Patient-Reported Functional Outcomes After Hypofractionated or Conventionally Fractionated Radiation for Prostate Cancer: a National Cohort Study in England

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ABSTRACT

Purpose

To determine patient-reported functional outcomes (PROs) in men with prostate cancer (PCa) undergoing moderately hypofractionated (H-RT) or conventionally fractionated radiotherapy (C-RT) in a national cohort study.

Patients and Methods

All men diagnosed with PCa between April 2014 and September 2016 in the English National Health Service undergoing C-RT or H-RT were identified in the National Prostate Cancer Audit and mailed a questionnaire at least 18 months after diagnosis. Differences in patient-reported urinary, bowel, sexual, and hormonal function (EPIC-26 domain scores on a 0-100 scale) and health-related quality of life (EQ5D5L on a 0-1 scale) were estimated using linear regression with adjustment for patient, tumour and treatment-related factors in addition to gastrointestinal (GI) and genitourinary (GU) baseline function with higher scores representing better outcomes.

Results

Of the 17,058 men in the cohort, 77% responded: 8,432 men had C-RT (64.2%) and 4,699 H-RT (35.8%). Men in the H-RT group were older (≥70 years: 67.5% versus 60.9%), fewer men had locally advanced disease (56.5% versus 71.3%), were less likely to receive ADT (79.5% versus 87.8%) and slightly more men had pre-treatment GU procedures (24.2% versus 21.2%). H-RT was associated with small increases in adjusted mean EPIC-26 sexual (3.3 points; 95% CI 2.1-4.5, p<0.001) and hormonal function scores (3.2 points; CI 1.8-4.6, p<0.001). These differences failed to meet established thresholds for a clinically meaningful

change. There were no statistically significant differences in urinary or bowel function and quality of life.

Conclusion

This is the first national cohort study comparing functional outcomes after H-RT and C-RT reported by patients. These 'real-world' results further support the use of H-RT as the standard for radiotherapy in men with non-metastatic PCa.

INTRODUCTION

Radical treatments for localised prostate cancer (PCa) are associated with adverse effects. External-beam radiation therapy (RT) is an established primary radical treatment option for men with localised or locally advanced PCa. A conventionally fractionated RT regimen (C-RT, 1.8 – 2 Gy doses per fraction) delivered over 7-8 weeks has traditionally been a standard for primary PCa. However, a moderately hypofractionated regimen (H-RT) which delivers >2Gy over 4 weeks, may offer a therapeutic and economic advantage by delivering an equivalent biologically effective dose in a shorter time period without increasing toxic effects.[1, 2]

Four recent large randomised clinical trials (RCTs) of modern radiotherapy using intensity-modulated radiotherapy (IMRT) have demonstrated the comparable efficacy of C-RT and H-RT without significant differences in 5-year biochemical or clinical failure-free survival.[3-7] A meta-analysis pooling data from three of these RCTs (each of non-inferiority design) demonstrated that H-RT was associated with a significantly increased risk of clinician-assessed acute (3 month) gastro-intestinal (GI) toxicity (predominantly grade 2 using Radiation Therapy Oncology Group criteria), which did not translate into late toxicity (median follow-up 5.2 – 6 years).[8] However, H-RT was reported to be associated with an increase in late Grade ≥2 genitourinary (GU) toxicity.[8]

It is generally accepted that patient-reported outcomes (PROs) detect more reliably adverse treatment effects relevant to patients than clinical data.[9-11] However, there is limited evidence on how PROs in urinary, bowel and sexual function vary by RT regimen. The largest RCT to date that reported PROs, the CHHiP study, found no significant differences urinary,

bowel and/or sexual functioning between C-RT and H-RT in men with predominantly intermediate risk PCa after two years of follow-up.[12]

Randomised controlled clinical trials (RCTs) in oncology enrol patients who meet strict protocol-specified criteria. Hence, patient populations encountered in clinical practice are essentially different from RCT-populations, questioning the representativeness of these trials. A 'real-world' evidence approach, using data from clinical practice, is increasingly employed to complement the information on drug safety and efficacy obtained from traditional clinical trials.

The National Prostate Cancer Audit (NPCA) evaluates the care and outcomes of all men with newly diagnosed PCa in the National Health Service (NHS) in England and Wales. The NPCA collected PROs for men undergoing radical treatment diagnosed between April 2014 and September 2016.[13] This national cohort includes more than 13,000 men undergoing C-RT or H-RT in England, collected at least 18 months after diagnosis, providing contemporary evidence on functional outcomes from large-scale 'real-world' clinical practice.[14]

MATERIALS AND METHODS

Study design and participants

All patients diagnosed with PCa in England between 1st April 2014 and 30th September 2016 as recorded in the English National Cancer Registry and who subsequently underwent RT were eligible for inclusion in the patient survey.

This study was exempt from NHS Research Ethics Committee approval because it involved analysis of de-identified linked data collected for the purpose of service evaluation

Survey design, administration and data handling

The NPCA patient questionnaire (Appendix 1) includes the Expanded Prostate Cancer Index Composite short-form (EPIC-26), a validated instrument comprising 26 items to measure patient function and bother in five domains and the EuroQol EQ-5D-5L.[15]

The EPIC-26 produces a validated summary score for each domain ranging from 0 to 100 with higher scores representing better function.[16] Thresholds for a minimal clinically important difference (MCID) have been estimated by domain, representing changes considered meaningful for patients.[17]

The urinary incontinence domain (MCID, 6 points) includes questions related to urinary frequency and leakage, and the urinary irritation/obstruction domain (MCID, 5 points) focuses on dysuria, haematuria and urinary frequency. The sexual function domain (MCID, 10-12 points) asks questions related to the quality and frequency of erections. The bowel function domain (MCID, 4 points) assesses bowel frequency, urgency, bleeding and pain, and the hormonal disturbance domain (MCID, 4 points), includes hot flushes, gynaecomastia, low energy and weight change.

The questionnaire in the second year of the study included three additional adapted EPIC-26 questions asking men to recall their urinary, bowel and sexual functioning at diagnosis: 'Overall, how big a problem was your urinary function/bowel habits/sexual function or lack of sexual function for you immediately before you were diagnosed with PCa?'

The EuroQol (EQ-5D-5L) describes generic Health Related Quality of Life (HRQoL) based on five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) with responses graded at five levels (no/slight/moderate/severe/extreme problems).[18] An index score on a scale from 0 representing 'death' to 1 'perfect health' is calculated by matching the pattern of the responses against a set of utilities derived from the general UK population.[19]

Questionnaires were mailed out to patients diagnosed between 1st April 2014 and 30th September 2016. Questionnaires were mailed to the homes of all identified men ≥18 months after diagnosis. Two reminders were sent to non-responders with the final reminder ≤ 8 weeks after the first mail out.

Survey response data were linked to records from the NPCA. This includes information on age at diagnosis, ethnicity, tumour characteristics according to TNM scores, Gleason biopsy score, pre-treatment PSA and receipt of androgen deprivation therapy (ADT) from the English National Cancer Registration and Analysis Service. [20] The survey questionnaire provided the data on comorbidities. Information on socioeconomic deprivation status was obtained from the Hospital Episode Statistics (HES), which records all admissions to English NHS providers.[21] The national Radiotherapy Dataset (RTDS), which records radiotherapy activity in each radiotherapy centre provided information on the RT treatment region (prostate bed only/whole pelvis), the use of IMRT (OPCS-4 code 'X671'), RT doses and number of attendances.[22]

The Royal College of Surgeons (RCS) Charlson score was used to identify comorbid conditions from HES records based on comorbidities coded in the year preceding their

prostate cancer diagnosis for the comparison of responders and non-responders only. [23] Socioeconomic deprivation was defined according to quintiles of the national ranking of the Index of Multiple Deprivation (IMD).[24] Cancer risk status (low-risk localised, intermediate-risk localised, locally advanced or advanced cancer) was based on TNM stage, Gleason score, and PSA level according to a modified D'Amico algorithm developed by the NPCA.[25]

Information about bowel/urinary function baseline function was derived from the presence of a GI or GU procedure code in the HES record up to one year prior to RT. The codes correspond to previously documented procedure codes used to flag RT treatment toxicity (Appendix 2). [26]

Inclusion and exclusion criteria

18,930 men who were diagnosed with PCa between 1st April 2014 and 30th September 2016 and underwent RT were identified from the NPCA database (Figure 1). We excluded patients who underwent an unclassified (n=1,159) or other RT regimens (n=431 men) The final study cohort comprised 17,058 eligible men undergoing RT with curative intent (Figure 1).

C-RT or H-RT regimens were defined on the basis of the UK RT dose fractionation guidance and the varying dose and fractionation schedules used in recent RCTs. [1, 4-6] C-RT was defined on the basis of the regimes most commonly used in UK practice including: 71.4 to 79.5 Gy in 35 – 40 fractions; 71.4 to 72.5 Gy/32 fractions; 69.4 to 70.5 Gy/35 fractions and 68.4 to 69.5 Gy/37 fractions . The overall median dose delivered for patients in the CRT cohort was 74 Gy in 37 fractions. H-RT was delivered following a moderately hypofractionated regimen with defined as 48.9 to 61.1 Gy in 16-20 fractions (median 60 Gy in 16, 19 or 20 fractions).

Outcomes

Primary outcome measures were the five EPIC-26 domain scores and the EQ-5D-5L index score.

Statistical analysis

Chi-squared tests were used to compare proportions. We used multivariable linear regression to estimate differences in outcomes between patients receiving C-RT and H-RT with adjustment for age, ethnicity, cancer risk group, year of diagnosis (14/15, 15/16, 16/17), time from RT to survey (months), comorbidities and IMD as categorical variables and ADT, RT type (IMRT), region (prostate only vs whole pelvis), GI and GU baseline procedures as binary variables. A random intercept was modelled for each RT centre to adjust for clustering within centres. P-values were based on the Wald test.[27]

Overall, the completeness of individual clinical data items was ≥90% with the exception of PSA at diagnosis (83.2% complete; Table 1). Missing patient response data to individual questions were handled in accordance with published guidelines. [15, 18] Completeness of the validated composite EPIC-26 scores ranged from 78% (urinary irritation/obstruction domain) to 89% (bowel domain), and was 96% for the EQ-5D-5L HRQOL composite score (Table 2).

Multiple imputation accounted for missing values of the adjustment variables and outcomes so that regression models included all 13,131 responders.[28] Missing values were replaced with 35 sets of plausible values and Rubin's rules were used to combine estimates and obtain adjusted differences with 95% confidence intervals (95% CI).[28]

All reported p-values are two-sided and p<0.05 was considered statistically significant without adjustment for multiple comparisons. Data analysis was undertaken using Stata version 14.

RESULTS

Response rate

Of the 17,058 included men, 13,131 (77.0%) responded to the survey (Figure 1). Responders were likely to be older (≥ 70 years), of white ethnicity, with fewer comorbidities, and were more often resident in the least socioeconomically deprived areas (Appendix 3). Overall, tumour and treatment characteristics were similar (Appendix 3). Responders who did not have a complete score for each of the five EPIC-26 domains were older than responders who did have complete scores but other characteristics were similar (Appendix 4).

Patient population

Among the 13,131 men who responded to the patient survey, 8,432 (64.2%) had C-RT and 4,699 (35.8%) had H-RT. IMRT was the predominant RT type (95.2% C-RT and 96.2% H-RT) and the use of H-RT increased four-fold during the 30-month study; Table 1). Most men underwent RT within 9 months of diagnosis (90.6%), and completed the survey ≥12 months after the start of RT (88.6%).

In the H-RT group men were older (67.5% versus 60.9%, ≥70 years, p<0.001), fewer men had locally advanced disease (56.5% versus 71.3%, p<0.001), were less likely to receive ADT (79.5% versus 87.8%, p<0.001) and slightly more men had pretreatment urinary procedures (24.2 % versus 21.2%, p<0.001) compared with C-RT. Pretreatment bowel procedures were similar between groups (5.5% versus 5.2%, p=0.4; Table 1).

Patient-reported outcomes according to RT regimen

Overall EPIC-26 domain and EQ5D5L scores are shown in Table 2. H-RT was associated with statistically significantly higher EPIC-26 sexual (adjusted mean difference 3.3 points; 95% CI 2.1-4.5, p<0.001) and hormonal function scores (adjusted mean difference (3.2 points; 95% CI 1.8-4.6, p<0.001) compared with C-RT (Table 3). However, these differences are below the established MCID. There was no significant difference in EPIC-26 urinary incontinence, urinary obstruction or bowel function scores or in EQ5D5L index scores between H-RT and C-RT groups (Table 3). These results were robust to including age and IMD as continuous variables in the regression model.

The effect of key patient, tumour and treatment characteristics on the EPIC-26 scores by domain are shown in Appendix 5.

The frequency of men who indicated that their functioning was a big problem at the time of diagnosis was similar between H-RT and C-RT groups: 10.8% (429/3,985) versus 12.2% (566/4,623) for urinary, 1.9% (91/3,991) versus 2.3% (90/4,629) for bowel, and 19.5% (756/3,870) versus 19.9% (891/4,487) for sexual function, respectively.

DISCUSSION

Key messages

In this contemporary, national cohort study of more than 13,000 men, predominantly surveyed more than one year after receiving primary C-RT or H-RT with a moderately hypofractionated regimen for prostate cancer, there were no clinically significant

differences in patient-reported urinary, bowel, sexual or hormonal function or HRQoL. H-RT was associated with slightly better sexual and hormonal function scores compared with C-RT but these differences were considerably smaller than changes considered meaningful for patients. These results reflect the outcomes of recent practice in the English NHS including patients diagnosed between 2014 and 2016, the majority of whom (95%) underwent IMRT.

Comparison with other studies

There is increasing evidence supporting the use of H-RT in PCa. In the HYPRO trial, combined clinician and patient-assessed acute GU toxic effects (≥2 RTOG-EORTC criteria) were similar between treatment groups up to 120 days after RT but GI toxicity was increased in the H-RT group. The cumulative incidence of severe late grade 3 or above GU toxicity was higher for H-RT but the incidence of ≥ grade 3 GI toxicity was similar (median follow-up = 60 months).[3,6]The QoL sub-study of the CHHiP trial, the largest RCT to date to report PROs following C-RT or H-RT, found no significant differences in patient-reported urinary, bowel or sexual functioning or HRQoL between men with clinically localised PCa receiving C-RT (74 Gy in 37 fractions, n=696) or one of two H-RT schedules (60 Gy in 20 fractions, n=698 or 57 Gy in 19 fractions, n=706 men) up to 24 months following radiotherapy.[12]

Compared with our study, the CHHiP trial had more men with intermediate-risk disease (71%), a narrower age-range (64-73 years), and included only 21 of 52 RT centres in England, which limits the generalisability of its results. Furthermore, the investigators used different instruments to measure functional outcomes (UCLA Prostate Cancer Index [UCLA-PCI] initially and the 50-item Expanded Prostate Cancer Index Composite [EPIC-50] later in the study), which may have resulted in fewer patients reporting rectal bleeding and faecal incontinence than would have been captured using EPIC-50 only.[12]

A recent trial comparing H-RT and C-RT in 962 low-risk prostate-cancer patients found no differences in patient-reported outcomes between 6 and 60 months after the start of treatment, expect for a statistically but not clinically significant decline in bowel function at 12 months only.[29]

Three smaller RCTs utilising IMRT have also reported no significant differences in patient-reported urinary, bowel, or sexual functioning measured using the EPIC-50 with short (3-month) [30] and long-term follow-up (≤ 5 years).[31,32]

The toxicity profiles will need to be reviewed in response to the introduction of other hypofractionation regimens.[33] For example, a phase-III RCT comparing ultra hypofractionation and conventional fractionation demonstrated that acute bowel and urinary toxicity was more pronounced with ultra-H-RT than with C-RT but that there were no differences in 5-year toxicity.

To our knowledge, our study is the first national population-based prospective study to compare PROs and HRQoL in men undergoing C-RT or H-RT. Previous observational studies have demonstrated similar clinician-reported GU/GI toxicities in retrospective comparisons with C-RT. [34,35]

Methodological considerations

A key strength of our study is that it reports recent real-world results in patients newly diagnosed in the English NHS between 2014 and 2016. Furthermore, a high response rate (77%) was achieved. The results reflect outcomes in an unselected national population because 95% of men diagnosed with PCa in England undergo treatment in the NHS[36,37]

The characteristics of men who had C-RT and H-RT were similar. In addition, the results from the survey are linked to patient level data from the NPCA database so that comparisons of PROs could be adjusted for the differences in the characteristics of men who had C-RT or H-RT. Consequently, the impact of residual 'confounding by clinical indication' is likely to be small.

Not all men completed sufficient information to generate an EPIC-26 score for each domain. However, the level of missingness did not vary by treatment group which makes it unlikely that it has affected differences in the PROs.

The lack of PROMs immediately before treatment could be considered a limitation in our study. However, baseline GI and GU function was measured on the basis of relevant bowel and urinary procedures up to one year prior to RT. There were no differences in bowel-related procedures and only small differences in urinary-related procedures between C-RT and H-RT groups, which were controlled for in our analyses. Furthermore, we did not find any differences in recalled urinary, bowel and sexual function immediately before diagnosis. Any effect is unlikely to be different between C-RT and H-RT groups which further supports the validity of our comparison.

The use of H-RT increased four-fold in the English NHS during this study period . Also, the type of RT regimen depended on where a patient had his treatment. For men diagnosed in the first six months of the diagnosis period, C-RT was the only regimen prescribed in 26 of the 52 RT centres in England but for men diagnosed in the last six months of the study H-RT was in use by the majority of RT centres (49/52), and the predominant regimen (≥80% of patients) in 13 of these centres. This pattern of H-RT use reflects a change in practice that

varies by centre over time and reduces the likelihood of patients being allocated to a RT regimen based on their individual risk characteristics.

Non-responders were younger, more often non-white, and more likely to live in less affluent areas. However, there were only small differences in response rate by radiotherapy regimen (30.2% of non-responders had H-RT compared with 28.1% of responders) and the impact of non-response on the findings in this study is likely to be small.

In our study, almost 90% of men reported their outcomes within two years from the start of ratidotherapy. It is possible that differences in outcomes according to type of radiotherapy become apparent 5 to 10 years after treatment. However, the results from the RCTs comparing C-RT versus H-RT do not demonstrate a consistent increase in late toxicity associated with hypofractionation.[38]

Clinical Implications

The benefits of H-RT for patients include greater convenience and shorter total duration of treatment. Recently published international, evidence-based guidelines recommend the routine use of H-RT with a moderately hypofractionated regimen for localised prostate cancer across all risk groups, independent of age, comorbidity, anatomy or baseline urinary function.[38]

PROs are increasingly being utilised to provide the patient perspective on comparative functional and HRQoL outcomes for treatments with similar efficacy and toxicity profiles.[39,40] Our results demonstrating a lack of clinically relevant differences in PROs and HRQoL add to the growing evidence base for the use of H-RT in men with non-metastatic PCa.

Conclusions

The results of this contemporary large national cohort study provide evidence that there are no clinically significant differences in functional outcomes and HRQoL between men receiving H-RT versus C-RT in real-world clinical practice. This supports recent guidelines that recommend H-RT with a moderately hypofractionated regimen as the standard of care for men with non-metastatic PCa.[40]

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Conflict of interest and financial disclosures

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Figure 1. Flow chart of men included in the study

Figure 1.

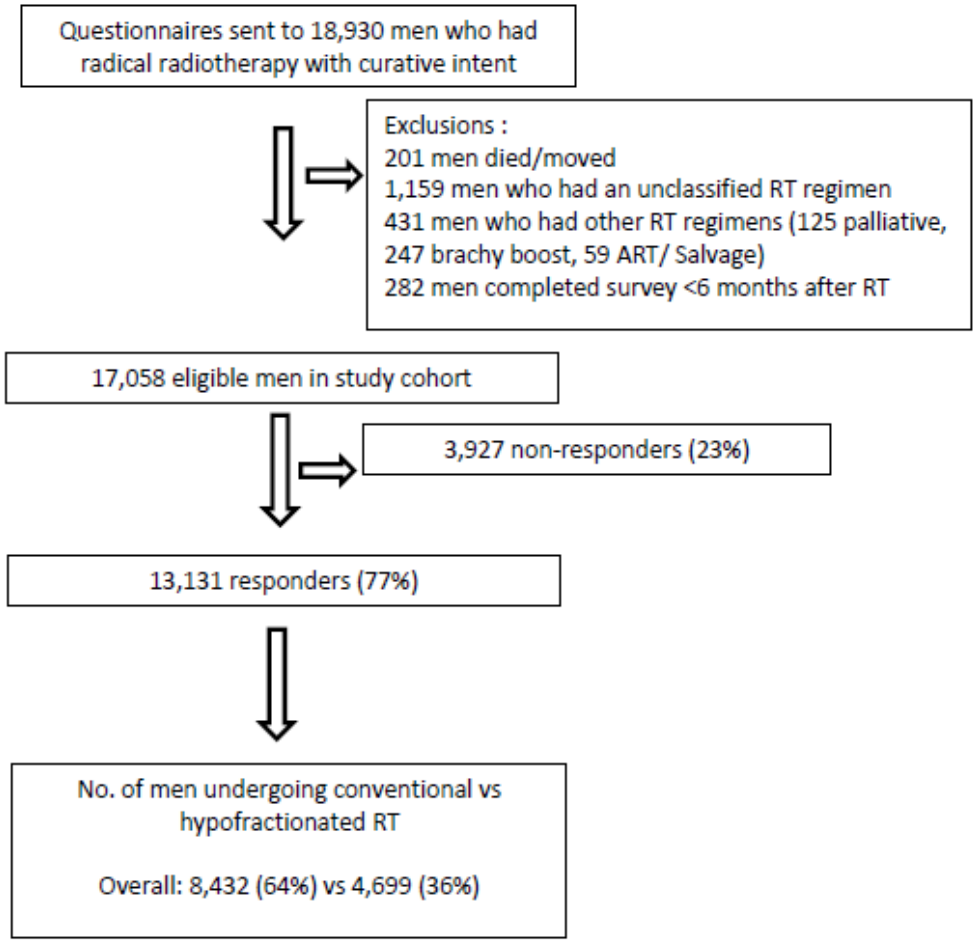

Table 1. Sociodemographic, tumour & treatment characteristics for men undergoing conventionally fractionated or hypofractionated radiotherapy who responded to the patient survey.

	Conventionally fractionated		Hypofractionated		Total	
	n	%	n	%	n	%
Patients	8,432 (64.2%)		4,699 (35.8%)		13,131	
Year of diagnosis						**p*<0.001**
Apr 14 – Mar 15	3,751	85.2	652	14.8	4,403	
Apr 15 – Mar 16	3,497	60.7	2,266	29.3	5,763	
Apr 16 – Sept 16	1,184	39.9	1,781	60.1	2,965	
Age						**p<0.001**
<60	361	4.3	154	3.3	515	3.9
61-70	2,935	34.8	1,372	29.2	4,307	32.8
71-80	4,688	55.6	2,795	59.5	7,483	57
>80	448	5.3	378	8.0	826	6.3
Ethnicity						**p=0.015**
White	7,181	96.1	4,010	95.5	11,191	95.9
Mixed	21	0.3	7	0.2	28	0.2
Asian/Asian British	83	1.1	76	1.8	159	1.4
Black/Black British	135	1.8	85	2.0	220	1.9
Other	49	0.7	23	0.5	72	0.6
Missing	*963*	*11.4*	*498*	*10.6*	*1,461*	*11.1*
Comorbidities**						**p<0.001**
0	1,609	19.1	815	17.3	2,424	18.5
1	2,602	30.9	1,361	29.0	3,963	30.2
≥2	4,221	50.1	2,523	53.7	6,744	51.4
Index of Multiple Deprivation						**p=0.002**
0	2,022	24.0	1,145	24.4	3,167	24.1
1	2,144	25.4	1,079	23.0	3,223	24.5
2	1,836	21.8	992	21.1	2,828	21.5
3	1,403	16.6	830	17.7	2,233	17.0
4	1,027	12.2	653	13.9	1,680	12.8
T stage						**p<0.001**
1	754	9.1	626	13.6	1,380	10.7
2	3,318	40.2	2,242	48.6	5,560	43.2
3	3,973	48.1	1,675	36.3	5,648	43.9
4	217	2.6	71	1.5	288	2.2
Missing	*170*	*2.0*	*85*	*1.8*	*255*	*1.9*
N stage						**p<0.001**

0	7,242	91.3	4,280	97.8	11,522	93.6
1	693	8.7	97	2.2	790	6.4
Missing	*497*	*5.9*	*322*	*6.9*	*819*	*6.2*
Gleason score						**p<0.001**
≤6	479	5.9	383	8.4	862	6.8
7	4,376	53.5	2,938	64.1	7,314	57.3
≥8	3,330	40.7	1,261	27.5	4,591	36
Missing	*247*	*2.9*	*117*	*2.5*	*364*	*2.8*
PSA (ng/ml)						**p<0.001**
<10	2,494	36.7	1,841	46.3	4,335	40.2
10-20	2,039	30.0	1,254	31.5	3,293	30.5
>20	2,270	33.4	885	22.2	3,155	29.3
Missing	*1,629*	*19.3*	*719*	*15.3*	*2,348*	*17.9*
Risk group						**p<0.001**
Locally advanced	5,927	71.3	2,610	56.5	8,537	66
Intermediate	2,336	28.1	1,951	42.2	4,287	33.1
Low risk	53	0.6	58	1.3	111	0.9
Missing	*116*	*1.4*	*80*	*1.7*	*196*	*1.5*
RT modality						**p=0.006**
3D conformal	408	4.8	179	3.8	587	4.5
IMRT	8,024	95.2	4,520	96.2	12,544	95.5
RT treatment region						**p<0.001**
Prostate and/or seminal vesicles	6,819	82.0	4,327	93.1	11,146	86.0
Whole pelvis incl. lymph nodes	1,499	18.0	319	6.9	1,818	14.0
Missing	*114*	*1.4*	*53*	*1,.1*	*167*	*1.3*
Hormonal treatment						**p<0.001**
No	1,031	12.2	964	20.5	1,995	15.2
Yes	7,401	87.8	3,735	79.5	11,136	84.8
Pretreatment urinary procedure						**p<0.001**
No	6,641	78.8	3,563	75.8	10,204	77.7
Yes	1,791	21.2	1,136	24.2	2,927	22.3
Pretreatment bowel procedure						**p=0.4**
No	7,994	94.8	4,440	94.5	12,434	94.7
Yes	438	5.2	259	5.5	697	5.3
Time from RT to survey						**p<0.001**

6-12 months	871	10.3	629	13.4	1,500	11.4
12-18 months	4,251	50.4	3,081	65.6	7,332	55.8
18-24 months	1,979	23.5	787	16.8	2,766	21.1
>=24 months	1,331	14.7	202	4.3	1,533	11.7
Time from diagnosis to RT						**p<0.001**
<=6 months	5,280	62.4	2,963	63.1	8,223	62.6
6-9 months	2,446	29.0	1,185	25.2	3,631	28.0
>=9 months	726	8.6	551	11.7	1,277	9.7

*p-value from chi-squared testsAbbreviations: PSA = prostate specific antigen; RT = radiotherapy

**The survey questionnaire provided the data on comorbidities

Table 2. Patient reported outcomes for men undergoing conventionally fractionated or hypofractionated radiotherapy – EPIC-26 summary scores for urinary incontinence, urinary obstructive/irritative, sexual, bowel and hormonal domains and EQ5D5L index scores for health-related quality of life based on five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).

	Conventionally fractionated	**Hypofractionated**
No. of patients	8,432 (22.9%)	4,699 (77.1%)
EPIC-26:overall domain scores		
Urinary (incontinence)		
Mean (SD)	86.7 (18.8)	85.5 (20.0)
Missing	*1,113 (13.2%)*	*653 (13.8%)*
Urinary (obstructive/irritative)		
Mean (SD)	86.7 (14.7)	85.2 (16.3)
Missing	*1,637 (19.4%)*	*985 (21.0%)*
Sexual		
Mean (SD)	17.0 (20.7)	19.7 (23.0)
Missing	*659 (7.8%)*	*423 (9.0%)*
Bowel		
Mean (SD)	85.7 (18.4)	86.2 (18.3)
Missing	*1,218 (14.4%)*	*700 (14.9%)*
Hormonal		
Mean (SD)	69.2 (23.4)	73.0 (22.9)
Missing	*1,001 (11.9%)*	*638 (13.6%)*
EQ-5D		
Overall score		
Mean (SD)	0.84 (0.19)	0.84 (0.19)
Missing	*223 (2.6%)*	*157 (3.3%)*

Abbreviations: EPIC-26 = Expanded Prostate Cancer Index Composite short-form; SD = standard deviation

Table 3. Relationship between patient-reported outcomes and type of radiotherapy regimen: unadjusted and adjusted* differences in EPIC-26 domain scores and EQ5D-5L score for men undergoing conventionally fractionated or hypofractionated radiotherapy.**

	Unadjusted difference (95% CI) H-RT vs C-RT, p value	**Adjusted difference (95% CI) H-RT vs C-RT, p value**
No. of patients		
EPIC-26		
Urinary (incontinence) MCID = 6-9		
	-1.31 (-2.01, -0.61), p<0.001	-0.46 (-1.25, 0.34), p=0.26
Urinary (obstructive/irritative) MCID = 5-7		
	-1.38 (-2.03, -0.72), p<0.001	-0.71 (-1.54, 0.13), p=0.098
Sexual MCID = 10-12		
	2.67 (1.88, 3.46), p<0.001	3.32 (2.11, 4.53), p<0.001 ↑ Hypofractionated RT
Bowel MCID = 4-6		
	0.45 (-0.27, 1.16), p=0.22	0.97 (-0.15, 2.08), p=0.09
Hormonal MCID = 4-6		
	3.15 (2.26, 4.04), p<0.001	3.20 (1.83, 4.57), p<0.001 ↑ Hypofractionated RT
EQ5D-5L		
	0.002 (-0.005, 0.009), p=0.50	0.0006 (-0.006, 0.008), p=0.87

*Multiple imputation by chained equations accounted for missing values of the adjustment variables and outcomes so that the multivariable linear regression model included all 10,206 men. Risk adjustment variables include diagnosis year, age, ethnicity, socioeconomic deprivation (IMD), number of comorbities, IMRT, radiotherapy region, disease status, time from radiotherapy to survey (months), hormone.

** MCID = minimal clinically important difference in EPIC-26 scores (Skolarus et al. 2015). The EPIC-26 urinary incontinence domain (MCID, 6 points) includes questions related to urinary frequency and leakage, and the urinary irritation/obstruction domain (MCID, 5 points) focuses on dysuria, haematuria and urinary frequency. The sexual function domain (MCID, 10-12 points) asks questions related to the quality and frequency of erections. The bowel function domain (MCID, 4 points) assesses bowel frequency, urgency, bleeding and pain. The fifth domain, hormonal disturbance (MCID, 4 points), includes hot flushes, gynaecomastia, low energy and weight change.

Abbreviations: H-RT = hypofractionated radiotherapy; C-RT = conventionally fractionated radiotherapy; EPIC-26 = Expanded Prostate Cancer Index Composite short-form; CI = confidence interval; IMD = Index of Multiple Deprivation

ONLINE SUPPLEMENTARY MATERIAL

Appendix 1. NPCA Patient Survey

https://www.npca.org.uk/content/uploads/2019/12/NPCA-Patient-Survey_051219.pdf

Appendix 2 (a) Genitourinary and (b) gastrointestinal procedures up to one year prior to treatment.[1]

2a. Genitourinary procedures

OPCS-4 code[2]	Description
H20.1/2/3/4/6/8/9 H21.2	Therapeutic colonoscopy
H22.1/9	Diagnostic colonoscopy +/- biopsies
H23.1-3/8/9 H24.2/8	Therapeutic fibreoptic sigmoidoscopy of lower bowel
H25.1/8/9	Diagnostic fibreoptic sigmoidoscopy of lower bowel +/- biopsies
H26.7	Therapeutic rigid sigmoidoscopy of lower bowel
H28.9	Diagnostic rigid sigmoidoscopy of lower bowel +/- biopsies
H62.6	Proctoscopy

2b. Gastrointestinal procedures

OPCS-4 code[2]	Description
M44.4/8	Other endoscopic operations on bladder
M45.5	Examination of bladder using rigid cystoscopy
M45.9	Unspecified endoscopic examination of bladder
M47.1	Urethral irrigation of bladder
M47.8/9	Other specified urethral catheterisation of bladder
M64.8	Other specified open operations on outlet of male bladder
M65.1-5	Endoscopic resection of prostate
M65.8/9	Other specified endoscopic resection of outlet of male bladder
M66.2	Endoscopic incision of outlet of male bladder

M66.8/9	Other specified therapeutic endoscopic operations on outlet of male bladder
M76.3	Optical urethrotomy
M76.4	Endoscopic dilation of urethra
M76.8/9	Other therapeutic endoscopic operations on urethra
M79.2	Dilation of urethra
M79.3/4	Internal urethrotomy
M64.2/3/6	Implantation of artificial urinary sphincter/prosthetic collar into outlet of male bladder

[1]GI and GU procedures previously reported in Sujenthiran A, Nossiter J, Charman SC, Parry M, Dasgupta P, van der Meulen J, et al. National Population-Based Study Comparing Treatment-Related Toxicity in Men Who Received Intensity Modulated Versus 3-Dimensional Conformal Radical Radiation Therapy for Prostate Cancer. *Int J Radiat Oncol Biol Phys* 2017;99: 1253-60.

[2] OPCS-4 classification of interventions and procedures (version 4).

Appendix 3. Sociodemographic, tumour & radiotherapy treatment characteristics of responders and non-responders to the patient survey.

	Non-responders		Responders		Total	
	n	%	n	%	n	%
Patients	3,927 (23.0%)		13,131 (77.0%)		17,058	
Age						
<60	352	9.0	515	3.9	867	5.1
61-70	1,410	35.9	4,307	32.8	5,717	33.5
71-80	1,953	49.7	7,483	57	9,436	55.3
>80	212	5.4	826	6.3	1,038	6.1
Ethnicity						
White	3,134	88.5	11,191	95.9	14,325	94.2
Mixed	21	0.6	28	0.2	49	0.3
Asian/Asian British	145	4.1	159	1.4	304	2.0
Black/Black British	186	5.3	220	1.9	406	2.7
Other	55	1.6	72	0.6	127	0.8
Missing	*386*	*9.8*	*1,461*	*11.1*	*1,847*	*10.8*
Comorbidities*						
0	2,819	71.8	10,240	78	13,059	76.6
1	749	19.1	2,012	15.3	2,761	16.2
≥2	359	9.1	879	6.7	1,238	7.3
Index of Multiple Deprivation						
0	674	17.2	3,167	24.1	3,841	22.5
1	797	20.3	3,223	24.5	4,020	23.6
2	802	20.4	2,828	21.5	3,630	21.3
3	820	20.9	2,233	17.0	3,053	17.9
4	834	21.2	1,680	12.8	2,514	14.7
T stage						
1	426	11.1	1,380	10.7	1,806	10.8
2	1,705	44.4	5,560	43.2	7,265	43.5
3	1,634	42.5	5,648	43.9	7,282	43.6
4	76	2.0	288	2.2	364	2.2
Missing	*86*	*2.2*	*255*	*1.9*	*341*	*2.0*
N stage						
0	3,431	93.7	11,522	93.6	14,953	93.6
1	230	6.3	790	6.4	1,020	6.4
Missing	*266*	*6.8*	*819*	*6.2*	*1,085*	*6.4*
Gleason score						
≤6	299	7.8	862	6.8	1,161	7.0
7	2,210	58.0	7,314	57.3	9,524	57.4

≥8		1,304	34.2	4,591	36.0	5,895	35.6
	Missing	*114*	*2.9*	*364*	*2.8*	*478*	*2.8*
PSA (ng/ml)							
<10		1,259	38.9	4,335	40.2	5,594	39.9
10-20		1,025	31.6	3,293	30.5	4,318	30.8
>20		955	29.5	3,155	29.3	4,110	29.3
	Missing	*688*	*17.5*	*2,348*	*17.9*	*3,036*	*17.8*
Risk group							
Locally advanced		2,511	65	8,537	66	11,048	65.8
Intermediate		1,305	33.8	4,287	33.1	5,592	33.3
Low risk		45	1.2	111	0.9	156	0.9
	Missing	*66*	*1.7*	*196*	*1.5*	*262*	*1.5*
RT modality							
3D conformal		194	4.9	587	4.5	781	4.6
IMRT		3,733	95.1	12,544	95.5	16,277	95.4
RT treatment region							
Prostate and/or seminal vesicles		3,348	86.2	11,146	86	14,494	86
Whole pelvis incl. lymph nodes		538	13.8	1,818	14.0	2,356	14.0
	Missing	*41*	*1.0*	*167*	*1.3*	*208*	*1.2*
Hormonal treatment							
No		735	18.7	1,995	15.2	2,730	16.0
Yes		3,192	81.3	11,136	84.8	14,328	84.0
Pretreatment urinary procedure							
No		3,013	76.7	10,204	77.7	13,217	77.5
Yes		914	23.3	2,927	22.3	3,841	22.5
Pretreatment bowel procedure							
No		3,710	94.5	12,434	94.7	16,144	94.6
Yes		217	5.5	697	5.3	914	5.4
RT regimen							
Standard		2,401	61.1	8,432	64.2	10,833	63.5
Hypofractionated		1,526	38.9	4,699	35.8	6,225	36.5

*The Royal College of Surgeons (RCS) Charlson score was used to identify comorbid conditions from HES records based on comorbidities coded in the year preceding their prostate cancer diagnosis for the comparison of non-responders and responders

Appendix 4. Patient characteristics for men with complete versus incomplete EPIC-26 information for each of the five functional domains (urinary incontinence, urinary irritative, sexual/bowel/hormonal function).

	Complete EPIC-26		Incomplete		Total	
	n	%	n	%	n	
Urinary (incontinence)						
Patients	11,365 (86.6%)		1,766 (13.4%)		13,131	
Age						
<60	478	4.2	37	2.1	515	3.92
61-70	3,859	34.0	448	25.4	4,307	32.8
71-80	6,356	55.9	1,127	63.8	7,483	57.0
>80	672	5.9	154	8.7	826	6.3
Comorbidities						
0	2,123	18.7	301	17.0	2,424	18.5
1	3,429	30.2	534	30.2	3,963	30.2
≥2	5,813	51.2	931	52.7	6,744	51.4
Risk group						
Locally advanced	7,384	66.0	1,153	66.2	8,537	66.0
Intermediate	3,710	33.2	577	33.1	4,287	33.1
Low risk	98	0.9	13	0.8	111	0.9
Missing	*173*		*23*		*196*	
Urinary (obstructive/irritative) function						
Patients	10,509 (80.0%)		2,622 (20.0%)		13,131	
Age						
<60	448	4.3	67	2.6	515	3.92
61-70	3,651	34.7	656	25.0	4,307	32.8
71-80	5,834	55.5	1,649	62.9	7,483	57.0
>80	576	5.5	250	9.5	826	6.3
Comorbidities*						
0	1,970	18.7	475	17.3	2,424	18.5
1	3,206	30.5	757	28.9	3,963	30.2
≥2	5,333	50.8	1,411	53.8	6,744	51.4
Risk group						
Locally advanced	6,809	65.9	1,728	66.6	8,537	66.0
Intermediate	3,439	33.3	848	32.7	4,287	33.1
Low risk	92	0.9	19	0.7	111	0.9
Missing	*169*		*27*		*196*	

Sexual function						
Patients	12,049 (91.8%)		1,082 (8.2%)		13,131	
Age						
<60	449	4.1	16	1.5	515	3.92
61-70	4,089	33.9	218	20.2	4,307	32.8
71-80	6,773	56.2	710	65.6	7,483	57.0
>80	688	5.7	138	12.8	826	6.3
Comorbidities						
0	2,199	18.3	225	20.8	2,424	18.5
1	3,618	30.0	345	31.9	3,963	30.2
≥2	6,232	51.7	512	47.3	6,744	51.4
Risk group						
Locally advanced	7,803	68.7	734	65.8	8,537	66.0
Intermediate	3,959	33.4	328	30.7	4,287	33.1
Low risk	104	0.9	7	0.7	111	0.9
Missing	*183*		*13*		*196*	
Bowel function						
Patients	11,213 (85.4%)		1,918 (14.6%)		13,131	
Age						
<60	468	4.2	47	2.5	515	3.92
61-70	3,853	34.4	454	23.7	4,307	32.8
71-80	6,254	55.8	1,229	64.1	7,483	57.0
>80	638	5.7	188	9.8	826	6.3
Comorbidities*						
0	2,079	18.5	345	18.0	2,424	18.5
1	3,415	30.5	548	28.6	3,963	30.2
≥2	5,719	51.0	1,025	53.4	6,744	51.4
Risk group						
Locally advanced	7,309	66.1	1,228	65.2	8,537	66.0
Intermediate	3,645	33.0	642	34.1	4,287	33.1
Low risk	96	0.9	15	0.8	111	0.9
Missing	*163*		*33*		*196*	
Hormonal function						
Patients	11,492 (85.4%)		1,639 (14.6%)		13,131	
Age						
<60	485	4.2	30	1.8	515	3.92
61-70	3,937	34.3	370	22.6	4,307	32.8
71-80	6,425	55.9	1,058	64.6	7,483	57.0
>80	645	5.6	181	11.0	826	6.3

Comorbidities*						
0	2,127	18.5	297	18.1	2,424	18.5
1	3,493	30.4	470	28.7	3,963	30.2
≥2	5,872	51.1	872	53.2	6,744	51.4
Risk group						
Locally advanced	7,497	66.2	1,040	64.4	8,537	66.0
Intermediate	3,730	33.0	557	34.5	4,287	33.1
Low risk	93	0.8	18	1.1	111	0.9
Missing	*172*		*24*		*196*	

***** The survey questionnaire provided the data on comorbidities

Appendix 5. The effect of key patient characteristics, risk group, treatment factors and pre-treatment GI/GU on the EPIC-26 scores for urinary, sexual, bowel, or hormone function – mean adjusted difference and 95% CI*

More advanced disease and higher socioeconomic deprivation status were associated with lower hormonal domain scores (p<0.001). Conversely, older age was associated with higher EPIC-26 scores for hormone function (p<0.001). Increasing age (p<0.001) and more advanced disease (p<0.001) were associated with lower sexual function scores. Pre-treatment GU procedures (p<0.001) were associated with lower urinary incontinence scores and pre-treatment GI procedures (p<0.001) with lower bowel function scores.

	Urinary (incont.) MCID** = 6-9	**Urinary (obst./irrit.)** MCID=5-7	**Sexual** MCID=10-12	**Bowel** MCID=4-6	**Hormonal** MCID=4-6
Patient characteristics					
Age	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
<60	0	0	0	0	0
61-70	2.4 (0.57, 4.31)	4.20 (2.56, 5.84)	-1.88 (-3.95, -0.17)	5.55 (3.47, 7.64)	7.92 (5.98, 9.87)
71-80	1.51 (-0.45, 3.47)	3.93 (2.05, 5.82)	-6.77 (-8.82, -4.73)	5.72 (3.60, 7.88)	11.26 (9.55, 12.97)
>80	-1.40 (-3.66, 0.86)	3.28 (0.98, 5.60)	-9.57 (-11.78, -7.35)	4.78 (2.53, 7.04)	12.07 (9.56, 14.59)
Ethnicity	p=0.003	p<0.001	p<0.001	p=0.55	p=0.16
White	0	0	0	0	0
Mixed	-2.98 (-10.58, 4.61)	-5.19 (-11.78, 1.40)	5.08 (-3.40, 13.52)	2.78 (-4.00, 9.57)	-0.47 (-10.37, 9.43)
Asian	-4.57 (-7.58, -1.55)	-7.61 (-10.86, -4.36)	2.04 (-1.24, 5.32)	-1.68 (-4.72, 1.37)	-4.20 (-8.61, 0.30)
Black	-3.86 (-7.04, 0.68)	-6.04 (-9.14, -2.95)	8.40 (5.42, 11.32)	0.86 (-2.40, 4.12)	-2.30 (-5.73, 1.21)
Other	-0.70 (-5.09, 3.68)	-2.53 (-6.63, 1.56)	3.44 (-2.71, 9.58)	0.44 (-4.62, 5.52)	3.75 (-1.59, 9.10)
Comorbidities* **	p=0.001	p<0.001	p<0.001	p<0.001	p=0.06
0	0	0	0	0	0
1	-1.61 (-2.51, -0.72)	-1.10 (-1.958, -0.25)	-2.44 (-3.40, -1.48)	-1.37 (-2.41, -0.32)	-0.77 (-1.98, 0.46)

≥2	-1.39 (-2.66, -1.26)	-2.25 (-3.36, -1.14)	-1.6 (-2.90, -0.36)	-2.7 (-4.14, -1.33)	-2.65 (-4.86, -0.44)
IMD	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
1 (least deprived)	0	0	0	0	0
2	-0.11 (-1.10, 0.85)	-0.48 (-1.32, 0.37)	-0.23 (-1.33, 0.87)	-0.09 (-1.07, 0.90)	-1.22 (-2.44, -0.13)
3	-1.28 (-2.17, 0.39)	-2.03 (-2.90, -1.153)	-1.96 (-3.12, -0.79)	-0.80 (-2.01, 0.41)	-2.50 (-3.80, -1.20)
4	-2.63 (-3.71, -1.56)	-2.75 (-3.76, -1.74)	-2.45 (-3.69, -1.21)	-1.94 (-3.04, 0.83)	-3.29 (-4.55, -2.02)
5 (most deprived)	-4.07 (-5.41, -2.74)	-4.18 (-5.945, -2.91)	-3.78 (-4.89, -2.67)	-2.8 (-4.04, -1.57)	-5.98 (-7.52, -4.21)
Risk group	p=0.12	p=0.001	p<0.001	p=0.46	p<0.001
Low	0	0	0	0	0
Intermediate	-2.33 (-4.79, 0.13)	3.29 (-5.97, 0.62)	-9.20 (-15.58, -2.81)	-2.31 (-6.58, 1.94)	-8.25 (-13.27, -3.22)
Locally advanced	-2.96 (-5.74,-0.17)	-4.51 (-7.33, -0.70)	-15.50 (-10.80, -9.09)	-2.68 (-7.13, 1.78)	-13.09 (-18.28, -7.90)
Treatment information					
EBRT regimen	p=0.26	p=0.10	p<0.001	p=0.0.09	p<0.001
C-RT	0	0	0	0	0
H-RT	-0.46 (-1.25, 0.34)	-0.71 (-1.55, 0.13)	3.32 (2.11, 4.53)	0.97 (-0.15, 2.08)	3.20 (1.83, 4.57)
ADT	p=0.12	p=0.79	p<0.001	p=0.08	p<0.001
No	0	0	0	0	0
Yes	0.54 (-0.38, 1.45)	0.12 (-0.74, 0.97)	-2.88 (-3.97, -1.79)	0.81 (-0.11, 1.72)	-2.19 (-3.30, -1.09)
IMRT	p=0.38	p=0.70	p=0.30	p=0.45	p=0.70
No	0	0	0	0	0
Yes	0.66 (-0.18, 1.50)	0.34 (-1.23, 1.92)	-0.89 (-0.80, 2.60)	0.70 (-1.09, 2.49)	0.39 (-1.59, 2.37)
RT region	p=0.86	p=0.07	p<0.001	p=0.24	p=0.01
Prostate only	0	0	0	0	0

Whole pelvis	-0.41 (-1.44, 0.61)	0.22 (-0.66, 1.10)	-3.18 (-4.40, -1.97)	0.70 (-0.48, 1.89)	-2.17 (-3.91, 0.44)
Pre-treatment procedures					
GI procedure	P<0.001	p=0.89	p=0.55	p<0.001	p=0.17
No	0	0	0	0	0
Yes	-3.07 (-4.48, 1.67)	-3.50 (-4.91, -2.08)	-0.50 (-2.10, 1.11)	-4.76 (-6.66, -2.87)	-2.09 (-3.80, 0.37)
GU procedure	P<0.001	p=0.89	p<0.001	p<0.001	p<0.001
No	0	0	0	0	0
Yes	-4.08 (-4.95, -3.21)	-2.98 (-3.75, -2.21)	-2.10 (-2.96, -1.25)	-1.98 (-2.85, -1.11)	-1.81 (-2.82, 0.80)

*Multiple imputation by chained equations accounted for missing values of the adjustment variables and outcomes so that the multivariable linear regression model included all 13,131 men. Risk adjustment variables include audit year, age, ethnicity, socioeconomic deprivation (IMD) imd, number of comorbities, IMRT, RT regimen, RT region, disease status, time from radiotherapy to survey, hormone use, pre-treatment urinary or bowel procedures. These results are estimated from the regression model in Table 3.

** MCID = minimal clinically important difference in EPIC-26 scores (Skolarus et al. 2015). The EPIC-26 urinary incontinence domain (MCID, 6 points) includes questions related to urinary frequency and leakage, and the urinary irritation/obstruction domain (MCID, 5 points) focuses on dysuria, haematuria and urinary frequency. The sexual function domain (MCID, 10-12 points) asks questions related to the quality and frequency of erections. The bowel function domain (MCID, 4 points) assesses bowel frequency, urgency, bleeding and pain. The fifth domain, hormonal disturbance (MCID, 4 points), includes hot flushes, gynaecomastia, low energy and weight change.

*** Patient-reported comorbidities

Abbreviations: EBRT = external beam radiation; RT = radiotherapy; H-RT = hypofractionated radiotherapy; C-RT = conventionally fractionated radiotherapy; EPIC-26 = Expanded Prostate Cancer Index Composite short-form; CI = confidence interval; IMD = Index of Multiple Deprivation; ADT = androgen deprivation therapy; GI = gastrointestinal; GU = genitorurinary.