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

Giovanna Dipasquale, MSc1, Thomas Zilli, MD2, Claudio Fiorino, PhD3, Véranne Achard, MD, PhD4, Michel Rouzaud, MSc5, Raymond Miralbell, MD6

1Division of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland, 2Division of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland, Geneva University Faculty of Medicine, Geneva Switzerland, 3Medical Physics San Raffaele Scientific Institute, Milan, Italy, 4Division of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland, Geneva University Faculty of Medicine, Geneva, Switzerland, 5Division of Radiation Oncology, Geneva University Hospital, Geneva, Switzerland, 6Geneva University Faculty of Medicine, Geneva, Switzerland

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 (EQD2Gy) per fraction, treatment techniques, and clinical factors potentially associated to severe GU toxicity were analyzed.

Results: At salvage-RT, the median EQD2Gy α/β = 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). V70 > 0 and V75 > 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 (EQD2Gy, α/β = 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.

J Contemp Brachytherapy 2022; 14, 3: 222–226
DOI: https://doi.org/10.5114/jcb.2022.117124

Key words: prostate cancer, prognostic factors, re-irradiation, urinary 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 published 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.

Address for correspondence: Véranne Achard, Department of Radiation Oncology, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, CH-1211 Genève 14, Switzerland, phone: +41-22-372-70-90, e-mail: verane.achard@hcuge.ch

Received: 27.02.2022
Accepted: 26.05.2022
Published: 14.06.2022

Creative Commons licenses: This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International (CC BY -NC -SA 4.0). License (http://creativecommons.org/licenses/by-nc-sa/4.0/).
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$_{20}$) per fraction (EQD$_{20}$, $\alpha/\beta$ 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$_{20}$ ($\alpha/\beta$ = 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$_{20}$, according to linear quadratic model, using a $\alpha/\beta$ = 1.5 Gy for prostate cancer and a $\alpha/\beta$ = 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 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 disease-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$_{75}$ (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, $\chi^2$ test). Similarly, the rate was 4/4 and 10/10 $V_{75} > 0$ and = 0 ($p =$ 0.019, $\chi^2$ 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$_{20}$ ($\alpha/\beta$ = 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$_{20}$ ($\alpha/\beta$ = 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 $\alpha/\beta$ 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$_{20}$ ($\alpha/\beta$ = 3 Gy) was
| Parameter                                                                 | Patient ID |
|--------------------------------------------------------------------------|------------|
| Age at 1<sup>st</sup> 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% CI > 20% > 20% > 20% > 20% > 20% |
| Primary RT treatment technique                                           | 6 fields 6 fields 4 fields  box + 6 fields 5 fields + 4 fields box + 4 fields box + 3 fields 6 fields 6 fields 4 fields box + 6 fields 4 fields box + 4 fields box 6 fields 6 fields 4 fields box + 6 fields 6 fields |
| Primary EBRT dose (Gy) × fraction                                         | 2 × 37 2 × 32 1.8 × 28 + 2 × 7 2.25 × 20 + 2.5 × 8 1.8 × 13 + 2 × 13 + 2.25 × 8 2 × 38 2 × 38 1.8 × 28 + 2 × 12 2 × 37 2 × 23 + 2 × 12 2 × 25 + 2 × 12 2 × 27 + 2 × 10 1.8 × 28 + 2 × 12 2 × 27 + 2 × 10 |
| Primary BT dose (Gy) × fraction                                          | – 7 × 2 7 × 2 – – – – – – – – – – – – – – – – – – |
| Primary RT EQD<sub>2Gy</sub> (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 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 × 22 + 4 × 6 2 × 21 + 4 × 6 2 × 25 1.8 × 25 1.8 × 25 1.8 × 25 1.8 × 25 + 4 × 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<sub>2Gy</sub> (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/ 77.1 75.6/ 85.2/ 85.2/ 80.1 85.2/ 85.2/ 85.2/ |
| Primary + salvage RT EQD<sub>2Gy</sub> (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/ 167.4 159.2/ 151.6 159.2/ |

*Table 1. Patients’ clinical and dosimetric characteristics*

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<sub>2Gy</sub> – 2 Gy equivalent dose.
Discussion

Although, the risk of severe GU toxicity after curative EBRT for prostate cancer is expected to rapidly increase with EQD$_{2a}$ 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 α/β ratio as low as 1 Gy for late GU toxicity [11, 12].

The corresponding EQD$_{2a}$ (α/β = 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$_{2a}$ (α/β = 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$_{20}$/V$_{75}$ of the first treatment and the increased risk of toxicity.

![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](image-url)
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 $E_{QD_{25Gy}} (\alpha/\beta = 3)$ 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.

References

1. Ghadjar P, Fiorino C, Munck AF Rosenschold P et al. ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer. Radiother Oncol 2019; 141: 5-13.

2. Ingrosso G, Becherini C, Lancia A et al. Nonsurgical salvage local therapies for radio-recurrent prostate cancer: a systematic review and meta-analysis. Eur J Radiol 2020; 135-197.

3. Augugliaro M, Marvagno G, Cambria R et al. Finding safe dose-volume constraints for re-irradiation with SBRT of patients with prostate cancer relapse: The IEO experience. Phys Med 2021; 92: 62-68.

4. Corkum MT, Mendez LC, Chin J et al. A novel salvage option for local failure in prostate cancer, reirradiation using external beam or stereotactic radiation therapy: systematic review and meta-analysis. Adv Radiat Oncol 2020; 5: 965-977.

5. Valle LF, Lehrer EJ, Markovic D et al. A systematic review and meta-analysis of local salvage therapies after radiotherapy for prostate cancer (MASTER). Eur Urol 2021; 80: 280-292.

6. 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.

7. Dipasquale G, Zilli T, Fiorino C et al. Salvage reirradiation for local failure of prostate cancer after curative radiation therapy: Association of rectal toxicity with dose distribution and normal-tissue complication probability models. Adv Radiat Oncol 2018; 3: 673-681.

8. Gay HA, Barthold HJ, O’Meara E et al. Pelvic normal tissue contouring guidelines for radiation therapy: A Radiation Therapy Oncology Group Consensus Panel Atlas. Int J Radiat Oncol Biol Phys 2012; 83: e353-e362.

9. Mahmood SS, Levy D, Vasan RS et al. The Framingham Heart Study and the epidemiology of cardiovascular disease: a historical perspective. Lancet 2013; 383: 999-1008.

10. Zeléfsky MJ, Levin EJ, Hunt M et al. Incidence of local rectal and urinary toxicities after three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for localized prostate cancer. Int J Radiat Oncol Biol Phys 2008; 70: 1124-1129.

11. Cozzarin C, Rancati T, Palorini F et al. Patient-reported urinary incontinence after salvage radiotherapy for prostate cancer: quantifying the dose-effect. Radiother Oncol 2017; 125: 101-106.

12. Fiorino C, Cozzarin C, Rancati T et al. Modelling the impact of fractionation on late urinary toxicity after postprostatectomy radiation therapy. Int J Radiat Oncol Biol Phys 2014; 90: 1250-1257.

13. Fuller D, Wurzer J, Shirazi R et al. Retreatment for local recurrence of prostate carcinoma after prior therapeutic irradiation: efficacy and toxicity of HDR-like SBRT. Int J Radiat Oncol Biol Phys 2020; 106: 291-299.

14. 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.

15. Jereczek-Fossa BA, Rojas DP, Zerini D et al. Reirradiation for isolated local recurrence of prostate cancer: Mono-institutional series of 64 patients treated with salvage stereotactic body radiotherapy (SBRT). Br J Radiol 2019; 92: 20180494.

16. Zerini D, Jereczek-Fossa BA, Fodor C et al. Salvage image-guided intensity modulated or stereotactic body reirradiation of local recurrence of prostate cancer. Br J Radiol 2015; 88: 20150197.

17. Jereczek-Fossa BA, Marvagno G, Zaffaroni M et al. Salvage stereotactic body radiotherapy (SBRT) for intraprostatic recurrence after prostate cancer radiotherapy: an ESTRO ACROP Delphi consensus. Cancer Treat Rev 2021; 98: 102206.

18. Leeman JE, Chen YH, Catalano P et al. Radiation dose to the intraprostatic urethra correlates strongly with urinary toxicity after prostate stereotactic body radiation therapy: a combined analysis of 23 prospective clinical trials. Int J Radiat Oncol Biol Phys 2022; 112: 75-82.

19. Zilli T, Lachen V, Guevelou JL. Intraprostatic urethra: the new kid on the block for prostate cancer radiation therapy? Int J Radiat Oncol Biol Phys 2022; 113: 92-95.

20. Ahmed AA, Egleston B, Alcantara P et al. A novel method for predicting late genitourinary toxicity after prostate radiation therapy and the need for age-based risk-adapted dose constraints. Int J Radiat Oncol Biol Phys 2013; 86: 709-715.

21. Mathieu R, Arango JD, Beckendorf V et al. Nomograms to predict late urinary toxicity after prostate cancer radiotherapy. World J Urol 2014; 32: 743-751.

22. Yahya N, Ebert MA, Bulsara M et al. Dosimetry, clinical factors and medication intake influencing urinary symptoms after prostate radiotherapy: an analysis of data from the RADAR prostate radiotherapy trial. Radiother Oncol 2015; 116: 112-118.

23. Solanki AA, Laiw SL. Tobacco use and external beam radiation therapy for prostate cancer: influence on biochemical control and late toxicity. Cancer 2013; 119: 2807-2814.