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ORIGINAL ARTICLE

A phase I/II study of acute and late physician assessed and patient-reported morbidity following whole pelvic radiation in high-risk prostate cancer patients

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ABSTRACT

Background: The aim of this study was to assess acute and late morbidity measured by the physician and patient-reported outcomes (PROs) in high-risk prostate cancer (PC) patients receiving whole pelvic intensity-modulated radiotherapy (IMRT) in the setting of a national clinical trial.

Material and methods: A total of 88 patients with adenocarcinoma of the prostate and high-risk parameters were enrolled from 2011 to 2013. All patients received 78 Gy in 39 fractions of IMRT delivering simultaneous 78 Gy to the prostate and 56 Gy to the seminal vesicles and lymph nodes. Physician-reported morbidity was assessed by CTCAE v.4.0. PROs were registered for gastro-intestinal (GI) by the RT-ARD score, genito-urinary (GU) by DAN-PSS, sexual and hormonal by EPIC-26, and quality of life (QoL) by EORTC QLQ-C30.

Results: Median follow-up (FU) time was 4.6 years. No persistent late CTCAE grade 3+ morbidity was observed. Prevalence of CTCAE grade 2+ GI morbidities varied from 0 to 6% at baseline throughout FU time, except for diarrhea, which was reported in 19% of the patients post-RT. PROs revealed increased GI morbidity (≥1 monthly episode) for "rectal urgency", "use of pads", "incomplete evacuation", "mucus in stool" and "bowel function impact on QoL" all remained significantly different ($p < .05$) at 60 months compared to baseline. CTCAE grade 2+ GU and sexual morbidity were unchanged. GU PROs on obstructive and irritative GU items (≥daily episode) increased during RT and normalized at 24 months. No clinically significant differences were found in sexual, hormonal, and QoL scores compared to baseline.

Conclusions: Whole pelvic RT resulted in a mild to the moderate burden of late GI morbidities demonstrated by a relatively high prevalence of PROs. Whereas, physician-assessed morbidity revealed a low prevalence of late GI morbidity scores. This emphasizes the importance of using both PROs and physician-reported scoring scales when reporting late morbidity in clinical trials.

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KEYWORDS
Prostate cancer; radiotherapy; morbidity; patient-reported outcomes; quality of life

Background

According to international guidelines, radiotherapy (RT) in combination with long-term androgen deprivation therapy (ADT) is an accepted standard treatment for patients with high-risk prostate cancer (PC) [1]. Because of the high risk of metastasis to loco-regional lymph nodes, RT will often include pelvic lymph nodes combined with high-dose irradiation to the prostate and seminal vesicles in case of stage T3b [1–3].

The cost and major concern with the use of whole pelvis radiotherapy (WPRT) in the treatment of high-risk PC is an increased risk of long-term morbidity [4]. Previous studies on WPRT for PC have focused on severe treatment-related morbidity [5–8]. Other studies suggest that moderate or even mild morbidity may alter the quality of life among PC patients treated with curative intent, and the use of patient-reported outcomes (PRO) are important in revealing the burden of symptoms experienced by patients [9–12]. The morbidity related to primary treatments for localized PC may have a negative impact on patients' quality of life (QoL) and it is important that the tools used for detecting these morbidities are specific and detailed enough to reveal the mild or moderate symptom-burden experienced by the patients and both physicians reported outcomes and PROs should be used to complement each other [13,14].

The aim of this study was to investigate acute and late physician-assessed morbidity and PROs in high-risk PC patients receiving WPRT.

Materials and methods

Trial design

The study was a national prospective, single-arm, multicenter phase I/II interventional clinical study (PROPEL). The study was approved by The Central Denmark Region Committee

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Supplemental data for this article can be accessed here.

on Health Research Ethics (reg. no. 20100203) and registered at clinicaltrials.gov (NCT01417676).

The current study followed the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies (Appendix A) [15].

Patient characteristics

A total of 88 patients were enrolled in the study from 2011 to 2013. Thirty-five patients were enrolled in cohort A (Nx) and 53 patients were enrolled in arm B (N1). Median follow-up (FU) was 4.6 years (range 3.8–6.5). Patient and treatment characteristics are shown in Table 1.

All patients had trans-rectal biopsies and were evaluated with bone scans and CT scans. The decision for radiotherapy (RT) was made at a Multi-Disciplinary Tumor Board (MDT). Patients were referred to departments of Oncology for RT. The study consisted of two patient cohorts. Cohort A included patients with confirmed adenocarcinoma of the prostate, T3NxM0 [16] (no surgical lymph node staging), Gleason 8–10 and PSA $\leq$70 or PSA $\geq$20 and PSA $\leq$70. Cohort B was selected by the same criteria as cohort A, but they had undergone laparoscopic lymph node dissection (limited/extended, according to local guidelines) and had a maximum of two micro-metastatic lymph nodes (maximum size of lymph node 2 cm). All patients, in both cohorts A and B, had to undergo abdominal CT and/or MRI scans revealing no metastasis including lymph node metastasis prior to inclusion in the protocol. For both cohorts, patients were younger than 75 years of age, had no history of previous pelvic RT, no prior pelvic surgery or inflammatory bowel disease or other serious comorbidities. All patients enrolled in the study were prescribed for a total of three years' androgen deprivation therapy, starting three months before RT.

Table 1. Patient and disease characteristics ($n = 88$).

Age, median in years (range)	65.5 (45.0–73.1)
Follow-up, median in years (range)	4.6 (3.8–6.4)
PSA, pretreatment median (range)	34 (1–72)
Gleason Score (*n*)	
2–6	1
7	27
8–10	60
T stage (*n*)	
T1c	3
T2a	1
T2b	6
T2c	4
T3a	50
T3b	24
N stage (*n*)	
Nx	34
N0	0
N1	54
M stage	
M0	88
Risk Groups (D'Amico)	
Low	0
Intermediary	0
High	88
Fiducial markers (*n*)	
Gold markers	81
Stents	7
PROPEL (*n*)	
A (no staging surgery)	34
B (staging surgery)	54
Dose (*n*)	
78Gy/56/39	88

Radiotherapy

The patients were treated with intensity-modulated RT (IMRT) and simultaneous integrated boost technique with 78 Gy to the prostate and 56 Gy to the pelvic lymph nodes. The daily set-up of patients was guided by orthogonal planar imaging and implanted gold fiducial markers. Weekly cone beam CTs were performed at some centers for verification of delivery of RT. Target and organs at risk were defined according to national guidelines [17]. The clinical target volume (CTV78) included the prostate and in the case of cT3b, the involved vesicles were also included. The planning target volume (PTV78) included the CTV78 with a margin of 5–7 mm transverse and 7–9 mm cranial-caudal, decided by the treating center. The pelvic lymph nodes and the seminal vesicles were included in CTV56/39, half of the length of the seminal vesicles were included unless cT3b. The PTV56/39 included the CTV56/39 with a transverse margin of 5 mm and an 8 mm margin cranial-caudal. The dose to pelvic lymph nodes was 56 Gy (1.4 Gy per fraction) and the dose prescribed (Dmean) to the PTV78 was 78 Gy (2 Gy per fraction). The treatment was delivered daily for a total of seven weeks and four days.

The treatment was delivered simultaneously to the lymph nodes and the prostate with the integrated boost to the prostate. The constraints for target coverages were PTV 78/39 D99% $\geq$ 70.3 Gy and PTV56/39 D99% $\geq$ 53.2 Gy. The dose-volume constraints for the rectum had the highest priority of any dose-volume constraints with D1cc $<$ 78 Gy, V70 Gy $\leq$ 10%, and the circumference of the rectum not enclosed by the 50 Gy isodose. Other constraints were bowel bag D2cc $<$ 70 Gy (max. 2 cm^3 received $\geq$ 70 Gy), femoral head Dmax $<$ 52 Gy, and bowel bag V35 Gy $\leq$ 40%.

Assessment of outcome

Overall, there were high response rates at all time points varying between 82% and 97%. At 60 months 58 patients were available for analysis of morbidity.

Clinical assessment of morbidity was performed at baseline, at the end of RT (post-RT), 3, 6, 12, 24, 36, and 60 months after RT. Morbidities were considered as acute if occurring within three months after RT and late if occurring 6 months or longer after completion of radiotherapy. The Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE v.4.0) was used to report physician-reported outcomes. Patient-reported outcomes (PROs) were assessed using single items from the RT-ARD score regarding gastrointestinal (GI) morbidity. Ratings were dichotomized into; "never or $<$ once a month" or "$\geq$ once a month" [18]. The DANPSS questionnaire was used for scoring genitourinary (GU) morbidity. Ratings were dichotomized into "no/rarely" or "daily/every time" [19]. The EPIC-26 questionnaire was used for hormonal and sexual domains; the domain scores

were calculated as recommended [20]. Patients' quality of life (QoL) was assessed by the EORTC-QLQ-C30 questionnaire [21].

Comparisons between cohort A and cohort B were performed for single items on the CTCAE scores and no differences were found between the two groups. Accordingly, morbidity analysis was performed with the patients pooled.

Statistical methods

Single GI, GU, and sexual items were analyzed separately by the CTCAE v. 4.0 at each time-point. Prevalence of grade 2+ morbidity at each time-point for single items regarding the CTCAE were calculated and compared to baseline by the use of the Chi-square test or Fisher's exact test as depending as prescribed for categorical data. The Kaplan-Meier product-limit method was used to calculate actuarial incidences of G1+, G2+, and G3+ CTCAE overall GI and GU morbidity. Time at risk was calculated from study entry until the event of interest occurred. Patients without an event of interest were censored at the end of the follow-up. Any morbidity at baseline was subtracted from subsequent scores. Prevalence grades of PROs at each time-point for the dichotomized GI and GU items were calculated and compared to baseline as mentioned above for categorical data. The EPIC-26 vitality/hormonal and sexual scores were calculated as recommended. Changes of more than 5 and 10 points were considered as clinically relevant regarding the vitality/hormonal and sexual EPIC-26 domains respectively [22]. EORTC-C30 QoL global health and functional scale analyses were performed after linear transformation of the scores on scales from 0 to 100, where 100 indicates the best functional level. A difference of >10 points was considered clinically significant [23].

All morbidity data were included with no imputation for missing data. *P*-values <.05 were considered statistically significant. Analyses were performed using STATA version 14.0 (StataCorp, College Station, TX).

Results

Physician reported morbidity

Prevalence of physician-reported morbidity at baseline revealed no grade 2+ CTCAE GI morbidity, except for one patient with grade 2 flatulence. GI grade 2+ morbidity did not rise significantly through FU except for diarrhea which worsened significantly post-RT, decreasing to insignificantly level at three months post-RT and remained low (Appendix B). Grade 3 diarrhea was present in 2 patients post-RT and at 3 months, one patient experienced grade 3 rectal bleeding post-RT. Overall GI morbidity is shown in Figure 1, including Kaplan-Meier estimates of GI grade 2+ of 31% (CI: 23%–43%) and 38% (CI: 28%–50%) at 24 and 60 months, respectively.

GU grade 2+ CTCAE morbidity at baseline showed prevalence frequencies ranging between 0 and 8%. Through FU bladder spasms and urinary frequency increased significantly post-RT compared to baseline, however declining to levels not different from pretreatment thereafter (Appendix C). One patient experienced grade 3 urinary incontinence at baseline, post-RT, and at 24 months FU. Two patients experienced grade 3 and 4 urinary infections at 60 months. Overall GU morbidity is displayed in Figure 1, with the corresponding actuarial estimates, revealing a 24 month of GU grade 2+

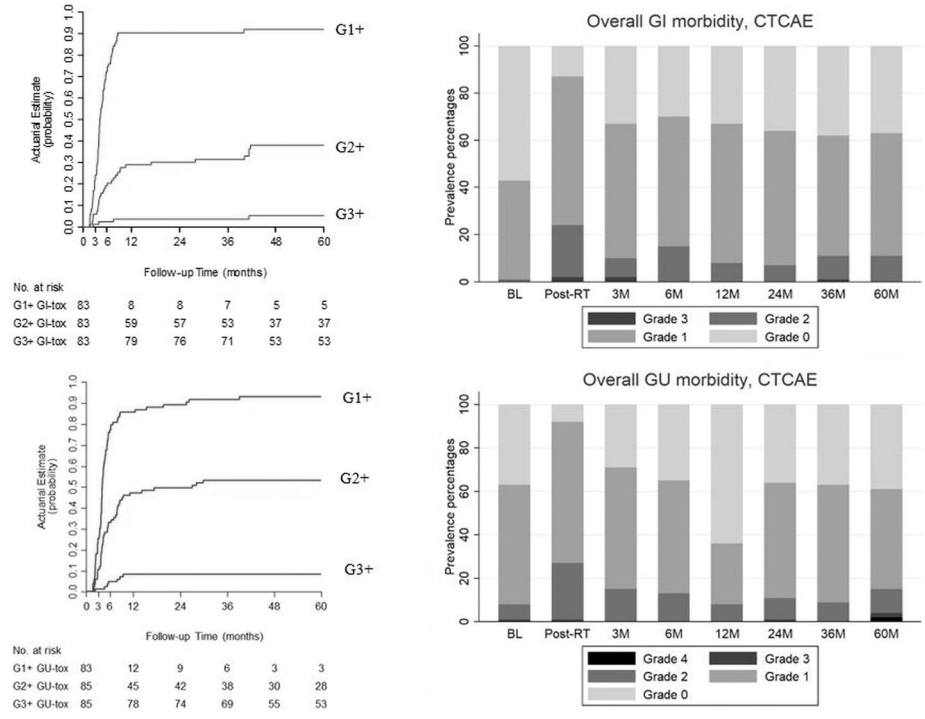

Figure 1. Overall gastro-intestinal and genitourinary physicians reported CTCAE morbidity. Actuarial estimates of G1+, G2+, and G3+ are shown in the Kaplan-Meier plot on the left. Prevalence rates for all grades for each follow-up are shown on the right. GI: gastro-intestinal; GU: genitourinary; G: grade.

Table 2. Patient-reported outcomes, gastro-intestinal morbidity at different time points.

	Baseline (*N* = 73–74)	Post-RT (*N* = 76–77)	3 months (*N* = 81–82)	6 months (*N* = 80–81)	12 months (*N* = 79–82)	24 months (*N* = 75–78)	36 months (*N* = 71–74)	60 months (*N* = 58–61)
Flatus*	27 (37)	39 (50)	41 (50)	36 (45)	31 (38)	37 (47)	35 (47)	26 (45)
Incontinence liquid stool*	5 (7)	20 (26)#	15 (18)#	11 (14)	20 (24)#	16 (21)#	15 (21)#	8 (14)
Incontinence solid stool*	1 (1)	9 (12)#	6 (7)	8 (10)#	8 (10)#	9 (12)#	6 (8)	4 (7)
Soiling*	23 (31)	31 (40)	29 (35)	35 (31)	40 (49)#	41 (53)#	36 (51)#	22 (37)
Use of pads*	1 (1)	12 (16)#	8 (10)#	8 (10)#	8 (10)#	10 (13)#	10 (14)#	7 (12)#
Change of lifestyle due to incontinence**	0	10 (13)#	4 (5)	3 (4)	6 (7)#	4 (5)	7 (10)#	2 (3)
Anti-diarrhoeal agents***	0	16 (21)#	8 (10)#	5 (6)	4 (5)	3 (4)	2 (3)	1 (2)
≥4 bowel movements daily	1 (1)	15 (20)#	9 (11)#	6 (7)	4 (5)	2 (3)	3 (4)	2 (3)
Nocturnal bowel movements*	1 (1)	17 (22)#	9 (11)#	6 (7)	8 (10)#	6 (8)	5 (7)	2 (3)
Urgency*	9 (12)	44 (58)#	34 (42)#	28 (35)#	37 (46)#	31 (41)#	25 (34)#	18 (30)#
Ability to defer defecation > 15 min.	53 (74)	25 (33)#	41 (50)#	42 (53)#	38 (46)#	35 (45)#	31 (43)#	28 (48)#
Clustering*	10 (14)	38 (50)#	27 (33)#	19 (23)	25 (31)#	22 (29)	20 (27)	17 (28)
Incomplete evacuation*	4 (6)	33 (43)#	24 (29)#	19 (24)	27 (34)#	28 (36)#	22 (30)#	20 (34)#
Obstructive sensation*	10 (14)	15 (20)#	12 (15)	10 (12)	15 (18)#	16 (21)#	14 (19)#	6 (10)
Strain to defecate*	10 (14)	19 (25)	17 (21)	10 (12)	14 (17)	21 (27)#	15 (21)	13 (22)
Pain at defecation*	4 (5)	16 (21)#	8 (10)	6 (7)	4 (5)	3 (4)	6 (8)	3 (5)
Tenesmus*	5 (7)	21 (28)#	10 (12)	9 (11)	9 (11)	10 (13)	9 (12)	4 (7)
Abdominal pain*	7 (10)	13 (17)	10 (12)	6 (7)	10 (12)	9 (12)	7 (10)	5 (8)
>5 min. per attempt to defecate	13 (18)	22 (29)	17 (21)	20 (25)	21 (26)	19 (25)	22 (31)	15 (25)
Defecation assistance***	4 (5)	5 (7)	4 (5)	9 (11)	8 (10)	8 (10)	9 (12)	9 (15)
Unproductive call to stool***	4 (5)	26 (39)#	14 (17)#	14 (17)#	11 (14)	11 (14)	15 (21)#	9 (15)
Mucus in stool*	0	23 (30)#	14 (17#)	21 (21)#	12 (15)#	12 (15)#	6 (10)#	6 (10)#
Blood in stool*	0	2 (39	2 (4)	2 (2)	8 (10)#	8 (10)#	3 (5)	3 (5)
Bowel function, impact on QoL**	13 (18)	46 (60)#	38 (48)#	40 (50)#	45 (58)#	45 (58)#	24 (40)#	24 (40)#

Numbers in () are percentages,*≥ 1 episode monthly, **some/a lot, ***the specific symptom/treatment being present/used, #significant different compared to baseline ($p < .05$).

morbidity of 53% (CI: 43%-64%) and not increasing any further at 60 months.

Sexual grade 2+ CTCAE morbidity revealed the prevalence of erectile dysfunction and decreased libido of 39% and 24% at baseline, respectively. Erectile dysfunction and decreased libido worsened significantly post-RT and erectile dysfunction remained significantly decreased through FU while decreased libido was less decreased at 60 months (Appendix C).

Patient-reported morbidity

Prevalence of PRO GI items at baseline ranged up to 37%. Most items increased significantly post-RT and several remained significantly different through FU compared to baseline, Table 2. The following items: "use of pads" ($p < .05$), "rectal urgency" ($p < .05$), "ability to defer defecation >15 min" ($p < .05$), "incomplete evacuation" ($p < .05$), "mucus in stool" ($p < .05$) and "bowel function impact on QoL" ($p < .05$) all remained significantly different at 60 months compared to baseline.

Prevalence of PRO GU items at baseline ranged between 0 and 30%. Several items increased significantly post-RT compared to baseline, declining to a non-significant level at 3 months except for nocturia which remained significantly different from baseline through FU, except at 60 months where the scores decreased to pretreatment levels (Appendix D).

Mean EPIC-26 sexuality score decreased clinical significantly from 28 at baseline to 13 post-RT and remained low through FU, increasing to 31 at 60 months. Mean EPIC-26 hormonal/vitality score was 83 at baseline declining clinically significantly to 73 post-RT and remained at this level until 60 months FU where it was increased to 85 (Appendix E).

EORTC-C30 QoL global health and functional scales mean scores did not decline with more than 10 points at any time-point except for "role function" which decreased from 94 to 81 points post-RT however increasing to an insignificant level thereafter (Appendix F).

Discussion

This study presents prospective data on acute and late morbidity assessed by a physician and patient-reported scoring systems in a national cohort of high-risk PC patients treated with WPRT, with a median FU of 4.6 years. There were very few cases of severe GI morbidities as scored by grade 3 CTCAE represented by two patients with grade 3 diarrhea at three months, one patient experiencing grade 3 rectal bleeding post-RT, and two patients experiencing grade 3 and 4 urinary infections at 60 months. Physician-reported morbidity revealed low rates of grade 2+ morbidity for all items at all time-points except for diarrhea, bladder spasms, and increased urinary frequency which had a prevalence rate of 19%, 10%, and 16%, respectively post-RT, declining to insignificant levels thereafter. The prevalence of PROs revealed a different pattern. Patient-reported outcomes both regarding GI and GU symptoms compared to physician assessed morbidity increased significantly post-RT compared to baseline and several GI items such as the use of pads, rectal urgency, incomplete evacuation, mucus in stool, and bowel function impact on QoL remained significantly elevated during FU. The findings in the current study revealed the different prevalence of the objective physician-reported morbidity assessed by CTCAE compared to the more subjective PROs.

The use of the CTCAE scale is important to elucidate the moderate and more severe and potential life-threatening morbidities, whereas PROs enlight the mild to moderate morbidities which may have a large impact on patients' quality of life. This emphasizes the importance of reporting both physician-assessed morbidity and PROs to complement each other when reporting morbidity in RT clinical trials as recommended in previous publications [13,14].

In our study, we found an underestimated rating of morbidity when comparing physician-reported morbidity and PROs except for diarrhea which was reported with the same prevalence rates post-RT. Previous studies have suggested that physicians often underestimate the symptoms patients might experience following RT [24,25]. Detailed reporting of RT morbidities may be important since items that are not captured by physician administrated scoring may still be of relevance to the patients' well-being [9,10]. In our study, the patients did not report a clinically decreased general QoL according to the EORTC C30 QoL scales. However, general QoL scores declined during FU it is most likely due to patients' increased age during FU as QoL scores are known to decline with age [26]. The patients in our study do report mild to moderate GI morbidity, but overall it did not have an impact on their general QoL.

The rate of severe morbidity in the current study seems to be in concordance with other studies on WPRT. The study by Dearnaley *et al.* comparing prostate only to pelvic lymph RT reported acute GI and GU grade 2 toxicity of 25% and 40% respectively, however, the acute morbidity was assessed by the RTOG scale which is characterized by grading between 1 and 4 of GI (diarrhea, proctitis and rectal bleeding) and GU (urinary urgency, frequency, and inability to pass urine). Late morbidity was assessed by the CTCAE and revealed rates of grade 2+ morbidity comparable to those found in our study. Similar results on late morbidity measured by the RTOG scale following WPRT were also found in the study by Murthy *et al.* Both studies also assessed PROs, however, the PROs were assessed by different scoring systems and outcomes were presented as composite scores. Insignificant changes or no changes were found in bowel function during FU compared to before radiation [5,27]. In a recent review by Vittrup *et al.* it has been suggested that morbidity should be reported by single grade items instead of composite scores as detailed information of important single items may be lost when using aggregated endpoints. In our study, we used single items to describe morbidity and several GI items were significantly increased at five year FU. This information might not have been apparent if we had presented our data as composite scores.

At baseline, several patients reported a prevalence of GI symptoms ranging between 0 and 37%. A study by Juul *et al.* on normative data of bowel function in the Danish population found that it is quite common in the general population to have some degree of bowel dysfunction [28]. This should be taken into consideration when interpreting GI symptoms measured by PROs. In our study, we reported the symptoms present at baseline and only items that increased significantly during FU were considered as relevant in regard to late morbidity.

The EPIC-26 sexual and hormonal morbidity scores declined clinical significantly post-RT and remained low until 60 months FU where they were at the same level as a baseline. Grade 2+ sexual morbidity scored by the CTCAE revealed nearly the same pattern. The reason for almost no discrepancy between the physician-reported assessed morbidity and PROs regarding sexual morbidity might be the knowledge of the physician that all patients enrolled in the study received a total of three years of ADT and thereby expected well-known sexual/hormonal morbidity that is related to ADT [29]. Testosterone was not included in the blood tests during FU.

The strengths of the current study are the reporting of individual grades regarding both physicians assessed morbidity and PROs, including five years of FU, with a high response rate at all time points. Data are presented by time to event analysis and the prevalence of different items at every timepoint regarding both physicians assessed morbidity and PROs, all complement each other and provides an overview of the pattern of the morbidity that high-risk PC patients experience following WPRT. However, the relatively small cohort of patients and the loss to FU at 60 months FU are limitations of the study.

In conclusion, this comprehensive analysis of morbidity including physician-assessed morbidity and detailed patient-reported outcomes on several items on both GI and GU morbidity at different time points provides an overview of the pattern and severity patients might experience following WPRT for high-risk PC. The patients experience mild to moderate late GI morbidity which was revealed by PROs, however, no significant change in general QoL was observed.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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