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Guidelines

Acute patient-reported intestinal toxicity in whole pelvis IMRT for prostate cancer: Bowel dose-volume effect quantification in a multicentric cohort study

Andrea Bresolin [a,b], Adriana Faiella [c], Elisabetta Garibaldi [d,1], Fernando Munoz [e], Domenico Cante [f], Vittorio Vavassori [g], Justina Magdalena Waskiewicz [h], Giuseppe Girelli [i], Barbara Avuzzi [j], Elisa Villa [g], Alessandro Magli [k], Barbara Noris Chiorda [j], Marco Gatti [d], Letizia Ferella [e], Angelo Maggio [d], Valeria Landoni [c], Stefania Aimonetto [e], Carla Sini [a,2], Tiziana Rancati [j,l], Giuseppe Sanguineti [c], Riccardo Valdagni [j,l], Nadia Di Muzio [a,m], Claudio Fiorino [a,*], Cesare Cozzarini [a]

[a] *San Raffaele Scientific Institute;* [b] *Fondazione Centro San Raffaele;* [c] *IRCCS Istituto Nazionale dei Tumori "Regina Elena", Rome;* [d] *Istituto di Candiolo – FPO-IRCCS, Candiolo;* [e] *Ospedale Regionale Parini-AUSL Valle d'Aosta, Aosta;* [f] *Ospedale di Ivrea, Ivrea;* [g] *Cliniche Gavazzeni-Humanitas, Bergamo;* [h] *Comprensorio Sanitario di Bolzano, ;* [i] *Ospedale degli Infermi, Biella;* [j] *Fondazione IRCCS Istituto Nazionale dei Tumori, Milan;* [k] *Azienda Ospedaliero Universitaria S. Maria della Misericordia, Udine;* [l] *Fondazione IRCCS Istituto Nazionale dei Tumori, Prostate Cancer Program, Milan; and* [m] *Dept. of Oncology and Hemato-Oncology, University Vita-Salute San Raffaele, Milan, Italy*

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ABSTRACT

Background and purpose: To assess bowel dose-volume relationships for acute patient-reported intestinal symptoms of patients treated with whole-pelvis intensity-modulated radiotherapy (WPRT) for prostate cancer.

Materials and methods: Complete data of 415 patients enrolled in a multi institute, prospective trial (#NCT02803086) treated with radical (31%), adjuvant (33%) and salvage (36%) intent at a median dose to pelvic nodes/lymph-nodal area of 53 Gy were available. The most severe changes between baseline and radiotherapy mid-point/end toxicity assessed by Inflammatory Bowel Disease Questionnaire (only Bowel Domain) were considered (ΔIBDQ). The 25th percentile values of these score variations were set as endpoints. DVHs of bowel loops for patients with/without toxicity were compared for each end-point, having excluded patients with baseline scores <5 (rate ranging between 2% and 7% according to the endpoint): the resulting best dosimetric predictors were combined with selected clinical parameters through multivariate logistic regression (MVA) to derive predictive models.

Results: ΔIBDQ ranged between 0.2–1.5 points considering separately each IBDQ symptom. Only four symptoms (IBDQ1 = frequency, IBDQ5 = diarrhea, IBDQ17 = gas passage, IBDQ24 = urgency) showed a median worsening ≥ 1; DVH predicted the risk of worse symptoms for IBDQ5, IBDQ24 and overall Bowel Domain. At multivariable analysis DVHs (best cut-off: V46Gy $\geq$80 cc) and baseline scores (Odd-Ratio:0.35–0.65) were independently associated to the three end-points. The resulting models were reliable (H&L test: 0.453–0.956), well calibrated (calibration plot: slope = 0.922–1.069, R^2 = 0.725–0.875) and moderately discriminative (Area Under the Curve:0.628–0.669). A bootstrap-based validation confirmed their robustness.

Conclusion: Constraining the bowel loops (V46 < 80 cc) may reduce the risk of several moderate intestinal symptoms, with a much greater impact for patients with lower IBDQ baseline scores.

Abbreviations: WPRT, whole-pelvis radiotherapy; QoL, quality of life; PRO, patient-reported outcomes; IBDQ, inflammatory bowel disease questionnaire; IBDQ-B, IBDQ bowel domain; IBDQ-E, IBDQ emotional domain; IBDQ-Sy, IBDQ systemic domain; IBDQ-So, IBDQ social domain; ΔIBDQ5, maximum variation of the "loose bowel movement" IBDQ item; ΔIBDQ24, maximum variation of the "urgency" IBDQ item; ΔIBDQ-B, maximum variation of the mean score relative to the IBDQ bowel domain; BMI, body mass index; DVH, dose-volume histogram; IHU-WPRT TOX, intestinal, hematologic and urinary toxicity from whole-pelvis radiotherapy cohort study; EPQ-R, Eysenck personality questionnaire (revised); RT, radiotherapy; PB-PTV, prostatic bed planning target volume; LN-PTV, lymph nodes planning target volume; UVA, univariable logistic regression analysis; MVA, multivariable logistic regression analysis; H&L, Hosmer and Lemeshow test; Vx, volume (cm^3) of small bowel loops receiving x Gy; PORT, post-prostatectomy radiotherapy; RAD, radical radiotherapy.

* Corresponding author at: Department of Medical Physics, IRCCS San Raffaele Scientific Institute, Via Olgettina, 60 – 20132 Milan, Italy.
E-mail address: fiorino.claudio@hsr.it (C. Fiorino).
[1] Currently Azienda Ospedaliera Nazionale SS. Antonio e Biagio e C. Arrigo, Alessandria, Italy.
[2] Currently Presidio Ospedaliero San Francesco, Nuoro, Italy.

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Intestinal toxicity is a common radiation induced side-effect in the treatment of pelvic and abdominal tumors [1], representing a limiting factor in the treatment of pelvic lymph-nodal areas with the intent to eradicate micrometastases in the treatment of rectal, gynecological and bladder cancers.

Whole-pelvis radiotherapy (WPRT) may be delivered in both radical and post-prostatectomy treatment of intermediate- and high-risk, clinically localized, prostate cancer, although its use is still controversial [2,3]. Despite the benefit of intensity-modulated radiation therapy (IMRT) in reducing intestinal toxicity [4–8], the possible detrimental effect of WPRT remains a significant issue owing to its poorly investigated impact on patient quality of life (QoL) [1,9–12]. The existence of a dose-volume effect for the bowel is known, having been recognized even in the pre-IMRT era when an association between the field extension and the risk of occurrence and severity of acute intestinal side-effects (primarily diarrhea) was reported [6,13]. With the advent of IMRT, the need for a more accurate quantitative assessment of dose-volume effect relationships became more urgent [14]. Surprisingly, the subject remains largely under-investigated, although recent studies have contributed to an improvement in the scenario [4–8,14–18]. There are several reasons for this inadequate knowledge, including the difficulty in objectively reporting intestinal radiation-induced symptoms, their correlation with individual clinical features (such as individual patient personality, microbioma, use of drugs) and dosimetric uncertainties due to bowel motion. In addition to this difficulty, there is a growing awareness that patient-reported scoring of bowel symptoms is to be preferred [1,4–9,11,12,14].

A prospective multi institute study was activated in 2014 [18,19]. The aim was to assess the dosimetric and clinical predictors of patient-reported intestinal toxicity in WPRT of prostate cancer. A first ad interim analysis referring to 206 patients treated after prostatectomy showed promising results, leading to the first quantification of bowel dose-volume effects referring to acute end-points [19]. The current analysis, extending these early findings, aimed to:

(1) quantify the acute changes of ten symptoms pertaining to the Bowel domain as measured by the Inflammatory Bowel Disease Questionnaire (IBDQ-B) [20–22], identifying the symptoms showing the most significant modifications;
(2) explore the association between bowel DVH and acute worsening of intestinal patient-reported symptoms;
(3) develop robust multi-variable predictive models of acute worsening of patient-reported intestinal toxicity combining DVH parameters and selected clinical factors.

Materials and methods

The multi institutional trial

IHU-WPRT TOX is a registered multi institutional cohort study (ClinicalTrials.gov identifier #NCT02803086) aimed at developing predictive models of Intestinal, Hematologic and Urinary Toxicity from WPRT [18,19,23]. Patients were enrolled from September 2012, firstly in a pilot study at the coordinating institute (San Raffaele Scientific Institute, Milan, Italy) [18,23] and then within the trial activated in February 2014 [19].

In the IHU-WPRT TOX protocol the sample size to detect a clinically significant variation of intestinal toxicity was estimated to be 351 patients on the basis of our previous retrospective studies [8] and recommendations from literature [24]. This study was approved by the institutional review boards of each institute.

Patient-reported intestinal toxicity

According to the instructions provided to each participating institute [18,19,23], the validated, licensed, Italian version of IBDQ [25] was prospectively administered and collected. The questionnaire was to be filled in at baseline, at radiotherapy mid-point and end, at 3 and 6 months after radiotherapy end, and thereafter every 6 months up to 5 years. The IBDQ form was found to be easy to understand by patients and hence the patients themselves completed the questionnaire at each time. It has indeed been demonstrated that IBDQ may be reliably used as a self-administered instrument in clinical trials [26].

The IBDQ comprises 32 questions analyzing four different domains: Bowel symptoms (IBDQ-B), Emotional health (IBDQ-E), Systemic symptoms (IBDQ-Sy) and their possible detrimental impact on Social functions (IBDQ-So). The score of each question ranges from 1 to 7 (lower number indicates worse symptoms).

The current study focused on the ten items pertaining to IBDQ-B, as derived from the questionnaires administered from the start to the end of the treatment. Questions assess the frequency of bowel movement and diarrhea (IBDQ1 and IBDQ5, respectively), abdominal cramps, pain and bloating (IBDQ9, IBDQ13 and IBDQ20, respectively), gas passage (IBDQ17), rectal bleeding (IBDQ22), urgency to defecate (IBDQ24), accidental soiling (IBDQ26) and nausea (IBDQ29).

Small bowel loops contouring

According to the guide for delineation of the IHU-WPRT TOX protocol [19], small bowel loops were contoured starting from the most cranial slice where lymph-node PTV was present and continuing on every CT slice up to the sigmoid flexure. These were manually delineated by a single observer from each institute, and contours reviewed by the coordinating institute.

Full planning data (planning CT, RT-Plan, RT-Dose, RT-Structure DICOM files) were collected in a dedicated software (VODCA, MSS Inc. [27]). Absolute DVHs were calculated in the range 2–70 Gy in steps of 2 Gy.

Patient characteristics

At the time of the analysis (May 2020), complete dosimetric data and IBDQ-B scores at baseline and RT-end were available for 410 patients (for 388/410 also at mid-point). Radiotherapy was delivered with different techniques (7% static-field IMRT, IMRT-SF, 38% TomoTherapy, 55% VMAT) and with differing intent (33% adjuvant, 36% salvage, 31% radical). Details pertaining to the rationale for WPRT delivery, definition of margins and treatment techniques were previously described [19].

The dose to the pelvic nodes ranged between 50 and 60 Gy with a median value of 53 Gy. Of note, patients were treated to the lymph-nodes/lymph-nodal area at a daily dose of 1.7–2.0 Gy for a total of 25–33 fractions, with the exception of 42 patients treated in one institute at 2.1–2.3 Gy/fr in 26 fractions. Considering the small difference from the reference 2 Gy daily dose and the small amount of bowel receiving doses near the prescribed dose, no correction for the fractionation was applied. Of note, the potentially critical group consisted of 26/42 patients treated to 2.2 Gy/fr (only 1 patient was treated to 2.3 Gy/fr); for this group, a sensitivity analysis whose results are shown in the Supplementary Material, confirmed the negligible impact of the different daily dose in current population.

General features (age and body mass index [BMI, kg/m^2]) as well as comorbidities such as diabetes, hypertension, hemorrhoids, smoking (yes *vs* no/stopped at least 5 years before radiotherapy

start), cardiopathies, chronic and autoimmune diseases were available. Additional information such as PSA at the diagnosis and pre-irradiation, pathologic stage, Gleason score, therapy intent, prescribed dose, fractionation, volume of the lymph-nodal PTV (in cc) and use of androgen deprivation were also included in the analyses.

Lastly, the abbreviated 24-item version of the revised Eysenck Personality Questionnaire (EPQ-R) [28] aimed at evaluating the individual levels of *extraversion, neuroticism psychoticism and tendency to lie* filled in by patients at baseline was considered in order to evaluate the possible impact of the patient's personality on the self-reported radiation-induced toxicities.

Endpoint definition

Analyses were focused on the "worst" decline observed from baseline between mid- and end-therapy timing (ΔIBDQ); in this way, possible improvements of specific symptoms/domains as the result of drugs prescribed during irradiation (with the aim of mitigating radiation-induced symptomatology) were mostly taken into account. ΔIBDQ referred *a priori* to the variation between baseline and end of treatment in 22/410 patients whose mid-point questionnaire was missing. For each question in IBDQ-B, a descriptive analysis of the maximum variation was performed and the 25th percentile values of the score variations were chosen as end-points of intestinal toxicity. In addition to these ten endpoints, an endpoint for the overall IBDQ Bowel Domain score was set in the same way.

Statistical analyses

Patients who exhibited moderate/severe bowel symptoms before radiotherapy (i.e. baseline score <5) were excluded from the analyses.

When only one answer for each IBDQ domain was missing (n = 19), imputation was accomplished using the most frequent value reported by those patients who answered similarly.

The mean baseline value of each main IBDQ domain (overall IBDQ-B, IBDQ-Sy, IBDQ-E, IBDQ-So) was evaluated as a possible predictive variable: the score for each domain was calculated as the sum of the scores of each domain divided by the number of items comprising each domain (10, 12, 5 and 5 respectively).

The statistical analyses consisted mainly of three steps. Firstly the average absolute DVH of bowel loops relative to patients with toxicity was compared for each endpoint against the ones without toxicity through a two-sided t-test [18]: when the difference was significant (p-values < 0.05), the endpoint was selected for the next step to be tested in a logistic regression analysis. In these cases, the analysis of the average absolute DVHs was also repeated considering separately patients who exhibited baseline symptoms higher and lower than the median baseline IBDQ score (see later for further explanation). The current study focused only on the IBDQ-based endpoints which showed a dose-volume effect in the DVH analyses.

In the second step, univariable logistic regression (UVA) was performed to assess the correlations between the endpoints selected in the DVH analyses and all clinical/dosimetric parameters. Given the larger number of cases, the current study fixed more stringent criteria than the previous one [19]: only variables with p-value <0.1 at UVA and without cross-correlations (Pearson or Spearman coefficient, according to the type of variables, in the range $[-0.25, 0.25]$) were entered into a backward stepwise multi-variable logistic regression (MVA). When significant variables at UVA were found to be correlated with each other, only the variable with the most clinically significant odds ratio was considered for MVA.

In the third and last step of analysis, MVA generated the final models with the most predictive and independent variables. Goodness of fit and predictive value were assessed by the Hosmer and Lemeshow test (H&L) [29] and the calibration plot (slope and R^2) [30]. Brier scores [31] were used to measure accuracy. Internal validation was performed by 1000 bootstrap resamplings [32], and optimism determined. Analyses were performed with the R software version 3.2.4 (©The R Foundation for Statistical Computing, Vienna, Austria). In particular, the *validate* function [33] was used for the bootstrap resampling: the upper limit of the resamples was set 1000 with the Akaike's information criterion (AIC) as stopping rule for the residual χ^2 of all variables deleted and significance level equal to 0.05.

Results

Table S1 (Supplementary material) summarizes patient characteristics.

The number of patients excluded (i.e. with baseline score < 5) ranged between 2% and 7% according to the endpoint.

Fig. S1 (Supplementary material) shows the longitudinal analysis of the mean IBDQ scores from the start (baseline) to the end of radiotherapy; each question evidenced a worsening trend, although mean differences were slight (0.2–1.5 points).

The quartile distribution of ΔIBDQ for each bowel symptom is shown in Fig. 1. Only four items (IBDQ1 = frequent bowel movement, IBDQ5 = diarrhea, IBDQ17 = gas passage, IBDQ24 = urgency) showed a median worsening ≥ 1, as well as overall IBDQ-B; in the other cases, no clinically important changes were observed.

The results of DVH analyses are plotted in Fig. S2: the difference between DVHs of patients with/without toxicities (considering the quartile of each bowel symptom variation as endpoint) was significant (p-value < 0.05) only for IBDQ5 and IBDQ24, with the best association for V40-V50Gy, as shown in Fig. 2. As the current work was focused on possible dose-volume effects, only these two bowel symptoms and overall IBDQ-B were selected for the subsequent analyses.

Table 1 reports the results of univariate analyses. Interestingly, diabetes and autoimmune diseases emerged as significant risk and protective factors of intestinal toxicity for overall IBDQ-B, respectively; due to their low frequency, however (n = 12 and 9), they were excluded from multivariate analyses. The findings of univariate analyses were matched with the cross-correlation analysis summarized in Fig. S3 (Supplementary material).

The resulting multivariable models are shown in Table 2 and Fig. 3. Endpoints were associated with DVH (V46Gy, OR:1.004–1.006) and their corresponding baseline scores (OR:0.35–0.65). The model regarding overall IBDQ-B was found to be dependent also on radiotherapy intent: patients treated with radical intent exhibited a higher risk (OR:1.79) compared to patients treated post-prostatectomy.

The importance of the baseline IBDQ score is highlighted by Fig. S4 and Fig. S5 (Supplementary material), which summarizes the DVH analyses for patients grouped according to the median baseline value taken as cut-off. The best association was again for V40-V50Gy, but only for the subgroup with the worst (although mild, having previously excluded patients with baseline score <5) baseline condition, while no dose-volume effect was evident for patients with a better baseline situation.

The three resulting models were reliable (H&L test: 0.453–0.956), well calibrated (slope: 0.922–1.069, R^2: 0.725–0.875) and moderately discriminative (AUC: 0.628–0.669). The bootstrap-based internal validation confirmed their robustness (Brier score optimism correction: 0.003–0.004). The calibration plot of each model and the corresponding ROC curve are shown in Fig. S6 (Supplementary Materials).

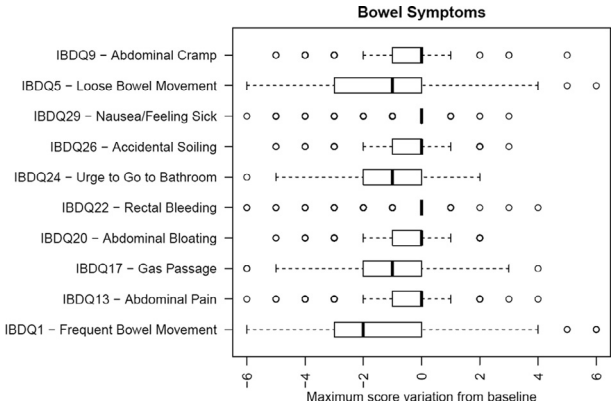


Fig. 1. Quartile distribution of the maximum score variation from baseline symptom for each IBDQ question in the Bowel Domain.

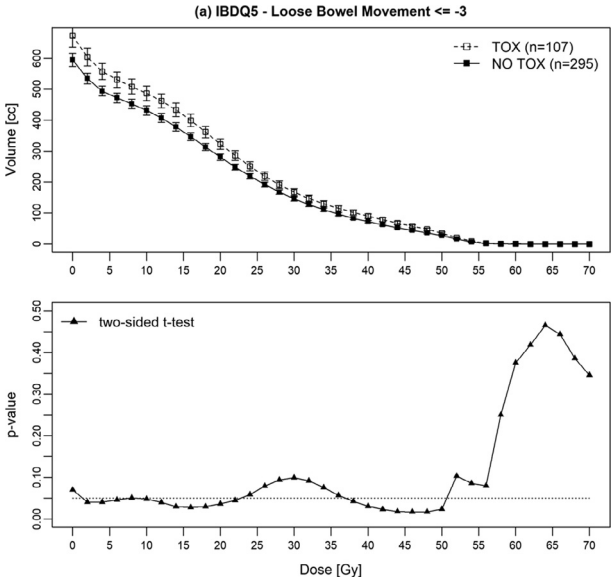


Fig. 2. In the upper plots: mean absolute DVHs of (a) diarrhea (IBDQ5), (b) urgency (IBDQ24) and (c) overall bowel symptoms (IBDQ-B) respectively for patients with and without toxicities (endpoint = 25th percentile value of the IBDQ score variation); error bars represent standard errors. In the bottom plots, the corresponding *p*-values were calculated both with two-sided t-test and univariable logistic regression.

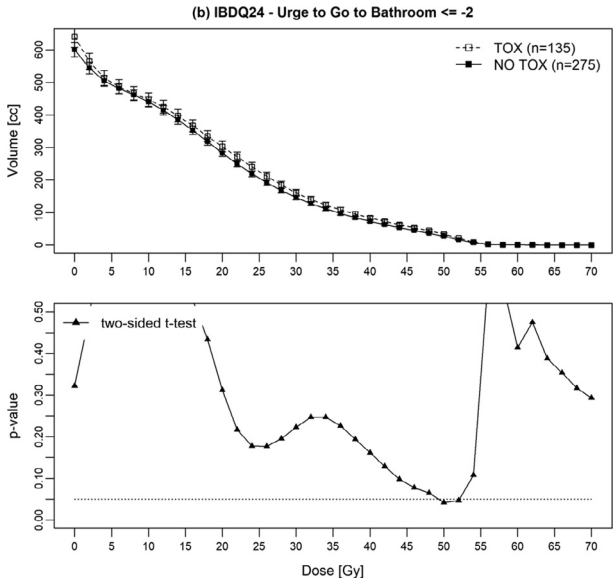


Fig. 2 (*continued*)

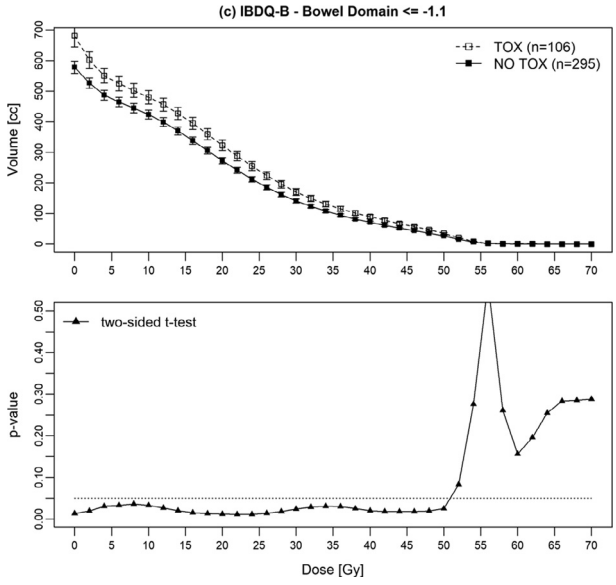


Fig. 2 (*continued*)

Discussion and conclusions

Since its advent, IMRT has significantly reduced the incidence and severity of intestinal toxicity from pelvic radiotherapy [4–6,14,34], owing to the efficient bowel sparing compared with 3DCRT. Nonetheless, bowel toxicity from WPRT remains an important issue due to the impact of intestinal symptoms on patients' daily QoL. Thus, the definition of proper bowel constraints, still largely uncertain, remains a clinically significant issue [12,17].

The need for prospective trials including a patient-reported assessment of intestinal symptoms is well evident, also in order to better understand dose-volume effects in the IMRT era, as well as the impact of clinical parameters potentially associated to an increased risk of bowel toxicity from pelvic irradiation.

The current study is, to our knowledge, the first attempt to address this question in a multi institute cohort study focused on patient-reported intestinal symptoms: data were considered appropriate for the assessment of dose-volume effects of acute worsening of intestinal symptoms, and the current analysis follows an early investigation [19] dealing with the pilot, single institute study that preceded the trial.

In general, our findings confirmed the good tolerability of WPRT in terms of patient—reported intestinal toxicity: the median worsening of IBDQ-B scores after IMRT-WPRT was relatively slight, and was $\geq$1 in only four out of ten questions. A bowel dose-volume effect was confirmed for diarrhea and urgency (questions 5 and 24 respectively), resulting in a similar dose-volume effect for the overall IBDQ-B score.

These results are partly consistent with the previous finding of Sini et al. [19] indicating evidence of a dose-volume effect only for IBDQ5 and overall IBDQ-B; the evidence of a similar effect also for IBDQ24 is a new finding, likely due to the more than doubled sample size.

An additional new finding with respect to the Sini et al. series concerns the strong impact of the baseline IBDQ scores, which was not considered in that investigation. It may be worth noting

Table 1
Results of the univariable logistic regression analysis: *p*-value and Odds-Ratio confidence interval of 95% in brackets. Significant values accepted for inclusion in subsequent multivariable analyses ($p < 0.1$) are marked in bold. The three endpoints are associated with the maximum variation of the score relative to "diarrhea" (ΔIBDQ5), "urgency" (ΔIBDQ24) and "overall" bowel symptoms (ΔIBDQ-B) in the patient-reported Inflammatory Bowel Disease Questionnaire.

Variables	ΔIBDQ5 ≤ -3	ΔIBDQ24 ≤ -2	ΔIBDQ-B ≤ -1.1
Patient characteristics			
Age (yr)	0.532	0.142	0.803
	(0.96–1.02)	(0.99–1.05)	(0.97–1.04)
BMI (kg/m^2)	0.498	0.424	0.237
	(0.96–1.09)	(0.92–1.04)	(0.90–1.02)
Comorbidities			
Hypertension (yes)	**0.083**	0.888	0.997
	(0.420–1.05)	(0.68–1.56)	(0.64–1.56)
Smoking (yes)	0.276	0.914	0.838
	(0.77–2.32)	(0.60–1.73)	(0.59–1.86)
Diabetes (yes)	0.977	0.222	**0.016**
	(0.22–3.61)	(0.63–6.68)	(1.31–14.6)
Hemorrhoids (yes)	0.638	0.767	0.433
	(0.66–1.94)	(0.65–1.78)	(0.72–2.07)
Cardiopathies (yes)	0.728	0.710	0.738
	(0.46–1.66)	(0.47–1.63)	(0.46–1.67)
Chronic diseases (yes)	0.653	0.572	0.201
	(0.20–7.73)	(0.03–3.63)	(0.52–15.8)
Autoimmune diseases (yes)	0.120	0.145	**0.057**
	(0.71–13.2)	(0.70–11.1)	(0.95–15.2)
Prostate cancer characteristics			
PSA pre-RT (ng/ml)	**0.014**	0.442	**0.053**
	(1.01–1.07)	(0.98–1.04)	(1.00–1.06)
Gleason score			
ISUP Groups 1–3	Ref.	Ref.	Ref.
ISUP Groups 4–5	0.774	0.691	0.440
	(0.634–1.88)	(0.67–1.86)	(0.72–2.22)
Stage T			
pT1 & pT2	Ref.	Ref.	Ref.
pT3a	0.886	**0.094**	0.145
	(0.64–1.64)	(0.43–1.06)	(0.42–1.13)
pT3b & pT4	0.785	0.212	0.327
	(0.56–1.52)	(0.85–2.09)	(0.78–2.06)
Stage T			
N0	Ref.	Ref.	Ref.
N1	0.439	0.582	0.943
	(0.48–1.35)	(0.55–1.39)	(0.59–1.60)
Nx	0.508	0.771	0.252
	(0.41–1.50)	(0.50–1.63)	(0.31–1.30)
Radiotherapy data			
Intent			
Post-prostatectomy RT	Ref.	Ref.	Ref.
Radical RT	0.301	0.205	**0.066**
	(0.80–2.03)	(0.86–2.04)	(0.97–2.46)
Prescribed dose (Gy)			
to PB-PTV	0.511	0.532	0.702
	(0.91–1.05)	(0.92–1.04)	(0.95–1.08)
to LN-PTV	0.182	0.168	0.986
	(0.96–1.21)	(0.97–1.19)	(0.89–1.12)
Hypofractionation (yes)			
for PB-PTV	**0.068**	**0.066**	0.973
	(0.97–2.57)	(0.98–2.37)	(0.64–1.61)
for LN-PTV	**0.073**	0.841	0.511
	(0.92–3.70)	(0.53–2.10)	(0.32–1.65)
LN-PTV volume (cc)	**<0.001** (1.000–1.002)	0.760	0.760
		(0.999–1.001)	(0.999–1.001)
Adjuvant hormonal therapy (yes)	0.855	0.351	0.121
	(0.61–1.53)	(0.80–1.92)	(0.91–2.38)
Patient-reported data at baseline			
EPQ-R			
Extraversion	0.988	**0.077**	0.431
	(0.88–1.14)	(0.80–1.01)	(0.83–1.08)
Neuroticism	0.558	**<0.001**	**0.012**
	(0.91–1.19)	(1.15–1.50)	(1.04–1.36)
Psychoticism	0.232	0.893	0.894
	(0.92–1.38)	(0.83–1.22)	(0.80–1.21)
Lie	0.532	0.736	0.171
	(0.78–1.14)	(0.82–1.15)	(0.75–1.06)
IBDQ			
Bowel symptoms	0.957	**<0.001**	0.814

Table 1 (*continued*)

Variables	ΔIBDQ5 ≤ -3	ΔIBDQ24 ≤ -2	ΔIBDQ-B ≤ -1.1
	(0.62–1.62)	(0.21–0.59)	(0.57–1.59)
Emotional functions	**0.010**	**<0.001**	**<0.001**
	(0.523–0.92)	(0.39–0.68)	(0.42–0.74)
Systemic symptoms	**0.002**	**0.001**	**0.038**
	(0.50–0.85)	(0.49–0.83)	(0.57–0.99)
Social functions	0.527	**0.025**	0.735
	(0.71–1.20)	(0.60–0.97)	(0.75–1.24)

IBDQ = Inflammatory Bowel Disease Questionnaire; ΔIBDQ5 = maximum variation of the "loose bowel movement" item; ΔIBDQ24 = maximum variation of the "urgency" item; ΔIBDQ-B = maximum variation of the mean score relative to the bowel domain; BMI = body mass index; RT = radiotherapy; PB-PTV = Prostatic Bed Planning Target Volume; LN-PTV = Lymph Nodes Planning Target Volume; EPQ-R = Eysenck Personality Questionnaire Revised.

Table 2
Results of the multi-variable logistic regression analysis relative to IBDQ items which showed significantly different DVHs with/without toxicities. The 25th percentile values of the IBDQ score variations were considered here as endpoints.

ΔIBDQ5 – variation in Loose Bowel Movement (Diarrhea)				
Endpoint: ΔIBDQ5 ≤ -3, *N* = 107/401 (27%),				
Excluded (IBDQ5 < 5 at baseline): 29 patients				
Predictors	**Coeff ± dev.std.**	***p*-value**	**OR**	**CI(95%)**
V46Gy [cc]	0.006 ± 0.002	0.010	1.006	(1.001–1.011)
Baseline IBDQ-Sy	−0.438 ± 0.139	0.002	0.65	(0.49–0.85)
Intercept	1.205			
H&L = 0.956	**Slope** = 1.069	R^2 = 0.875	**Brier score** = 0.191 (optimism **=** −0.003)	**AUC** = 0.628 (optimism **=** 0.008)
ΔIBDQ24 – variation in Urge to Go to Bathroom (Urgency)				
Endpoint: **Δ**IBDQ24 ≤ -2, *N* = 130/400 (32%),				
Excluded (IBDQ24 < 5 at baseline): 19 patients				
Predictors	**Coeff ± dev.std.**	***p*-value**	**OR**	**CI(95%)**
V46Gy [cc]	0.004 ± 0.002	0.059	1.004	(1.000–1.009)
Baseline IBDQ-B	−1.049 ± 0.266	<0.001	0.35	(0.21–0.59)
Intercept	6.676			
H&L = 0.619	**Slope** = 0.922	R^2 = 0.725	**Brier score** = 0.212 (optimism **=** −0.003)	**AUC** = 0.628 (optimism **=** 0.007)
ΔIBDQ-B – variation in Bowel Domain (Overall Bowel Symptoms)				
Endpoint: ΔIBDQ-B ≤ -1.1, *N* = 103/392 (26%),				
Excluded (IBDQ-B < 5 at baseline): 9 patients				
Predictors	**Coeff ± dev.std.**	***p*-value**	**OR**	**CI(95%)**
RAD vs. PORT	0.580 ± 0.251	0.021	1.79	(1.09–2.92)
V46Gy [cc]	0.006 ± 0.002	0.009	1.006	(1.002–1.011)
Baseline IBDQ-E	−0.614 ± 0.146	<0.001	0.54	(0.40–0.72)
Intercept	2.081			
H&L = 0.453	**Slope** = 0.992	R^2 = 0.812	**Brier score** = 0.185 (optimism **=** −0.004)	**AUC** = 0.669 (optimism **=** 0.009)

H&L = Hosmer and Lemeshow test; IBDQ = Inflammatory Bowel Disease Questionnaire; IBDQ-Sy = IBDQ Systemic Domain; IBDQ-B = IBDQ Bowel Domain; IBDQ-E = IBDQ Emotional Domain; Vx = volume (cm^3) of small bowel loops receiving × Gy; optimism = optimism correction in the Brier Score and AUC calculated by 1000 bootstrap resamplings; RAD vs. PORT = radical radiotherapy *versus* post-prostatectomy radiotherapy.

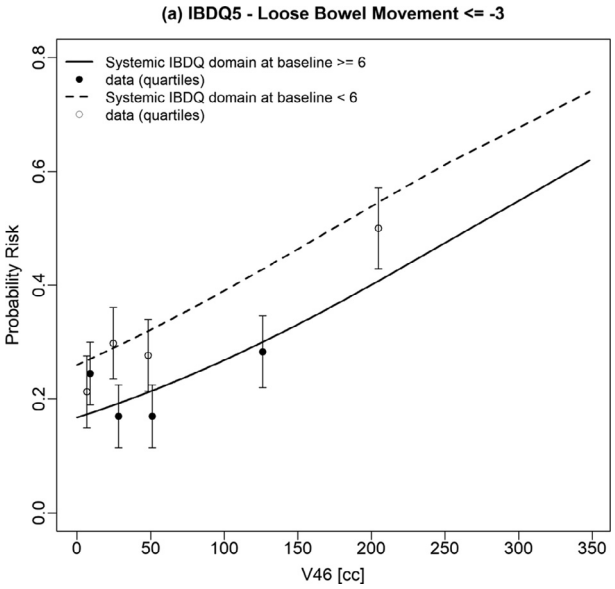
that patients with moderate/severe symptoms (score <5) were excluded from both analyses: consequently, the impact actually found regarding baseline score concerns relatively mild symptoms, likely impossible to capture without a patient-reported evaluation.

In other words, the presence of mild bowel symptoms (scores of around 5–6) is the major predictor of the risk of experiencing moderate/severe worsening of symptoms, here coincident with a decrease (=worsening) ≥ 2–3 points.

Another difference relative to the series by Sini et al. [19] concerns the impact of age, previously reported as a significant predictor. Of note, the median age of the population in the current study was 69 years against 65 years in the previous work, suggesting that older patients may be less sensitive to moderate worsening of diarrhea symptoms.

Another new finding concerns the impact of radiotherapy intent for overall IBDQ-B, suggesting a higher likelihood of acute worsening for patients treated with radical compared to post-prostatectomy intent. A possible explanation could be derived from the higher doses delivered to the intact prostate when compared to those delivered to the prostatic bed, resulting in a worse rectal (and sigmoid) dose-volume profile for the former.

The major result of the current investigation is the quantification of the dose-volume effect for the moderate worsening of patient-reported diarrhea and urgency as well as of the overall IBDQ-B score. In particular, the previously suggested predominant impact of the dose delivered in the V40-V50 range was confirmed [19], with V46 emerging as the strongest predictor for acute diarrhea and urgency. In sum, reducing the fraction of bowel loops receiving doses ≥46 Gy to below 80 cc should translate into a reduction of moderate worsening of IBDQ-B scores to less than 15–25 % and 25–35 % of patients without or with only "mild" baseline symptoms, respectively. Looking at Fig. 3, it emerges that toxicity rates are quite constant for patients with V46 < 80 cc: a possible interpretation lies in the unavoidable fraction of the bowel included in the high-dose region, which cannot be spared without a significant and potentially harmful underdosage of lymph-nodal PTV. The picture of this phenomenon is further jeopardized by the simultaneous irradiation of the rectum and sigmoid colon and by the potentially large and difficult to quantify impact of bowel loops inter- and intra-fraction motion, which is expected to have a relatively higher impact on patients with small bowel volumes overlapping with the 45–50 Gy isodoses at the planning CT.



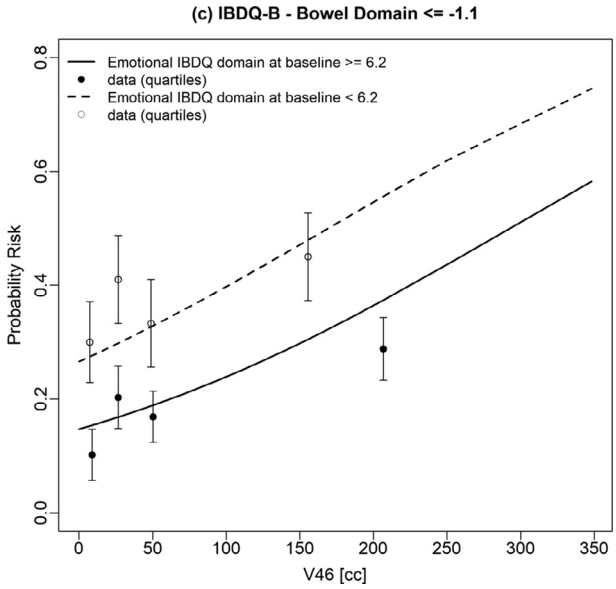


Fig. 3. Probability risk according to bowel loop volumes receiving 46 Gy and to different baseline IBDQ scores related to (a) diarrhea (IBDQ5), (b) urgency (IBDQ24) and (c) overall bowel symptoms (IBDQ-B) respectively.

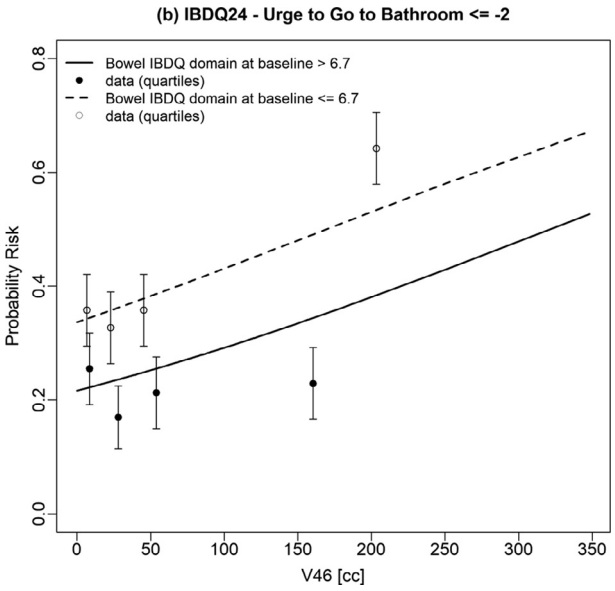


Fig. 3 (*continued*)

Fig. 3 (*continued*)

Very interestingly, the dose volume effect was found to be far more pronounced for patients with mild baseline symptoms: constraining V46 < 80 cc could be particularly beneficial for such patients, as evident in Fig. 3 and in Figs. S4-S5 of the Supplementary material.

The results of current work, obtained in a large multi institute series, were quite consistent with recent findings, and corroborated and refined the values of operative constraints for the bowel previously suggested by our group (V20 < 470 cc, V30 < 245 cc, V42 < 110 cc) [19]; the addition of V46 < 80 cc is in line with them, and compares favorably also with most recently reported findings in the field of pelvic radiotherapy (without chemotherapy) and pelvic lymph-nodal irradiation. Based on a comprehensive review, Rancati and Fiorino [12] suggested that constraining V40 < 150 cc and V50 < 100 cc could be helpful in keeping the risk of acute Grade 2 gastrointestinal toxicity below about 10–15%; considering physician-assessed end-points, McDonald et al. [35] suggested multiple constraints between 30 and 65 Gy, including V45 < 120 cc. More similarly to our study, Res Ferreira [11] proposed constraints in the 45–60 Gy range, including V55 < 30 cc and V50 < 110 cc. In Fig. 4, a summary plot of the recently suggested constraints in the case of WPRT for prostate cancer is shown, indicating quite good agreement between studies. Not surprisingly, owing to the milder end-points considered in this analysis for patient-reported acute intestinal toxicity, the constraints proposed here seem to be more restrictive when compared to those derived from physician-reported moderate/severe end-points.

In conclusion, moderate worsening of patient-reported diarrhoea and urgency were the most frequent acute symptoms after IMRT-WPRT for prostate cancer. The risk of experiencing moderate toxicity was largely dependent on the baseline intestinal situation, showing that mild symptoms before radiotherapy are the major predictors; in addition, a dose-volume effect was found, more evident for patients with baseline symptoms. Constraining bowel DVHs on the whole dose range [19], with V46 < 80 cc being the most robust constraint, seems to be efficient in reducing the risk

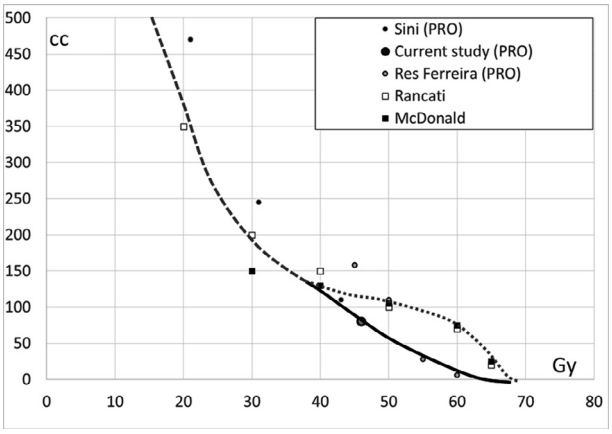


Fig. 4. Summary of DVH constraints for bowel to reduce acute GI toxicity in pelvic nodes IMRT for prostate cancer: tentative suggestions for moderate PRO scores (continuous) and grade 2 or higher physician-based scores (dotted). The corresponding expected rates if respecting the constraints are approximately 15–20 % and 10–15%.

of acute worsening of mild-moderate intestinal symptoms roughly to below 20%. A further risk reduction does not seem to be feasible by stressing plan optimization, while current models should help clinicians achieve an early individuation of patients at higher risk of radiation-induced toxicity when evaluating the cost-benefit of WPRT and the possible suggestion of preventive/support therapies to reduce both severity and incidence of these symptoms. The current study is expected to provide significant findings concerning how acute symptoms may translate into late transient or chronic impairment of intestinal functionality, an aspect of paramount importance in correctly assessing the real impact of intestinal toxicity on QoL, hopefully to be improved in the future.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.02.026.

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