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ORIGINAL ARTICLE

Living alone, obesity and smoking: Important factors for quality of life after radiotherapy and androgen deprivation therapy for prostate cancer

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Abstract

Background. While effective treatment of prostate cancer with radiotherapy and hormones increase survival, adverse effects may reduce quality of life (QoL). The aim of this study was to investigate frequency and severity of self-assessed late adverse effects, and identify the patients most exposed. **Material and methods.** QoL of 317 cancer survivors with primary stage T1–T3 prostate cancer treated with conformal radiotherapy (70–78 Gy) and androgen deprivation therapy was analyzed by using SF-12 and EPIC-26 questionnaires. Patients were stratified into three groups, filling out the questionnaires 1–2, 2–3, and 3–4 years after radiotherapy. Differences between groups were tested with ANOVA and the χ^2 test. The influence of marital status, severe obesity, smoking, stage of disease, and applied dose of radiotherapy on QoL was evaluated with multiple linear and logistic regression analyses. **Results.** Of 337 patients, 317 (94%) answered the questionnaire. The sexual and hormonal summary scores in the EPIC significantly improved during time since radiotherapy ($p < 0.001$). Current smoking had a negative effect on SF-12 Physical Component Summary (PCS) and the Mental Component Summary (MCS) scores, on EPIC bowel overall bother (OR 7.8; $p = 0.003$), on EPIC mean urinary incontinence scores, and on the sexual domain. Severe obesity had a negative influence on SF-12 PCS and vitality. Severe obesity also was a negative predictor for moderate-to-severe problems in the EPIC urinary incontinence, and in the hormonal domain. Living alone was associated with lower SF-12 PCS, MCS scores, and SF-12 general health, social functioning, and the EPIC hormonal domain. The stage of disease or the radiation dose had no statistically significant impact on QoL. **Conclusion.** Results showed significant negative associations between smoking, severe obesity and living alone on self-assessed late adverse effects after radiotherapy for prostate cancer. This information may guide rehabilitation.

Prostate cancer is the most common cancer among men in Europe, the incidence reaching 338,000 in the EU in 2008 [1]. In Denmark, the incidence of prostate cancer increased more than 50% in the period 2000 to 2009; close to 4000 cases are expected in 2012. The combination of higher incidence and treatment improvements means that more than 20,000 Danish men with prostate cancer are alive today [2]. External beam conformal radiotherapy (3D-CRT), carried out as 39 fractions up to a total of 78 Gy, is frequently used as the treatment of stage T1–T3 primary prostate cancer [3]. 3D-CRT is usually combined with androgen deprivation treatment

(ADT), started three months before radiotherapy [4], and for T3 patients ADT may be given for up to three years.

Adverse physiological effects are, however, seen in these patients: impotence in 40–50% [5], incontinence in 5–10%, and bowel problems in up to 20% [6]. ADT reduces upper extremity strength, measured as a 2 kg decline in grip strength, within three months after start [7], and may feminize the body image because subcutaneous fat mass increases from 9% to 11% within the first year [6]. In addition to these somatic and sexual problems, prostate cancer patients face an 81% increase in hospitalization

due to depression during the first 10 years after diagnosis [8].

Therefore, monitoring quality of life (QoL) after radiotherapy and ADT is important for at least three reasons: 1) to evaluate and follow the development of side effects, (2) to inform and educate patients how to cope with side effects, and (3) to determine the most severe side effects in order to conduct targeted interventions.

Some single-arm prospective studies have been published: a Spanish study by Pardo et al. [9] of 127 3D-CRT patients with stage T1-T2 showed that radiotherapy with 74 Gy but without ADT caused significant urinary irritative-obstructive symptoms, sexual dysfunction, and bowel-related adverse effects three years after treatment compared to pretreatment scores. These results were not adjusted for smoking or obesity. A prospective study from the USA by Sanda et al. [10] on 292 stage T1-T2 patients identified determinants of QoL after radiotherapy. The study included an adjustment for obesity [defined as Body Mass Index (BMI) ≥ 35]. The authors observed that a large prostate (not defined) and ADT (31% of the patients) were significantly associated with decreased QoL scores by at least one measure point six months or later after treatment.

However, both studies cited here and the majority of the other studies in this area included only stage T1 and T2 patients and only a few patients treated with ADT. We, therefore, studied a group of patients with T1, T2 or stage T3 prostate cancer treated with radiotherapy and ADT to investigate frequency and severity of self-assessed late adverse effects. Several explanatory variables that could influence the outcome were investigated to identify the most exposed patients.

Material and methods

From patient files at Odense University Hospital, Denmark, 384 prostate cancer patients treated with 3D-CRT in a three-year period from 1 January 2006 to 31 December 2008 were retrospectively identified. Patients ($n = 33$) given radiotherapy either immediately after operation or as salvage for local relapse of prostate cancer were excluded. A total of 13 patients (3%) died after the treatment period, and one patient was lost to follow-up, leaving 337 patients eligible for inclusion. Before being contacted by mail, the vital status of all patients was checked in the Central Person Register. This continuously updated registry, since 1 April 1968, has stored information on all Danish residents via a 10-digit unique personal identification number which includes date of birth, gender, and information

on emigration, disappearance, or change of vital status.

The questionnaires consisted of socio-demographic data, the generic Short-Form 12 version 1 (SF-12) [11], and 26 disease-specific questions, the Expanded Prostate Index Composite (EPIC-26) [12,13].

The SF-12 includes eight concepts commonly represented in health surveys. Each concept includes one or two items. Concepts with one item: general health, social functioning, bodily pain, and vitality. Concepts with two items: physical functioning, role limitations due to physical health problems, role limitations due to emotional problems, and mental health. SF-12 results have the opportunity to be expressed in terms of two continuous meta-scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These two meta-scores are standardized to the US population normative values, with a mean score of 50 and a SD of 10. Higher scores represent better health [11]. Furthermore, the results of single-item concepts of SF-12 may be expressed in categorical variables.

The EPIC-26 consists of items concerning urinary symptoms, bowel symptoms, sexual function, and hormonal symptoms. For each domain, a summary score is constructed. In addition, two urinary scales that distinguish irritative/obstructive symptoms and incontinence are obtained. All EPIC items are answered on a five-point Likert scale from no problems to severe problems ("big problems" in the questionnaire). All domains, except the hormonal domain, have a unifying question about the overall bother. Similar to the SF-12 instrument, the scores of the EPIC domains can be transformed linearly to a scale of 0 to 100, with higher scores indicating better QoL [12,13]. Scores from single-items EPIC can be expressed in categorical variables.

A low inter-scale correlation observed between SF-12 and EPIC domains supports the concurrent use of EPIC with SF-12 for an efficient and comprehensive assessment of QoL among prostate cancer patients [12].

Medical information was obtained by review of all individual medical records and included Gleason score, TNM-staging, prostate-specific antigen values, and initial treatments with ADT.

Statistical methods

Statistics were calculated with STATA 11. Socio-demographic and clinical characteristics of all patients were described by using means for continuous variables and frequencies for categorical variables. Patients

were divided into three groups: 1–2 years (mean 1.8), 2–3 years (mean 2.6), and 3–4 years (mean 3.6) after treatment.

In some of the returned questionnaires data were missing. According to the methods described for SF-12 and EPIC, some domains could be used with single answers missing, while in other domains all questions should be answered [11,12]. Answers with insufficient data were removed from the analysis.

Differences of QoL scores between the periods were tested with one-way analysis of variance (ANOVA) or the χ^2 test depending on the nature of variables. Continuous outcome measures were first analyzed with multiple linear regression models using the summary scores (PCS and MCS) of SF-12, and the summary scores from the EPIC domains, respectively.

Then, the categorical outcome variables from the single items of SF-12 and EPIC were divided as binary outcomes into none-to-minor problems (patients responding 1, 2 and 3 in the questionnaire) or moderate-to-severe problems (patients responding 4 and 5 in the questionnaire). One single-item concept, SF-12 vitality with a scale from 1–6, was divided into none-to-minor problems (patients responding 1–4) and moderate-to-severe problems (patients responding 5–6).

The binary data were analyzed with multiple logistic regression models and were adjusted for age at treatment and time since radiation. The purpose was to develop an explanatory model of the exposures, in this case: smoking, severe obesity ($\text{BMI} \geq 30$), living alone, the stage of disease, and the radiotherapy treatment dose applied, because these could influence the outcome and serve as a guide for rehabilitation. P-values < 0.05 were considered statistically significant. Reported p-values were two-sided.

Ethics and data protection

The study was approved by the local Scientific Research Ethics Committee (File number S-200 90142), and by the Danish National Data Protection Agency (File number 2009-41-3948).

Results

Study population

A total of 317 of 337 prostate cancer patients (94%) filled in the questionnaire. The non-responders ($n = 20$) were significantly younger, with a mean age of 64 years at diagnosis ($p = 0.008$). No significant differences in medical characteristics were observed by comparing responders to non-responders. According to protocol all patients were liable to ADT, but

four patients were not treated (Table I). Unfortunately, the reason why was not documented in the patient files. It may have been due to patient refusal or the doctors' clinical decision.

Frequency and severity of late effects

Basic descriptions of the means of the SF-12 and EPIC scores are shown in Table II. Time since radiotherapy improved the sexual and hormonal domains in the EPIC significantly ($p < 0.001$). Figure 1 shows the trajectory over time of percentage of patients with moderate-to-severe overall bother in the EPIC domains (urinary, bowel and sexual), and individual items in the hormonal domain. The single items that changes significantly are included. Figure 1a show no significant change in the overall urinary bother, but during the period significant more patients, from 6% to 16%, had a need for daily diapers. Figure 1c show no significant change in the overall sexual bother, but several of the single sexual items had changed significantly. Age had a significant influence on the single item quality of erection ($p < 0.004$, data not shown).

Possible explanatory factors for QoL

The adjusted multiple linear regression analysis (data not shown) revealed a statistically significant negative influence of current smoking on the EPIC domains. Mean urinary incontinence score was lower (-9.6 ; $p = 0.019$) in smokers compared to non-smokers on a score from 0 to 100. Furthermore, smoking reduced the mean bowel score (-9.3 ; $p = 0.023$), and the mean sexual score (-9.9 ; $p = 0.023$). On the SF-12, smoking reduced the mean PCS score (-4.1 ; $p = 0.036$), and the mean MCS score (-4.8 ; $p = 0.010$). The logistic regression analysis showed that current smokers had increased risk of moderate-to-severe problems with: SF-12 vitality [Odds Ratio (OR) 2.8; $p = 0.034$]; with the EPIC bowel overall bother (OR 7.8; $p = 0.003$), and with EPIC sexual overall bother (OR 2.6; $p = 0.035$) (Figure 2).

Severe obesity, defined as a $\text{BMI} \geq 30$, had a significant negative influence on the EPIC mean urinary incontinence score, and the mean hormonal summary score (-10.2 ; $p = 0.001$) compared to patients with a lower BMI. Severe obesity reduced the mean PCS score (-4.6 ; $p = 0.001$), and increased the risk of moderate-to-severe problems with SF-12 vitality (OR 2.2; $p = 0.018$) (Figure 2).

Living alone as compared to living with a spouse was likewise a significant negative explanatory variable for worse QoL on the SF-12 mean PCS score (-6.0 ; $p = 0.001$); the mean MCS score (-5.9 ; $p = 0.001$),

Table I. Socio-demographic and biological characteristics of 317 survivors with primary prostate cancer included in a retrospective survey after radiotherapy and androgen deprivation therapy, 2006–2008 Odense, Denmark.

	Responders (n = 317)	Non-responders (n = 20)	p-value
Socio-demographic characteristics			
Age at treatment (years)			
Mean (range)	67.3 (49–77)	64.1 (48–74)	0.008 ^a
Weight (kg) reported at time of questionnaire			
Mean (range)	86.8 (62–159)	NA	
Unknown	3		
Body mass index (BMI) kg/m ²			
Mean (CI)	28.2 (27.7; 28.7)	NA	
Range	19.6–63.5		
Unknown	11		
Relation reported at time of questionnaire		NA	
Living alone	41 (13.0%)		
Living with a spouse	275 (87.0%)		
Unknown	1		
Education		NA	
Basic (less than 10 years)	130 (41.5%)		
Youth (high school)	101 (32.3%)		
Medium (profession)	62 (19.8%)		
Higher (university)	20 (6.4%)		
Unknown	4		
Smoking status reported at time of questionnaire		NA	
Never smoker	93 (29.6%)		
Past smoker	175 (55.7%)		
Current smoker	46 (14.7%)		
Unknown	3		
Medical characteristics			
PSA pretreatment serum ng/ml:			
Mean (range)	23.8 (2–172)	26.4 (6–85)	0.618 ^a
Gleason score:			0.135 ^b
< 7	104 (32.9%)	5 (25%)	
7	146 (46.2%)	6 (30%)	
> 7	66 (20.9%)	8 (40%)	
Unknown	1	1	
Degree of malignancy:			0.162 ^b
T1	18 (5.7%)	2 (10%)	
T2	111 (35.2%)	3 (15%)	
T3	186 (59.1%)	15 (75%)	
Unknown	2		
Radiation dose:*			0.378 ^b
70 Gy	56 (17.7%)	2 (10%)	
78 Gy	261 (82.3%)	18 (90%)	
Hormone therapy:			
No	4 (1.3%)	2 (10%)	
Androgen deprivation therapy (ADT)**	313 (98.7%)	18 (90%)	

^at-test. p-values are two-sided and <0.05 were considered statistically significant.^bχ² test.

*Radiotherapy was delivered in 2.0 Gy daily fractions, 5 days per week.

**Luteinizing hormone-releasing hormone (LHRH) analogue and/or androgen every third month, usually until one year after radiotherapy or three years in T3 patients.

and the mean hormonal summary score (−9.7; $p = 0.013$). The risk of moderate-to-severe problems with general health (OR 2.8; $p = 0.008$), and the reporting problems with social functioning were likewise increased (Figure 2). Furthermore,

living alone increased the risk of hot flashes, and feeling depressed (OR 3.2; $p = 0.013$).

The stage of disease (data not shown) or the radiation doses had no statistically significant impact on QoL.

Table II. General quality of life (QoL) scores (SF-12) and disease-specific QoL scores (EPIC) overall and at different times after radiotherapy among 317 survivors with primary prostate cancer included in a retrospective survey after radiotherapy and androgen deprivation therapy, 2006–2008. Odense, Denmark.

		SF-12 and epic mean qol scores (95% CI) score 0 to 100*				
QoL after treatment	n	Overall n (317)	1–2 years n (101)	2–3 years n (109)	3–4 years n (107)	p-value ^a
SF-12 domain:						
Physical (PCS)	283	46.2 (45.0–47.4)	46.6 (44.6–48.6)	46.8 (44.8–48.7)	45.3 (43.0–47.6)	0.536
Mental (MCS)	283	53.4 (52.3–54.5)	51.9 (49.8–53.9)	54.3 (52.5–56.1)	54.0 (52.1–55.8)	0.157
EPIC domain:						
Urinary summary	300	81.3 (79.2–83.5)	81.2 (77.4–85.0)	83.3 (79.6–87.0)	79.4 (75.5–83.3)	0.347
Urinary incontinence	300	84.9 (82.4–87.5)	85.9 (81.9–90.0)	87.4 (83.0–91.7)	81.4 (76.5–86.2)	0.141
Urinary irritative	300	79.1 (77.0–81.3)	78.7 (74.8–82.6)	81.7 (78.6–84.7)	76.9 (72.7–81.1)	0.190
Bowel summary	295	80.7 (78.3–83.1)	79.4 (75.2–83.5)	83.9 (79.8–87.9)	78.8 (74.5–83.2)	0.176
Sexual summary	301	17.2 (14.6–19.9)	9.3 (6.1–12.5)	20.5 (15.4–25.6)	21.3 (16.8–25.9)	< 0.001
Hormonal summary	299	72.9 (70.3–75.5)	64.5 (60.3–68.6)	74.1 (69.6–78.6)	79.9 (75.6–84.2)	< 0.001

*Higher scores indicating better QoL. Note: SF-12 is standardized to the US population normative values, with a mean score of 50 and a SD of 10.

^aAnalysis of variance. Reported p-values are two-sided, and $p < 0.05$ considered statistically significant.

Discussion

In this study, self-assessed general and disease-specific QoL was measured at one point within a time period of one to four years after radiotherapy and ADT for primary prostate cancer. The study points out that smoking, severe obesity and living alone are important factors that have a significant negative influence on QoL.

There is no consensus when a difference in QoL is of clinical “significance” or relevance in intervention studies, but half a standard deviation has been suggested as a threshold value [14]. The factors reducing QoL of the men in the present descriptive study were “living alone” and the lifestyle risk factors smoking or obesity. Using the half a standard deviation approach these factors were just significant, or borderline significant.

Late adverse effects

Compared with a study by Wei et al. of a group of 127 radiated patients with a mean age of 70.9 years, and a healthy control group of 112 men [15], the patients in our study expressed lower QoL scores in all EPIC domains. However, the affected QoL may be explained by both the prostate cancer and the treatment. Compared to the study by Pardo et al. [9] who investigated radiated patients without ADT, our patients of comparative age had lower EPIC scores;

so most likely, the ADT used in our study had a negative impact on QoL. In line with this, Wei et al. [15] found lower QoL scores in prostate cancer patients given ADT.

These late adverse effects, however, have to be assessed in relation to the clinical characteristics of the patients. The patients in our study had a mean PSA value of 23.8 ng/ml, and 59% were defined as clinical stage T3, while the previously described studies [9,10] included patients with stage T1 and T2. However, our patients with stage T3 did not show significantly more problems than patients with lower stages.

The finding that, with time, more patients used diapers and few patients reported moderate-to-severe urinary problems could indicate that patients adapted to the situation. Our data showed no correlation between radiation dose and increased occurrence of disease-specific late adverse effects. This may indicate that radiation dose does not completely explain toxicity. Other factors, e.g. the treated target volume/radiation field, QoL before treatment, co-morbidity, and pre-diagnostic urinary function may be of importance. However, we were not able to adjust for these factors in the analysis.

Smoking

A survey [16] of Danish men aged 65–74 years ($n = 12,677$) show that 21.5% were current smokers.

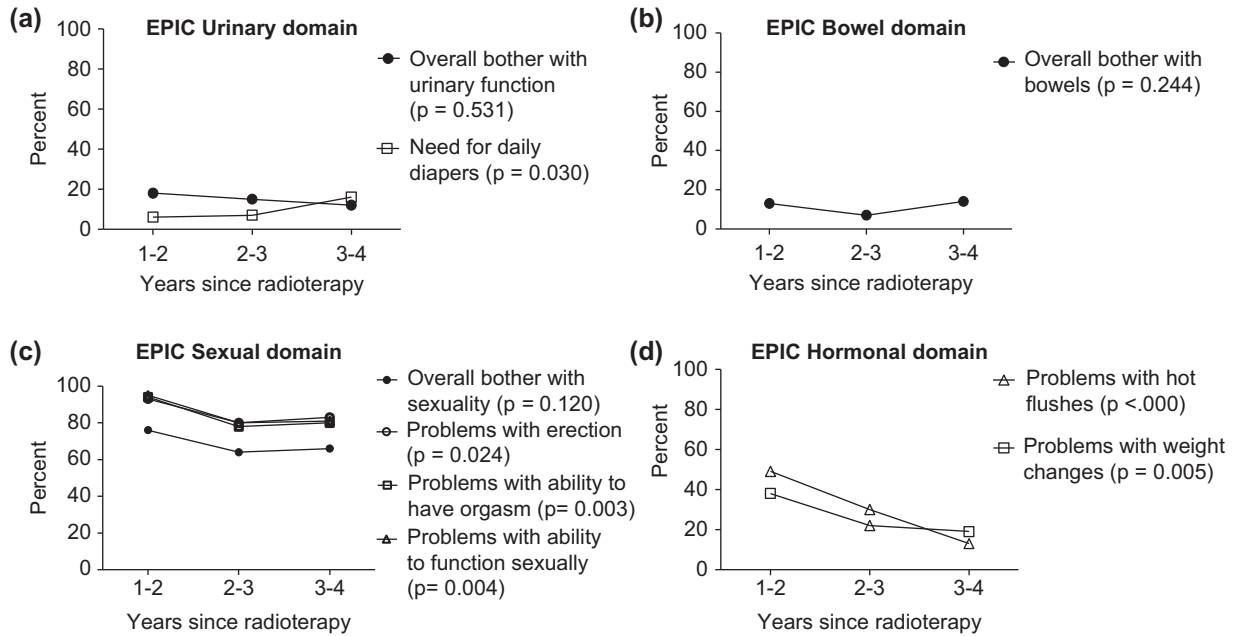


Figure 1. Proportion of patients responding the EPIC questionnaire with moderate-to-severe urinary, bowel, sexual, and hormonal problems among 317 Danish survivors of primary prostate cancer treated with radiotherapy and androgen deprivation therapy, 2006–2008. Odense, Denmark. The overall bother question in each domain is shown and single items within the domains that changes significantly.

In our study 15% were current smokers, and a large group (56%) were past smokers. We found that current smoking had a significant negative impact on both general and disease-specific QoL after radiotherapy

for prostate cancer, especially on patients who experienced bowel problems. This is consistent with the findings one year after pelvic radiotherapy reported in a prospective study (n = 193) by Wedlake et al.

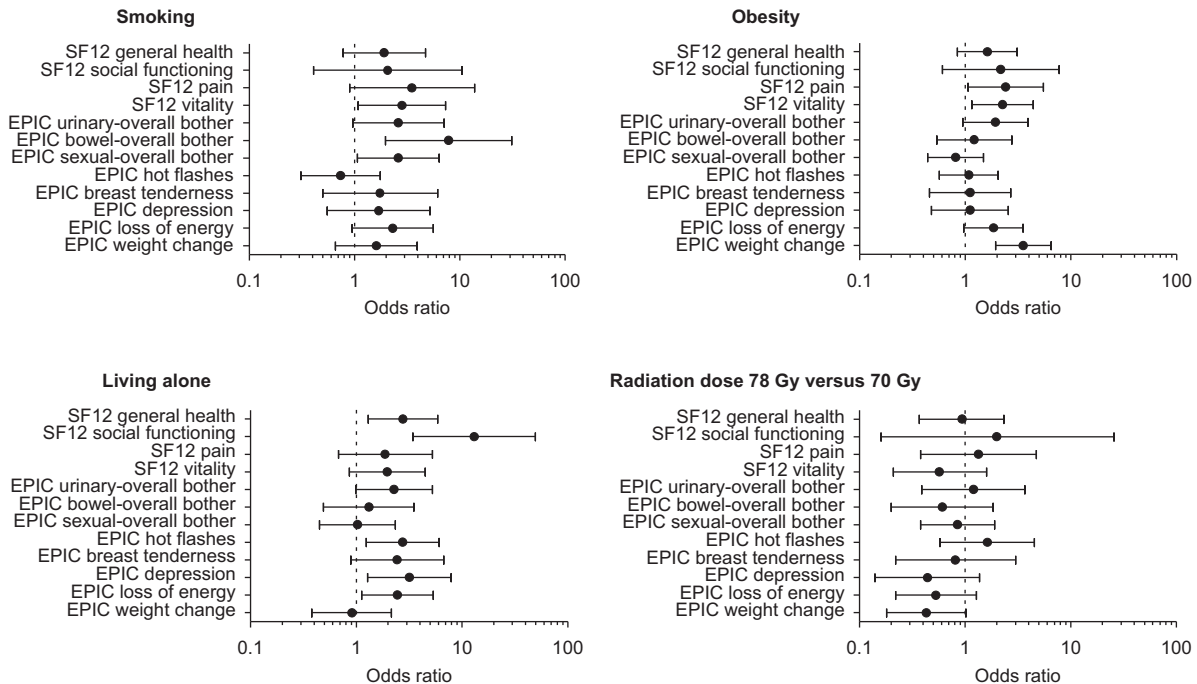


Figure 2. Forest plot with hypothesized factors associated to moderate-to-severe reduction of QoL among 317 Danish survivors with primary prostate cancer treated with radiotherapy and androgen deprivation therapy, 2006–2008. Odense, Denmark. Odds ratios are given for SF-12 single-item concepts, and the EPIC overall bother items concerning the domains “urinary”, “bowel” and “sexual”. Since the hormonal domain has no overall bother item, all single items are shown. *Logistic regression analysis adjusted for patient age and time (years) since radiotherapy. ^aReported p-values are two-sided and p < 0.05 considered statistically significant.

[17], and a recent retrospective Swedish study ($n = 836$) by Alsadius et al. [18] who found a prevalence ratio of 2.8 for diarrhea in current smokers compared to never-smokers.

Severe obesity

The prevalence of severe obesity ($\text{BMI} \geq 30$) in Danish men aged 65–74 years is 17.4% [16]. In this study, 23% of the patients had $\text{BMI} \geq 30$. This difference could be attributable to treatment with ADT, started three months before radiotherapy, as weight increase is a known side effect of this treatment [19]. The data showed that $\text{BMI} \geq 30$ was significantly associated with a lower QoL regarding incontinence and PCS after radiotherapy, consistent with the findings of Sanda et al. [10]. However, Sanda defined obese BMI as ≥ 35 , so even less obesity has a negative influence on QoL.

Living alone

The prevalence of men living alone in Denmark (age 65–74 years) is 21% [20]. A total of 13% of the men in our study lived alone. This life situation had a significant negative impact on QoL after radiotherapy. Previous research showed that married men with prostate cancer turned to spouses for support and assistance [21], and that some prostate cancer patients with no partner have specific coping needs that have to be obviated [22]. Therefore, men living alone may need special attention.

Rehabilitation

Smoking, obesity, and living alone had negative impact on QoL after radiotherapy for prostate cancer. These results are of interest from the rehabilitation perspective [23], since a focused intervention after radiotherapy directed toward smokers, severely obese persons, and men living alone could benefit the QoL of prostate cancer survivors.

Some rehabilitation studies regarding prostate cancer patients are emerging. An Australian randomized study by Galvão et al. [24] with 57 radiated prostate cancer patients treated with ADT longer than two months showed that combined resistance and aerobic training twice weekly for 12 weeks increased lean mass with 1 kg and improved muscle mass, strength, and physical function. A Danish study by Rottmann et al. [25] of 507 cancer patients included 99 with prostate cancer. The patients were randomized to either a six-day residential psychosocial rehabilitation course, or to usual care. No significant impact on psychological distress was found

at six months. However, most rehabilitation studies concern breast cancer patients, and intervention studies regarding smoking cessation, weight control, and psychological support in radiated prostate cancer patients are sparse. Thus, further research is needed.

Limitations and strengths

Our study has several advantages. It was conducted in a society characterized by a public health system, and this almost excludes socioeconomically based selection bias into the study. In addition, our response rate was quite high, which further excludes a disease-specific selection bias. During the time period of inclusion, the treatment protocol was uniform, excluding change in treatment strategy as an explanation for the observed results. However, the study has limitations which, in principle, arise from the retrospective design: the lack of information on co-morbidity and on urinary and sexual function at the time of diagnosis, and the use of data acquired at one point in time.

Conclusion

This study investigated the self-rated frequency and severity of late adverse effects among primary prostate cancer patients one to four years after radiotherapy. Individual patient characteristics showed that the men prone to a reduced QoL were those living alone and those with lifestyle risk factors such as smoking and obesity. While personal factors such as ability to cope and satisfaction with life may influence QoL, identifying vulnerable patients may strengthen the impact of future rehabilitation interventions and research.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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