Reports of Practical Oncology and Radiotherapy 25 (2020) 157–162

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

Helical tomotherapy re-irradiation for patients affected by local radiorecurrent prostate cancer

Cristina Mariucci[a], Gianluca Ingrosso[a,*], Vittorio Bini[b], Simonetta Saldi[c], Marco Lupattelli[c], Alessandro Frattegiani[c], Elisabetta Perrucci[c], Isabella Palumbo[a], Lorenzo Falcinelli[c], Giuseppe Centofanti[a], Rita Bellavita[b], Cynthia Aristei[a]

[a] Radiation Oncology Section, Department of Surgical and Biomedical Science, University of Perugia, Italy
[b] Internal Medicine, Endocrine and Metabolic Science Section, University of Perugia, Italy
[c] Radiation Oncology Section, Perugia General Hospital, Italy

ARTICLE INFO

Article history:
Received 1 July 2019
Received in revised form 3 December 2019
Accepted 20 January 2020
Available online 22 January 2020

Keywords:
Radiorecurrent prostate cancer
Re-treatment
Helical tomotherapy
Toxicity

ABSTRACT

Background: Salvage re-irradiation in patients affected by radiorecurrent prostate cancer might be a valid as well as challenging treatment option. The aim of this study was to evaluate feasibility and toxicity of salvage external beam radiotherapy (EBRT) re-treatment in patients affected by radiorecurrent prostate cancer within the prostate gland or the prostate bed.
Materials and Methods: 15 patients underwent EBRT re-treatment using helical tomotherapy (HT), with daily Megavolt computed tomography image-guidance. We registered toxicity according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Biochemical relapse was defined as a PSA increase > 20% compared with the pre-EBRT re-treatment value. Survival curves were calculated using the Kaplan-Meier method.
Results: All patients received a total dose of 50 Gy (25 × 2 Gy), and 7 (46.6%) had concomitant androgen deprivation therapy (median duration of 12 months). With a median follow-up of 40.9 months, the 2-year and 4-year biochemical relapse-free survival were 55% and 35%, respectively. Acute and late genito-urinary (GU) toxicity ≥2 were recorded in 4 (26.6%) and 5 (33.3%) patients, respectively, and the 4-year late GU toxicity was 30%. Acute gastrointestinal toxicity ≥2 was recorded in 2 (13.3%) cases, whereas no patient experienced late toxicity.
Conclusions: Despite the inherent bias of a retrospective analysis, our long-term results showed a low toxicity profile with a relatively low rate of biochemical control for HT re-treatment in patients affected by local radiorecurrent prostate cancer. Prospective trials are needed to investigate the role of EBRT in this setting.

1. Introduction

Biochemical recurrence after primary radiotherapy (RT) for localized prostate cancer (Pca) occurs within 5 years from the treatment in about 25–30% of the cases.[1–3] It is defined as a rise by 2 ng/ml or more above the prostate specific antigen nadir (nPSA).[4] Patients affected by only intra-prostatic relapse after primary RT can be managed with salvage radical prostatectomy (SRP), obtaining a biochemical recurrence-free survival ranging between 47 and 82% at 5 years but with complications impairing quality of life, such as urethral anastomotic stricture and incontinence, in up to 40% of the cases.[5] Salvage re-irradiation might be a valid as well as challenging treatment option,[6–8] and brachytherapy is the most used RT modality in such setting.[8–10] Some experiences of external beam radiotherapy (EBRT) have been reported, with different techniques and different results in term of toxicity,[11,6,12] not only in the re-treatment of intra-prostatic disease but also of radio-recurrent disease within the prostate bed.[13–15] It is to say that only about 20% of radio-recurrent Pca patients undergo local salvage therapy, whereas androgen deprivation therapy (ADT) and observation are currently the most frequent treatment options.[16]

The aim of the present study was to evaluate feasibility and toxicity of salvage EBRT re-treatment in patients affected by radiorecurrent Pca within the prostate gland or the prostate bed. More specifically, biochemical control and long-term toxicity,

* Corresponding author.
E-mail addresses: gianluca.ingrosso@unipg.it, gianluca.ingrosso@libero.it (G. Ingrosso).

https://doi.org/10.1016/j.rpor.2020.01.005
1507-1367/

Table 1
Patients and treatment features at first diagnosis (n = 15).

	Median (IQR)	IQR	Number (%)
Age (y)	67.7	65–71	
PSA (ng/ml)	12.28	10.4–43.9	
Gleason score			
≤ 6			4 (26.6)
7			6 (40)
≥ 8			2 (13.3)
Unknown			3 (20)
cT-stage			
T1c			2 (13.3)
T2a			1 (6.6)
T2b			1 (6.6)
T2c			3 (20)
T3a			1 (6.6)
T3b			1 (6.6)
pT-stage			
pT2a, R1			1 (6.6)
pT2c, R1			2 (13.3)
pT3a			1 (6.6)
Unknown			2 (13.3)
Risk class			
Intermediate			10 (66.6)
High			5 (33.3)
Radical EBRT			9 (60)
Post-operative EBRT			6 (40)
Radical EBRT (Gy)	70	70–74	
Post-operative EBRT (Gy)	70	70–70.15	
PSA nadir (ng/ml)	0.07	0.02–0.41	
Time from EBRT to salvage therapy (months)	120	93–148	

after helical tomotherapy (HT) intensity-modulated radiation therapy (IMRT) with volumetric image-guidance (Megavolt computed tomography) were analyzed.

2. Material and methods

Between December 2012 and November 2018, 15 patients affected by radiorecurrent Pca underwent EBRT re-treatment using HT, in our Department. At the first diagnosis of localized Pca, 9 patients underwent radical EBRT and 6 radical prostatectomy followed by post-operative EBRT. Median age at first diagnosis was 67.7 years (IQR, 65–71) and the median PSA level was 12.28 ng/ml (IQR, 10.4–43.9). Six patients (40%) had a Gleason score 7, and ten (66.7%) were in the intermediate risk class (Table 1). All patients underwent three-dimensional conformal radiotherapy (3DCRT). The median total dose was 70 Gy in the radical (IQR, 70–74 Gy) and in the post-operative (IQR, 70–70.15 Gy) setting, with a daily fractionation of 2 Gy. The PSA nadir after the treatment for localized prostate cancer was 0.07 ng/ml (IQR, 0.02–0.41). The median time from the end of the first EBRT treatment to the diagnosis of radiorecurrence was 120 months (IQR, 93–148). At the time of biochemical recurrence, all patients underwent choline-PET and multiparametric MRI (mp-MRI) to assess local recurrence and exclude distant metastases. The intra-prostatic recurrence was defined by the presence of choline-PET and/or MRI findings within the irradiated gland. The radiorecurrence within the prostate bed was based on the detection of a macroscopic lesion on choline-PET and/or MRI. No patient had confirmatory biopsy. For every patient, we reviewed the first EBRT plan and evaluated the occurrence of late toxicity in order to decide for EBRT re-treatment. Regarding the re-treatment planning, all patients underwent CT (2.5 mm slice thickness) in supine position in empty rectum and comfortably full bladder condition. We used knee fix and foot fix (Combifix®, CIVCO Medical Solutions, Orange City, IA, USA) for immobilization, and performed an urethrography before the CT scan, to better identify the apex of prostatic gland or vescico-urethral anastomosis. CT images were transferred to a treatment planning system (Pinnacle®; Philips, Fitchburg, WI, USA) to delineate the clinical target volume (CTV), that encompassed the whole prostate (for intra-prostatic radiorecurrent cancer) or the radiorecurrent lesion within the prostate bed (for patients who received radical prostatectomy and post-operative radiotherapy at first treatment). Organs at risks (OARs) were rectum, bladder, penile bulb and femoral heads. Treatment plans were delivered by HT (helical slice 6 MV photon beam), with a field width of 1 or 2.5 cm, a pitch value of 0.287 and a modulation factor ranging from 1.8 to 3. A total dose of 50 Gy (2 Gy × 25) was prescribed. A criterion of 95% of the target volume receiving 95% of prescribed dose was satisfied for all plans.

Megavoltage CT was performed before the daily treatment session, to correct patient setup (according to bone and soft tissue anatomy) and to take into account inter-fraction variability. Median duration of a single daily treatment was 211.15 seconds (IQR, 180–245). Patients were monitored weekly during re-treatment for acute side effects and every 3 months afterward. Toxicity was registered according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Acute (within 90 days from the start of radiotherapy) and late (>90 days from the start of radiotherapy) genito-urinary (GU) and gastro-intestinal (GI) toxicities were analyzed. Biochemical relapse was defined as a PSA increase >20% compared with pre-EBRT re-treatment value.[6,12]

Regarding dosimetric data, we recorded EBRT re-treatment maximum and mean doses to the OARs, and the cumulative maximum and mean doses derived from the 2 plans, the one at primary treatment and the one at radiorecurrence. More specifically, we calculated cumulative doses assuming that every patient received from each treatment the corresponding mean and maximum dose on the same sub-volume of the OAR.

Survival curves were calculated using the Kaplan–Meier product-limit method, followed by log-rank test to evaluate differences in expected event probability between groups. The Cox proportional hazard regression model was used for multivariate analysis. Statistical significance was set at $p \leq 0.05$. All calculations were carried out with IBM-SPSS® version 25.0 (IBM Corp., Armonk, NY, USA, 2017).

3. Results

Median age at re-treatment was 79.5 years (IQR 74–81), median PSA value was 4.6 ng/ml (IQR 2.8–8.7). Patients received a total dose of 50 Gy (25 × 2 Gy), and 7 (46.6%) had concomitant ADT, with a median ADT duration of 12 months (IQR, 9–12). The median follow-up after EBRT re-treatment was 40.9 months (IQR, 35–51) (Table 2). At the time of analysis, of the 6 (40%) patients in biochemical control two were dead from other cause (1 patient from bladder cancer, and 1 from ischemic heart disease). The 2-year biochemical relapse-free survival (b-RFS) was 55% (Fig. 1a). The median PSA nadir (nPSA) after EBRT re-treatment was 0.63 ng/ml (IQR, 0.2–1.05). At the time of the analysis, of the nine (60%) patients in biochemical failure, 5 were in biochemical progression without evidence of disease. Two patients had lymph node metastases (1 patient 2 pelvic nodes treated with pelvic EBRT, and 1 patient lombo-aortic nodes treated with intermittent ADT) and 2 patients had bone metastases (low volume of disease, treated with ADT + EBRT). We performed the Kaplan-Meier analysis splitting intra-prostatic radiorecurrent patients from prostate bed radiorecurrent patients, with no differences in biochemical control rates between the two settings (Fig. 1b).

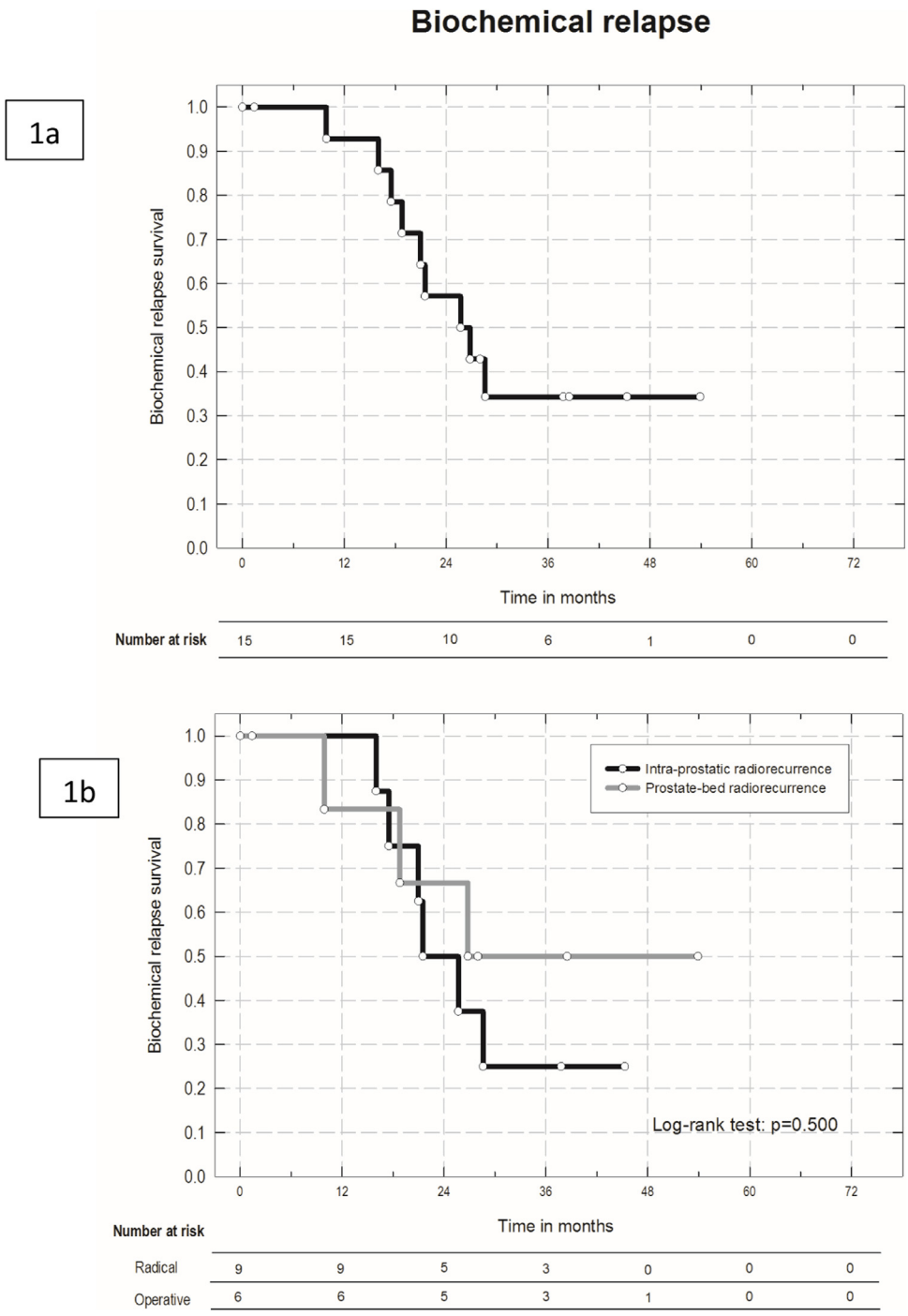

Fig. 1. Biochemical relapse-free survival (b-RFS) for the whole cohort (1a), and splitting intra-prostatic radiorecurrent patients from prostate bed radiorecurrent patients (1b).

Toxicity data are shown in Table 2 and 3. Acute and late GU toxicity ≥ 2 were recorded in 4 (26.6%) and 5 (33.3%) patients, respectively (Table 3). More specifically, regarding late GU toxicity we recorded grade 2 hematuria in 3 (26.6%) patients (one occurring at 70 months from the end of re-treatment), and grade 3 obstruction/retention in 2 patients (Table 2). Acute GI toxicity ≥ 2 was recorded in 2 (13.3%) cases, whereas no patient experienced late toxicity. The 2-year late GU toxicity was 30% (Fig. 2a), which remained stable at 4 years. We performed the Kaplan–Meier analysis splitting intra-prostatic radiorecurrent patients from prostate bed radiorecurrent patients, with no differences in terms of late GU toxicity between the two settings (Fig. 2b). Regarding rectum and bladder dosimetric data of EBRT re-treatment and cumulative doses, we reported maximum and mean values on Table 4. At univariate analysis, late grade ≥2 GU toxicity was not correlated with cumulative maximum and mean dose to the bladder for the whole cohort ($p = 0.22$ and $p = 0.46$, respectively). In separate Cox multivariate regression models, we analyzed the correlation between late grade ≥2 GU toxicity and cumulative maximum and mean dose to the bladder adjusted for the two settings (intra-prostatic recurrence and prostate bed recurrence) finding no significance ($p = 0.18$ and $p = 0.81$, respectively).

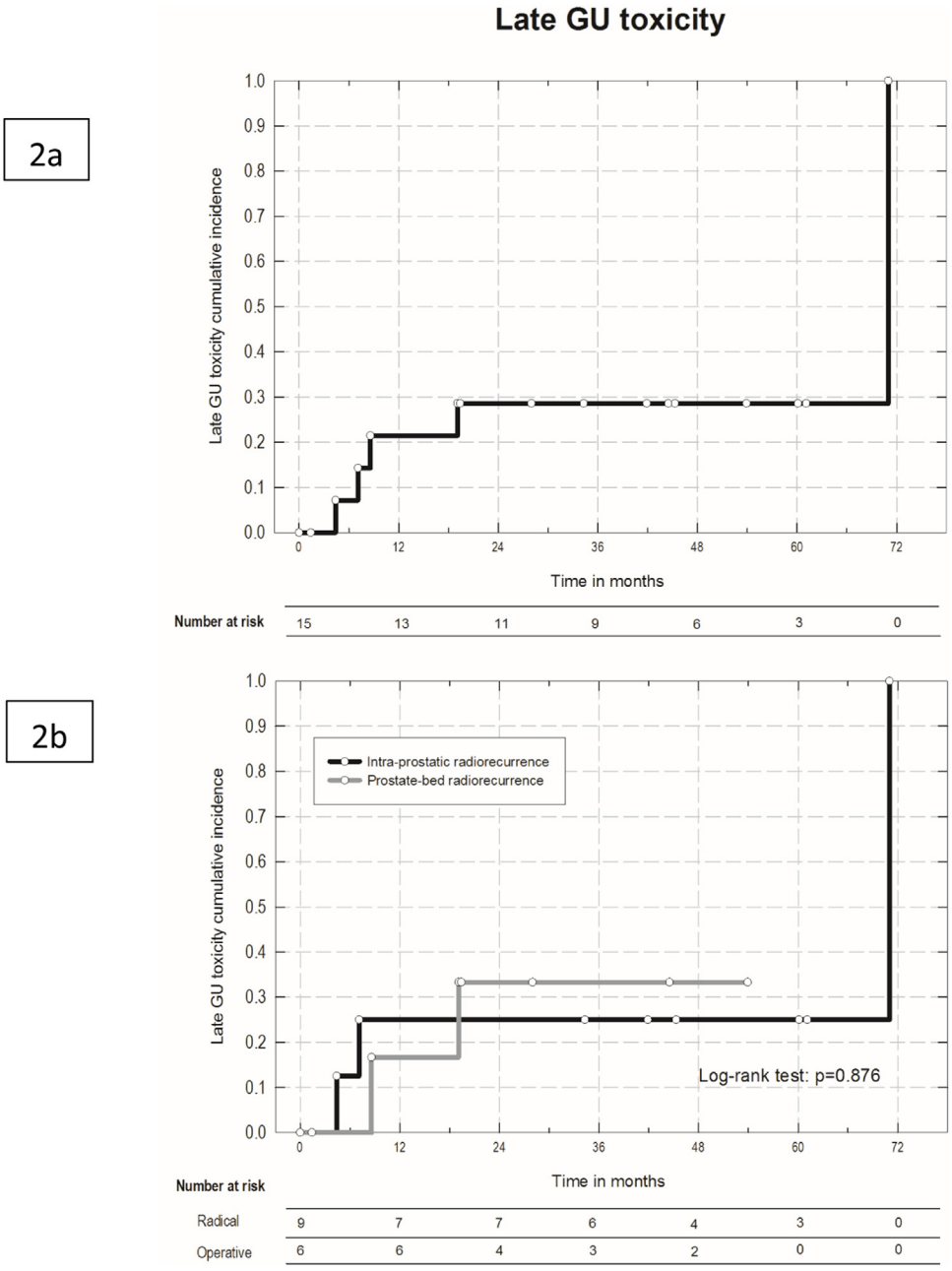

Fig. 2. Actuarial late grade ≥2 toxicity for the whole cohort (2a), and splitting intra-prostatic radiorecurrent patients from prostate bed radiorecurrent patients (2b).

4. Discussion

Radiorecurrent Pca is a potentially curable disease frequently managed with indiscriminate ADT, which may have a negative impact on quality of life (e.g. increased risk of metabolic syndrome and cardiovascular events) in patients who still could receive a local salvage therapy.[17] Local assessment of radiorecurrence and systemic staging have a crucial role in the definition of a truly localized recurrence, in order to offer the personalized local treatment. Multiparametric magnetic resonance imaging (mp-MRI)[18] and nuclear medicine imaging (e.g. choline-PET, fluciclovine-PET and, more recently, 68Ga-PSMA PET)[19,20] have shown great efficacy in the detection of disease, even at low PSA levels.[21]

To our knowledge, this series is the first in the literature reporting long-term results after HT re-irradiation with conventional fractionation for patients affected by radiorecurrent Pca within the prostate gland or the prostate bed. With a median follow-up of 40.9 months, for the whole cohort we had a 2-year and 4-year b-RFS of 55% and 35%, respectively (Fig. 1a). Delivering a total dose of 50 Gy (2 Gy × 25) to the target volume, we obtained the same rate of b-RFS as reported by other authors.[11,22] For instance, in the study with the longest follow-up (94 months) after EBRT re-irradiation, Zilli et al.[11] reported in 14 patients a 5-year b-RFS of 34%, similar to our findings. Data in literature show that salvage radical prostatectomy (SRP) after RT yields to a biochemical recurrence-free survival ranging between 47 and 82% at 5 years.[5] Regarding non-surgical salvage local therapies, pooled results from a recent systematic review showed an overall rate of biochemical control of 69% in patients re-treated with EBRT, which was delivered mainly with stereotactic body radiotherapy (SBRT) technique using extreme hypofractionation.[23] Studies on SBRT showed high rates of b-RFS at 1 year, ranging from 70% to 80%, but long-term

Table 2
Patients' features at local relapse and after EBRT re-treatment (n = 15).

	Median	IQR	Number (%)
Age (y)	79.5	74–81	
PSA (ng/ml)	4.6	2.8–8.7	
Imaging for local relapse and staging			
MRI			15 (100)
Choline-PET			15 (100)
Total dose at radiotherapy re-treatment (Gy)	50	50	
Concomitant androgen deprivation therapy			
Yes			7 (46.6)
No			8 (53.4)
Androgen deprivation therapy duration (months)	12	9–12	
Follow-up (months)	40.9	35–51	
PSA nadir (ng/ml)	0.63	0.2–1.05	
Biochemical control			
Yes			6 (40)
No			9 (60)
Toxicity scale CTCAE v4.0			
Late toxicity			
Incontinence			2 (13.3); G1 in 2 pts
Hematuria			4 (26.6); G1 in 1 pt; G2 in 3 pts
Obstruction/retention			2 (13.3); G3 in 2 pts
Proctitis			1 (6.6); G1 in 1 pt

Table 3
CTCAE v4.0 toxicity (15 patients).

	Genito-urinary		Gastro-intestinal	
	Acute (%)	Late (%)	Acute (%)	Late (%)
G0	7 (46.6)	7 (46.6)	12 (80)	14 (93.4)
G1	4 (26.6)	3 (20)	1 (6.6)	1 (6.6)
G2	4 (26.6)	3 (20)	2 (13.3)	0 (0)
G3	0 (0)	2 (13.3)	0 (0)	0 (0)

Table 4
Dosimetric features of re-irradiation and cumulative doses to OARs (n = 15).

	Median	IQR
Planning target volume (cm^3)	29.16	15.18–50.32
PTV mean dose (Gy)	49.85	47.8–49.95
Rectum		
Maximum dose (Gy)	44.86	38.80-47.68
Mean dose (Gy)	8.48	4.70–10.13
Maximum cumulative dose (Gy)	114.86	111.30–118.15
Mean cumulative dose (Gy)	46.60	44.15–62.55
Bladder		
Maximum dose (Gy)	48.58	39.70–51.08
Mean dose (Gy)	1.38	0.73–2.28
Maximum cumulative dose (Gy)	119.33	114.16–121.03
Mean cumulative dose (Gy)	59.46	48.09–62.16

results are lacking.[7,12] To date few studies have been published about EBRT re-treatment in the prostate radio-recurrent setting, and there is a growing interest in this treatment modality, which could be a valid option because of its efficacy and good toxicity profile, although some series have been reported showing a high rate of late GU and GI toxicity.[11] In fact, in the study by Zilli et al.,[11] the 5-year probability of grade ≥2 GU and grade ≥2 GI toxicity were 58.3% and 71.4%, respectively. It is to say that the majority of the patients received prostate re-irradiation with 3-dimensional conformal RT techniques, which could explain the high rates of toxicity reported. Cutting-edge technologies, such as SBRT, volumetric modulated arc therapy (VMAT) and image-guidance might help improving the role of EBRT in the local recurrence setting. Loi et al.[13] have recently published a retrospective series of 50 patients affected by intra-prostatic or prostate bed recurrence, treated with SBRT to a total dose of 30 Gy in 5 fractions. With a median follow-up of 21.3 months, late grade ≥ 2 GU toxicity was observed in 4 (8%) patients and late grade ≥2 GI toxicity in 2 (4%) patients. Jereczek-Fossa et al.[6] re-treated 19 patients (15 on the whole-prostate and 4 on the prostate bed for peri-anastomotic recurrence) with SBRT, reporting a late grade ≥2 GU and GI toxicity of 10.5% (2 patients) and of 5.2% (1 patient), respectively. In our series, we reported late grade ≥2 GU toxicity in 5 (33.3%) patients, whereas no patient developed late grade ≥2 GI toxicity. Despite the inherent bias of a retrospective analysis, our long-term results showed a low toxicity profile with a relatively low rate of biochemical control for HT radiotherapy in the local radiorecurrent setting. Our data, which are hypothesis generating, seem to confirm the feasibility and safety of prostate EBRT re-treatment, and the relatively poor impact on long-term biochemical control might be related to the total dose delivered to the tumor, which might be insufficient for the cure of radiorecurrent prostate cancer. Short-term outcome from retrospective series on ablative SBRT seems to be promising in terms of outcome and toxicity.[6,7,12] However, data are sparse with differences in terms of treatment technique and schedule, and length of follow-up. Prospective trials are needed to investigate the role of EBRT for the re-treatment of radiorecurrent prostate cancer.

Conflict of interest

None declared.

Financial disclosure statement
None declared.

Compliance with ethical standards

On behalf of all Authors, the Corresponding Author states that the work is compliant with Ethical Standards and that there is no conflict of interest.

Ethical approval for retrospective study

We performed this retrospective analysis complying with the specific requirements of Italy. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee (SMM-Perugia General Hospital) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards."

Informed consent

Informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

References

1. Peeters ST, Heemsbergen WD, Koper PC, et al. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol*. 2006;24:1990–1996.
2. Dearnaley DP, Sydes MR, Graham JD, et al. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol*. 2007;8:475–487.

3. Beckendorf V, Guerif S, Le Prisé E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys*. 2011;80:1056–1063.
4. Roach 3rd M, Hanks G, Thames Jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix consensus Conference. *Int J Radiat Oncol Biol Phys*. 2006;65:965–974.
5. Chade DC, Eastham J, Graefen M, et al. Cancer control and functional outcomes of salvage radical prostatectomy for radiation-recurrent prostate cancer: a systematic review of the literature. *Eur Urol*. 2012;61:961–971.
6. Jereczek-Fossa BA, Beltramo G, Fariselli L, et al. Robotic image-guided stereotactic radiotherapy, for isolated recurrent primary, lymph node or metastatic prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82:889–897.
7. Janoray G, Reynaud-Bougnoux A, Ruffier-Loubière A, et al. Stereotactic body re-irradiation therapy for locally recurrent prostate cancer after external-beam radiation therapy: initial report. *Cancer Radiother*. 2016;20:275–281.
8. Barbera F, Triggiani L, Buglione M, et al. Salvage low dose rate brachytherapy for recurrent prostate cancer after external beam radiotherapy: results from a single institution with focus on toxicity and functional outcomes. *Clin Med Insights Oncol*. 2017;11:1–6.
9. Kollmeier MA, McBride S, Taggar A, et al. Salvage brachytherapy for recurrent prostate cancer after definitive radiation therapy: a comparison of low-dose-rate and high-dose-rate brachytherapy and the importance of prostate-specific antigen doubling time. *Brachytherapy*. 2017;16:1091–1098.
10. Maenhout M, Peters M, van Vulpen M, et al. Focal MRI-guided salvage high-dose-rate brachytherapy in patients with radiorecurrent prostate Cancer. *Technol Cancer Res Treat*. 2017;16:1194–1201.
11. Zilli T, Benz E, Dipasquale G, et al. Reirradiation of prostate cancer local failures after previous curative radiation therapy: long-term outcome and tolerance. *Int J Radiat Oncol Biol Phys*. 2016;96:318–322.
12. Mbeutcha A, Chauveinc L, Bondiau PY, et al. Salvage prostate re-irradiation using high-dose-rate brachytherapy or focal stereotactic body radiotherapy for local recurrence after definitive radiation therapy. *Radiat Oncol*. 2017;12:49.
13. Loi M, Di Cataldo V, Simontacchi G, et al. Robotic stereotactic retreatment for biochemical control in previously irradiated patients affected by recurrent prostate cancer. *Clin Oncol (R Coll Radiol)*. 2018;30:93–100.
14. Detti B, Bonomo P, Masi L, et al. Stereotactic radiotherapy for isolated nodal recurrence of prostate cancer. *World J Urol*. 2015;33:1197–1203.
15. Créhange G, Roach 3rd M, Martin E, et al. Salvage reirradiation for locoregional failure after radiation therapy for prostate cancer: who, when, where and how? *Cancer Radiother*. 2014;18:524–534.
16. Cooperberg MR, Vickers AJ, Broering JM, et al. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. *Cancer*. 2010;116:5226–5234.
17. Jones JS. Radiorecurrent prostate cancer: an emerging and largely mismanaged epidemic. *Eur Urol*. 2011;60:411–412.
18. Abd-Alazeez M, Ramachandran N, Dikaios N, et al. Multiparametric MRI for detection of radiorecurrent prostate cancer: added value of apparent diffusion coefficient maps and dynamic contrast-enhanced images. *Prostate Cancer Prostatic Dis*. 2015;18:128–136.
19. Evans JD, Jethwa KR, Ost P, et al. Prostate cancer-specific PET radiotracers: a review on the clinical utility in recurrent disease. *Pract Radiat Oncol*. 2018;8:28–39.
20. Afshar-Oromieh A, Haberkorn U, Schlemmer HP, et al. Comparison of PET/CT and PET/MRI hybrid systems using a 68Ga-labelled PSMA ligand for the diagnosis of recurrent prostate cancer: initial experience. *Eur J Nucl Med Mol Imaging*. 2014;41:887–897.
21. Buergy D, Sertdemir M, Weidner A, et al. Detection of local recurrence with 3-Tesla MRI after radical prostatectomy: a useful method for radiation treatment planning? *In Vivo*. 2018;32:125–131.
22. Leroy T, Lacornerie T, Bogart E, et al. Salvage robotic SBRT for local prostate cancer recurrence after radiotherapy: preliminary results of the Oscar Lambret center. *Radiat Oncol*. 2017;12:95.
23. Ingrosso G, Becherini C, Lancia A, et al. Nonsurgical salvage local therapies for radiorecurrent prostate cancer: a systematic review and meta-analysis. *Eur Urol Oncol*. 2019 [Epub ahead of print].