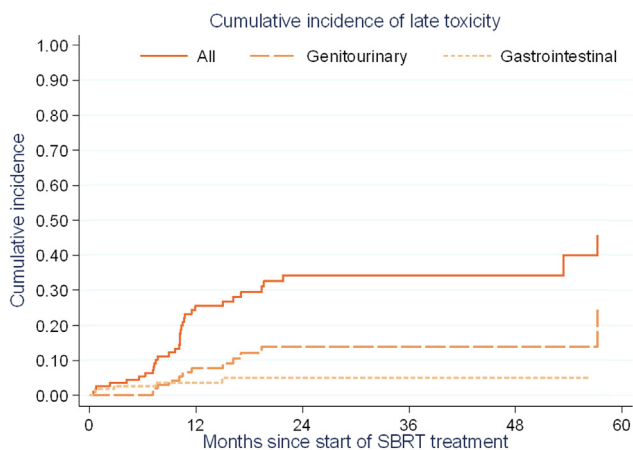
Late GI toxicities affected seven patients: two patients had grade 1, three had grade 2, and two had grade 3 toxicities, with a large majority experiencing proctitis (Supplementary Table 4). The cumulative incidence of late GU or GI toxicity, regardless of grade, was estimated to be 25% (95% CI, 17–34) at 1 yr and 34% (95% CI, 24–44) at 2 and 3 yr (Fig. 2). The cumulative incidence of grade ≥2 late GU or GI toxicity was estimated to be 13% (95% CI, 7–21) at 1 yr and 18% (95% CI, 10–26) at 2 and 3 yr.

In the multivariable cause-specific Cox analysis (Table 4), a recurrence in contact with the urethrovesical anastomosis

Table 4 – Factors associated with late toxicities (any grade): multivariable cause-specific Cox models (N = 97)

Characteristics	Adjusted cs-HR (95% CI)	p value
Time interval between end of EBRT and start of SBRT (mo)		0.2
HR/1 mo	1.01 (0.99–1.01)	
Location of recurrence (MD = 8)		0.002
UV anastomosis only	3.65 (1.61–8.24)	
Other	1 (ref)	
GU or GI residual toxicity (MD = 1)		0.5
No	1 (ref)	
Yes	1.30 (0.60–2.83)	
D2% bladder (Gy; MD = 10)		0.02
HR/10 Gy	1.88 (1.12–3.16)	

Adjusted cs-HR = cause-specific hazard ratio estimated in the multivariable model including all variables listed in the table; 95% CI = 95% confidence interval; EBRT = external beam radiation therapy; GI = gastrointestinal; GU = genitourinary; HR = hazard ratio; MD = number of patients with missing data; ref = reference; SBRT = salvage stereotactic body radiotherapy; UV = urethrovesical.

and D2% of the bladder were significantly associated with late toxicities of any grade (HR = 3.65 [95% CI, 1.61–8.24], p = 0.002; HR/10 Gy = 1.88 [95% CI, 1.12–3.16], p = 0.02, respectively). The time interval between the end of EBRT and the start of SBRT, and GU or GI residual toxicity were not significantly associated with late toxicity of any grade (p = 0.2 and p = 0.5, respectively).

In the multivariable Cox model, we did not find any significant association between grade ≥2 late toxicities and time interval between the end of EBRT and the start of SBRT (p = 0.4), GU or GI residual toxicity (p = 0.4), and D2% bladder (p = 0.15). Furthermore, a recurrence in contact with the urethrovesical anastomosis was also significantly associated in the multivariable analysis with an increase of grade ≥2 late toxicities (HR = 3.74 [95% CI, 1.23–11.39], p = 0.02; Supplementary Table 5).

Fig. 2 – Cumulative incidence of late toxicity (any grade: all, GU, and GI). GI = gastrointestinal; GU = genitourinary; SBRT = stereotactic body radiotherapy.

4. Discussion

To our knowledge, this is the largest retrospective series (117 patients) of stereotactic reirradiation for local recurrence in the prostatic bed. Our strength is the identification of factors associated with recurrence (size of recurrence and recurrence in contact with the urethrovesical anastomosis unrelated to another location) and toxicity (D2% of the bladder and a recurrence in contact with the urethrovesical anastomosis). Our study is the only study to report dosimetric data according to the ICRU 91 report.

Our results are relatively consistent according to the literature: Jereczek-Fossa et al [16] found a biochemical PFS rate of 40% at 2 yr in patients also treated for intraprostatic recurrence, Olivier et al [15] and Janoray et al [17] showed a biochemical PFS rate of around 80% at 1 yr; and Perennec et al [21] performed a larger study with 48 patients and found biochemical PFS rates of 80% and 52% at 1 and 2 yr, respectively.

In our study, a PSA rate of ≥0.2 ng/ml confirmed by a second increasing measure was used as the definition of BCR. However, there is no consensus regarding the definition of BCR in this setting. Olivier et al [15] used the same criteria as in our study. Jereczek-Fossa et al [16] chose an increased PSA rate at two successive measures above the pre-SBRT PSA. Perennec et al [21] preferred an absolute increase in PSA of >0.2 ng/ml above the nadir. Janoray et al [17], Detti et al [18], Loi et al [19], and D'Agostino et al [20] did not specify the criteria for BCR.

We identified factors significantly associated with poorer PFS: the size of the recurrence (GTV) and contact with the urethrovesical anastomosis unrelated to another location. A possible explanation to the association between the site of recurrence and PFS is the difficulty of tumor contouring when in contact with the urethrovesical anastomosis. Perennec et al [21] found that the PSA rate before SBRT was a prognostic factor of BCR only in their univariate analysis.

Toxicity rates have been relatively uniform in the literature. To the best of our knowledge, this is the first study to identify the factors significantly associated with toxicity. D2% of the bladder and a recurrence in contact with the urethrovesical anastomosis were associated with a poorer toxicity profile. The proximity of these recurrences to the urinary tract makes salvage SBRT difficult and explains the risk of toxicity. It is important to note that the salvage SBRT dose did not differ according to location.

Notably, the role of ADT in this setting remains unclear. Our series recorded the use of ADT with SBRT in 41% of our patients with a mean duration of 7 mo, which is greater than the rate reported in the literature; however, we failed to show a benefit in terms of PFS. It remains possible that ADT could have been prescribed for patients who had a worse prognosis.

The use rate of PSMA PET-CT to identify recurrence in the prostate bed was low because of the inclusion period. With improved availability in the next coming years, PSMA PET-CT could increase the diagnosis of concomitant metastases due to the higher sensitivity and allow a better selection of patients for salvage reirradiation.

Our study has several limitations, the main one being its retrospective nature. In addition, some data, such as sexual toxicity, were assessed poorly. The high number of missing values also precludes any reliable conclusion regarding the association between the PSA doubling time and the risk of progression. We noticed heterogeneity in the target volumes and SBRT schedules, which might make reproducibility difficult. Lastly, although it is the largest series in this setting so far, the sample size precludes any definitive conclusion about prognostic factor analyses.

Few other salvage treatments have been evaluated in the context of relapse after postoperative radiotherapy. High-intensity focused ultrasound was evaluated as salvage treatment in a case series of four patients previously treated with RP and salvage EBRT (in three patients), with 50% resulting in failure [25]. Another case series of 15 patients reported 60% BCR after cryoablation as a salvage treatment in the prostatic bed without previous EBRT [26]. Brachytherapy has also been less reviewed than SBRT in reirradiation of the prostatic bed [27,28]. Salvage surgery after RP for recurrence in the prostatic bed was reported in a recent retrospective series of 40 patients, with 83% of them receiving adjuvant or salvage EBRT. They reported comparable median biochemical PFS of 23.7 mo [29].

Further prospective studies are needed on this topic. Of note, one study is already ongoing: the REPAIR GETUG P16 (NCT04536805) study may precisely determine the role of salvage SBRT and the target population in this context.

5. Conclusions

Salvage stereotactic reirradiation for local recurrence in the prostatic bed may offer encouraging control and acceptable toxicity. Prospective studies are ongoing to confirm these oncological outcomes and to better define the population that could benefit from this treatment.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euo.2023.03.005.

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