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RESEARCH ARTICLE

Assessment of acute bowel function after radiotherapy for prostate cancer: Is it accurate enough?

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Abstract
Background and purpose Pelvic radiotherapy for prostate cancer can be associated with bowel toxicity, which may have a significant impact on quality of life. Our aim was to assess the adequacy of the tools currently used to assess bowel symptoms after radiotherapy, including physician and patient reported outcomes. This sub-study on acute toxicity was part of a prospective trial assessing long-term bowel dysfunction.
Materials and methods Between February 2013 and July 2015, 75 patients with prostate cancer who received radiotherapy completed the LENT/SOMA and the EPIC questionnaires baseline and 2 weeks after the treatment. The Bristol stool scale and two additional questions on faecal urgency were added. Physicians assessed toxicity using Common Terminology Criteria for Adverse Events v.4.0. Agreement between patients and clinicians was assessed using the Cohen's κ coefficient.
Results Acute toxicity during radiotherapy was very low. The pattern of overall bowel bother was similar before and after treatment. Faecal urgency significantly increased after radiotherapy compared to baseline but was only detected by the additional questions and not by the physicians or the patient-reported outcomes (PRO) questionnaires. Correlation between physician and PRO was poor for most symptoms.
Conclusion Bowel symptoms such as urgency may remain undetected by usual tools to assess toxicity after radiotherapy. Assessment of bowel toxicity should be reappraised in order to identify those patients who may have symptoms with an impact on their quality of life.

Keywords Radiotherapy · Prostate cancer · Bowel dysfunction · Faecal urgency · Quality of life

Introduction

Prostate cancer is the third most frequent cancer in Europe, accounting for an incidence of 22.8% in males [1]. The increase in tumour detection at an earlier stage has resulted in a decrease in the age of patients at diagnosis [2] and, therefore, patients may potentially live many years after the treatment. In this scenario, the assessment of treatment side effects is crucial and should take into account the impact on patients' quality of life (QoL).

Several studies have shown that external beam radiotherapy (RT) for prostate cancer may be associated with bowel complaints [3–5]. The total dose of RT is limited by dose-dependent toxicity to the normal adjacent tissues such as the gastrointestinal tract. Bowel dysfunction caused by radiation is important mainly for two reasons: first, the risk of acute and late severe gastrointestinal symptoms might limit optimal RT doses; and second, long-term toxicity might be associated with a significant reduction in QoL

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[6–8]. It has been reported that among all the potential adverse effects of pelvic RT, gastrointestinal symptoms are those with the greatest impact on QoL [7]. However, bowel dysfunction after radiotherapy might not be properly evaluated by the most commonly used questionnaires. Faecal urgency has a significant impact on quality of life and is one of the most frequent symptoms in studies assessing late anorectal symptoms [9–14], but it is not systematically assessed by most questionnaires.

In February 2013, a prospective trial to assess long-term bowel dysfunction in patients undergoing RT for prostate cancer was started at our institution, in which toxicity was recorded both by the physician and the use of self-reported questionnaires. The present paper reports the early outcomes of the cohort, as an initial substudy assessing their acute bowel toxicity.

The aim of our study was to evaluate the adequacy of the tools currently used to assess bowel symptoms after radiotherapy for prostate cancer, including physician- and patient-reported outcomes. A secondary aim was to investigate the agreement between patient and physician measures for acute bowel symptoms after RT for prostate cancer.

Materials and methods

Patients and treatment

Between February 2013 and July 2015, all consecutive patients with histologically confirmed prostate cancer were included in the study. Inclusion criteria were a prescribed RT dose >66 Gy both in radical or postoperative setting, and both with and without androgen deprivation. Exclusion criteria were refusal of the patient to participate in the study and intellectual or language difficulties to fill in the questionnaires appropriately.

All patients were simulated with a computed tomography acquired in the supine position with a 3-mm thickness and knee immobilization. Patients were asked to come with a comfortably filled bladder and had previous dietary counseling [10]. The clinical target volume (CTV) encompassed the prostate (with or without the seminal vesicles) or the visible mass (GTV) in the case of recurrence with a 3-mm margin. If indicated, the volumes for prophylactic nodal irradiation were defined according to the RTOG guidelines [15]. The planning target volume (PTV) for prostate was 1 cm around the prostate, except in the posterior direction, where a margin of 7 mm was added. In the postoperative setting, an additional margin of 5 mm was added for PTV. The organs at risk (OAR) were defined according to the RTOG pelvic normal tissues guidelines [16]. The total dose was prescribed according to the ICRU guidelines. The delivered dose ranged from 64 to 80 Gy (64–70 Gy for postoperative patients and 74–80 Gy if radical approach), and the prophylactic dose to pelvic lymph nodes ranged from 45 to 50.4 Gy at standard fractionation. A non-action level protocol of image-guided RT (IGRT) was used, based on either cone-beam CT or portal vision according to the treatment modality, geometrical conditions of the target and/or OAR.

The rectal volumes were contoured following the RTOG recommendations. In addition, the anal canal and the "anatomic rectum" (that was defined as the rectal RTOG volume excluding the canal anal) were contoured as well. The contouring process was guided by an experienced specialist in radiology imaging.

Symptoms assessment

All patients were followed up weekly by the same experienced radiation oncologist during the RT and 2 weeks after the end of treatment. Subsequently, patients were followed by the urologist and the radiation oncologist every 6 months.

Patient-reported outcomes

Patient-reported outcomes (PRO) were assessed by the Spanish version of the expanded prostate cancer index composite questionnaire (EPIC) [17].

The EPIC questionnaire was designed to evaluate function (presence and severity) and bother after prostate cancer treatment. It includes 50 questions on four domains (urinary, bowel, sexual and hormonal symptoms). For this study, only data on the bowel domain of the EPIC questionnaire were included. The bowel subscale is a seven-item subscale that rates frequency of bowel movements, rectal urgency, uncontrolled leakage of stool, loose or liquid stool, bloody stool, painful bowel movements and crampy pain in the abdomen, pelvis or rectum. Response options for each EPIC question are transformed linearly to a 0–100 scale, with higher scores representing better health-related QoL.

In order to improve the assessment of faecal urgency, two additional questions were included: "Do you even need to rush to the toilet to open your bowels? and "Are you able to defer defecation for 15 min?". Questions were phrased as in the scores commonly used to assess faecal incontinence [18].

Patients were also asked to fill in the LENT/SOMA questionnaire to complete the patient-reported treatment toxicity. Stool consistency was assessed by the Bristol stool scale [19].

Questionnaires were completed by the patient without the physician's participation at baseline (before the first

radiation treatment), 2 weeks after RT and every 6 months.

Physician-reported outcomes

During RT and follow-up, bowel toxicity was assessed by the radiation oncologist and graded according to the common terminology criteria for adverse events scale (CTCAE v.4.0) [20] for the following symptoms: proctitis, urgency and faecal incontinence, rectal bleeding, rectal/anal pain, diarrhoea, flatulence and constipation.

Correlation between the patient- and physician-reported outcomes

Seven bowel toxicity items assessed by the physician were correlated with the analogous items of the EPIC and LENT/SOMA questionnaires, which had been completed by the patient alone.

Ethical issues

Surveys were conducted according to the accepted standards of good clinical practice in agreement with the latest version of the Declaration of Helsinki. The study was approved by the Ethics Committee of the Consorci Sanitari de Terrassa. All patients provided written informed consent for the study.

Statistical analysis

Results are presented as means, standard deviation and range for quantitative variables and as absolute and relative frequencies for qualitative variables. A Chi squared test was applied to assess differences between the study groups for qualitative parameters or Fisher's exact test as appropriate. The agreement between patients' response and physicians' assessment was measured with the Cohen's κ coefficient. The interpretation of k was performed by correlating its value with a qualitative scale, which includes six levels of strength of agreement: poor (<0.00), slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80) and almost perfect (0.81–1.00) simplifying its comprehension. A p value <0.05 was considered statistically significant. Data analysis was performed using the statistical package SPSS version 20.

Results

Of the 75 patients who were initially enrolled in this study, three were excluded for the following reasons: one patient interrupted treatment due to a psychiatric disorder, one was finally treated at another hospital and one received treatment with brachytherapy.

Finally, 72 patients were included with a mean age of 68 ± 6 years (range 53–84).

According to treatment modality, 20 (27.8%) patients received only RT; 20 (27.8%) RT as adjuvant treatment to surgery; 24 (33.3%) RT and hormonal therapy; and 8 (11.1%) were treated with surgery, RT and hormonal therapy.

RT was delivered using a 3D-conformal technique in 51 patients and using VMAT in 21. Mean dose was 73 ± 4 Gy (range 64–80), with only three patients receiving less than 66 Gy. There were no cases of clinical or biochemical relapse during follow-up.

Mean dose to the RTOG rectum, canal anal and "anatomic rectum" was 40.08 Gy (34.9–49.9), 31.8 Gy (15.9–45.1) and 44.3 Gy (39.2–50.1), respectively. V25, V50 and V70 was 78.5% (66.6–98.9), 38.1% (23.7–42.4) and 8.5% (2–14.7) for the RTOG rectum; 52.3% (25.9–87.4), 19.5% (5.2–47.8) and 0.4% (0.2–9.8) for the anal canal; and 89.8% (67.1–100), 39.5% (26.9–44.7) and 9.9% (2.4–16.5) for the "anatomic rectum".

Patient-reported outcomes

The EPIC questionnaire after RT (Table 1) revealed a significant increase in the number of patients experiencing tenesmus ($p = 0.000$) and increased bowel frequency ($p = 0.000$). The mean change between the EPIC assessment before and after treatment is shown in Table 2.

The answers to the two additional questions about faecal urgency revealed an increase of patients experiencing urgency, from 7.5% at baseline to 9.4% after treatment ($p = 0.030$). Stool consistency did not differ significantly between baseline and after RT when assessed using the Bristol stool scale, although there were slightly more patients with Bristol 5 (loose stools) after RT (Fig. 1).

Most patients experienced a slight increase in all bowel symptoms, which was only statistically significant for tenesmus ($p = 0.017$) and for the need for antidiarrhoeal medication ($p = 0.031$) according to the LENT/SOMA responses (Table 3).

The pattern of overall bowel bother was similar at baseline and after RT, with very few patients reporting either moderate or big bothers (Fig. 2).

Physician-reported outcomes

Acute toxicity was very low and no patients experienced grade 3 or 4 toxicity (Table 4). Most common symptoms were diarrhoea (23.6%), grade 1–2 proctitis (38.9%) and constipation (22.2%).

Table 1 EPIC at baseline (V0) and immediately after RT (V1)

		V0	V1	*p*
Tenemus	Never/≤once a week	52 (76.5%)	43 (64.2%)	0.000
	≥once a week	16 (23.5%)	24 (35.8%)	
Faecal incontinence	Never/≤once a week	65 (90.3%)	64 (95.5%)	0.136
	≥once a week	3 (4.2%)	3 (4.5%)	
Diarrhoea	Never or few times	55 (82.1%)	56 (83.6%)	0.089
	At least half of the times	12 (17.9%)	11 (16.4%)	
Bleeding	Never or few times	65 (95.6%)	66 (98.5%)	0.953
	At least half of the times	3 (4.4%)	1 (1.5%)	
Pain during defecation	Never or few times	64 (94.1%)	60 (89.6%)	0.056
	At least half of the times	4 (5.9%)	7 (10.4%)	
Frequency	2 or less	56 (82.4%)	48 (71.6%)	0.000
	3–4	12 (17.6%)	16 (23.9%)	
	>5	0 (0%)	3 (4.5%)	
Abdominal pain	Never/≤once a week	56 (82.4%)	46 (68.7%)	0.093
	≥once a week	12 (17.6%)	21 (31.3%)	

Table 2 Quality of life scores (EPIC) before (V0) and after RT (V1)

	V0	V1	Mean change (SD) from baseline
EPIC bowel	91.5 (10.2)	86.1 (14.7)	−5.3 (13.4)
Function	90.2 (10.5)	85 (14.5)	−5.5 (15)
Bother	92.6 (12.1)	87.2 (16.7)	−5.2 (14.7)

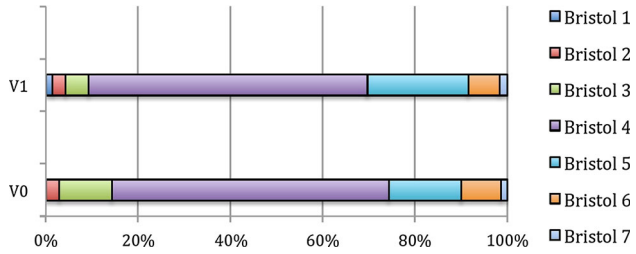

Fig. 1 Bristol stools scale at baseline (V0) and after RT (V1)

Correlation between patient- and physician-reported outcomes

The agreement was poor for diarrhoea, slight for bleeding and fair for pain and constipation. The only substantial agreement was for antidiarrhoeal medication (kappa = +0.660) (Table 4). We did not find an analogous item for the CTCAE term "proctitis" in PRO questionnaires, and no patient presented other rectal symptoms

Table 3 LENT/SOMA at baseline (V0) and immediately after RT (V1)

	V0		V1		*p*
	No	Yes	No	Yes	
Tenesmus (once a week or more)	57 (85.1%)	10 (13.9%)	45 (68.2%)	21(31.8%)	0.017
Urgency (once a week or more)	60 (88.2%)	8 (11.8%)	49 (73.1%)	18 (26.9%)	0.059
Faecal incontinence	68 (98.6%)	1 (1.4%)	61 (91%)	6 (9%)	0.092
Diarrhoea	66 (95.7%)	3(4.3%)	57 (85.1%)	10 (14.9%)	0.059
Antidiarrhoeal medication	68 (98.6%)	1 (1.4%)	65 (97%)	2 (3%)	0.031
Bleeding	62 (91.2%)	6 (8.8%)	62 (92.5%)	5 (7.5%)	0.065
Pain during defecation	63 (90%)	7 (10%)	50 (74.6%)	17 (25.4%)	0.053
Constipation	68 (98.6%)	1 (1.4%)	59 (88.1%)	8 (11.9%)	0.108

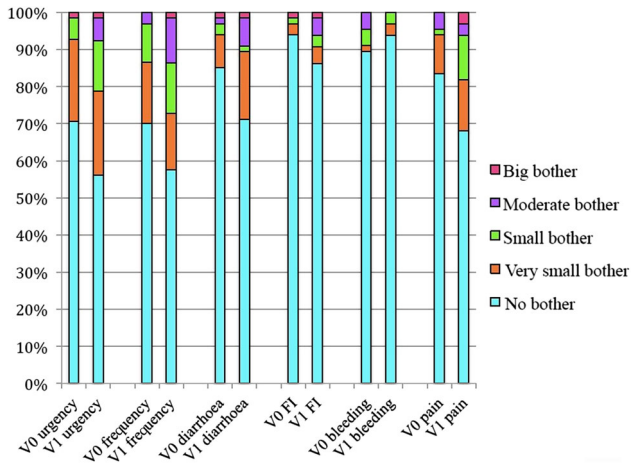

Fig. 2 Bowel bother at baseline (V0) and after RT (V1). FI: faecal incontinence

classified as CTCAE ≥grade 3 by physicians. Six patients (9.4%) referred faecal urgency after RT, but no patients were classified as "proctitis grade 3" ("faecal urgency or stool incontinence") by physicians. Kappa coefficient could not be calculated for faecal incontinence and proctitis due to imbalances in the distribution of cells of agreements, disagreements and marginal totals.

Discussion

The main findings of our study were that current tools may not be accurate enough to assess bowel dysfunction after RT and that the correlation between physician- and patient-reported outcomes is poor. PRO questionnaires showed a slight increase in all bowel symptoms after RT, which were only statistically significant for tenesmus and increased bowel frequency. However, this questionnaire does not evaluate faecal urgency. Other authors [14] have previously reported that faecal urgency has been underestimated in many studies, although being the most frequent and persistent symptom after RT. Interestingly, the additional questions to improve the assessment of urgency showed a statistically significant increase from baseline. The relevance of this symptom is that faecal urgency may be an extremely stressful condition, as patients feel the sudden need to rush to the toilet and experience a constant fear of having a bowel leakage. This situation may lead to a significant limitation of their activities, fear of leaving home and social isolation.

Conformal 3D and intensity-modulated IMRT have been associated with clinically meaningful reductions in acute bowel symptoms during RT [21]. Despite the advances in technology, RT for prostate cancer may increase bowel frequency, defecatory urgency, faecal incontinence and/or G2 rectal bleeding that can occur in up to 7% of patients in the acute period [22]. Acute toxicity may be reduced when IGRT techniques are used, resulting in only 1.1% according to the CTCAE v 3.0 scale [23]. In our experience, acute toxicity was low with few patients reporting either moderate or severe bowel bother. Although acute toxicity may be of minor relevance in the treatment of prostate cancer, it has been reported that acute toxicity may be a predictor for late toxicity [24]. Regardless of whether acute or late adverse effects are measured, making sure that toxicity is adequately assessed is of great importance. There are numerous studies on rectal bleeding, but anorectal dysfunction associated with RT has not been well characterized and few authors have addressed other aspects of pelvic radiation disease such as faecal urgency or faecal incontinence, despite a significant impact on QoL [7]. More than 50% of patients treated with RT for prostate cancer report an alteration of bowel habit, with bowel symptoms causing considerable distress in 9% of patients 1 year after RT [12, 25, 26]. Unfortunately, there is a limitation of our study that prevents us to correlate the dosimetric parameters to the OARs and the toxicity. The study allowed the inclusion of a variety of treatments (intact prostate, prostatectomy, prophylactic lymph node irradiation, androgen deprivation) that may also impact the rates of the potential chronic toxicity.

There are several considerations to be made regarding the physicians' assessment. The RTOG/EORTC scale, the most commonly used tool to assess bowel toxicity, does not include an evaluation of anorectal symptoms such as urgency and faecal incontinence, and therefore, bowel dysfunction was rarely identified in previous studies and clinical trials [27]. The common terminology criteria for adverse events (CTCAE) do not include faecal urgency as an adverse event either, although it does include a question on urinary urgency. Moreover, faecal incontinence is solely graded based on the need to wear pads and the impact on quality of life is not taken into account, resulting in a tendency to consider it as a minor problem because it is classified as grade 1–2 toxicity. Finally, the definition of the term "proctitis" can be vague and misleading, and this may explain why physicians did not identify any of the six patients who suffered faecal urgency in our study. Andreyev et al. reported that the term "proctitis" suggests that the pathology is exclusively rectal, although changes in other anatomical locations such as the sigmoid colon may contribute to the symptoms. Moreover, different symptoms grouped together under the term "proctitis" may have different pathophysiological causes [28].

Another point to highlight is that a proportion of patients undergoing RT may have pre-existing bowel symptoms, which are not usually systematically assessed before treatment. In our study, 13.9% reported tenesmus and

Table 4 Physician- *vs.* patient-reported outcomes after RT

	Physician		Patient reported outcomes		Kappa	*p*
Diarrhoea	G0 (normal)	54 (75%)	No	57 (85.1%)	−0.057	0.575
	G1 (increase of <4 stools)	17 (23.6%)	<4/day	7 (10.4%)		
	G2 (4–6 stools)	1 (1.4%)	4–6/day	3 (4.5%)		
	G3 (≥7 stools)	0 (0%)	>7/day	0 (0%)		
Antidiarrhoeal medication	Yes	2 (2.8%	Yes	2 (3.1%)	0.660	0.000
	No	70 (97.2%)	No	63 (96.9%)		
Faecal incontinence	G0 (no)	72 (100%)	No	61 (91%)		
	(Yes)	0 (0%)	Yes	6 (9%)		
	G1 (pads required)	0 (0%)	Pads required	0 (0%)		
	G2 (daily use of pads)	0 (0%)	Daily use of pads	0 (0%)		
	G3 (severe symptoms)	0 (0%)	Severe symptoms	1 (1.4%)		
Bleeding	G0 (no)	66 (91.7%)	Never	60 (89.6%)	0.040	0.706
	G1 (mild, no treatment)	5 (6.9%)	Few times	6 (9%)		
	G2 (moderate, medical intervention or minor cauterization)	1 (1.4%)	Frequent	1(1.4%)		
	G3 (transfusion or treatment)	0 (0%)	–	–		
Proctitis	G0 (no)	44 (61.1%)	–	–	–	
	G1 (rectal discomfort)	18 (25%)	–	–		
	G2 (medical intervention indicated)	10 (13.9%)	–	–		
	G3 (faecal urgency or stool incontinence)	0 (0%)	–	–		
	G4 (life-threatening conseq; urgent intervention)	0 (0%)	–	–		
Pain	G0 (no)	64 (88.9%)	No	47 (74.2%)	0.215	0.045
	G1 (mild pain)	8 (11.1%)	Minimal	17 (25.8%)		
	G2 (moderate pain)	0 (0%)	Moderate	0 (0%)		
	G3 (severe pain)	0 (0%)	Severe	0 (0%)		
Constipation	G0 (no)	55 (76.4%)	No	59 (88.1%)	0.254	0.024
	G1 (occasional use of stool softeners)	16 (22.2%)	Occasional laxatives	4 (5.5%)		
	G2 (regular use of laxatives or enemas)	1 (1.4%)	Regular laxatives	4 (5.5%)		
	G3 (manual evacuation indicated)	0 (0%)	–	–		

11.8% faecal urgency according to the LENT/SOMA questionnaire at baseline, and figures were even higher in the EPIC questionnaire (tenesmus more than once a week was reported by 23.5% patients). Our results are consistent with previous studies [14] that reported 17 and 24% of urgency of defecation before RT in 3D and 2D, respectively, and rates of faecal incontinence of 3–5%. The absence of a baseline evaluation both in studies and in daily clinical practice raises the question whether toxicity is adequately evaluated. Although the oncological outcome is a priority, it is well known that quality of life may be adversely affected by long-term side effects of the treatments, and therefore, assessment of functional outcomes is of key importance to allow an adequate informed consent and a shared decision making process.

The advantage of patient-reported outcomes is that measurements are directly reported by the patient and not only include the severity of symptoms, but also the patient's subjective bother. These tools are especially useful when QoL plays an essential role, such as in cancer treatments and for prostate cancer in particular, given that most patients will cure and a long survival is expected. In this respect, the EPIC questionnaire is considered to be one of the best choices when assessing prostate cancer patients [29, 30]. However, in our opinion, faecal urgency may not be properly questioned. There is a question on "rectal urgency" but it specifies "felt like I had to pass stool, but did not", which refers more to tenesmus than to faecal urgency. These definitions have been standardized in a recent report of two international societies (International Urogynecological Association and International Continence Society) specifically for female anorectal dysfunctions. Although our study was performed in males, these definitions apply perfectly. Faecal urgency is defined as "the complaint of a sudden compelling desire to defecate that is difficult to defer". Tenesmus is defined as "desire to

evacuate the bowel, often accompanied by pain, cramping, and straining, in the absence of faeces in the rectum" [31]. Given that faecal urgency is one of the symptoms that most bothers the patients, it should be properly assessed and this is why we added two specific questions. Likewise, we felt that the Bristol stool scale is the tool that best clarifies stool consistency.

Regarding the correlation between physician- and patient-reported outcomes, our results are consistent with those of a recent systematic review [32] which reported that agreement between CTCAE and PRO ratings was moderate at best. The authors concluded that there is a need to integrate PRO with physician reporting of adverse events. An example of these discrepancies is that six patients reported faecal incontinence in the PRO, while none of them was identified by the physicians, probably because patients are too embarrassed to disclose their symptoms. In this respect, the recently validated PRO-CTCAE, a PRO measure designed to be used together with the CTCAE, will be used in future US-based clinical trials in oncology [9]. This tool includes assessment of several gastrointestinal disorders (abdominal pain, bloating, constipation, diarrhoea, dry mouth, dyspepsia, dysphagia, faecal incontinence, flatulence, oral mucositis and vomiting) but, however, does not evaluate faecal urgency.

Recently, Petersen et al. [11] developed and validated the RT-ARD score to assess late anorectal dysfunction after radiotherapy for prostate cancer. By applying binomial regression on patient responses, the five issues that most bothered patients were selected: incontinence for solid stool, ability to defer defecation, unproductive call to stool, clustering of stool and mucus in stool. The most prevalent symptom in the questionnaires sent to patients was faecal urgency (53% cases). Unfortunately, our study started before the publication of this score and could not be included.

Consequently, according to the results of our study, we should emphasize the need to systematically assess bowel symptoms that may affect QoL after treatment of prostate cancer. Both terminology and the usual scores used to evaluate bowel changes after RT should be reappraised and include the assessment of faecal urgency, which is one of the most frequent and bothering symptoms.

Conclusions

Bowel dysfunction after radiotherapy might not be properly evaluated by the most commonly used questionnaires and faecal urgency may remain undetected, although it may have a negative impact on QoL. The correlation between physician-recorded toxicities and patient-reported outcomes remains low, and may not be a surrogate for the analysis of QoL. The assessment of bowel toxicity should be reappraised in order to identify patients whose quality of life may be impaired.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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