Excess dose-related parameters (Vex, Rex, and iRex): novel predictors and late toxicity correlations in cervical cancer image-guided adaptive brachytherapy

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Abstract

Purpose: In this paper, excess dose is originally proposed to represent the dose outside the target volume that encompass only organs at risk (OARs), not the whole dose volume of isodose surface volume (ISV). By means of spatial consideration, excess dose-related parameters would also compensate inconsistent applicator positions and OARs motion, which may deviate the identical dose small-volume assumption of D_{2cc}. Late toxicity correlations of these parameters were investigated.

Material and methods: A retrospective review was performed on cervical cancer high-dose-rate image-guided adaptive brachytherapy (HDR-IGABT). From ISVs of 60 to 100 Gy EQD_2 ($a/\beta = 3$), excess dose-related parameters were derived as following: toxicity negligible volume (Vneg = V_{60} of toxicity negligible organs; high-risk clinical target volume – HR-CTV, uterus, and vagina), excess dose volume (Vex = ISV – Vneg), Vneg normalized parameters of excess dose volume ratio (Rex = Vex/Vneg), and indirect excess dose volume ratio (iRex = ISV/Vneg). Relationships between toxicity and these parameters were analyzed using a mean difference and a probit analysis method. Net reclassification indices (NRIs) were used to compare iRex60 and D_{2cc} gastrointestinal (GI) toxicity prediction.

Results: From 143 cases with an incidence of 34.9% and 10.5% of 3-year grade 2-4 GI and genitourinary (GU) toxicity, respectively, comparisons of means showed significant difference between grade 0-1 and 2-4 toxicities for late GI toxicity for all parameters, except ISV. There was a dose-response relationship with toxicity for each parameter across the range of 60-100 Gy EQD_2. ED_{10} of iRex60 and iRex70 were 2.1 and 1.2, respectively. By comparing iRex60 and D_{2cc}, additive and absolute NRIs were +6.45 and +7.69%, respectively. The reclassification significantly occurred in range of 65-75 Gy of rectum D_{2cc}.

Conclusions: Excess dose-related parameters, including Vex, Rex, and iRex, showed significant mean differences and parameter-toxicity relationships for late GI but not for GU toxicities. Positive NRIs suggest iRex60 utilization for spatial control of dose expansion, in addition to high-dose control with OAR small volumes. Further investigations are needed to define the optimum use of these predictors.

Purpose

In image-guided adaptive brachytherapy (IGABT) for cervical cancer, inconsistent applicator positions, and movement of organs at risk (OARs) cause both inter- and intrafraction variation in dose conformation between each brachytherapy (BT) fraction [1,2,3,4,5,6,7,8], which may affect toxicity prediction. The International Commission on Radiation Units and Measurements (ICRU) 89 mentioned the potential dose volume parameter called "isodose surface volume (ISV)" as the volume encompassed by clinically relevant equi-effective dose (EQD_2) levels of combined external beam radiation therapy (EBRT) and BT doses [9]. The ISV includes not only the radiation target but also the mobile OARs, thus raising the probability of predicting OAR toxicity. In a retrospective series of 642 cervical cancer cases, a dose volume defined by the half product of height, width, and thickness (HWT), demonstrated significant correlations with rectal and soft tissue complications [10]. Total reference air kerma (TRAK), on which ISVs are based, was shown to correlate with morbidity [11,12]. For ISV, a large retrospective study of 1,253 patients failed to demonstrate any correlation between 60 and 160 Gy ISVs and tumor control [13]. The relationship between ISV and toxicity has not been studied.

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In the present study, the outside target volume dose or excess dose are originally proposed as the novel toxicity predictor. Since the excess dose includes only the space in which OAR may be located and moved, contrary to ISVs, of which the volume covers both target and OARs. Excess dose-related parameters are proposed to be more specific to OAR toxicity than ISV. Furthermore, spatial consideration of excess dose concept may compensate for the uncertainty of identical small-volume assumptions of dose-volume histogram parameters, e.g. D_{2cc} and $D_{0.1cc}$, from inconsistent applicator and OAR alignment.

In this study, excess dose volume (Vex) and its derivatives, including excess dose volume ratio (Rex) and indirect excess dose volume ratio (iRex) were proposed. Correlations between late gastrointestinal (GI) and genitourinary (GU) toxicity and these excess dose-related parameters were investigated as late toxicity predictors.

Material and methods

The study was approved by the Institutional Review Board, protocol number 713/2560 (EC1).

Patient selection, treatment procedure, and clinical evaluation

A retrospective review was performed on all cervical cancer patients receiving radical three-dimensional conformal radiotherapy (3D-CRT) with or without chemotherapy (CMT) between January 2012 and December 2015. Treatment was delivered in accordance with the Gynaecologic Groupe Européen de Curiethérapie-European Society for Radiation Oncology (GEC-ESTRO) recommendations [14,15], using high-dose-rate image-guided adaptive brachytherapy (HDR-IGABT). In cases of central shielding, parametrial or pelvic lymph node boosts, or re-irradiation, patients were excluded due to interference with ISV dose calculation as well as those patients with a follow-up time less than 6 months or incomplete data.

IGABT was guided with computer tomography (CT) or magnetic resonance imaging (MRI). In every BT fraction, after catheterization, the bladder was filled with 50 ml of contrast solution and rectal deflation using a rectal catheter was performed, while applicators were inserted and removed after radiation delivery.

Patient characteristics, imaging modalities, intracavitary (IC) with or without interstitial (IS) applicators, and dose parameters, including maximum dose to 2 cc of OARs (D_{2cc}) were recorded. Late GI and GU toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [16]. Patients were classified into 0-1 and 2-4 grades of GI and GU late toxicities occurring six months or more after completion of the treatment. Lower GI toxicity included hemorrhage, proctitis, colitis, GI tract fistula, and perforation, and GU toxicities consisted of hematuria, cystitis, and GU fistula.

Excess dose volume (Vex) and toxicity negligible volume (Vneg)

Excess dose volume (Vex = ISV – Vneg) was defined as ISV with the toxicity negligible volume (Vneg) subtraction.

Vneg describes the radiation target and the close-to-applicator normal organs, which have less impact on quality of life. By hindering the applicator, Vneg was also considered as an OAR motion limiter, since it is located close to the applicators and reflects blockage of OARs motion toward the radiation source, sparing OARs irradiation.

Excess dose volume ratio (Rex) and indirect excess dose volume ratio (iRex)

Absolute values of ISV and Vex would not reflect identical free space in each individual patient. Even with equal absolute values, ISVs and Vexs differ between each individual, due to different dose distributions and variation in the size of individual tumors and pelvic organs, which constitute Vneg. The individually varied conformations of ISV or Vex demonstrate unevenly covered OARs, leading to unequal toxicity correlations as described in Supplementary material. Hence, ISVs and Vexs would not alone be accurate, unless compared to Vneg. Excess dose volume ratio (Rex) and indirect excess dose volume ratio (iRex) were therefore proposed as the parameters, which should be normalized with Vneg and would compensate for conformationally omitted absolute values of ISV and Vex.

Rex, defined as Vex/Vneg = (ISV – Vneg)/Vneg, normalizes values for Vex between each individual. Vex and Rex have the advantage of directly reflecting the permitted space for OAR motion, but subtracted volumes and ratios of Vex and Rex were not yet supported by the automatic optimization with current treatment planning systems (TPS). iRex, derived from ISV/Vneg, was an alternative parameter of Rex, and was obtainable from automatic optimization in current TPSs. iRex was therefore favored as a potential excess dose-related parameter.

Proposed parameter delineation and calculation in each BT fraction

Each of the novel parameters were generated as follows:
ISVs were transformed from isodose lines of absorbed doses corresponding to total EQD_2 ($a/\beta = 3$) of 60, 70, 80, 90, and 100 Gy from the combined EBRT and BT dose, for example, absorbed dose of 2.34 Gy for one fraction corresponded to a total EQD_2 ($a/\beta = 3$) of 60 Gy (Supplementary material). Vneg was constituted from high-risk clinical target volume (HR-CTV) and the toxicity negligible organs, such as uterus and vagina. Uterine and vaginal toxicities were considered negligible in this study, compared to bowel and bladder toxicities. Delineation of toxicity negligible organs included HR-CTV, uterus up to fundus, and vagina downward below lower border of generated ISV60s. Vneg60 was defined as volume of Vneg exposed to 60 Gy EQD_2 ($a/\beta = 3$) and was used in Vex delineation as well as in Rex and iRex calculations.

Vex (= ISV60, …, 100 – Vneg60) was generated by subtracting Vneg60 from each corresponding dose of ISV.

Each Rex (= Vex60, …, 100/Vneg60) was calculated by dividing corresponding Vex with Vneg60, and similarly, ISV was divided by Vneg60 for iRex (= ISV60, …, 100/Vneg60).

Delineations and ratio calculations are summarized in Figure 1.

A — Isodose surface volume (ISV) 60-100 Gy EQD$_2$ ($\alpha/\beta = 3$)

B — Excess dose-related parameter delineations and ratio calculations

ISV — volume encompassed by 60-100 Gy EQD$_2$ ($\alpha/\beta = 3$) of combined EBRT and BT dose

Vneg — radiation target and OAR with less QOL disturbing toxicity considered as other OARs motion limiter (HR-CTV $\cup$ uterus $\cup$ vagina)

Vneg60 = V60 Gy EQD$_2$ ($\alpha/\beta = 3$) of Vneg

Vex = ISV – Vneg

$$Rex = \frac{Vex}{Vneg60} = \frac{ISV - Vneg}{Vneg60}$$

$$iRex = \frac{ISV}{Vneg60}$$

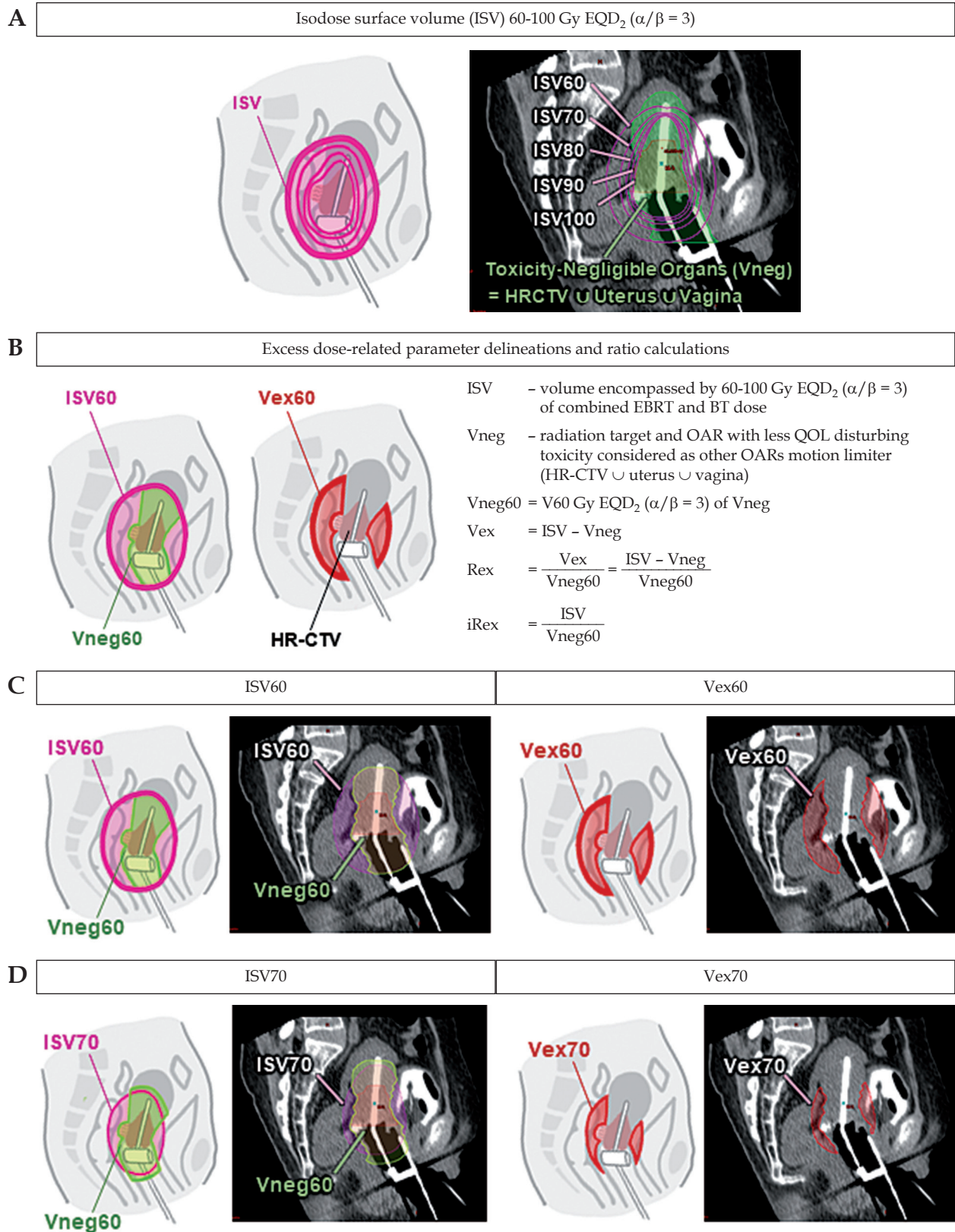**C** — ISV60 | Vex60

D — ISV70 | Vex70

Fig. 1. A) Isodose surface volume (ISV) encompassing organs at risk, delineated in pink lines. Toxicity negligible organs included HR-CTV, uterus, and vagina delineated in the green line. **B)** Excess dose-related parameter delineations and ratio calculations. **C)** Depicts ISV60 and Vex60 example. **D)** Depicts ISV70 and Vex70 example

Vneg – toxicity negligible volume, Vex – excess dose volume, Rex – excess dose volume ratio, iRex – indirect excess dose volume ratio, ISV60 – isodose surface volume of 60 Gy EQD$_2$, Vex60 – excess dose volume of 60 Gy EQD$_2$, QOL – quality of life

Toxicity – novel parameter correlation analysis and statistical method

Mean ISV, Vex, Rex, and iRex data for every patient were calculated for each of the prescribed 3-5 fractions. Relationships between toxicity and novel parameters were analyzed for mean difference, and probit analysis was performed using PASW statistics, version 18.0.0. Mathematical means of these mean values were compared between grade 0-1 and 2-4 toxicities, using Mann-Whitney test. The dose-response relationship between means of parameters and grade 2-4 toxicities was analyzed with probit analysis.

iRex60 vs. D_{2cc} GI toxicity prediction reclassification analysis

Net reclassification indices (NRI) [17] were used to compare iRex60 and D_{2cc} GI toxicity prediction. An effective dose for 10% and 15% toxicity probability (ED_{10} and ED_{15}) cut points of 2.1 and 2.3 from the iRex60 probit result were used, while D_{2cc} values of 65 and 75 Gy for rectum were selected as defined in the image-guided intensity-modulated external beam radiochemotherapy and MRI-based adaptive BRAchytherapy in locally advanced CErvical cancer (EMBRACE II) protocol [18,19].

Table 1. Patient characteristics (median follow-up time, 37 months)

Parameters	Total n (%)	GI toxicity			GU toxicity		
		Grade 0-1	Grade 2-4	p-value	Grade 0-1	Grade 2-4	p-value
Total number (%)	143	93 (65.1%)	50 (34.9%)		128 (89.5%)	15 (10.5%)	
Age (years), median (range)	57 (24-84)	53 (24-84)	62 (24-84)	< 0.001[t]	58 (32-84)	47 (24-79)	0.019[t]
FIGO 2009 staging							
IB1	4 (2.8%)	0	4	0.198[χ]	3	1	0.383[χ]
IB2	7 (4.9%)	6	1	–	7	0	–
IIA	17 (11.9%)	10	7	–	17	0	–
IIB	44 (30.8%)	29	15	–	36	8	–
IIIA	2 (1.4%)	0	2	–	2	0	–
IIIB	59 (41.3%)	39	20	–	54	5	–
IVA	10 (6.9%)	9	1	–	9	1	–
Concurrent chemotherapy							
Yes	130 (90.9%)	84	46	0.739[χ]	117	13	0.546[χ]
No	13 (9.1%)	9	4	–	11	2	–
Imaging							
CT-based BT	101 (70.6%)	65	36	0.792[χ]	92	9	0.338[χ]
MRI-based BT	42 (29.4%)	28	14	–	36	6	–
Applicator							
IC alone	84 (58.7%)	52	32	0.349[χ]	75	9	0.917[χ]
IC/IS	59 (41.3%)	41	18		53	6	–
Mean HR-CTV ±SD, cc	35.12 ±25.40	36.37 ±28.88	32.79 ±17.15	0.423[t]	35.35 ±26.31	33.07 ±16.01	0.743[t]
Mean D_{2cc} ±SD, Gy EQD_2 (a/β = 3)							
Rectum	69.75 ±5.95	68.55 ±5.48	71.98 ±6.18	0.001[t]	–	–	–
Sigmoid	60.12 ±6.33	60.17 ±6.37	60.02 ±6.32	0.887[t]	–	–	–
Bowel	64.78 ±10.50	63.86 ±10.24	66.49 ±10.88	0.154[t]	–	–	–
Bladder	85.08 ±7.08	–	–	–	84.96 ±7.25	85.95 ±5.72	0.591[t]

D_{2cc} – maximum dose to 2 cc, EQD_2 – 2 Gy equi-effective dose, HR-CTV – clinical target volume for high-risk region, IC – intracavitary, IS – interstitial implantation, n – number, SD – standard deviation, [t] – Student's t-test, [χ] – chi-square test

Results

A total of 143 cases from 364 cervical cancer patients treated over the study period were reviewed. 221 cases were excluded due to central shielding (n = 92), parametrial and pelvic lymph nodal boost (n = 104), pelvic re-irradiation (n = 2), and follow-up time less than 6 months or incomplete data (n = 23). Median follow-up time was 37 (range, 6-70) months. Patient characteristics and DVH parameters are presented in Table 1.

For BT, imaging modalities were classified into MRI-based and CT-based BT. MRI-based BT included patients who underwent MRI for every fraction (MR alone) or MRI for only first fraction of BT (MR first fraction), which accounted for 42 (29.4%) patients. CT-based BT includ-
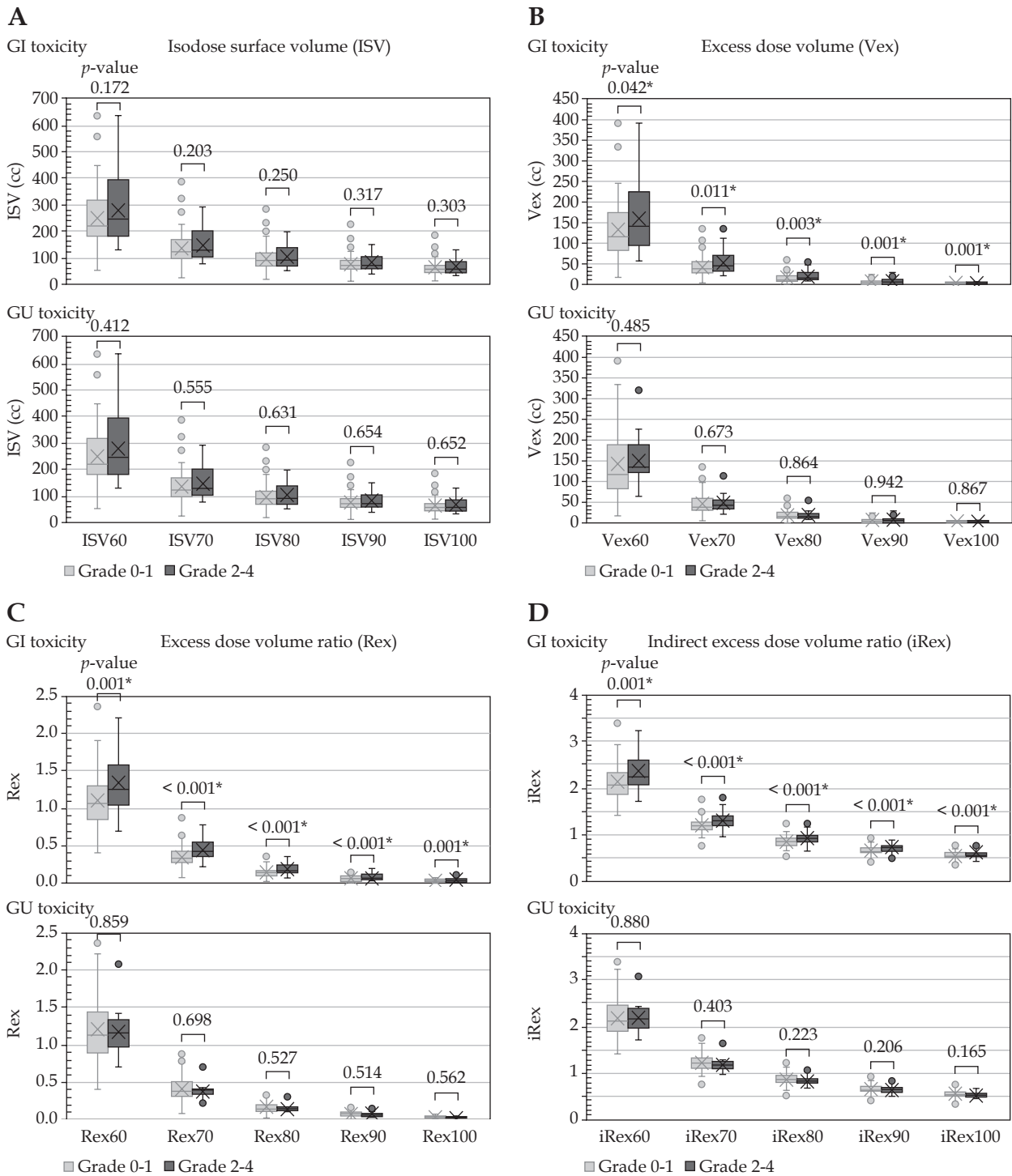

Fig. 2. Boxplots of mean of ISV, Vex, Rex, and iRex according to grade 0-1 and 2-4 GI and GU toxicities

ed patients who underwent only CT for every fraction (CT alone) with or without fusion of pre-brachytherapy MRI (MR pre-BT), which occurred in 101 (70.6%) patients. IC applicators were used for 84 (58.7%) patients and in combination with IS for 59 (41.3%) patients.

The total number of grade 2-4 late GI toxicities was 50 (34.9%), while late GU toxicities was 15 (10.5%). The total number of grade 3-4 late GI toxicities was 19 (13.3%), while

late GU toxicities was 5 (3.5%). All 19 cases of grade 3 and 4 late GI toxicities were confirmed with endoscopic examination, and included 12 rectal, 3 rectosigmoid, 2 anorectal, and 1 case of both sigmoid and rectal telangiectasia. The remaining patient developed a grade 3 rectal ulcer with anal telangiectasia at 1 year after the treatment, followed by a grade 4 jejunal perforation, 5 years after the treatment.

The mathematical mean of mean Vex, Rex, and iRex for each patient demonstrated significant differences between grade 0-1 and 2-4 late GI toxicity from 60 to 100 Gy EQD_2 ($\alpha/\beta = 3$). No significant mean differences were observed for ISV and all late GU toxicities (Figure 2 and Supplementary material).

There was a significant correlation with toxicity at each radiation dose for all parameters studied (see Supplementary material). The mean ISV exhibited a significant probit analysis for 70 to 100 Gy EQD_2 ($\alpha/\beta = 3$) of ISV (ISV70 to ISV100), except for ISV60. The mean Vex showed a significant dose-response relationship with grade 2-4 late GI toxicities for Vex80 and Vex90. The mean Rex demonstrated a significant dose-response relationship with grade 2-4 late GI toxicities for Rex60. The mean iRex exhibited a significant dose-response relationship with grade 2-4 late GI toxicities for iRex60 and iRex70, with an ED_{10} of 2.129 and 1.211, respectively (Figure 3 and Supplementary material). When comparing iRex60 and D_{2cc} toxicity prediction, additive and absolute NRIs were +6.45 and +7.69%, respectively. The reclassification occurred most strongly in the 65-75 Gy range for the D_{2cc} of rectum (Figure 4).
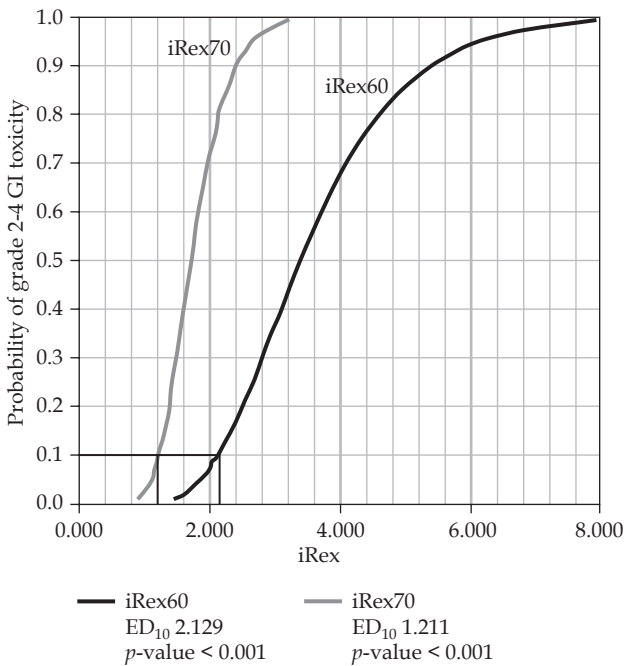
Discussion

In this study, the discrepantly higher toxicity was observed, comparing to tolerable D2cc doses. As hypothesized, the effect of inconsistent applicator positions and

Fig. 3. Dose-response relationship of indirect excess dose volume ratio (iRex) and grade 2-4 late GI toxicity by probit analysis

A No. of grade 2-4 GI late toxicities ($n = 50$, 34.9% of total)

D_{2cc} rectum	iRex60			
	< 2.1	≥ 2.1 − < 2.3	≥ 2.3	Total
≤ 65 Gy	4	0	1	5
> 65 − ≤ 75 Gy	7	10	11	28
> 75 Gy	3	2	12	17
Total	14	12	24	50

B No. of grade 0-1 GI late toxicities ($n = 93$, 65.1% of total)

D_{2cc} rectum	iRex60			
	< 2.1	≥ 2.1 − < 2.3	≥ 2.3	Total
≤ 65 Gy	21	3	2	26
> 65 − ≤ 75 Gy	26	16	17	59
> 75 Gy	1	1	6	8
Total	48	20	25	93

C Reclassification indices calculation

	Grade 2-4 (events)	Grade 0-1 (non-events)	
Correct reclassification	12	28	Additive NRI +6.45
Incorrect reclassification	12	22	Absolute NRI +7.69%
Net reclassification	0	6	

Fig. 4. iRex60 vs. D_{2cc} GI toxicity prediction reclassification analysis

D_{2cc} – maximum dose to 2 cc, iRex60 – indirect excess dose volume ratio of 60 Gy EQD_2 ($\alpha/\beta = 3$), NRI – net reclassification indices

OARs motion may deviate the identical dose-volume assumption of small-volume dose. Excess dose-related parameters, proposed to represent the dose outside the target and to compensate the OAR motion factor, established significant correlations with late GI toxicity only for Vex, Rex, and iRex, but not ISV. No correlation was observed with GU toxicity.

There was no significant correlation between ISV and GI toxicity. In previous studies, which have reported significant correlation [10,11,12], ISV or TRAK and toxicity correlation may have been confused by the dose outside target, not the whole dose volume.

Vex showed a significant relationship with GI toxicity, with a significant dose-response relation at 80-90 Gy. The lack of a dose-response relation for Vex100 resulted from the exceedingly small volumes of Vex100. The absence of toxicity correlation with Vex60 and Vex70 could reflect the uncertainty in toxicity prediction using absolute dose volumes at low doses. At low-dose levels, with larger territory of dose coverage, the distribution of dose is more varied compared to high-dose level. The equal absolute values for low-dose levels of ISV and Vex between each individual fraction could not reflect the different shape and coverage of the OAR outside Vneg. Therefore, the poor correlation with toxicity at low-dose levels was demonstrated by examples included in Supplementary material.

In contrast, for Rex and iRex, the lower dose levels were predictive of toxicity, in particular Rex60 and iRex60-70, comparable to the higher predictive dose levels of ISV and Vex. The low-dose prediction of Rex and iRex emphasizes the normalization effect on Vneg from calculating Rex and iRex, which compensates for the varied conformations of ISV and Vex. Both Rex and iRex demonstrated the same significant correlations between Rex60, iRex60, and iRex70 for late GI toxicity. These results confirm that iRex may be used instead of Rex.

The absence of a relation between GU toxicity and any parameter may be explained by the low number of events (10.5%), compared to GI toxicity events (34.9%).

Excess dose-related parameters could be more accurate as toxicity predictors because they compensate for OAR motion, which is not captured in dose-volume histogram (DVH) parameters. Based on the analysis presented here, Rex and iRex were recommended as having a significant correlation with toxicity in low-dose regions and the Vneg relative properties. Positive NRIs also suggested iRex60 utilization for dose expansion spatial control, in addition to high-dose control with OAR small volumes.

Although, Rex (Rex = Vex/Vneg) directly reflects the excess dose, unfortunately this was not currently derived during the optimization process within a commercial TPS. However, iRex (iRex = ISV/Vneg) as an indirect measure of Rex, was produced by the TPS, and it was therefore proposed that iRex was used until Rex could be produced by the TPS automatically.

A limitation of these conclusions was that the comparison of ISV, Vex, Rex, and iRex with dose to small volumes (D_{2cc} and $D_{0.1cc}$) in predicting toxicity has not been fully validated. Toxicity measurement was retrospective with inherent inaccuracies. There was a variation in imaging, using both CT and MRI, which would have altered OAR volume accuracy; CT volumes were tending to be larger than those defined by MRI. This study assumed a uniform dose of EBRT. Its validity when a pelvic boost was used, which would interfere with ISV dose calculation should yet be explored. Future studies with multivariate analysis as well as prospective studies and DVH parameter comparison are crucial in further validation and development of these novel toxicity predictors.

Conclusions

Excess dose-related parameters, including Vex, Rex, and iRex, were significantly related to late GI but not GU toxicity. iRex60 is the most suitable parameter, as it can be derived directly from a commercial TPS, with an ED_{10} of 2.1. Further investigations are needed for robust validation of these toxicity predictors to be used for spatial control of dose expansion in addition to control of high-dose regions by conventional DVH parameters for OAR small volumes, such as D_{2cc} and $D_{0.1cc}$.

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Disclosure

The authors report no conflict of interest.

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Supplementary material

Table S1. Fractional absorbed doses corresponded to equi-effective dose (EQD$_2$) (α/β = 3) of 60, 70, 80, 90, and 100 Gy from combined external beam radiation therapy (EBRT) and brachytherapy (BT) dose

Total EBRT dose, Gy	Number of BT fractions	Fractional absorbed doses corresponded to EQD$_2$ (α/β = 3), Gy				
		ISV60	ISV70	ISV80	ISV90	ISV100
46	4	2.94	4.18	5.19	6.07	6.85
46	5	2.53	3.62	4.52	5.30	6.00
50	3	2.85	4.47	5.73	6.80	7.75
50	4	2.34	3.72	4.80	5.73	6.55
50	5	2.00	3.22	4.18	5.00	5.73

Table S2. The comparison of mean differences of all parameters between grade 0-1 and 2-4 late toxicity groups, with median follow-up time of 37 months

Grade			GI toxicity			GU toxicity		
			Grade 0-1	Grade 2-4	*p*-value	Grade 0-1	Grade 2-4	*p*-value
Isodose surface volume (ISV) Mean ±SD, cc	ISV60	261.5 ±117.5	251.2 ±113.0	280.6 ±124.3	0.172	260.2 ±119.8	272.4 ±98.3	0.412
	ISV70	143.3 ±59.7	139.0 ±60.2	151.4 ±58.7	0.203	143.0 ±61.0	146.5 ±48.8	0.555
	ISV80	101.2 ±41.1	98.4 ±41.9	106.2 ±39.3	0.250	101.0 ±42.1	102.5 ±32.4	0.631
	ISV90	78.9 ±31.7	77.1 ±32.7	82.2 ±29.7	0.317	78.8 ±32.4	79.9 ±24.8	0.654
	ISV100	65.2 ±26.2	63.7 ±27.0	68.0 ±24.7	0.303	65.1 ±26.9	65.8 ±20.5	0.652
Excess dose volume (Vex = ISV – Vneg) Mean ±SD, cc	Vex60	142.7 ±75.8	132.6 ±70.0	161.5 ±83.1	0.042	142.1 ±77.1	148.0 ±66.0	0.485
	Vex70	46.3 ±24.6	42.3 ±22.6	53.6 ±26.7	0.011	46.3 ±25.0	46.3 ±22.1	0.673
	Vex80	18.1 ±10.7	16.3 ±9.7	21.6 ±11.7	0.003	18.2 ±10.9	17.8 ±9.5	0.864
	Vex90	7.4 ±5.0	6.4 ±4.5	9.1 ±5.6	0.001	7.4 ±5.1	7.0 ±4.4	0.942
	Vex100	3.1 ±2.6	2.6 ±2.2	4.0 ±2.9	0.001	3.1 ±2.6	2.9 ±2.3	0.867
Excess dose volume ratio (Rex = Vex/Vneg) Mean ±SD	Rex60	1.20 ±0.40	1.12 ±0.37	1.36 ±0.42	0.001	1.20 ±0.41	1.19 ±0.33	0.859
	Rex70	0.39 ±0.15	0.36 ±0.13	0.46 ±0.15	< 0.001	0.40 ±0.15	0.37 ±0.11	0.698
	Rex80	0.16 ±0.07	0.14 ±0.07	0.19 ±0.07	< 0.001	0.16 ±0.07	0.14 ±0.05	0.527
	Rex90	0.06 ±0.04	0.06 ±0.04	0.08 ±0.04	< 0.001	0.07 ±0.04	0.06 ±0.02	0.514
	Rex100	0.03 ±0.02	0.02 ±0.02	0.04 ±0.02	0.001	0.03 ±0.02	0.02 ±0.01	0.562
Indirect excess dose volume ratio (iRex = ISV/Vneg) Mean ±SD	iRex60	2.22 ±0.41	2.13 ±0.37	2.38 ±0.44	0.001	2.22 ±0.42	2.20 ±0.33	0.880
	iRex70	1.22 ±0.17	1.18 ±0.15	1.30 ±0.18	< 0.001	1.23 ±0.18	1.19 ±0.15	0.403
	iRex80	0.87 ±0.12	0.84 ±0.11	0.92 ±0.12	< 0.001	0.87 ±0.12	0.84 ±0.09	0.223
	iRex90	0.68 ±0.09	0.66 ±0.08	0.71 ±0.08	< 0.001	0.68 ±0.09	0.65 ±0.07	0.206
	iRex100	0.56 ±0.07	0.54 ±0.07	0.59 ±0.07	< 0.001	0.56 ±0.07	0.54 ±0.06	0.165

Table S3. Probability of isodose surface volume (ISV) for grade 2-4 late toxicities for the incidence rates shown in 95% confidence interval

ISV	5%	10%	20%	*p*-value
GI toxicity				
ISV60	134.9 (128.8-140.7)	194.6 (189.0-200.0)	303.2 (296.6-310.2)	0.078
ISV70	78.0 (74.2-81.6)	109.3 (105.9-112.6)	164.6 (160.8-168.7)	0.006
ISV80	56.0 (53.2-58.6)	77.6 (75.2-80.0)	115.4 (112.6-118.2)	< 0.001
ISV90	43.8 (41.5-45.9)	60.4 (58.4-62.3)	89.3 (87.1-91.5)	< 0.001
ISV100	36.3 (34.5-38.0)	50.1 (48.4-51.6)	73.9 (72.1-75.7)	< 0.001
GU toxicity				
ISV60	280.3 (269.7-291.0)	437.5 (416.0-463.5)	750.3 (686.7-833.7)	1.000
ISV70	150.2 (144.8-155.7)	230.5 (219.7-243.5)	387.2 (355.5-428.7)	1.000
ISV80	104.9 (101.1-108.6)	160.6 (153.2-169.7)	269.5 (247.3-298.6)	1.000
ISV90	81.5 (78.6-84.5)	124.7 (118.10-131.7)	208.7 (191.5-231.2)	1.000
ISV100	67.4 (65.1-69.8)	102.8 (98.1-108.5)	171.3 (157.4-189.5)	1.000

Table S4. Probability of excess dose volume (Vex) for grade 2-4 late toxicities for the incidence rates shown in 95% confidence interval

Vex	5%	10%	20%	*p*-value
GI toxicity				
Vex60	70.8 (67.5-74.1)	106.1 (102.8-109.3)	173.0 (168.7-177.5)	0.851
Vex70	24.6 (23.6-25.7)	36.1 (35.1-37.1)	57.4 (56.0-58.9)	0.101
Vex80	9.54 (9.03-10.02)	14.2 (13.7-14.7)	23.1 (22.4-23.9)	0.001
Vex90	3.67 (3.45-3.88)	5.69 (5.45-5.91)	9.65 (9.31-10.0)	< 0.001
Vex100	1.32 (1.24-1.39)	2.21 (2.13-2.30)	4.15 (4.01-4.30)	0.273
GU toxicity				
Vex60	150.7 (144.3-157.3)	250.0 (236.6-266.2)	461.5 (418.8-517.5)	1.000
Vex70	47.3 (45.2-49.3)	79.1 (74.9-84.2)	147.6 (133.9-165.7)	0.998
Vex80	17.7 (16.8-18.9)	31.6 (29.8-33.9)	63.8 (57.2-72.6)	0.317
Vex90	6.90 (6.46-7.34)	13.3 (12.3-14.5)	29.4 (25.6-34.7)	0.009
Vex100	2.62 (2.44-2.81)	5.90 (5.45-6.46)	15.8 (13.6-18.8)	0.768

Table S5. Probability of excess dose volume ratio (Rex) for grade 2-4 late toxicities for the incidence rates shown in 95% confidence interval

Rex	5%	10%	20%	*p*-value
GI toxicity				
Rex60	0.884 (0.856-0.909)	1.105 (1.081-1.128)	1.449 (1.422-1.477)	< 0.001
Rex70	0.289 (0.282-0.296)	0.368 (0.361-0.374)	0.492 (0.484-0.500)	0.176
Rex80	0.104 (0.101-0.107)	0.140 (0.137-0.143)	0.201 (0.197-0.205)	0.722
Rex90	0.037 (0.035-0.038)	0.054 (0.052-0.055)	0.086 (0.083-0.088)	0.920
Rex100	0.012 (0.011-0.013)	0.020 (0.019-0.021)	0.037 (0.036-0.038)	1.000
GU toxicity				
Rex60	1.232 (1.197-1.267)	1.727 (1.667-1.796)	2.598 (2.439-2.799)	1.000
Rex70	0.386 (0.373-0.398)	0.562 (0.542-0.586)	0.888 (0.830-0.962)	0.263
Rex80	0.147 (0.141-0.154)	0.231 (0.220-0.244)	0.399 (0.366-0.442)	0.019
Rex90	0.057 (0.054-0.060)	0.103 (0.098-0.109)	0.209 (0.189-0.235)	0.208
Rex100	0.023 (0.021-0.024)	0.050 (0.046-0.054)	0.129 (0.112-0.152)	0.998

Table S6. Probability of indirect excess dose volume ratio (iRex) for grade 2-4 late toxicities for the incidence rates shown in 95% confidence interval

| iRex	5%	10%	20%	*p*-value
GI toxicity				
iRex60	1.865 (1.825-1.901)	2.129 (2.098-2.158)	2.499 (2.467-2.532)	< 0.001
iRex70	1.099 (1.085-1.112)	1.211 (1.201-1.222)	1.363 (1.352-1.375)	< 0.001
iRex80	0.785 (0.778-0.793)	0.860 (0.854-0.865)	0.959 (0.953-0.965)	0.395
iRex90	0.615 (0.610-0.621)	0.670 (0.666-0.674)	0.743 (0.739-0.748)	1.000
iRex100	0.507 (0.502-0.512)	0.553 (0.550-0.557)	0.615 (0.611-0.618)	0.918
GU toxicity				
iRex60	2.265 (2.226-2.302)	2.766 (2.709-2.833)	3.525 (3.395-3.687)	0.940
iRex70	1.199 (1.180-1.216)	1.431 (1.406-1.459)	1.772 (1.714-1.846)	0.681
iRex80	0.841 (0.829-0.853)	0.992 (0.977-1.010)	1.212 (1.176-1.258)	0.767
iRex90	0.659 (0.649-0.667)	0.768 (0.757-0.781)	0.926 (0.900-0.958)	0.986
iRex100	0.541 (0.533-0.548)	0.636 (0.627-0.647)	0.774 (0.751-0.803)	0.823
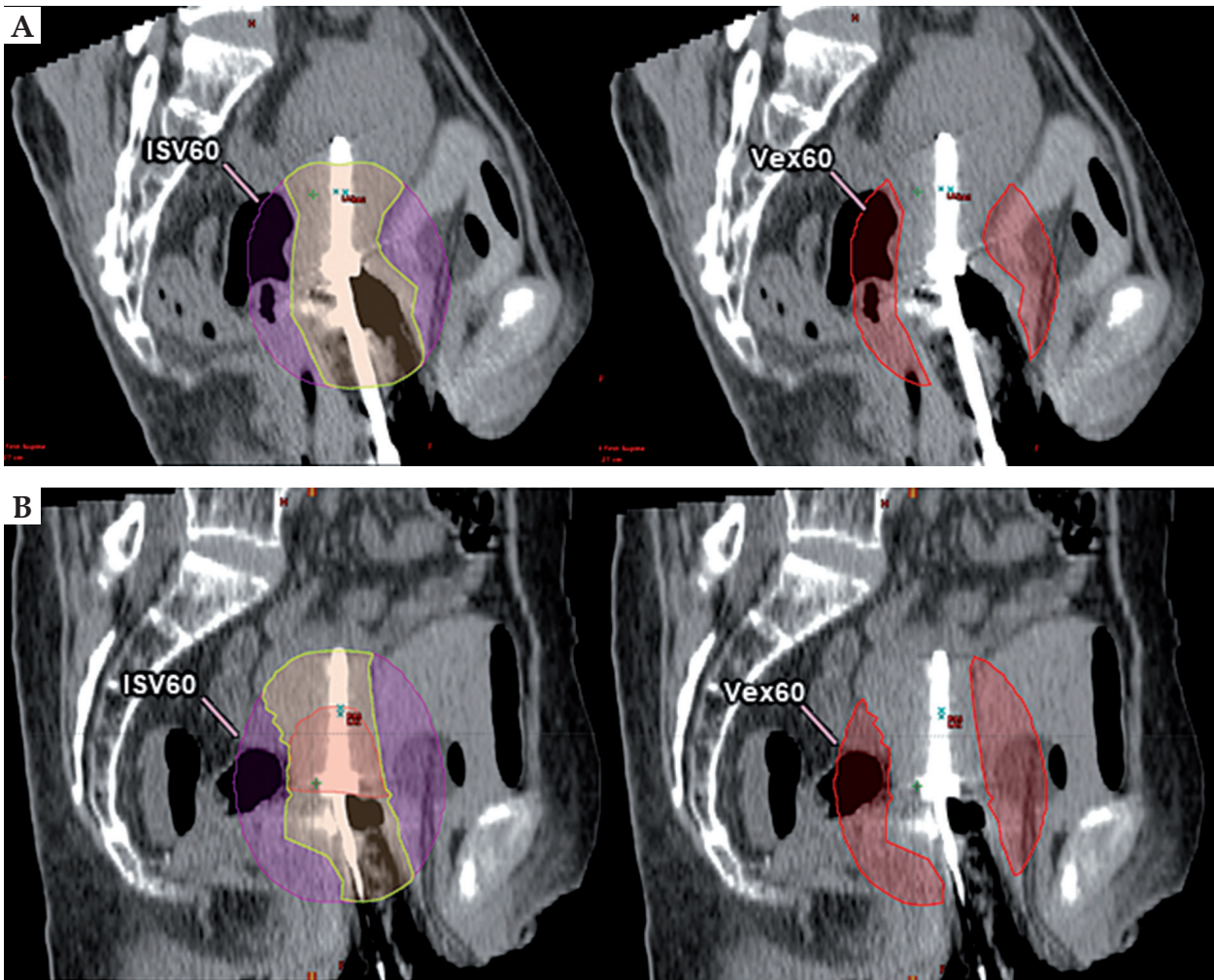
Fig. S1. A, B) Equal ISVs values but different in their conformations between each individual, due to different dose distributions and sizes of individual tumors and pelvic organs; the compositions of Vneg. The varied conformations precipitate the unequal encompassment for organ at risk motion, leading to unequal toxicity correlations. Of note, Rexs and iRexs differed in each case and correlated more to GI toxicity, highlighting the relative property of ratio parameters. As summarize in Table S7

Table S7. Patient characteristic, dose parameters, and radiation toxicity according to cases presented in Fig. S1

Patient	Age (year)	Stage	Vneg (cc)	HR-CTV (cc)	ISV60 (cc)	Vex60 (cc)	Rex60	iRex60	D_{2cc} rectum (Gy)	GI toxicity grade	GU toxicity grade	F/U time (month)
S1-A	59	3B	98.31	19.5	215.5	116.4	1.186	2.194	72.82	0	0	40
S1-B	69	3B	87.33	25.5	215.5	127	1.446	2.461	72.78	3*	0	42

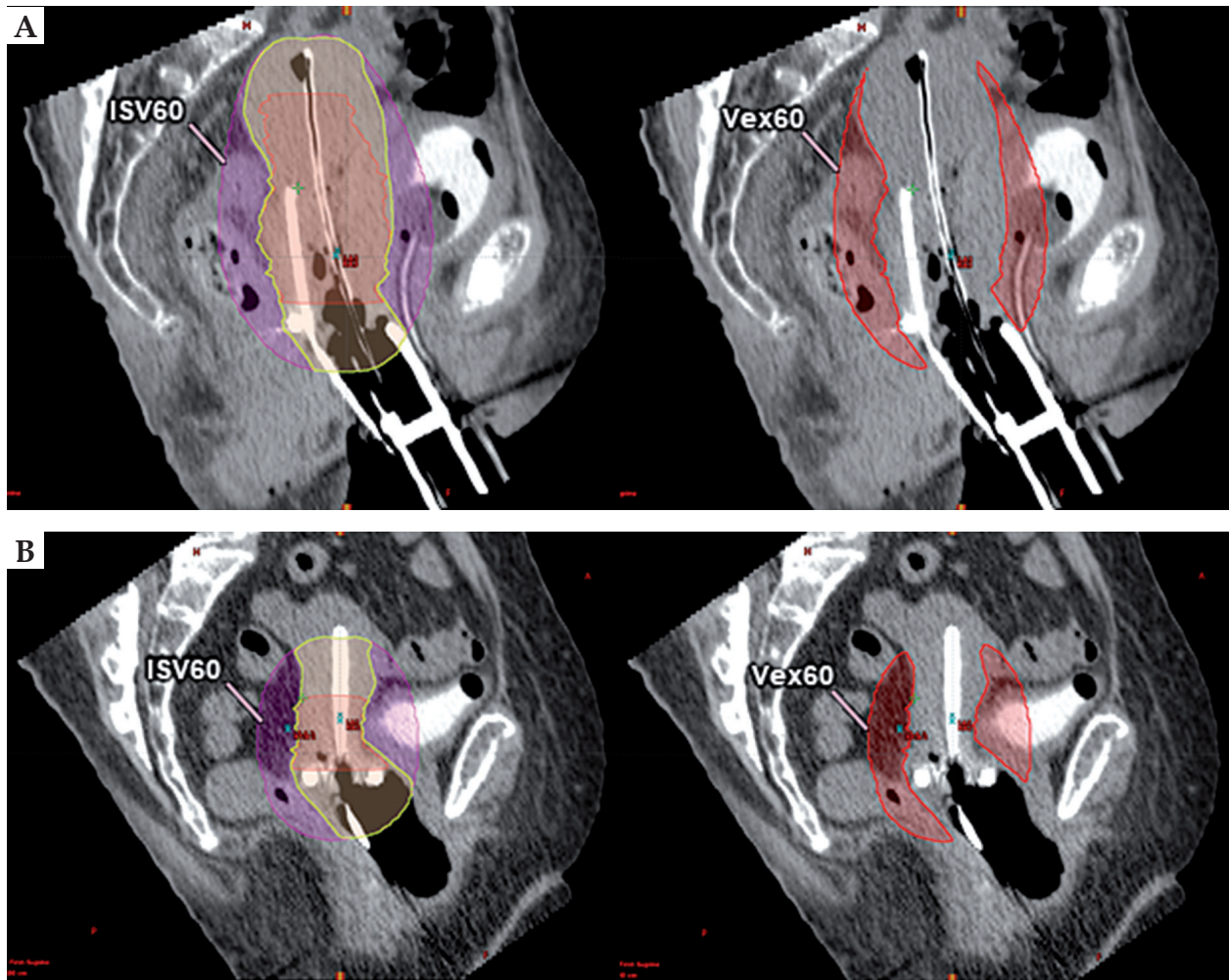*Telangiectasia at rectum and anal canal

Fig. S2. A, B) Equal Vexs values but different in their conformations between each individual, due to different dose distributions and sizes of individual tumors and pelvic organs; the compositions of Vneg. The varied conformations precipitate the unequal encompassment for organ at risk motion, leading to unequal toxicity correlations. Of note, Rexs and iRexs differed in each case and correlated more to GI toxicity, highlighting the relative property of ratio parameters. As summarize in Table S8

Table S8. Patient characteristic, dose parameters, and radiation toxicity according to cases presented in Fig. S2

Patient	Age (year)	Stage	Vneg (cc)	HR-CTV (cc)	ISV60 (cc)	Vex60 (cc)	Rex60	iRex60	D_{2cc} rectum (Gy)	GI toxicity grade	GU toxicity grade	F/U time (month)
S2-A	76	3B	244.3	160.5	406.25	158.71	0.649	1.663	69.73	0	0	41
S2-B	68	3B	85.77	95	245.25	158.97	1.859	2.864	75.03	3*	0	34

Telangiectasia at rectum and sigmoid colon