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Scientific Letter

Reirradiation of Prostate Cancer Local Failures After Previous Curative Radiation Therapy: Long-Term Outcome and Tolerance

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Summary

In this retrospective study we evaluated the long-term results of 14 prostate cancer patients treated with salvage external beam radiation therapy (EBRT) for exclusive local failure after primary EBRT. Whole-gland reirradiation resulted in a high rate of severe radiation-induced side effects and poor long-term biochemical and local control. Alternative salvage reirradiation modalities should be explored for selected cases of local relapse in accurately designed prospective trials.

Purpose: To evaluate the safety, feasibility, side-effect profile, and proof of concept of external beam radiation therapy (EBRT) with or without a brachytherapy (BT) boost for salvage of exclusive local failure after primary EBRT for prostate cancer.

Methods and Materials: Fourteen patients with presumed exclusive local recurrence after primary EBRT with or without BT were considered eligible for reirradiation. The median normalized total dose in 2-Gy fractions (NTD_{2Gy}, α/β ratio = 1.5 Gy) was 74 Gy (range, 66-98.4 Gy) at first irradiation. Median time between the first irradiation and the reirradiation was 6.1 years (range, 4.7-10.2 years).

Results: Between 2003 and 2008 salvage treatment was delivered with a median NTD_{2Gy} of 85.1 Gy (range, 70-93.4) to the prostate with EBRT with (n = 10) or without (n = 4) BT. Androgen deprivation was given to 12 patients (median time of 12 months). No grade $\geq$3 toxicity was observed during and within 6 weeks after RT. After a median follow-up of 94 months (range, 48-172 months) after salvage RT, 5-year grade $\geq$3 genitourinary and gastrointestinal toxicity-free survival figures were 77.9% $\pm$ 11.3% and 57.1% $\pm$ 13.2%, respectively. Four patients presented with combined grade 4 genitourinary/gastrointestinal toxicity. The 5-year biochemical relapse-free, local relapse-free, distant metastasis-free, and cancer-specific survival rates were 35.7% $\pm$ 12.8%, 50.0% $\pm$ 13.4%, 85.7% $\pm$ 9.4%, and 100%, respectively.

Conclusion: Salvage whole-gland reirradiation for patients with a suspicion of exclusive local recurrence after initial RT may be associated with a high rate of severe radiation-induced side effects and poor long-term biochemical and local control.

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T.Z. and E.B. contributed equally to this study.
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Introduction

Although there is no consensus about standard of care for local-only recurrence after definitive external beam radiation therapy (EBRT) (1), reirradiation may offer a valid local salvage treatment option as an alternative to palliative androgen deprivation therapy.

Most of the available data on reirradiation stem from retrospective studies using brachytherapy (BT) techniques (2-5) owing to its optimal conformity and good rectal sparing. Preliminary results with salvage stereotactic body irradiation (SBRT) have been reported (6, 7), although long-term data after salvage SBRT are lacking.

The purpose of this study was to evaluate the safety, feasibility, side-effect profile after long follow-up, and proof of concept of reirradiation of the whole gland with or without a BT boost for salvage of local-only failure after primary EBRT for prostate cancer.

Methods and Materials

Between 2003 and 2008, 14 patients with presumed exclusive local recurrence after primary ERBT with or without a BT boost were considered eligible for reirradiation. Inclusion criteria were as follows: the presence of a local prostatic recurrence documented by multiparametric endorectal MRI and/or ^{18}F-choline or ^{11}C-acetate positron emission tomography−computed tomography scans with or without confirmatory biopsies; >5-year life expectancy; interval between the first RT course and reirradiation of at least 4 years; and no severe residual late toxicity after the first irradiation.

Table 1 Patient and tumor characteristics at first diagnosis (n = 14)

Characteristic	n
Age at diagnosis (y), median (range)	59 (52-74)
PSA at diagnosis (ng/mL), median (range)	26.7 (4.8-116)
AJCC cT-stage	
T1c	1 (mrT2a)
T2a	1 (mrT2a)
T2b	1 (mrT3b)
T3a	10
T3b	1
NCCN risk classes	
Intermediate	2
High	12
Gleason score	
≤6	10
7	3
≥8	1
PSA nadir after RT (ng/mL), median (range)	0.44 (0.04-3.9)

Abbreviations: AJCC = American Joint Committee on Cancer; mr = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen; RT = radiation therapy.
Values are number unless otherwise noted.

Table 2 Patient and tumor characteristics at recurrence (n = 14)

Characteristics	n
Age at recurrence (y), median (range)	68 (60-80)
Time between 1st RT and 1st relapse (y), median (range)	4.4 (2.3-7.4)
PSA at reirradiation (ng/mL), median (range)	7.4 (3.3-27.4)
PSA-DT at reirradiation (mo), median (range)	11 (2.5-36)
Positive DRE (n = 14)	
Yes	9
No	4
Unknown	1
AJCC T-restaging at relapse	
T2a	4
T2b	3
T2c	1
T3a	1
T3b	5
Gleason score (n = 11)	
≤6	8
7	2
≥8	1
Bilateral relapse on biopsies (n = 11)	
Yes	4
No	7
Radiological restaging	
PET-CT (choline/acetate)	11 (8/3)
erMRI	12
Bone scan	11
Abdominal CT	8

Abbreviations: DRE = digital rectal examination; erMRI = endorectal magnetic resonance imaging; PET-CT = positron emission tomography−computed tomography; PSA = prostate-specific antigen; PSA-DT = PSA doubling time. Other abbreviations as in Table 1.
Values are number unless otherwise noted.

Patient and tumor characteristics at diagnosis and recurrence are summarized in Tables 1 and 2, respectively. At recurrence most patients were free of gastrointestinal (GI) or genitourinary (GU) toxicity. Only 2 patients were scored as having grade 2 GU toxicity. Salvage reirradiation was delivered with EBRT only (n = 4) or EBRT + BT (n = 10). Table 3 summarizes treatment characteristics of both irradiation courses.

Statistical analysis was performed with the SPSS statistical package (v.22; IBM, Armonk, NY). Five-year survival actuarial rates with corresponding standard errors for late toxicity and clinical outcomes were calculated using the Kaplan-Meier method.

Results

All 14 patients completed the salvage RT treatment as planned. The worst acute GU and GI toxicity scores by Common Terminology Criteria for Adverse Events toxicity

Table 3 Treatment characteristics (n = 14)

Primary irradiation, May 1992-March 2002	
Normalized total RT dose (α/β = 1.5 Gy), median (range)	74 (66-98.4)
Pelvis RT	
Yes	6
No	8
Median dose, Gy (range)	50.2 (46-50.4)
BT boost	
Yes	2 (7 Gy × 2 fractions with HDR)
No	12
RT technique	
2D-RT	4
3D-CRT	10
ADT	
Yes	9
No	5
ADT duration (mo), median (range)	6 (4-8)
Salvage reirradiation, March 2003-June 2008	
Interval time primary RT and reirradiation (y), median (range)	6.1 (4.7-10.2)
Normalized total RT dose (α/β = 1.5 Gy), median (range)	85.1 (70-93.4)
Pelvis RT	
Yes	0
No	14
EBRT dose to the whole prostate (Gy), median (range)	45 (44-72)
Boost (n = 13)*	
BT†	10
EBRT‡	3
RT technique	
3D-CRT	10
IMRT	4
ADT	
Yes	11
No	3
ADT duration (mo), median (range)	12 (8-17)

Abbreviations: 2D-, 3D-CRT = 2-, 3-dimensional conformal RT; ADT = androgen deprivation therapy; BT = brachytherapy; EBRT = external beam RT; HDR = high-dose-rate; IMRT = intensity modulated RT.

Values are number unless otherwise noted.

* One patient was treated with IMRT to the whole prostate with 72 Gy in 2.25 Gy per fraction.

† High-dose-rate (3 × 6 Gy, n = 2; 3 × 7 Gy, n = 6; 5 × 4 Gy, n = 1); pulse-dose-rate (25 Gy in 50 hourly fractions, n = 1).

‡ IMRT (5 × 4 Gy, n = 2; 6 × 4 Gy, n = 1 on alternate days).

Table 4 Acute genitourinary (GU) and gastrointestinal (GI) toxicity scores (CTCAE v3.0 scale): toxicity at the end of the second RT and at 6 weeks

	Acute CTCAE toxicity (% of patients)			
	GU		GI	
Grade	End RT	6 wk	End RT	6 wk
0	2 (14)	7 (50)	6 (43)	6 (43)
1	2 (14)	4 (29)	6 (43)	6 (43)
2	10 (72)	3 (21)	2 (14)	2 (14)
3	-	-	-	-
4	-	-	-	-

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events. Other abbreviation as in Table 1.

scale (CTCAE v3.0) criteria are presented in Table 4. No grade ≥3 acute GU or GI toxicity was observed during RT or 6 weeks after completing RT.

Table 5 presents the worst late GU and GI toxicity scores observed during follow-up. With a median follow-up of 94 months (range, 48-172 months) after reirradiation, the 5-year probability for grade ≥2 and grade ≥3 late GU toxicity-free survival was 41.7% ± 13.5% and 77.9% ± 11.3% (Fig. 1a), respectively, whereas the corresponding rates at 8 years were 25% ± 12.2% and 55.7% ± 15.6%. The 5-year probability for grade ≥2 late GI toxicity-free survival was 28.6% ± 12.1%, with the majority of events occurring during the first 5 years of follow-up. Correspondingly, the 5- and 8-year probability for grade ≥3 late GI toxicity-free survival was 57.1% ± 13.2% and 27.2% ± 14.3%, respectively (Fig. 1b).

After reirradiation, 10 and 8 patients presented with biochemical and local relapse, respectively. Among the 8 patients with a local relapse (5 and 3 treated with a BT and EBRT boost, respectively), histologic confirmation was available in 5 cases (in all but 1 patient with undifferentiated recurrent adenocarcinoma Gleason score ≥8), whereas in 3 subjects the suspicious local recurrence was identified on the basis of positron emission tomography–computed tomography studies. The 5-year actuarial biochemical relapse-free survival (bRFS) according to the Phoenix definition, nadir prostate-specific antigen value + 2 ng/mL (8), and local relapse-free survival rates were 35.7% ± 12.8% and 50.0% ± 13.4%, respectively. Four patients, 3 with concomitant local relapse, developed distant metastases. A total of 5 deaths were observed, with 2 patients dying from prostate cancer. The 5- and 8-year distant metastasis-free survival, overall survival, and competing risk cancer-specific survival rates were 85.7% ± 9.4% and 76.2% ± 12.2%, 92.9% ± 6.9% and 76% ± 12.2%, and 100% and 91.6% ± 8.5%, respectively. At last follow-up, 4 patients were alive without evidence of progression.

Discussion

To our knowledge, our series is the first in the literature to report long-term results after whole-gland reirradiation with EBRT with or without a dose-escalated BT boost for patients with local-only recurrence of prostate cancer after primary EBRT.

Comparing series of patients treated with salvage irradiation is difficult given the range of techniques, different definitions of biochemical failure, the use of adjuvant

Table 5 Late genitourinary (GU) and gastrointestinal (GI) toxicity scores (CTCAE v3.0 scale): maximum score after reirradiation (n = 14)

	Late CTCAE toxicity (% of patients)			
	GU		GI	
Grade	Worst score		Worst score	
0	-		1 (7)	
1	3 (21)		1 (7)	
2	3 (21)		3 (21)	
3†	4 (29)	• Dysuria, pain, and urgency not responding to medication treated with HBOT (n = 1) • Actinic cystitis treated with HBOT and obstructive problems requiring permanent catheterization (n = 1) • Obstruction by urethral stenosis requiring dilatation, suprapubic catheterization, and TURP (n = 1) • Bladder neck stenosis requiring an endoscopic stricture incision (n = 1)	4 (29)	• Rectal bleeding requiring topical formalin (n = 2) or argon plasma coagulation (n = 1) • Rectal pain and urgency which had to be treated with HBOT (n = 1)
4†	4 (29)*	• Rectal-prostatic (n = 2) and vesico-prostatic (n = 1) fistulae formation requiring salvage surgery (pelvic exenteration with cysto-prostatectomy and terminal colostomy) • Actinic cystitis requiring cystectomy followed 3 years later by a rectal-bowel-prostatic fistula formation treated by bowel resection (n = 1)	5 (36)*	• Rectal-prostatic (n = 2) and vesico-prostatic (n = 1) fistulae formation requiring salvage surgery (pelvic exenteration with cysto-prostatectomy and terminal colostomy) • Actinic cystitis requiring cystectomy followed 3 years later by a rectal-bowel-prostatic fistula formation treated by bowel resection (n = 1) • Rectal necrosis and stenosis requiring permanent colostomy (n = 1)

Abbreviations: HBOT = hyperbaric oxygen therapy; TURP = transurethral prostate resection.

* In 2 patients the final histology after surgical resection showed the presence of persistent Gleason 5 + 4 adenocarcinoma.

† Exclusive EBRT techniques (n = 4): no grade ≥3 GU toxicity; 2 patients with grade ≥3 GI toxicity (1 with grade 4) (50%). Brachytherapy boost (n = 10): 8 patients with grade ≥3 GU toxicity (4 with grade 4) (80%); 7 patients with grade ≥3 GU toxicity (4 with grade 4) (70%).

androgen deprivation therapy, and the length of follow-up. Nonetheless, published 5-year bRFS rates concerning salvage BT range from 20% to 75% (9). In one of the largest published BT series with a follow-up as long as 64 months, Grado et al (10) observed in 49 patients a 5-year bRFS of 34%, similar to our findings.

Regarding SBRT, Jereczek-Fossa et al (6) reported a complete biochemical response after a follow-up time of

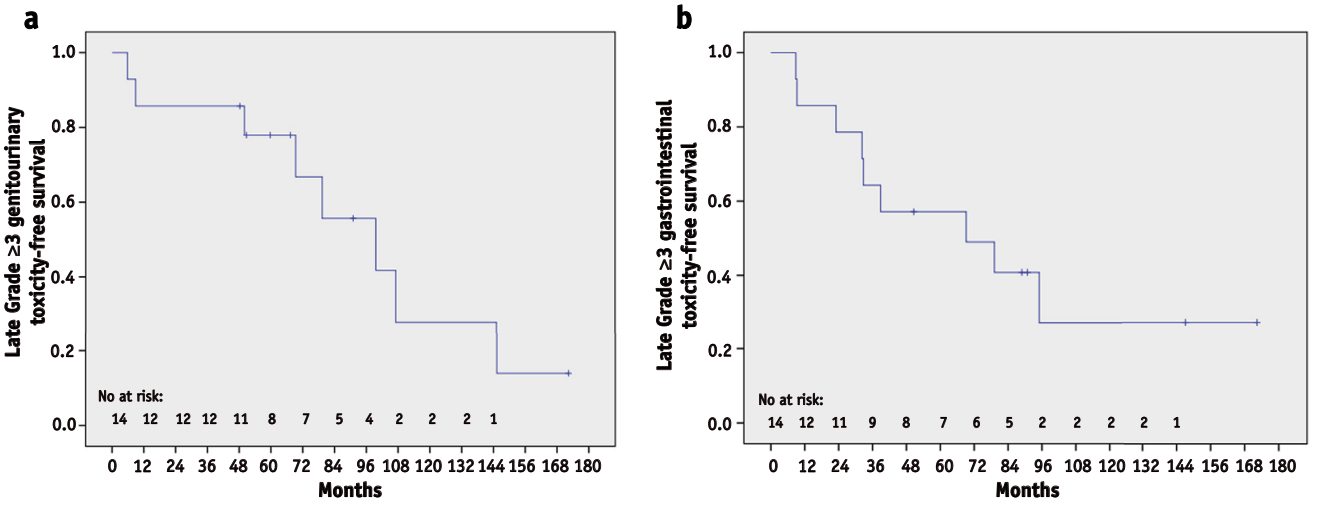

Fig. 1. Late grade ≥3 genitourinary (a) and gastrointestinal (b) toxicity-free survival Kaplan-Meier estimates.

9.5 months in 6 of 9 patients with isolated intraprostatic recurrence and salvaged with CyberKnife SBRT (30 Gy in 5 fractions). In an additional series of 23 patients reirradiated with SBRT (36 Gy in 6 fractions), Leroy et al (7) observed a 2-year disease-free survival of 55.6%, including 5 local recurrences. Although the preliminary results of these 2 series look promising, mostly because of the low toxicity rates reported by the authors, their very short follow-ups limit any further conclusion regarding the long-term benefit of salvage extreme hypofractionation delivered with SBRT techniques.

As far as toxicity is concerned, we observed a high rate of severe radiation-induced side effects. In contrast, Ramey et al (9), in a review of salvage BT after primary EBRT, reported lower rates of severe side effects (though with a shorter follow-up than ours), with an overall risk of grade 3 to 4 late GU and GI toxicities at 4 to 5 years of 13% (range, 0%-47%) and 5% (range, 0%-20%), respectively. Three of 25 patients (13%) experienced fistulae formation after salvage BT in a phase 2 trial by Nguyen et al (11), with an interval of <4.5 years between courses of RT as the most predictive prognostic factor. Conversely, 4 of 14 patients (29%) in our series experienced fistula formation. Even in the absence of clinical signs of toxicity after first RT and a long interval between the 2 RT courses, reirradiation of the whole gland using mostly 3-dimensional conformal RT techniques may probably explain the higher toxicity rates of our series.

Despite the inherent bias of this small retrospective series, whole-gland EBRT with or without BT boost as salvage option may result in a relatively poor long-term outcome with a fairly high rate of severe side effects. Focal SBRT to the recurrent intraprostatic tumor (12) with internal organ immobilization (13) and rectal sparing (14), as well as combination of hyperthermia and RT (15) or delivery of pulsed low-dose-rate schedules (16), should be explored in very selected cases as alternative reirradiation modalities in accurately designed prospective trials.

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