

Scientific Article

# 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

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## Abstract

**Purpose:** This study aimed to assess the impact of radiation dose on rectal toxicity after salvage external beam radiation therapy (EBRT) with or without a brachytherapy boost for exclusive local failures after the primary EBRT for prostate cancer.

**Methods and materials:** Fourteen patients with no severe residual late toxicity after primary EBRT ± brachytherapy were reirradiated after a median time interval of 6.1 years. The median normalized total dose in 2 Gy fractions (NTD<sub>2Gy</sub>,  $\alpha/\beta$  ratio = 1.5 Gy for prostate cancer cells) was 74 Gy at primary EBRT and 85.1 Gy at reirradiation. Rectal dose-volume histograms (converted to NTD<sub>2Gy,  $\alpha/\beta = 3$  Gy</sub>) and the corresponding normal-tissue complication probability (NTCP) values for gastrointestinal (GI) toxicity were evaluated for 2 groups: High GI toxicity (grade  $\geq 3$ ) and low GI toxicity (grade  $\leq 2$ ).

**Results:** The 5-year grade  $\geq 3$  GI toxicity-free survival rate was 57.1%. The median rectal V<sub>70Gy</sub> and maximum dose to 1 cm<sup>3</sup> (D1cc<sub>rect</sub>) at primary EBRT were both predictive for grade  $\geq 3$  GI toxicity (9% vs 0%;  $P = .04$  and 72.2 Gy vs 66.8 Gy;  $P < .01$ , respectively). When adding primary radiation therapy (RT) and reirradiation plans, the median D1cc<sub>rect</sub> was 139.8 Gy versus 126.7 Gy ( $P < .01$ ) for high and low GI toxicity groups. NTCP >10% at primary RT was predictive for high GI toxicity at reirradiation ( $P < .05$ ).

Predictors for rectal toxicity were studied from dosimetric data of fourteen prostate cancer patients treated with salvage external beam radiotherapy (EBRT) for exclusive failure after primary EBRT.

Threshold dose constraints (rectal V<sub>70Gy</sub> at 1st EBRT and a cumulative maximum dose to 1 cc of rectum > 130 Gy) and NTCP models were both predictors of severe gastrointestinal toxicities after re-irradiation and may be integrated in optimization of salvage-RT plans.

Conflicts of interest: The authors have no conflicts of interest to declare.

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**Conclusions:** Even in the absence of residual toxicity after primary RT, rectal doses >70 Gy and NTCP >10% calculated for a first irradiation may be associated with a higher risk of developing high GI toxicity at reirradiation with a possible  $D_{1cc_{rect}}$  threshold of 130 Gy.

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## Introduction

There is no wide consensus with regard to the optimal management of recurrent prostate cancer after external beam radiation therapy (EBRT). Androgen deprivation therapy is still the most frequently used salvage strategy, even if its long-term use may lead to a marked decline in quality of life<sup>1-4</sup> and its efficacy may fade over time. Alternative approaches of local salvage treatment with curative intent may be proposed for selected cases, in particular for patients with a long life expectancy.

The best salvage modality after exclusive local failure following primary radiation therapy (RT) is still unknown. Several authors have reported their experience with reirradiation with brachytherapy (BT), EBRT, or stereotactic body radiation therapy (SBRT).<sup>5-7</sup> With SBRT, high doses can be delivered with steep dose gradients. Improvements in technology and image guidance as well as a better understanding of the fractionation sensitivity of prostate cancer supports SBRT as a challenging alternative to BT for salvage treatment.

Although a few promising preliminary results (up to 2 years of follow-up) with salvage SBRT have been reported,<sup>7,8</sup> longer follow-up intervals are needed to establish the benefits and toxicity of SBRT reirradiation for salvage therapy because severe radiation-induced side effects and relatively poor long-term biochemical control have been reported with >5-year follow up.<sup>9</sup>

The purpose of this study was to assess the value of the dosimetric data for 14 patients with prostate cancer who were reirradiated with salvage whole-gland EBRT for exclusive local failure after primary RT and with long follow-up times.<sup>9</sup> We aimed to study potential risk predictors of severe gastrointestinal (GI) toxicity after salvage reirradiation.

## Methods and materials

Fourteen patients with recurrent prostate cancer who had been previously treated with primary RT between 1992 and 2002 were reirradiated between 2003 and 2008 using an EBRT ± BT technique. The median time interval between the 2 RT courses was 6.1 years (range, 4.7-10.2 years). All patients had local-only relapses as confirmed by prostate biopsy (n = 11) and/or radiologic staging images. At recurrence, most patients were free of GI or genitourinary (GU) toxicity. Toxicity was scored in accordance with the

Common Terminology Criteria for Adverse Events toxicity scale version 3.0 (<http://ctep.cancer.gov/>). While on treatment, patients were seen in status-check visits once weekly, followed by a follow-up visit 6 to 8 weeks after treatment completion, then every 3 months during the first year, and every 6 months thereafter. Follow-up visits involved prostate-specific antigen (PSA) measurements, a digital rectal examination, and an assessment of GI and GU toxicities. Patient and tumor characteristics at diagnosis and recurrence have been previously reported.<sup>9</sup> Table 1 (and eTables 1 and 2; available as supplementary material online only at [www.practical.radonc.org](http://www.practical.radonc.org)) presents the material description with urinary and rectal toxicity grading as recently published by our group.<sup>9</sup>

A median normalized total dose in 2 Gy-fractions (also referred to as 2 Gy equivalent dose;  $NTD_{2Gy}$ ,  $\alpha/\beta$  ratio = 1.5 Gy for prostate cancer cells) of 74.0 Gy was delivered with the first irradiation. At reirradiation, 10 patients were salvaged with combined EBRT and BT, and the remaining 4 were salvaged with EBRT only (median  $NTD_{2Gy}$  = 85.1 Gy). Treatment setup verifications for salvage EBRT and intensity modulated RT (IMRT) were performed using an offline protocol and appropriate patient repositioning was performed on the basis of bone-matching on portal images.

To analyze the data and assess the radiation dose parameters and clinical factors that potentially predict severe long-term GI toxicity, the study population was divided into 2 subgroups: Low-grade toxicity (grade ≤2) and high-grade (≥3) toxicity with 5 and 9 patients, respectively. To analyze GI toxicity, the physical doses (EBRT and BT) were converted into  $NTD_{2Gy}$ , using the linear quadratic formula and  $\alpha/\beta$  ratio of 1.5 Gy (prostate) and  $\alpha/\beta$  ratio = 3 Gy (rectum):

$$NTD_{2Gy} = D \times (d + (\alpha/\beta)) / (2 + (\alpha/\beta))$$

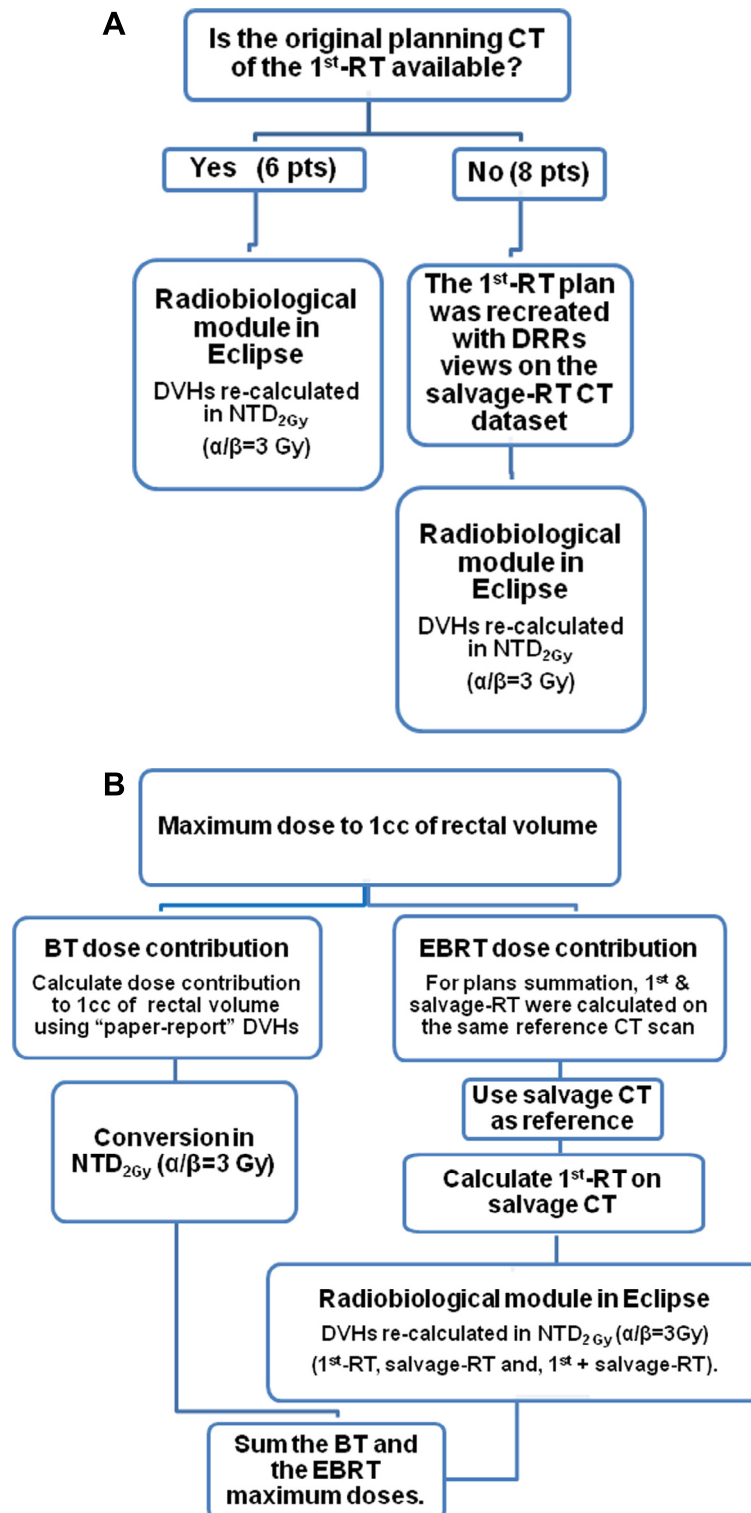
where  $NTD_{2Gy}$  is the dose delivered in 2 Gy fractions that is biologically equivalent to a total physical dose D (Gy), with d (Gy) the dose per fraction and  $\alpha/\beta$  (Gy) the dose at which the linear and quadratic components of cell kill are equal.<sup>10</sup> The results of the  $NTD_{2Gy}$  prescription doses are reported per patient in Table 1, for  $\alpha/\beta$  = 1.5 Gy.

Although salvage EBRT treatment plans were available for all patients and could be recovered from the treatment planning system (TPS; Eclipse, Varian, Palo Alto, CA), EBRT treatment plans for the first irradiation could only be retrieved for 6 of 14 patients. For the remaining 8 patients, the primary RT plans were reconstructed on the

**Table 1** Patients' clinical and dosimetric characteristics

Patient ID	1	2	3	4	5	6	7
Late GI toxicity (grade)	0	1	2	2	2	3	3
Age at first diagnosis (y)	66	63	57	54	52	68	58
Age at relapse (y)	72	70	64	59	60	73	64
Interval time between primary and salvage RT (y)	5.6	6.7	6.6	5.3	7.4	5.2	4.9
Framingham score	>20%	<20%	>20% CI	<20%	<20%	>20%	>20%
Primary RT treatment technique	6 fields	6 fields	4-fields box+6 fields	5 field+4-fieldsbox	4-fields box+4-fields box+ 3 fields	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
Primary BT dose (Gy) × fraction	—	7 × 2	7 × 2	—	—	—	—
Primary RT NTD <sub>2Gy</sub> (αβ = 1.5 Gy)	74.0	98.0	95.5	71.1	67.3	74.0	76.0
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
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
Salvage BT dose (Gy) × fraction	7 × 3	—	—	6 × 3	0.5 × 50	7 × 3	7 × 3
Salvage RT NTD <sub>2Gy</sub> (αβ = 1.5 Gy)	91.7	81.7	79.7	88.6	56.7	73.9	93.4
Primary + salvage RT NTD <sub>2Gy</sub> (αβ = 1.5 Gy)	165.7	179.7	175.2	159.7	124.1	147.9	169.4
Patient ID	8	9	10	11	12	13	14
Late GI toxicity (grade)	3	3	4	4	4	4	4
Age at first diagnosis (y)	58	74	59	56	67	65	57
Age at relapse (y)	66	80	70	65	76	71	62
Interval time between primary and salvage RT (y)	7.4	5.2	10.2	8.8	6.4	5.8	4.7
Framingham score	>20%	>20% CI	>20%	>20% CI	>20%	>20%	>20%
Primary RT treatment technique	4-fields box+6 fields	6 fields	4-fields box+4-fields box	4-fieldsbox+4-fields box	6 fields+6 field	4-fields box+6 fields	6 fields+6-fields
Primary EBRT dose (Gy) × fraction	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	—	—	—	—	—	—	—
Primary RT NTD <sub>2Gy</sub> (αβ = 1.5 Gy)	76.0	71.5	70.0	70.0	71.5	71.5	74.0
Salvage RT treatment technique	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	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	6 × 3	—	—	7 × 3	7 × 3	4 × 6	7 × 3
Salvage RT NTD <sub>2Gy</sub> (αβ = 1.5 Gy)	93.4	81.0	77.1	93.4	93.4	80.1	93.4
Primary + salvage RT NTD <sub>2Gy</sub> (αβ = 1.5 Gy)	169.4	152.5	147.1	163.4	164.9	151.6	167.4

BT, brachytherapy; CI, cardiovascular incident (infarctus, angor, or stent); EBRT, external beam radiation therapy; GI, gastrointestinal; ID, identification number; IMRT, intensity modulated radiation therapy; NTD<sub>2Gy</sub>, normalized total dose in 2 Gy equivalent fraction; RT, radiation therapy.



**Figure 1** Dosimetric study workflow.

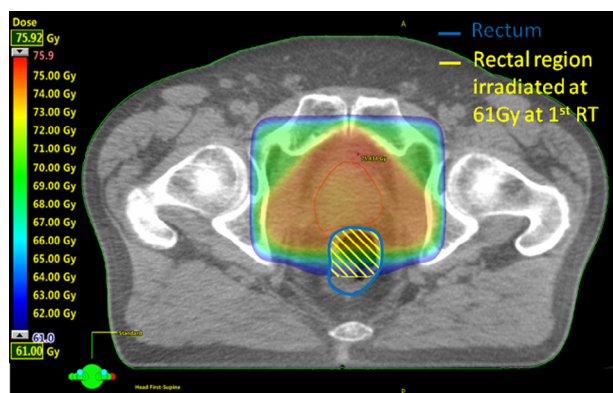
computed tomography (CT) data sets of the reirradiation plans (second CT scan) using treatment records in hard-copy format, including simulation and treatment portal films. The study workflow is shown in [Figure 1A](#). The dose-volume histogram (DVH) analysis of treatments plans

considered both the percentage of rectal volume and the absolute rectal volume (in  $\text{cm}^3$ ) receiving a given dose. DVH paper prints from all primary RT treatment plans were also used to assess the correlation between dose to the rectum at primary treatment and GI toxicity.

The rectal structures used for the EBRT dose analysis were recontoured on the CT data sets by an expert radiation oncologist using the Male Pelvis Normal Tissue Radiation Therapy Oncology Group Contouring guidelines.<sup>11</sup> The rectum was contoured as a solid structure (including the contents) and as a wall structure with a wall thickness of 5 mm (rectal wall). The analytical anisotropic algorithm version 10 was used to calculate the dose distribution for all plans (imported and reconstructed) with a calculation grid resolution of 2.5 mm.

To take into account the heterogeneity of the dose prescriptions (Table 1), Eclipse Biological Evaluation Module version 11 was used to convert the DVH data into equivalent doses delivered in 2 Gy fractions ( $\alpha/\beta = 3$  Gy for the rectum) in accordance with the linear-quadratic model. To use the Biological Evaluation Module to convert the prescribed dose and DVH data for the primary + salvage RT treatment plans, they were calculated on the same CT data set. Thus, patients' salvage RT data sets were used for the summed plan analysis. The addition of doses in the Biological Evaluation Module was performed without modeling normal tissue recovery time.

DVH metrics disregard dose distribution spatial information; therefore, different approaches were used to analyze the DVH data: (1) maximum dose to 1 cm<sup>3</sup> of the entire rectum (D1cc<sub>rect</sub>) from the summed (primary + salvage) EBRT; and (2) maximum dose to 1 cm<sup>3</sup> of the pre-irradiated high-dose rectal region (D1cc<sub>1st-irr\_rect</sub>). This is defined hereafter as the portion of the rectum that is encompassed by the 61 Gy isodose line (ie, 95% of 64 Gy, the lowest prescription dose at first irradiation; Table 1) as shown in Figure 2. The 1 cm<sup>3</sup> rectal volume choice was driven by several facts: (1) restricting the analysis to the rectum receiving 61 Gy from the initial plan resulted in 1 patient with a volume of approximately 1 cm<sup>3</sup>; (2) a hot spot as defined by 62 International Commission on Radiation Units<sup>12</sup> is approximately 1.8 cm<sup>3</sup> in volume (volume of a sphere of diameter of 15 mm); (3) ICRU 83<sup>13</sup> recommends describing the maximum dose as D2% of the entire organ, which



**Figure 2** Example of delineation of the portion of rectal wall treated at 61 Gy at primary radiation therapy.

corresponds to 1 cm<sup>3</sup> for our series, considering that our median rectal volumes are approximately equal to 50 cm<sup>3</sup>.

The BT treatment plans were calculated using the Plato TPS (Nucletron-Odelft, Veenendaal, The Netherlands).<sup>14</sup> The contribution of the BT dose to the rectum could not be recovered in the EBRT TPS because the plans were no longer accessible in digital format. However, the BT dose to the rectum was available in the form of hard-copy DVH reports. From the BT DVH data, the maximum dose to 1 cm<sup>3</sup> of the rectum from the BT plan could be determined. Rectal doses from BT were converted to NTD<sub>2Gy</sub> (linear quadratic formula,  $\alpha/\beta = 3$  Gy) for late rectal toxicity.

The BT dose to 1 cm<sup>3</sup> of the rectum, as delineated in the BT plans, was summed with the maximum dose to 1 cm<sup>3</sup> of the rectum from the EBRT plans (Fig 1B). This approach is based on the assumption that the part of the rectum that is directly adjacent to the prostate is the part that receives the highest dose and that the same rectal portion is abutting the prostate in both treatment scenarios.

Normal-tissue complication probability (NTCP) models were used to estimate the risk of grade  $\geq 2$  and  $\geq 3$  rectal toxicity on the basis of dosimetric data for all primary RT treatment plans. NTCP values were calculated using the Lyman-Kutcher-Burman model<sup>15,16</sup> using parameters from the literature (Table 2).<sup>17-21</sup> NTCP included models with an  $\alpha/\beta$  value  $> 3$  Gy.

Patient-related factors that potentially influence the severity of vascular morbidity and thus increase the risk for rectal reirradiation damage are age, sex, high blood pressure, diabetes, and high cholesterol levels. The Framingham risk score, which is estimated with all these risk factors, was conceived to predict the 10-year cardiovascular risk of an individual and was chosen in our analysis to stratify patients into 2 groups with a standard cutoff of 20%: one with a low score ( $< 20\%$  risk) and another with a high score ( $\geq 20\%$  risk).<sup>22</sup> Both risk groups were correlated with rectal toxicity severity after reirradiation.

A Mann-Whitney test was used to evaluate independently several factors between the patients stratified in low- and high-grade GI toxicity groups (time-interval between primary RT and reirradiation, age, DVH parameters, and NTCP data). A two-tailed Fisher exact test was used for the cross-comparison between the Framingham score and pelvic RT versus toxicity (grade 0-2 vs grade 3-4). The statistical analysis was performed using the SPSS package (SPSS Statistics version 22.0; IBM, Armonk, NY).

## Results

The median rectal volumes for patients with ( $n = 9$ ) or without ( $n = 5$ ) grade  $\geq 3$  GI toxicity were similar (51 vs 59 cm<sup>3</sup>;  $P > .05$ ). The median time-interval between primary RT and salvage RT for the low- and high-grade toxicity groups were similar (6.6 vs 5.8 years;  $P > .05$ ). Age (median) was not statistically different between the 2 toxicity groups



**Table 2** Rectal toxicity NTCP (Lyman-Kutcher-Burman) after first irradiation for the 14 patients in the study by different models

Reference	Toxicity grade/endpoint	Rectal organ segmentation	D50, Gy	$\alpha/\beta$ , Gy	n	m	NTCP median (range) Grade 0-2/Grade 3-4	P-value
Dale et al. <sup>17</sup>	Grade $\geq 3$ /late effects	Rectal wall	80	3.9	<b>0.06</b>	0.15	<b>6.0 (1.8-12)/11 (5.5-20.0)</b>	<b>.05</b>
Rancati et al. <sup>18</sup>	Grade $\geq 3$ /bleeding	Rectum solid organ	78.6	3	<b>0.06</b>	0.06	<b>0.0 (0.0-3)/0.2 (0.0-7.4)</b>	<b>.05</b>
Michalski et al. <sup>19</sup>	Grade $\geq 2$ /bleeding	Rectum solid organ	76.9	3	0.08	0.13	4.3 (0.7-10.7)/8.2 (1.6-18.4)	.16
Tucker et al. <sup>20</sup>	Grade $\geq 2$ /bleeding	Rectum solid organ	77.9	4.8	<b>0.08</b>	0.15	<b>6.7 (0.9-14.0)/11.2 (4.2-30.8)</b>	<b>.03</b>
Gulliford et al. <sup>21</sup>	Grade $\geq 2$ /bleeding	Rectum solid organ	68.9	3	0.18	0.16	14.8 (1.3-25.0)/22.5 (2.8-56.4)	.26
Rancati et al. <sup>18</sup>	Grade $\geq 2$ /bleeding	Rectum solid organ	81.8	3	0.29	0.22	10.2 (1.8-15.4)/7.7 (1.5-13.8)	.64

D50, dose giving a 50% response probability; n, volume dependence factor; NTCP, normal tissue complication probability; m, slope of the response curve.

at the time of the first (57 vs 59 years;  $P > .05$ ) and salvage irradiation (64 vs 70 years;  $P > .05$ ). No differences between the 2 groups were observed with regard to pelvic node RT ( $P > .05$ ). Only 3 of the 13 patients in the study presented with a Framingham risk score  $< 20\%$ , and all 3 belonged to the low-grade toxicity group ( $P = .03$ ).

As shown in Figure 3, primary EBRT treatment plans using simulation CT data for salvage showed that the percent of rectal volume that received  $\geq 70$  Gy ( $\text{NTD}_{2\text{Gy}} \text{D1cc}_{\alpha/\beta = 3}$ ) was statistically significant for grade  $\geq 3$  versus grade  $\leq 2$  GI toxicity at reirradiation (9% vs 0%;  $P = .04$ ; Fig 3). The corresponding median volume that received 70 Gy was 6  $\text{cm}^3$  (range, 1-31  $\text{cm}^3$ ) and 0  $\text{cm}^3$  (range, 0-13  $\text{cm}^3$ ) for the high- and low-grade toxicity groups, respectively (Fig 3). Using original DVH paper prints, the percentage of rectal volume that received  $\geq 70$  Gy was correlated significantly with grade  $\geq 3$  versus grade  $\leq 2$  GI toxicity at reirradiation (6% vs 0%;  $P = .04$ ). The corresponding median volumes that received 70 Gy were 3  $\text{cm}^3$  (range, 1-17  $\text{cm}^3$ ) and 0 cc (range, 0-8  $\text{cm}^3$ ) for the high- and low-grade toxicity groups, respectively.

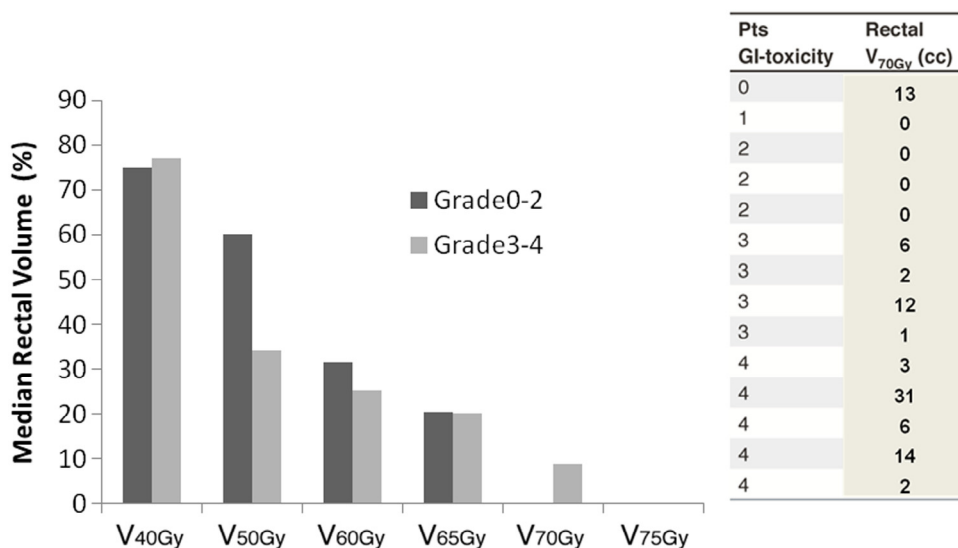
Although the median (range) value of the maximum  $\text{NTD}_{2\text{Gy}} \text{D1cc}_{\text{1st-irr\_rect}}$  at first irradiation was statistically different between the high- and low-grade GI toxicity groups (ie, 72.2 Gy [71.0-75.6 Gy] vs 66.8 Gy [59.5-70.6 Gy], respectively;  $P < .01$ ), no statistical difference was seen at salvage RT (ie, 67.6 Gy [54.7-69.2 Gy] vs 55.9 Gy [39.6-70.0 Gy], respectively;  $P > .05$ ). When summing the first irradiation and reirradiation treatment plans, including BT, the median (range)  $\text{NTD}_{2\text{Gy}} \text{D1cc}_{\text{1st-irr\_rect}}$  was 139.8 Gy (126.7-147.8 Gy) versus 125.9 Gy (99.4-133.1 Gy;  $P = .01$ ) for the high- and low-grade GI toxicity groups, respectively (Fig 4).

When analyzing the added total dose to the entire rectum, the median (range) value of the maximum  $\text{NTD}_{2\text{Gy}} \text{D1cc}_{\text{rect}}$  was significantly different (139.8 Gy [127.0-147.8 Gy] vs 126.7 Gy [124.4-133.1 Gy];  $P < .01$ ) between the high- and low-grade GI toxicity groups. For all but 1 patient, the portion of the high dose to the rectum at reirradiation was within the region of the high dose at primary RT. Only in 1 patient (patient 3), the 1  $\text{cm}^3$  rectal volume that received the maximum dose at the first and salvage irradiation regions were located in different spots within the rectal wall.

As shown in Table 2, NTCP estimations after primary RT using the model by Tucker et al. ( $\alpha/\beta = 4.8$  Gy for late severe GI rectal toxicity;  $P = .03$ ) showed the best results to predict toxicity after reirradiation.<sup>20</sup> We used this  $\alpha/\beta$  value to recalculate DVHs and BT doses for the plan sum. We observed that the median (range) value of the maximum  $\text{NTD}_{2\text{Gy}} \text{D1cc}_{\text{rect}}$  was still significantly different (135.3 Gy [120.2-140.9 Gy] vs 125.8 Gy [116.3-129.8 Gy];  $P = .03$ ) between the high- and low-GI toxicity groups.

## Discussion

To minimize toxicity and optimize the success of local salvage treatment, the appropriate selection of patients is

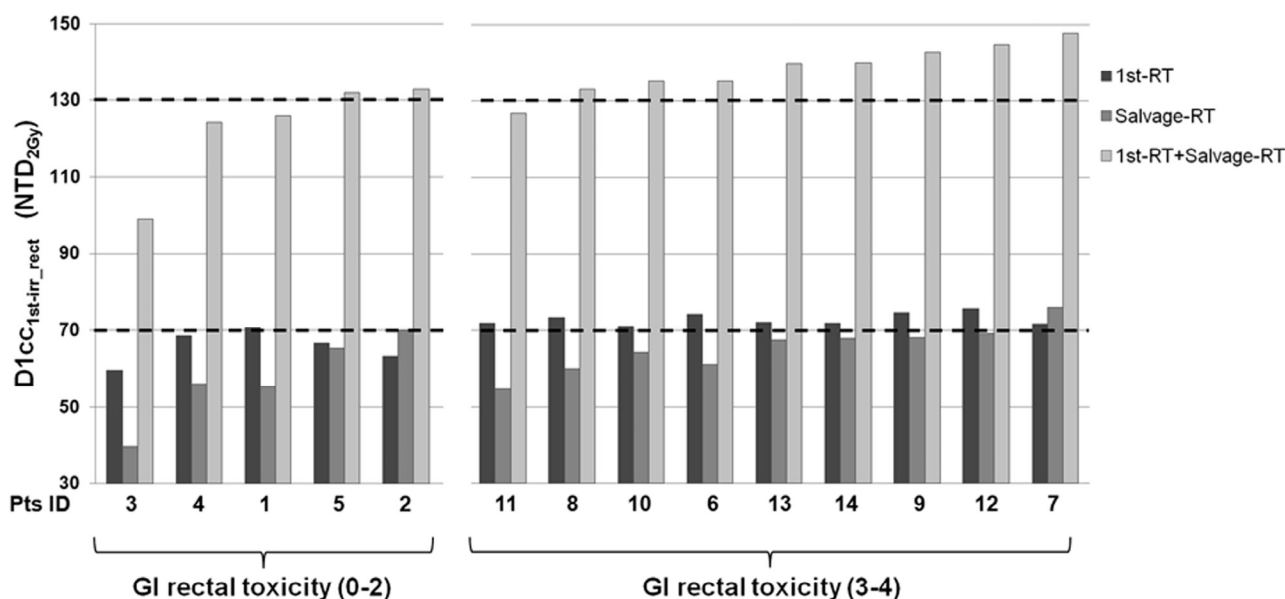


**Figure 3** Histograms representing the percentage of median rectal volume receiving a specific dose with the first irradiation. Patients are stratified into 2 groups by GI toxicity severity (grade 0-2 vs grade 3-4). V<sub>70Gy</sub> (in cm<sup>3</sup>) for every patient, on the right side of the figure.

of paramount importance. A long PSA doubling time, a low PSA value at relapse, an interval between first treatment and PSA failure of >3 years, and a low Gleason score at re-biopsy are factors that suggest a reasonable likelihood of isolated recurrence within the prostate.<sup>3,6</sup> However, when salvage reirradiation is considered, the residual biological harm to the rectum from previous irradiation treatment needs to be taken into account. In the present study, the impact of dose on long-term rectal toxicity after reirradiation of the prostate with EBRT ( $\pm$ BT) has been assessed in a small

population of 14 patients with local recurrence after primary EBRT ( $\pm$ BT).

To our knowledge, this is the first report to assess the value of dosimetric and clinical parameters at first irradiation as risk indicators for severe late complications after salvage reirradiation. Our observations suggest that the ability of the rectum to repair damage from a second EBRT salvage irradiation may depend on the dose received by the same rectal portion from the first irradiation, as well as on the total dose received by the rectum after salvage RT.



**Figure 4** Maximum dose (NTD<sub>2Gy</sub>,  $\alpha/\beta = 3$  Gy) to 1 cm<sup>3</sup> of rectum treated at high doses at first irradiation (D1cc<sub>1st-irr-rect</sub>) as a function of treatment for each patient.

Although a long-enough time interval (>4 years) between primary and salvage RT has been proposed as a safe measure to reduce the severity of GI toxicity at reirradiation,<sup>3,23</sup> we were unable to confirm this hypothesis in our study. Instead, the volume of the rectum irradiated to high doses ( $\geq 70$  Gy) at first RT correlated well with the severity of late GI toxicity, regardless of the time interval between primary and salvage RT.

Furthermore, we observed a significant risk for late grade  $\geq 3$  toxicity for summed doses above 130 Gy to 1 cm<sup>3</sup> of rectal volume. The influence of the dose to the rectum after primary EBRT was observed both with the DVH analysis and with well-known NTCP models. Indeed, NTCP values obtained from primary EBRT treatment plans were estimated using several models (Table 2).

Restricting the analysis to the hottest portion of the rectum from the first and salvage irradiations suggests the existence of a threshold dose ( $NTD_{2Gy,\alpha/\beta = 3 Gy}$ ) of 130 Gy for rectal high-grade GI toxicity (both for  $\alpha/\beta = 3$  or 4.8 Gy). In the present study, the delivery of a relatively low dose at first irradiation and a more focal reirradiation (IMRT, BT boost) keeping the  $D1cc_{rect} < 130$  Gy might have helped reduce the risk of severe rectal side effects. The hypothesis may be supported by reports on BT for salvage RT because reducing the dose to the rectum at reirradiation can limit the incidence of grade 3 to 4 rectal toxicity to <5% (range, 0-20%).<sup>24</sup>

Additional data from the literature support the concept of threshold. Kim et al.<sup>25</sup> reported that, for dose-escalated prostate SBRT, an increased risk of late rectal toxicity correlated with a concomitant high percentage of the circumference of the rectal wall that was irradiated to higher dose levels (39 Gy in 5 fractions) and 3 cm<sup>3</sup> of rectum irradiated to 50 Gy in 5 fractions. Interestingly, their fractionation and dose correspond to a  $NTD_{2Gy}$  of 130 Gy, ( $\alpha/\beta = 3$  Gy). The study by Kim et al.<sup>25</sup> might also point out the importance of a rapid dose fall-off around the hot spot in the rectum (ie, dose-volume effects), which might help RT damage repair and possibly explain the low rate of rectal toxicities reported by BT studies.<sup>24,26</sup>

The knowledge of the dose distribution for the rectum is essential to correlate toxicities with plans. As visible for 2 patients (Table 1; patients 2 and 3) who were treated with a BT boost at primary RT, the  $NTD_{2Gy,\alpha/\beta = 3 Gy}$  prescription dose was high while the dose to 1 cm<sup>3</sup> of rectum was much smaller (Fig 4). Furthermore, 2 patients were treated with exclusive EBRT, both at primary and salvage RT (patients 9 and 10), and both developed GI toxicity grade  $\geq 3$ . Nevertheless, only future studies using a segmental DVH analysis of the rectum might improve the knowledge of geometrical and dose-volume effects on GI toxicity.<sup>27</sup>

Furthermore, the NTCP parameters proposed by Tucker et al.<sup>20</sup> were the most reliable predictors for rectal toxicity after reirradiation. The estimated NTCP with low  $n$  values suggested, not surprisingly, that high doses are most determinant,<sup>28</sup> with the rectum responding radio-biologically

like a serial organ. In addition, Brenner<sup>29</sup> speculated on late rectal bleeding as an intermediate between a classic late effect and early response, with  $\alpha/\beta$  values intermediate between 3 Gy and 8 Gy.

We wish to highlight that in this study, the incidence of late severe rectal toxicity at reirradiation was extremely high, though much alike the reported toxicity in one dose escalation SBRT study, which delivered a  $NTD_{2Gy,\alpha/\beta = 3 Gy}$  of 130 Gy.<sup>25</sup>

For salvage RT in the NRG02526 trial, Crook et al.<sup>30</sup> observed a 14% crude rate of grade 3 toxicity at a median follow up of 54 months, which is below the 20% rate that is considered unacceptable. However, in this trial, reirradiation was performed using permanent seed BT, a technique known to minimize reirradiation of the rectal wall. A longer follow-up period is probably needed to confirm that grade 2 late toxicity does not evolve in grade 3 adverse events as observed in our series. In fact, as previously demonstrated by Kaplan-Meier estimations,<sup>9</sup> the occurrence of grade  $\geq 3$  side effects was a late event in our population, with a median onset occurring after 5 years of follow-up (late Grade  $\geq 2$  GU: median toxicity free-survival 39 months [range, 6-145 months]; late grade  $\geq 3$  GU: median toxicity free-survival 97 months [range, 6-145 months]; late grade  $\geq 2$  GI: median toxicity free-survival 15 months [range, 6-69 months]; late grade  $\geq 3$  GI: median toxicity free-survival 69 months [range, 9-95 months]). With a median follow-up time after reirradiation of 94 months (range, 48-172 months), the 5- and 8-year probability for grade  $\geq 3$  late GI toxicity-free survival was  $57.1\% \pm 13.2\%$  and  $27.2\% \pm 14.3\%$ , respectively. For GU, the toxicity-free survival rates were  $77.9\% \pm 11.3\%$  and  $55.7\% \pm 15.6\%$ , respectively, at 5 and 8 years.

There are several flaws and pitfalls that may have biased the reported results in this retrospective, small assessment. Among these, the most significant may be the approximate estimations and assumptions that were made to reconstruct the dosimetric contribution of the BT boosts and the missing of some original treatment plans that were only available on paper; the absence of IMRT/image guided RT at primary RT to ensure that the planned doses were accurately and precisely delivered at each fraction; the lack of patient-reported outcomes and quality-of-life assessments; and other clinical or dosimetric variables that were not taken into account in this study. Indeed, as the severity of post-reirradiation rectal toxicity may also be influenced by patients' cardiovascular health status and its possible impact on the peripheral microvasculature,<sup>31</sup> stratifying patients by Framingham risk score at the time of first treatment appears to correlate with toxicity, which adds a confounding factor in the genesis of post-reirradiation rectal damage.

## Conclusions

As for any late-responding normal tissue, the rectal mucosa exposed to high RT doses harbours silent subclinical



damage that predisposes patients to severe side effects after reirradiation. The estimated risk of rectal toxicity after the first irradiation may predict the severity of late rectal side effects after reirradiation. A safe threshold dose for the rectum, aiming to optimally prevent the risk of grade  $\geq 3$  rectal toxicity may be to keep the summed dose below 130 Gy to any hot spot in the rectum. Salvage whole-gland reirradiation should be used with extreme care.

## Supplementary data

Supplementary material for this article (<https://doi.org/10.1016/j.adro.2018.06.001>) can be found at [www.practicalradonc.org](http://www.practicalradonc.org).

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