



## Original Research Article



# Late Adverse Health Outcomes and Quality of Life after curative radiotherapy + long-term ADT in Prostate Cancer Survivors: Comparison with men from the general population

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## ABSTRACT

**Background:** Few studies have described the impact of urinary, bowel and sexual Adverse Health Outcomes (AHOs) on Quality of Life (QoL) in Prostate Cancer Survivors living for more than 5 years after curative radiotherapy (“long-term PCaSs”), and compared the findings with those in men from general population. Here we assess self-reported AHOs in such PCaSs focusing on the association between problem experience and QoL. The findings are compared to corresponding symptoms in age-similar men from the general population without a PCa diagnosis (Norms).

**Methods:** Nine years (mean) after curative radiotherapy 1231 PCaSs and 3156 Norms completed the EPIC-26 questionnaire and the EORTC QLQ-C30 instrument. Domain Summary Scores (DSSs) for the urinary, bowel and sexual domains, the percentages of moderate/big dysfunctions and the proportions of overall problems were determined. Inter-cohort differences were interpreted based on cut-off values for published Minimal Clinically Important Differences (MCIDs). Multivariable linear regression models analyzed the associations between QoL and domain-related overall problems.

**Results:** Only the inter-cohort differences regarding bowel and sexual DSSs exceeded the respective MCIDs. Among PCaSs 54% had at least one moderate/big problem (Norms: 30%). In PCaSs and Norms, QoL increased with decreasing urinary and bowel problems. For sexuality this association was weaker in Norms and was almost lacking in PCaSs. Multivariable-adjusted QoL was similar in PCaSs and Norms, with general health being the strongest covariate.

**Conclusions:** During follow-up of long-term PCaSs health professionals should be aware of the survivors’ persisting moderate/big urinary, bowel or sexual problems associated with reduced QoL. In particular, alleviation of urinary and bowel problems can increase the men’s QoL.

## 1. Introduction

Radiotherapy (RT) with or without adjuvant androgen deprivation treatment (ADT) of varying duration represents a curative treatment of non-metastatic prostate cancer (PCa), the survival rates dependent on the radiation dose. However, with rising target doses the risk of urinary,

bowel and sexual Adverse Health Outcomes (AHOs) (“typical AHOs”) increases, with eventual negative impact on Quality of Life (QoL). New radiotherapy (RT) techniques such as Intensity- modulated radiotherapy (IMRT), Image Guided Radiotherapy, Volumetric Modulated Arc Therapy (VMAT) and new brachytherapy techniques are expected to reduce this risk [1].

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Typical post-RT AHOs have in PCa survivors (PCaSS) been described in multiple studies [2–11] but few reports, often from non-European institutions, have dealt with PCaSS living for more than five years after RT (“Long-term PCaSS”) [2–4,5,8–11]. Moreover, the numbers of evaluated long-term PCaSS have often been limited (<200). On the background of PCa patients’ 10-year post-RT overall survival of  $\geq 75\%$  [12] and the considerable between-country variability of self-reported AHOs [13] more and larger studies should deal with post-RT AHOs and related Quality of Life (QoL) in European long-term PCaSS, comparing the findings with corresponding symptoms in age-similar men from the general population (Norms).

The two co-primary aims of this nation-wide observational cohort study in long-term PCaSS are therefore.

1. To describe the severity of patient-reported typical AHOs after RT combined with ADT as well as the prevalence of moderate or big typical dysfunctions and related problems.

and

2. To assess the associations between overall urinary, bowel and sexual problems and QoL.

All findings in PCaSS are compared with corresponding observations in Norms.

## Patients and methods

### General

For each PCa patient diagnosed in the country the Cancer Registry of Norway (CRN) documents basic diagnosis- and treatment-related data, collects data on total and daily radiation doses and the number of daily fractions. Following the Norwegian guidelines from 2009 and 2015 (<http://www.helsedirektoratet.no>) curative RT for PCa implied a total dose of  $\geq 70$  Gy, applied by a 3- or 4- field conformal technique most often combined with 2–3 years of neoadjuvant ADT. Since 2011 IMRT was gradually used by the country’s nine radiotherapy units. MVAT was first introduced in 2017. The most frequent daily dose was 2 Gy. High-dose rate brachytherapy combined with external beam RT (HDR / EBRT) was also used at one hospital [14] and hypo-fractionated RT (HYPO-RT) [15] at another center. Margins of 10 mm to the rectum were viewed acceptable, with weekly verifications of the target volume.

### PCa survivors

Based on a previous study [16] we identified relapse-free 4306 PCaSS diagnosed from 2004 to 2015 who started curative RT to the prostate before 2017 and were  $\leq 80$  years old per August 1st, 2021. These PCaSS were invited to complete a questionnaire presented to them on a specified Internet page.

### Norms

The CRN had randomly identified 10,843 men from the general population (2017–2019) without a PCa diagnosis but similarly aged as men with PCa. Totally 9509 of these men, aged within the age range of the study’s PCaSS, were invited to complete the same questionnaire as presented to the PCaSS, omitting PCa-related questions.

### The questionnaire

The questionnaire contained the Norwegian versions of EPIC-26 [17] and the EORTC QLQ-C30 instrument [18]. The current analyses disregard the hormonal domain of EPIC-26, but uses Question 13c (depression) and Question 13d (lack of energy) for descriptive purposes. The

urinary, bowel and sexual Domain Summary Scores (DSSs) were calculated (<https://medicine.umich.edu/>), each DSS reflecting the severity of the domain’s AHOs, ranging from 0 (worst) to 100 (absent). Minimal Clinically Important Differences (MCIDs) assessed differences between DSSs [19]: Urinary incontinence: 6; Urinary obstruction/irritation: 5; Bowel 4; Sexual : 10. The percentage of non-valid EPIC-26 domains was  $\leq 6\%$ , and  $< 1\%$  of responders had no valid domain. Cronbach alpha was  $> 0.75$  for each of the valid DSSs.

Each domain in EPIC-26 covers aspects of functional impairment (“dysfunctions”). Within the bowel and sexual domain one additional question and question 5 of EPIC-26 assess overall urinary, bowel and sexual problems, ranked as “No problem”, “Very small problems”, “Small problems”, “Moderate problems” and “Big problems”. Following Downing et al [5] we determined the proportions of men with the two worst response alternatives of each EPIC-26 item, briefly called “substantial dysfunction” or “substantial problem”.

Responses to Item 30 of the EORTC QLQ-C30 reflected QoL. The original scale of item 30, ranging from 1 to 7, was transformed covering 0 (worst) to 100 (best) points or was dichotomized: 1–4: (poor QoL) versus 5–7 (satisfactory QoL) [18]. Inter-cohort differences of  $> 10$  points were viewed as moderate”, contrasting “small” differences ( $\leq 10$  points) [20]. Based on a previous study [21] we also included the following variables from C30: General health (Item 29, operationalized as Item 30), work capacity (Item 6), leisure activity (Item 7), and social activity (Item 27) the latter three responses dichotomized: 1–2 (Not limited) versus 3–4 (Limited).

### Statistics

Standard descriptive methods were used, presenting means and corresponding standard deviations (SDs) of continuous variables, and absolute and relative frequencies of categorical variables. Due to considerable differences in the age distribution between PCaSS and Norms, descriptive statistics for Norms were age-adjusted, based on three age categories ( $< 70$ ,  $70 - < 75$ ,  $\geq 75$  years).

Following the principles laid out by causal inference theory it can be argued that sexual, bowel and urinary problems affect overall health, social function and other parts of everyday life [21] so that such factors may be considered to mediate the effect of the three AHO-related overall problems on QoL. The first linear regression model (Model 1) therefore assessed the associations between levels of QoL and the five degrees of sexual, bowel and urinary overall problems, only adjusting for age and level of education ( $< \text{college}$  vs  $\geq \text{college}$ ) as confounders. Interaction terms between case-control status and all other covariates were included together with the before mentioned confounders. Model 2 also included general health, work capacity, leisure activity and social activity as covariates. Predicted levels of QoL for selected covariate patterns were obtained at the means of all other covariates. We used likelihood ratio tests to test the models including interaction effects with age group, but these were not close to significant. These added complexities were thus deemed unnecessary. Statistical significance:  $p < 0.05$ . SPSS version 26.0 and Stata version 17.0 were used.

### Ethics

The Regional Committee for Medical Research Ethics South-East approved this study (no.165867).

## 3. Results

With similar response rates in both groups 1,231 relapse-free PCaSS, and 3,156 Norms were finally evaluable (suppl. Fig. 1). Adjusting for age significantly more PCaSS than Norms reported poor general health, limited work capacity and problems with leisure or social activity (Table 1). Also depression and lack of energy were in PCaSS significantly increased. The target dose was  $> 70$  Gy in 90 % of the PCaSS, and about

**Table 1**  
PCaSs and Norms: Characteristics.

	PCa Survivors n: 1231 (%)	Norms n: 3156 (%)	
		Age-adjusted	Age-Unadjusted
<b>Demographics</b>			
<b>Age at Survey</b>			
All*	74.5 (4.3)	73.4 (4.9)	68.7 (5.9)
55 – 69.9 years	195 (16%)	500 (16%)	1646 (52%)
70 – 74.9 years	405 (33%)	1038 (33%)	986 (31%)
≥75 – 80 years	631 (51%)	1618 (51%)	524 (17%)
<b>Civil status</b>			
Married/living together	1010 (82%)	2509 (80%)	2507 (80%)
Single	215 (18%)	620 (20%)	623 (20%)
<b>Education</b>			
<College	580 (48%)	785 (58%)	1689 (54%)
College /University	635 (52%)	1332 (42%)	1434 (46%)
<b>EORTC QLQ- C30</b>			
<b>Limited Work capacity</b>			
No (Score 1–2)	1032 (84%)	2840 (91%)	2854 (91%)
Yes (Score 3–4)	196 (16%)	287 (9%)	277 (9%)
<b>Limited Leisure activity</b>			
No (Score 1–2)	1041 (85%)	2818 (91%)	2851 (92%)
Yes (Score 3–4)	189 (15%)	277 (9%)	258 (8%)
<b>Limited Social activity</b>			
No (Score 1–2)	1022 (83%)	2882 (92%)	2910 (93%)
Yes (Score 3–4)	200 (16%)	237 (8%)	220 (7%)
<b>General health</b>			
All*	71.2 (27.9)	81.2 (19.8)	81.5 (19.6)
Satisfactory (score 5–7)	888 (72%)	2734 (87%)	2761 (88%)
Poor(score 1–4)	342 (28%)	410 (13%)	387 (12%)
<b>EPIC-26</b>			
<b>Depression</b>			
All*	86.5 (23.7)	91.7 (18.4)	91.3 (18.8)
No/Very small/Small	1114 (93%)	2910 (97%)	2958 (97%)
Moderate/Big	68 (7%)	91 (3%)	94 (3%)
<b>Lack of Energy</b>			
All*	68.9 (31.0)	81.2 (24.7)	81.5 (24.5)
No/Very small/Small	957 (86%)	2797 (92%)	2848 (94%)
Moderate/Big	137 (14%)	226 (8%)	226 (6%)

\*Mean (Standard Deviation).

60 % had undergone IMRT. HDR / EBRT had been applied in 140 PCaSs and HYPO-RT had been applied in 219 men (suppl. Table 1).

In spite of statistically significant differences between the age-adjusted DSSs ( $p < 0.01$ ), only the inter-cohort differences of the bowel and the sexual DSSs exceeded the respective MCIDs (Table 2). Compared to all Norms the sexual DSS in the group of PCaSs was almost

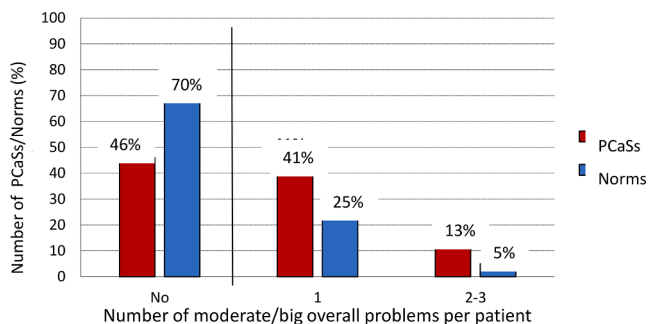
halved (31.9 vs 55.4). Further, age- related differences of sexual DSSs were in PCaSs larger than in Norms, without similar findings for the urinary or bowel DSSs. The DSSs in PCaSs who had IMRT or HYPO-RT were similar to figures after RT without IMRT (suppl. Table 3). PCaSs who had undergone HDR / EBRT had the most favorable DSSs.

Forty-six percent of the PCaSs did not record any substantial problem

**Table 2**  
A. Domain Summary Scores (DSSs) and mean Overall problems (EPIC-26); B: Quality of Life (QLQ-C30).

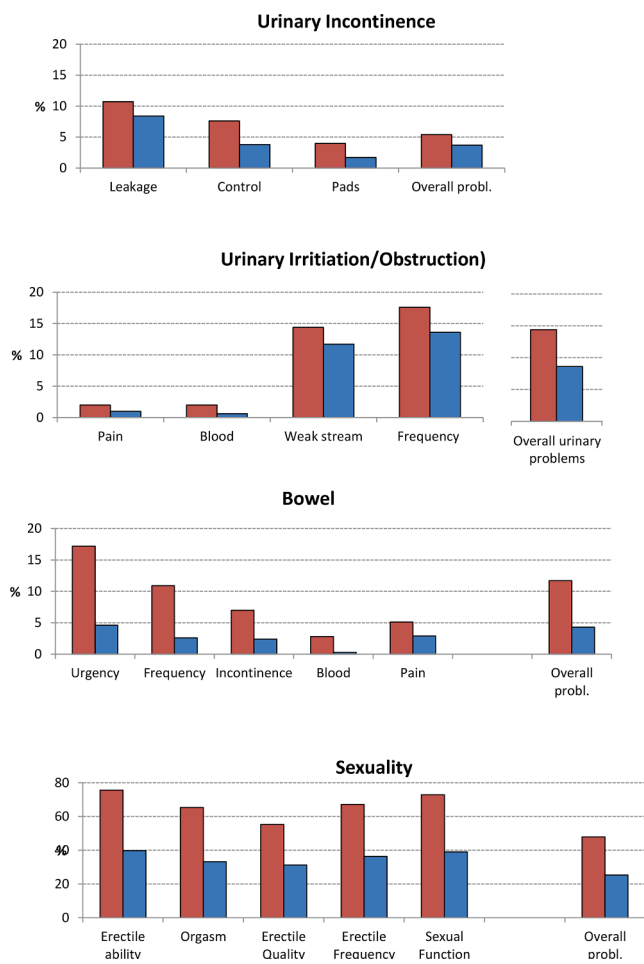
A: EPIC-26	PCaSs				Norms				
	<70y	70–74.9y	≥75y	Total	Age-adjusted			Age-Un-adjusted	
DSS/ overall urinary problems	<70y	70–74.9y	≥75y	Total	<70y	70–74.9y	≥75y	Total	
<u>Urinary incontinence</u> DSS (SD)*	88.8 (19.9)	88.1 (18.7)	86.1 (20.7)	87.2 (20.0)	93.5 (12.7)	90.9 (15.4)	89.6 (17.6)	90.7 (16.2)	92.0 (14.5)
<u>Urinary Irrit./Obstr.</u> DSS (SD)*	82.7 (16.8)	82.1 (17.0)	82.1 (14.4)	82.2 (16.9)	87.7 (14.0)	85.1 (14.0)	84.4 (15.1)	85.5 (14.6)	86.5 (14.2)
<u>Overall urinary problem</u> Mean (SD)*	73.8 (28.7)	74.7 (26.4)	73.3 (29.0)	73.8 (28.1)	82.9 (23.1)	78.7 (25.2)	78.8 (25.8)	79.4 (25.2)	80.9 (24.3)
<u>Bowel</u> DSS (SD)	82.8 (19.9)	82.4 (20.0)	84.0 (18.0)	83.3 (19.1)	93.5 (11.9)	93.9 (18.6)	92.2 (13.0)	93.0 (12.5)	93.4 (12.1)
<u>Sexuality</u> DSS (SD)*	43.7 (27.2)	33.7 (25.8)	27.0 (22.8)	31.9 (25.3)	73.3 (25.6)	58.8 (28.1)	47.5 (28.9)	55.4 (29.6)	64.6 (28.6)
<b>B: QLQ-C30</b>									
<u>Quality of Life</u> (Item 30)Mean (SD)*									
	74.4 (24.1)	73.5 (23.5)	73.0 (22.7)	73.4 (23.2)	83.2 (19.9)	84.5 (18.6)	82.6 (20.3)	83.3 (19.7)	83.5 (19.6)
Satisfactory (5-7)	148 (76%)	303 (75%)	483 (77%)	934(76%)	443 (89 %)	941 (91 %)	1411 (87 %)	2795 (89 %)	2811 (89 %)
Poor (1-4)	47(24%)	102(25%)	147(23%)	296 (24%)	56 (11 %)	93 (9 %)	207 (13 %)	356 (11 %)	339 (11 %)

\*Mean (Standard Deviation).



**Fig. 1.** Age-adjusted percentages of PCaSS and Norms with no, 1 or 2–3 moderate or big overall problems within the urinary, bowel or sexual domains. ( $P < 0,01$  for all inter-group differences).

compared to 70 % of the Norms (Fig. 1). All proportions of PCaSS with substantial dysfunctions or overall problems exceeded the corresponding percentages among Norms (Fig. 2, suppl. Table 2). About 15 % of the PCaSS reported substantial urinary or bowel problems, while the prevalence of sexual problems was almost 50 %. Further, compared to the Norms the urinary and sexual problems were almost doubled in the PCaSS along with a nearly threefold increase of bowel problems. Notably, substantially reduced sexual function (EPIC item no 11) was described by 73 % of the PCaSS, but only 48 % reported substantial overall sexual problems. The corresponding figures among Norms were 40 % and 25 %.



**Fig. 2.** Age-adjusted percentages of PCaSS and Norms with domain-specific moderate or big AHOs or overall problems ( $p < 0,01$  for all inter-group differences except for pain [ $p:0.02$ ]).

Table 3 documents the independent associations between QoL and the rankings of urinary, bowel and sexual problems. According to the regression coefficients in Model1 the associations between QoL and urinary or bowel problems are in the PCaSS much stronger than between QoL and sexual problems. After adjusting for the mediating variables and covariates (Model 2), the reduction of urinary and bowel problems remained significantly associated with increasing QoL levels, though weaker than in Model1. In particular, the association between sexual problems and QoL became less evident. Both in the PCaSS and the Norms general health was the dominating predictor of QoL. Importantly, the mean QoL levels based on Model 2 were similar in PCaSS and Norms (PCaSS: 79 [range: 78–80]; Norms: 81 [range: 81–82]).

Fig. 3 visualizes the above findings. In PCaSS and Norms an almost linear increase of QoL is documented along with reduction of bowel and urinary problems (Fig. 3a). A much less steep improvement of QoL emerged in the Norms along with reduced sexual problems. In the PCaSS the QoL levels remained almost unchanged in men reporting Moderate, Small, Very small or None sexual problems. Reduction of urinary and bowel problems from Big to None increased QoL in PCaSS by nearly 30 points with less QoL improvement along with reduction of sexual problems (9 points). The corresponding QoL differences were generally lower in Norms. Controlling for mediating variables (Fig. 3b) reduced the absolute impact of urinary, bowel and sexual problems, but supported the effect of decreasing urinary and bowel problems on QoL improvement. The weaker impact of reducing sexual problems was confirmed, in particular for PCaSS. For each step of problem experience the QoL differences between PCaSS and Norms were small.

#### 4. Discussion

In this nation-wide survey, 54 % of long-term PCaSS but only 30 % of Norms reported at least one moderate or big post-RT urinary, bowel or sexual overall problem. An almost linear QoL increase emerged in PCaSS and Norms along with decreasing overall urinary and bowel problems. The corresponding association regarding overall sexual problems was weaker in Norms and was almost lacking in PCaSS. Adjusted QoL was similar in PCaSS and Norms.

The DSSs and the means of overall problems in our PCaSS are comparable to published figures from EPIC-based surveys performed in PCA survivors >5 years after RT (Table 4), and our findings in Norms correspond well with those in age-similar men from the general population in Northern Ireland [22]. None of the relevant publications in PCaSS provide data on the duration of ADT, though a negative long-term impact of adjuvant ADT on sexual DSS has been indicated by Downing et al [5] and Hoffman et al [3]. Notably, the most favorable sexual DSS combined with a relatively high prevalence rate of preserved sexual function (64 %) emerged in Donovan et al’s [10] patients. Compared to our PCaSS the UK patients were, however, younger and had undergone ADT for maximum six months (Personal communication, M. Mason). Adjuvant ADT for 2–3 years has, on the other hand been “clinical practice” in Norway before 2017. High age, long-lasting ADT and insufficient recovery from hypogonadism represent the most probable explanation for the substantial erectile dysfunction in 75 % of our PCaSS and the >20 points inter-cohort difference of the sexual DSSs. RT-induced atherosclerosis of the pudental vessels [23] and scattered testicular irradiation [24] may have contributed to the development of late hypogonadism and of the low sexual DSS.

Long-lasting hypogonadism rises the risk of physical and mental morbidity [25], and explains the increased prevalence of depression and energy loss in our PCaSS. This finding, possibly more than sexual dysfunction itself, warrants the consideration of testosterone replacement therapy in long-term tumor-free PCaSS with severe symptoms and low serum testosterone [26], and supports today’s shorter ADT duration, whenever possible.

More PCaSS than Norms reported substantial overall urinary problems (14 % versus 9 %;  $p < 0.01$ ), mostly due to increased micturition

**Table 3**  
Multivariate regression analyses with QoL as dependent variable.

Variables	Model 1		Model 2	
	PCaSS	Norms	PCaSS	Norms
Age (ref: <70 years)				
70-74	2.6 (1.3,4.0) <sup>1</sup>	2.6 (1.3,4.0)	1.4 (0.5,2.4)	1.4 (0.5,2.4)
75+	2.1 (0.6,3.6)	2.1 (0.6,3.6)	1.8 (0.7,2.9)	1.8 (0.7,2.9)
Education (ref: <College)				
College/University	2.6 (1.5,3.7)	2.6 (1.5,3.7)	0.6 (-0.2,1.4)	0.6 (-0.2,1.4)
General health (ref: Satisfactory)				
Poor	NR	NR	-28.0 (-30.1,-26.0)	-29.2 (-31.0,27.3)
Limited leisure activity (ref: No)				
Yes	NR <sup>2</sup>	NR	-9.9 (-12.1,-6.7)	-2.9 (-5.6,-0.1)
Limited work capacity (ref: No)				
Yes	NR	NR	-1.9 (-5.0,1.1)	-6.5 (-9.1,-3.9)
Limited social activity (ref: No)				
Yes	NR	NR	-6.7 (-9.4,-4.0)	-10.0 (-12.4,-7.6)
Urinary problem (ref: Big)				
Moderate	11.7 (5.1,18.3)	4.0 (-2.3,10.4)	4.10 (-0.7,8.9)	5.4 (0.8,10.0)
Small	14.1 (7.5,20.6)	11.5 (5.3,17.7)	5.6 (0.9,10.4)	6.0 (1.5,10.4)
Very small	21.5 (15.2,27.7)	15.0 (9.0,21.0)	7.5 (2.9,12.0)	7.2 (2.9,11.6)
None	26.3 (20.0,32.6)	18.7 (12.7,24.7)	11.4 (6.8,16.0)	10.8 (6.4,15.1)
Bowel problem (ref: Big)				
Moderate	14.9 (8.0,21.8)	4.7 (-4.0,13.4)	2.5 (-2.5,7.5)	1.1 (-5.4,7.6)
Small	21.6 (14.9,28.3)	10.3 (1.9,18.8)	3.8 (-1.0,8.7)	4.1 (-2.1,10.4)
Very small	23.4 (17.0,29.9)	16.3 (8.1,24.4)	3.6 (-1.1,8.4)	5.6 (-0.5,11.6)
None	28.8 (22.4,35.2)	22.7 (14.6,30.8)	7.1 (2.5,11.8)	9.52 (3.5,15.5)
Sexual problem				
Moderate	7.0 (3.9,10.0)	2.8 (-0.3,5.8)	2.9 (0.7,5.1)	-1.1 (-3.4,1.1)
Small	7.0 (3.9,10.1)	5.0 (2.1,8.0)	2.8 (0.6,5.1)	-0.3 (-2.4,1.9)
Very small	8.0 (4.8,11.2)	7.5 (4.7,10.4)	3.8 (1.5,6.1)	1.3 (-0.7,3.4)
None	8.6 (5.2,12.0)	8.8 (6.1,11.6)	3.7 (1.3,6.2)	2.7 (0.7,4.7)

<sup>1</sup> Non-standardized regression coefficients (95% confidence interval); <sup>2</sup>Not Relevant.

frequency and weak stream, neither uncommon in our Norms. Post-RT pelvic and bladder wall fibrosis [27] adds to the age-related micturition dysfunction reported by Norms.

Our bowel DSS is lower than Bergengren et al's [11] EPIC-26-based nation-wide results. Our figures are also considerably below Donovan et al's figures in patients initially included in the ProtecT trial [10]. The latter difference is possibly related to the common outcome differences between individuals selected to participate in trials and those included in population-based surveys [28]. Further, older age of our PCaSS, larger primary tumors and increasing post-RT fibrosis along with expanded time since RT contributes the differences between our and the UK findings.

We could not confirm data on reduced post-RT toxicity using IMRT [29], but document slightly more favorable findings after the use of HDR / EBRT. Gradual increase of the total dose for EBRT may be one explanation for this disappointing finding together with the acceptance of a 10 mm posterior margin. In agreement with published findings Hypo-RT did not increase the severity of typical AHOs [30].

EPIC-26 is internationally recommended for assessment of post-treatment AHOs in PCaSS [31]. The instrument is often referred to as a QoL instrument, though the questionnaire does not cover items important for a PCaSS' generic QoL such as work capacity and leisure or social activities [21]. In some studies EPIC-26 has therefore been supplemented by a generic QoL instrument [3–5] such as the EORTC QLQ-C30 in the current study [18]. This approach increases the understanding of the associations between PCaSS' QoL and the PCa- typical AHOs. Not surprisingly, our data indicate that the stepwise reduction of urinary bowel and problems increases QoL in PCaSS and Norms. As also discussed by others [2,4–6] for the sexual domain this association was in our PCaSS only moderate or weak: Only about two thirds of our PCaSS reporting substantial erectile dysfunction also described big or moderate sexual function problems. We can only speculate about an explanation of the limited association between sexual problems and QoL in PCaSS. In contrast to the age-related gradual decrease of sexual function in the Norms, PCaSS experience loss of sexual functions soon after ADT start,

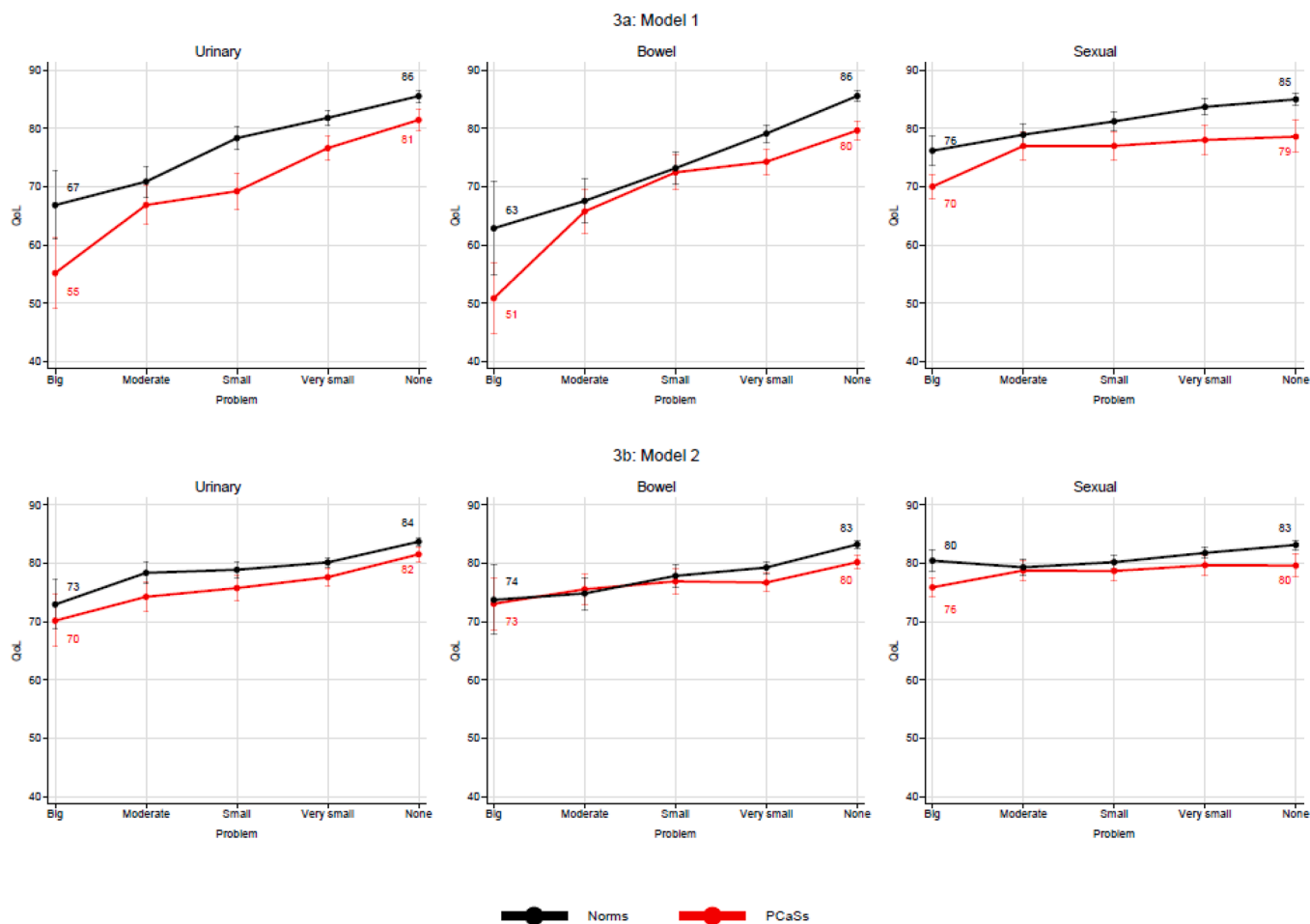
not rarely with insufficient recovery after 2–3 years of ADT. Response shift [32] and satisfactory social and leisure activities [21] may have reduced the survivor's view on the importance of sexual function for his QoL. Further, important emotional and relational issues of sexuality, strongly associated with elderly men's QOL, are not covered by EPIC-26.

In agreement with other studies [3–5] the inter-cohort differences of QoL were small in Model 2, and we document the highly significant association between QoL and general health. Without access of relevant pre-treatment characteristics, the causal influence of RT on our PCaSS' general health cannot be quantitated. On the other hand, RT, combined with long-lasting ADT has most probably contributed to the excess rates of energy loss and depression in PCaSS, these conditions impacting on a PCaSS' experience of poor general health.

#### Limitations and strengths

Our registry-based study has several limitations. Only about one third of the invited men participated in the survey, the low compliance possibly related to the men's high age, reduced health and lack of Internet competence. Further, the RT techniques used could only be broadly described, disabling to study more detailed correlations between RT and AHOs. Neither do we have any information on therapeutic procedures performed to reduce severe problems in individual PCaSS. As detailed data on comorbidity were lacking, Item 29 of the C30 questionnaire served as a measure of general health, while only Item 30 reflected QoL thus slightly deviating from the recommended operationalization [18]. Further, we collected data from only one Northern-European country. Inter-country culture-dependent variations of self-reported urinary symptoms and, in particular, of sexuality among PCaSS and in men from the general population should not be ignored [13,33]. Finally, our PCaSS were relatively old (mean age 74 years), and different results, not at least regarding sexual problems, are to be expected in younger men.

The large sample size of populations-based cohorts and the long observation time of the PCaSS represent the study's advantages. The



**Fig. 3.** Associations between QoL and overall problems in PCaSs and Norms based on Model 1 (3a) and Model 2 (3b). (The numbers in each panel indicate the level of QoL for PCaSs and Norms associated with the respective ranking of Overall problems).

**Table 4**  
Published observations on DSSs and/or overall problems >5 years after curative radiotherapy of prostate cancer.

First author (ref. nr)	Observation time/#PCaSs	Urinary incontinence	Urinary irrit./obstr.	Overall urinary probl./funct.	Bowel	Sexual
Taylor (8)	10 yrs n: 110			84 (2)	84 (2.7) <sup>2</sup>	28 (5.8) <sup>2</sup>
Resnick (2)	15 yrs n: 491 <sup>4</sup>			~78 <sup>3</sup>	~78	~17
Miller (9)	6.2 yrs n: 147	86 (81–90) <sup>1</sup>	84 (80–87)		84 (81–86)	35 (29–41)
Punnen (7)	5–10 yrs n: 158			~88	~85	~28
Pinkawa (6)	9–12 yrs n: 191				~85	~9
Donovan (10)	6 yrs n: ~450	89 (14) <sup>2</sup>	93 (8)	90 (11)	91 (11)	41 (25)
Current study	9 yrs n: 1231	87 (20)	82 (17)	74 (28)	83 (19)	32 (25)

<sup>1</sup>Mean (range); <sup>2</sup>Mean (SEM/ Standard deviation); <sup>3</sup>Figure extracted from a relevant graph; <sup>4</sup>Number of patients at start of the longitudinal study.

real-world design minimizes selection bias which must be considered when PCaSs from trials or single institutions are evaluated [28].

As far as we know, this is the first European report which compares post-RT long-term urinary, bowel and sexual AHOs between PCaSs and men from the general population and describes the associations between related problems and QoL.

**5. Conclusion**

About 10–15 % of long-term PCaSs suffer from post-RT big or moderate urinary or bowel problems, with sexual problems in 50 % of them. Such problems are two-to threefold increased compared to age-similar men from the general population, and they are inversely associated with the men’s QoL. Improvement of post-RT QoL can be expected by therapeutic tasks which alleviate these problems, in particular

within the urinary and bowel domain. Overall, PCa patients can during pre-treatment counseling be informed that their long-term QoL after RT most probably will be similar to that of non-irradiated age-comparable peers. Future studies should address whether modern RT-techniques and today's reduced ADT duration decrease the prevalence of moderate/big long-term post-RT problems thereby increasing QoL.

#### Authors' contribution

Fosså SD / Myklebust TAA: Principal co-investigators, manuscript writing, statistical analyses.

Johannessen TB / Gjelsvik Y: Data provision, comments to and interpretation of the findings.

Dahl AA / Storås AH: Comments to and interpretation of the findings.

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#### Declaration of Competing Interest

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

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ctro.2022.08.003>.

#### References

- Cellini F, Tagliaferri L, Frascino V, Alitto AR, Fionda B, Boldrini L, et al. Radiation therapy for prostate cancer: what's the best in 2021. *Urologia* 2022;89(1):5–15.
- Resnick MJ, Koyama T, Fan K-H, Albertsen PC, Goodman M, Hamilton AS, et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med* 2013;368(5):436–45.
- Hoffman KE, Penson DF, Zhao Z, Huang L-C, Conwill R, Laviana AA, et al. Patient-reported outcomes through 5 years for active surveillance, surgery, brachytherapy, or external beam radiation with or without androgen deprivation therapy for localized prostate cancer. *JAMA* 2020;323(2):149.
- Mazariego CG, Egger S, King MT, et al. Fifteen year quality of life outcomes in men with localised prostate cancer: population based Australian prospective study. *BMJ* 2020; 371: m3503. Oct 7;371:m3503. doi: 10.1136/bmj.m3503. PMID: 33028540; PMCID: PMC7539021.
- Downing A, Wright P, Hounsfield L, Selby P, Wilding S, Watson E, et al. Quality of life in men living with advanced and localised prostate cancer in the UK: a population-based study. *Lancet Oncol* 2019;20(3):436–47.
- Pinkawa M, Gharib A, Schlentner M, Timm L, Eble MJ. Quality of life more than 10 years after radiotherapy for localized prostate cancer-impact of time after treatment and prescription dose. *Qual Life Res* 2021;30(2):437–43.
- Punnen S, Cowan JE, Chan JM, Carroll PR, Cooperberg MR. Long-term health-related quality of life after primary treatment for localized prostate cancer: results from the CaPSURE registry. *Eur Urol* 2015;68(4):600–8.
- Taylor KL, Luta G, Miller AB, Church TR, Kelly SP, Muenz LR, et al. Long-term disease-specific functioning among prostate cancer survivors and noncancer controls in the prostate, lung, colorectal, and ovarian cancer screening trial. *J Clin Oncol* 2012;30(22):2768–75.
- Miller DC, Sanda MG, Dunn RL, Montie JE, Pimentel H, Sandler HM, et al. Long-term outcomes among localized prostate cancer survivors: health-related quality-of-life changes after radical prostatectomy, external radiation, and brachytherapy. *J Clin Oncol* 2005;23(12):2772–80.
- Donovan JL, Hamdy FC, Lane JA, Mason M, Metcalfe C, Walsh E, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med* 2016;375(15):1425–37.
- Bergengren O, Garmo H, Bratt O, Holmberg L, Johansson E, Bill-Axelsson A. Satisfaction with care among men with localised prostate cancer: a nationwide population-based study. *Eur Urol Oncol* 2018;1(1):37–45.
- Fosså SD, Wiklund F, Klepp O, Angelsen A, Solberg A, Damber J-E, et al. The Scandinavian Prostate Cancer Group-7 Investigators. Ten- and 15-yr prostate cancer-specific mortality in patients with nonmetastatic locally advanced or aggressive intermediate prostate cancer, randomized to lifelong endocrine treatment alone or combined with radiotherapy: final results of the Scandinavian prostate cancer group-7. *Eur Urol* 2016;70(4):684–91.
- Storås AH, Sanda MG, Garin O, Chang P, Patil D, Crociani C, et al. A prospective study of patient reported urinary incontinence among American, Norwegian and Spanish men 1 year after prostatectomy. *Asian J Urol* 2020;7(2):161–9.
- Wedde TB, Småstuen MC, Brabrand S, Fosså SD, Kaasa S, Tafjord G, et al. Ten-year survival after high-dose-rate brachytherapy combined with external beam radiation therapy in high-risk prostate cancer: a comparison with the Norwegian SPCG-7 cohort. *Radiother Oncol* 2019;132:211–7.
- Ekanger C, Helle SI, Heinrich D, Johannessen DC, Karlsdóttir Á, Nygård Y, et al. Ten-year results from a phase II study on image guided, intensity modulated radiation therapy with simultaneous integrated boost in high-risk prostate cancer. *Adv Radiat Oncol* 2020;5(3):396–403.
- Fosså SD, Aas K, Müller C, Jerm MB, Tandstad T, Lilleby W, et al. Definitive radiotherapy for prostate cancer in Norway 2006–2015: temporal trends, performance and survival. *Radiother Oncol* 2021;155:33–41.
- Fosså SD, Storås AH, Steinsvik EA, Myklebust TA, Eri LM, Loge JH, et al. Psychometric testing of the Norwegian version of the expanded prostate cancer index composite 26-item version (EPIC-26). *Scand J Urol* 2016;50(4):280–5.
- Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Dues NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85(5):365–76.
- Skolarus TA, Dunn RL, Sanda MG, Chang P, Greenfield TK, Litwin MS, et al. Minimally important difference for the expanded prostate cancer index composite short form. *Urology* 2015;85(1):101–6.
- Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16(1):139–44.
- Fosså SD, Dahl AA. Global quality of life after curative treatment for prostate cancer: what matters? a study among members of the Norwegian Prostate Cancer Patient Association. *Clin Genitourin Cancer* 2015;13(6):518–24.
- Donnelly DW, Donnelly C, Kearney T, Weller D, Sharp L, Downing A, et al. Urinary, bowel and sexual health in older men from Northern Ireland. *BJU Int* 2018;122(5): 845–57.
- Zelevsky MJ, Eid JF. Elucidating the etiology of erectile dysfunction after definitive therapy for prostatic cancer. *Int J Radiat Oncol Biol Phys* 1998;40(1):129–33.
- Farhood B, Mortezaee K, Haghi-Aminjan H, Khanlarkhani N, Salehi E, Nashtaei MS, et al. A systematic review of radiation-induced testicular toxicities following radiotherapy for prostate cancer. *J Cell Physiol* 2019;234(9):14828–37.
- Barone B, Napolitano L, Abate M, Cirillo L, Reccia P, Passaro F, et al. The role of testosterone in the elderly: what do we know? *Int J Mol Sci* 2022;23(7):3535.
- Fode M, Salonia A, Minhas S, Burnett AL, Shindel AW. Late-onset hypogonadism and testosterone therapy – a summary of guidelines from the American urological association and the European association of urology. *Eur Urol Focus* 2019;5(4): 539–44.
- Dohm A, Sanchez J, Stotsky-Himelfarb E, Willingham FF, Hoffs S. Strategies to minimize late effects from pelvic radiotherapy. *Am Soc Clin Oncol Educ Book* 2021;41:158–68.
- Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. *Br J Cancer* 2014;110(3):551–5.
- 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(5): 1253–60.
- Staffurth JN, Haviland JS, Wilkins A, Syndikus I, Khoo V, Bloomfield D, et al. CHHiP trial management group. Impact of hypofractionated radiotherapy on patient-reported outcomes in prostate cancer: results up to 5 yr in the CHHiP trial (CRUK/06/016). *Eur Urol Oncol* 2021;4(6):980–92.
- Martin NE, Massey L, Stowell C, Bangma C, Briganti A, Bill-Axelsson A, et al. Defining a standard set of patient-centered outcomes for men with localized prostate cancer. *Eur Urol* 2015;67(3):460–7.
- Ilie G, Bradfield J, Moodie L, et al. The role of response-shift in studies assessing quality of life outcomes among cancer patients: a systematic review. *Front Oncol* 2019; 9:783. doi: 10.3389/fonc.2019.00783. PMID: 31482068; PMCID: PMC6710367.
- Hald GM, Graham C, Štulhofer A, Carvalheira A, Janssen E, Traen B. Prevalence of sexual problems and associated distress in aging men across 4 European Countries. *J Sex Med* 2019;16(8):1212–25.