

## Partial prostate re-irradiation for the treatment of isolated local recurrence of prostate cancer in patients previously treated with primary external beam radiotherapy: short-term results of a monocentric study

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Many different therapeutic options are available for locally recurrent prostate cancer (PCa). However, standard treatment has not yet been established. We conducted a partial prostate re-irradiation (PPR) program for the treatment of isolated and limited-size intraprostatic recurrences, in patients who previously underwent external beam radiation therapy (EBRT) as primary treatment for prostatic cancer (PCa). The analysis of this experience in terms of feasibility, toxicity, and efficacy is reported. The inclusion criteria of this retrospective analysis were: previous definitive EBRT, evidence of biochemical recurrence, radiological detection of isolated local relapse, and PPR as local salvage therapy. Gastrointestinal (GI) and genitourinary (GU) toxicities were registered according to the RTOG/EORTC criteria. Between July 2012 and May 2019, 44 patients were treated with PPR. All patients completed the planned treatment. The median follow-up was 25.4 months. Tumor progression was observed in 18 patients (40.9%). Two-year local control, biochemical failure-, and clinical relapse-free survival rates were 90.1%, 58.3%, and 67.9%, respectively. The occurrence of biochemical failure after PPR is lower for patients with the time interval between the primary EBRT and first biochemical failure >4 years; local control results strongly associated with a biologically effective dose (BED) at first EBRT >177 Gy. No acute grade 3 or greater toxic events were observed. Two late grade 3 GU toxicities were reported. Although retrospective in design, our study indicates that PPR appears as a feasible, well-tolerated, and effective salvage treatment for isolated local PCa recurrence. Long term data are required in order to confirm these results.

*Key words: prostate cancer, salvage therapy, recurrence, re-irradiation*

External beam radiotherapy (EBRT) and surgery represent a therapeutic milestone in the treatment of localized prostate cancer (PCa) [1]. In recent years, advances in radiation therapy techniques have resulted in a significant improvement of both tumor control and toxicity associated with treatment [2, 3]. However, about half of prostate cancer patients undergoing EBRT as their primary treatment develop a biochemical disease recurrence within ten years [4, 5]. At imaging re-evaluation, a percentage ranging from 30–60% of these patients show a recurrence limited to the prostate gland [6, 7].

Historically, the most common treatment choice for locally recurrent PCa was androgen deprivation therapy (ADT). However, a downside of this approach is its detrimental

effect on the quality of life as well as the risk of promoting a castration-resistant disease. Nowadays, international guidelines suggest a local approach (i.e. salvage prostatectomy, re-irradiation with brachytherapy or EBRT, cryotherapy, and high intensity focused ultrasound) to manage this clinical picture. However, the most effective strategy for recurrent PCa remains still unknown. Additionally, no agreement has been reached so far as to which is the optimal patient selection for each local approach [8].

In recent years, there has been a growing interest in re-irradiation, due to the introduction of advanced radiation therapy techniques (i.e. Stereotactic Body Radiotherapy or SBRT), which allow to administer ablative doses to small volumes, thus sparing adjacent healthy tissues [9].

At the same time, advancements in radiological and nuclear medicine fields, with the development and improvement of multiparametric Magnetic Resonance Imaging (MRI) and Positron Emission Computed Tomography (PET-CT) with choline and the most recent Prostate Specific Membrane Antigen (PSMA), respectively, have improved the capacity to detect with greater accuracy the site of disease recurrence and its local extension [10]. These technological and diagnostic advancements have had a significant impact on the radiation therapy field and they have also contributed to the idea of limiting re-irradiation to intraprostatic recurrence only.

Irradiation of intraprostatic recurrence only has the two-fold aim of limiting the irradiation volume, thus allowing the delivery of ablative doses to the true lesion, and of reducing the dose to the previously irradiated adjacent areas, with a favorable impact on treatment-related toxicity.

To date, few studies have been reported in the literature on Partial Prostate Re-irradiation (PPR); however, these have been conducted on heterogeneous patient populations by primary treatment or by volume of re-irradiation, with most patients receiving re-treatment to the entire prostatic gland and a minority to the site of recurrence only.

Based on these premises, we conducted a retrospective analysis on PPR for the treatment of isolated and limited-size intraprostatic recurrences, in patients who previously underwent EBRT as primary treatment for prostatic cancer. The goal of the present study is to evaluate PPR in terms of feasibility, toxicity, and efficacy.

## Patients and methods

**Patients' selection.** We retrospectively reviewed the medical records of 51 consecutive patients treated with PPR between July 2012 and May 2019 for isolated local recurrence of PCa after radical EBRT at the Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy.

For all patients, a biochemical recurrence (BCR) according to Phoenix criteria (PSA nadir + 2 ng/ml) was recorded [11]. Subsequent imaging investigations included pelvic and prostatic MRI (T2-weighted-T2W, diffusion-weighted-DWI, and dynamic contrast-enhanced-DCE) and/or [11C]-choline PET-CT. Patients were eligible to PPR only if they met the following criteria: diagnosis of local recurrence 12 months or more after primary EBRT, Karnofsky performance status > 80, absence or minimal gastrointestinal and genitourinary late effects after the primary irradiation, imaging documenting an isolated intraglandular recurrence occupying less than 50% of the prostate. Prostate biopsy was not mandatory if all diagnostic findings were univocal in presence of a body of evidence (PSA kinetic, prostate MRI, and/or [11C]-choline PET-CT findings) in favor of a local recurrence. Four patients were excluded due to metastatic disease (oligometastatic) at the time of re-irradiation, one patient was excluded because of another local salvage treatment between first EBRT and PPR, and two patients because

of a follow-up shorter than 6 months, thus leaving 44 eligible patients. All patients included in this study had been evaluated at the time of recurrence by a multidisciplinary tumor board and signed written informed consent for PPR.

The study was approved and retrospectively registered by the Institutional Review Board and by the Ethics Committee (Comitato Etico Unico Regionale) (study registration number: CRO 2020-14).

**PPR protocol.** PPR was delivered by Linac-based external beam radiation. All patients received a total dose of 35 Gy in seven daily fractions of 5 Gy, five fractions/week, which translates into a biologically effective dose (BED) of 151.7 Gy (for  $\alpha/\beta$  1.5 Gy). No rectal spacer or fiducial markers were used. Patients underwent a non-contrast-enhanced multi-slice CT scan with a 2 mm slice thickness. Patient immobilization during CT acquisition and treatment was obtained by knee-fix<sup>®</sup> and feet-fix<sup>®</sup> (CIVCO Medical Solutions, Kalona, IA, USA). All patients were asked to empty the bowel (oral and written instructions for diet and enema were given) and to have full urinary bladder for computed tomography (CT) planning and during all treatment fractions (patients were educated to drink half a liter of water 30 minutes before the procedure). PCa local recurrence was detected by MRI (as the area showing low signal intensity on T2W + focal hypointensity on the ADC map and hyperintensity on high b-value imaging on DWI + hyperenhancement on DCE) [12] and/or by [11C]-choline PET-CT (as the area delineated with a semiautomated technique using a fixed threshold of 40% of the maximum signal intensity) [13]. This area was defined as the gross tumor volume (GTV). MRI and/or [11C]-choline PET-CT images fusion based on rigid transformations (Registration; Varian Medical Systems, Palo Alto, CA) was used to delineate GTV on planning CT. Clinical Target Volume (CTV) was defined as the GTV plus 3 mm [14]. The Planning Target Volume (PTV) included the CTV and a margin of 3 mm [15]. On each slice, contouring of organs at risk was also performed: rectum, bladder, penile bulb, and femoral heads. The planning objectives for the target were the following: at least 98% of the CTV to be covered by 98% of the prescribed dose (V98% >98%) and at least 99% of the PTV to be covered by 95% of the dose (V95% >99%). Hot spots >107% were accepted only if inside the CTV. Patients were treated by Linac Volumetric Modulated Arc Therapy (VMAT) technique (RapidArc<sup>®</sup>, Varian Medical Systems, Palo Alto, CA) with 2 arcs. In particular, in this study all treatment plans were optimized and delivered on a Trilogy<sup>®</sup> or a TrueBeam<sup>®</sup> Linac (Varian Medical Systems, Palo Alto, CA, USA), with 18-MV or 10-MV flattening-filter-free photon beams, respectively; the maximum dose rate available was 600 MU/min and 2400 MU/min, respectively. The treatment planning system in use was Eclipse version 13.6 with Anisotropic Analytical Algorithm version 13.6.23 (Varian Medical System, Palo Alto, CA, USA) with a grid resolution of 2.5 mm or less. Avoidance sectors were planned in the case of metal implants in the femoral heads of patients. Dose-volume

objectives applied during plan optimization for organs at risk (OARs) were as follows: for rectum, V10 Gy <40%, V18 Gy <20%, V26 Gy <10%; for bladder, V10 Gy <25%, V18 Gy <15%, V26 Gy <10%; for femoral heads, V10 <1%; for penile bulb, V10 <5%. Image guidance was performed before each fraction. In particular, before each fraction, a cone beam CT (CBCT) was performed to verify the correct position as well as full bladder and empty rectum. Set up corrections were performed after automatic matching of CBCT images to reference planning CT (using the integrated algorithm on the Varian on-board imager console) followed by manual adjustments with an action level of 1 mm. When set up corrections were greater than 5 mm, or bladder and rectum preparation was not correct, the patient was repositioned and re-verified. The entire process, starting from the CBCT acquisition to the end of radiation delivery, always took less than 6 minutes.

Short-term ADT with luteinizing hormone-releasing hormone agonist (LHRHa) was prescribed in the case of PSA doubling time <12 months.

**Follow-up after PPR.** After PPR, PSA level dosage was recorded at 3 months after treatment, every 3 months for the following 2 years, every 6 months until the fifth year, then annually. Likewise, the primary treatment, BCR after PPR was defined as PSA nadir + 2 ng.ml<sup>-1</sup> above the nadir according to Phoenix Consensus criteria. In the case of BCR, a further [11C]-choline-PET-CT was performed to define local, regional, or metastatic failure. Depending on the type of disease progression, patients received additional therapies. The vital status, the date, and the underlying cause of death (i.e., the condition that led to death) were ascertained up to December 31<sup>st</sup>, 2019.

Acute (<3 months) and late (>3 months) toxicities were registered according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria during PPR, and subsequently every 3–6 months up to the fifth year from PPR [16]. Gastrointestinal (GI) and genitourinary (GU) events were registered. Sexual dysfunction was not analyzed due to the lack of baseline evaluation.

**Statistical analysis.** For each patient, the time at risk was computed as the time elapsed from the end of PPR to the occurrence of the events of interest which were: PSA increase (defined as above) for biochemical failure-free survival (BFFS); radiological detection of local or distant disease for clinical relapse-free survival (CRFS); radiological diagnosis of prostatic recurrence for local control (LC); radiological diagnosis of distant locoregional or metastatic disease for distant relapse-free survival (DRFS); death for overall survival (OS).

The survival probabilities were estimated by means of the Kaplan-Meier method and survival differences were tested through the log-rank test [17]. Differences in clinical outcomes (i.e., OS, BFFS, CRFS, LC, DRFS) according to potential predictors were evaluated through the log-rank

test [17]. Statistical significance was claimed for  $p < 0.05$  (two-tailed).

## Results

**Patient and tumor characteristics.** Patients characteristics are shown in Table 1. At primary EBRT, our population was mainly constituted by patients initially presenting with high-risk disease (23 patients, 52.3%) according to D'Amico classification [18]; low-risk and intermediate-risk disease was reported in 7 (15.9%) and 14 (31.8%) patients, respec-

**Table 1. Clinical characteristics of 44 prostate cancer patients with isolated recurrence.**

Characteristics	n
Prior RT	
Age at diagnosis [years], median (range)	68 (51–81)
Initial PSA [ng.ml <sup>-1</sup> ], median (range)	8.7 (2.6–46)
Initial Gleason Score, median (range)	7a (6–9)
Prior RT modality	
3DCRT	28 (64%)
IMRT	16 (36%)
BED* (Gy), median (range)	177.3 (151.7–186.7)
Number of fractions, median (range)	37 (27–42)
Prophylactic pelvic irradiation	2 (4%)
Interval between first RT and BCR [months], median (range)	60 (16.9–615.5)
PPR	
Age at PPR [years], median (range)	76 (56–89)
Pre-PPR PSA [ng.ml <sup>-1</sup> ], median (range)	2.6 (2–7.68)
Concomitant androgen deprivation to PPR	
Yes (%)	12 (27%)
No (%)	32 (73%)
Duration [months], median (range)	4.2 (2.9–7.1)
Biopsy of the target lesion	
Yes (%)	5 (11%)
Gleason score (range)	6 (6–7a)
No (%)	39 (89%)
Histological +/-Radiological diagnosis	
Biopsy + PET-CT + MRI	1
Biopsy + MRI	2
Biopsy + PET-CT	2
PET-CT only	27
PET-CT + MRI	2
MRI only	10
Target lesion	
left lobe	15
right lobe	16
apex	2
bilateral anteriorly	2
bilateral posteriorly	9

\*BED was calculated for  $\alpha/\beta$  1.5 Gy; Abbreviations: 3DCRT-Conformal radiotherapy; BCR-Biochemical recurrence; BED-Biologically effective dose; IMRT-Intensity modulated radiotherapy; MRI-Magnetic Resonance Imaging; PET-CT Positron Emission Computed Tomography; PPR-Partial Prostate Re-irradiation; PSA-Prostate specific antigen; RT-Radiotherapy

tively. The first EBRT included 3D-CRT in 28 (64%) patients (median BED: 177.3 Gy; the median number of fractions: 38) and IMRT in 16 (36%) (median BED: 180.3 Gy; the median number of fractions: 28). Twenty-seven (61%) patients were treated with conventional fractionation, and 17 (39%) received moderate hypofractionation. In the study population, BED of first EBRT was not associated with D'Amico risk classification (data not shown).

According to risk group evaluation, concurrent ADT was added to primary radiation therapy in 37 (84%) patients.

The median time between first EBRT and BCR was 81.1 months, 67.3 months, and 54 months in low-risk, intermediate-risk, and high-risk disease patients, respectively.

**Table 2. Dosimetric parameters in 44 patients receiving Partial Prostatic Re-irradiation.**

Dosimetric parameter	Median	Mean	Q1	Q3
CTV (cm <sup>3</sup> )	16	16.3	6	23
PTV (cm <sup>3</sup> )	26	27.9	15.1	37.5
Maximum bladder dose (Gy)	34.4	29.4	28.8	36.2
Mean bladder (Gy)	2.7	6.4	2	10.2
Bladder V90% (cm <sup>3</sup> )	0.1	1.3	0	2.4
Bladder V100% (cm <sup>3</sup> )	0	0.5	0	0.5
Maximum rectal dose (Gy)	35.4	34.3	33.8	35.6
Mean rectal dose (Gy)	6.6	7.4	5.6	9.3
Rectal V90% (cm <sup>3</sup> )	0.3	0.5	0	0.8
Rectal V100% (cm <sup>3</sup> )	0	0.1	0	0

Abbreviations: CTV-Clinical target volume; PTV-Planning target volume; Q1-First quartile; Q3-Third quartile; V90%-Volume receiving 90% of the prescribed dose; V100%-Volume receiving 100% of the prescribed dose

**Table 3. Description of 18 relapses in prostate cancer patients undergoing Partial Prostate Re-irradiation.**

Outcome	n (%)
Biochemical relapse only	4 (22%)
Clinical recurrence	
Local	4 (22%)
Local and distant	3 (17%)
Distant	7 (39%)
Locoregional nodes and metastatic sites	1 (6%)
Locoregional nodes	5 (28%)
Metastatic sites	1 (6%)

**Table 4. Toxicities in 44 prostate cancer patients undergoing Partial Prostate Re-irradiation (PPR).**

Grade	Acute toxicity		Grade	Late toxicity	
	GU	GI		GU	GI
G0	30 (68%)	40 (92%)	G0	28 (64%)	41 (93%)
G1	10 (23%)	2 (4%)	G1	8 (18%)	3 (7%)
G2	4 (9%)	2 (4%)	G2	6 (14%)	0
G3	0	0	G3	2 (4%)	0
Total patients	44	44	Total patients	44	44

Abbreviations: GU-Genitourinary; GI-Gastrointestinal

Prostatic recurrence was documented by [11C]-choline PET-CT, pelvic MRI, or both in 29 (66%), 12 (27%), and 3 (7%) patients, respectively. Biopsy of the radiologically documented recurrent lesion was performed in 5 (11%) patients. For the remaining 39 (89%) patients, the diagnosis of isolated local recurrence of prostate cancer was based on PSA levels indicating a BCR and on the radiological confirmation. In most cases, local recurrence had clear laterality: it occurred within the right lobe in 16 (36%) patients and within the left lobe in 15 (34%) patients, respectively.

Concomitant ADT was used in 12 (27%) patients for a median time of 4.2 months (2.9–7.1 months). The median PTV volume was 26 cm<sup>3</sup> (5.7–56 cm<sup>3</sup>). Dosimetry details of target volumes and organs at risk are available in Table 2.

**Tumor outcome.** All patients completed the planned treatment. The median PSA nadir after PPR was 1.1 ng.ml<sup>-1</sup> (0.07–4.92 ng.ml<sup>-1</sup>). Details of the post-PPR progressive disease are summarized in Table 3.

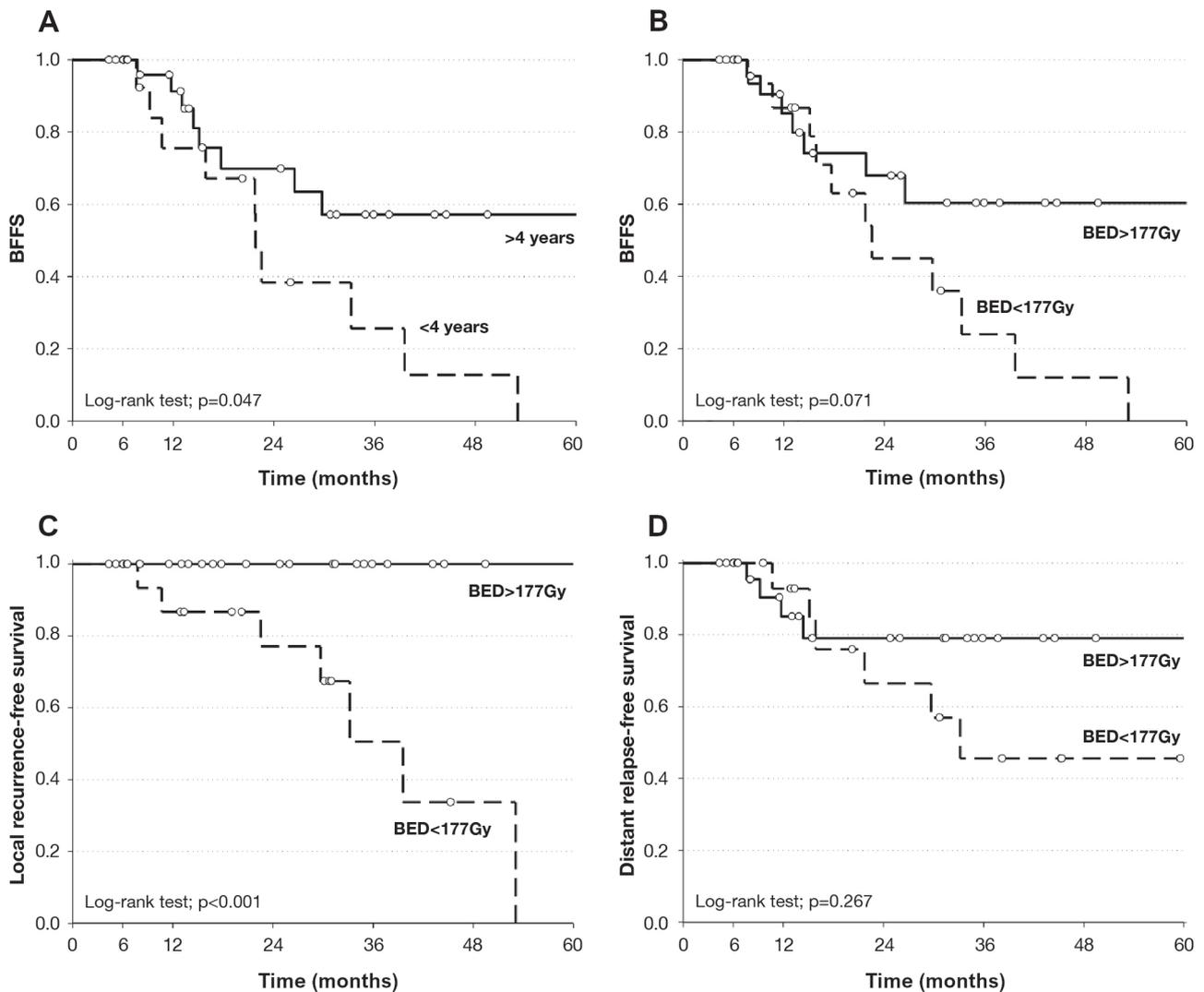
After a median follow-up of 25.4 months (6.7–81.5 months), biochemical failure was observed in 18 (41%) patients with a median time to relapse of 16.8 months (7.6–53 months). In all cases, clinical relapse was preceded by biochemical failure.

At restaging, in 7 (39%) out the 18 patients, post-PPR recurrence was located in the prostate (four patients in the prostate only, 2 in prostate and locoregional nodes, 1 in prostate and bone metastases); all prostatic recurrences were inside the treatment field.

The 1- and 2-year actuarial rates were 85.9% and 58.3% for BFFS, 85.9% and 67.9% for CRFS, 94.4% and 90.1% for LC, and 88.4% and 73.8% for DRFS, respectively. No patient died during the first two years after PPR (OS = 100%).

At the last follow-up, 43 (98%) patients were alive, 26 (59%) patients showed no evidence of disease, and 17 (39%) were alive with biochemical or clinical disease. One (2%) patient with clinical recurrence died of other causes. Metastatic disease was reported in 4 (9%) patients, 2 of them developed metastatic castration-resistant prostate cancer (mCRPC).

Late recurrence (i.e., the time interval between primary EBRT and first BCR >4 years) was a favorable prognostic factor for BFFS (p=0.046), with a 5-year rate of 67% in patients with late recurrence versus 0% in patients with early recurrence (i.e., the time interval between primary EBRT and first BCR <4 years; Figure 1A). Similarly, patients with BED of the first radiotherapy >177 Gy had a 5-year BFFS rate of 60% compared to 0% in patients with BED <177 Gy (p=0.071; Figure 1B). Furthermore, BED of the first radiotherapy was strongly correlated with LC, and no patient receiving a BED >177 Gy experienced a local recurrence (p<0.001; Figure 1C); whereas there was no statistically significant association between BED >177 Gy and DRFS (p=0.267; Figure 1D). The radiation dose of primary EBRT was converted into BED using  $\alpha/\beta=1.5$  Gy: since there is no consensus on the value of  $\alpha/\beta$  for prostate cancer, as a sensitivity analysis on  $\alpha/\beta$ , analyses were performed with different



**Figure 1.** Biochemical failure-free survival according to time to first recurrence (A) and BED (B); local recurrence-free survival (C) and distant relapse-free survival (D) according to BED. Abbreviations: BFFS-Biochemical failure-free survival; BED-Biologically effective dose

values of  $\alpha/\beta$  (2 Gy, 3.5 Gy, 5 Gy) [19], showing no substantial differences (data not shown).

Patients undergoing ADT concomitant to PPR reported a better BFFS than those who did not receive ADT (5-year BFFS: 45% and 16%, respectively), but the difference was not statistically significant ( $p=0.119$ ). Similarly, non-significant effect of concomitant ADT was found for CRFS ( $p=0.197$ ), LC ( $p=0.276$ ), and DRFS ( $p=0.191$ ).

**Toxicity.** Overall acute toxicities were assessed in 17 (39%) patients (Table 4).

Considering the maximum grade of toxicity observed up to 3 months after PPR, 27 (61%) patients had no acute toxicities. No patient experienced acute Grade 3 GU or GI toxicity. Two (5%) patients experienced a late Grade 3 GU event consisting of frequent macroscopic hematuria requiring

blood transfusion. No patient developed late Grade 3 GI or Grade 4–5 GU or GI toxicities.

In 13 (30% of our series) patients monitored for more than 36 months after PPR, only two Grade  $\geq 2$  GU/GI events were reported (one GU Grade 3 and one GU Grade 2). We found no association between toxicities PPR-related and BED of the first radiotherapy, the time interval between initial EBRT and PPR, and re-treatment volumes.

## Discussion

In patients with isolated local recurrence of PCa, local salvage therapies could represent a valid alternative to ADT, because they may offer, unlike hormone therapy, curative prospects. On the other hand, since local salvage therapies

Table 5. Comparison of results from previous experiences including Partial Prostate Re-irradiation and the present study.

Author, year of publication (Ref)	N	Initial treatment modality	Treated Volume	Technique	Total Dose and Fractionation	Median follow up (months)	Toxicity	Outcome
Janoray, 2016 [20]	21	Postprostatectomy RT: 10 pts Radical EBRT: 11 pts	Prostate bed recurrence: 10 Partial Prostate: 11	CK	36.25 Gy/5 fr to the 80% isodose line (95% PTV coverage)	11.7	Acute Grade 2: 1	1 year LC: 95.2% 1 year BFFS: 83.3%
Leroy, 2017 [28]	23	Radical EBRT: 19 pts Radical BRT: 4 pts	Whole gland: 19 Partial Prostate: 3 Hemi-prostate: 1	CK	36 Gy/6 fr to the 80% isodose line (95% PTV coverage)	22.6	Time of onset: not reported Grade 1: 13 Grade 2: 9 Grade 3: 3 Grade 4: 0	2 year LC: 76% 2 year DFS: 54%
Mbeutcha, 2017* [21]	18*	Radical EBRT: 3 pts Radical BRT: 15 pts	Partial Prostate: 18	CK	35 Gy/5 fr to the 80% isodose line	14.5	Acute: Grade 2: 2 GU, 2 GI Late: Grade 2: 1 GU, 1 GI Grade 4: 1 GU	14.5 months BFFS: 55.6%
Loi, 2018 [23]	50	Postprostatectomy RT: 22 pts Radical EBRT: 28 pts	Partial Prostate: 28 Prostate bed recurrence: 22	CK	30 Gy/5 fr to the 80% isodose line (95% PTV coverage)	21.3	Acute: Grade 2: 1 GU, Grade 3: 1 GU Late: Grade 2: 3 GU, 2 GI	1 year BFFS: 80%
Jerezek-Fossa, 2019 [29]	64	Postprostatectomy RT: 19 pts Radical EBRT: 40 pts Radical BRT: 4 pts Radical EBRT+BRT: 1 pts	Partial Prostate: 4 Whole gland: 40 Whole gland +DIL: 1 Prostate bed recurrence: 19	CK (3 pts) Vero (54 pts) RapidArc (7 pts)	Median total dose 30 Gy Median number of fractions 5	26.1	Acute: Grade 2: 3 GU, 1 GI Grade 3: 1 GU Late: Grade 2: 6 GU, 1 GI Grade 3: 1 GU	2 year LC: 75% 2 year BFFS: 40% 2 year CRFS: 53%
Scher, 2019 [26]	42	Postprostatectomy RT: 9 pts Radical EBRT: 33 pts	Prostate bed recurrence: 9 Partial Prostate: 33	CK	36 Gy/6 fr to the 80% isodose line	21	Acute: Grade 2: 9 GU, Grade 3: 1 GU Late: Grade 2: 2 GU	21 months BFFS: 75% 21 months LC: 100%
Pasquier, 2019 [30]	100	Radical EBRT: 80 pts Radical BRT: 17 pts Radical EBRT+BRT: 3 pts	Partial Prostate: 32 Hemi-prostate: 18 Whole gland: 49 Seminal vesicles only: 1	CK (81 pts) Vero (19 pts)	Median total dose 36 Gy Median number of fractions 6	29.3	Acute: Grade 2: 8 GU Grade 3: 1 GU Late: 3-year Grade ≥ 2 GU: 20.8% 3-year Grade ≥ 2 GI: 1%	2 year BFFS: 73% Intraprostatic recurrence: 10 (4 in PTV, 6 out PTV)
Present study	44	Radical EBRT: 44 pts	Partial Prostate: 44	RapidArc	35Gy/7fr	25.4	Acute: Grade 2: 4 GU, 2 GI Late: Grade 2: 6 GU Grade 3: 2 GU	2 year LC: 90.1% 2 year BFFS: 58.3% 2 year CRFS: 67.9%

\*Only patients retreated with EBRT are included. Abbreviations: BFFS-Biochemical failure-free survival; BRT-Brachytherapy; CK-CyberKnife; CRFS-Clinical relapse-free survival; DFS-Disease free survival; DIL-Dominant intra-prostatic lesion; EBRT-External beam radiation therapy; GI-Gastrointestinal; GU-Genitourinary; LC-Local control; PTV-Planning target volume

act on already treated tissues (surgically or with radiation therapy), it is a priority that any local treatment option should guarantee an acceptable profile of toxicity. Among the spectrum of local salvage therapies available, PPR could represent a valid approach. In this retrospective study, we focused on PPR with the aim of evaluating its efficacy, feasibility, and toxicity profile.

Several investigations evaluating the efficacy of salvage re-irradiation for locally recurrent PCa were published [20–30]; however, the comparability of our results with other reports is hindered by the different selection criteria adopted by the authors. Some papers included in the same case series patients with local recurrence of PCa after primary EBRT, after BRT, or after salvage post-prostatectomy radiotherapy [20–30]. In addition, investigations evaluating intraprostatic recurrence after primary EBRT reported re-irradiation with mixed approaches delivering radiation therapy to the entire prostatic gland or to hemi prostate or to part of the prostate [28–30]. In our retrospective cohort, we included only patients who underwent EBRT as primary treatment and who were subsequently treated with PPR for an isolated intraprostatic recurrence.

Our results in terms of BFFS and LC rates are in agreement with updated literature (Table 5).

Janoray et al. [20] using a CyberKnife® linac and a total dose of 36.25 Gy in five fractions, treated a population of 21 patients with biochemical failure with focal salvage radiotherapy. Eleven of these patients had been previously treated with radical EBRT with a 1-year biochemical response rate and local control of 83.3% and 95.2%, respectively.

Similarly, Mbeutcha et al. [21] analyzed a total population of 28 patients with local recurrence after definitive EBRT. Eighteen of these patients underwent focal radiotherapy using CyberKnife® linac and received a total dose of 35 Gy in five daily fractions. Within a median follow-up of 14.5 months, 10 out of 18 patients remained alive with no evidence of disease; among the patients who experienced BCR, only 3 (20.0%) developed a loco-regional disease recurrence.

The largest series on salvage re-irradiation has been reported in a retrospective multicenter study recently published by Pasquier et al. [30]. On a total of 100 cases of local relapse, 32 were treated with PPR with different radiation doses. The authors reported excellent outcomes with a 2-year overall BFFS of 73% and only four in-field recurrences.

In our study, the toxicity profile after PPR resulted highly favorable, with a very low rate of GU and GI side effects. In fact, none of our patients discontinued PPR for acute toxicity and only two Grade 3 late toxicity events were reported (equivalent to 4% of the total patient population). No Grade  $\geq 4$  toxicity was recorded. Our data are in agreement with those reported in the literature; however, our median follow-up, although similar to those reported in most investigations dedicated to PCa re-irradiation, might be too short for an accurate estimate of late toxicity.

Our results on late toxicity differ greatly from those published by Zilli et al. [25] who, in a series of 14 patients treated with whole prostate re-irradiation, at a longer median follow-up of 94 months, reported a high rate of both late GU and GI toxicities (eight GU Grade  $\geq 3$  toxicity events and nine Grade  $\geq 3$  GI events). It should be noted that in the series by Zilli et al. conformal radiotherapy (3DCRT) + brachytherapy boost was the modality predominantly used for re-irradiation of patients who had been previously treated also with conventional radiotherapy (2DRT). This may indicate the importance of using advanced techniques in the setting of re-irradiation. In addition, we reported no event of urinary incontinence, which is a typical late event occurring in a significant percentage of patients undergoing salvage treatments after post-EBRT failure, in particular in those undergoing salvage prostatectomy [31, 32]. Similar to the recent findings by Pasquier et al. [30], also in our study the biochemical control of disease post-PPR is correlated with the duration of the time interval between first EBRT and disease recurrence. Therefore, since our patient population was made up mostly of patients at high risk at initial diagnosis, the time interval to recurrence could identify a subset of patients with a better response to re-treatment.

Even more fascinating is the correlation between dose at first EBRT and local control after PPR. Assuming that the role of dose escalation in the improvement of all oncological outcomes including local control is a well-established data [2], an interpretation of this correlation as well as the finding that all prostatic recurrences occurred within the PPR treatment field [33], could be higher BED in the first treatment reduces the number of surviving clonogens, which could lead to a lower number of clonogens in the second treatment.

The role of the combination of ADT and radiotherapy in the patient setting evaluated in our study remains unclear. Because in our study the radiation re-treatment was considered as a possible alternative to systemic therapy, concomitant ADT was administered only to a minority of selected patients and for a short period of time. However, in our study, the role of concomitant ADT in disease control after PPR could not be determined. This is consistent with the data reported in most of the published literature, although the number of patients receiving concomitant ADT and the duration of the periods of ADT administration differs substantially among studies. We observed a trend for better biochemical control in patients undergoing combination treatment. A similar finding was also reported by Shipley et al. [34] and Carrie et al. [35] in patients treated with post-operative radiotherapy in association with Bicalutamide and Goserelin, respectively. The short follow-up time and the retrospective design of our study are two major shortcomings, which limit the evaluation of the role of ADT in these patients. A longer follow-up is necessary to determine which oncologic outcomes may potentially be improved by concomitant ADT. In addition, the statistical design of

future studies should include the administration of ADT in this patient population and the comparison of outcomes by ADT in pre-determined subsets of patients.

A distinctive feature of our study is the use of the same radiation therapy technique and schedule in all patients at re-treatment. Although the radiation dose we employed in our patient population is in line with those reported in most papers, our patients received, at their first EBRT, a higher median radiation dose compared to patients treated in other studies. However, in spite of a high cumulative dose, the safety profile of PPR treatment remains excellent. Jereczek-Fossa et al. [29] found a statistically significant improvement in a 1-year biochemical progression-free survival rate and a 1-year clinical progression-free survival rate when a BED  $\geq 130$  Gy was prescribed. In our study, a BED of 151.7 Gy was prescribed to all patients with comparable 1-year outcomes and higher 2-years BFFS and 2-years CRFS suggesting that a dose escalation in this population could lead to improved outcomes.

To date, it is not yet clear what is the absolute and mutual role of the factors, which pose a limit to dose escalation in the re-treatment setting, namely: dose received by OARs and treatment volumes at primary EBRT, elapsed time, residual toxicity, re-irradiation volumes, and comorbidity. Therefore, dose-finding trials are necessary in this patient setting.

Although the rationale for PPR is to obtain the same or better oncological outcomes of re-irradiation of the entire gland but with an improvement in toxicity profile, its major limitation lies in the definition of the target volume. Even if we used fusion plans with MRI and/or [11C]-choline-PET, these imaging modalities have significant sensitivity limits that could result in an underestimation of the presence of tumor in the remaining prostate [36–39]. Nowadays, MRI is considered the best imaging modality to drive both diagnostic and therapeutic strategies for locally recurrent prostate cancer after primary radiotherapy [40]. Detection of recurrent prostate cancer is also feasible with choline PET/CT [41]: it should be noted that comparing data between choline PET and MRI in this setting of patients is still lacking. Recently, PSMA PET has been proposed in patients with BCR after primary treatment for prostate cancer. Although PET PSMA seems to have higher sensitivity to detect distant metastases and/or local relapse after radical prostatectomy with lower PSA values [42, 43], it remains unclear its superiority with respect to choline PET in the detection of local recurrence after primary EBRT with PSA values over Phoenix threshold [44]. The evaluation of the impact on the focal treatment of PSMA tracer could represent an object of future investigation.

Similarly, to most published investigations evaluating salvage re-irradiation for locally recurrent PCa [20–29], the small number of biopsies made represents a limitation of our study. The histological proof could in fact determine a potential modification of the volumes defined on the basis of imaging only [45]. However, we could assume that the

imaging employed has been adequate in target definition since no intraprostatic out-field failure has been recorded. Additionally, other limitations of our study can be found in the retrospective nature of this report, in the limited number of patients treated, and in the relative shortness of the median follow-up. In particular, a longer follow-up is needed to obtain data on late toxicity, which is essential to determine the role of PPR.

Some caveats of our study need to be overcome to fulfill an effective long-time study. The aforementioned small number of biopsies made and the heterogeneity of diagnostic imaging at BCR represent crucial points to improve the patient selection with a larger number of biopsy-proven relapses and to homogenize treatment procedures (i.e. target delineation based on the same diagnostic tools). On these bases, a prospective long-term trial would confirm our results and provide more robust data on PPR.

Conversely, the homogeneity of our treatment modality both in the primary setting and in the recurrent disease, as well as the radiation technique employed can be regarded as points of strength of the present study.

There are some aspects of improvements in our study. Our PPR program has achieved efficacy results similar, or at least not inferior, to those reported in the literature but with an improved acute-toxicity profile. As for PPR feasibility, all patients completed the planned treatment, and the data on late toxicity, although not definitive, are very encouraging.

The statistical findings of our study seem to stress previously underestimated characteristics of recurrent prostate disease, such as the time to recurrence after primary EBRT and the cumulative dose in prostatic re-irradiation. Moreover, it must be emphasized that no out-field recurrences were reported, which confirms the validity of modern radiological and nuclear medicine techniques in the identification of recurrent disease and, consequently, in the definition of the radiation treatment volume.

The short-term results reported in this paper may provide the scientific community with updated information for a better understanding of PPR and for the implementation of this approach in patients with isolated intraprostatic recurrence.

To the best of our knowledge, this is the largest series exclusively dedicated to the PPR approach for isolated local PCa recurrence after primary EBRT. Even if retrospective, our study showed that PPR is a feasible and well-tolerated approach with a promising tumor control rate. These short-term results may contribute to the growing evidence of PPR as a valid option in the context of focal salvage therapies for locally recurrent PCa. Long-term toxicity and the impact on disease control and patient survival will be evaluated with a longer follow-up time.

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