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FULL PAPER

Reirradiation for isolated local recurrence of prostate cancer: Mono-institutional series of 64 patients treated with salvage stereotactic body radiotherapy (SBRT)

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Objective: To evaluate high-precision external beam reirradiation (re-EBRT) for local relapse of prostate cancer (PCa) after radiotherapy.
Methods: This retrospective study included patients with biochemical failure and evidence of isolated local recurrence of PCa after radical/salvage EBRT or brachytherapy that received salvage stereotactic body radiation therapy (SBRT, re-EBRT). Biopsy was not mandatory if all diagnostic elements were univocal (prostate specific antigen evolution, choline-positron emission tomography or magnetic resonance imaging). Salvage SBRT (re-EBRT) was delivered with image-guided radiation therapy (RapidArc®, VERO® and CyberKnife®).
Results: Data of 64 patients were included, median age at salvage SBRT was 73.2 years, median pre-salvage SBRT prostate specific antigen was 3.89 ng ml^{-1} . Median total dose was 30 Gy in five fractions, biologically effective dose (BED) of 150 Gy. One acute G3 genitourinary event and one late G3 genitourinary event were observed. No G ≥ 3 bowel toxicity was registered. At the median follow-up of 26.1 months, tumor progression was observed in 41 patients (64%). 18 patients (28%) experienced local relapse. 2-year local control, biochemical and clinical relapse free survival rates were 75, 40 and 53%, respectively. With BED ≥130 Gy 1-year biochemical and clinical progression-free survival rate were 85 and 90%, respectively.
Conclusions: Salvage SBRT (re-EBRT) for isolated local PCa recurrence is a safe, feasible and noninvasive salvage treatment. Further investigation is warranted to define the optimal patient selection, dose and volume parameters.
Advances in knowledge: Salvage SBRT reirradiation for the locally recurrent PCa offer a satisfactory tumor control and excellent toxicity profile, if BED ≥130 Gy is administered.

INTRODUCTION

External beam radiotherapy (EBRT) is widely used as primary treatment for localized prostate cancer (PCa).[1] A recent randomized study with a median 10 years follow-up demonstrated that, in localized low and intermediate risk PCa, EBRT achieves results similar to radical prostatectomy in terms of tumor control and disease specific mortality.[2] In recent years, the development of modern techniques such

as intensity modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT) and stereotactic body irradiation (SBRT), in addition to the progressive escalation of the prescribed dose, resulted in good tumor local control and enhanced overall survival in patients affected by localized PCa.[3,4] However, still approximately 22–69% of patients develop biochemical failure after radical EBRT or radical prostatectomy.[5,6]

Currently, the standard treatment for locally recurrent PCa is not uniquely defined[7,8] and different therapeutic options are available, including systemic therapy, *i.e.* androgen deprivation therapy (ADT), or local salvage approaches with curative intent, such as salvage prostatectomy, re-irradiation, cryotherapy and high intensity focused ultrasound (HIFU). The majority of the patient series is small and includes heterogeneous patients and treatments without a long follow-up. No randomized trials comparing salvage local and systemic strategies are available.[7,9,10] The most effective local therapy has not been established yet and remains controversial in the absence of consensus.[11–13] At present, patients with biochemical failure mainly receive longlasting ADT with negative impact on the quality of life and other health aspects. In selected patients with prostate specific antigen (PSA) <10 ng ml^{-1} and a good life expectancy (>10 years) a local treatment with radical intent can be considered.[7,12]

As far as reirradiation is concerned, the vast majority of patient series were treated with brachytherapy (BRT). In the last years, along with the improvement in radiotherapy (RT) planning and delivery technology, several reports on salvage EBRT have been published[14–27] (Table 1).

Our Division, equipped with high precision RT systems, has a long experience of reirradiation.[19,28–30] Our reports include numerous primary tumor sites, and the majority of studies are focused on the recurrent PCa.[14,15,19,28–34] In particular, the preliminary retrospective analysis published by Zerini et al[14] with a mean follow-up of 21.3 months, reported good local tumor control and low toxicity profile in a series of 32 patients treated with IG-IMRT for isolated local recurrence of PCa. The aim of the current study was to present the outcome in the larger patient series treated with salvage SBRT (re-EBRT), including updated information of some patients from Zerini's series.[14]

METHODS AND MATERIALS

Study protocol

Inclusion criteria for this retrospective study were: (1) isolated local recurrence of PCa after primary EBRT, BRT or salvage post-prostatectomy RT; (2) salvage with SBRT (re-EBRT) at the European Institute of Oncology between November 2009 and November 2016; (3) written informed consent for radiation treatment; (4) written informed consent for use of anonymized clinical and imaging data for research and education purpose; (5) minimum follow-up of 3 months; (6) no evidence of metastatic disease. No other local salvage treatment for the recurrent PCa was permitted.

This study is a part of the research notified to the Ethical Committee of the European Institute of Oncology (notification Nr 79: clinical and dosimetric aspects of IGRT for PCa). Data of some patients were shared with the French Genito-Urinary Group (GETUG) and a separate analysis will be performed. The GETUG analysis will regard exclusively the cases with biopsy-proven intraprostatic recurrence" (unpublished data).

Biochemical failure

Biochemical failure after the primary therapy was defined as two consecutive risings in PSA level >0.2 ng ml^{-1} post-radical prostatectomy and PSA nadir +2 ng ml^{-1} above the nadir after primary RT, according to the Radiation Therapy Oncology Group (RTOG) and American Society for Radiation Oncology (ASTRO) Phoenix Consensus.[35]

The diagnosis of local recurrence was based on the biochemical failure confirmed by imaging studies, *i.e.* [11C]-choline positron emission tomography with co-registered CT (PET/CT), whole body MRI (WB-MRI) including multiparametric MRI (mpMRI) of the prostate, whole body CT scan. Choline-PET/CT and MRI were used after the diagnosis of biochemical recurrence to confirm local recurrence and choline PET/CT was also used to exclude nodal and bone metastasis.[36–40] Biopsy was not mandatory[41] if all diagnostic elements were univocal (PSA evolution stating for biochemical recurrence, [11C]-choline-PET/CT or MRI findings). All cases were discussed in the multidisciplinary uro-oncology tumor board.

Treatment procedures

Salvage SBRT (re-EBRT), was delivered with IGRT, employing CyberKnife® (Accuray, Inc., Sunnyvale, CA), Vero® (Mitsubishi Heavy Industries, Ltd., Japan and BrainLab AG, Feldkirchen, Germany) or RapidArc® (Varian Medical Systems, Palo Alto, CA) systems whose technical characteristics have been published elsewhere.[14] Patients treated with CyberKnife had fiducial markers implanted into the target. 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 simulation CT and all treatment fractions. Gross tumor volume (GTV) contouring was based on the mpMRI and PET/CT co-registration. Clinical target volume (CTV) included the whole prostate or intraprostatic lesion or prostate bed recurrence with margins. The CTV to planning target volume (PTV) margins were 5 mm in all directions except for the posterior margin where 3 mm margin was added. For CyberKnife treatments and in case of short interval between two RT courses, comorbidity or unfavorable anatomy or dose volume histograms (DVH) data, margins were reduced of 1 mm. This decision was supported by the steep dose gradient that could be achieved with CyberKnife and intra fraction organ motion control performed in all CyberKnife treatments. The organs at risk (OARs) included rectum (and its posterior part), urinary bladder, penile bulb, penis, testis, femoral heads, peritoneal cavity and cauda equina. Dose–volume constraints were: Dose given to 30% of rectal volume <13.5 Gy; Dose given to 60% of rectal volume <6.7 Gy; Dose given to 30% of urinary bladder volume <10.6 Gy (based on our previous series data reported by Jereczek-Fossa et al).[19] Extreme hypofractionated schedules were employed and the fractions were delivered on alternating days. Before every fraction image guided procedures were performed

Table 1. Published clinical series including patients treated with external beam reirradiation for locally recurrent prostate cancer>.>

Author, year of publication [Ref]	N	Initial treatment modality	Median relapse time (range)	Treated volume	RT technique	Total Dose and fractionation	ADT	Median follow-up (range)	Toxicity	Local control/ pattern of failure	Overall survival
Kalapurakal, 2003[24]	13	Group A: EBRT ± ADT: 8 pts Group B: ADT : 4 pts prostatectomy + orchiectomy: 1	Not reported	PTV: GTV + 1–2 cm	3D-CRT + hyperthermia	Median total dose 39.6 Gy/ 22 fr (prior RT) Median total dose 66.6 (59.4–70.2) fr (no prior RT)	Neoadjuvant: 1 pts	Group A: 14 (4–48) months Group B: 15 (6–32) months	Acute: Grade 4: 1 GI Late Grade 1: 3 GI, 1 GU Grade 2: 1 GI Grade 4: 2 GU	Group A: Median duration of CR/PR: 12 (4-27) months Group B Median duration of CR/PR: 15 (2-32) months	N.A.
Vavassori, 2010[15]	6	EBRT	Not reported	Whole gland	SBRT	30 Gy/ 5 fr	Neoadjuvant: 4 pts	11.2 (9.6–18.6) months	Acute: Grade > 2: 0 pts Late Grade > 2: 0 pts	Median time to clinical progression: 9.9 (9.2–10) months (1 regional, 2 distant)	11.2 months OS: 100%
Jereczek-Fossa, 2012[19]	34 pts/38 lesions	EBRT ± ADT: 20 pts Radical prostatectomy ±RT ± ADT: 14 pts	66 (24–180) months	Local recurrence (15 pts) Anastomosis recurrence (4 pts) Lymph node recurrence (16 lesions) Metastasis (3 lesion)	SBRT	*Local recurrence* Median total dose 30 Gy/4.5 fr *Anastomosis recurrence* Median total dose 30 Gy/5 fr	Concomitant, 5 pts Concomitant, 2 pts	9.5 (3–28.9) months 23 (3.9–30.6) months	Local and anastomosis recurrence Acute: Grade 1: 3 GU, 1 GI Grade 2: 2 GU Grade 3: 1 GU Late: Grade 1: 1 GU Grade 2: 1 GU, 1 GI Grade 3: 1 GU	30 months PFS (%) (95% CI): 22.2 (0–58.2) Median PFS (%) (95% CI):: 13 (10, > 30) 30 months PFS (%) (95% CI) : 33.0 (0–68.7) Median PFS (%) (95% CI): 14 (10, > 30)	Not reported
Zerini, 2015[14]	32	EBRT ± ADT: 10 pts Radical prostatectomy ±RT ± ADT : 22 pts	99.7 (23–208.4) months	Whole gland (22 pts) Prostate bed (10 pts)	SBRT	Median total dose 25 Gy/ median dose/fr 5 Gy (if no prior surgery); median total dose 25 Gy/ 5 fr (if prior surgery)	Concomitant, 11 pts	21.3 (2–53) months	Acute: Grade 1: 6 GU, 2 GI Grade 2: 2 GU, 1 GI Late: Grade 1: 6 GU Grade 2: 1 GU	Median time to biochemical progression: 9.4 (4.9–27.8) months Median time to clinical progression: 13.2 (2–53) months (4 local, 1 regional, 7 metastatic)	21.3 months cancer-specific OS: 93.7%
Fuller, 2015[16]	29	EBRT	88 (32–200) months	Whole gland	SBRT	34 Gy/5 fr	No	24 (3–60) months	Late Grade 2: 3 Grade 3: 1 Grade 4: 1	Actuarial 2 year BFFS: 82% 2 year DFS: 100%	2 year OS: 100%
Arcangeli, 2015[25]	1	Radical prostatectomy +RT	42 months	PTV: CTV + 5 mm	SBRT	30 Gy/5 fr	No	6 months	Acute: Grade 1 GU, Late: Grade 0	6 months LC: 100% 6 months BFFS: 100%	6 months: 100%

(Continued)

Table 1. (Continued)

Author, year of publication [Ref]	N	Initial treatment modality	Median relapse time (range)	Treated volume	RT technique	Total Dose and fractionation	ADT	Median follow-up (range)	Toxicity	Local control/ pattern of failure	Overall survival
Lee, 2015[27]	2	EBRT	Case1: 102 months Case 2: 35 months	Whole gland	IMRT	Case 1: 66 Gy/30 fr Case 2: 69 Gy/30 fr	no	Case 1: not reported Case 2: 4 years	Acute: Grade > 3: 0, Late: Grade > 3: 0	Not reported	Not reported
Zilli, 2016[22]	14	EBRT: 12 pts Primary EBRT ±BRT boost: 2 pts	4.4 (2.3–7.4) years	Whole gland	3D-CRT (10 pts) IMRT (4 pts) boost BRT (10 pts) boot EBRT (3 pts)	Median normalized dose in 2 Gy fr: 85.1 (70–93.4) Gy, α/β: 1.5 Gy	12 months (median time) ADT: 12 pts	94 (48–172) months	Acute: Grade 1: 4 GU, 6 GI Grade 2: 3 GU, 2 GI Late Grade 1: 3 GU, 1 GI Grade 2: 3 GU, 3 GI Grade 3: 4 GU, 4 GI Grade 4: 4 GU, 5 GI	5 year BFFS: 35.7±12.8% 5 year LRFS: 50.0±13.4% 5 year DMFS: 85.7±9.4%	5 year cancer-specific survival: 100%
Rutenberg, 2016[21]	11	Prostate BRT	49.2 (12.9–135.5) months	Whole pelvis: 8 pts Prostate +proximal SVs: 1 Prostate only: 2	3D-CRT (2 pts), IMRT (9 pts);	median total dose: 70.2 (64.8–75.6) Gy	6 months ADT: 3 pts 2 year ADT: 2 pts	26.5 (1–53.6) months	Acute: G2: 1 Late: Grade 2: 2 Grade 3: 2	Actuarial 3 year BFFS: 69% Median time to local relapse: 17.7 months (4 pts)	Actuarial 3 year OS: 77%
Janoray, 2016[17]	21	Radical prostatectomy +RT: 10 pts Primary RT only: 11 pts	111 (38–398) months	CTV: GTV + 1 or 2 mm per D'Amico risk stratification (low/intermediate *vs* high)	SBRT	36.25 Gy/5 fr to the 80% isodose line (95% PTV coverage)	Concomitant (2 pts)	11.7 (2.5–46.5) months	Acute Grade 2: 1	1 year BFFS: 83.3% 1 year LR: 95.2% (1 pt, in field)	11.7 months OS: 100%
Detti, 2016[18]	16	Radical prostatectomy: 8 pts Radical prostatectomy +RT: 8 pts	10.5 (3.5–21.4) years	Prostatic bed	SBRT	30 Gy/5 fr (if previous RT); 35 Gy/5 fr (if no previous RT)	Adjuvant (5 pts)	10 (2–21) months	Acute: Grade 1: 1 Late: G2:1	Biochemical response: 15 pts Median time to relapse: 9.3 months (7, distant relapse)	10 months OS: 100%
Leroy, 2017[20]	23	EBRT: 19 pts BRT: 4 pts	65 (28–150) months	Whole gland: 19 Focal: 3 Hemi-prostate: 1	SBRT	36 Gy to the 80% isodose line (95% PTV coverage)	Concomitant (14 pts)	22 (6–40) months	Time of onset: not reported Grade 1: 13 Grade 2: 9 Grade 3: 3 Grade 4: 0	2 year DFS: 54% 20 months DFS: 60.9% (5 local, 1 nodal and 3 metastatic recurrences)	2 year OS: 100%

(Continued)

Table 1. (Continued)

Author, year of publication [Ref]	N	Initial treatment modality	Median relapse time (range)	Treated volume	RT technique	Total Dose and fractionation	ADT	Median follow-up (range)	Toxicity	Local control/ pattern of failure	Overall survival
Mbeutcha, 2017[26]	28	HDRB: 16 pts EBRT: 12 pts	69 months (IQR: 55–85) 49 months (IQR: 37–70)	PTV: CTV + 1 mm	BRT (10 pts), SBRT (18 pts)	35 Gy/5 fr 35 Gy/5 fr	Concomitant (2 pts) Concomitant (10 pts)	22.5 months (IQR: 8–42) 14.5 months (IQR: 7–23)	Acute: Grade 1: 2 GU, 1 GI Grade 2: 7 GU Late: Grade 1: 1 GI Grade 2: 6 GU Grade3: 1 GU Acute: Grade 1: 5 GU, 1 GI Grade 2: 2 GU, 2 GI Late: Grade1:4 GU Grade 2: 1 GU, 1 GI Grade 4: 1 GU	BRT: Biochemical recurrence free survival: 44.4% at 19.5 months (IQR: 14–36) SBRT: Biochemical recurrence free survival: 33.3% at 7 months (IQR: 4–7)	N.A.
Loi, 2018[23]	50	Post-prostatectomy RT: 22 pts Radical EBRT: 26 pts	76 (9–205) months	Whole gland, DIL	SBRT	30 Gy to the 80% isodose line (95% PTV coverage)	Concomitant (11 pts)	21.3 (6.1–49.2)	Acute: Grade 1: 9 GU, 4 GI Grade 2: 1 GU Grade 3: 1 GU Late: Grade 1: 9 GU, 1 GI Grade 2: 3 GU, 2 GI Grade 3: 1 GU, 1 GI	1 year BFFS: 80% 1 year DMFS: 92%	N.A.
Current study	64[a]	Post-prostatectomy RT: 19 pts Radical EBRT: 40 pts Radical BRT: 4 pts Radical EBRT + BRT: 1 pts	99.7 (23–208.4) months	PPI: 4 Whole gland: 40 Whole gland +DIL: 1 Prostate bed recurrence: 19	IMRT (50 pts) SBRT (14pts)	Median total dose 30 Gy/ 6 fr, Median dose/fraction 6 Gy (3–12). Median number of fractions 5 (2–10)	Concomitant (16 pts)	26.1 (3.1–82.4) months	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 Clinical free survival: 53%	2 year OS: 92%. 2 year PCSS: 95%

3D-CRT, 3 dimensional-conformal radiation therapy; ADT, androgen deprivation therapy; BFFS, biochemical failure free survival; BRT, brachytherapy; CR/PR, complete response/partial response; CTV, clinical target volume; DFS, disease-free survival; DIL, dominant intraprostic lesion; DMFS, distant metastases free survival; EBRT, external beam radiation therapy; fr, fraction; GTV, gross tumor volume; GTVGI, gastrointestinal; GU, genitourinary; IMRT, intensity modulated radiation therapy; LC, local control; N.A, not available; OS, overall survival; PCSS, prostate cancer specific survival; PPI, partial prostate irradiation; pt, patient; RT, radiation therapy; SBRT, stereotactic radiation therapy;

[a]27 pts from Zerini et al[14] with up-dated follow-up.

(with cone beam CT in Vero and Rapidarc patients) or intrafraction control was used (CyberKnife). Additionally, automated infrared marker-based patient-positioning device integrated into the Vero system was employed (ExacTrac, BrainLab AG Feldkirchen, Germany).The patients received premedication with dexamethasone and α-blockers.

Outcome assessment

Acute and chronic toxicity was registered by a radiation oncologist according to the RTOG/European Organization for Research and Treatment of Cancer Guideline (RTOG/EORTC) during salvage SBRT (re-EBRT), and subsequently every 6–12 months after the end of salvage SBRT (re-EBRT) . Gastrointestinal (GI) and genitourinary (GU) events were registered whereas sexual dysfunction was not analysed here due to lack of baseline evaluation. Serum PSA level was tested every 3 months until any biochemical or clinical progression. In patients with a reduction or stabilization of PSA levels at follow-up, non-additional radiological or nuclear medicine evaluation was requested.

Likewise, the primary treatment, biochemical failure after reirradiation was defined as PSA nadir +2 ng ml^{-1} (Phoenix consensus).[35] In post-prostatectomy patients, biochemical progression was defined as a continuous increase in PSA over the pre-re-EBRT value confirmed by at least two tests.[14] In case of local relapse, the data were censored for toxicity in order to avoid the misinterpretation of local symptoms of relapse as GI and GU events. Biochemical progression-free survival was measured as the time from the beginning of salvage SBRT (re-EBRT) to the PSA increase after salvage SBRT (re-EBRT). Clinical progression-free survival was measured as the time from the beginning of re-EBRT to the radiological detection of local progression or distant disease. LC was measured from the beginning of salvage SBRT (re-EBRT) and the radiological diagnosis of in-field relapse.

In patients treated by ADT and salvage SBRT (re-EBRT), the PSA value before the start of ADT was considered as pre-salvage SBRT (re-EBRT) PSA level. The prescribed dose of reirradiation was converted to biologically effective dose (BED) calculated using an α/β ratio 1.5 Gy.

STATISTICAL ANALYSIS

Patient and tumor characteristics were represented as frequencies and percentages when classified with categorical variables and with median values and range for continuous variables.[42] The correlation between treatment doses and clinical outcome were investigated with Cox proportional-hazards regression. Survival analysis was performed with Kaplan–Meier approach, and differences between groups were evaluated with log-rank test.[43] A p-value < 0.05 was considered significant.

RESULTS

Patient data

Between November 2009 and November 2016, 73 patients with biochemical failure and evidence of isolated local relapse of PCa after radical/salvage EBRT or BRT were treated with salvage SBRT (re-EBRT) in our department. For this retrospective analysis, 64 patients were eligible according the inclusion criteria. Nine patients were excluded due to metastatic disease at the time of reirradiation and one patient was excluded for the reirradiation technique (three-dimensional conformal radiotherapy, 3D-CRT). 27 out of 32 patients included in Zerini's series[14] fulfilled the criteria of the current study and their updated follow-up data have been included here. The median follow-up for the whole series was 26.1 months (range 3.1–82.4 months).

Patient and tumor characteristics

Patient and tumor characteristics are listed in Table 2. Local relapse was documented by [11C]-choline PET/CT, pelvic MRI, and total body CT scan in 53 (83%), 40 (63%) and 4 (6%) patients, respectively. Biopsy of the radiologically documented recurrent lesion was performed in 28 patients (44%). For the remaining 41 patients (non-biopsied or non-positive at biopsies), diagnosis of isolated local recurrence of prostate cancer was based on PSA levels (stating for biochemical recurrence) and radiological confirmation with PET, CT scan and/or MRI. All cases were discussed with the multidisciplinary uro-oncology tumor board and the clinical decision was taken jointly.

Previous EBRT included 3D-CRT in 55 patients (median dose: 70.2 Gy), IMRT in 4 patients (median dose: 66.1 Gy) and 4 patients received low dose rate interstitial BRT (median dose: 145 Gy). At the first EBRT, the most of the patients were treated with a conventional fractionation, and 9 patients received moderate hypofractionation.

Treatment

Salvage SBRT (re-EBRT) was performed for intraprostatic recurrence and for post-prostatectomy bed recurrence in 45 (70%) and 19 (30%) cases, respectively. CTV of reirradiation included the whole prostate in 40 patients (63%), mpMRI-identified intraprostatic relapse (partial prostate reirradiation) in 4 patients (6%), whole prostate and simultaneous boost to intraprostatic relapse in 1 patient (1%) and prostatic surgical bed nodule in 19 patients (30%). The schedules used for salvage SBRT (re-EBRT) are presented in the Table 3.

Extreme hypofractionation was employed in the majority of patients. Median dose was 30 Gy (range: 20–30 Gy) given in five fractions (range: 2–10). The choice of the schedule was based on the clinical situation (age, comorbidity, time interval between two RT courses ìetc.) and was at the physician discretion. In three patients, hypofractionated SBRT was employed due to important comorbidity

Patients treated with a total salvage SBRT (re-EBRT) BED <130 Gy had major comorbidities (*i.e.* ischemic cardiopathy, previous percutaneous transluminal coronary angioplasty), previous abdominal surgery and antiplatelet/anticoagulant therapy.

Concomitant ADT included luteinizing hormone-releasing hormone agonist (LHRHa), antiandrogens and combined androgen blockade (CAB) in 8, 4 and 4 patients, respectively.

Table 2. Patient characteristics (*N* = 64 patients)

Characteristics	All patients, *n* = 64	Prostate, *n* = 45	Prostate bed, *n* = 19
PRIOR RT			
Initial PSA [ng ml^{-1}], *median (range)*	11.4 (0.5–228.5)	11.69 (3.4–228.5)	16.7 (0.5–110)
Initial Gleason Score, *median (range)*	7 (2–9)	6 (4–8)	7 (2–9)
Prior RT modality			
3D	55	38	17
3D + BRT	1	1	
BRT	4	4	
IMRT	4	2	2
Dose (Gy), *median (range)*	70.2 (45–145)	75 (50–145)	70 (45–77.4)
Interval between first RT and re–EBRT [months], *median (range)*	99.7 (23–208.4)	102.6 (23–208.4)	93.9 (27.9–183.3)
Re–EBRT			
Age at re–EBRT [years], *median (range)*	73.2 (52.6–81.7)	65.2 (47–81.7)	59.4 (48.8–70.5)
Pre re–EBRT PSA [ng/ml], *median (range)*	3.89 (0.17–51.8)	4.29 (0.24–21)	3 (0.17–51.8)
Androgen deprivation			
Yes (%)	16 (25%)	10	6
No (%)	48 (75%)	35	13
Duration [months], *median (range)*	17.8 (3.0–38.1)	14.7 (7.6–37.9)	20.6 (3.0–38.1)
Biopsy of the target lesion			
Yes (%)	28 (44%)	21	7
Positive	23	18	5
Gleason score[a] (range)	7 (6–9)	7 (6–9)	
No (%)	36 (56%)	24	12
Histological +/–Radiological diagnosis			
Biopsy + PET + MRI	11		
Biopsy + MRI	6		
Biopsy + PET	11		
MRI + PET	15		
PET only	12		
PET+CT+MRI	3		
PET+CT	1		
MRI only	5		
Target lesion			
Prostate	45 (70%)	45 (70%)	
PPI	4 40	4 40	
Whole gland	1	1	
Whole gland+ Intraprostatic relapse	19 (30%)		19 (30%)
Prostate bed recurrence			
Total dose [Gy], *median (range)*	30 (20–30)	30 (20–30)	25 (25–30)
Dose/fraction [Gy], *median (range)*	6 (3–12)	6 (3–12)	5 (5–6)

(Continued)

Table 2. (Continued)

Characteristics	All patients, $n = 64$	Prostate, $n = 45$	Prostate bed, $n = 19$
Number of fractions, *median (range)*	5 (2–10)	5 (2–10)	5

3D, three-dimensional conformal RT; BRT, brachytherapy; CT, whole body computer tomography; PPI, partial prostate irradiation; PET, [11C]-choline positron emission tomography with co-registered computed tomography; PPI, partial prostateirradiation; PSA, prostate specificantigen; re-EBRT, external beam re-irradiation; RT, radiotherapy; IMRT, intensity modulated radiation therapy;
[a]available in 10 patients

Tumor outcome

At the median follow-up of 26.1 months from salvage SBRT (re-EBRT) (range: 3.1–82.4 months), progressive disease was observed in 41 patients (64%) (Table 4). In all cases, clinical progression followed biochemical progression. 18 patients (28%) experienced clinically/radiologically evident local relapse. Median time to progression was 14 months (range: 3.1–65.9 months), which was similar in both groups, namely 13.8 months (range 3.4–51.8) for prostate-bed subgroup and 14 months (range 3.1–65.3) for prostate subgroup. Patients irradiated at prostate-bed appear to have higher proportion of clinical relapse, whether patients treated on prostate presented a higher proportion of biochemical recurrence only. However, differences between groups were not statistically significant at χ^2 test (we added these results in Table 4).

The 2 year actuarial biochemical progression-free survival and clinical progression free survival rates were 40 and 53%, respectively. Local control at 2 years was 75%. Overall survival and PCa specific survival rates at 2 years were 92 and 95%, respectively. Five patients with a second clinical and biochemical relapse underwent a new re-EBRT.[44] At the last follow-up, 59 patients were alive. 23 (36%) patients showed no evidence of disease, 35 patients (44%) were alive with biochemical or clinical disease and 1 was lost to follow-up. Five patients (8%) died: three for disease progression, one for another type of tumor and one of unknown cause.

Considering salvage SBRT (re-EBRT)BED (≥130 Gy *vs* <130), statistically significant differences were found for the 1-year biochemical progression-free survival rate (85 *vs* 60%, *p*-value = 0.0006) and 1-year clinical progression-free survival rate (90 *vs* 73%, *p*-value = 0.0026), as shown in the Kaplan–Meier curves (Figure 1). No statistically significant differences between patients treated with a total BED <130 Gy or ≥130 Gy were found for local control at 2 years (85% *vs* 65%, *p*-value = 0.09) and overall survival at 2 years (95% *vs* 90%, *p*-value = 0.38).

For patients treated with addition of ADT and without ADT, biochemical progression was observed in 12/16 patients (75%) and in 25/48 (52%) patients, respectively.

Considering salvage SBRT (re-EBRT) setting (prostate in place and post-prostatectomy tumor bed), tumor progression was observed in 27/45 patients (60%) and 14/19 (74%) patients, respectively.

Toxicity

Acute toxicity was assessed in 64 patients (Table 5). Considering the maximum grade of toxicity observed at the end or during the first 6 months after salvage SBRT (re-EBRT), 46 patients (72%) had no acute toxicity. One patient experienced acute Grade 3 GU event represented by transitory macroscopic hematuria.

Late toxicity was evaluated in 62 patients (Table 5). One patient experienced late Grade 3 GU event represented by permanent reduction in urinary bladder capacity. Late toxicity was missing for two patients (follow-up <6 months). No patient developed Grade 4 or 5 toxicity.

To evaluate long-term toxicity in our series, we reviewed the data of the patients with follow-up longer than 36 months. In 20 patients monitored for more than 36 months after salvage SBRT (re-EBRT (31% of our series), only 1 Grade 3 GU event was registered (reduction in urinary bladder capacity).

Table 3. Treatment schedules

Total dose [Gy] (Dose/fraction [Gy] × num. fractions)		**30 (3 × 10)**	**25 (5 × 5)**	**30 (5 × 6)**	**30 (6 × 5)**	**20 (10 × 2)**	**24 (12 × 2)**
BED [Gy] (α/β = 1.5 Gy)		**90**	**108.3**	**130**	**150**	**153.3**	**216**
LINAC	**Total (%)**	**Number of patients**					
CyberKnife®	3 (5%)	–	1	–	–	1	1
VERO®	54 (84%)	3	18	1	28	–	–
Trilogy® (RAPIDARC)	7 (11%)	–	8	–	3	–	–

BED: biologically effective doseIMRT, intensity modulated radiation therapy;

Table 4. Patterns of failure evaluated on 41 patients

Outcome	All patients (%)	Prostate	Prostate bed	*p*-value
Biochemical relapse only	11 (27%)	9 (33%)	2 (14%)	0.19
Whole gland		8		
PPI		1		
Concomitant ADT	3	2	1	
Clinical recurrence IN-FIELD[a]	13 (32%)	8 (30%)	5 (36%)	0.69
Concomitant ADT	5	3	2	
Clinical recurrence IN-FIELD and OUT-FIELD[b]	5 (12%)	2 (7%)	3 (21%)	0.19
Concomitant ADT	2	0	2	
Clinical recurrence OUT-FIELD[a]	12 (29%)	8 (29%)	4 (29%)	0.94
Locoregional relapse with metastatic relapse	2 (5%)	1 (4%)	1 (7%)	.62
Concomitant ADT	0	0	0	
Locoregional relapse	5 (12%)	5 (18%)	0	–
Concomitant ADT	1	1	0	
Metastatic relapse	5 (12%)	2 (7%)	3 (21%)	0.19
Concomitant ADT	1	1	0	
TOTAL	41	27	14	

ADT: Androgen deprivation therapy PPI: partial prostate irradiation
Medianfollow-up was 26.1 months. Statisticalanalysis is performed with χ^2 test.
[a]And biochemical relapse
[b]With biochemical relapse and metastatic relapse out-field

No significant difference was observed between the groups with regard to acute toxicity. As concerning late toxicity, Grade 2 genitourinary events appear to be more frequent in patients who received reirradiation to prostate bed (5 events out of 19 patients in prostate-bed subgroup against 1 event out of 45 patients in prostate subgroup, *p*-value = 0.002, χ^2 test).

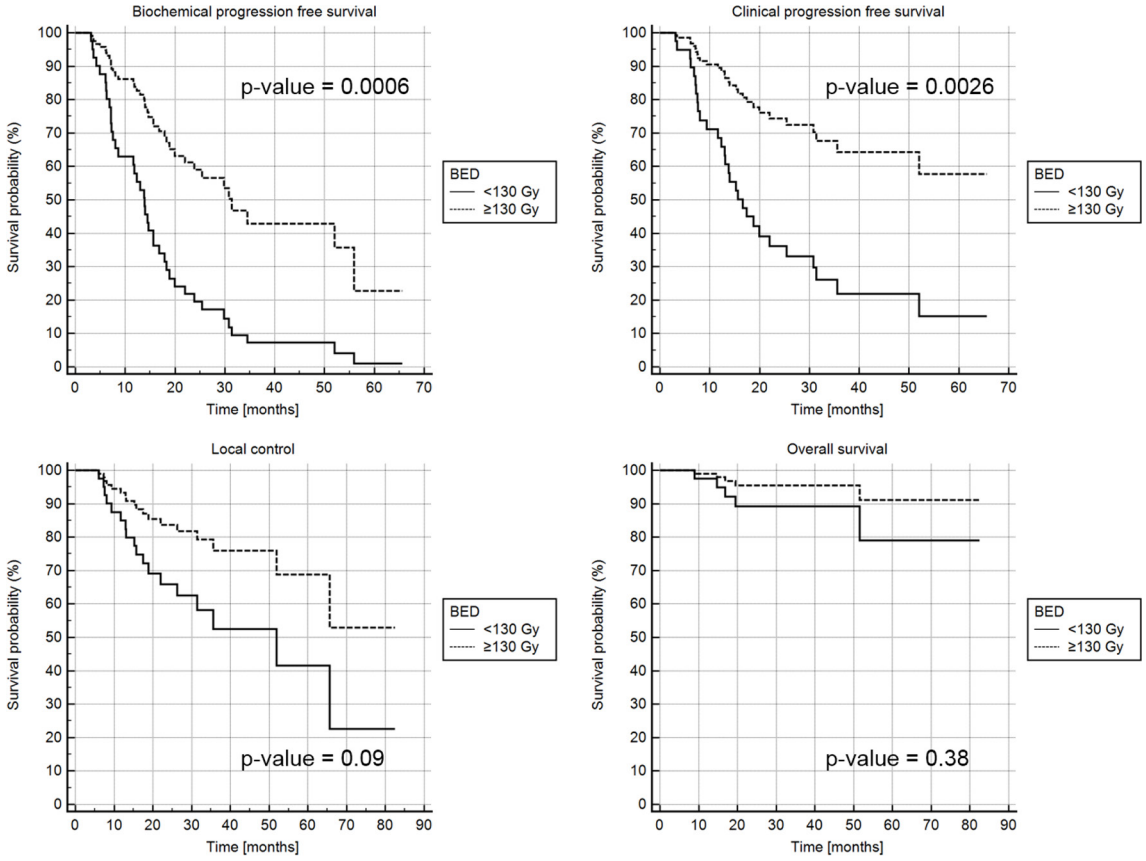
DISCUSSION

To the best of our knowledge, this is the largest series on the salvage SBRT (re-EBRT) of isolated local PCa recurrence. Our study including 64 patients showed that local salvage SBRT (re-EBRT) is safe and offers promising tumor control. Indeed, only one patient experienced late Grade 3 toxicity and almost half of the patients were free of progression and in consequence free of new therapies at 2 years after salvage SBRT (re-EBRT).

Our excellent rates of GU and GI side effects confirm the good profile of toxicity reported also by other investigators in smaller series.[17,18,20,21,23,25] For example, Leroy et al[20] in a series of 23 patients treated with SBRT (36 Gy in 6 fractions) did not observe Grade 4 or 5 toxicity. Importantly, in our series no patient experienced urinary incontinence, a typical complication of other salvage local therapies. Urinary incontinence has been observed in a range of 35–65% for patients treated with salvage prostatectomy, 10–40% with HIFU, 10.4% with BRT and 3–19% with cryotherapy.[7,9,45,46] Salvage SBRT (re-EBRT), might be considered a valid tool in the armamentarium of local salvage approaches. Its noninvasive character represents a particular benefit in patients with contraindications to more invasive therapies, like surgery, cryoablation, HIFU or even BRT (advanced age, medical conditions including coagulopathy, severe obesity, anesthesia contraindications etc.).two-dimensional

The efficacy of salvage reirradiation for locally recurrent PCa has been evaluated by several investigations.[14–19,22–26,28–34] The first report on re-EBRT by Vavassori et al[15] including six cases treated by CyberKnife, showed the feasibility of reirradiation with an acceptable rate of acute and early chronic toxicity (median follow-up was 11.3 months). These preliminary findings were then confirmed by the successive series.[14,16–19,28–34] All but one report concluded that salvage re-EBRT is safe.[14–21,23–27] Zilli et al[22] published the data of 14 patients treated with whole prostate reirradiation, with the median follow-up of 94 months, showing low acute but very high late GU and GI toxicity rates (29% of patients experienced combined Grade 4 GU/GI injury). Contrarily to the Zilli's series, we observed only 1 Grade 3 GU event among 20 males with follow-up >36 months. This huge difference between observed toxicity profiles most probably results from differences in re-EBRT techniques. All our patients received salvage SBRT whereas in the report of Zilli et al. 71% of patients were retreated with 3D-CRT BRT boost. Moreover, the first RT course in the Zilli's series included two-dimensional irradiation in 30% of patients, probably with important exposure of rectum and urinary bladder to high doses. These findings underline the absolute necessity to use the best available techniques and extremely careful planning when reirradiation is considered. In our practice, we employ the dosimetric constraints based on the OAR doses in the first patients treated with CyberKnife re-EBRT for isolated local recurrence. [19]

Figure 1. (a) b-PFS rate, (b) c-PFS rate, (c)LC, (d) OS by BED <130 Gy (solid line) and BED ≥130 Gy (dashed line). BED,biologically effective dose; b-PFS, Biochemical progression free survival rate; c-PFS, Clinical progression free survival rate; LC, local control; OS, Overall survival.



The satisfactory toxicity profile in our series opens the question of dose escalation. Indeed, we observed a statistically significant difference for the biochemical progression free survival and clinical progression-free survival, as shown in the Kaplan–Meier curves. Since toxicity our series was very low despite the inclusion of numerous patients with comorbidities, we do believe that BED ≥130 Gy should be considered in all patients undergoing salvage SBRT (re-EBRT). Higher doses were employed by some investigators[15,17,20,21,23,24,26] still maintaining acceptable toxicity level and somehow higher tumor control when compared to our findings. We do believe that these somehow suboptimal tumor control might be explained both by inclusion of patients with aggressive disease (high PSA and Gleason score at the first diagnosis and at the diagnosis of recurrent cancer) and relatively low doses prescribed in our series. For example, in the series presented by Loi et al, 1-year biochemical relapse-free survival was 80%, comparable with 85% 1-year biochemical progression free survival rate in our series when BED ≥130 Gy was administered. Nonetheless, we have to considered that most our patients received a relatively low dose at the first course of RT (median dose of 70.2 Gy), while for patients recently treated in the dose escalation era with higher BED at first treatment, the safe dose of re-EBRT still have to be defined, especially for the risk of late rectal toxicity.[47]

The benefit of combined use of ADT in salvage local RT is not clear. Two recent randomized trials showed a progression-free survival and/or overall survival improvement when LHRHa or bicalutamide was added to salvage post-prostatectomy RT (the benefit was greater in case of more aggressive tumors and higher pre-salvage RT PSA).[48,49] However, no data are available for combined ADT and RT in the re-EBRT setting.[10,45,50] In our series, concomitant ADT was prescribed in 16 (25%) patients, this percentage being lower than in other series.[20,46] Whenever possible, exclusive local therapy was proposed, reserving ADT for future tumor progression. Ideally, local therapy should minimize the burden of systemic therapies and their side effects. Interestingly, lower tumor control was observed in patients treated with concomitant ADT, and this can be at least partially explained by the selection of patients in whom ADT was added to re-EBRT (*i.e.* high initial PSA, initial castration resistance etc.). Several questions, including addition of ADT and treated volume, must still be answered in local salvage therapy of PCa. A consensus on the salvage BRT has been recently published in order to help clinicians managing intraprostatic recurrence.[13] Consensus for salvage EBRT still needs to be undertaken.

CONCLUSION

Salvage SBRT (Re-EBRT), is a safe, feasible and noninvasive salvage treatment for the locally recurrent PCa, offering

Table 5. Acute and late toxicity. Genito-urinary and gastro-intestinal toxicity is presented for all patients and for prostate and prostate-bed subgroups. Statistical analysis is performed with Chi-square test

Acute toxicity (available in 64 patients)								
	All patients		**GU**			**GI**		
Grade	**GU**	**GI**	**Prostate**	**Prostate bed**	***p*-value**	**Prostate**	**Prostate bed**	***p*-value**
G0	46 (72%)	58 (90%)	31 (69%)	15 (79%)	0.41	42 (93.5%)	16 (84%)	0.25
G1	13 (20%)	5 (8%)	11 (24.5%)	2 (11%)	0.21	2 (4.5%)	3 (16%)	0.12
G2	3 (5%)	1 (2%)	2 (4.5%)	1 (5%)	0.88	1 (2%)	0	–
G3	1 (1.5%)	0	1 (2%)	0	–	0	0	–
NE	1[a] (1.5%)	0	0	1 (5%)	–	0	0	–
Total patients	64	64	45	19		45	19	
Late toxicity (available in 62 patients)								
Grade	**All patients**		**GU**			**GI**		
	GU	**Prostate**	**Prostate**	**Prostate bed**	***p*-value**	**Prostate**	**Prostate bed**	***p*-value**
G0	36 (57%)	57 (89.5%)	24 (54%)	12 (63%)	0.47	41 (91%)	16 (84.1%)	0.42
G1	18 (28%)	4 (6%)	18 (40%)	0	–	3 (7%)	1 (5.3%)	0.73
G2	6 (9%)	1 (1.5%)	1 (2%)	5 (26.4%)	0.002	0	1 (5.3%)	–
G3	1 (1.5%)	0	1 (2%)	0	–	0.	0	–
NE	1[a] (1.5%)	0	0	1 (5.3%)	–	0	0	–
Missing data	2 (3%)	2 (3%)	1 (2%)	1 (5.3%)	0.41	1 (2%)	1 (5.3%)	
Total patients	64	64	45	19		45	19	

GI, gastrointestinal; GU, genitourinary; NE, Not evaluable;

Genitourinary and gastrointestinal toxicity is presented for all patients and for prostate and prostate-bed subgroups. Statistical analysis is performed with χ^2 test.

[a]toxicity not evaluable in one patient with urinary catheter positioned before reirradiation.

a satisfactory tumor control and excellent toxicity profile, if BED ≥130 Gy is administered. Further prospective studies are warranted to define the optimal patient selection and establish the optimal dose and volume parameters for this particular clinical scenario.

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CONFLICT OF INTEREST

The authors whose names are listed above certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants;participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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