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Original Article

# Worsening of 2-year patient-reported intestinal functionality after radiotherapy for prostate cancer including pelvic node irradiation

Giuseppe Sanguineti<sup>a</sup>, Maddalena Pavarini<sup>b</sup>, Fernando Munoz<sup>c</sup>, Alessandro Magli<sup>d</sup>, Domenico Cante<sup>e</sup>, Elisabetta Garibaldi<sup>c</sup>, Andrea Gebbia<sup>b</sup>, Barbara Noris Chiorda<sup>f</sup>, Giuseppe Girelli<sup>g</sup>, Elisa Villa<sup>h</sup>, Adriana Faiella<sup>a</sup>, Justyna Magdalena Waskiewicz<sup>i</sup>, Barbara Avuzzi<sup>f</sup>, Alice Pastorino<sup>j</sup>, Eugenia Moretti<sup>k</sup>, Luciana Rago<sup>1</sup>, Teodora Statuto<sup>m</sup>, Marco Gatti<sup>n</sup>, Tiziana Rancati<sup>o</sup>, Riccardo Valdagni<sup>f</sup>, Vittorio Luigi Vavassori<sup>h</sup>, Nadia Gisella Di Muzio<sup>p,q</sup>, Claudio Fiorino<sup>b</sup>, Cesare Cozzarini<sup>p,\*</sup>

<sup>a</sup> Radiotherapy, IRCCS Istituto Nazionale dei Tumori "Regina Elena", Roma, Italy

- <sup>b</sup> Medical Physics, IRCCS San Raffaele Scientific Institute, Milano, Italy
- <sup>c</sup> Radiotherapy, Ospedale Regionale Parini-AUSL Valle d'Aosta, Aosta, Italy
- <sup>d</sup> Radiotherapy, Azienda Ospedaliero Universitaria S. Maria della Misericordia, Udine, Italy
- <sup>e</sup> Radiotherapy, ASL TO4 Ospedale di Ivrea, Ivrea, Italy
- <sup>f</sup> Radiotherapy, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
- <sup>g</sup> Radiotherapy, Ospedale degli Infermi, Biella, Italy
- <sup>h</sup> Radiotherapy, Cliniche Gavazzeni-Humanitas, Bergamo, Italy
- <sup>i</sup> Radiotherapy, Comprensorio Sanitario di Bolzano, Bolzano, Italy
- <sup>j</sup> Radiotherapy, A.O.SS. Antonio e Biagio, Alessandria, Italy
- <sup>k</sup> Medical Physics, Azienda sanitaria universitaria Friuli Centrale, Udine, Italy
- <sup>1</sup> Radiotherapy, Centro di Riferimento Oncologico della Basilicata (IRCCS-CROB), Rionero in Vulture, Italy
- <sup>m</sup> Laboratory of Clinical Research and Advanced Diagnostics, Centro di Riferimento Oncologico della Basilicata (IRCCS CROB), Rionero in Vulture, Italy
- <sup>n</sup> Radiotherapy, Istituto di Candiolo Fondazione del Piemonte per l'Oncologia IRCCS, Candiolo, Italy
- ° Unit of Data Science, Department of Epidemiology and Data Science, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy
- <sup>p</sup> Radiotherapy, IRCCS San Raffaele Scientific Institute, Milano, Italy
- <sup>q</sup> Medicine and Surgery, Vita-Salute San Raffaele University, Milano, Italy

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## ABSTRACT

*Background and Purpose*: To quantify patient-reported 2-year intestinal toxicity (IT) from pelvic nodal irradiation (PNI) for prostate cancer. The association between baseline/acute symptoms and 2-year worsening was investigated.

*Materials and Methods*: Patient-reported IT was prospectively assessed through the Inflammatory Bowel Disease Questionnaire (IBDQ), filled in at baseline, radiotherapy mid-point and end, at 3 and 6 months and every 6 months until 5 years. Two-year deterioration of IBDQ scores relative to the Bowel Domain was investigated for 400 patients with no severe baseline symptoms and with questionnaires available at baseline, 2 years, RT midpoint and/or end and at least three follow-ups between 3 and 18 months. The significance of the 2-year differences from baseline was tested. The association between baseline values and  $\Delta_{Acute}$  (the worst decline between baseline and RT mid-point/end) was investigated.

Results: In the IBDQ lower scores indicate worse symptoms. A significant (p < 0.0001) 2-year mean worsening, mostly in the range of -0.2/-0.4 points on a 1–7 scale, emerged excepting one question (IBDQ29, "nausea/feeling sick"). This decline was independent of treatment intent while baseline values were associated with 2-year absolute scores. The  $\Delta_{Acute}$  largely modulated 2-year worsening: patients with  $\Delta_{Acute}$  greater than the first quartile (Q1) and  $\Delta_{Acute}$  less or equal than Q1 showed no/minimal and highly significant (p < 0.0001) deterioration, respectively. Rectal incontinence, urgency, frequency and abdominal pain showed the largest

\* Corresponding author at: Department of Radiotherapy, IRCCS San Raffaele Scientific Institute, Via Olgettina, 60 20132, Milan, Italy. *E-mail address:* cozzarini.cesare@hsr.it (C. Cozzarini).

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Received 11 July 2023; Received in revised form 31 December 2023; Accepted 2 January 2024 Available online 8 January 2024 0167-8140/© 2024 Elsevier B.V. All rights reserved. mean changes (-0.5/-1): risk of severe worsening (deemed to be of clinical significance if  $\leq$  2) was 3–5 fold higher in the  $\Delta_{Acute} \leq$  Q1 vs  $\Delta_{Acute} >$  Q1 group (p < 0.0001).

*Conclusion:* A modest but significant deterioration of two-year patient-reported intestinal symptoms from PNI compared to baseline was found. Patients experiencing more severe acute symptoms are at higher risk of symptom persistence at 2 years, with a much larger prevalence of clinically significant symptoms.

## Introduction

Intestinal toxicity (IT) is a clinically relevant side-effect of radiotherapy delivered for pelvic cancers owing to the irradiation of the bowel, and the number of patients who develop chronic gastrointestinal symptoms after pelvic radiotherapy is greater than those with Crohn's disease[1]. Pelvic nodal irradiation (PNI) is delivered with the intent of eradicating lymph-nodal micrometastases, in both radical and postprostatectomy settings, in the treatment of pelvic malignancies such as prostate, rectal or gynecologic cancers. In the treatment of prostate cancer (PCa), thanks to recent evidence of its clinical efficacy, PNI is becoming increasingly chosen for selected categories of patients, although its use is not yet fully consolidated [2-7]. One of the main worries potentially limiting the use of PNI is the potential increase of IT. Intensity-modulated radiation therapy (IMRT) has been demonstrated to effectively limit IT from PNI [8-10]; however, although several investigations have apparently reported full recovery from intestinal symptoms after acute reactions [11–13], there is a clear lack of longterm prospective investigations based on patient-reported quantitative scores, known to better reflect the true impact of IT on patient quality of life (QoL) [14–21].

Very importantly, a worsening of patient-reported symptoms, even if of only apparently modest extent, may potentially translate into a persistent deterioration of QoL in a non-negligible fraction of patients, even years after irradiation. The individuation of such patients is important, for both a thorough evaluation of the real cost-benefit balance of PNI and the timely activation of medical intervention aimed at preventing or at least limiting the severity of persistent symptoms [1,22,23].

A prospective multi-Institute observational study was activated in 2014 [16,24] with the aim of developing sophisticated predictive models of patient-reported intestinal, urinary and hematological toxicity from PNI in the treatment of PCa, and of identifying the major clinical and dosimetric predictors of these sequelae. Concerning IT, the Inflammatory Bowel Disease Questionnaire (IBDQ) [25,26], whose reliability and sensitivity for the assessment of IT from pelvic radiotherapy had previously been demonstrated [27], was used.

Two previous ad interim analyses focused on acute intestinal symptoms, leading to the first quantification of bowel dose-volume effects as well as the impact of baseline bowel functionality [16,19].

Given the availability of a sufficiently large number of patients with complete data at two years, the current analysis was focused on late worsening of intestinal symptoms, with the major aims of: a) evaluating the changes of IBDQ Bowel Domain (IBDQ-B) scores in the first two years after treatment and determining whether the 2-year scores differed significantly from baseline values; b) testing any impact of therapy intent (radical *vs* post-prostatectomy, including any difference between salvage and adjuvant intent); c) quantifying any possible impact of baseline scores, and of the intensity of acute IT on 2-year worsening.

# Materials and methods

#### The IHU-WPRT TOX study

The IHU-WPRT TOX (Intestinal Hematologic Urinary Toxicity from Whole-Pelvis Radiotherapy) is a registered prospective cohort study (ClinicalTrials.gov identifier #NCT02803086) involving 14 Italian Institutes; the main goal is the development of predictive models of toxicity from PNI delivered for PCa. Initially, a pilot study was conducted at the Coordinating Center (San Raffaele Scientific Institute, Milan, Italy) starting in September 2012. Subsequently, the IHU-WPRT-TOX trial was activated in February 2014. Overall, 886 patients were enrolled in the two studies. The IHU-WPRT-TOX study was approved by the IRB of the Coordinating Institute (San Raffaele Scientific Institute) and by the IRB of each participating Center. Patients were treated with either radical or post-prostatectomy (both adjuvant and salvage) intent. Further information regarding the study can be found elsewhere [16,24,28].

#### Using the IBDQ to quantify patient-reported IT

Based on the assumption that symptoms scored as manifestations of radiation-induced IT have great similarities with those due to bowel disorders unrelated to cancer therapies, both Khalid *et al.* and Olopade *et al.* reported that the IBDQ gives reliable and sensitive measures of IT from pelvic radiotherapy, offering greater insight into the severity and range of symptoms when compared to the RTOG (Radiation Therapy Oncology Group) grading [27,29]. For this reason the IBDQ is considered a powerful tool, and was selected in order to offer a detailed description of IT symptoms; it was already used in previous analyses within the IHU-WPRT TOX study [16,19] as well as others [27,30]. It is worthwhile, in this context, to highlight how other scales, such as RTOG or CTCAE, aimed at quantifying the radiation induced gastrointestinal symptoms, tend to over-represent rectal bleeding, which reflects only the dose delivered to the anterior rectal wall and is not caused by radiotherapy in a non-negligible fraction of patients [1].

According to the study requirements, the validated and licensed Italian version of the IBDQ is to be filled in by patients at baseline, at radiotherapy mid-point and end, at 3 and 6 months after its conclusion, and thereafter every 6 months until five years after radiotherapy. The IBDQ includes 32 Likert-type scale questions whose score ranges from 1 to 7, with lower scores corresponding to worse symptomatology. It is also divided into four Domains to assess the severity of Bowel symptoms (IBDQ-B, 10 items) and their possible detrimental impact on Emotional (IBDQ-E, 12 items), Social (IBDQ-So, 5 items) and Systemic (IBDQ-Sy, 5 items) Domains. Only the ten questions pertaining to the IBDQ-B were analyzed in the present study, concerning: 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), urge to defecate (IBDQ24), accidental soiling (IBDQ26) and nausea/feeling sick (IBDQ29).

# Patient population

This analysis pertains to 400 of the 886 recruited patients; a more detailed description of inclusion/exclusion criteria is reported in the Results section. Patients were treated with different techniques: 8 % static-fields IMRT, 42 % TomoTherapy and 50 % VMAT. For patients treated with postoperative irradiation (n = 252) the median 2 Gy-equivalent dose (EQD2, assuming  $\alpha/\beta$  = 3 Gy) to the pelvic nodal area was 50.2 Gy (Interquartile Range, IQR: 49.9–51.8) with 72 Gy (IQR: 70–74) being delivered to the prostatic bed. In the case of radical intent (n = 148), the median EQD2 dose to the pelvic lymph-nodes was 51.8 Gy (IQR: 51.1–59.5), while that to the prostate was 80 Gy (IQR: 77–80.1). Radiotherapy to prostatic bed/prostate planning target volume (PB/P-

PTV) was delivered with both conventional fractionation (172/400, 43 %) or moderate hypo-fractionation (228/400, 57 %). Median prescribed daily dose to PB/P-PTV was 2 Gy (IQR: 2–2.4) and 2.5 Gy (2.4–2.7) for post-operative and radical treatments, respectively, while the dose to the lymph-nodal PTV was 1.8 Gy (IQR: 1–8-1.9) for men who underwent surgery and 2 Gy (1.8–2.2) for patients treated with radical intent.

#### Statistical analysis

Bowel symptoms were assessed analysing the variation of the 10 single IBDQ-B scores from the baseline at each of the following times: radiotherapy mid-point and end, 3, 6, 12, 18 and 24 months after radiotherapy conclusion. At each time point, in the case of a single missing question score, the average value of IBDQ-B Domain for that specific patient calculated on the nine remaining items was adopted as a replacement. Only complete and single-question-imputed question-naires were considered, and the IBDQ-B score was calculated as the mean of the 10 IBDQ-B values.

Patients were included if the following criteria were satisfied:

- a) both baseline and 2-year scores were available;
- b) no more than one Bowel Domain score from 3 to 18 months was missing;
- c) at least one between radiotherapy mid-point and end IBDQ-B scores was available.

Although it was plausible that patients with lower baseline scores continued to exhibit low scores after radiotherapy, possibly as the result of causes unrelated to irradiation, we decided to limit the role of preexisting severe intestinal dysfunctions as potential confounders and effect modifiers. No patient had to be excluded due to total Bowel Domain score as these were always  $\geq$  5. On the other hand, in order to focus on single symptoms mostly attributable to irradiation, patients with moderate/severe symptoms before the beginning of radiotherapy (i.e., baseline score < 5) were excluded from the study of IBDQ-B individual questions, as in previous investigations [16,19]. The percentage of patients who for this reason were excluded from the analysis of the single questions ranged from 1 % (for IBDQ22 - Rectal Bleeding and IBDQ29 -Nausea/Feeling Sick) to 11.5 % (for IBDQ20 - Abdominal Bloating and IBDQ17 - Gas Passage) with a median value of 3.9 %. If both scores at radiotherapy mid-point and end were available (90 % of analyzed patients), the worst between the two and its corresponding variation with respect to baseline ( $\Delta_{Acute}$ ) was considered in the analysis. For each score, men were split into two subgroups according to the maximum decrease (=worsening) of the  $\Delta_{Acute}$ : threshold values were set as the first quartiles (thereafter Q1) of their distributions. Patients were also stratified into similar groups by the first quartile of their baseline Bowel Domain score. Patients were finally also grouped according to treatment intent: adjuvant (ADV) vs salvage (SALV) vs radical (RAD) as well as radical (RAD) vs post-prostatectomy (POSTOP). When investigating the possible detrimental impact of radiation-induced acute toxicity on 2year worsening of intestinal function, two thresholds to identify subgroups of patients at risk were proposed: a reduction (=worsening) at two years from radiotherapy end with respect to the baseline of at least one point (the minimum possible reduction) and of at least two points of both the overall IBDQ-B domain and the ten single intestinal items.

Wilcoxon signed-rank tests were performed to assess any statistically significant difference between baseline and 2-year scores for both the overall Intestinal Domain (IBDQ-B) and the 10 single Bowel items for the entire population and for each of the subgroups considered. In addition, Mann-Whitney tests with Bonferroni corrections were performed to test for any possible difference in terms of bowel symptoms at baseline, at radiotherapy mid-point/end and at 2 years between the considered subgroups (RT intent, baseline above *vs* below Q1 and  $\Delta_{Acute}$  above *vs* below Q1). All analyses were performed with Python programming language version 3.7.9 (Python Software Foundation, https://www.py

thon.org/) and the SQL Server Management Studio (SSMS) software version 18.11.1 (Microsoft Corporation).

# Results

# Patient characteristics

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram for this study is reported in Fig. 1, displaying the progress of all participants throughout the trial.

Overall, 400 of the 886 recruited and treated patients, who satisfied the criteria for inclusion in the current analysis were considered.

Table S1 (Supplementary Materials) shows a summary of the patient characteristics, grouped by radiotherapy intent (radical *vs* postprostatectomy). Androgen deprivation therapy (ADT) concurrent and adjuvant to irradiation was prescribed to 261 men for a median time of 24 months (IQR: 24–25 months). Mann-Whitney U-Tests (significance level: p < 0.05) were conducted at each time point of interest up to 2 years after RT completion. The difference in Bowel Domain Score between men who underwent ADT and those who did not was not statistically significant (p-values > 0.069).

#### Longitudinal behavior and 2-year changes of IBDQ scores

In order to investigate the temporal trend of the Bowel Domain, firstly, the IBDQ Bowel Domain score was calculated for each questionnaire as the mean of the scores of the ten IBDQ-B items. Secondly, for each patient, the IBDQ-B domain score during radiotherapy (acute phase) was taken as the lower (=worse) IBDQ Bowel Domain score between radiotherapy mid-point and end. Of note, for 90 % of the patients included in this analysis, complete IBDQ-B questionnaires were available at radiotherapy mid-point and end. It was therefore possible to accurately report (Fig. 2) the trend over time of average IBDQ-B for the entire population, showing a non-negligible decrease in the acute phase (-0.76) followed by improvement. Interestingly, the recovery was never complete: despite the relatively small changes compared to baseline, the difference between each time point against baseline starting from 3 months remained significant. A similar trend was seen for all the ten Bowel items: as a Summary, in Table 1 the absolute values at baseline and 2 years as well as the corresponding delta values are shown. The differences always proved to be significant, with the sole exception of the symptom "Nausea/Feeling Sick", and ranged mostly between -0.2and -0.4. The items showing the largest variations were "Frequent Bowel Movement", "Gas Passage", "Rectal Bleeding" and "Accidental Soiling" (IBDQ items #1, 17, 22 and 26, respectively).

Table S2 (Supplementary Materials) focuses on the longitudinal behavior of average IBDQ-B stratified by Institute: no significant differences were found when considering patients available for each Institute.

#### Impact of radiotherapy intent and of baseline values

The summary curves, reported in the Supplementary Materials, compare both men treated with radical *vs* post-prostatectomy intent, and patients submitted to radical *vs* adjuvant *vs* salvage irradiation (Figure S1). The influence of radiotherapy intent on IBDQ-B was not statistically significant at any of the time points analyzed with the sole exception of at 18 months when comparing RAD *vs* SALV and RAD *vs* POSTOP cohorts (Mann Whitney *U* test p-values: 0.02 and 0.04, respectively). Since no statistically significant differences between the radiotherapy intent and surgery groups either before or this single time point emerged, we attributed this finding at 18 months as only the result of a very probable fluctuation in the data. In any case in future works, when additional mature data is available, we will investigate this issue more thoroughly.

The impact of baseline symptoms on overall IBDQ-B Domain and the



Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram for our present study.



**Fig. 2.** Temporal trend of the average IBDQ-B Domain score of the analyzed patients from baseline until 2 years after radiotherapy. At the time named "Acute" for each patient the Bowel Domain score was the lowest (worst) between radiotherapy mid-point and end.

evolution of the ten single IBDQ-B items over time was investigated by stratifying patients according to their baseline IBDQ-B scores, above and below their respective first quartile (Q1) values. Results are summarized in the Supplementary Materials (Figure S2 and Table S3). It turned out that no patient had to be excluded from the analysis due to the impact of baseline symptoms on overall Bowel Domain score, as these were always  $\geq$  5 or higher. On the other hand, when focusing on the ten specific IBDQ-B items, men reporting a baseline score < 5 for a specific IBDQ-B item had to be removed from the investigation of that particular symptom. Patients with lower (=worse) scores at baseline ( $\leq$ Q1)

# Table 1

Mean (and SD) values for each of the ten IBDQ-B questions and IBDQ-B Domain at baseline (BL), at 2-years and delta ( $\Delta$ ) values.

	Mean BL Score ± SD	Mean 2 y Score ± SD	Mean 2 y Δ ± SD	p-value
IBDQ1 - Frequent	$\textbf{6.85} \pm \textbf{0.43}$	$6.41 \pm 1.31$	$-0.43$ $\pm$	< 0.001
Bowel Movement			1.36	
IBDQ5 - Loose Bowel	$6.71 \pm 0.57$	$\textbf{6.47} \pm \textbf{0.87}$	$-0.24~\pm$	< 0.001
Movement			0.89	
IBDQ9 - Abdominal	$\textbf{6.88} \pm \textbf{0.38}$	$6.66\pm0.73$	$-0.22~\pm$	< 0.001
Cramp			0.74	
IBDQ13 - Abdominal	$6.78 \pm 0.51$	$6.63 \pm 0.78$	$-0.15~\pm$	< 0.001
Pain			0.83	
IBDQ17 - Gas Passage	$6.32 \pm 0.78$	$5.88 \pm 1.11$	$-0.44~\pm$	< 0.001
			1.11	
IBDQ20 - Abdominal	$\textbf{6.47} \pm \textbf{0.69}$	$6.21 \pm 1.06$	$-0.27~\pm$	< 0.001
Bloating			1.06	
IBDQ22 - Rectal	$6.95\pm0.21$	$6.62\pm0.93$	$-0.33~\pm$	< 0.001
Bleeding			0.91	
IBDQ24 - Urge to Go	$\textbf{6.74} \pm \textbf{0.54}$	$6.53\pm0.86$	$-0.21~\pm$	< 0.001
to Bathroom			0.89	
IBDQ26 - Accidental	$6.78\pm0.50$	$6.48 \pm 0.99$	$-0.29~\pm$	< 0.001
Soiling			0.94	
IBDQ29 - Nausea/	$6.94\pm0.27$	$6.88\pm0.5$	$-0.06~\pm$	0.063
Feeling Sick			0.54	
IBDQ-B - Bowel	$6.56\pm0.5$	$6.41 \pm 0.64$	$-0.15~\pm$	< 0.001
Domain			0.61	

maintained significantly lower IBDQ-B scores at all subsequent time intervals when compared to men with higher (=better,  $\geq$ Q1) baseline values. On the other hand, the overall IBDQ-B scores at 2 years remained roughly unchanged when compared to baseline in patients with worse ( $\leq$ Q1) baseline scores, while they emerged as significantly lower (=worsened) in patients starting radiotherapy with higher (=better)

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baseline values. The same behavior was confirmed for the majority of the ten single IBDQ-B items, for which the changes were very limited, typically within or around -0.2.

#### Impact of acute toxicity ( $\Delta_{Acute}$ ) on 2-year worsening of intestinal function

The distributions of the 2-year changes relative to baseline scores for six of the ten IBDQ-B items showing the largest variations are displayed in the Supplementary Materials (Figure S3): they were grouped by  $\Delta_{Acute}$  values into the first quartile of the population ( $\Delta_{Acute} \leq Q1$ ) and the remaining part of the distribution ( $\Delta_{Acute} > Q1$ ). Each item exhibited left-skewed and unimodal distributions with the one of  $\Delta_{Acute} \leq Q1$  shifted to the right relative to that of  $\Delta_{Acute} > Q1$ . Fig. 3 shows the longitudinal trend of the mean scores of the same six items, namely: "IBDQ1 - Frequent Bowel Movement", "IBDQ5 - Loose Bowel Movement", "IBDQ9 - Abdominal Cramp", "IBDQ13 - Abdominal Pain", "IBDQ24 - Urge to defecate" and "IBDQ26 - Accidental Soiling". For all these six symptoms the mean scores were grouped by  $\Delta_{Acute}$  values. At baseline the two cohorts are nearly indistinguishable, resulting then

very well separated during radiotherapy and at its end (acute worsening); subsequently, starting three months after radiotherapy conclusion, they become much closer and remain more or less unaltered until two years after irradiation. An identical plot is shown in Fig. 4, referring to the overall IBDQ-B. In Table S4 (Supplementary Materials) the significance of the differences between IBDQ scores at 2 years and at baseline stratified by  $\Delta_{Acute}$  are reported.

Patients with only modest acute worsening ( $\Delta_{Acute} > Q1$ ) showed no/ minimal mean changes (<0.2) at 2 years. On the contrary, patients with moderate-severe acute worsening ( $\Delta_{Acute} \leq Q1$ ), did not achieved a full recovery of symptoms at two years (p < 0.0001): the symptoms showing the largest mean changes (0.5–1 points) were "Frequency of bowel movement", "Loose bowel movement", "Abdominal pain", "Accidental soiling" and "Urge to defecate" (items # 1, 5, 13 and 24, respectively). In order to try to provide an overview of possible "clinically significant" worsening of the ten intestinal symptoms and of the overall IBDQ-B Domain, in Table 2, the rates of patients with 2-year worsening greater than or equal to 1 or 2, are shown for all ten IBDQ specific questions and for the overall IBDQ-B Domain, stratified according the



**Fig. 3.** Trend over time of the average scores of six out of ten IBDQ-B items: first quartile values (Q1) of Delta Acute distributions stratify the populations with "Frequent Bowel Movement" (Q1 = -4), "Lose Bowel Movement" (Q1 = -3), "Abdominal Cramp" (Q1 = -1), "Abdominal Pain" (Q1 = -1), "Urge to Go to Bathroom" (Q1 = -2) and "Accidental Soiling" (Q1 = -1).

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Fig. 4. Trend over time of average IBDQ-B Domain scores when patients are split according to the first quartile value (Q1 = -1.2) of Delta Acute distribution.

 $\Delta_{Acute}$  ( $\Delta_{Acute} \leq Q1 \ vs \ \Delta_{Acute} > Q1$ ). The rates were significantly higher in the  $\leq Q1$  group for most items and were particularly high for "Loose Bowel Movement", "Abdominal Pain", "Gas Passage", "Abdominal Bloating", "Urge to Defecate" and "Accidental Soiling". Specifically, in the ( $\Delta_{Acute} \leq Q1$  group the risk of 2-year worsening of at least < 1 point = the minimum possible worsening), was between 1.9 and 3.1 times greater than in the ABOVE group, with the sole exception of "Rectal Bleeding" and "Nausea/Feeling Sick" where differences were not statistically significant. The corresponding risks for patients with a  $\Delta_{Acute}$  of at least 2 points ranged between 1.7 and 6.9 fold.

#### Discussion

Intensity-modulated radiotherapy significantly reduced the incidence and severity of IT from pelvic radiotherapy, owing to efficient bowel sparing. This important result, combined with recent evidence of the beneficial role of PNI in both radical and post-prostatectomy settings [2,5], translated into a continuously growing fraction of PCa patients treated with PNI. Although most modern investigations showed small rates of late IT and scanty or null impact on OoL [9,11,12,14,17,19,31,32], there is a clear lack of sufficiently powered studies to identify patients who may evolve toward chronic bowel symptomatology, with likely important consequences for QoL. Two prospective trials [20,21] and one recent review [33] have underlined that PNI may negatively affect late QoL scores in a non-negligible fraction of patients, while highlighting that patient-reported scores should be preferred for an adequate investigation of this issue. The need for prospective trials including a careful patient-reported assessment of intestinal symptoms on sufficiently large populations is evident and, in part with this aim, the IHU-WPRT TOX study was activated and completed patient enrollment in 2021. In this multi-centric observational trial, IT was carefully assessed by means of the IBDQ, whose "Bowel" domain includes 10 questions providing a detailed description of intestinal symptoms, and which has already been successfully used in patients treated with pelvic radiotherapy [16,19,23,27,30,34]. In previous analyses, acute toxicity was investigated, showing the impact of baseline scores and, secondarily, of bowel DVH parameters on its severity [16,19]. The current study exploited the maturity of the data to focus on the 2-year worsening of intestinal symptoms when compared to baseline.

The first significant result is that the mean worsening of intestinal symptoms at 2 years is generally mild, and greater only for specific symptoms such as frequency, gas passage, rectal bleeding and accidental soiling. The temporal trend is similar for all items and shows a maximum decrease (=worsening) during and/or at radiotherapy end (acute phase), followed by a significant improvement though without a full recovery at two years; at that time for all the investigated symptoms with the sole except of "Nausea/Feeling Sick" (IBDQ29) a significant worsening with respect to baseline emerged. Several recent studies have reported similar trends using different questionnaires, mainly the EPIC [17,20,21]. Akhtar et al. [21] for instance, analyzing 199 patients found no clinically significant change after a median follow-up of 33 months in the bowel domain in the post-prostatectomy setting. Interestingly, our results showed, to our knowledge for the first time in a prospective multi-Institute trial, that radiotherapy intent (radical vs postprostatectomy) had no impact on radiation-induced worsening of intestinal symptoms.

Another significant finding concerns the association between baseline and late symptoms. Regarding the absolute values, baseline scores are clearly associated with both acute and late scores, in agreement with our previous findings relative to the acute setting [16,19] and reasonably suggesting that patients with modest/moderate symptoms at baseline are likely to continue to experience them. Nevertheless, evidence of a consequential pattern concerning patient-reported IT in a large prospective cohort, to our knowledge, is reported here for the first time. The result is in line with the recently reported findings by Leufgens *et al.* [35], referring to patient-reported IT in a cohort of 287 patients treated without PNI and using large margins for PTV definition, whose pattern of toxicity should be expected to depend mostly on rectum irradiation.

Regarding the worsening relative to baseline, our findings showed that patients with modest/moderate symptoms already present at baseline did not experience significant radiation-induced deterioration, while a small decrease (=worsening) was more frequently detected in patients with absent/almost null baseline symptoms. Very importantly,

Table 2

Rates of 2-year severe worsening (of at least one or two points when compared to baseline) split between Delta Acute  $\leq vs >$  its first quartile (Q1) for each IBDQ-B question and for the total IBDQ-B Domain. Patients with baseline score < 5 were removed from the analyses relative to the ten single IBDQ-B questions. The p-values of the Chi-square test for independence between the two groups are reported.

		2-year severe worsening relative to baseline of at least:						
		1 point			2 points			
	Q1	$\Delta_{Acute} \leq Q1$	$\Delta_{Acute} > Q1$	p-value	$\Delta_{Acute} \leq Q1$	$\Delta_{Acute} > Q1$	p-value	
IBDQ1 – Frequent Bowel Movement	-4	35.1 %	17.7 %	0.001	20.6 %	9.1 %	0.005	
IBDQ5 – Loose Bowel Movement	-3	46.7 %	17.3 %	< 0.001	11.4 %	6.6 %	0.182	
IBDQ9 – Abdominal Cramp	$^{-1}$	29.3 %	13.9 %	< 0.001	8.6 %	3.2 %	0.037	
IBDQ13 – Abdominal Pain	$^{-1}$	31 %	10 %	< 0.001	10.8 %	2.2 %	< 0.001	
IBDQ17 – Gas Passage	$^{-2}$	60.2 %	32.4 %	< 0.001	31 %	7.9 %	< 0.001	
IBDQ20 – Abdominal Bloating	$^{-1}$	46.7 %	15.5 %	< 0.001	19.8 %	3.7 %	< 0.001	
IBDQ22 – Rectal Bleeding	0	19.1 %	40 %	0.546	9.2 %	20 %	0.958	
IBDQ24 – Urge to defecate	$^{-2}$	33.6 %	15.1 %	< 0.001	12.4 %	3.3 %	0.001	
IBDQ26 – Accidental Soiling	$^{-1}$	38.9 %	17.7 %	< 0.001	14.6 %	2.9 %	< 0.001	
IBDQ29 - Nausea/Feeling Sick	0	5.9 %	0 %	1	2.1 %	0 %	1	
IBDQ-B – Bowel Domain	-1.2	11.4 %	5.1 %	0.046	4.8 %	0.7 %	0.021	

this result was obtained by excluding, for each of the ten IBDQ item, patients with severe baseline symptoms (scores < 5), aiming to limit the interplay between irradiation and other pre-existing severe intestinal dysfunctions. Of note, it would be of interest to conduct an analysis focused on this relatively small (<10 %) subgroup of patients, also considering the expected increased number of cancer patients with intestinal problems at baseline, following the reported increment in the general population [36,37]. With respect to this analysis, the scanty sample size of patients with baseline severe intestinal symptoms did not allow the performance of statistical analyses providing accurate and reliable results. With the continuation of data retrieval, hopefully there will be room for this kind of analysis in future research.

Probably the major achievement of the current investigation is the clear identification of acute severe toxicity (expressed in our analysis as  $\Delta_{Acute} \leq Q1$ ) as a strong modulator of 2-year intestinal function. In particular, the fraction of patients with a 2-year change of at least 2 points (on a 1–7 scale) was 3–5-fold higher for patients experiencing severe acute symptoms ( $\Delta_{Acute} \leq Q1$ ) when compared to patients with less severe acute toxicity for most symptoms likely to significantly affect QoL, such as urgency, frequency, accidental soling and abdominal pain. Very importantly, the mean 2-year worsening of symptoms in patients with  $\Delta_{Acute} > Q1$  was very mild (<0.2) and non-significant for several items.

These findings suggest that "radio-sensitive" patients experiencing more severe acute toxicity should be regarded as those with the highest probability of suffering from chronic late radiation-induced worsening of intestinal function. Once identified, these patients may be offered thorough and personalized multidisciplinary targeted intervention aimed at mitigating any possible further evolution toward chronic symptomatology, starting immediately after radiotherapy conclusion [22,23]. On the other hand, the detection of pre-irradiation potential predictors may help in better refining the identification of "patients at risk" before radiotherapy. Very interestingly, it is likely that the severity of acute toxicity measured by  $\Delta_{Acute}$  is, at least in part, a surrogate marker for a genetically pre-existing poorer repair capacity of the radiation-induced damage [38]. It could also be an indicator of the presence of an individual microbiome making some patients more sensitive to radiation [39,40] and/or of other individual features associated with inflammatory response, immune regulation, or vascular response.

An additional interesting finding of this series pertains to the lack of significant differences in terms of IT over time observed in patients treated with different intent (radical *vs* adjuvant *vs* salvage) in the two years following irradiation, possibly as the result of the rather similar doses delivered to prostate and prostatic bed in the three cohorts analyzed, which could have mitigated any possible difference in terms of radiation induced IT.

Still, one might think that the findings presented in this paper could be too optimistic as a considerable number of treated patients were excluded from the analysis due to a lack of questionnaires, as required by the inclusion criteria. To overcome this concern, the two conditions on the presence of baseline, 2 year, 3, 6, 12 and 18 month questionnaires were dropped, and the results on IT were documented in the <u>Supplementary Materials</u> (Figure S4). No difference was found with regard to the IBDQ-B score, corroborating the impression that the lack of questionnaires is not related to the loss of patients with particularly major worsening of symptoms.

Moreover, the possible impact of bowel symptom deterioration on the other domains of IBDQ, dealing with the impact of bowel symptoms on QoL, is a significant issue and will be the aim of further analyses on the current population.

## Conclusions

Late worsening of intestinal symptoms after radiotherapy including PNI may be significant, although mild for the large majority of patients. In our analysis, it was found to be independent of therapy intent and only minimally influenced by baseline intestinal status. Patients experiencing severe acute symptoms are at higher risk of symptom persistence two years after irradiation, likely impairing QoL. The rate of patients in the first quartile of  $\Delta_{Acute}$  experiencing severe worsening (defined as a score decrease of two or more points on a 1-7 scale) of bowel symptoms likely to have a serious impact on QoL, such as urgency, frequency, accidental soiling and abdominal pain is in the 10-20 % range. On the other hand, a general warning concerns the possible perception of PNI as a treatment without any cost in terms of late bowel toxicity. Although the current study does not compare the IT of patients receiving and not receiving PNI, it appears reasonable that prophylactic lymph-nodal area irradiation could be most responsible for the reported findings. The cost may be non-negligible and it should be considered in the cost-benefit clinical evaluation, especially for certain categories of patients for whom the benefit deriving from PNI may be slight, if any. This issue is particularly debatable in the salvage setting: despite recent confirmation of the benefit of PNI [2], it is likely to be insignificant for most "low risk" patients, as shown in a recent retrospective study [41]. Analysis of the impact on OoL domains of IBDO (Emotional, Social and Systemic) of the patient-reported 2-year worsening of bowel symptoms is ongoing.

#### CRediT authorship contribution statement

Giuseppe Sanguineti: Data curation, Writing - review & editing. Maddalena Pavarini: Data curation, Formal analysis, Methodology, Writing - original draft, Writing - review & editing. Fernando Munoz: Data curation, Writing - review & editing. Alessandro Magli: Data curation, Writing - review & editing. Domenico Cante: Data curation, Writing - review & editing. Elisabetta Garibaldi: Data curation, Writing - review & editing. Andrea Gebbia: Data curation, Formal analysis, Writing - review & editing, Software. Barbara Noris Chiorda: Data curation, Writing - review & editing. Giuseppe Girelli: Data curation, Writing - review & editing. Elisa Villa: Data curation, Writing - review & editing. Adriana Faiella: Data curation, Writing - review & editing. Justyna Magdalena Waskiewicz: Data curation, Writing review & editing. Barbara Avuzzi: Data curation, Writing - review & editing. Alice Pastorino: Data curation, Writing - review & editing. Eugenia Moretti: Data curation, Writing - review & editing. Luciana Rago: Data curation, Writing - review & editing. Teodora Statuto: Data curation, Writing - review & editing. Marco Gatti: Data curation, Writing - review & editing. Tiziana Rancati: Data curation, Formal analysis, Methodology, Supervision, Writing - original draft, Writing review & editing. Riccardo Valdagni: Data curation, Writing - review & editing. Vittorio Luigi Vavassori: Data curation, Writing - review & editing. Nadia Gisella Di Muzio: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing original draft, Writing - review & editing. Claudio Fiorino: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing - original draft, Writing - review & editing. Cesare Cozzarini: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing - original draft, Writing - review & editing.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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#### Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110088.

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