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FULL PAPER

Salvage image-guided intensity modulated or stereotactic body reirradiation of local recurrence of prostate cancer

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Objective: To retrospectively evaluate external beam re-irradiation (re-EBRT) delivered to the prostate/prostatic bed for local recurrence, after radical or adjuvant/salvage radiotherapy (RT).
Methods: 32 patients received re-EBRT between February 2008 and October 2013. All patients had clinical/radiological local relapse in the prostate or prostatic bed and no distant metastasis. re-EBRT was delivered with selective RT technologies [stereotactic RT including CyberKnife™ (Accuray, Sunnyvale, CA); image-guidance and intensity-modulated RT etc.]. Toxicity was evaluated using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria. Biochemical control was assessed according to the Phoenix definition (NADIR + 2 ng ml^{-1}).
Results: Acute urinary toxicity: G0, 24 patients; G1, 6 patients; G2, 2 patients. Acute rectal toxicity: G0, 28 patients; G1, 2 patients; and G2, 1 patient. Late urinary toxicity (evaluated in 30 cases): G0, 23 patients; G1, 6 patients; G2, 1 patient. Late renal toxicity: G0, 25 patients; G1, 5 patients. A mean follow-up of 21.3 months after re-EBRT showed that 13 patients were free of cancer, 3 were alive with biochemical relapse and 12 patients were alive with clinically evident disease. Four patients had died: two of disease progression and two of other causes.
Conclusion: re-EBRT using modern technology is a feasible approach for local prostate cancer recurrence offering 2-year tumour control in about half of the patients. Toxicity of re-EBRT is low. Future studies are needed to identify the patients who would benefit most from this treatment.
Advances in knowledge: Our series, based on experience in one hospital alone, shows that re-EBRT for local relapse of prostate cancer is feasible and offers a 2-year cure in about half of the patients.

Modern external beam irradiation (EBRT) is considered a cornerstone of the radical treatment of localized prostate cancer. Technological advances have been progressively introduced, using highly conformed techniques and dose escalation. In spite of this, the rate of biochemical failure ranges between 33% and 69%.[1–4] New imaging modalities such as ^{11}C-choline positron emission tomography/CT (PET/CT) or multiparametric MRI (mpMRI) are now able to detect clinically evident disease with a rate up to 75% for ^{11}C-choline-PET/CT at a prostate specific antigen (PSA) value >3 ng ml^{-1}.[5] In up to 50% of patients with PET/CT-positive scans, isolated local relapse is diagnosed.[5]

In the case of solid tumours, the approach to isolated local relapse is local treatment [surgery, radiotherapy (RT) etc.], whenever possible, and systemic therapy is rarely used. Paradoxically, in the case of prostate cancer local relapse, systemic androgen deprivation therapy (ADT) is the standard-of-care approach [National Comprehensive Cancer Network (NCCN) guidelines].[6] Such treatment has a mainly palliative intent and is continued life long, giving rise to numerous side effects, deterioration in the quality of life and high social costs.

According to the NCCN guidelines, a local approach including surgery, cryotherapy or brachytherapy should be considered for patients candidated for local salvage treatment: patients with documented recurrent local disease of limited aggressiveness (low Gleason score, stage and initial PSA), a long time interval between primary EBRT and recurrence and a slow PSA evolution. Indeed, in this clinical scenario, effective local

Table 1. Patient characteristics ($N = 32$ patients)

Characteristics	All patients, $N = 32$
Age (years), at the re-EBRT	
Mean ± standard deviation	73 ± 5.96
Median (range)	73 (60–83)
Initial PSA (ng ml^{-1})*	$n = 31$
Initial PSA (unknown)	$n = 1$
Median (range)	15 (4.5–110.0)
Initial Gleason score*	$N = 29$
Initial Gleason score (unknown)	$N = 3$
Median (range)	6 (4–9)
Initial disease category (National Comprehensive Cancer Network)[6]	$N = 22$[a]
Low	5
Intermediate	7
High	9
Unknown	1
Initial treatment	
RT ± ADT	10
Radical retropubic prostatectomy ± lymphadenectomy ± ADT ± RT	22
Interval between diagnosis of prostate cancer and re-EBRT	
Mean (months) (range)	115 (33–182)
Former radiotherapy	
External beam radiotherapy	29
Brachytherapy	3

ADT, androgen deprivation therapy; PSA, prostate specific antigen; re-EBRT, external beam reirradiation; RT, radiotherapy.
*Data are available only for this number of patients and not for the 32 patients analysed.
[a]Operated patients excluded.

therapy appears a more convenient strategy for controlling local disease, and it reduces the burden of systemic therapy. Radical salvage surgery is rarely used in this situation although recent studies suggest that it is more effective than other salvage treatment modalities, such as cryotherapy, high-intensity focus ultrasound (HIFU) or brachytherapy, in terms of biochemical control.[7] The disadvantage of salvage surgery includes the risk of severe perioperative and post-operative complications owing to previous therapies and the advanced age of the patients (comorbidities). Brachytherapy might be an option for some patients, however low-dose-rate (LDR) brachytherapy requires general anaesthesia and hospitalization. It is important to note that modern technologies with image-guided intensity-modulated RT (IG-IMRT) or stereotactic body RT (SBRT) allow for the precise delivery of high radiation doses. Several dosimetric planning studies confirm that the target dose distribution might be similar between high-dose-rate brachytherapy and non-invasive EBRT, such as CyberKnife™ (Accuray, Sunnyvale, CA).[8,9] Ablative hypofractionation regimens are commonly chosen for high-precision RT, which may increase the chance of killing prostate cancer cells, owing to their low alpha/beta ratio. Recently, several reports on stereotactic prostate reirradiation have been published: Vavassori et al[10] reported the preliminary results on six patients treated with Cyberknife SBRT (30 Gy in five fractions over five consecutive days). This study was later updated by Jereczek-Fossa et al:[11] complete response was obtained in six out of nine patients (without any systemic therapy) with a low toxicity profile (no rectal toxicity and few urinary events). The pattern of failure was predominantly out of field (four out of five events). The authors concluded that CyberKnife reirradiation is a feasible and safe approach and offers excellent in-field tumour control.

On this basis, we present a retrospective analysis of the series of patients who underwent salvage re-EBRT using highly selective modalities (IG-IMRT or SBRT) for local recurrence after radical or post-prostatectomy/salvage RT.

METHODS AND MATERIALS

Study protocol

The inclusion criteria for this retrospective study were as follows: (1) isolated local recurrence of prostate cancer after radical or post-prostatectomy RT, (2) salvage re-EBRT performed in the Radiotherapy Department of the European Institute of Oncology, Milan, Italy, between February 2008 and October 2013, (3)

Table 2. Patient and external beam re-irradiation (re-EBRT) characteristics ($N = 32$ patients)

Characteristics	Prostate, $n = 22$	Prostate bed, $n = 10$
Pre re-EBRT PSA (ng ml^{-1})		
Median (range)	3.9 (0.8–16.9)	2.3 (0.7–51.8)
Biopsy of the target lesion		
Yes	13	6
No	8	4
Unknown	1	0
ADT added to re-EBRT		
Yes	8	3
Type of ADT added to radiotherapy		
Complete androgen blockade	3	2
Luteinizing hormone releasing factor alone	2	1
Antiandrogen alone[a]	3	0
re-EBRT data		
Median total dose (Gy)	25 (25–30)	25 (15–25)
Dose/fraction	5 (3–6)	5
Number of fractions	5 (5–10)	5 (3–5)
Mean overall re-EBRT duration (days)	10	9
Median (days)	10	9

ADT, androgen deprivation therapy; PSA, prostate specific antigen.
[a]Bicalutamide.

Table 3. Treatment outcome ($N = 32$)

Outcome	Prostate, $n = 22$	Prostate bed, $n = 10$
Acute toxicity of re-EBRT		
Urinary toxicity[a]	7	1
G1	5	1
G2	2	0
Rectal toxicity[a]	3	1
G1	3	0
G2	0	1
Late toxicity of re-EBRT		
Urinary toxicity[a]	6	1
G1	6	0
G2	0	1
Not available (two patients)[b]		
Rectal toxicity[a]	4	1
G1	4	1
Not available (two patients)[b]		
Status at the last observation (September 2014)		
No evidence of disease	13	
Alive with disease	15	
Biochemical relapse	3	
Clinical local relapse	4	
Clinical locoregional relapse	1	
Clinical metastatic relapse	7	
Dead	4	
Metastatic disease	2	
Other tumour	1	
Other cause	1	

re-EBRT, external beam re-irradiation.
[a]According to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria.[12]
[b]Death of the patients before late toxicity check-point.

minimum follow-up of 12 months and (4) written consent for re-EBRT and for the use of clinical data for scientific or educational purposes (anonymously). No other local therapy (surgery, cryotherapy, HIFU etc.) for the recurrent lesion was permitted.

Radiotherapy procedures

The first RT course included three-dimensional conformal RT (3D-CRT) to 29 patients to a median dose of 74 Gy (range, 50–80 Gy). Three patients received an LDR brachytherapy implant to a dose of 145 Gy.

The re-EBRT technique was developed in the Radiotherapy Department of the European Institute of Oncology, Milan, Italy. First, image-guided 3D-CRT (IG-3D-CRT) was used: up to December 2010, our standard treatment technique (i) consisted of a three-dimensional conformal dynamic arc therapy with two lateral arcs of 100° compass (220°–320° and 40°–140°). Treatment was performed using three different modalities: the 15-MV X-ray beam generated by our Saturno 43 (General Electric Medical Systems) and equipped with the Elekta (Stockholm, Sweden) micro-multileaf collimator (μMLC); the 6-MV X-ray beam generated by a Clinac® 600 (Varian® Medical Systems, Palo Alto, CA) and equipped with the M3® (BrainLab AG, Feldkirchken, Germany) μMLC; the 18-MV X-ray beam generated by a Clinac® 2100 (Varian® Medical Systems, Palo Alto, CA) and equipped with the Millennium80® multileaf collimator (MLC).

In 2010, IG-IMRT with Rapid Arc® (Varian® Medical Systems, Palo Alto, CA) was implemented with a treatment schedule of 25 Gy in five fractions, given every other day within an overall treatment time of 10 days: the technique consisted of one or two coplanar arcs: the first arc was 280° wide (from 220° to 140°) with a 340° collimator; the second one was 350° wide (from 175° to 185°) with a 20° collimator. If two arcs were used, they were optimized simultaneously and rotated in opposite directions (clockwise and counterclockwise). Collimator rotation was used to minimize the tongue and groove effect during arc rotation and to make use of leaf trajectories that are non-coplanar with respect to the patient's axis.[12] In 2012, IG-IMRT was implemented with Vero™ (BrainLab AG, Feldkirchen, Germany) and CyberKnife™ and the same five-fraction schedule was prescribed, although some modifications (5–6 Gy per fractions) were made according to the retreated volume, the interval between the two RT courses, the shape of the recurrence and its localization, and the patient's comorbidities.

Vero is a joint product of BrainLab AG and Mitsubishi Heavy Industries Ltd (Tokyo, Japan). The Vero system is a small and light 6-MV C-band linear accelerator (linac) with a fast MLC mounted on an O-ring gantry (BrainLab AG, Feldkirchken, Germany). The MLC allows a maximum field size of 150 by 150 mm, and the maximum leaf speed is 50 mm s^{-1}. Two orthogonal gimbals hold the linac-MLC assembly, allowing pan and tilt motions of the linac and therapeutic beam. This mechanism offers the possibility to perform real-time tracking of moving tumours, decoupled from the dynamic MLC and intensity modulation of the dose. The maximum excursion of the beam axis is 4.4 cm at the isocentre plane (or 2.5) in both pan and tilt directions.

In addition to an electronic portal imaging device for megavoltage portal imaging, the Vero system is equipped with two orthogonal kilovoltage imaging systems attached to the O-ring at 45° from the megavoltage beam axis. This imaging system allows cone beam CT (CBCT) and simultaneous acquisition of orthogonal radiographs and fluoroscopy. An ExacTrac (BrainLab AG) automated infrared marker-based patient-positioning device is integrated into the Vero system.

For CyberKnife SRT, Multiplan® v. 2.0.5 was employed. If feasible, a radio-opaque fiducial marker was introduced into the target lesion. 1 week after the implant, a simulation CT scan was performed using contrast medium. Gross tumour volume (GTV) was

Table 4. Acute and late toxicities (only positive events registered) in relation to radiotherapy (RT) fractionation

Acute toxicity	RT fractionation			Number of patients
	30 Gy (6 × 5 fr), number of patients 5	25 Gy (5 × 5 fr), number of patients 25	30 Gy (3 × 10 fr), number of patients 1	
GU G1	0	5	1	6
GU G2	1	1	0	2
GI G1	0	3	0	3
GI G2	0	1	0	1

Late toxicity	RT fractionation		Number of patients
	30 Gy (6 × 5 fr) number of patients 5	25 Gy (5 × 5 fr) number of patients 25	
GU G1	2	5	7
GU G2	0	1	1
GI G1	1	4	5

fr, fraction; GI, rectal and intestinal events; GU, genitourinary events.

contoured on the CT scan. A 1-mm margin was added to the GTV to take account of submillimetre fiducial marker detection inaccuracy. Fiducial marker detection was used to target the planning target volume (PTV) during the treatment. For patients with no fiducial marker, the Xsight® (Accuray, Sunnyvale, CA) spine detecting system was used.

All patients underwent supine CT simulation, and for some patients, fusion with mpMRI was carried out. All the patients were treated with a full bladder (the patients were instructed to drink 0.5 l of water 1 h before starting the RT session) and to empty the rectum (the patients had an enema before the CT simulation, and this was repeated during the treatment if necessary, that is, when the CBCT showed large rectal volume).[13] The patients were asked to follow dietary instructions given to them during the first visit.

Clinical target volume (CTV) included the whole prostate or the site of clinical nodule relapse in the prostatic bed [partial prostate irradiation (PPI)]. In two patients, who underwent three courses of RT, PPI was performed for the third course of RT. The expansion from the CTV to the PTV varied according to the technique and was in the range of 3 mm posteriorly and 5 mm in the other directions for highly conformal techniques such as Cyberknife or Vero, to 5 mm posteriorly and 7 mm in the other directions for IG-3D-CRT. The organs at risk contoured included the rectum (and the posterior part of the rectum for IMRT plans), urinary bladder, penile bulb, penis, testis, femoral heads, peritoneal cavity and cauda equina. Dose–volume histograms were based on a previous study reported by Jereczek-Fossa et al[11] and included mean dose to 30% of the rectal volume (DR30), <13.8 Gy; mean dose to 60% of the rectal volume (DR60), <6.69 Gy; mean dose to 30% of the bladder volume (DB30), <10.58 Gy for prostate reirradiation; and mean DR30, <8.4 Gy; mean DR60, <4.08 Gy; and mean DB30, <3.94 Gy for prostatic bed re-irradiation. These constraints were applied in the later years of the study.

End points and patient monitoring

In order to diagnose isolated local recurrence of prostate cancer, in the prostate or prostatic bed, staging was required and included total body CT, ^{11}C-choline PET/CT scan and pelvic MRI and, if

Table 5. Acute and late toxicities (only positive events registered) with or without concomitant androgen deprivation therapy (ADT)

Acute toxicity	RT concomitant with ADT		Number of patients
	Yes (patients 11)	No (patients 21)	
GU G1	2	4	6
GU G2	0	2	2
GI G1	1	2	3
GI G2	0	1	1

Late toxicity	RT concomitant with ADT		Number of patients
	Yes (patients 11)	No (patients 21)	
GU G1	2	5	7
GU G2	0	1	1
GI G1	2	3	5

GI, rectal and intestinal events; GU, genitourinary events.

Table 6. Outcome with or without concomitant androgen deprivation therapy

Number of patients	Outcome	Radiotherapy concomitant with androgen deprivation therapy	
		Yes (number of patients, 11)	No (number of patients, 21)
13	No evidence of disease	3	10
3	Biochemical relapse	1	2
4	Clinical local relapse	2	2
1	Locoregional relapse	0	1
7	Metastatic relapse	2	5
4	Dead[a]	3	1

[a]Only two patients died as a result of disease progression.

possible, mpMRI. All patients were discussed on a multidisciplinary basis, and were monitored clinically before and during RT. Following the course of treatment, the patients were seen by a radiation oncologist every 6 months and their PSA was tested every 3 months. In the case of biochemical response (PSA reduction or stabilization), no radiologic or nuclear medicine imaging evaluation was requested.

Acute and late toxicity was the primary end point of the present study. Toxicity was evaluated using Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer guidelines.[14] Biochemical response was evaluated according to the Phoenix Consensus definition for prostate re-irradiation, that is, the American Society for Radiation Oncology (ASTRO) definition.[15] We considered the NADIR + 2 ng ASTRO definition as valid to define biochemical failure also in the patients treated with concomitant ADT.

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). When possible, the radiologic response was also evaluated.

RESULTS

Patient population

Between February 2008 and October 2014, 50 patients with local prostate cancer relapse after a primary irradiation were treated with re-EBRT at the Radiotherapy Department, European Institute of Oncology, Milan, Italy. All patients gave written consent for re-EBRT and for data analysis. 32 patients fulfilled the inclusion criteria (treated up to October 2013, *i.e.* follow-up of at least 12 months) and were the subjects of the present study.

The baseline characteristics of the patients at re-EBRT are listed in Tables 1 and 2.

In 22 patients (68.7%), the first RT course was delivered to the prostate ± seminal vesicle with radical intent, whereas 10 patients (31.3%) had previous surgery and were irradiated in a post-operative or salvage setting.

A choline-PET/CT scan was performed and was positive in 28 patients. 14 patients also had a positive pelvic MRI (mpMRI in 4 cases). Three patients had a positive MRI alone and one patient had a CT and pelvic ultrasound that indicated the presence of disease at a radiological level; the initial histology and PSA evolution were considered, all suggesting local failure.

Biopsy was performed in 19/32 patients (59.3%) and was positive in 15 patients (46.8%). 17 patients with either no biopsy or with a negative one were reirradiated on the basis of the radiological diagnosis of isolated local recurrence: of these patients, a positive choline-PET/CT scan; for 16 of them, a positive pelvic MRI (mpMRI in 2 cases); and for 1, a pelvic CT were carried out, all of which indicated local failure.

In all, re-EBRT included 3D-CRT with image-guided RT (IGRT), SBRT, IMRT, SBRT + IMRT and CyberKnife, respectively, in 1, 13, 15, 1 and 2 patients. The schedules used are reported in Table 2; all had treatment on alternate days: the choice of fractionation was guided by the technological developments in our department (availability of image guidance) and the favourable level of toxicity observed in the first patients of the current series. Then from 2012, we introduced IG-IMRT hypofractionated schemes, regardless of the relapse pattern (prostate or post-prostatectomy bed).

Three patients had a particular clinical course; two of them because they were irradiated three times: after a primary 3D-CRT, they received EBRT + brachytherapy boost. Both patients received salvage re-EBRT with Cyberknife and IG-IMRT Vero, respectively. Later, after a second biochemical and clinical relapse, both patients underwent a re-EBRT with a new IG-IMRT course. In this case, we censored the toxicity and tumour control data after the second course of RT, in order to present the data in a homogeneous way (the outcome of the first re-irradiation).

The other patient had previously been treated with IG-IMRT for lymph node recurrence with complete remission.

It is important to note that in the current series of patients, ADT was permitted if prescribed earlier by the referring physician. In these cases, it was continued until the completion of RT and then stopped. Obviously, PSA NADIR was strongly influenced in the ADT group, but we considered NADIR + 2 ng ml^{-1} (ASTRO definition) valid to define biochemical failure in this situation as well.

Toxicity of external beam reirradiation

The toxicity is reported in Table 3, the toxicity in relation to the fractionation schedules is reported in Table 4, and, in Table 5,

the events registered with or without concomitant ADT: the re-EBRT was well tolerated in the majority of the patients, with 24 (75%) and 28 (87.5%) patients free from acute urinary and rectal events, respectively, and no grade 3 acute/late toxicity was reported.

Tumour control data

At the median follow-up of 21.3 months (range, 2–53 months), 13 patients (40.6%) were alive with no evidence of disease (NED), while 15 patients (46.9%) were alive with active disease and 4 (12.5%) had died, 2 from metastatic progression, 1 from a second tumour and with metastatic disease, 1 from an acute ischaemic heart attack and NED.

Tumour progression (biochemical or clinical) was observed in 15 patients: after a median period of 9.4 months following the end of re-EBRT for biochemical progression (range, 4.9–27.8 months), and after a median period of 13.2 months following treatment for clinical progression (range, 2–53 months). At present, biochemical failure alone has been reported in three males. Clinical progression was present in 12 males: the pattern of failure included local progression in 4 males (30%) and regional or metastatic progression in 1 and 7 males, respectively. In all cases, clinical progression followed biochemical progression.

11 patients received concurrent ADT during re-EBRT: Table 6 shows patient outcome with or without ADT.

DISCUSSION

Our series of 32 patients, all from the same hospital, showed that re-EBRT for local relapse in prostate cancer, using highly selective modalities, is feasible and very well tolerated, with the vast majority of the patients free of acute or late side effects. Only single grade 2 events were observed, and no severe (>grade 2) toxicity was reported.

This excellent toxicity profile has to be compared with other local salvage therapies, for both acute and late events. In the case of salvage surgery, perioperative toxicity is common and correlated mortality is a risk. As in the case of other focal therapies, anaesthesia is necessary, which can be contraindicated in some patients because of their age and concomitant medical conditions.[7] The late toxicity profile of re-EBRT is extremely favourable when compared with late events reported following other local salvage therapies.

Tumour control in this unselected patient series was good, with 40.6% of the patients NED after a median follow-up of 21.3 months after re-EBRT. This compares well with the figures reported for other local salvage therapies.[4] Unfortunately, it is impossible to compare patterns of failure and the degree of local control with other local salvage therapies since this is rarely reported.[4]

In our series, local control was excellent with only four events of local recurrence. The majority of patients with progressive disease experienced metastatic dissemination. These findings may be at least partially explained by the lack of strict inclusion criteria in our series. In fact, not all our patients would be classified as good candidates for local salvage treatment according to the NCCN guidelines (indeed, one-third of the patients had high-risk disease initially).[6] However, these cases were discussed individually with a multidisciplinary board and the patient, proposing salvage re-EBRT as a way to postpone the systemic palliative approach or to avoid an invasive local approach (surgery or brachytherapy). The effect of the dose prescribed for re-EBRT also warrants further investigation: the extremely low toxicity profile observed in our series raises the possibility of dose escalation. Concomitant ADT was not seen to affect the re-EBRT outcome; however, this result might be biased by the limited number of cases.

Our findings suggest that re-EBRT might be a safe and non-invasive alternative to other salvage modalities that are being investigated for isolated primary recurrent prostate cancer, including prostatectomy, brachytherapy, HIFU, cryotherapy, radiofrequency interstitial tumour ablation and photodynamic therapy, with some of these reporting severe late toxicities, including rectal fistula after HIFU and a high rate of rectal dysfunction, and urinary incontinence, or retention, owing to urethral stricture, after cryotherapy.[16]

The strengths of our series include the use of modern selective RT techniques (IGRT, SBRT, IMRT etc.). All cases were discussed in the multidisciplinary setting both before re-EBRT and, if necessary, after re-irradiation. We are well aware of the limitations of our study, including short follow-up, the retrospective character of the study, the limited number of patients, the heterogeneity of the clinical cases (regarding previous therapies, concomitant systemic treatment, type of previous RT etc.), RT techniques and doses.

Longer follow-up and a bigger patient series is warranted in order to confirm these promising early findings and better define the category of patients that can really benefit from a salvage local procedure.[17] More selective inclusion criteria and further dose escalation might improve tumour control rates.

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