Urinary toxicity after salvage re-irradiation for prostate cancer local failure after definitive radiotherapy: a clinical and dosimetric prognostic factors analysis

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Abstract

Purpose: Predictors of long-term toxicity after prostate cancer re-irradiation are scarce. In this study, we retrospectively assessed the impact of clinical/dosimetric data on late genitourinary (GU) toxicity on fourteen radio-recurrent prostate cancer patients treated with salvage radiotherapy (RT).

Material and methods: To identify dose parameters and clinical factors potentially associated to severe long-term GU toxicity, study population was stratified in two groups according to toxicity, including one low-grade group (grade ≤ 2, $n = 6$) and one high-grade group (grade ≥ 3, $n = 8$). Dose prescription at primary and salvage-RT in 2 Gy equivalent dose (EQD_{2Gy}) per fraction, treatment techniques, and clinical factors potentially associated to severe GU toxicity were analyzed.

Results: At salvage-RT, the median EQD_{2Gy} $\alpha/\beta = 3$ Gy was significantly higher in the high-toxicity group (85 Gy, range, 71-85 Gy) compared to the low-toxicity group (77 Gy, range, 61-85 Gy) ($p = 0.01$). All patients treated using salvage-RT with a brachytherapy (BT) boost and with a baseline Framingham risk-score of > 20% ($n = 8$) developed severe GU toxicity, while none of the remaining patients developed a grade 3 or more GU toxicity ($p = 0.0003$). $V_{70} > 0$ and $V_{75} > 0$ of the primary treatment were associated with an increased rate of toxicity.

Conclusions: Our analysis shows that the delivery of doses up to 75-80 Gy (EQD_{2Gy}, $\alpha/\beta = 3$ Gy) in salvage-RT can be safe in terms of severe GU toxicity avoidance. Furthermore, concomitant cardiovascular comorbidities seem to increase the risk to develop severe GU toxicity.

Purpose

Nowadays, the interest of salvage treatments for locally relapsed prostate cancer after primary radiotherapy (RT) are boosting among radiation oncologists due to progress in image guidance and precision in dose delivery [1, 2]. Little has been reported on gastro-intestinal (GI) and genitourinary (GU) toxicity developing years after re-irradiation, while analyses correlating dosimetric and clinical parameters with long-term tolerance are scarce [3-5]. Indeed, in 2016, we have reported the long-term GI and GU toxicity profile for a group of 14 patients salvaged with external beam radiotherapy (EBRT) with or without a brachytherapy (BT) boost, for exclusive local failures following previous EBRT [6]. In a later report in 2018 [7], we have published an analysis on the correlation of rectal toxicity for the same patients with rectal dose-volume parameters quantifying late GI toxicity, with normal tissue complication models (NTCP).

The purpose of the present study was to retrospectively assess the possible association between treatment and dosimetry features and GU toxicity, thus aiming to identify potential predictors for severe GU toxicity after re-irradiation.

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Material and methods

A cohort of 14 locally recurrent prostate cancer patients treated at the Radiation Oncology Department of the Geneva University Hospital between 1992 and 2008 was analyzed. Median (minimum-maximum) time interval between salvage and primary RT treatments was 6.1 years (range, 4.7-10.2 years). All but two patients with grade 2 GU toxicity were free of any GI or GU toxicities at salvage RT [6] as assessed using common terminology criteria for adverse events version 3. Patients were regularly seen for status verification during and after treatment completion [7]. Tables 1 and 2 present clinical characteristics, dose prescription, treatment techniques, and GU toxicity grading for the 14 patients as previously reported [6].

Median dose delivered to the prostate in 2 Gy-equivalent dose (EQD_{2Gy}) per fraction (EQD_{2Gy}, α/β ratio = 1.5 Gy) was 74 Gy at primary irradiation. For salvage RT, four patients were treated with exclusive EBRT, and the remaining 10 patients were treated with a combination of EBRT and BT boost. Median EQD_{2Gy} (α/β = 1.5) of the whole group at re-irradiation was 85 Gy (Table 1). High-dose-rate (HDR) BT boost was delivered in three or more consecutive days. When using intensity-modulated radiation therapy (IMRT) and salvage treatments, set-up verifications were performed using electronic portal imaging on bony anatomies, and an off-line protocol as previously reported [7].

In order to explore the data, and to assess dose parameters and clinical factors potentially associated with severe long-term GU toxicity, study population was stratified into two groups according to toxicity, including one low-grade group (grade ≤ 2, n = 6) and one high-grade group (grade ≥ 3, n = 8). Physical dose was translated to EQD_{2Gy}, according to linear quadratic model, using a α/β = 1.5 Gy for prostate cancer and a α/β = 3 Gy for bladder and urethral late toxicity [7].

In order to analyze the data appropriately, contouring guidelines [8] were applied to re-contour the bladder both as a solid structure and as the bladder wall (defined as a wall thickness of 5 mm). An experienced radiation oncologist (TZ) contoured all patients and structures to eliminate inter-contouring variability effects from different radiation oncologist contouring in the analysis. Eclipse version 10 (Varian, Palo Alto, USA) treatment planning system was used for contouring. For primary treatments, it was possible to obtain BT dose contribution to the urethra and bladder in the form of dose-volume histogram (DVH) by using paper hard copies. This allowed us to investigate dose-volume relationships and if doses received at primary treatment could predict toxicity at re-irradiation.

In order to consider factors that might reduce the capability of each patient to recover from the irradiation, such as pre-existing vascular morbidity, which could increase the risk of damage to the bladder and urethra at re-irradiation, Framingham risk score was applied. For each patient, the predicted 10-year cardiovascular risk was calculated and was used to divide patients into high-risk and low-risk score groups using a cut-off value of 20% [9].

Mann-Whitney test was applied to evaluate the impact of continuous variables; for cross-comparison between toxicity (grade 0-2 vs. grade 3-4) and dichotomous variables, such as Framingham risk score (with/without BT boost), BT boost, and pelvic RT, a two-tailed Fisher exact test was used. SPSS software, version 22.0 (IBM USA) was employed for statistical analysis. This study was carried out within a retrospective research project on prostate cancer hypofractionation approved by local ethical committee (project No. 2018-00614). No signed informed consent was required.

Results

With a median follow-up after re-irradiation of 94 months (range, 48-172 months), the 5- and 8-year probability (± SD) for grade ≥ 3 late GU toxicity-free survival were 77.9 ±11.3% and 55.7 ±15.6%, respectively. Four cases of grade 3 and four cases of grade 4 GU toxicity were observed (Table 2). The estimated 5-year biochemical relapse-free survival was 36% [6]. The median time-interval between primary RT and salvage RT (6.6 vs. 5.7 months) as well as the median age at primary RT (58 vs. 62 years old) or at salvage RT (67 vs. 69 years old) were similar for the low- and high-grade toxicity groups (p = not significant [N.S.]). Whole pelvis RT at primary RT was not associated with the development of severe GU toxicity as well as the size of the bladder volume at salvage RT (p = N.S.).

The median bladder wall V_{75Gy} (volume receiving 75 Gy) at primary RT was predictive for grade ≥ 3 GU toxicity; 1 cc vs. 0 cc, p = 0.05 (Figure 1). In addition, both $V_{70} > 0$ cc and $V_{75} > 0$ cc were significantly associated with an increased toxicity: the rate was 8/10 vs. 0/4 for $V_{70} > 0$ and = 0 (p = 0.008, χ^2 test). Similarly, the rate was 4/4 and 4/10 $V_{75} > 0$ and = 0 (p = 0.019, χ^2 test).

Late grade ≥ 3 GU toxicity was observed in 8 out of 10 patients treated with salvage EBRT and BT boost, while no patient out of the 4 treated with highly conformal EBRT developed severe GU toxicity (p = 0.008). If considering one patient treated with a pulse-dose-rate BT (0.5 Gy × 50) with EBRT only, the corresponding proportions became 8/9 patients vs. 0/5 patients (p = 0.002) (Table 1).

All patients salvaged with a BT boost and presenting with a baseline Framingham risk score of > 20% (n = 8) developed severe GU toxicity, while none of the six remaining patients developed grade 3 or more GU toxicity (p = 0.0003) (Table 1). Of note, 3 patients with a Framingham score of < 20% presented grade 1 GU toxicity only.

At primary RT, the median delivered EQD_{2Gy} (α/β = 3 Gy) was 74 Gy (range, 72-76 Gy) and 73 Gy (range, 67-92 Gy) for the high- and the low-toxicity groups, respectively (p = N.S.). On the other hand, at salvage RT, the median EQD_{2Gy} (α/β = 3 Gy) was significantly higher in the high-toxicity group (85 Gy, range, 71-85 Gy) compared with the low-toxicity group (77 Gy, range, 61-85 Gy) (p = 0.01). Differences were even more significant between the low- and the high-toxicity groups by using a α/β ratio of 1.5 Gy instead of 3 Gy (p = 0.007).

By cumulating the primary and salvage RT courses, the median delivered total EQD_{2Gy} (α/β = 3 Gy) was

Table 1. Patients' clinical and dosimetric characteristics

Parameter	Patient ID													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age at 1st diagnosis	66	63	57	54	52	68	58	58	74	59	56	67	65	57
Age at relapse	72	70	64	59	60	73	64	66	80	70	65	76	71	62
Interval time primary salvage RT (years)	5.6	6.7	6.6	5.3	7.4	5.2	4.9	7.4	5.2	10.2	8.8	6.4	5.8	4.7
Late GU toxicity (grade)	3	1	2	1	1	3	3	3	2	2	4	4	4	4
Framingham score	> 20%	< 20%	> 20% CI	< 20%	< 20%	> 20%	> 20%	> 20%	>20% CI	> 20%	> 20% CI	> 20%	> 20%	> 20%
Primary RT treatment technique	6 fields	6 fields	4 fields box + 6 fields	5 fields + 4 fields box	4 fields box + 4 fields box + 3 fields	6 fields	6 fields	4 fields box + 6 fields	6 fields	4 fields box + 4 fields box	4 fields box + 6 fields box	6 fields + 6 fields	4 fields box + 6 fields	6 fields + 6 fields
Primary EBRT dose (Gy) × fraction	2×37	2×32	$1.8 \times 28 + 2 \times 7$	$2.25 \times 20 + 2.5 \times 8$	$1.8 \times 13 + 2 \times 13 + 2.25 \times 8$	2×38	2×38	$1.8 \times 28 + 2 \times 12$	2×37	$2 \times 23 + 2 \times 12$	$2 \times 25 + 2 \times 12$	$2 \times 27 + 2 \times 10$	$1.8 \times 28 + 2 \times 12$	$2 \times 27 + 2 \times 10$
Primary BT dose (Gy) × fraction	–	7×2	7×2	–	–	–	–	–	–	–	–	–	–	–
Primary RT EQD$_{2Gy}$ (α/β = 3 and 1.5 Gy)	74.0/74.0	92.0/98.0	90.4/95.5	69.3/71.1	67.4/67.3	76.0/76.0	76.0/76.0	72.4/71.5	74.0/74.0	70.0/70.0	74.0/74.0	74.0/74.0	72.4/71.5	74.0/74.0
Salvage-RT treatment technique	4 fields box	5 fields IMRT + 5 fields IMRT	5 fields IMRT + 5 fields IMRT	5 fields IMRT	6 fields	6 fields	6 fields	6 fields	3 fields + 7 fields IMRT	5 fields IMRT	6 fields	6 fields	6 fields	6 fields
Salvage EBRT dose (Gy) × fraction	1.8×25	$2 \times 22 + 4 \times 6$	$2 \times 21 + 4 \times 6$	2×25	1.8×25	1.8×25	1.8×25	1.8×25	$1.8 \times 25 + 4 \times 5$	2.25×32	1.8×25	1.8×25	1.8×25	1.8×25
Salvage BT dose (Gy) × fraction	7×3	–	–	6×3	0.5×50	7×3	7×3	6×3	–	–	7×3	7×3	4×6	7×3
Salvage-RT EQD$_{2Gy}$ (α/β = 3 and 1.5 Gy)	85.2/93.4	77.6/81.7	75.6/79.7	82.4/88.6	60.7/56.7	85.2/93.4	85.2/93.4	75.6/81.0	71.2/73.9	75.6/77.1	85.2/93.4	85.2/93.4	76.8/80.1	85.2/93.4
Primary + salvage RT EQD$_{2Gy}$ (α/β = 3 and 1.5 Gy)	159.2/167.4	169.6/179.7	166.0/175.2	151.7/159.7	128.1/124.1	161.2/169.4	161.2/169.4	148.0/152.5	145.2/147.9	145.6/147.1	159.2/167.4	159.2/167.4	149.2/151.6	159.2/167.4

Patient ID – patient identification number, GU – genitourinary, CI – cardiovascular incident: acute myocardial infarction, angina, or stent, RT – radiation therapy, EBRT – external beam radiotherapy, BT – brachytherapy, IMRT – intensity-modulated radiation therapy, EQD$_{2Gy}$ – 2 Gy equivalent dose

Table 2. Late genitourinary (GU) toxicity scores (CTCAE v.3.0 scale)

Worst score	n subjects (%)	
0	0 (0.0)	
1	3 (21.0)	
2	3 (21.0)	
3	4 (29.0)	• 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) • Bladder neck stenosis requiring an endoscopic stricture incision (n = 1) • Obstruction by urethral stenosis requiring dilatation, suprapubic catheterization, and TURP (n = 1)
4	4 (29.00)	• Rectal-prostatic (n = 2) and vesico-prostatic (n = 1) fistula formation requiring salvage surgery (pelvic exenteration with cysto-prostatectomy and terminal colostomy) • Actinic cystitis requiring cystectomy 3 years later by a rectal-bowel-prostatic fistula formation, treated by bowel resection (n = 1)

HBOT – hyper-baric oxygen therapy, TURP – trans-urethral prostate resection, Re-printed with permission from Zilli T et al. [4]
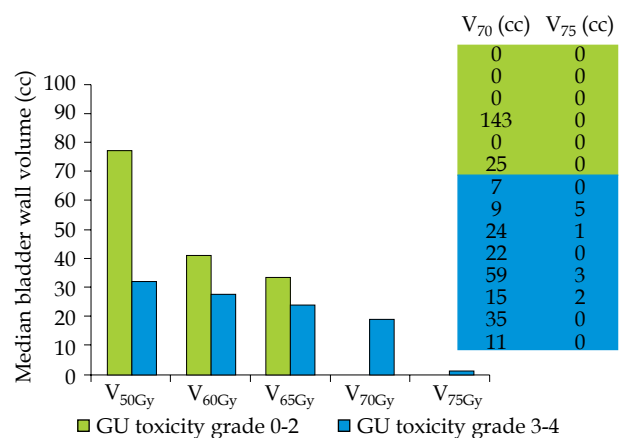
159 Gy (range, 145-161 Gy) and 156 Gy (range, 128-170 Gy) for the high- and low-toxicity groups, respectively (p = N.S.). A $\alpha/\beta = 1.5$ Gy did not discriminate between the two groups.

Discussion

Although, the risk of severe GU toxicity after curative EBRT for prostate cancer is expected to rapidly increase with EQD_{2Gy} above 80 Gy [10], our data suggests that a partial, though incomplete, repair of the bladder wall after first irradiation may allow a second irradiation to radical doses, especially if the interval between treatments is of at least 3-4 years, and a dose to the bladder lower than 75 Gy after first irradiation attempt. In the present study, by lowering the α/β ratio from 3 Gy to 1.5 Gy, we were able to better distinguish the effect of salvage dose prescription between patients with or without severe toxicity after re-irradiation. This result is consistent with data from previously published literature, suggesting an α/β ratio as low as 1 Gy for late GU toxicity [11, 12].

The encouraging results on early and late toxicities after stereotactic body RT (SBRT) re-irradiation [2, 3, 13-16] with doses ranging between 25 Gy and 36.25 Gy in 5 fractions, are consistent with our findings. Indeed, the corresponding EQD_{2Gy} ($\alpha/\beta = 3$) of SBRT salvage schedules ranged between 40 Gy and 74 Gy, well below the 80 Gy threshold emerging from our analysis. Moreover, in these series, the use of modern image-guided techniques for re-positioning and reduced treatment margins [1], together with SBRT treatments delivered to the local relapse only and not the whole prostate gland as in our series [17], can certainly attenuate the dose-effect relationship for severe GU toxicity observed in our study at re-irradiation, showing that safe salvage RT can be delivered with lower salvage doses. Nevertheless, the compromise may be a lower probability of disease control when primary and salvage EQD_{2Gy} ($\alpha/\beta = 3$ Gy) doses are lower than 130 Gy to the prostate [3]. There is strong need to investigate the dose limits and possible threshold effects on organs at risk.

Leeman *et al.* [18, 19] analyzed 23 studies (n = 2,232 patients) and have shown that even after SBRT as primary treatment, urinary toxicity can be the determining factor and strongly correlates with high-doses received by the urethra. Patients with 146 Gy maximum urethral dose metric had an estimated 5% risk of late grade 3 GU toxicity, with a predictive curve showing that above this value, toxicity may increase dramatically with a possible threshold dose of 150-160 Gy.

In the absence of complete DVH data on the two treatments, we considered the prescribed dose to the target to be a surrogate of the dose received by a portion of the bladder and by the prostatic urethra, as both were within planning target volume (PTV) and clinical target volume (CTV). Unlike exclusive EBRT, combined EBRT and BT treatments may have resulted in a marked inhomogeneous dose distribution within the target and nearby organs at risk, such as the bladder and urethra. This and the very high-dose per week delivered via brachytherapy at salvage RT may explain high-rate of severe GU complications due to the implant itself as well as the absence of correlation with total prescribed dose. Perhaps, this is what has limited our ability to define a combined 'primary and salvage' threshold dose for GU toxicity. On the other hand, it is worth mentioning the association between V_{70}/V_{75} of the first treatment and the increased risk of toxicity.

	V_{70} (cc)	V_{75} (cc)
	0	0
	0	0
	0	0
	143	0
	0	0
	25	0
	7	0
	9	5
	24	1
	22	0
	59	3
	15	2
	35	0
	11	0

Fig. 1. Median bladder wall volume (cc) receiving a dose of 50, 60, 65, 70 and 75 Gy as a function of the GU toxicity grade: low vs. high

As for the clinical factors observed for late severe GI toxicity [7], Framingham risk score at primary RT correlated with grade ≥ 3 late GU toxicity, and may help to select optimal candidates for salvage RT. These results are somewhat consistent with other studies that have reported age [20, 21], vascular problems [22], and smoking [23] to be associated with an increased risk of late GU symptoms after primary irradiation. Our study, besides the small sample size and its' retrospective nature, presents a main flaw, which is the impossibility to evaluate the salvage RT dose contribution of BT to the bladder and the urethra in terms of DVH and/or dose distribution.

Conclusions

In summary, in the present study, we were able to identify possible dosimetric and clinical factors that could be involved with the development of long-term severe GU side effects after re-irradiation of a prostate cancer local failure. Our data support that salvage re-irradiation to EQD_{2Gy} ($\alpha/\beta = 3$) below 75-80 Gy to the bladder and urethra, may result in safe and acceptable long-term GU toxicity. Concomitant cardiovascular comorbidities, according to the Framingham risk score, may also predict the risk to develop severe GU toxicity.

Data availability statement

All data used in this study are available in the paper via Figure 1, and Tables 1 and 2.

Disclosure

The authors report no conflict of interest.

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