

Ph.D. Thesis

Rehabilitation in Prostate Cancer Care

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**University of Southern Denmark
2013**



Keld Moseholm - A detail of “The Obelisk”

This statue, made by a local artist, symbolises for me the challenge men with prostate cancer face and the bravery they demonstrate.

Karin Brochstedt Dieperink

PhD thesis

Rehabilitation in Prostate Cancer Care

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Preface

This PhD thesis is based on studies planned and carried out during my employment as a graduate student from 2009 to 2013 at the Department of Oncology, Odense University Hospital and at the Faculty of Health Sciences, University of Southern Denmark.

I have worked with cancer patients in different settings, and connection with different nursing job positions. It has always interested me how the disease affected the patient and family, and how it was possible to include their resources in patient care. In rehabilitation this is a pivotal factor.

Research in cancer rehabilitation is a new and interesting area and calls for an interdisciplinary approach and thoughts about the continuity of care. Unfortunately, a way of thinking that is challenging in the present organization of health services with increasing specialization and different opaque sectors. Nevertheless, this project has shown how to overcome some of the obstacles.

This project has shown me that cancer rehabilitation has to be looked from various perspectives and methods, and each piece together may improve the existing knowledge just a little bit.

Acknowledgements

I am deeply indebted to a number of persons who made this work possible. First of all, I am grateful to the patients and spouses involved in the studies. They have opened my eyes for the depth of the needs of rehabilitation in prostate cancer.

Second, I want to express my sincere gratitude to my supervisors Olfred Hansen, Lis Wagner, and Steinbjørn Hansen for their valuable guidance, discussions, and support in the field of research. Furthermore, I owe thanks to my other co-writers and to my special ad hoc supervisor (M) Christoffer Johansen from the Danish Cancer Society, who shared with me his large knowledge of cancer rehabilitation.

I wish to thank the Department of Oncology for providing excellent working conditions; to the leaders: Merete Bech Poulsen, Niels Holm, Peter Sørensen, Tina Storm Larsen, Susanne Falck Schmidt, doctors from the A-team, and the secretary staff: Annette Sindberg Nissum, Mona Algren Hansen, Dorthe F. Hansen, and Trine Gren Sørensen, who despite busy working days supported my research.

I want to express a special gratitude to the professionals who executed the intervention. The nurses from the A-team: Tina Vinther Boldsen, Heidi McLachlan, Inger Dalsgaard, Anne-Birgitte Truelsen, Mette Møhlenborg Rye, Anders Månsson, Rebekka K. Jørgensen, and Elsebeth Kjærsgaard. A particular thanks to Tina Vinther Boldsen, who handled the randomisations. Likewise, a warm thank to the physiotherapists from the Department of Rehabilitation: Tove Boe, Daniela Fritz, Kirsten Larsen, Lise Svarrer, and Margit Kjær.

Likewise, I want to express my appreciation to Lene Sigaard, who supervised the staff within the method of motivational interviewing, and the staff from the Department of Clinical Research who managed the randomisation list and the development of the database: Christina Nordenbæk and Ulrich Heide Køhler. The fellowship with my colleague students in the hut and in the Research Unit of Nursing was invaluable.

Finally, I want to thank my family Anders, Sabine, Mathilde, and Hans for being there for me. A particularly thanks and love to my husband Hans for continuing support, fruitful discussions, and advice.

Karin Brochstedt Dieperink

Financial disclosures

The studies in this PhD thesis were supported and/or funded by:

The Department of Oncology, Odense University Hospital (OUH)

The Department of Rehabilitation, OUH

The University of Southern Denmark

The Odense University Hospital Research Foundation

CIRRO – The Lundbeck Foundation Center for Interventional Research in Radiation
Oncology

The Danish Cancer Society

The Mette Hede Nielsen Memorial Foundation

The Scholarship Funds of the Physician Council OUH

The Nurses Research Foundation

The Danish Nurses Organization Research Foundation

The professional society of urology nurses

The professional society of cancer nurses

The professional society of nurses working with research and development

The Propa Vita Foundation

The Sister Marie Dalgaard Foundation

We are grateful to all.

We have no financial relationship with any commercial company or institution related directly or indirectly to the subject of this PhD study.

List of terms and abbreviations

| | |
|---------|---|
| PCa | Prostate Cancer |
| PSA | Prostate-specific Antigen |
| Gy | Grey – Dose of Radiation |
| ADT | Androgen Deprivation Therapy |
| QoL | Quality of Life |
| SF-12 | Short Form 12 |
| EPIC | Expanded Prostate Index Composite |
| MAC | Mental Adjustment to Cancer |
| MiniMac | Mini Mental Adjustment to Cancer |
| PFM | Pelvic Floor Muscles |
| MI | Motivational Interviewing |
| RCT | Randomised Controlled Trial |
| SD | Standard Deviation |
| CI | Confidence Interval |
| OR | Odds Ratio |
| UCSF | University of California, San Francisco |
| KBD | Karin Brochstedt Dieperink |
| LW | Lis Wagner |

List of publications

This thesis is based on the following papers and manuscript:

Paper I:

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

Dieperink KB, Hansen S, Wagner L, Johansen C, Andersen KK, Hansen O.

Acta Oncology 51(6), 722-729. 2012

Manuscript II:

The Effect of Counseling in Pelvic Floor Muscle Exercise and Psychosocial Support: A Randomized Study among Primary Prostate Cancer Patients.

Dieperink KB, Johansen C, Hansen S, Wagner L, Andersen KK, Minet L, Hansen O.

Submitted

Paper III:

Embracing life after prostate cancer. A male perspective on treatment and rehabilitation.

Dieperink KB, Wagner L, Hansen S, Hansen O.

European Journal of Cancer Care 2013, *In press*.

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Introduction

This thesis addresses rehabilitation in prostate cancer (PCa) patients treated with radiotherapy and androgen deprivation therapy (ADT).

The Western countries are experiencing an increasing number of cancer survivors, including PCa survivors [1]. This has raised a debate about follow-up, control, treatment of late effects, and rehabilitation. Evidence of this debate can also be found in the Danish National Cancer Plans, with overriding recommendations of rehabilitation services to be put into practice [2-5]. Some of these recommendations rest on fragile foundation since research has mostly investigated late effects, and are focused on the rehabilitation needs of women treated for breast cancer. There is a special need for studies that include the male perspective [6] because men react differently than women [7], and there is a growing demand for development of interventions, implemented in clinical practice, that take into consideration the complex situation with early and late effects experienced by PCa patients as a result of disease and treatment. Patients need for supportive care during and after the end of a cancer treatment may be multimodal [8], and more knowledge is needed about the transition period between end of treatment and long-term survivorship. In 2010, the Danish National Board of Health published a medical technology report [9]. Only a few recommendations regarding rehabilitation interventions for PCa patients were presented due to lack of research. Pelvic floor exercises were cautiously recommended as a response to urinary incontinence. This recommendation was based on randomised studies of patients treated with prostatectomy [10-13]. Apparently, PCa patients treated with radiotherapy and ADT have a different profile of adverse effects, with more bowel problems and irritative urinary symptoms than patients treated with prostatectomy [14-17]. Thus, there is a lack of knowledge of both the extent and type of adverse effects, but also a lack of knowledge of what to do about them, and not least how patients themselves relate to these problems.

Approaching a topic from different perspectives or paradigms may help to gain a holistic perspective and a broader bio-psycho-social understanding of the concept of rehabilitation [18]. As Whyte et al. point out, no single research strategy can address all the important questions related to rehabilitation [19].

Aims of the thesis

The theoretical frame of the thesis is within health promotion and rehabilitation.

The thesis is delimited within the male perspective of early and late effects after curative intended radiotherapy for prostate cancer, and the patients' lived experiences of the rehabilitation applied.

The research aims and strategies in this thesis were threefold:

1. To identify the extent and category of late effect after radiotherapy for localised or locally advanced prostate cancer, and to identify the patients most exposed to late effects.
2. To examine whether a multimodal individually focused multidisciplinary intervention influences the generic and disease specific QoL and coping strategies after radiotherapy for prostate cancer. Our hypothesis was that the intervention within 6 months would reduce irritative urinary problems.
3. To explore how prostate cancer patients experience the treatment and the rehabilitation process in their new, everyday life, and to clarify the importance of the involvement of spouses.

Background

Prostate cancer

PCa is the most frequent male cancer disease in Europe, with an incidence in 2008 reaching 338,000 in the European Union member states [1]. In Denmark, with a population of 5.8 million people, 4,258 men were diagnosed with prostate cancer in 2011 [20]. The mortality was stable, with approximately 1,200 deaths annually [21], while the prevalence of men living with PCa increased to 26,608.

The prostate is located deep in the pelvis between the bladder and the external urinary sphincter, anterior to the rectum, behind the pubic bone, and over the pelvic floor muscles. The function of the prostate is to secrete a slightly acidic fluid that includes the proteolytic enzyme prostate-specific antigen (PSA) into the seminal coagulum where it liquefies semen and allows sperm to swim freely. The pelvic floor muscles (PFM) are associated with a sphincteric, supportive function. Several well-recognisable muscles form the muscular layer of the pelvic floor: levator ani, striated urogenital sphincter, external anal sphincter, ischiocavernosus, and bulbospongiosus [22]. Contraction of the PFM causes elevation and occlusion of all soft tissues of the pelvic floor and closure of the pelvic openings to resist downward forces through the pelvic area.

Because of the placement of the prostate gland at this critical juncture, urinary, sexual, and bowel functions are jeopardised by both the cancer and the antineoplastic treatment [23]. Known risk factors for developing clinical PCa are increasing age, ethnicity, and heredity [24], but these factors cannot explain all cases. A suspected diagnosis of PCa is made on the basis of a digital rectal examination and a serum tests for PSA performed in appropriately counselled patients in whom there is clinical suspicion of PCa [25]. A prostate biopsy with transrectal ultrasound, staging, and risk assessment leads to the final diagnosis [26].

The measurement of PSA in the blood has led to an increasing number of patients diagnosed, but current evidence is insufficient to warrant population-based screening with a test for PSA [24].

The increasing incidence of PCa and the increased prevalence of PCa survivors explain a growing interest in evaluating the impact of treatment on patients' quality of life (QoL).

Radiotherapy

PCa is a disease that is curable when it is still localised to the prostate gland. To cure localised or locally advanced PCa, radiotherapy is an option as an alternative to surgery [27]. Still, there are no scientifically sound, randomised studies that have compared surgery with radiotherapy [28], but a similarity is seen in survival rates associated with these two treatments.

About 1,500 Danish patients are treated with radiotherapy annually, although this number is not limited to curative intent [29]. Three-dimensional conformal radiotherapy (3D-CRT) is the gold standard, and intensity-modulated radiotherapy (IMRT), an optimised form of 3D-CRT, is becoming more widely used as image-guided radiotherapy [24]. Randomised trials have demonstrated that higher doses of radiotherapy improve local tumour control [30, 31]. However, dose escalation is limited by the occurrence of adverse effects.

The standard radiotherapy for curative treatment in stage T1-T3 primary prostate cancer implies 78 Gy in 39 fractions [32], delivered in daily fractions of 2.0 Gy, 5 days per week for 7 to 8 weeks.

Androgen deprivation therapy

The value with respect to survival of neoadjuvant, concomitant, and adjuvant endocrine therapy in conjunction with radiotherapy has been investigated [33]. High-risk patients benefit with a halved 10-year PCa-specific mortality from treatment with a luteinising hormone-releasing hormone (LHRH) analogue delivered 3 months before, during, and up to 3 years after the radiotherapy [34], according to the D'Amico system [35].

The patient trajectory at Odense University Hospital is shown in Figure 1.

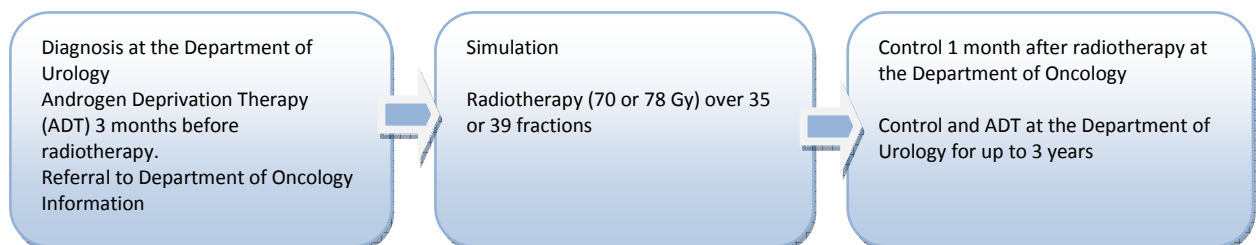


Figure 1. The patients' trajectory from diagnosis to radiotherapy to control.

Adverse effects after radiotherapy

The prospects of life after treatment with radiotherapy are good, but in spite of refinements of the radiation technology, treatment may still be accompanied by acute or late adverse effects and reduced QoL [17, 36]. Late adverse physiological effects after radiotherapy are incontinence in 5–10%; irritative urinary symptoms causing pain, hematuria, weak urine stream, frequency, nocturia, urgency, or urge incontinence in up to 25% [36]; bowel problems in up to 20% [37]; and impotence in 40–50% [38]. The prevalence of acute adverse effects is associated with an increased incidence of late adverse effects [39, 40].

Even though the magnitude of late effects after radiotherapy seems to be considerable, there is a lack of knowledge about their exact frequency and severity, and how late effects influence daily living. This lack of knowledge curtails health initiatives aimed at improving patient trajectories.

Adverse effects after androgen deprivation therapy

ADT as neo-adjuvant to radiotherapy benefits survival in patients with localised PCa [33, 34]. However, some adverse effects are secondary to ADT, e.g. loss of sexual desire in up to 90%, which for some may influence intimacy and marital relations [41]. In addition, ADT may in up to 70% of patients cause development of secondary female characteristics, with increased body fat especially around the waist, hips, and thighs [42, 43] and the occurrence of hot flushes [44]. Furthermore, muscle decay in large muscle groups [45, 46], osteoporosis, and increased risk of metabolic syndrome are reported [47, 48].

Rehabilitation

The definition of rehabilitation according to the WHO [49] is as follows:

“Rehabilitation of people with disabilities is a process aimed at enabling them to reach and maintain their optimal physical, sensory, intellectual, psychological, and social functional levels. Rehabilitation provides disabled people with the tools they need to attain independence and self-determination”

However, for this study the Danish definition of rehabilitation from “Hvidbogen” was selected [50], although the definition is still discussed [51].

“Rehabilitation is a focused and temporary process of cooperation between the patient, relatives, and the professionals. The purpose for the patient is to achieve an independent and meaningful life, even if he has, or is at risk of a significant decline in his physical, mental, or social functions. Rehabilitation is based on the patient’s whole life situation and consists of a coordinated, interconnected, and knowledge-based effort” [50].

(own translation)

Thus, the definition is broad, and it is therefore essential to relate the definition to applied clinical practice. In this particular case, it is used in a perspective of nursing and physical therapy in oncology practice.

Prostate cancer rehabilitation

Research regarding cancer rehabilitation from the male perspective is sparse. A literature search in March 2013 of randomised controlled trials in the database PubMed from 2003 to 2013, using the keywords: “prostate cancer” or “prostatic neoplasm” (MeSH) and “rehabilitation” resulted in 55 hits.

In Denmark, the incidences of PCa and breast cancer are almost identical [20], but in comparison the number of hits was 217 for randomised controlled trials with the keywords “breast cancer” or breast neoplasms (MeSH) and “rehabilitation” in the same period. Furthermore, if the search was restricted to PCa patients treated with external beam radiotherapy, the number of randomised studies with rehabilitation interventions indexed in PubMed 2003 to 2013 showed only six publications, and two of these were report protocols [52, 53]. However, data on rehabilitation are often not disaggregated from other health care services [54], and studies could have been indexed with different keywords. Therefore, the last search was expanded with the word “exercise”, and a few more studies were added. The published randomised studies with exercise interventions are briefly described in Table 1. According to the definition, rehabilitation also has to focus on mental or social problems, and the literature search was expanded with the word “psychological” or “psychosocial”. These published randomised studies are listed in brief in Table 2.

The rehabilitation studies mentioned in Tables 1 and 2 have different endpoints, are relatively small, some with mixed populations, and are of a varying quality. Nevertheless, these studies deliver evidence that exercise in general is beneficial for irradiated PCa patients. The psychological interventions also showed positive results. Additional studies on the psychological perspective were reported in a review by Cockle-Hearne et al. concerning PCa patients in general and focusing on studies offering a self-management approach [55]. They concluded that targeting participants’ needs, promoting motivation, and maintaining programme adherence were important factors to ensure positive health outcomes.

Table 1. Literature search March 2013 of randomised controlled studies including exercise rehabilitation interventions focusing on prostate cancer patient treated with curative radiotherapy.

| Author | Participant demographics | Intervention | Endpoint measures | Reported results | Comments |
|---------------------------|--|---|--|---|------------------------------------|
| Windsor et al. 2004 [56] | PCa (n=66) | Home-based, moderate-intensity walking for 30 min at least 3 days a week during radiotherapy. | Incidence of fatigue during radiotherapy. Fatigue measured each week. | Significant improvement in physical functioning and no increase in reported fatigue. Kapur et al. 2010 [57] showed later lower rectal toxicity in the same sample population. | 52 Gy in 20 fractions over 4 weeks |
| Monga et al. 2007 [58] | PCa (n=21) randomised to exercise (n=11) or control group (n=10) | Supervised exercise-group received radiotherapy plus aerobic exercise 3 times a week for 8 weeks; the control group received radiotherapy without exercise. | Cardiac fitness, fatigue, depression, functional status, physical, social, and functional well-being, leg strength, and flexibility were examined within and between groups. | Significant improvements in: cardiac fitness ($P<.001$), fatigue ($P=.02$), (FACT-P) ($P=.04$), physical well-being ($P=.002$), social well-being ($P=.02$), flexibility ($P=.006$), and leg strength ($P=.000$). | Small study |
| Griffith et al. 2009 [59] | 126 patients, of whom n=70 with PCa | Home-based walking intervention 20-30 min each week | Cardio-respiratory fitness, physical function and pain | Significant improvements in cardio-respiratory fitness and self-reported physical function, and reduced pain | |
| Mustian et al. 2009 [60] | Breast and PCa patients (n=38) of whom n=11 with Pca | Home-based aerobic and resistance training | Fatigue, aerobic capacity, strength, muscle mass, QoL | Significant improvements in fatigue, QoL | Pilot study |
| Segal et al. 2009 [61] | PCa (n=121) | Supervised 24 weeks training with 3 times a week usual care n=41 aerobic n=40 resistance n=40 | Fatigue, QoL, physical fitness, body composition | Both resistance and aerobic exercise significant mitigated fatigue, and increased QoL | |

Table 2. Literature search March 2013 of randomised controlled studies including mental rehabilitation interventions focusing on prostate cancer patient treated with curative radiotherapy.

| Author | Participant demographics | Intervention | Endpoint measures | Reported results | Comments |
|-------------------------|---|--|--|--|---------------------|
| Penedo et al. 2004 [62] | (n=92) men treated with radiotherapy or prostatectomy | 10 week group-based cognitive-behavioural stress management versus 1 day seminar (control-group) | QoL, perceived stress-management skill | Significant improvement in general QoL | |
| Canada et al. 2005 [63] | 3-5 month survivors PCa (n=84) one third treated with radiotherapy and the rest with prostatectomy. All patients were in a relationship | 4 sessions of sexual counselling, together or the man alone. | Sexual satisfaction and medical treatment for erectile dysfunction | 51/84 couples completed (61%) Improvement in overall distress, male global sexual function, and female global sexual function at 3 month but regression towards baseline a 6 month. | Large drop-out rate |
| Beard et al. 2011 [64] | PCa (n=54) | Relaxation response therapy weekly, or Reiki therapy twice weekly or waiting list | Anxiety, depression and QoL | Relaxation response therapy improved emotional well being and eased anxiety in participants. Reiki therapy also had a positive effect in anxious patients. | Pilot study |

Irritative urinary symptoms

A major concern for irradiated patients is irritative urinary symptoms, as more than 25% experience this [36], but none of the randomised studies in Tables 1 and 2 had irritative urinary symptoms as a primary endpoint.

Faithfull et al. showed improvements in lower urinary tract symptoms in a pilot study in which 22 irradiated patients with defined urinary problems completed a self-management intervention with a combination of cognitive-behavioural techniques and pelvic floor exercises [65].

Dr. Arnold Kegel was the first to report that training of the pelvic floor muscles (PFM) was effective in management of urinary incontinence in women [66]. Since then, several randomised controlled trials have supported his results, and in men PFM training has been shown to significantly improve post-prostatectomy urinary continence, post-micturition dribble, and erectile function [10-13, 67], showing more effectiveness with more intensive supervised training [68]. As noted, pelvic floor exercises have shown effects regarding incontinence in patients treated with a prostatectomy, but there is a lack of knowledge as to whether this method also has an effect on irritative urinary symptoms in irradiated patients.

Patients and Methods

Study design

The thesis was designed as three separate studies called Study I, Study II, and Study III. Each study refers to a separate paper or manuscript, Table 3. The thesis is based on a cross-sectional survey investigating late effects after radiotherapy, a prospective randomised controlled trial investigating the effects of a multidisciplinary programme, and a qualitative study with focus group interviews of prostate cancer patients investigating the patients' perspectives of treatment and rehabilitation.

Table 3. The studies represented in the thesis.

| | Study I | Study II | Study III |
|-----------------|--|---|--|
| Methods | Cross-sectional survey. | Randomised controlled trial (RePCa). | Focus group interviews. |
| Data-generation | Questionnaires from 317 participants irradiated between 2006 and 2008. | QoL questionnaires and physiotherapy tests from 161 participants included in the study between 2010 and 2012. | Two interviews conducted January 2012 with 13 participants who completed the intervention in Study II. |
| Analyses | ANOVA, Chi2 test, multiple linear and logistic regression analysis. | Descriptive and multiple linear regression analysis. | Meaning condensation inspired by Giorgi and interaction analysis inspired by Goffman. |

Empirical data were gathered over a period of 3 years, from 2010–2012. The various methods for collecting data were processed simultaneously, but in the analysis, the data were separated between methods. In Study I, data were collected using Danish versions of the questionnaires of general QoL (SF-12), and disease specific QoL (EPIC-26). In Study II, the same instruments were supplemented with data describing coping strategies derived from the questionnaire (MiniMac), and with assessments of the pelvic floor. In Study III, qualitative data were collected with tape recording of two focus group interviews.

Patients

In the three studies, 491 patients with primary prostate cancer were included. The patients followed the contemporary treatment guidelines for the Department of Oncology, OUH, during the recruitment period, based on the guidelines from the Danish Urology Cancer Group (DUCG) [69]. They were all treated with radiotherapy, 70 or 78 GY, and the majority (96%) with ADT.

Assessment of QoL

SF-12

The Medical Outcomes Study Short Form 12-item Health Survey (SF-12) measures generic health concepts relevant across age, disease, and treatment groups [70]. The SF-12 was derived from SF-36 [71], and designed to measure general health status from the patient's point of view. It provides a comprehensive, psychometrically sound, and efficient way to measure health by scoring standardised responses to standard questions.

The SF-12 questionnaire is designed for self-administration, reducing the burden of data collection for health care providers. Most patients can complete the SF-12 in less than 3 minutes without assistance. The SF-12 includes eight concepts commonly represented in health surveys: physical functioning, role limitation due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Results can be expressed in terms of two meta-scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS), or expressed by the single concepts. The SF-12 is scored so that a high score indicates better QoL. To calculate the PCS and MCS scores, test items are scored and normalised in an algorithm. The PCS and MCS scores have a range of 0 to 100 and were designed to have a mean score of 50 and a standard deviation of 10 in a representative sample of the United States population. Thus, scores that are greater than 50 represent above average health status. On the other hand, people with a score of 40 function at a level lower than 84% of the population (one standard deviation) and people with a score less than 30 function at a level lower than approximately 98% of the population (two standard deviations).

In this study, the SF-12 version 1 was selected because this version is usually combined with the EPIC. The SF-12 was licensed for this study.

EPIC-26

The 50-item Expanded Prostate Cancer Index Composite (EPIC) instrument was developed and validated in the United States to expand the scope of the 20-item University of California, Los Angeles, Prostate Cancer Index (UCLA-PCI) [72], by adding items on irritative urinary symptoms, and to assess the effect of hormonal therapy. The EPIC-50 instrument measures disease specific QoL and includes urinary incontinence and irritation / obstruction items, along with bowel, sexual, and vitality/hormonal domains, each with function and bother sub domains. However, its initial 50-item version is a lengthy tool to administer, and its length is even more problematic when combined with other questionnaires, especially when the responders are elderly. Therefore the reduced-length EPIC-26 was selected for this study. The EPIC-26 has a high degree of correlation with the EPIC-50, while the correlation between the different domains is low, confirming that EPIC-26 has the ability to discern the five distinct QoL domains. The internal consistency and test-retest reliability for EPIC-26 (Cronbach's alpha > 0.70 and $r > 0.69$) for all five QoL domains support its validity [73]. Just as in the original EPIC, all domains for EPIC-26 are reported using a 0–100 score, with higher scores representing favourable QoL [74].

The Danish prostate database (DanCaP) performed the translation of EPIC-26 (unpublished). Standard translation procedures were followed. The first step involved forward translation of the original questionnaire into Danish by two Danes speaking fluent English. Differences in translation were discussed. The next step was to translate the EPIC-26 back into English. The Danish version of the questionnaire was pilot tested in three different hospitals in Denmark: Aarhus Sygehus, Skejby, and Rigshospitalet.

A low inter-scale correlation observed between SF-12 and EPIC domains supports the concurrent use of EPIC with SF-12 as an efficient and comprehensive assessment of QoL among prostate cancer patients [72]. The EPIC-26 has no copyright.

Assessment of coping styles

Mini-Mac

Over the last decades, there has been a growing interest in coping with cancer. The most widely spread definition of coping is Lazarus and Folkman's definition:

“Constantly changing cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person”[75].

Related to Lazarus and Folkman's theory of coping is the theory of mental adjustment to cancer, developed by Watson and Greer, where mental adjustment is defined as: "*the cognitive and behavioural responses the patient makes to the diagnosis of cancer*" [76]. It comprises the person's assessment of the implications of cancer and furthermore the emotional reactions in relation to the disease. So, "mental adjustment" is more comprehensive than coping, and therefore chosen for this study.

The Mental Adjustment to Cancer (MAC) scale was developed in the United Kingdom to measure self-rated cognitive and behavioural responses of patients suffering from cancer [76, 77]. The original MAC had 40 items to measure four adjustment styles. A new refined and shortened scale was developed in 1994 and called The Mini-Mental Adjustment to Cancer Scale (Mini-MAC). This scale was extended with the possibility to measure avoidance as a coping response [78]. The Mini-MAC is a 29-item 4-point Likert Scale ranging from (1 = it definitely does not apply to me; to 4 = it definitely applies to me). The scale measures how the person is coping with cancer with regard to five adjustment styles:

- ***Fighting Spirit FS*** – four items (the tendency to confront and actively face the illness, e.g. "I see my illness as a challenge")
- ***Helplessness-Hopelessness HH*** – eight items (the tendency to adopt a pessimistic attitude about the illness e.g. "I feel like giving up")
- ***Anxious Preoccupation AP*** – eight items (feelings of anxiety and the tendency of feeling over-worried concerning the illness e.g., "I am a little frightened")
- ***Fatalism FA*** – five items (resigned and fatalistic attitudes about the illness, e.g. put themselves in the hands of God or fate and take one day at a time e.g., "I've had a good life, what's left is a bonus")
- ***Cognitive Avoidance CA*** – four items (tendency to distract one-self about thoughts of illness and to avoid confrontation with it "Not thinking about it helps me cope")

The original factor structure was used to obtain scores on the five subscales. The raw scores are summed up for each subscale. A higher score represents a higher level of the respective adjustment style. The adjustment styles can be scored separately through simple addition, and the mean score can be calculated by dividing the sum with the number of items.

The Mini-MAC is a validated and well-known tool [79-81] and, in the Scandinavian cultural sphere, was translated and validated in Norway [82]. The Mini-Mac is used in a Swedish study of patients with laryngeal cancer [83] and, in Denmark, in a study of women with breast cancer [84]. However, the psychometric properties of the Danish version of the Mini-Mac

have not been tested, and the original 5-factor structure has been debated. Bredal et al. suggested a 4-factor structure, which combines Fighting spirit and the Fatalism subscales into a “positive attitude” adjusting style [82], but as underlined by Ho et al., the Fatalism in the original Mini-MAC is presumed to measure a patient’s tendency to accept the situation as unavoidable or “fate”, and it should be conceptually separated from Fighting Spirit, which measure a patient’s tendency to take active steps to try to cure the disease or to ameliorate its effects [79]. Cooper et al. studied Australian men with localised and advanced prostate cancer, and found that a fatalistic coping pattern near the time of diagnosis was predictor for a later depression in men with localised disease [85].

The MiniMac was used with permission from Professor Maggie Watson.

Assessment of pelvic floor strength

Digital palpation

The original Oxford Scale for digital palpation was first developed in women by Laycock [86], but before 1996, there was no recognised method of assessing the strength of the PFM in men. In 1996, Wyndaele and Van Eetvelde found that digital anal assessment of the PFM, grading from 0 (nil) to 5 (strong), was a reliable method [87], but due to a ceiling effect Professor Grace Dorey argued for the need for another digital anal grade for men, including grade 6 (very strong) [88]. Unfortunately, there is no “gold standard” for PFM measurement [22], so the Modified Oxford Scale 0–6 was chosen for this study to measure strength because it is a commonly used scale for PFM assessment amongst physiotherapists, and the scale has been evaluated to have a good intra-therapist reliability [89].

In all patients, a correct PFM contraction was confirmed on digital palpation by the assessor with one finger in the patients’ rectum before making the test. The instruction used for each contraction was “squeeze and lift” the pelvic floor, and then the assessor determined the strength on a scale of 0–6. A standardised protocol for ensuring a correct and reproducible technique was used for all tests of the pelvic floor. This protocol was developed after pilot testing in seven patients, and used subject lateral positioning, exact wording of instructions in each repetition, and avoidance of muscles other than those of the pelvic floor. Data from the pilot test were not shown in Manuscript II.

In our study, the static endurance was measured as the number of seconds to hold one contraction at 50% of maximal strength, and the dynamic endurance as a number of contractions with 50% of maximal strength using a hold for 6 seconds and a release for 6

seconds. We considered 60 seconds and 40 contractions as evidence of the optimal performance of endurance.

Electromyography (EMG)

In Study II, EMG using an anal probe was a supportive measurement to the digital palpation. EMG Biofeedback is a method of recording and quantifying the electrical activity produced by the muscle fibres of activated motor units. The depolarisation and repolarisation of the surface membrane of the muscle fibres are the source of the electrical potential changes detected. EMG is useful to demonstrate the time of activation and in the grossest form the amount of EMG activity of a given muscle. In EMG a range of possible errors are seen, e.g. the EMG signal may be affected by physiological parameters such as movements, intervening fatty tissue, muscle temperature, etc., and interpretation of the signals from the surface EMG must be made with caution due to the risk of cross talk from other muscles [90]. To counteract some of the above-mentioned potential errors in our study, we secured the EMG information with a clinical observation and a hand on the stomach when the patient made a squeeze to avoid the use of abdominal muscles.

The surface EMG instrument used in Study II was The NeuroTrac™ MyoPlus [91], and the Anuform™ analprobe. Regarding the instruments, there was an on-line support from Verity Medical in the U.K. during the study.

Each patient was tested with a Work/Rest Assessment in the programme “Incontinence” using five trials with a work time of each contraction of 5 seconds and a rest time of 8 seconds.

The variables derived from the EMG were as follows: average activity indicated the average work microvolt level of the EMG signals during the work periods; average rest indicated the average microvolt level of the EMG signals during the rest periods, as shown in Figure 2.

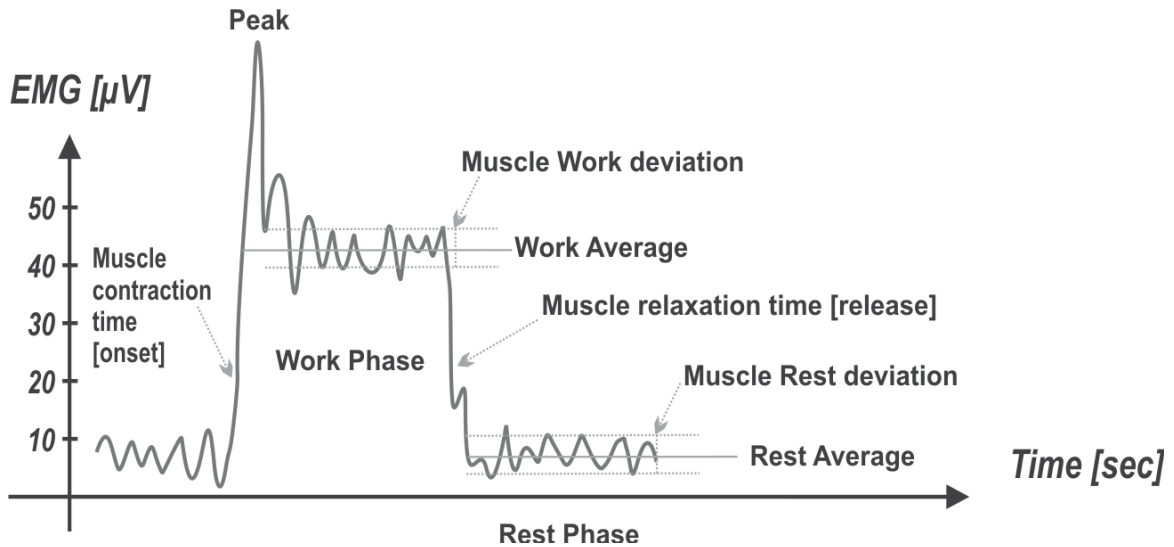


Figure 2. EMG interpretations [91]

Study I - Cross-sectional survey

To guide the rehabilitation process in a Danish setting, we found it important to have a precise knowledge of the nature and extent of late adverse effects. The first study therefore implied a cross-sectional survey.

A number of 351 patients were treated from 2006 to 2008. Thirteen patients died after the end of treatment, and one patient was lost to follow-up. In the spring 2010, 337 patients were sent a generic (SF-12) and a disease-specific QoL questionnaire (EPIC-26) with an accompanying letter and a pre-paid answering envelope. Initially, 36 patients failed to answer, and they received a reminder within 1 month. This yielded 16 more answers.

Data quality

All data entry was done by (KBD). To minimise typing errors, the database was set up like the questionnaire, and followed a pre-scribed codebook [92]. A gold standard for data entry is called “double entry”, but this standard is time and resource demanding [93], and was therefore deselected. Instead, a quality control was made with the procedure as recommended by King et al. [94]. Dataset of 2006–2008: 62/317 (20%) questionnaires were checked. One error was found in questionnaire no. 6003 and corrected.

The dataset was adjusted for missing data, Table 4.

SF-12 and the EPIC domains: urinary incontinence and urinary irritative are not possible to analyse with any missing data [70, 72]. Answers within the domains with missing data are therefore removed from the analysis. The EPIC domains: urinary summary, bowel summary, sexual summary, and hormonal summary allow one missing answer [72]. Outliers were controlled with original data and corrections were documented in file.

Table 4. The number of **removed / cleaned** data in study I

| | SF12 | Urinary summary | Urinary incontinence | Urinary irritative | Bowel summary | Sexual summary | Hormonal summary |
|--|------|-----------------|----------------------|--------------------|---------------|----------------|------------------|
| 2006 n=90 | 13/- | 4/1 | 4/- | 4/- | 9/0 | 5/7 | 7/3 |
| 2007 n=109 | 10/- | 8/3 | 8/- | 7/- | 8/5 | 5/5 | 7/2 |
| 2008 n=118 | 11/- | 5/1 | 5/- | 6/- | 5/7 | 6/3 | 4/2 |
| Completeness in the data to analyse n (317) | 283 | 300 | 300 | 300 | 295 | 301 | 299 |

After the above adjustments of the dataset, the available response rate to analysis in SF-12 was 84% and from 89% of the EPIC domains.

Study II - Randomised controlled trial (RePCa)

This prospective randomised study was ongoing between February 2010 and October 2012. Data were collected on three occasions: 1) before start of radiotherapy (preliminary), 2) at baseline 4 weeks after radiotherapy, and finally 3) at post intervention 6 month after radiotherapy, Figure 3. The results were reported in accordance with the guidelines from the CONSORT statement referring to randomised trials of non-pharmacologic treatment [95] and with graphical methods for reporting complex interventions [96].

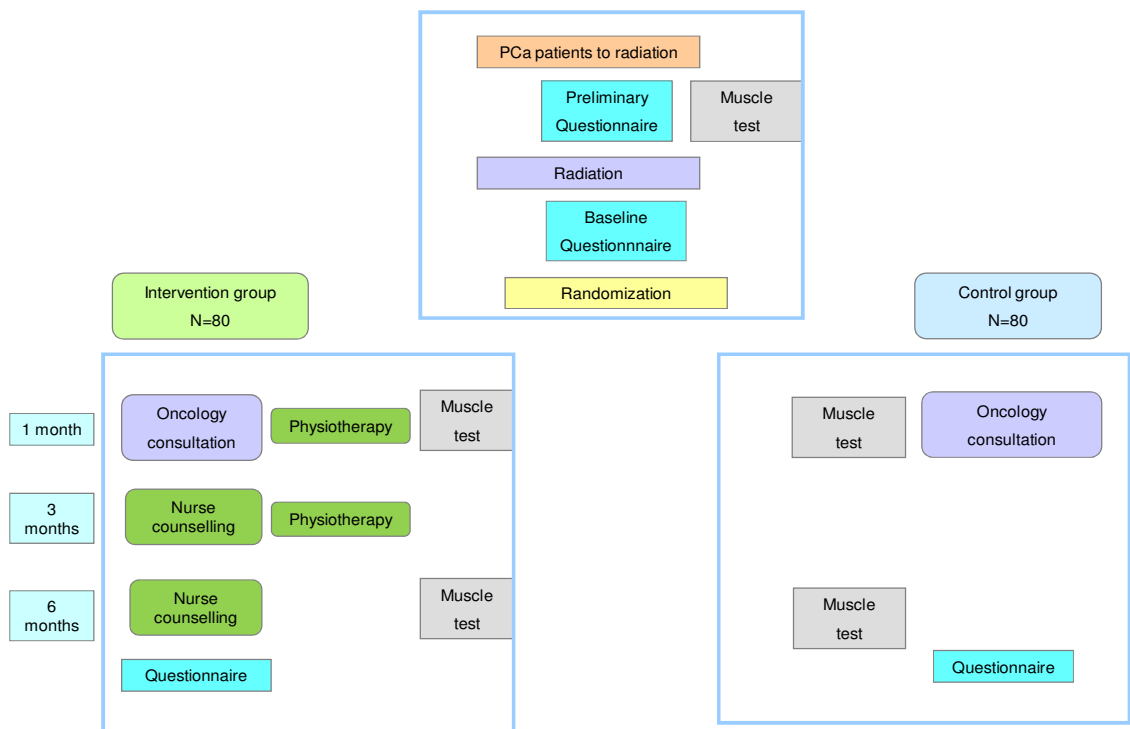


Figure 3. The study design in the RePCa study.

Inclusion and exclusion criteria

Men were eligible if they had localised or locally advanced PCa, were 18 years of age or older, and were referred to curative primary radiotherapy. Men were excluded if they had a prostatectomy, were in palliative treatment, preferred treatment at another hospital, or did not speak Danish.

Primary endpoint

The EPIC-26 urinary irritative sum-score was selected to be the primary endpoint in Study II because this is a frequently registered acute symptom during and after radiotherapy and includes dysuria, hematuria, weak urine stream, frequency, urgency, or urge incontinence [36, 37]. Furthermore, results from Study I showed that 15% of the patients reported moderate-severe urinary problems as late effects with extensively impact on the urinary irritative sum-score, with a mean EPIC 0–100 score of 79.1 (SD 18.9). The primary endpoint was a self-reporting and subjective measurement, and to have an objective measurement, we

supplemented the secondary endpoints with measurements of the pelvic floor, as the pelvic floor function is closely related to bladder capacity or voiding dysfunction [22]. The patients were not informed about the exact primary endpoint of the study.

Data collection and rationale for measurement points

Between February 2010 and January 2012, 161 patients were enrolled in the study. The clinical characteristics were similar for both groups; Table 1 in Manuscript II.

The measurement points were chosen to represent quite different situations. At the preliminary measurement point, the patients were awaiting start of treatment with radiotherapy, and the experience of receiving the cancer diagnosis was expected to be fresh in their minds and the outcome of the disease still unclear. At this point most of the patients had been treated with ADT for about 3 months.

One month after radiotherapy (baseline), some of the patients were expected to have suffered from acute side effects, especially urinary and bowel problems.

Six months after radiotherapy (post-intervention), the situation was expected to be quite different; most patients would have returned to daily living and have received information about their health status.

Medical treatment was not part of the intervention. All participants, irrespective of participation in the allocated group, therefore underwent the same radiotherapy and ADT and physician follow-up 4 weeks after radiotherapy.

Randomisation

Following written consent, patients were randomly assigned to the intervention group or standard follow-up (control-group) in a ratio of 1:1 using a computer random assignment program. The randomisations were handled by the department of Clinical Research, and the allocation sequence was concealed from the research team. Randomisation was done after radiotherapy, and the patients were informed after filling out baseline questionnaires.

Difficulties recruiting patients determined that we also included patients with metastasis to one lymph node (n=6). These patients were stratified, with three patients allocated to each arm; Figure 1 in Manuscript II.

Blinding

In a rehabilitation intervention, it is not possible to blind patients or care providers. However, to avoid detection bias, the three observers who executed the assessments of the pelvic floor were blinded to the allocated group, and patients were told not to inform the observers.

Theoretical frameworks for the intervention

The intervention in Study II was based on the approaches described below.

The Primacy of Caring

The nursing intervention in Study II is above all inspired by Patricia Benner and Judith Wrubel's philosophy of nursing described in: "The Primacy of Caring" [97]. Secondly, Virginia Henderson's methodical approach in the literary classic: "Basic Principles of Nursing" [98] has been applied to ensure that possible problems are identified in accordance with instructions from the Odense University Hospital practice of nursing documentation. Benner and Wrubel's philosophy has also been the primary indicator in the coding of the text material in Study III. This frame of reference is important to have in mind to understand the extent of the intervention. The following chapter describes briefly the focal points in the philosophy of Benner and Wrubel.

Patricia Benner, RN, PhD, FAAN, is a professor in the Department of Physiological Nursing at the School of Nursing, University of California, San Francisco (UCSF), and Judith Wrubel, PhD is a Research specialist in the Department of Medicine, UCSF.

The theoretical perspective taken by Benner & Wrubel is based on the phenomenology of Martin Heidegger and Maurice Merleau-Ponty, and inspired by Dreyfus and Lazarus. Benner and Wrubel's philosophy is that nursing is a caring practice based on perceptions of both mental and physical health and is always situated in a social context. The nurse has to have an open mind to find out what the patient cares about (someone or something), and this places the patient in the situation in such a way that certain aspects show up as important. Then the nurse has the possibility of giving help. In other words, caring sets up what counts as stressful and what coping options are available. Regarding Benner & Wrubel, expert oncology nurses set for themselves the goal of understanding the patient's "insiders" illness experience [97].

Motivational Interviewing as a communicative platform

The relationship between patient, relatives, and professionals frames the intervention in the RePCa study. To support a trustful and confidential relationship, communication is essential. The Motivational Interviewing (MI) was selected to be the common communication approach used by nurses and physiotherapists. This method was primarily selected because of its spirit, but after a diagnosis of cancer, a window of opportunity is created for patients to review and maybe modify lifestyle habits [99].

The theory of MI was first described by Professor in Psychology William R. Miller in 1983 based on his experiences in treating alcoholism [100]. The theory has developed over the years with the collaboration of psychologist Steven Rollnick, and the intervention in Study II is based on the MI described in the second edition from 2002 by Miller and Rollnick [101], which has been translated into Danish [102]. MI draws, among other sources, from Carl Rogers' theory of client-entered psychotherapy and Prochaska and DiClementes' model of change [101].

Miller and Rollnick define MI as a “*client-centred directive method for enhancing intrinsic motivation to change by exploring and resolving ambivalence*”[101] p. 47.

The foundation of MI is consistent with the theory of Benner and Wrubel, as MI is based on a humanistic view of humanity, and the patients' responsibility and right of self-determination are in focus. The evidence of MI has been summed up in two meta-analyses [103, 104].

Experienced healthcare professionals can learn to use MI within a few hours of education, and with support they are able to maintain the ability over time [105].

Education of the multidisciplinary team

The seven oncology nurses and the two physiotherapists who performed the intervention were all experienced staff. The nurses were specially trained and examined radiation therapists, and the physiotherapists were skilled within male incontinence. Before the research project was initiated, the multidisciplinary team spent time together on a three-day course with the topics:

- The male perspective [106]
- Prostate cancer
- Radiotherapy and Androgen Deprivation Therapy
- Incontinence and the male pelvic floor
- Sexuality and intimacy

- Depression and fear of recurrence
- Social possibilities, e.g. the Danish Prostate Cancer patients association PROPA [107].

The team was furthermore instructed in a 3-day course of Motivational Interviewing (MI) by two MI trainers from the Motivational Interviewing Network of Trainers in the Nordic countries. The course included theoretical introduction to strategies, and critical dimensions of MI, empathy, and the MI spirit. The course included role playing involving relevant cases of prostate cancer patients and video recording. To support this new knowledge, the course was followed by supervision in real patient situations of the nurses every second month as long as the intervention was ongoing. The physiotherapists were supervised whenever needed.

To clarify whether the nurses competence in MI increased after the supervision phase, and to stimulate self-knowledge and development, the seven nurses in the RePCa team filled out anonymous questionnaires just before the supervision started (January 2011), and after 12 months. The questionnaire was a tool of evaluation developed by University College Lillebælt containing 12 questions regarding the use of MI [108]. The results from a t-test showed a statistically significant increase in mean VAS score (1–10) of 11.7 points $P < .000$ (95% CI 7.7; 15.6). This was a satisfactory improvement; however, some of the nurses still commented on MI as being difficult.

The rehabilitation intervention

Nursing counselling

Nursing intervention in Study II consisted of two sessions, each lasting 40 minutes, performed during the third month and 6 months after radiotherapy. The fundamental basis of the nursing consultations was to know the patient's particular illness trajectory. The aim was to provide psychological support, and to identify problems or dilemmas regarding the disease experienced by the patient and his spouse. Problems that could mean something to him, and he wanted to talk about. The nurses initiated the dialogue based on needs, and if needed the nurse was able to give information about late side effects, make an individual rehabilitation plan with the patient's personal goals, and give counselling regarding toilet habits, smoking cessation, weight control, sexuality, and psychological problems after treatment. The nurse could refer to other collaborators depending on the problem, e.g., doctors, sexologist, or social workers.

Physiotherapy counselling

Physical therapy intervention in Study II consisted of two sessions, each lasting 1 hour, performed on the first and third month after radiotherapy. The aim of the intervention was to identify the patient's need for increased pelvic floor muscle function and general physical activity level.

During the sessions, the patient's own subjective descriptions of his symptoms were explored, including pelvic floor muscle functions such as control over urine, flatulence, and faeces. The patient's level of functioning before the illness and the current level of functioning were identified, as well as the patient's physical activity level. If necessary, patient pelvic floor muscle function could be guided using Biofeedback, a method to help the patients increase their awareness and proprioception of the muscle so that they could discriminate between muscle contraction and muscle relaxation. Biofeedback is in general a technique by which information about a normally unconscious physical process is presented to the patient, in our study as a visual signal [88].

The main problem or problems experienced by the patients were identified in relation to their severity and duration, as well as to whether the problem or problems limited quality of life and activity level. Patient goals were set concerning pelvic floor muscle function and physical activity level.

The second session was used to follow-up on the patient's goals, amending goals and creating new patient-identified goals if necessary. It was possible to refer patients who needed further rehabilitation to a community/municipal training centre.

Pelvic floor muscle function

When identifying pelvic floor muscle function, patients were questioned about their understanding of 1) pelvic floor muscle anatomy and function, 2) how to correctly perform muscle contractions, and 3) the importance of pelvic floor muscle exercises to improve and maintain pelvic floor muscle function. At this point, the physical therapist assessed whether or not the patient required further clarification. If this was the case, the patient was offered the opportunity to decide whether or not they wanted further information.

For patients who required increased pelvic floor muscle function, patient-identified goals were established, i.e. goals expressed by the patients themselves. The physical therapist collaborated with the patient to identify the effort(s) required to meet the goal(s).

Physical activity level

When identifying the patients' general physical activity level, the patients were questioned on their understanding of how physical activity has a positive influence on endurance, muscle strength, balance, and quality of life. For patients who required increased general physical activity, patient-identified goals were established. Based on the patient's preferences, an exercise training programme was established, and the patient was motivated to return to previous sports activities.

Self-training home programme

Through motivational interviewing the physical therapist offered the patient a self-training home programme based on patient-identified goals and the patient's level of muscle function, such as exercise type (strength and/or endurance exercises and at times together with functional activity training), number of repetitions for each exercise, frequency, and how many times the programme should be performed daily.

The physical therapist provided a written pamphlet created specifically for the purpose of this study. The pamphlet contained information about how PCa treatment can affect both physical and general health and a self-training home programme consisting of pelvic floor muscle exercises, exercises for the major muscle groups that included muscle endurance and muscle strength and balance exercises, and pictures of possible exercises. If necessary, general physical activities were recommended, such as daily walks or other similar activities.

Pilot study

A standardised protocol of testing the pelvic floor was developed after pilot tests of seven patients not included in Study II. The pilot study examined the subjects lateral positioning, exact wording of instructions used for each repetition, and avoidance of muscles other than the pelvic floor.

Data quality

All data entry was performed by the first author (KBD). To minimise typing errors, the database was set up like the questionnaire, and followed a prescribed codebook [92]. A

quality control was made using the procedure recommended by King et al. [94]. A dataset of 25/161 (15.5%) questionnaires was checked. No errors were found.

Inter-rater reliability

The tests of the pelvic floor strength were made by three observers. The observers were experienced physiotherapists. The method used to assess how similar the observers performed the digital evaluation was Cohen's kappa (κ), which is the index of choice for measurement of observer agreement in categorical, nominal data because it corrects for agreement expected by chance alone [109].

Fifteen random records were examined regarding the inter-rater variability between two different observers testing digital evaluation. Each physiotherapist was involved in ten records, Table 10. A κ value of ≥ 0.60 with a $P < 0.05$ was considered adequate.

Reliability between digital palpation and EMG

Correlation between methods of digital evaluation with the Modified Oxford Scale and with EMG was measured with Spearman's correlation. A Spearman correlation is used when one or both of the variables cannot be assumed to be normally distributed, but are ordinal. The values of the variables are converted in ranks and then correlated [110].

Study III - Focus group interviews

A qualitative phenomenological approach was chosen to explore the participants' experiences with treatment and rehabilitation, and on how they interpreted those experiences in a social interaction with fellow patients. Data were formed through narrations from patients participating in focus groups. Focus group interviews give the researchers access to a variety of the participants' ideas, views, and experiences of how to return to everyday life after radiotherapy for PCa. The interactive and synergistic nature of focus group interviews allowed us to explore the participants' experiences with the treatment and rehabilitation.

The phenomenological approach

This study was inspired of the phenomenological approach, a qualitative research tradition with roots in philosophy that focuses on the lived experience of humans. There are two "schools" of phenomenology: descriptive phenomenology developed first by Edmund Husserl and interpretive phenomenology (hermeneutic) described by Martin Heidegger [111]. In the phenomenological approach it is important that the researcher places her prior understanding of the concept in brackets in order to bring the participants' experiences in front.

Study design and participants

Former patients who within the last year fulfilled the complete intervention programme in Study II could be included. In November 2011, 17 former patients were invited to participate in the focus groups planned in January 2012. The invitation included a statement of consent, and a prepaid answering envelope.

To seek a neutral ground, the focus group interviews were held at a convenient location in the Patients' Hotel at Odense University Hospital away from the participants' homes and not directly connected to the Department of Oncology where the treatment was delivered. Two focus group interviews both lasting 2 hours were conducted and recorded. The first author (KBD) moderated the focus groups, and a senior researcher and co-author (LW) assisted during both focus group interviews by supervising, taking notes, watching the time, and asking additional questions. Through the focus group interviews, each participant was encouraged to be honest and candid about his experiences and position regarding the rehabilitation delivered.

To ensure that all participants had ample opportunity to express their own views and experiences, the focus groups comprised a maximum of six to eight patients. We sought

maximal variation in the participants with regard to age and severity of problems during the rehabilitation process as documented in the patient files. Furthermore, the participants were stratified into two groups depending on whether the participant had involved his spouse actively in the nursing consultations and/or the guidance of physiotherapists, or not. A total of 13 patients accepted the invitation and participated in one of the two focus group interviews, as illustrated in Figure 4. One patient refused, and three patients were not able to participate at the suggested time.

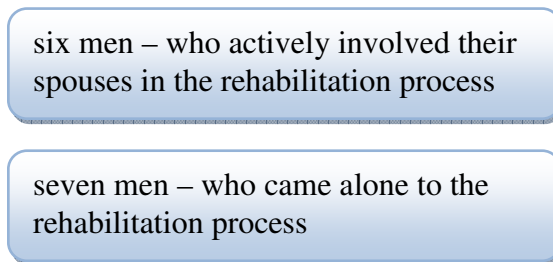


Figure 4. Patients included in Study III.

None of the participants knew each other beforehand, although the treatment with radiotherapy was delivered at the same place, and some of the participants could have met each other in the waiting room. They were in the age range of 66 to 77 years. Educational levels ranged from lower secondary school to professional bachelor's degree. Two participants had a connection to the labour market. Eleven participants were married or lived with a spouse, and two lived alone. None came from an ethnic minority. They all lived in the Southern Region of Denmark; four men in Jutland, eight in Funen, and one in Langeland.

Focus group and appurtenances

First, the focus group was informed about the aim of the study. Each participant was briefly introduced with name and age. Information about educational level or civil status was not shared since we wanted the participants' to feel equal.

The focus groups interviews were guided by the research questions and a semi-structured interview guide. The interview guide was a typically funnel model with a few open questions and then a number of more specific questions at the end. The questions were only asked if the participants did not by themselves answer the questions. To inspire the participants to talk, and remember, appurtenances consisting of pictures from the Department of Radiotherapy and pamphlet/probe from the physiotherapist were placed on the table during the interviews. Both interviews were recorded on two tape recorders. The first author transcribed the interviews as part of the analysis [112]. Data were transcribed in full using a simple list of transcription codes [113]:

| | |
|------------------|---------------------------------------|
| []: | overlaps in speech |
| (): | incomprehensible speech |
| Capital letters: | Speaker underlines with tone of voice |
| [laughter): | other oral expressions |
|: | pause less than 5 seconds |
| [pause]: | pause more than 5 seconds |

Statistics

Data from Study I and III involved descriptive and analytical statistics. Socio-demographic and clinical characteristics for patients were described using means for continuous variables and frequencies for categorical variables.

In Study I, data were divided into three groups, with a median time since treatment of 1.8, 2.6, and 3.6 years. Differences in QoL scores between the groups were tested with one-way analysis of variance (ANOVA) and the chi-square test depending on the nature of variables. The clinical data from records of the 20 non-responders were analysed as well. First, continuous outcome measures were analysed with multiple linear regression models. Second, the individual categorical outcome variables were dichotomised as binary outcomes and analysed with multiple logistic regression models.

In Study II, sample size calculation were calculated by tools created for EPIC [114]. With one primary endpoint, the urinary irritative score, and an effect size of 0.5, a level of significance at 0.05; and a level of power at 80%, 64 patients in each group were necessary. We adjusted for an expected 20% drop-out rate during the study period. As a result, 160 patients had to be randomised. The Department of Oncology at Odense University Hospital treated in 2009 about 140 patients with curative intended radiotherapy. We estimated it possible to recruit 110 patients annually, but during the study period another hospital in the Region of Southern Denmark started to offer radiotherapy to PCa patients. Consequently, the period of inclusion was extended to last from February 2010 to January 2012.

To compare differences between groups from baseline to post-intervention, the analyses were made with multiple linear regression models adjusted for baseline score or Wilcoxon rank-sum test. Cohen's *d* at 6 months was calculated as effect size, by dividing group mean differences with mean standard deviation. Subgroup analyses were conducted to find the patients who benefitted the most from the intervention, and correlations between variables were tested with linear regression models. Inter-rater reliability of the pelvic floor observers was tested in a random sample of 15 records with Cohen's Kappa coefficient. Intervention and control groups were analysed with intention-to-treat, meaning that no patient was withdrawn from the analysis. Data from the 41/48 patients who refused to participate in the randomised part of the study but replied to the questionnaire before radiotherapy, were analysed as well.

Statistical analyses were performed using STATA version 11 [115]. *P* values < 0.05 were considered statistically significant. As analyses were exploratory; all reported *P* values were 2-sided.

Qualitative analysis

Data from Study III were transferred to NVIVO 9 [116, 117]. The text analysis was made in two parts. At first, a content analysis was done consisting of meaning condensation [118], which gave the opportunity to understand what was of most importance for these men during their trajectories [97]. Second, to strike a balance between the interaction in the group and the content of the data [113], the interaction between the men was analysed inspired by Goffman's approach to social interaction. The patients' statements were translated verbatim into English by a native English speaker.

Meaning condensation

The content analysis was inspired by the methods developed by the American psychologist Amedeo Giorgi. Giorgi's method of meaning condensation was developed on the basis of phenomenological philosophy. The analysis of the focus groups involved five steps [118, 119]:

1. Read and reread the whole interview in order to gain a sense of the whole.
2. Identify the "natural meaning units" as expressed by the informants.
3. Identify the dominant themes in the meaning units, as understood by the researcher.
4. Relate the meaning units to the research question.
5. Condense the themes in descriptive statements.

Social interaction

The interaction analysis, which was secondary to the meaning condensation, was inspired by the Canadian micro-sociologist Erving Goffman's main point: "*How people in social interaction attempt to sustain their self-narratives*" Goffman believed that individuals will attempt to control or guide the impression that others might have of them by changing their setting, appearance, and manner. At the same time, the person the individual is interacting with is trying to form and obtain information about the individual. He furthermore believed that all participants in social interactions are engaged in certain practices to avoid being

embarrassed or embarrassing others. This led to Goffman's dramaturgical analysis, in which people's interaction with most others happens "front stage", but that there is a hidden or private place "back stage" where the individual can be themselves and get rid of their role or identity in society [120].

Ethical considerations

Ethical aspects were in all stages of the study given careful considerations, and the studies were conducted in compliance with the Helsinki Declaration [121]. The Ethics Committee of the Region of Southern Denmark approved the studies (ref. no. S-20090142). The Danish National Data Protection Agency (ref. no.2009-41-3948; ref. no. 2012-41-1175) gave their formal consent. The study was performed in accordance with the Ethical Guidelines for Nursing Research in the Nordic Countries (SSN) [122]. The ClinicalTrial.gov identifier for Study II is NCT01272648.

All participants gave informed verbal and written consent. It was emphasised that the anonymity of the participants would be maintained in the reporting of results.

The studies included questions and interventions regarding the genital area, and this could have made them intimate and tabooed. The establishment of a relationship of trust and confidence between the professionals and the participants had first priority, and was a precondition for a successful intervention. The fact that 6/7 of the nurses and all physiotherapists were women has generated considerations about the influence of gender on the intervention delivered, and this question was included in the interviews in Study III.

In some countries, rehabilitation after cancer treatment is integrated into the protocol used, and is a legal right [123]. This is not the case in Denmark, and therefore the control patients could be stratified to a no rehabilitation group.

Results

Study I – Cross-sectional survey

Aim

To identify the extent and category of late effects after radiotherapy for localised or locally advanced PCa, and to identify the patients most exposed to late effects.

Summary of main result Study I

The main results are reported in Paper I [124]. Study I showed a diversity of problems after radiotherapy, as listed in Table 5. Patients who smoked, were severely obese, or lived alone had a reduced QoL.

Additionally results

The patients (n=317) stated a history of cancer in the family as follows: breast cancer: 15.0%, most among mothers or sisters; ovarian cancer: 4.2%, most among mothers; prostate cancer: 20.1%, most among fathers or brothers.

Table 5. QoL in 317 prostate cancer patients 1.5 to 4 years after radiotherapy.

| SF-12 | n | % |
|---|-----|------|
| Moderate-severe poor physical condition | 64 | 20.3 |
| Moderate-severe poor health | 61 | 19.3 |
| Health limits activities | 101 | 32.4 |
| Health limits climbing several flight of stairs | 149 | 47.2 |
| Need of personal care | 8 | 2.5 |
| Have accomplished less due to physical health | 103 | 33.3 |
| Limited in the kind of work | 95 | 31.7 |
| Have accomplished less due to emotional problems | 78 | 25.2 |
| Were less carefully than usual | 42 | 14.0 |
| Pain complicates daily activities | 32 | 10.3 |
| None of the time or only a little time felt calm and peaceful | 17 | 5.5 |
| None of the time or only a little of the time felt a lot of energy | 55 | 17.7 |
| All of the time or most of the time felt downhearted and blue | 19 | 6.2 |
| Physical health or emotional problems interfered with social activities | 13 | 4.1 |
| EPIC-26 | n | % |
| Moderate-severe urinary problems* | 47 | 14.9 |
| Moderate-severe bowel problems | 36 | 11.4 |
| Moderate-severe sexual problems | 206 | 68.4 |
| Moderate-severe problems with hot flushes | 93 | 30.3 |
| Moderate-severe problems with breast tenderness | 30 | 10.2 |
| Moderate-severe problems with depression | 36 | 12.0 |
| Moderate-severe problems with loss of energy | 68 | 22.2 |
| Moderate-severe problems with weight change | 80 | 26.1 |

*Moderate-severe problems indicate patients answering 4 or 5 on the question: How big a problem has your urinary function been for you during the last 4 weeks?

Study II - Randomised controlled trial

Aim

To examine whether an individually focused multidisciplinary intervention influenced the generic and specific QoL and coping strategies after radiotherapy for PCa.

Summary of main result Study II

The main results are reported in Manuscript II. The main result showed that clinically significant improvements were seen in the intervention group compared to the control group regarding the primary end-point self-reported urinary irritative sum-score (5.8 point (CI 1.4; 10.3, $P = 0.011$)), overall urinary sum-score, hormonal sum-score, and PCS QoL.

Additionally results

The moderate-severe problems between groups at 6 months after radiotherapy (post-intervention) were improved in most of the items in favour of the intervention group, as shown in Table 6.

Table 6. QoL in 161 prostate cancer patients 6 months after radiotherapy.

| SF-12 n(%) | Control group n=77 | Intervention group n=76 |
|---|--------------------------|-------------------------------|
| Moderate-severe poor physical condition | 12(15.6%) | 7(9.2%) |
| Moderate-severe poor health | 12(15.6%) | 6(7.9%) |
| Health limits activities | 28(36.4%) | 17(22.4%) |
| Health limits climbing several flight of stairs | 35(45.5%) | 29(38.2%) |
| Need of personal care | 4(5.2%) | 1(1.3%) |
| Have accomplished less due to physical health | 29(38.2%) | 20(26.3%) |
| Limited in the kind of work | 26(33.8%) | 17(22.7%) |
| Have accomplished less due to emotional problems | 23(30.3%) | 15(20%) |
| Were less carefully than usual | 11(14.3%) | 8(10.5%) |
| Pain complicates daily activities | 10(13.0%) | 4(5.3%) |
| None of the time or only a little time felt calm and peaceful | 5(6.5%) | 5(6.6%) |
| None of the time or only a little of the time felt a lot of energy | 15(19.5%) | 10(13.2%) |
| All of the time or most of the time felt downhearted and blue | 2(2.6%) | 3(3.9%) |
| Physical health or emotional problems interfered with social activities | 0(0%) | 2(2.6%) |
| EPIC-26 n(%) | Control group | Intervention group |
| Moderate-severe urinary problems* | 9(11.7%) | 3(4.0%) |
| Moderate-severe bowel problems | 9(11.7%) | 5(6.6%) |
| Moderate-severe sexual problems | 50(67.6%) | 43(60.6%) |
| Moderate-severe problems with hot flushes | 37(48.1%) | 36(48%) |
| Moderate-severe problems with breast tenderness | 6(7.8%) | 7(9.2%) |
| Moderate-severe problems with depression | 10(13.0%) | 2(2.7%) |
| Moderate-severe problems with loss of energy | 17(22.1%) | 10(13.3%) |
| Moderate-severe problems with weight change | 16(20.8%) | 13(17.3%) |

*Moderate-severe problems indicate patients answering 4 or 5 on the question: How big a problem has your urinary function been for you during the last 4 weeks?

Inter-Rater Reliability

Inter-rater reliability was calculated between the three blinded observers testing the pelvic floor with the Modified Oxford Scale, Table 7. A κ value of ≥ 0.60 with a $P < 0.05$ was considered adequate.

Table 7. Kappa coefficient between the three blinded observers.

| Modified Oxford Scale | Kappa (κ) | Physiotherapist A against B & C | Physiotherapist B against A & C | Physiotherapist C against A & B |
|-----------------------|--------------------|---------------------------------|---------------------------------|---------------------------------|
| Muscle strength | | 0.84 ($P < 0.001$) | 0.83 ($P < 0.001$) | 0.72 ($P < 0.001$) |

Reliability between digital palpation and EMG

The pelvic floor strength was measured before radiotherapy, 1 month after, and post-intervention. The pelvic floor results are given in Table 8.

At post-intervention in the overall population, a significant correlation was found between muscle strength measured by digital evaluation and EMG $\rho = 0.5698$ ($P < .001$).

Table 8. Pelvic floor muscle strength in prostate cancer patients treated with radiotherapy in RePCa: a randomised controlled rehabilitation study.

| Pelvic floor Muscle strength mean (95% CI) | Intervention group n=79 | | Control group N=82 | | P- value* | |
|---|--|--------------------------------|-----------------------|--------------------------------|---------------------|-----------------------|
| | Study population pre- radiation | post- radiation baseline | post- intervention | post- radiation baseline | | post- intervention |
| no. of participants | n=156 | n=73 | n=68 | n=75 | n=71 | |
| Digital evaluation ^a | 4.0 (3.8;4.1) | 3.8 (3.5;4.0) | 3.9 (3.6;4.1) | 3.8 (3.6;4.1) | 3.7 (3.5;4.0) | NS |
| Static strength no. of seconds to hold one contraction | 34.4 (31.1;37.7) | 35.2 (30.2;40.2) | 36.1 (31.0;41.2) | 31.6 (26.6;36.6) | 32.9 (28.0;37.8) | NS |
| Dynamic strength no. of contractions during 60 seconds | 22.2 (19.9;24.5) | 21.2 (17.7;24.7) | 22.7 (18.9;26.5) | 19.1 (15.9;22.3) | 19.2 (15.9;22.6) | NS |
| no. of participants | n=156 | n=72 | n=66 | n=71 | n=71 | |
| EMG average activity (μ V) | 38.2 (34.8;41.6) | 31.3 (27.9;34.8) | 24.7 (21.7;27.7) | 31.6 (27.3;35.9) | 23.3 (20.4;26.2) | NS |
| EMG average rest (μ V) | 6.8 (6.2;7.5) | 5.8 (5.0;6.6) | 4.8 (4.0;5.5) | 5.5 (4.9;6.1) | 4.9 (3.6;6.2) | NS |

^aMeasured by Modified Oxford Scale 0-6.

^{*}Post-intervention differences between groups. Wilcoxon Sign-rank test. Reported *P* values are 2-sided and < 0.05 was considered statistically significant.

Coping

The mental adjustment to cancer styles was measured before radiotherapy, 1 month after, and post-intervention, Table 9, showing a stable fighting spirit in the intervention group compared with controls.

Table 9. Mental adjustment styles pre-radiation, post-radiation, and post-intervention 6 months after radiotherapy.

| Mini-MAC | Intervention Group | | | Control Group | | | <i>P</i> * |
|-------------------------------|-----------------------|------------------------------------|---------------------------|-----------------------|------------------------------------|---------------------------|------------|
| | Mean (95%CI) | | | Mean (95%CI) | | | |
| | pre-radiation n=75 | post-radiation baseline n=77 | post-intervention n=76 | pre-radiation n=79 | post-radiation baseline n=76 | post-intervention n=73 | |
| Fighting spirit | 12.0 (11.4;12.6) | 12.1 (11.6;12.6) | 12.1 (11.5;12.6) | 12.2 (11.6;12.7) | 12.2 (11.6;12.8) | 11.6 (11.0;12.2) | 0.025 |
| Fatalism | 12.7 (12.1;13.3) | 12.5 (11.9;13.1) | 12.3 (11.7;13.0) | 12.5 (11.9;13.1) | 12.3 (11.7;12.9) | 12.2 (11.6;12.8) | 0.991 |
| Cognitive avoidance | 9.9 (9.3;10.5) | 9.6 (9.0;10.3) | 9.7 (9.0;10.3) | 9.8 (9.2;10.4) | 9.7 (9.0;10.5) | 9.8 (9.0;10.5) | 0.853 |
| Anxious preoccupation | 16.6 (15.4;17.7) | 15.4 (14.3;16.6) | 14.8 (13.9;15.7) | 15.6 (14.7;16.6) | 14.5 (13.4;15.5) | 14.2 (13.1;15.3) | 0.841 |
| Helplessness/ Hopelessness | 11.1 (10.4;11.8) | 10.9 (10.2;11.7) | 10.3 (9.6;10.9) | 11.2 (10.4;11.9) | 10.5 (9.7;11.3) | 10.7 (10.0;11.5) | 0.076 |

*Numbers refer to the *P* value between groups at post-intervention in a linear regression model adjusted for baseline score.

Reported *P* values are two-sided, and *P* < 0.05 considered statistically significant.

Study III – Focus group interviews

Aim

The aim of this study was threefold: First of all, we wanted to broaden our understanding of the patients' experiences regarding the treatment and the participation in the rehabilitation offered in Study II. Secondly, we wanted to learn how these men coped with the possible adverse effects in everyday life. Finally, we wanted to explore the men's attitude towards spousal involvement in rehabilitation after treatment with radiotherapy for prostate cancer.

Summary of result Study III

The main results are reported in paper III [125].

The main results showed that rehabilitation after treatment is seen as an important support, but calls for awareness that interventions should take male culture into account. Spousal involvement in rehabilitation may reflect the relationship the couple had beforehand, and it is therefore important to let the man decide whether or not he wants to involve his spouse. ADT severely influences masculinity and male identity and in consequence affects everyday life; therefore patients must be given careful information about ADT and adverse effects.

Discussion

Methodological considerations

This PhD project used quantitative and qualitative methodologies, as we saw the methods as complementary, with the aim of uncovering different perspectives in a novel research area [126]. As underlined by Albaugh and Hacker, quantitative and qualitative methods of QoL research should be combined to capture the broad range of experiences among men with PCa [127]. However, the use of different methodologies calls for awareness of various epistemological traditions to obtain a richer and more comprehensive picture of the issue under investigation [128], in this case rehabilitation of PCa patients.

Because different terms are used, the discussion about the validity is discussed separately for the quantitative studies and the qualitative study.

Rehabilitation as a definition in research

Rehabilitation is as described in the definition page 6 based on a holistic view of the cancer patient and his family, not only treating the disease, but considering both early and late adverse effects with regard to the patient's daily life, family, resources, occupational life, leisure activities, etc. Rehabilitation can therefore be seen as an essential part of the continuing health care of cancer survivors [123]. However, in research this broad definition can be in conflict with the precondition in randomised controlled trials that one or a few primary endpoints are selected. In Study II, we selected the urinary irritative sum-score and on the basis of this primary endpoint determined whether the intervention was successful or not. As Wade et al. point out, rehabilitation research involves a complex, and sometimes complicated intervention, and should have at least one "process" measure, and not rely on a single primary outcome [18]. Thus, Study III was our "process" measure to support or explain the findings from Study II.

Internal validity

Internal validity refers to the extent to which it is possible to conclude that the independent variable influences dependent variable inference [111]. To maintain internal validity in the quantitative studies, we attempted to minimise systematic errors, e.g., selection bias, information bias, and confounding bias [129].

Selection bias stems from the procedure of selecting subjects for the study. Therefore in Study I, we double-checked in the treatment calendar Mosaic and the patients administrative system FPAS whether all patients treated between 2006 and 2008 had been found. In Study II, a double-check was done by the secretarial staff and the nurses in the prostate cancer team in order to find eligible patients.

To minimise selection bias, only a few exclusion criteria were used, and both studies came out with high response and adherence rates. The non-responders in Study I ($n = 20$) were significantly younger, and significantly more of the non-responders in Study II ($n = 48$) were classified in a marginally lower risk-group. However, a strength in Study II was that most of the non-responders filled out questionnaires before radiotherapy, and these showed no differences in the adverse effects before radiotherapy.

Currently, radiotherapy to PCa patients is offered in a uniform way at all Danish centres, and therefore the patients referred to our study were comparable to other primary PCa patients treated with curative intended radiotherapy.

Information bias arises due to errors that cause misclassification of patients. To minimise information bias, the patients were encouraged to fill out every questionnaire. When possible, the questionnaires were checked by a nurse to achieve good data quality.

Confounding bias arises when there is a mixing or confusion of known or unknown variables influencing the effects. To counteract confounding bias, the randomised design in Study II served to distribute confounders equally between groups. One example of a confounder could be a urine infection causing irritative urinary symptoms. Another possible confounder could be medication prescribed to treat urinary tract symptoms. We did not register this information, but presumed an equal distribution between intervention and control groups. The analysis with multivariate regression models furthermore took realised confounders into account, e.g., age and time since radiotherapy in Study I. Several possible confounders were checked in Study II, e.g., age, BMI, marriage status, and smoking, but were not found significant.

Bias in the qualitative Study III, in the sense of undesirable or hidden skewness, was counteracted by using two researchers to supplement and contest the statements [126].

Furthermore, reflexivity was sought by explicating the researchers' preconceptions and meta positions.

As noted, consideration about the researchers pre-understanding in qualitative research is important and attempted to be explicated. In quantitative research, this is often not required as

the researcher is considered neutral. However, we have realised that a shared precondition between the different methods is that the researchers pre-understanding could influence every research process, especially in the interpretation of data. Therefore, previous agreements about the hypothesis in the quantitative studies were followed during analysis and interpretation.

External validity

External validity refers to the extent to which the research findings can be generalised to other settings or samples [111].

The relatively large number of patients in Study I and the RCT design with baseline homogeneity in Study II allow the possibility to generalise the results to a larger but similar population. Men who attended the Department of Oncology and entered the studies lived in cities and towns as well as rural areas of Denmark, and the samples were considered representative. However, only one patient in the RCT was not an ethnic Dane, and this limits the generalisation from the findings into a broader context.

The qualitative study give no opportunity to generalise in the same way, but as Malterud describes, qualitative research methods are founded on an understanding of research as a systematic and reflective process for development of knowledge that can be contested and shared, implying ambitions of transferability beyond the study setting, and therefore the contextual background material, such as demographics and study setting is explained, and the interpretation of the analysis is described seeking a transparent, systematic procedure [126]. The sample size with two focus groups was considered adequate as this study was a supplementary study and because we reached data saturation [113]. Giorgi's analysis relies solely on the researcher. His view is that it is inappropriate to return to the participants to validate the findings or to use external judges to review the analysis [111].

Reliability

Reliability refers to the degree of consistency with which an instrument measures the characteristics it is designed to measure [111]. Each of the applied methods had its strengths and weaknesses. In the following section the measurements used will be discussed.

Questionnaires

QoL is a multidimensional construct generally consisting of physical, psychological, and social dimensions [130], and that is why a combination of generic, disease-specific, and coping questionnaires was selected.

In Study I, SF-12 and EPIC-26 were used together as recommended [72]. In Study II, the SF-12 and EPIC-26 were supplemented with the mental adjustment questionnaire MiniMac. The questionnaires in the quantitative studies were all well validated and had undergone comprehensive evaluation of quality [131].

The generic QoL questionnaire SF-12 has been valid in detecting changes between groups associated with physical and mental health [70]. The reliability of SF-12 was tested in two datasets and showed a test-retest summary measure of 0.89 in the United States and 0.86 in the United Kingdom. The SF-12 is widely used, and Danish people are used to fill out this kind of questions, e.g., in the large national health survey [132]. SF-12 demands a close review with the data quality as the sum-scores PCS and MCS cannot be calculated if one answer is missing. Furthermore SF-12 is licensed with a relatively large fee, which weighs heavily in a research budget.

The disease-specific EPIC-26 was considered a natural choice because it especially addresses PCa patients' unique situations [72]. In our studies, the questions were well understood, and the patients felt that it was easy to answer them. The EPIC questionnaire consisted at first of 56 questions, but during the development to EPIC-26, questions were removed, e.g., about the time-frame of urinary urgency problems and questions about sexual libido. The lack of these questions was unfortunate in our studies because irradiated men often have urinary urgency problems especially at night and have problems with affected libido due to ADT.

The MiniMac was developed for cancer patients [78], and has been validated in a Norwegian setting [82] but not in a Danish setting. Although Danish and Norwegian societies have common characteristics, this may have affected some of the answers, and especially one question regarding faith: "I have surrendered to God" was by some patients seen as provocative. Danish society has moved into a more secular culture, and questions about

religion and faith are for some more taboo than questions about sexuality. An argument supported by the findings from the qualitative study; the men did not want to talk much about faith but happily shared problems about declining sexuality.

The high response-rate in completing questionnaires in Study I (94%) constituted a solid and valid basis for the survey. Likewise, the response rate in Study II (92%) and the repeated questionnaires validated the answers.

Measurements of the pelvic floor

To support the patient-reported data in Study II, we used methods measuring the strength of the pelvic floor as surrogate markers [133], assuming a causal connection between pelvic floor strength and urinary problems [67].

Digital evaluation was made with the modified Oxford Scale 0–6. We saw no ceiling effect as only 6 (4%) of the examined patients reached the maximal score. The inter-rater reliability scores between the blinded observers furthermore confirmed this measurement as reproducible. The measurement of EMG was an additional objective measurement and proved to be a sensitive instrument, showing a decline in the pelvic floor strength during the patient trajectory from before radiotherapy to 6 months after.

The intervention

The multidisciplinary multimodal intervention in Study II was designed to counteract the complexity of physical and emotional problems an irradiated PCa patient may experience during transition from patient to survivor. However, the shortcoming of a combined programme like this is to determine which elements were responsible for the effects found, and this challenges the assumptions made in traditional medical trials [134].

Unfortunately, the timeframe of this PhD projects caused some constraining factors, since the results from Study I could have focused the intervention in Study II even more on the smokers, the severely obese patients, and the men living alone.

The design of Study II with home-based training allows no assessment of the patients' pelvic floor exercise and physical activity. Physical activity could have been assessed, e.g., with the Godin Leisure-Time exercise questionnaire [135]. However, this scale was not developed for cancer patients and was therefore deselected. Despite the low-impact intervention and the theoretical risk that patients from the control group could make pelvic floor exercises by themselves, the results showed an effect. This could indicate that even greater effects could be

achieved if the pelvic floor exercises were supervised to bring the intensity to a higher level, as has been mentioned as an important issue in a recent review examining exercise interventions to cancer patients in general [136]. Due to concerns about the impact of radiotherapy on the pelvic floor muscles, the intervention started 1 month after radiotherapy, although we are aware of the recommendation that rehabilitation is started at diagnosis. Some of the patients complained of rectal tenderness when pelvic floor strength was tested, and this indicates that this was a correct decision. However, counselling by the nurse could have started during treatment without any complications.

The use of motivational interviewing as the common communicative platform between nurses and physiotherapists was shown to be appropriate. First of all, it encouraged the patients to talk about their own agenda. Second, if the patients gave any kind of hint of a wish to change lifestyle, the health professionals were able to investigate his motivation and to support him. However, the target group were elderly men, and some of them were accustomed to letting the health professionals decide what to talk about, and this communicative u-turn required adaptation by both patients and professionals. Bennett et al. have shown that motivational interviewing promotes increased physical activity in a mixed population of cancer survivors [137]. However, our study did not focus on motivational interviewing as the primary intervention but as one of more components to reach improvements with regard to irritative urinary symptoms.

Discussion of the findings

This section discusses the results of the thesis in a broader context.

Study I showed that PCa patients treated with radiotherapy and ADT experienced serious late physical and psychosocial problems. Furthermore, that smoking, severe obesity, and living alone were negatively predictors of QoL.

Study II showed that a multidisciplinary rehabilitation programme consisting of individually targeted psychosocial support by a nurse and physical therapy counselling were able to facilitate statistically significant and clinically relevant improvements in self-reported urinary irritative symptoms, overall urinary symptoms, hormonal symptoms, and PCS QoL in the intervention group. These changes were accompanied by a stable fighting spirit to face the new daily life.

Study III revealed that the patients saw the rehabilitation as supportive, but calls at the same time for awareness that each component of the intervention take male culture into account.

Spousal involvement in the rehabilitation may reflect the relationship the couple had beforehand, and it is therefore important to let the man decide whether or not he wants to involve his spouse. ADT severely influences masculinity and male identity, and in consequence affects everyday life; therefore patients find information about ADT and adverse effects important.

Late adverse effects

In accordance with our results, others have found that radiotherapy and ADT reduce QoL [16, 17, 138]. However, most studies investigated patients with a more beneficial stage of disease or without ADT. Others studies have confirmed the impact of smoking as substantial on bowel problems [139, 140], while the impact of obesity [17] and the impact of living alone are other known factors important for QoL [141, 142]. However, no previous study has brought this knowledge into the discussion about rehabilitation.

Irritative urinary symptoms

Our result showed clinically relevant and statistically significant improvements in self-reported irritative urinary symptoms in the intervention group as hypothesised. To estimate the magnitude of the effect, we calculated Cohen's *d* between the intervention and control group. Although Cohen's *d* may be difficult to interpret in a clinical setting, it is often used to compare RCT studies with similar study design features [143]. However, the interpretation of an effect size still requires evaluation of the meaningfulness of the clinical change, and Osaba et al. have shown that at least a 5-point change is clinically significant on a 0–100 scale, although this was not PCa patients but breast and lung cancer patients with different symptoms [144]. The meaningfulness was furthermore confirmed by the patients included in Study III, as they experienced the intervention as useful in everyday life.

We are not aware of other studies examining the effect of rehabilitation on irritative urinary symptoms after radiotherapy and ADT in a randomised setting, but components of the intervention were inspired by others who have successfully investigated urinary problems with pelvic floor exercises in PCa patients treated with prostatectomy and showed a decreased duration of symptoms and degree of incontinence [10-13].

The choice of irritative urinary symptoms as primary outcome in Study II was due to awareness that these symptoms are frequent and closely related to radiotherapy.

RCT studies with physical exercises in irradiated PCa patients but using different endpoints have supported our result that physical exercise benefits the patients [56-58, 61, 145].

However, it is not possible to make direct comparisons between these studies and ours because our intervention was multimodal, and none of these studies had irritative urinary symptoms as primary endpoint.

Only two multimodal studies with a self-management approach to PCa patients combined physical and physiological components. Zhang et al. (n = 29) included patients with urinary incontinence 6 months post-surgery and offered the intervention group 3 month of educational, behavioural, and psychosocial support and practice of pelvic floor exercises. This study showed an improved continence associated with reduced depression and symptom distress over time, but only a weak effect on QoL. The Swedish “Between Men” study from Berglund et al. included PCa patients (n = 211) with different stages and treatments, hence 21 with radiotherapy, in a rehabilitation programme consisting of four groups: physical activity, information, combined information and physical activity, and controls. The study showed no effect on anxiety or depression, perhaps due to a lack of power [146]. Thus, at the time of writing there is a lack of multimodal intervention studies targeted PCa patients, but several studies are in progress [147-149].

We found that patients with objective and subjective impairments at baseline benefitted the most, and this may lead to a further discussion and studies to define how patients can be selected for intervention.

Secondary outcomes

The intervention furthermore reduced the overall urinary and hormonal problems and increased PCS QoL. The self-reported urinary improvements were in contradiction to the clinical measurements of the pelvic floor, since the pelvic floor strength was stable as judged by repeated digital evaluation, and declined as judged by EMG. Therefore, there was no clear-cut causal relationship between the subjective dimensions of QoL and the objective measurements of the pelvic floor. However, pelvic floor muscle strength is of some importance for urinary irritative sum-score, as the intervention improved urinary irritative sum-score especially in patients with impaired muscle strength after radiotherapy. Since this is the first study to investigate the pelvic floor in PCa patients treated with radiotherapy, it remains to be seen whether the finding can be reproduced in future studies.

However, it could be discussed whether effects from a rehabilitation intervention have to be measurable in an objective way to be called successful, or is it enough to rely on patients' subjective statements of being helped? Anyway, irritative urinary symptoms are clinically meaningful for irradiated patients, and a lot is accomplished if the patients feel helped, as more than every 10th cancer patient feels abandoned by the health care system after being discharged from the hospital, according to a new national survey from the Danish Cancer Society [150].

Most of the mental adjustment styles remained remarkably stable during the patient trajectory except anxious preoccupation, which declined from before radiotherapy to post-intervention in both intervention and control groups. Also, fighting spirit declined in the control group, but remained stable in the intervention group at post-intervention. Only a few studies have used MiniMac to investigate PCa patients, but Cooper et al. investigated 211 Australian patients with early PCa and found that a fatalistic coping pattern at diagnosis predicted a later depression [85].

All data, especially pelvic floor data and coping, were not fully presented in the current papers. Therefore, these data will be addressed in future articles.

Patient perspectives

The patients perspective is important in evidence-based medicine [133], and especially important to investigate in the evaluation of new strategies. The focus groups were investigated in Study III in order to obtain an insight into the patients' experiences with treatment and rehabilitation, and also to learn whether the intervention was feasible, and to understand benefits and disadvantages. Furthermore, the focus groups gave insight into the patients' unconscious needs for peer contact and support, as they really enjoyed being together. The findings of treatment experiences are consistent with other studies [151, 152], but the experience with rehabilitation has provided new knowledge in PCa patients.

Main conclusions

Based on the results from the three studies in this thesis, the following main conclusions were drawn:

Prostate cancer patients treated with radiotherapy and androgen deprivation therapy have serious late adverse effects to deal with including urinary, bowel, sexual, and hormonal problems. The condition of life of living alone and a lifestyle that includes smoking or obesity are associated with late adverse effects.

A multimodal and multidisciplinary intervention of nursing counselling and physical therapy counselling improved early irritative urinary symptoms. The intervention group benefitted by having fewer overall urinary symptoms, less severe hormonal symptoms, and a better physical QoL than did a control group. Furthermore, the fighting spirit in the intervention group was stable. Patients with impairments at baseline benefitted the most.

Patient perspectives on treatment and rehabilitation revealed that androgen deprivation therapy had pivotal influences on daily life, and androgen deprivation therapy-related adverse effects call for more information and attention from professionals. The rehabilitation delivered was experienced as supportive if the intervention was tangible and targeted the individual's premises, and if the patient felt motivated to cooperate with the health professionals.

These results stress the importance and relevance of rehabilitation that both considers and addresses the patients' individual needs.

Implications for clinical practice

To counteract early or late adverse effects after radiotherapy and ADT for PCa, rehabilitation needs a tool box to lean onto. Based on the results from this thesis, it is suggested that:

- Men are informed about the exact risk of late adverse effects after treatment, and especially about the risk if they smoke, are obese, or if they live alone.
- To reduce early irritative urinary symptoms, men can be offered a multidisciplinary programme with nursing psychosocial support, and psychical therapy counselling including pelvic floor exercises, as described in Study II, especially if they have objective or self-reported impairments after radiotherapy.
- Rehabilitation to PCa is tailored to the male culture, so that initiatives appeal to them, and communication about initiatives is aimed directly at the individual.

An even closer cooperation between urologists, oncologists, nurses, and physiotherapists could be rational when a shift towards a combination of follow-up and supported self-management approach is being discussed [153]. However, we have some obstacles in cancer rehabilitation because the common language within rehabilitation, known as the International Classification of Functioning, Disability and Health concept (ICF) [154], is not shared between all involved health professionals. Furthermore, we have to improve coordination of care between primary care providers, e.g., in a shared care model [155], to change patient perspectives from being a cancer victim to a cancer survivor.

Implications for further research

This thesis uncovers a corner of the phenomenon of rehabilitation in PCa care after radiotherapy and androgen deprivation therapy. Further research is important.

Late effects of 3D-CRT radiotherapy for PCa are well described, but interest has been sparse on explanatory factors involving why and how patients are able to be rehabilitated. Study I showed that smoking, obesity, and living alone were factors with a significant negative impact on QoL after radiotherapy for PCa. This knowledge may guide future rehabilitation research. Future studies could initiate rehabilitation at diagnosis and before treatment. More studies are needed to clarify the exact intervention needed in order to address different impairments. Likewise, there is a lack of knowledge of other explanatory factors regarding late adverse effects, e.g., comorbidity, and/or medication. The radiation dose in this study had no impact on QoL, but the importance of the treated target volume/radiation field remains to be clarified.

Hot flushes and affected sexuality were in all three studies described as the most frequent symptoms. Further intervention studies are needed to deal with these symptoms.

The intervention in Study II achieved to alleviate irritative urinary symptoms. However, further research is needed to adjust the intervention to the target group, and to clarify long-term effects. Follow-up studies are needed, and studies with focus on sub-groups with impairments at baseline are important. The significant decline in the pelvic floor muscle strength seen in both groups would be interesting to investigate in depth.

Regarding the male perspective of coping with PCa and adverse effects, it is important to clarify the exact intervention wanted and needed. Men need tangible interventions, but maybe more innovative interventions are also needed? One example of this is the FC Prostate project from (CIRE) Rigshospitalet, which investigates PCa patients playing football as a combined physical and psychosocial intervention. Other self-management interventions combining health promotion with psychosocial support, including new technology, e.g., internet blogs, smartphones, and apps, could be tailored to the specific male culture [156]. The male perspective after PCa has to be seen in relation to the psychosocial environment, and those giving supportive care must not forget to include the family involved.

Summary

This PhD study was carried out during my employment at the Institute of Clinical Medicine, University of Southern Denmark, and in affiliation with the Department of Oncology at Odense University Hospital.

Prostate cancer is the most common male cancer. More men are long-term survivors after prostate cancer because of improved treatment. Focus is increasingly on the adverse effects that may result due to the disease and treatment and the rehabilitation interventions needed to counteract these.

The aim of this PhD study was to investigate rehabilitation after radiation and androgen deprivation therapy for prostate cancer. The study has a special focus on acute adverse effects, late adverse effects, and the patient's quality of life in relation to achieving the tools to master these consequences.

The study includes three studies presented in two papers and one manuscript. The studies used different methodological approaches: a cross-sectional study in the form of a questionnaire, a randomised clinical controlled trial, and a qualitative study with focus group interviews.

In the first study (Paper I) general and disease-specific quality of life were studied in 317 previously irradiated patients using questionnaires SF-12 and EPIC-26. The results showed that quality of life was particularly affected in patients who live alone and have a lifestyle involving smoking and obesity.

In the second study, RePCa (Manuscript II), 161 patients were randomised to intervention (n = 79) or control (n = 82). The intervention consisted of an individually tailored rehabilitation programme with psychosocial support from nurses, and physiotherapy guidance in self-managed pelvic floor exercises and physical training. The primary endpoint was an irritative urinary summary score, and secondary endpoints were overall quality of life, urinary, bowel, sexual or hormonal problems, strength of the pelvic floor, and coping. The intervention group 6 months after radiation therapy reported significantly fewer irritative urinary symptoms than the control group (Cohen's $d=0.40$; $P=0.011$), fewer overall urinary symptoms ($P=0.023$), less hormonal problems ($P=0.018$), better physical quality of life ($P=0.002$), and retained the coping strategy called fighting spirit ($P=0.025$). Both treatment groups had a decrease in the strength of the pelvic floor musculature, measured by EMG ($P=0.001$). Analysis showed that patients who live alone or who had impairments at baseline had the greatest effect of the intervention.

The third study (Paper III) consisted of two focus group interviews with 13 men (66–77 years). The informants were men who completed the rehabilitation process in Study II. One focus group consisted of men who came alone to the intervention, and the second focus group of men who had actively involved their partner in the process. Focus group interviews lasted approximately 2 hours and were transcribed verbatim. A thematic interview guide was used, and in a phenomenological approach inspired by Giorgi condensation of meanings was used as an analytical tool. In addition, the social interaction in the focus groups was analysed. The study revealed that especially androgen deprivation therapy affected masculinity and identity, elucidating a need for improved information in this field. The men mastered life with a singular male humour. Whether rehabilitation was perceived as useful depended on the health professional's specific approach and the patient's motivation and ability to translate new knowledge into strategies in everyday life. Involvement of a partner can be a support but should be up to the individual patient.

Conclusion: The quality of life and living conditions have consequence for the incidence of late effects after radiotherapy and androgen deprivation therapy for prostate cancer. A multidisciplinary rehabilitation intervention may reduce acute irritative urinary symptoms and improve quality of life. Also, the approach of the health professionals in the intervention and the patient's ability and motivation to contribute to health improvement are important factors.

Summary in Danish (Dansk Resumé)

Denne Ph.d. afhandling blev udført under min ansættelse på Klinisk Institut, SDU, tilknyttet Onkologisk afdeling, OUH.

Prostatakræft er den mest hyppige mandlige kræftsygdom. Flere mænd overlever prostatakræft og lever længe på grund af forbedret behandling. Fokus rettes i stigende grad på de følgevirkninger som sygdom og behandling kan medføre, samt på de rehabiliteringsinterventioner som kan modvirke disse.

Formålet med dette Ph.d. studie var at undersøge rehabilitering efter stråle- og hormonbehandling for prostatakræft. Undersøgelsen har særligt fokus på akutte bivirkninger, senfølger samt patientens livskvalitet i forhold til at opnå redskaber til at mestre disse følger. Undersøgelsen indbefatter tre undersøgelser, som præsenteres ved to artikler og et manuskript. I undersøgelserne anvendes forskellige metodologiske tilgange: en tværsnitsundersøgelse med spørgeskemaer, en randomiseret klinisk kontrolleret undersøgelse og en kvalitativ undersøgelse med fokusgruppeinterviews.

I første undersøgelse (artikel I) blev generel og sygdomsspecifik livskvalitet undersøgt hos 317 tidligere strålebehandlede patienter ved hjælp af spørgeskemaerne SF-12 og EPIC-26. Resultaterne viste, at livskvaliteten i særlig grad var påvirket hos patienter som lever alene, og som har en livsstil med rygning og svær overvægt.

I anden undersøgelse - RePCa (Manuskript II) blev 161 patienter randomiseret til intervention (n=79) eller kontrol (n=82). Interventionen bestod af et individuelt tilrettelagt rehabiliteringsprogram bestående af psykosocial støtte fra sygeplejersker samt fysioterapeutisk vejledning i et hjemmeprogram bestående af bækkenbundstræning og fysisk træning. Det primære endepunkt var irritativ urinscore, og sekundære endepunkter: generel livskvalitet, urin-, tarm-, seksuelle-, eller hormonelle problemer, styrke i bækkenbunden samt mestring.

Resultaterne viste at interventionsgruppen 6 måneder efter strålebehandlingen rapporterede signifikant færre irritative symptomer end kontrolgruppen (Cohens $d=0.40$; $P=0.011$), færre samlede urinproblemer ($P=0.023$), færre hormonelle problemer ($P=0.018$), bedre fysisk livskvalitet ($P=0.002$) samt bevarede sin coping strategi kaldet fighting spirit stabilt ($P=0.025$). Begge grupper havde i behandlingsforløbet et fald i styrken i bækkenbunden målt med EMG ($P=0.001$). Analyser viste at de patienter som lever alene, eller som havde det dårligste udgangspunkt ved baseline havde størst effekt af interventionen.

Tredje undersøgelse (artikel III) bestod af to fokusgruppeinterviews med 13 mænd (66-77 år). Informanterne var mænd som havde fuldendt rehabiliteringsforløbet i RePCa undersøgelsen.

Den ene fokusgruppe bestod af mænd som mødte alene til interventionen, og den anden fokusgruppe af mænd som aktivt havde inddraget sin samlever i interventionen.

Fokusgruppeinterviewene varede ca. 2 timer og blev transskriberet ordret. Der blev anvendt en tematisk interviewguide, og med en fænomenologisk tilgang inspireret af Giorgi, blev meningskondensering anvendt som analytisk redskab. Desuden blev den sociale interaktion i fokusgrupperne analyseret.

Fundene viste at især hormonbehandling påvirker maskulinitet og identitet, og der er et behov for bedre information på dette område. Mændene mestrede livet med en særegen mandlig humor. Hvorvidt rehabiliteringen blev opfattet som brugbar afhang af de sundhedsprofessionelles konkrete tilgang samt den enkeltes motivation og evne til at omsætte ny viden til strategier i hverdagslivet. Involvering af evt. samlever kan være en støtte men bør være op til den enkelte patient.

Samlet kan konkluderes at livskvalitet og livsvilkår har betydning for omfanget af senfølger efter stråle- og hormonbehandling for prostatakraft. En tværfaglig rehabiliteringsintervention kan reducere omfanget af akutte irritative urin problemer, og øge livskvaliteten. Ligeledes har den sundhedsprofessionelles tilgang i interventionen betydning samt patientens evne og motivation til at bidrage til egen sundhedsfremme.

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Appendix

Paper I

Manuscript II

Paper III

Paper I

ORIGINAL ARTICLE

Living alone, obesity and smoking: Important factors for quality of life after radiotherapy and androgen deprivation therapy for prostate cancerKARIN B. DIEPERINK¹, STEINBJØRN HANSEN¹, LIS WAGNER²,
CHRISTOFFER JOHANSEN³, KLAUS K. ANDERSEN³ & OLFRED HANSEN¹¹Department of Oncology, Odense University Hospital, Odense, Denmark, ²Research Unit of Nursing, Clinical Institute, University of Southern Denmark, Odense, Denmark, and ³Survivorship, Danish Cancer Society Research Center, Copenhagen, Denmark**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 (BMI ≥ 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 BMI ≥ 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.

^b χ^2 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.

| QoL after treatment | n | SF-12 and epic mean qol scores (95% CI) score 0 to 100* | | | | p-value ^a |
|----------------------|-----|--|----------------------|----------------------|----------------------|----------------------|
| | | Overall n (317) | 1–2 years n (101) | 2–3 years n (109) | 3–4 years n (107) | |
| 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.

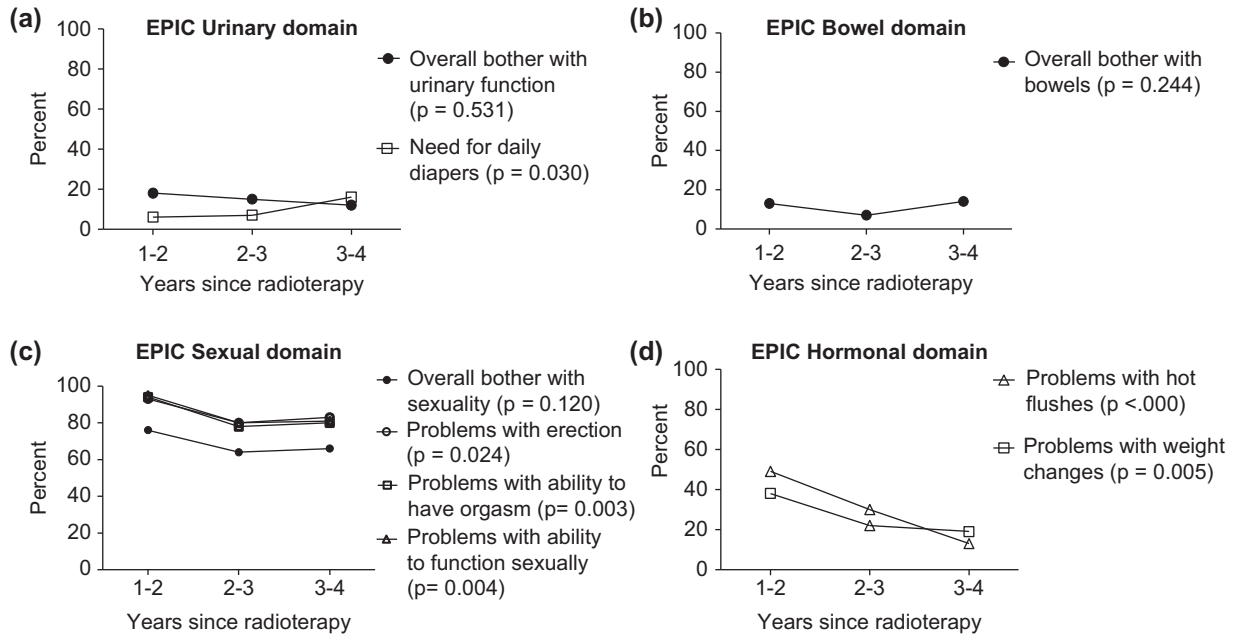


Figure 1. Proportion of patients responding the EPIC questionnaire with moderate-to-severe urinary, bowel, sexual, and hormonal problems among 317 Danish survivors of primary prostate cancer treated with radiotherapy and androgen deprivation therapy, 2006–2008. Odense, Denmark. The overall bother question 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.

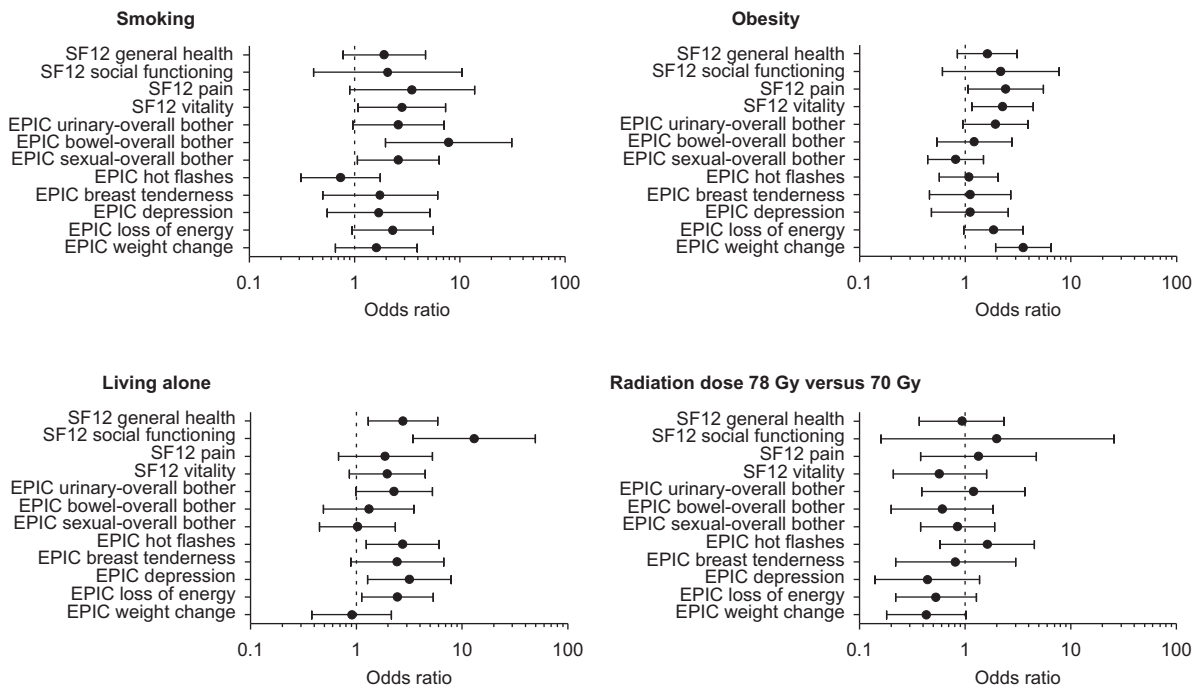


Figure 2. Forest plot with hypothesized factors associated to moderate-to-severe reduction of QoL among 317 Danish survivors with primary prostate cancer treated with radiotherapy and androgen deprivation therapy, 2006–2008. Odense, Denmark. Odds ratios are given for SF-12 single-item concepts, and the 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 (BMI \geq 30) in Danish men aged 65–74 years is 17.4% [16]. In this study, 23% of the patients had 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 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 \geq 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.

Acknowledgements

We especially wish to thank the cancer patients who participated in the study for their valuable contributions. This study was funded by Odense University Hospital (OUH) Research Foundation, the University of Southern Denmark, the Danish Cancer Society, CIRRO – The Lundbeck Foundation Center for Interventional Research in Radiation Oncology, the Department of Oncology, OUH, the Mette Hede Nielsen Foundation, the Scholarship Funds of the Physician Council, OUH, the Nurses Research Foundation, the Danish Nurses Organization Research Foundation, and the Propa Vita Foundation.

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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Manuscript II

The Effects of Counseling in Pelvic Floor Muscle Exercise and Psychosocial Support: A Randomized Study among Primary Prostate Cancer Patients

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Conflict of interest statement:

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

Abstract

Purpose: Effectiveness of a multidisciplinary rehabilitation program compared to usual care on treatment-related adverse effects, QoL in patients with prostate cancer (PCa).

Patients and Methods: In a single-center oncology unit in Odense, Denmark, 161 PCa patients treated with radiotherapy and the majority with androgen deprivation therapy were randomly assigned to either a program of two nursing counseling sessions and two counseling sessions with a physical therapist (n= 79), or to usual care (n= 82). Primary outcome was EPIC-26 (0-100) urinary irritative sum-score, measuring irritative and obstructive voiding symptoms.

At baseline, 4 weeks after radiotherapy, and after the 20-week intervention, measurements were made in self-reported disease-specific QoL (EPIC-26), including urinary, bowel, sexual, and hormonal symptoms. Furthermore, general QoL (SF-12), mental adjustment styles (Mini-MAC), digital evaluation of the pelvic floor muscle strength (Modified Oxford Scale) by blinded assessors, and electromyography were undertaken. To evaluate changes between groups, intention-to-treat analyses were made with linear regression adjusted for baseline scores.

Results: In the intervention group urinary irritative symptoms improved compared with controls, 5.8 point, Cohen's $d = 0.40$; $P = .011$. The program also improved urinary sum-score $d = 0.34$; $P = .023$, the hormonal sum-score $d = 0.19$; $P = .018$, and the SF-12 Physical Component Summary (PCS) $d = 0.35$; $P = .002$, and stabilized the mental adjustment style fighting spirit $P = .025$. Patients with impairments at baseline gained the most. However, pelvic floor muscle strength declined significantly in both groups $P = .0001$.

Conclusions: Multidisciplinary rehabilitation in irradiated PCa patients improved urinary and hormonal symptoms, SF-12 (PCS), and kept fighting spirit stable.

Keywords: prostate cancer; radiotherapy; physical therapy; pelvic floor; nursing counseling; quality of life; urinary irritative symptoms; rehabilitation

Introduction

Prostate cancer (PCa) is the most frequent male malignancy in the Western world.¹ The development of treatment with radiotherapy combined with androgen deprivation therapy (ADT) has in locally advanced or high-risk PCa increased the 10-year survival rates from around 60% to more than 70%.² Following these improvements in survival, a growing interest has emerged in evaluating the impact of the overall treatment on quality of life (QoL),^{3,4} and clinical attention has been directed toward how the adverse effects of the treatment may be counteracted.⁵⁻⁷ Adverse effects are categorized into acute disorders occurring within 6 months of radiotherapy, or late complications after 6 months or more.⁸

In particular, urinary irritative problems causing frequency, nocturia, urgency or urge incontinence are of major concern for these patients.^{9,10} The incidence of acute urinary tract symptoms after intensity-modulated radiotherapy (IMRT) is estimated to occur in one or even two out of every four patients.⁹ In a follow-up study from the USA with 1571 patients who experienced acute urinary symptoms during treatment, the risk of having grade 2 (CTC 3.0) late adverse effects after 10 years was found to be significantly increased from 12% to 35%.¹¹

In randomized trials, home-based training of pelvic floor exercises has been confirmed as an effective non-invasive treatment of post-prostatectomy incontinence, showing significantly decreased duration and degree of incontinence.^{12,13} However, this concept has not been investigated in a randomized designed study following treatment of PCa with radiotherapy and ADT.¹⁴ Here, we present data from the first RCT to investigate a multidisciplinary rehabilitation program comparing usual care with psychosocial support and counseling in pelvic floor exercises to primarily reduce urinary irritative problems, and secondarily to increase overall QoL.

Methods

Setting and participation

The study was approved by the local Scientific Research Ethics Committee (File no. S-20090142), the Danish National Data Protection Agency (File no. 2012-41-1175), and registered by ClinicalTrials.gov (Study number, NCT01272648). All participants provided written informed consent.

Design:

The design was organized as a two-armed randomized, controlled trial recruiting among 226 patients referred to curative radiotherapy from February 1, 2010 to January 31, 2012 at Odense University Hospital, Denmark. A total of 209 patients fulfilled the inclusion criteria and were eligible for participation, as shown in the CONSORT diagram,¹⁵ Figure 1.

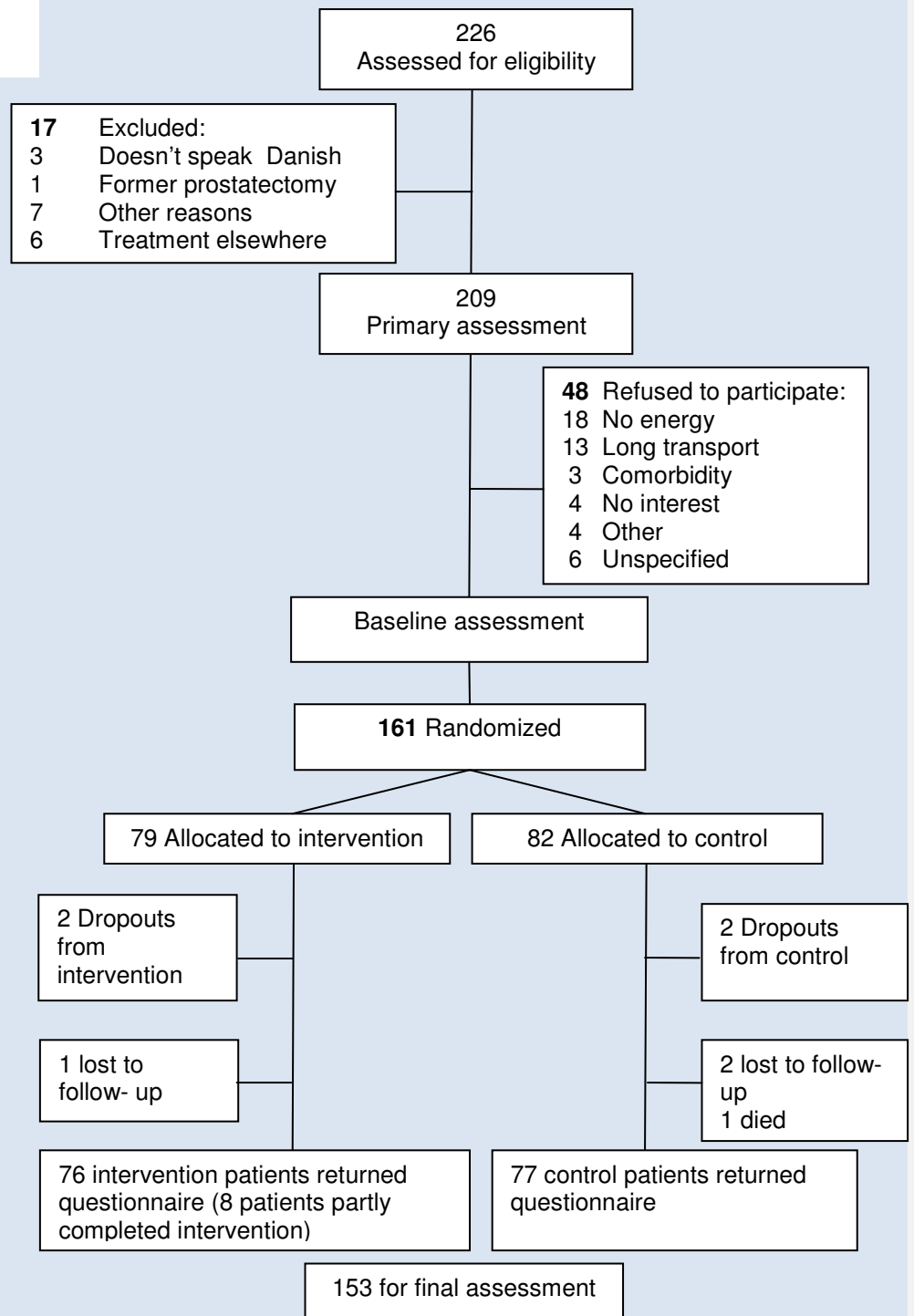
Inclusion criteria: men \geq 18 years old with biopsy documented adenocarcinoma of the prostate. Exclusion criteria: former prostatectomy, not able to speak Danish, or included in other protocols.

Information about Gleason score, TNM-staging, prostate-specific antigen values (PSA), and comorbidity was obtained from the medical records, and patients were stratified into risk groups as described by D'Amico et al.¹⁶ with regard to determining the treatment plan.

IMRT used a prescription dose of 78 Gy in 39 fractions given in five fractions per week. Inter-fractional prostate displacement was corrected by daily-IGRT using implanted gold markers. Target volume was the prostate gland including the proximal 2 cm of the seminal vesicles in high-risk patients and adding a 7-mm margin. Three patients in each randomization group received pelvic radiotherapy due to metastatic lymph nodes. ADT was started 3 months before radiotherapy; in T3 patients, ADT is given for up to 3 years.

Patients were randomly assigned to the intervention group or usual care during follow-up (control group) in a ratio of 1:1. The randomizations were externally handled by the Department of Clinical Research at Odense University Hospital, Denmark, and the allocation sequence was concealed from the research team.

Figure 1. CONSORT-
Flow chart



Intervention

The intervention took place in an outpatient setting at the Department of Oncology, and the Department of Rehabilitation. At 4 weeks post-radiation, baseline data were obtained from all patients in the study and the intervention initiated.

The control group received usual care during follow-up, consisting of one physician visit 4 weeks after radiotherapy. In addition to usual care, the patients in the intervention group were instructed in an individually suited multidisciplinary program during two nursing counseling and during two additional sessions of counseling by physical therapists, Figure 2. The patient was recommended to bring his spouse along for all counseling and instruction in order to increase understanding of and compliance with the exercises suggested.

The above-mentioned intervention was provided by dedicated staff members at each site. The seven project oncology nurses engaged in the intervention activities were specially trained and qualified radiation therapists, and the two physical therapists had more than 10 years' clinical experience in the instruction and training of men to address incontinence, including pelvic floor training. This group of nine staff members were all enrolled in a 6-day course with seven 45-minute lectures per day containing the topics PCa and treatment, the male perspective, incontinence and the pelvic floor, sexuality, depression and fear of recurrence, social support, and finally the method of motivational interviewing¹⁷ that was used as a communicative platform. To ensure consistency, the course was followed by 12 supportive, 60-minute reinforcing sessions every second month provided by a motivational interview trainer.

Nursing counseling

The nursing counseling sought to provide psychological support and enable identification of problems regarding the disease experienced by the patient and his spouse, Figure 2. In accordance with the nursing approach of Patricia Benner,¹⁸ the nurses initiated the dialogue based on needs. With this approach the nurses identified information needs about late adverse effects, established an individual rehabilitation plan based on the patients' personal goals, and if needed, provided advice on lifestyle changes concerning smoking, alcohol, general fitness, diet, weight control, and further suggested solutions to other problems, e.g., toilet habits, sexuality, and psychological problems. The project oncology nurses had the authority to refer patients in the

intervention group to medical specialists, public/community rehabilitation centers, sexologists, and social workers.

Physical therapy counseling

The physical therapy started out by identifying the individual patient's need for increased pelvic floor muscle function and general physical activity level, Figure 2. Symptoms related to pelvic floor muscle function were explored, e.g., urination control, flatulence, and defecation. If necessary, the patient was guided by biofeedback, a visual signal presenting the pelvic floor strength to the patient.¹⁹

A written pamphlet was created specifically for the purpose of this study and explained how PCa treatment affects physical and general health. The self-training home program consisted of pelvic floor muscle exercises, and exercises for the major muscle groups including muscle endurance and strength and balance exercises. General physical activities were recommended to inactive patients. The second session was used as a follow-up on the individual goals of each patient.

Figure 2. Graphical depiction of the intervention in a randomized rehabilitation study with 161 participants with prostate cancer, Odense, Denmark.

| Time line | Intervention group | Control group |
|------------------------------|--|---------------|
| 12 weeks before radiotherapy | Primary assessment with questionnaires and test of muscle strength by blinded assessors. | |
| | Radiotherapy | |
| | Randomization | |
| Baseline | Ⓐ Ⓑ | Ⓐ Ⓑ |
| 4 weeks after radiotherapy | Ⓒ | |
| 12 weeks from baseline | Ⓓ Ⓔ | |
| 24 weeks from baseline | Ⓕ Ⓑ | Ⓑ |
| 25–26 weeks from baseline | Outcome questionnaires were received by mail. | |

Notes:

- Ⓐ 25-minute follow-up visit at the Department of Oncology with oncologist. Baseline questionnaires were received and checked by nurse. Patients were informed about group allocation.
- Ⓑ 30-minute muscle strength test by blinded observers.
- Ⓒ 60-minute first individual visit with the physical therapist. Guidance of functional home training and pelvic floor exercises depending on the muscle strength test. A pamphlet with the individual training goals was handed out.
- Ⓓ 40-minute first individual visit with the oncology nurse, identifying patient's needs and response to them, e.g. psychological support, counseling about lifestyle, toilet habits, sexual problems.
- Ⓔ 45-minute second individual visit with the same physical therapist. Follow-up guidance.
- Ⓕ 40-minute second individual visit with the same oncology nurse. Follow-up and perspectives on the new everyday life.
- Ⓑ 30-minute muscle strength test by blinded observers. The last questionnaire was handed out with a pre-paid envelope, and the patient was asked to send it in within a few weeks.

Primary and Secondary Outcome Measures

Study outcomes were preliminary assessed before radiotherapy, as baseline-measurements at 4 weeks post-radiation, and after 20 weeks of intervention, Figure 2. The primary outcome was defined as the urinary irritative sum-score based on the Expanded Prostate Cancer Index Composite (EPIC-26). Secondary outcomes included QoL arising from the Medical Outcome Study Short-form-12 (SF-12), urinary incontinence, bowel, sexual and hormonal sum-scores as measured by the EPIC-26, mental adjustment styles (Mini-Mac), and assessment of the pelvic floor.

SF-12

The generic extensively validated QoL questionnaire SF-12²⁰ includes eight concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. Results are expressed in two meta-scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). These meta-scores are standardized to the United States population normative values, with a mean score of 50 and a SD of 10. Higher scores represent better health.²⁰

EPIC

The disease-specific validated EPIC-26 consists of domains concerning urinary symptoms, bowel symptoms, sexual function, and symptoms related to ADT. For each domain, a sum-score is constructed. In addition, two urinary scales that distinguish irritative/obstructive symptoms and incontinence were obtained. EPIC items are answered on a 5-point Likert scale from no problems to severe problems. Scores are transformed linearly to a scale of 0 to 100, with higher scores indicating better QoL.^{21,22} A low inter-scale correlation observed between SF-12 and EPIC domains supports the concurrent use of EPIC with SF-12.²²

MiniMac

Mini-MAC²³ is a 29-item version of the Mental Adjustment to Cancer Scale,²⁴ which elicits cognitive and behavioral responses to cancer in five subscales: fighting spirit, fatalism, cognitive avoidance, anxious preoccupation, and helplessness-hopelessness. The raw scores, ranging from 1 to 4, are summed up for each subscale. A higher sum-score represents a higher level of the respective adjustment style. Mini-Mac is validated in Norway,²⁵ a country comparable to Denmark with regard to public welfare.

Pelvic floor Assessment

A standardized protocol ensuring a correct and reproducible technique was used for all tests. This protocol was developed after pilot tests of seven patients, including subject lateral positioning, exact wording of instructions, and avoidance of muscles other than the pelvic floor. Pilot test data were not included in this study.

In all patients, a correct pelvic floor muscle contraction was confirmed on digital rectal evaluation by the assessor before making the test. The instruction used for each contraction was “squeeze and lift” the pelvic floor. Muscle strength was measured by the ability to contract. Digital evaluation was done according to the modified 6-point Oxford Scale.²⁶ Surface anal electromyography (EMG) was performed with NeuroTrac™ MyoPlus with an Anuform™ analprobe. The three assessors of the pelvic floor function were blinded and independent of the research team. The patients were told not to give the assessors information about group assignments.

Sample Size Calculation and Statistical Analyses

Sample sizes were based on expected between-group differences obtained from the EPIC-26 questionnaire.²⁷ With a power of 0.80, $\alpha = 0.05$, corresponding to an effect size of 0.5, the sample size was estimated to be 80 patients per group, providing for 20% dropouts and withdrawals.

Socio-demographic and clinical characteristics were described using means for continuous variables and frequencies for categorical variables. Differences regarding QoL and mental adjustment styles (continuous) between intervention and control groups were tested with multiple linear regression models adjusted for baseline scores.

Differences in the strength of pelvic floor muscles were tested with Wilcoxon rank-sum test. Inter-rater reliability between assessors was tested in a random example of 15 records with Kappa statistics. Groups were analyzed with intention-to-treat according to the allocated group.

Correlations between variables were tested with linear regression models. Cohen's d as effect size was calculated by group mean differences post-intervention divided by mean standard deviation.

P values < 0.05 were considered statistically significant and were reported two-sided. Questionnaires with insufficient data were removed from the analysis.^{20,22}

Statistics were calculated with STATA 11.

Table 1. Socio-demographic and biological baseline characteristics of 161 participants and 48 refusers with primary prostate cancer included in a randomized controlled trial after radiotherapy and androgen deprivation therapy, 2010–2012 Odense, Denmark.

| SOCIO-DEMOGRAPHIC CHARACTERISTICS | Intervention Group (n = 79) | Control Group (n = 82) | Refusers (n=48) |
|---|--------------------------------|---------------------------|--------------------|
| Age at first radiotherapy date (years) mean (SD): | 68.2 (4.8) | 69.0 (5.2) | 68.7 (6.4) |
| Weight (kilo) reported at baseline mean (SD) | 84.7 (12.7) | 86.3 (14.8) | 85.9 (15.6) |
| unknown | 1 | 3 | 7 |
| Body mass index (BMI) kg/m ² mean (SD) | 27.1 (3.6) | 27.4 (4.1) | 27.2 (4.6) |
| unknown | 1 | 3 | 7 |
| Social status reported at baseline: | | | |
| living alone | 10 (13%) | 12 (15%) | 8 (19%) |
| living with a spouse | 68 (87%) | 67 (85%) | 33 (81%) |
| unknown | 1 | 3 | 7 |
| Education: | | | |
| basic (less than 10 years) | 31 (40%) | 36 (46%) | 21 (52%) |
| youth (high school) | 24 (31%) | 23 (29%) | 12 (30%) |
| medium (profession) | 18 (23%) | 18 (23%) | 6 (15%) |
| higher (university) | 5 (6%) | 2 (2%) | 1 (3%) |
| unknown | 1 | 3 | 8 |
| Smoking status at baseline: | | | |
| never smoker | 33 (42%) | 32 (41%) | 12 (29%) |
| past smoker | 30 (39%) | 35 (44%) | 20 (49%) |
| current smoker | 15 (19%) | 12 (15%) | 9 (22%) |
| unknown | 1 | 3 | 7 |
| MEDICAL CHARACTERISTICS | | | |
| PSA pre-treatment serum mean ng/ml (SD) | 21.5 (17.7) | 19.8 (16.8) | 21.6 (18.4) |
| Gleason score: | | | |

| | | | |
|---|----------|----------|----------------------|
| <7 | 10 (13%) | 17 (21%) | 10 (21%) |
| 7 | 47 (59%) | 44 (54%) | 25 (52%) |
| >7 | 22 (28%) | 21 (25%) | 13 (27%) |
| Degree of malignancy: | | | |
| T1 | 8 (10%) | 9 (11%) | 6 (12%) |
| T2 | 34 (44%) | 35 (43%) | 23 (48%) |
| T3 | 36 (46%) | 38 (46%) | 19 (40%) |
| unknown | 1 | | |
| Risk group: | | | |
| low | 1 (1%) | 3 (4%) | 6 (12%) ^a |
| intermediate | 19 (24%) | 13 (16%) | 8 (17%) |
| high | 59 (75%) | 65 (80%) | 34 (71%) |
| unknown | | 1 | |
| Hormone therapy: | | | |
| no | 3 (4%) | 2 (3%) | 5 (11%) ^b |
| Androgen Deprivation Therapy (ADT) | 76 (96%) | 79 (97%) | 42 (89%) |
| unknown | | 1 | 1 |
| Patient reported comorbidity at baseline: | | | |
| Charlson index score 1 | 20 (25%) | 19 (23%) | 13 (27%) |
| score 2 | 4 (5%) | 5(6%) | 1 (2%) |
| score 3 | 0 | 0 | 0 |
| score 6 | 0 | 0 | 0 |

^aFisher's exact $P = 0.028$

^bFisher's exact $P = 0.049$

Results

Groups were balanced at baseline, Table 1. Patient flow before and after randomization of 161 patients is shown in Figure 1, leaving 153 patients (95%) for the analysis. A total of 71/79 of the intervention group patients (90%) completed the entire intervention program.

PCa patients in the intervention group benefitted significantly with regard to urinary irritative symptoms with 5.8 point Cohen's $d = 0.40$; $P = .011$ (Table 2, 3 and Figure 3).

No significant interactions between groups and baseline scores were seen. Covariates (age, body mass index, risk group, PSA, education, smoking, and marital status) showed no significant correlation with the urinary irritative sum-score. PCS and MCS correlated with improved urinary irritative sum-score ($P = .007$ and $P = .040$), respectively.

Subanalysis showed that improvements in the urinary sum-score were most pronounced in patients living alone (12.0 point $P = .021$), that baseline urinary bother (score >3) indicating moderate to severe problems gained (13.1 point; $P = .034$), and a baseline urinary irritative sum-score below the study mean value of 68 point predicted a higher intervention effect with (10.1 point; $P = .031$).

Urinary sum-score, hormonal sum-score, and physical QoL (PCS) improved significantly in the intervention group compared to controls, whereas pelvic floor muscle strength measured by digital evaluation (Modified Oxford Scale 0–6) did not change significantly during the study period: mean 3.9 and 3.7 at post-intervention in the intervention and the control groups, respectively. Muscle strength measured by EMG declined concurrently ($P = .001$), 31.3 to 24.7 μV in the intervention group and 31.6 to 23.3 μV in the control group, with no significant differences between the two groups.

In the intervention group compared with the control group, the urinary irritative sum-score improved in patients with impaired pelvic floor strength at baseline, < 5 Modified Oxford Scale, (7.4 point; $P = .012$) as did the urinary irritative sum-score in patients with low EMG at baseline, $< 21\mu\text{V}$, (9.2 point; $P = .012$).

In the digital evaluation, inter-rater reliability among the three assessors had Kappa values of 0.72, 0.83, and 0.84.

The score of fighting spirit as adjustment style remained stable in the intervention group compared to the control group ($P = .025$). A higher score of fighting spirit significantly correlated with improved urinary irritative sum-score ($P = .004$), while higher scores of helplessness-hopelessness and anxious preoccupation significantly correlated with a decline in the urinary irritative sum-score ($P = .022$) and ($P = .011$), respectively.

Table 2. Mean changes in QoL (Quality of Life) scores among 161 Danish prostate cancer survivors included in a randomized rehabilitation study, Odense, Denmark.

| | | Effect (Coef)* | CI | P[#] |
|---|---------------------|-----------------------|-----------|----------------------|
| Intervention group versus control group | SF12 | | | |
| | Physical (PCS) | 3.6 | 1.3; 5.8 | 0.002 |
| | Mental (MCS) | 0.7 | -1.6; 3.0 | 0.549 |
| | EPIC domains | | | |
| | Urinary | 4.5 | 0.6; 8.4 | 0.023 |
| | Incontinence | 2.6 | -1.8; 6.9 | 0.242 |
| | Irritative | 5.8** | 1.4; 10.3 | 0.011 |
| | Bowel | 3.0 | -1.9; 8.0 | 0.224 |
| | Sexual | 3.6 | -0.9; 8.0 | 0.117 |
| | Hormonal | 4.8 | 0.8; 8.8 | 0.018 |

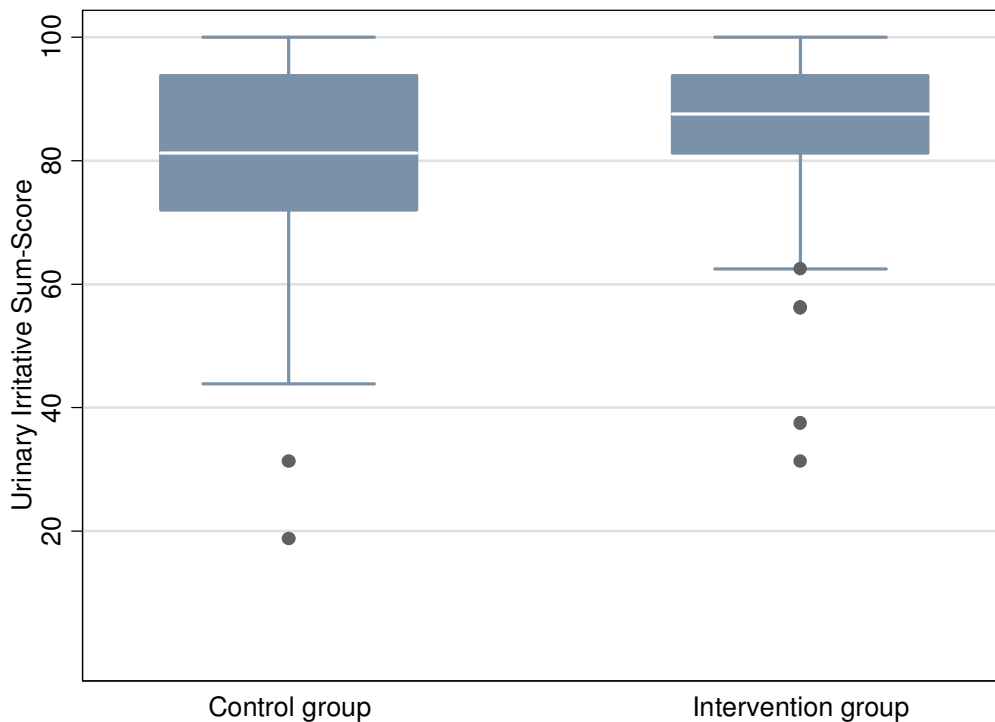
CI: 95% Confidence interval

Reported *P* values are 2-sided and < 0.05 was considered statistically significant.

*Multiple linear regression analysis adjusted for baseline scores.

**Example: if the patient is in the intervention group, his mean QoL score (0-100) regarding urinary irritative sum-score increases with 5.8 point compared with the controls.

Figure 3. Box-plot median urinary irritative sum-score post-intervention in a randomised rehabilitation study with 161 participants with prostate cancer, Odense, Denmark.



The whiskers show the lower/upper adjacent value and the box the 25th-75th percentile. The dots show outliers.

Table 3. Baseline levels and changes in disease-specific QoL (Quality of Life) scores (EPIC), and general QoL scores (SF-12) in intervention and control groups at 4 weeks (baseline) and 24 weeks after radiotherapy (post-intervention) among 161 survivors with primary prostate cancer included in (RePCa) a prospective randomized rehabilitation study, 2010–2012 Odense, Denmark.

| EPIC AND SF12 MEAN QOL (SCORE 0 TO 100)* | | | | | |
|---|--|--|--|--|-------------------------------------|
| QoL mean (SD) | Intervention group <i>n</i> = 79 | | Control group <i>n</i> = 82 | | <i>Cohen's d</i>^a |
| | baseline level 4 weeks after radiotherapy | difference between follow-up and baseline level at 6 months | baseline level 4 weeks after radiotherapy | difference between follow-up and baseline level at 6 months | |
| EPIC domain: | | | | | |
| Urinary irritative | 67.7 (18.7) | 17.6 (18.1) | 68.1 (18.7) | 11.6 (16.5) | 0.40 |
| Urinary incontinence | 82.5 (17.5) | 7.3 (14.9) | 82.2 (21.7) | 4.9 (15.8) | |
| Urinary sum-score | 73.5 (14.5) | 13.3 (13.9) | 73.1 (17.4) | 9.0 (12.9) | 0.34 |
| Bowel sum-score | 77.6 (19.9) | 9.7 (20.3) | 77.0 (20.0) | 7.6 (16.4) | |
| Sexual sum-score | 15.0 (19.5) | -1.3 (13.7) | 14.0 (20.1) | -4.1 (16.4) | |
| Hormonal sum-score | 71.6 (18.8) | 2.3 (13.2) | 72.8 (18.9) | -2.8 (12.8) | 0.19 |
| SF12 domain: | | | | | |
| Physical (PCS) | 47.4 (8.3) | 1.9 (6.7) | 47.5 (9.0) | -1.7 (7.9) | 0.35 |
| Mental (MCS) | 53.0 (8.7) | 2.3 (7.1) | 51.7 (9.6) | 2.3 (8.9) | |

*Higher scores indicating better QoL. Note: SF12 is standardized to the United States population normative values, with a mean score of 50 and a SD of 10.

^aCohen's *d* effect size = group mean differences at patients post-intervention divided by mean SD.

Discussion

We found that the multidisciplinary rehabilitation program had a significant effect compared to usual care on the primary outcome, urinary irritative symptoms, among a large sample of irradiated PCa patients. As secondary outcomes, we observed benefits of the intervention in improvement in overall urinary symptoms, hormonal symptoms, and physical QoL. Our intervention improved urinary irritative symptoms by more than 5 points on a 0–100 scale compared to a control group, which is clinically significant.²⁸

Consistent with our finding, Faithfull et al²⁹ in a small phase II trial including 22 irradiated patients observed significant improvements, with a median score change of 5, on lower urinary tract symptoms following an intervention consisting of a program almost the same as used in this study (self-management program comprising pelvic floor exercises, bladder training, patient education and problem solving). However, Faithfull et al. included only patients with moderate to severe symptoms, and their pelvic floor exercises were conducted as group sessions, whereas we included all patients with an individualized intervention, aiming at the targeted and exact need of each individual patient.

Our results parallel those from two randomized studies ($N = 102$ and $N = 300$) among PCa patients treated with prostatectomy using a single component pelvic floor exercise program to improve incontinence.^{12,13}

Pelvic floor function is closely related to bladder capacity or voiding dysfunction. Previous research has examined pelvic floor muscle strength in men treated with prostatectomy, but there is no gold standard of measurement.³⁰ The pelvic floor strength measured by digital evaluation was stable during the period, but as measured by EMG, the pelvic floor strength declined significantly. Thus, EMG may be more sensitive in detecting changes in muscle strength. Studies show that ADT causes a decline in large muscle groups,^{31,32} and perhaps this includes the muscles of the pelvic floor.

The patients in the control group met the blinded assessors only when being tested. However, patients were able to obtain information from the internet or elsewhere, and this may, in theory, have watered down the intervention. Pelvic floor exercises are difficult to learn without instructions,³⁰ and consequently we offered the intervention group meticulous instructions in order to give the best opportunity to counteract adverse effects, which may have come about through information from other sources, e.g. the internet.

Our intervention group maintained a stable and significantly higher score of fighting spirit at 6 months after treatment than did controls. Fighting spirit is the tendency to confront and actively face the illness,²³ and this may be an important adjustment style in a self-management approach including home-based training.

Our recently published cross-sectional survey including 317 prostate cancer patients³³ showed that risk factors (e.g. smoking, severe obesity BMI>30, and the condition of

living alone) were associated with increased risk of late adverse effects after radiotherapy. The present study showed that patients living alone had a better outcome after intervention. These results imply a need for integration of not only the adverse effects but also personal factors as lifestyle and life conditions during intervention. Screening before intervention may identify patients with a potential for improvement and the motivation to make an effort. The present study showed that patients with baseline objective (i.e. digital evaluation < 5 or EMG < 21) or subjective (i.e. EPIC irritative sum-score below 68 points) impairment improved the most. Therefore, screening with these measures may be considered in future rehabilitation intervention studies.

This study has a number of advantages. The accrual procedures made it possible to obtain information about the majority of the patients who denied participation, as 41/48 filled out questionnaires before radiotherapy. This group of patients differed from patients included in the randomization by having a statistically significant, but marginally lower D'Amico risk. We find it unlikely that was related with not joining the study. In addition, this group included more patients living alone, and they had a lower level of education and a higher incidence of smoking than did the randomized patients. Taken together, these factors should be taken into account if the intervention tested in this study is used as a standard of care.³⁴

Internal validity was maintained due to the randomization and the homogeneity of the groups. The study provided good feasibility with a high inclusion rate, and few drop outs, although we could not monitor the patients' compliance to the recommended self-training home exercises. The intervention did not have any negative effects on the outcomes measured. The relative unrestricted inclusion and exclusion criteria allow generalization of the results because the study sample was representative of a population of irradiated PCa patients. However, the design permits only causal conclusions about the combined program of nursing and physical therapy counseling and not about the components separately.

Based on the results of this study, it can be recommended that patients treated with radiotherapy of the prostate could be offered a combined nurse-physiotherapist intervention program. Timing, duration, and more focus on the empowerment aspects of this intervention need further study.

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Paper III

Embracing life after prostate cancer. A male perspective on treatment and rehabilitation

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DIEPERINK K.B., WAGNER L., HANSEN S. & HANSEN O. (2013) *European Journal of Cancer Care* Embracing life after prostate cancer. A male perspective on treatment and rehabilitation

This study explores prostate cancer patients' experiences of rehabilitation after radiotherapy with androgen deprivation therapy (ADT). Patients who had completed a multidisciplinary rehabilitation programme with psychosocial support and physiotherapy were interviewed in two focus groups: Group 1 consisted of six men who came to the rehabilitation with their spouses, and Group 2 of seven men who came alone. Meaning condensation was used to analyse the interviews. Radiotherapy was described as full-time work. Adverse effects due to ADT influencing masculinity and identity were emphasised. The men embraced life with a particular sense of humour. Whether rehabilitation was experienced as useful depended on the health professionals' approach, and on the patients' motivation and effort to contribute to health promotion, and to convert experiences into coping strategies. The supportive role of the spouse was emphasised by several, but some men preferred to handle the process alone. In conclusion, men undergoing ADT should be carefully informed of the consequences. Spousal involvement in rehabilitation must be decided by the patient. The focus group interviews themselves had a positive impact on the men's understanding of their rehabilitation processes. The specific male approach and differences between the needs of female and male cancer patients are important to understand when planning rehabilitation.

Keywords: prostate cancer, radiotherapy, androgen deprivation therapy, survivor, rehabilitation, male perspective.

INTRODUCTION

Prostate cancer is the most common cancer among men in Europe (Ferlay *et al.* 2010). More than 20 000 Danish men live with prostate cancer (Sundhedsstyrelsen 2010) due to a combination of increased incidence and improvements

in treatment. The growing number of survivors requires attention to the challenges after treatment and the possibilities of rehabilitation.

Patients treated with radiotherapy and androgen deprivation therapy (ADT) have several problems with urinary, bowel, sexual, and hormonal function (Dieperink *et al.* 2012). Dieperink *et al.* found that men living alone had a lower quality of life after treatment for prostate cancer, and this motivated our focus on the spousal role.

Only a few studies have dealt with patients' perspectives on treatment. Kelsey *et al.* (in the UK) explored the experiences of 17 men with prostate cancer treated with external beam radiotherapy 3D-CRT (Kelsey *et al.* 2004) and found that an altered sex life as a result of the treatment was the most severe experience. Hedestig *et al.*

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Accepted 15 January 2013

DOI: 10.1111/ecc.12061

European Journal of Cancer Care, 2013

described the experiences of 10 Swedish men given 3D-CRT and found that the men reconciled themselves to a new everyday life (Hedestig *et al.* 2005). At present 3D-CRT treatment, usually combined with ADT, has been replaced by intensity-modulated radiotherapy (IMRT). A recent Norwegian study interviewed eight patients treated with ADT alone and found that loss of libido and impotency were significant side effects influencing masculinity (Ervik & Asplund 2012).

These studies present information important for the understanding and management of the concerns of men with prostate cancer. Nevertheless, the knowledge of a male perspective regarding a combined treatment consisting of both radiotherapy and ADT followed by rehabilitation is sparse. Furthermore, very little is known of men's approach to spousal involvement in rehabilitation. For this reason, the present study was planned as a part of a larger randomised study of rehabilitation in prostate cancer patients. The present work describes patients' perspectives on the treatment and the rehabilitation delivered.

AIMS

The overall aims of the study were to:

- 1 Explore the participants' experiences of treatment with radiotherapy and ADT, and the participating in a rehabilitation programme.
- 2 Explore the participants' thoughts and approach to spousal involvement in the rehabilitation process.

STUDY DESIGN AND METHODS

This study was a qualitative focus group interview study to supplement a randomised controlled study (RePCa) investigating the effect of a multidisciplinary rehabilitation programme after radiotherapy for primary prostate cancer.

Data collection

Two focus group interviews were undertaken in January 2012 with Danish prostate cancer survivors treated with IMRT radiotherapy 78 Gy over 39 fractions and ADT during the years 2010–2011. Focus group interviews were selected because this method has the advantage of making use of group dynamics to stimulate discussion, gain insights, and generate ideas in order to pursue a topic in greater depth (Morgan 1997; McLafferty 2004; Freeman 2006).

Seventeen patients with a wide age range were invited. The inclusion criterion was that all patients had taken part in an active group as part of the rehabilitation programme (RePCa) during a period of maximum 18 months. The RePCa study is explained below. Patient hospital files documented small to severe problems during the rehabilitation process. The participants' were stratified into two groups depending on whether the participant had involved his spouse actively in the nursing consultations (FG 1) or not (FG 2), Table 1.

The focus group sessions were facilitated by an experienced female nurse (first author), and moderated by a senior researcher. Each session group lasted 2 h, was audio-recorded, and transcribed verbatim. The focus group sessions were guided by the research questions and a

Table 1. Characteristics of 13 Danish focus group participants, of patients radiated for localised prostate cancer

| (Participants) No. | Age* | Stage of disease | Androgen deprivation therapy | Cohabitation | Education‡ | Socio-economic group | Experience with prostate cancer in the family |
|-------------------------------------|------|------------------|------------------------------|--------------|------------|----------------------|---|
| Focus Group 1 – Men involved spouse | | | | | | | |
| FG1-1 | 71 | IIIa | Ongoing | Married | Basic | Retired | No |
| FG1-2 | 77 | IIa | Discontinued† | Married | Basic | Retired | No |
| FG1-3 | 74 | Ic | Ongoing | Married | Youth | Retired | Brother |
| FG1-4 | 71 | IIIb | Ongoing | Married | Youth | Retired | No |
| FG1-5 | 76 | IIa | Discontinued† | Cohabiting | Youth | Retired | No |
| FG1-6 | 66 | IIIb | Ongoing | Cohabiting | Basic | Retired | No |
| Focus Group 2 – Men came alone | | | | | | | |
| FG2-7 | 69 | IIc | Ongoing | Divorced | Youth | Retired | No |
| FG2-8 | 67 | IIIa | Ongoing | Married | Basic | Retired | Father |
| FG2-9 | 73 | IIb | Completed | Cohabiting | Medium | Retired | No |
| FG2-10 | 66 | Ic | Ongoing | Married | Youth | Self-employed | Brother |
| FG2-11 | 75 | III | Discontinued† | Widower | Medium | Retired | No |
| FG2-12 | 71 | IIIb | Ongoing | Married | Youth | Retired | No |
| FG2-13 | 67 | IIIa | Ongoing | Married | Basic | Employee | No |

*At time of focus group.

†Discontinued before schedule due to adverse effects on patient request.

‡Basic = <10 years, Youth = high school, Medium = profession, High = university.

semi-structured interview guide. Each participant was encouraged to be honest and candid about his experiences and his position regarding the topics discussed. To inspire the participants to talk and remember, pictures from the Department of Oncology and a pamphlet from the physiotherapist were placed on the table during the interviews. To seek a neutral ground and a safe environment, the focus group interviews were not held at the participant's homes but at a convenient location not directly connected to the Department of Oncology where the treatment had been given.

The rehabilitation intervention

All participants completed the rehabilitation programme (RePCa) that consisted of two individual nursing counsellings and two sessions of guidance from a physiotherapist within 6 months after the radiotherapy. We recommended the patient to be accompanied by his spouse.

The nursing consultations were based on the philosophy of Patricia Benner (Benner & Wrubel 1989). The nurse identified problems or dilemmas important for the patient, and gave him psychosocial support and the opportunity of counselling regarding, e.g. toilet habits, smoking cessation, weight control, sexuality, and psychological problems. The nurse could refer to other collaborators depending on the problem, e.g. doctors, sexologists, or social workers. The guidance from the physiotherapist contained instructions in pelvic floor exercise and physical exercise on the basis of individual tests of the strength of the pelvic floor.

The method of motivational interviewing (Miller & Rollnick 2002) was a communicative platform common for nurses and physiotherapists.

Ethical issues and approval

Verbal and written informed consent to participate was obtained, and participants were informed about the aim of the study and that anonymity would be preserved. The study was approved by the local Scientific Research Ethics Committee (File number S-20090142), and by the Danish National Data Protection Agency (File number 2009-41-3948).

Data analysis

The initial analysis was performed by two of the authors. The software program NVivo 9 was used to code and retrieve data.

At first, an analysis with meaning condensation was made which gave the opportunity to understand what was

of most importance during the patients' trajectory (Benner & Wrubel 1989). Meaning condensation is a frequently applied method in analysing text materials. Meaning condensation involves a reduction of large interview texts into briefer more succinct formulations (Kvale & Brinkmann 2009). The analysis was inspired by Giorgi's phenomenological approach (Giorgi 1975), a descriptive process which contains the following steps (Kvale & Brinkmann 2009):

The first step was to achieve an overall understanding by reading the entire transcript in order to derive a global sense of the whole. This was done with maximum of openness without taking the specific aim of the study into account, and a summary of each focus group session was made. The second step was to break the text into natural meaning units by rereading the transcripts, as expressed in the participants' own words. Text unrelated to the phenomenon in focus was deleted. The meaning units were considered as expressions related to the main themes 'treatment and side effects', 'rehabilitation', and 'spousal involvement'. The third step was to examine and transform each meaning unit of the participants' own language into the researcher's language, searching for essential aspects of the phenomenon. This was done by adding memos to each meaning unit. The fourth step was to investigate the meaning units on the basis of the research questions, and the last step was to reveal the essential structure and to synthesise the transformed meaning units into descriptive statements (example in Table 2).

To balance the content and the interaction in the groups (Halkier 2010), some short reflections on the interaction between the participants were made inspired by Erving Goffman's approach to social interaction (Goffman 1959).

The researchers' approach

Our epistemological assumption was that the participants' experience of treatment and rehabilitation was a pre-existent individual experience modified by the situated encounter between the participants in the focus groups. It was therefore important to analyse the interaction as well. Examples from the two focus groups in the form of quotes representative of both focus groups are presented in the results. The quotes are used to illustrate the analytical points and are not intended to give quantitative estimates.

RESULTS

Participants

In total, 13 patients participated in two focus groups (age range 66–77, mean 71 years) (Table 1). Four patients

Table 2. Example of steps 2, 3 and 4 in the process of analysis as part of the main theme: ‘Spousal Involvement’ and the subtheme: ‘Co-player or line player’

| Focus Group | Step 2 Natural meaning units described by patients | Step 3 Essential aspects described by researcher | Step 4 Patients’ experiences |
|-------------------------------------|---|---|---|
| Focus Group 1 – Men involved spouse | ‘I just sat there and listened. They asked about other things that we would ask about. One thing is coming home and telling about this and that.. but things have a different weight when they come from a doctor or nurse, and here too its that four ears hear more and better than two, so I think it’s really good that my partner is also there’ (FG1-5) | Men/Women, Patients/Relatives have different wishes regarding information The health professionals’ authority means something with regard to information A wish that one did not miss any information | Questions asked by the spouse were of benefit for the patient too, as they revealed different perspectives. |
| Focus Group 2 – Men came alone | ‘I ask my wife if she wanted to go with me, but she said no, it’s not necessary, you’ll do just fine by yourself, and yes that I do (smiles)’ (FG2-10) | A wedded couple can have different priorities Support can be given at different levels | The men were used to handle things themselves. Their spouses seemed to be at the sideline. |

declined to participate. Three patients were not able to participate on the proposed date, and one patient declared a lack of interest. All participants had primary prostate cancer (stages T1–T3) and had been treated with radiotherapy and ADT. None of the participants experienced a relapse of the disease. None came from an ethnic minority. All lived in their own homes.

The main themes derived from the analysis across both focus groups are described in the following section. In a separate paragraph, the spousal involvement will be mentioned. Figure 1 illustrates the main themes with subthemes derived from the analysis.

Main theme: treatment with radiotherapy and androgen deprivation therapy

The main essence, ‘the participants’ experiences of the treatment’, was identified as the following five subthemes:

Like a working day

The influence on everyday life was substantial as it meant 8 weeks with a daily visit to the hospital to receive radiotherapy. Most of the participants drove themselves, and some had long distances to drive (>100 km). The majority of the participants were retired, but the daily visit had extensive impact on everyday life, as one describes:

It was a kind of work – in a way – to have to take that trip every day (FG1-2)

The schedule of the radiotherapy felt overwhelming. Vacations periods and holidays gave a feeling in some patients that the treatment dragged on and on.

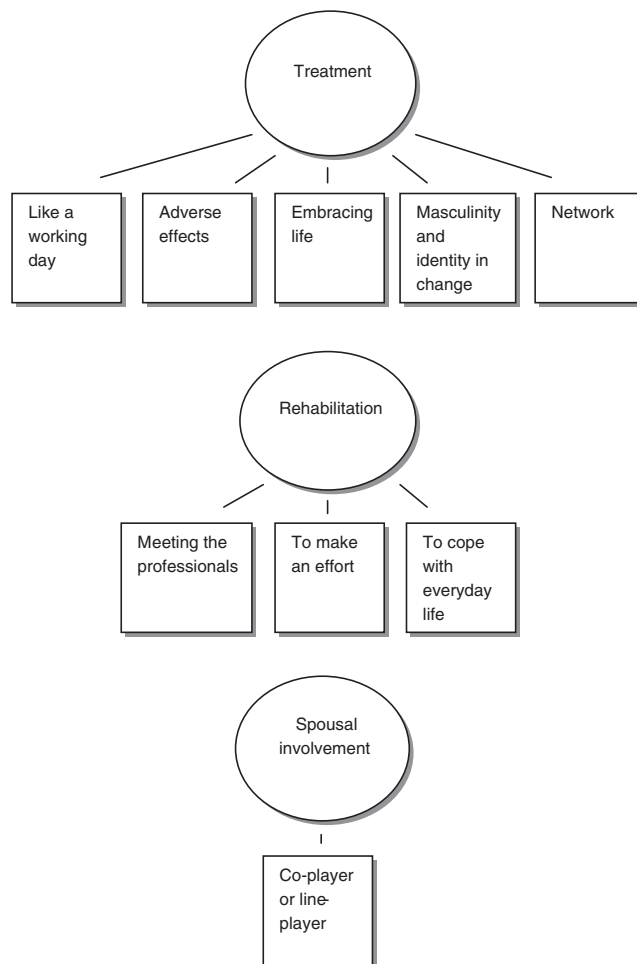


Figure 1. Main themes and subthemes derived from the analysis.

The radiotherapy was less complicated than the participants expected beforehand, and no pain during treatment was described. The nurses as persons were described as caring, flexible and humorous. This humour was important and made the men feel alive.

The treatment with ADT was described differently. Inconsistent information from the health professionals regarding adverse effects and duration caused uncertainty. One man was not informed about the sexual consequences, but the others felt well informed. However, they all wanted better information about how long the adverse effects would persist after the treatment was completed.

Adverse effects

Adverse effects from the radiotherapy were primarily described as related to the bladder and bowels. These problems were frequent in the acute phase but decreased over time. Most of the participants described irritative bladder symptoms necessitating voiding about three times every night and in some also every second hour during the day. Adverse effects from the bowels were bloody stools, pain and irritation, stinging and itching. This bother decreased significantly after the radiotherapy. A few still had problems. One man said:

Almost every day between 11 and 1 o'clock, if I have to pass wind, some mucus also comes out. I have a little pad in my underpants (FG2-9)

ADT-related adverse effects were experienced by all participants. The complaints were increasing weight, changed body image, and hot flashes. The lack of sexuality affected the men in both a physical and mental way.

Nine were still actively being treated with ADT, one had completed the scheduled therapy, and three had found the hot flashes so intense that they decided to stop before the scheduled end of the therapy (Table 1). However, all patients were still suffering from adverse effects. The hot flashes were described as worst in the evening and at night, whenever they rested. The intensity varied from a light facial flush to extensive sweating with the need to change bedclothes every night. Together with the nocturia, the hot flashes resulted in lack of sleep and reduced quality of life in some.

The impact on sexuality was described as significant, even though the participants agreed that other life values were important too. Libido and function were affected in all but one participant. Five of them expressed hope for improvement after treatment, but had difficulty believing it. One participant complained that he was not informed about the treatment's impact on sexuality.

The importance of having both oral and written information about the adverse effects was described as essential. Only a few participants had previously had any symptoms before the diagnosis of prostate cancer, partly explaining why the experience of adverse effects was distressing.

Embracing life

Despite adverse effects, the participants expressed gratitude to being alive, as one said:

We still cling to life despite everything. And it's not so bad. . . . even without a sex life (FG1-2)

Most of the participants were told to consider themselves as cured after the radiotherapy. Nevertheless, their thoughts circled around this issue. They agreed that they had to rely on the information given by the health professionals. Except for the shock felt on learning of the diagnosis, the participants denied psychological problems; on the contrary, they claimed to accept things as they came. They spoke openly about death, with a distinctive male humour and sarcasm, and wanted to get the most out of the time left. Several of the participants had other health problems, and some had seen family members die of cancer. The present illness gave an involuntary opportunity to reflect on what is important in life.

In most cases, they limited their hopes to being able to participate in specific events, e.g. a child's wedding day or driving a veteran car. Religious thoughts increased, but these thoughts were kept to themselves.

Masculinity and identity in change

During the treatments some bodily changes occurred. All gained weight, increased fatty tissue appearing particularly on the stomach, breasts, buttocks, as their body became feminised. The testicles shrank, and along with hot flushes, some similarity with menopausal women was evident. The participants ribbed each other:

You're almost a women with those hot flashes (FG-5)

These bodily changes and lack of sexual ability had an important impact on how the participants felt like men, as one said:

We don't feel like men anymore (FG2-10)

Age had an impact on how they accepted the situation. It was more acceptable to have sexual problems in old age, and not to be able to do the same things as before. Nevertheless, the participants experienced the decline in

sexuality as a loss, and with sadness they realised the influence on their marital life.

Network

This subtheme dealt with close relations, especially the spouse, and the peripheral relations, other family members, friends, and the remaining formal or informal network. The majority of the participants lived in cohabitation, but one man was divorced, and one man had recently lost his wife to cancer. The spouse was described by FG1 as a key support during the entire cancer journey. Some of the men ($n = 4$) were living in new partnerships, and one man had a much younger wife. These couples were particularly affected by the lack of sexuality. The men did not directly express concern as to whether the spouses would leave, but there was a feeling of loss because of the changed interplay between man and wife. The romance was gone. Furthermore, they expressed concern about the women's need to be satisfied.

Other things committed the couples to each other, like love for each other and children together. However, several of the men in new relationships expressed hope for sexual recovery after treatment.

The other family was only involved if they had certain competences, e.g. having prostate cancer themselves, and friends were typically not involved unless they asked.

So it's just within a very small circle that one (talks about it) . . . and so only with those who know something about it (FG2-13)

Two of the participants had a good contact with their general practitioner but most had not been in contact since referral to hospital, and consequently did not see the general practitioner as a support.

The men met fellow patients in the radiotherapy waiting room. They were confronted with the suffering of others and reflected. Some made new acquaintances and reported that these gave support during the patient trajectory.

Main theme: rehabilitation

The main essence: 'the participants' experiences of the rehabilitation programme' was identified as the following three subthemes:

Meeting the professionals

The participants in the rehabilitation study RePCa met nurses and physiotherapists. The approach of the health

professionals was described as important. Kindness and courtesy were essential, but also knowledge of what the individual patient had been through.

They were unbelievably informal and open talks . . . and I was VERY pleased with them, you know, and my wife was also present FG1-1

At the same time, it was important that the patient was acknowledged as a person and that the discussion was relevant and important.

Yes, because she had such a good approach . . . she didn't come and say we had to talk about it . . . because you think anyway, no, damn it, we aren't going to do it that way . . . not me . . . she started with some good, err, quiet . . . just to get the conversation going (FG2-7)

The participants had been in treatment for a long time and were dependent on the staff. The rehabilitation gave the men a sense of security during the change to everyday life.

The participants described that they had had the opportunity to select the topic to be discussed, including physical, mental or social concerns of everyday life. They related that they were given knowledge and support on how to act themselves, and some specific advice was provided regarding, for example, urination, bowel function, and referral to a sexologist.

Some difficulties were seen regarding telling doctors from nurses, but the profession was not pivotal. The gender of the health professionals was of importance for some of the men, because they felt bashful towards their own gender regarding sexuality.

Good personal contact with the health professionals was described as important to get the most out of the intervention.

To make an effort

In general, the men expressed satisfaction with the intervention given by both the nurses and physiotherapists. Most had good conversations with the nurses. Three of the participants wanted more specific initiatives in the nurse consultation, but the men disagreed about this. Others mentioned the importance of contributing to their own rehabilitation. The men experienced the visits to the physiotherapists as relevant, with information about the risk of decline in muscle strength due to ADT, and guidance regarding pelvic floor and physical exercises. Some of the participants exercised actively and felt this as beneficial. Others did not do the exercises.

When I haven't been physically active to the point of tiredness . . . so that I sweat a little and such, but, err, I've discovered that when I make an effort with the pelvic exercises and to be more active in general, the more exercise the better, then I feel good again (FG1-2)

To talk with the physiotherapists was experienced as motivational, and there were several reasons for doing the exercises. Present problems motivated some, and others were worried about the consequence of weak muscles. On the other hand, if the men did not have problems the motivation decreased.

To cope with everyday life

The men appreciated the ability to sustain a normal everyday life. Most of them did the same things as before, but adapted their life to the frequent visits to the lavatory. One truck driver, using pelvic floor exercises, learned to hold back until the next highway pull over. Others modified their lifestyles.

The men handled the adverse effects mostly by themselves, but welcomed advice from the professionals, e.g. psyllium seeds for stool control. The participants attempted to maintain normalcy, and believed that some of their problems were due to ageing.

We're old men you know. Men without prostate cancer also have to get up at night (FG1-5)

Humour was a dominant and much used coping mechanism and was used to shift focus.

Some of the men needed to change behaviour due to hot flushes. One man said that he always brought along an extra shirt to social events. Several of the men felt embarrassed when they started to flush among strangers, because then they needed to explain the cause.

Main theme: spousal involvement

The participants' attitude towards spousal involvement in the rehabilitation is described in the subtheme co-player or line-player. Significant differences between FG 1 and 2 are described by examples in Table 2.

Co-player or line-player

All patients in the RePCa study were advised to bring their spouses to the intervention. The participants in FG 1 chose to bring their spouses to every nursing consultation, but the participants in FG 2 came alone. FG 1 experienced the spousal involvement as important because of the

opportunity to be together and talk about treatment, adverse effects, and future possibilities. Furthermore, the participants in FG 1 believed that the involvement had a calming impact on their spouses.

I think that just because she's there and gets told about this and that . . . this calms her down, because actually she was more nervous about it than me (FG1-6)

Questions asked by the spouses were of benefit for the patient too, as they revealed different perspectives.

To bring his spouse to the interviews was often motivated by the advice given by the health professionals. Active spousal involvement in the intervention enhanced the men's motivation to follow the planned programme.

I trained with my wife. She did exactly the same exercises . . . and she's the one who often asked: shouldn't we have a go at it? FG1-4)

FG 2 did not bring spouses (two had no spouses). It was obvious that in this group, the men were used to handling things themselves.

No, it's much better to be alone, so could we ask about what we wanted (FG2-13)

Main theme: interaction in the groups

The interaction between the participants is often seen as a key to the focus groups (Freeman 2006). In the following section, we will describe how the men interacted in the focus groups, with Goffman's main message in mind: people in social interaction attempt to sustain their self-narratives (Goffman 1959).

The atmosphere in both focus groups was relaxed, but in FG 2 (no spouse involved in rehabilitation) there was a much more male jargon with a lot of laughter. A text count in NVivo showed that the word laughter was used 31 times in FG 1 and 60 times in FG 2. All participants were active in the discussion, although some were more talkative.

There was a large degree of consensus in both focus groups, and they agreed especially about the experience of treatment, adverse effects, and that the prostate cancer did not affect them mentally. The self-narrative of being a man in a Western culture has been described as the hegemonic masculinity, e.g. characterised by toughness, stoicism, little or no emotional sensitivity (Cecil *et al.* 2010), and none of the participants went against this self-narrative (Table 3).

However, some disagreements were seen regarding the information given by the health professionals and the experience of the nursing consultations. The men were

Table 3. Examples of the specific male culture expressed by the participants

| |
|--|
| Rely on the information given by the health professionals. |
| Denied psychological problems, and accept things as they come. |
| A distinctive male humour and sarcasm due to death and a feminised body. |
| Age had an impact on how they accepted their situations. |
| Want specific information and initiatives relevant for the individual. |
| Seek support with people who know something about the disease. |

happy to share experiences of how to cope with adverse effects friendly teased each other, e.g. one man said that he hoped for a better sexuality after treatment, and the others said that this was only because of his young age. He was 66. At one point the men were discussing the levels of prostate-specific antigen (PSA), and it was almost like a competition to relate the lowest figure. FG 2 expressed that this kind of being together (in a focus group) was seen as an added bonus and could be an alternative function/path in rehabilitation instead of the individual nursing consultations, although they still wanted a nurse to contribute.

DISCUSSION

The present study explored a male approach and experiences of treatment with IMRT, ADT, and rehabilitation with or without spousal involvement.

Treatment

The treatment with IMRT was experienced with satisfaction, and only minor problems were reported. However, ADT caused significant adverse effects regarding body image, hot flashes, and sexuality, consistent with the results from previous quantitative studies (Harrington *et al.* 2009; Dieperink *et al.* 2012). These problems were complicated by a lack of or inconsistency in the information given by the health professionals. Indeed, if patients dropped out of ADT before scheduled completion of therapy because of unclear information, it could be fatal because ADT postpones relapse (Bolla *et al.* 2010). Therefore, the information about ADT should be more in focus.

We found that humour was a particular male coping strategy, and together with maintaining normalcy they embraced life one day at a time, as thoughts about death were always present. This finding is supported by the findings of Ervik *et al.* (Ervik & Asplund 2012), who described the specific humour used as gallows humour. The diminished masculinity and changes in identity

involved body and mind, and the men had to accept an influence on their partnerships as well. However, the spouse was still described as the key support during treatment, consistent with the findings of Arrington, and Kelsey *et al.* (Kelsey *et al.* 2004; Arrington 2005).

All things considered, as also found by Hedestig *et al.*, the specific male culture could be the reason why these men did not share experiences of prostate cancer with friends and family, unless they had specific knowledge of the subject (Hedestig *et al.* 2005).

Rehabilitation

In contrast with previous studies regarding patient perspectives on treatment, this study adds knowledge about what prostate cancer patients see as supportive during the rehabilitation process. The patients in the RePCa study met nurses and physiotherapists two times each during the first 6 months after radiotherapy. The participants valued the professionals approach, with room and time for discussing present needs. O'Brien *et al.* found during a qualitative study that psychosexual problems gained importance over time, even for the very elderly (O'Brien *et al.* 2011), and consequently, rehabilitation has to contain the possibility of appointments with the health professionals at variable times after treatment, as in the RePCa study. However, to be supportive the intervention had to be specific, and the individual man to be motivated to make an effort of his own, otherwise he was not able to convert this new knowledge for use in daily life. A few participants did not benefit much from the rehabilitation process. These men did not wish to change health behaviours. This is in line with the expectations of the method of motivational interviewing viewed as being particular useful for clients who are reluctant to change or who are ambivalent about changing their behaviour (Rubak *et al.* 2005). Hence, the difficulties integrating health behaviour and psychosocial support are underlined here. Maybe the patient's motivation should be determined before entering a rehabilitation process?

The findings in our study hinted that the focus group itself provided an unplanned added bonus regarding a supportive environment among peers. This was also seen in another Danish rehabilitation study of 17 men with various cancers (Adamsen *et al.* 2001).

The specific male approach and differences between the needs of female and male cancer patients are important to understand when planning rehabilitation. The findings in several mixed rehabilitation studies have been difficult to generalise to the entire cancer population due to under-representation of male cancer patients (Hoybye *et al.*

2008; van Weert *et al.* 2010). Maybe this could be due to a devaluation of the male perspective in the interventions provided.

Spousal involvement in rehabilitation

Differences were seen between FG 1 and FG 2 regarding the men's attitude towards spousal involvement in rehabilitation; while FG 1 enhanced the involvement as important, FG 2 played it down. Maybe this difference reflected the relationship between the couple. Walker and Robinson found that loss of sexuality due to ADT frequently leads to changes in the marital relationship, and recommended that interventions should support a strong relational bond (Walker & Robinson 2010). Participants in FG 1 related that the spouses felt calmed by the involvement. Bruun *et al.* found in a qualitative study that being a partner of a man with prostate cancer could be lonely (Bruun *et al.* 2011), and Tanner *et al.* described several difficulties experienced by the partner (Tanner *et al.* 2011). However, the spouses were not interviewed and could have contributed with interesting results about being either included or not in the rehabilitation process.

Interaction

Some things may not turn up in a focus group, and the similarity with Goffman's dramaturgical analysis is striking: that people's interaction with most others happens 'frontstage', and the private and hidden place 'backstage' is where individuals can be themselves and get rid of their role or identity in society (Goffman 1959). However, the men in this study also enjoyed being with peers, with whom they revealed sensitive issues, so maybe the stage has several levels.

Trustworthiness

In this study two focus groups were established. Stewart and Shamdasani suggest that there are no general rules as to the optimal number of focus groups (Stewart & Shamdasani 1990), but Krueger suggests a minimum of three groups (Krueger 1994). However, the principle of saturation was used in this study, as the participants were homogeneous with regard to a potential general population. Furthermore, pragmatic reasons including limitations of time and resources were important for the decision. The sample size in the groups was six and seven participants. This seemed to be ideal as all participants had the opportunity to speak, and the moderator was able to manage the groups.

Strength and limitations

As far as we know, this study is one of the first studies exploring men's experiences of rehabilitation after treatment with IMRT and ADT for prostate cancer. The inclusion rate was quite high, as 13 patients out of 17 invited participated. In this way, we suggest that our findings give a good understanding of Danish prostate cancer patients' experiences of treatment and this specific rehabilitation. However, the qualitative study is supported by a concurrent quantitative research in the ongoing RePCa study that examines the effect of the rehabilitation intervention in a larger sample using questionnaires.

None of the men reported any impact on their mental health, but the design of the study may not be optimal in exposing emotional problems. Men living up to the ideals of hegemonic masculinity would object to admitting such things in a group of other men, and maybe especially to female researchers (Cecil *et al.* 2010), but, as described in the results, some of the men could also have problems discussing sexual issues with male persons.

CONCLUSION AND IMPLICATIONS FOR CLINICAL PRACTICE

Because ADT severely influences masculinity and male identity and in consequence affects everyday life, patients must be given carefully information about its adverse effects.

Rehabilitation after treatment is seen as an important support, but calls for an awareness that the interventions take male culture into account. Spousal involvement in rehabilitation may reflect the relationship the couple had beforehand, and it is therefore important to let the man decide whether or not he wants to involve his spouse.

Understanding the male perspectives on treatment and rehabilitation will allow us to tailor and develop interventions designed to improve the quality of life of survivors after prostate cancer.

ACKNOWLEDGEMENTS

We especially wish to thank the cancer patients who participated in the study for their valuable contributions. This study was funded by Odense University Hospital (OUH) Research Foundation, the University of Southern Denmark, the Danish Cancer Society, CIRRO – The Lundbeck Foundation Center for Interventional Research in Radiation Oncology, the Department of Oncology, OUH, the Mette Hede Nielsen Foundation, the Nurses Research Foundation, the Danish Nurses Organization Research Foundation, and the Propa Vita Foundation.

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Keywords: radiotherapy; physical therapy; pelvic floor; nursing; quality of life; urinary irritative symptoms

The effects of multidisciplinary rehabilitation: RePCa—a randomised study among primary prostate cancer patients

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Background: The objective of this study is the effectiveness of multidisciplinary rehabilitation on treatment-related adverse effects after completed radiotherapy in patients with prostate cancer (PCa).

Methods: In a single-centre oncology unit in Odense, Denmark, 161 PCa patients treated with radiotherapy and androgen deprivation therapy were randomly assigned to either a programme of two nursing counselling sessions and two instructive sessions with a physical therapist ($n=79$) or to usual care ($n=82$). Primary outcome was Expanded Prostate Cancer Index Composite (EPIC-26) urinary irritative sum-score. Before radiotherapy, pre-intervention 4 weeks after radiotherapy, and after a 20-week intervention, measurements included self-reported disease-specific quality of life (QoL; EPIC-26, including urinary, bowel, sexual, and hormonal symptoms), general QoL (Short-form-12, SF-12), pelvic floor muscle strength (Modified Oxford Scale), and pelvic floor electromyography. Intention-to-treat analyses were made with adjusted linear regression.

Results: The intervention improved, as compared with controls, urinary irritative sum-score 5.8 point (Cohen's $d=0.40$; $P=0.011$), urinary sum-score ($d=0.34$; $P=0.023$), hormonal sum-score ($d=0.19$; $P=0.018$), and the SF-12 Physical Component Summary, $d=0.35$; $P=0.002$. Patients with more severe impairment gained most. Pelvic floor muscle strength measured by electromyography declined in both groups, $P=0.0001$.

Conclusion: Multidisciplinary rehabilitation in irradiated PCa patients improved urinary and hormonal symptoms, and SF-12 physical QoL.

Prostate cancer (PCa) is the most frequent male malignancy in the Western world (Ferlay *et al*, 2010). The development of treatment with radiotherapy combined with androgen deprivation therapy (ADT) has, in locally advanced or high-risk PCa, increased the 10-year survival rates from ~60% to >70% (Widmark *et al*, 2009). Following these improvements in survival, a growing interest has emerged in evaluating the impact of the overall treatment on quality of life (QoL) (Miller *et al*, 2005; Sanda *et al*, 2008), and clinical attention has been directed towards how the

adverse effects of the treatment may be counteracted (Johansen, 2007; Armes *et al*, 2009; World Health Organization, 2012). Adverse effects are categorised into acute disorders occurring within 6 months of radiotherapy or late complications after 6 months or more (Grise and Thurman, 2001).

In particular, urinary irritative problems causing frequency, nocturia, urgency or urge incontinence are of major concern for these patients (Michaelson *et al*, 2008; Budaus *et al*, 2012). The incidence of acute urinary tract symptoms after

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Received 15 June 2013; revised 6 October 2013; accepted 8 October 2013; published online 29 October 2013

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intensity-modulated radiotherapy is estimated to occur in one or even two out of every four patients (Budaus *et al*, 2012). Furthermore, the risk of late urinary adverse effects is increasing in patients with acute disorders. In a follow-up study from the United States of America with 1571 patients who experienced acute urinary symptoms during treatment, the risk of having grade 2 (CTC 3.0) late adverse effects after 10 years was found to be significantly increased from 12 to 35% (Zelevsky *et al*, 2008).

In randomised trials, home-based training of pelvic floor exercises has been confirmed as an effective non-invasive treatment of post-prostatectomy incontinence, showing significantly decreased duration and degree of incontinence (Van Kampen *et al*, 2000; Filocamo *et al*, 2005). However, this concept has not been investigated in a randomised designed study following treatment of PCa with radiotherapy and ADT (Cockle-Hearne and Faithfull, 2010), and especially not with urinary irritative problems as the primary end point. Here, we present data from the first RCT to investigate a multidisciplinary rehabilitation programme comparing usual care with psychosocial support from nurses and counselling in pelvic floor exercises primarily to reduce urinary irritative problems and secondarily to increase overall QoL.

MATERIALS AND METHODS

Setting and participation. The study called RePCa was approved by the local Scientific Research Ethics Committee (File no. S-20090142), the Danish National Data Protection Agency (File no. 2012-41-1175), and registered by ClinicalTrials.gov (Study number, NCT01272648). All participants provided written informed consent.

Design. The design was organised as a two-armed randomised, controlled trial recruiting from 226 patients referred to curative radiotherapy from 1 February 2010 to 31 January 2012 at Odense University Hospital, Denmark. A total of 209 patients fulfilled the inclusion criteria and were eligible for participation as shown in the CONSORT diagram (Boutron *et al*, 2008), Figure 1. The patients were informed about the RePCa study from a project nurse at the first meeting at the Department of Oncology.

Inclusion criteria: men ≥ 18 years old with biopsy-documented adenocarcinoma of the prostate.

Exclusion criteria: former prostatectomy, not able to speak Danish, or included in other protocols.

Information about Gleason score, TNM-staging, prostate-specific antigen values, and comorbidity was obtained from the medical records, and patients were registered in risk groups as described by D'amico *et al* (1998) with regard to determining the treatment plan.

Intensity-modulated radiotherapy used a prescription dose of 78 Gy in 39 fractions given in five fractions per week. Inter-fractional prostate displacement was corrected by daily IGRT using implanted gold markers. Target volume was the prostate gland including the proximal 2 cm of the seminal vesicles in high-risk patients and adding a 7-mm margin. Three patients in each randomisation group received pelvic radiotherapy due to metastatic lymph nodes. Androgen deprivation therapy was started 3 months before radiotherapy; in T3 patients, ADT is given for up to 3 years.

Patients were randomly assigned to the intervention group or usual care (control group) in a ratio of 1:1 after the completion of radiotherapy. The randomisations were externally handled by the Department of Clinical Research at Odense University Hospital, Denmark, and the allocation sequence was concealed from the research team.

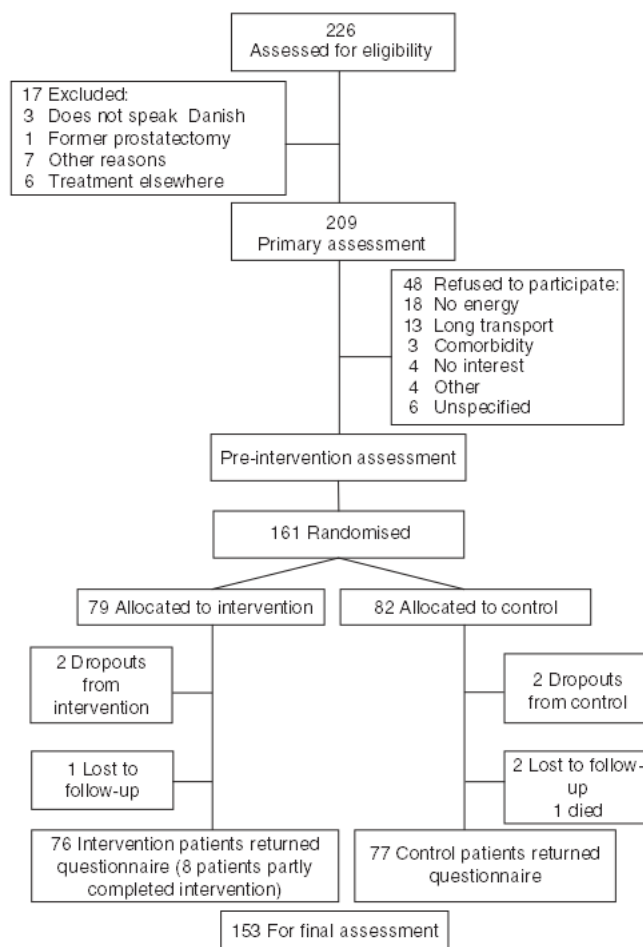


Figure 1. CONSORT-Flow chart.

Intervention. The intervention was based on the following definition: 'Rehabilitation is a focused and temporary process of cooperation between the patient, relatives, and the professionals. The purpose for the patient is to achieve an independent and meaningful life, even if he has, or is at risk of a significant decline in his physical, mental, or social functions. Rehabilitation is based on the patient's whole life situation and consists of a coordinated, interconnected, and knowledge-based effort' (Rehabiliteringsforum, 2004).

The intervention took place in an outpatient setting at the Department of Oncology and the Department of Rehabilitation. At 4 weeks post radiation, pre-intervention data were obtained from all patients in the study and the intervention was initiated.

The control group received usual care during follow-up. The usual care consisted of one physician visit 4 weeks after radiotherapy. No systematic education for the control group was provided during the trajectory. In addition to usual care, the patients in the intervention group were instructed in an individually suited multidisciplinary programme during two nursing counselling sessions and during two additional sessions of counselling by physical therapists aiming the exact need of each individual patient; Figure 2. The patient was recommended to bring his spouse along for all counselling and instructions in order to increase understanding of and compliance with the exercises suggested.

The above-mentioned intervention was provided by dedicated staff members at each site. The seven project oncology nurses engaged in the intervention activities were specially trained and qualified radiation therapists, and the two physical therapists had more than 10 years of clinical experience in the instruction and

| Time line | Intervention group | Control group |
|--|--|---------------|
| 12 Weeks before radiotherapy | Primary assessment with questionnaires and test of muscle strength by blinded assessors. | |
| | Radiotherapy | |
| | Randomisation | |
| Pre-intervention 4 weeks after radiotherapy | (a) (b) (c) | (a) (b) |
| 8 Weeks from pre-intervention | (d) (e) | |
| 20 Weeks from pre-intervention | (f) (b) | (b) |
| 21–22 Weeks from pre-intervention | Outcome questionnaires were received by mail. | |

Notes:

- (a) 25-Min follow-up visit at the Department of Oncology with oncologist. Pre-intervention questionnaires were received and checked by nurse. Patients were informed about group allocation.
- (b) 30-Min muscle strength test by blinded assessors.
- (c) 60-Min first individual visit with the physical therapist. Guidance of functional home training and pelvic floor exercises depending on the muscle strength test. A pamphlet with the individual training goals was handed out.
- (d) 40-Min first individual visit with the oncology nurse, identifying patient’s needs and response to them, for example psychological support, counselling about lifestyle, toilet habits, sexual problems.
- (e) 45-Min second individual visit with the same physical therapist. Follow-up guidance.
- (f) 40-Min second individual visit with the same oncology nurse. Follow-up and perspectives on the new everyday life.
- (b) 30-Min muscle strength test by blinded assessors. The last questionnaire was handed out with a pre-paid envelope, and the patient was asked to send it in within a few weeks.

Figure 2. Graphical depiction of the intervention in a randomised rehabilitation study with 161 participants with PCa, Odense, Denmark.

training of men in order to address incontinence, including pelvic floor training. This group of nine staff members were all enrolled in a 6-day course with seven 45 min lectures per day containing the topics PCa and treatment, the male perspective, incontinence and the pelvic floor, sexuality, depression and fear of recurrence, social support, and finally the method of motivational interviewing (Miller and Rollnick, 2002) that was used as a communicative platform. To ensure consistency in the intervention, the staff had 12 supportive, 60-min reinforcing sessions every second month provided by a motivational interview trainer. Communication between the multidisciplinary staff members was provided during structured documentation in the patients files.

Nursing counselling. The nursing counselling sought to provide psychological support and enable identification of problems regarding the disease experienced by the patient and his spouse, Figure 2. In accordance with the framework for nursing (Benner and Wrubel, 1989), the nurses initiated the dialogue based on the patients needs. With this approach and secondarily with the

professional knowledge of possible themes important for PCa patients written in a guideline, the nurses identified information needs about adverse effects, established an individual rehabilitation plan based on the patients’ personal goals, and, if needed, provided advice on lifestyle changes concerning smoking, alcohol, general fitness, diet, weight control, and further suggested solutions to other problems, for example, toilet habits, sexuality, and psychological problems. The project oncology nurses had the authority to refer patients in the intervention group to medical specialists, public/community rehabilitation centres, sexologists, and social workers.

Physical therapy counselling. The physical therapy identified the individual patient’s need for increased pelvic floor muscle function and general physical activity level; Figure 2. Symptoms related to pelvic floor muscle function were explored, for example, urination control, flatulence, and defecation. If necessary, the patient was guided by biofeedback, a visual signal presenting the pelvic floor strength to the patient (Dorey, 2006).

A written pamphlet was created specifically for the purpose of this study and explained how PCa treatment affects physical and general health. The self-training home programme consisted of pelvic floor muscle exercises integrated in daily activities, for example, during driving the car, walking, or working in the garden. The exercises for the major muscle groups included muscle endurance and strength and balance exercises, for example, three sessions of 10–12 repetitions for each muscle group. General physical activities were recommended to inactive patients for at least 30 min per day. The agreement about the self-training programme was noted in the pamphlet. The second session was used as a follow-up on the individual goals of each patient.

Primary and secondary outcome measures. Study outcomes were preliminary assessed before radiotherapy, as pre-intervention measurements at 4 weeks post radiation and after the 20 weeks of intervention; Figure 2. The 20 weeks of intervention were used to allow for muscle training and a change from 'being a patient' to 'being a cancer survivor'.

The primary outcome was defined as the urinary irritative sum-score based on the Expanded Prostate Cancer Index Composite (EPIC-26). The irritative sum-score was derived from four items regarding pain, bleeding, weak stream, or frequent urination. Secondary outcomes included QoL arising from the Medical Outcome Study Short-form-12 (SF-12), urinary incontinence, bowel, sexual and hormonal sum-scores as measured by the EPIC-26, and assessment of the pelvic floor by clinical examination and electromyography.

EPIC-26. The disease-specific validated EPIC-26 consists of domains concerning urinary symptoms, bowel symptoms, sexual function, and symptoms related to ADT. The internal consistency and test-retest reliability for EPIC-26 (Cronbach's $\alpha > 0.70$ and $r > 0.69$) for all domains support its validity. For each domain, a sum-score is constructed. In addition, two urinary scales that distinguish irritative/obstructive symptoms and incontinence were obtained. For the primary outcome, the urinary irritative sum-score, Cronbach's α was 0.74 and $r > 0.80$ (Szymanski *et al*, 2010). Expanded Prostate Cancer Index Composite items are answered on a 5-point Likert scale from no problems to severe problems. Scores are transformed linearly to a scale of 0–100, with higher scores indicating better QoL (Wei *et al*, 2000; Szymanski *et al*, 2010). A low inter-scale correlation observed between SF-12 and EPIC domains supports the concurrent use of EPIC with SF-12 (Wei *et al*, 2000).

SF-12. The generic extensively validated QoL questionnaire SF-12 (Ware *et al*, 1996) includes eight concepts: physical functioning, role limitations due to physical health problems, body pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health. The reliability of SF-12 was tested in two data sets and showed a test-retest summary measure of 0.89 in the United States of America and 0.86 in the United Kingdom. Results are expressed in two meta-scores: the Physical Component Summary and the Mental Component Summary. These meta-scores are standardised to the population normative values of the United States of America, with a mean score of 50 and a s.d. of 10. Higher scores represent better health (Ware *et al*, 1996).

Pelvic floor assessment. A standardised protocol ensuring a correct and reproducible technique was used for all tests. This protocol was developed after pilot tests of seven patients, including subject lateral positioning, exact wording of instructions, and avoidance of muscles other than the pelvic floor. Pilot test data were not included in this study.

In all patients, a correct pelvic floor muscle contraction was confirmed on digital rectal evaluation by the assessor before

making the test. The instruction used for each contraction was 'squeeze and lift' the pelvic floor. Muscle strength was measured by the ability to contract. Digital evaluation was done according to the modified 6-point Oxford Scale (Dorey, 2007). Surface anal electromyography (EMG) was performed with NeuroTrac Myo-Plus (Verity Medical Ltd., Hampshire, England) with an Anuform analprobe (Patterson Medical UK Ltd, Nottinghamshire, UK). The three assessors of the pelvic floor function were blinded and independent of the research team. The patients were told not to give the assessors information about group assignments.

All data entry was done by the first author. A quality control was made with the procedure as recommended by King and Lashley; the first 10 questionnaires in the data set were controlled, and then every 10 questionnaire until errors occurred. Further, each questionnaire was controlled until 10 were without errors (King and Lashley, 2000).

Sample size calculation and statistical analyses. The power calculation was based on a two-sided *t*-test on difference between programs in the mean reduction in the EPIC-26 urinary irritative sum-score (Michigan, 2012) corresponding to a Cohens *d* of 0.5 (mean change divided by s.d.). We applied a significance level of 5% and power of 80%. The sample size of 160 patients was found by taking into account a maximal drop-out rate of 20%.

Socio-demographic and clinical characteristics were described using means for continuous variables and frequencies for categorical variables. Differences regarding disease-specific and general QoL (continuous) between intervention and control groups were tested with multiple linear regression models adjusted for pre-intervention scores. Differences in the strength of pelvic floor muscles were tested with the Wilcoxon rank-sum test. Inter-rater reliability between assessors was tested in a random example of 15 records with Kappa statistics. Groups were analysed with intention-to-treat according to the allocated group.

Correlations between variables were tested with linear regression models. We checked the model assumptions, that is, linearity, normality, homogeneity, and serial correlation of residuals, by relevant scatter plots followed by visual inspection.

As only one primary end point was selected and secondary end points have to be tested in future studies, adjustments for multiple comparisons were not made. *P*-values ≤ 0.05 were considered statistically significant and were reported two-sided.

In some of the returned questionnaires, data were missing. According to the methods described for EPIC urinary irritative sum-score and incontinence sum-score and SF-12, all questions should be answered to be analysed. Questionnaires with insufficient data were therefore removed from the analysis. The EPIC domains: urinary, bowel, sexual, and hormonal sum-scores allow one missing answer (Ware *et al*, 1996; Wei *et al*, 2000). Statistics were calculated with STATA 11 (StataCorp LP, College Station, TX, USA).

RESULTS

A number of 226 patients were screened for eligibility, but 48 patients refused to participate because of several reasons; Figure 1. Groups were balanced at pre-intervention, and we had some information of the patients who refused; Table 1. Patient flow before and after randomisation of 161 patients is shown in Figure 1, leaving 153 patients (95%) for the analysis. The attrition rate was 5% as four patients dropped out, one died, and three were lost to follow-up. A total of 71 out of 79 patients in the intervention group (90%) completed the entire intervention programme that included two nursing counselling and two physical therapy counselling sessions, but data from all patients were analysed according to the allocated group. Data (150 out of 153; 98%) regarding the primary end point urinary irritative symptoms were completed.

Table 1. Socio-demographic and biological pre-intervention characteristics of 161 participants and 48 refusers with primary prostate cancer included in a randomised controlled trial after radiotherapy and androgen deprivation therapy, 2010–2012 Odense, Denmark

| | Intervention group (n = 79) | Control group (n = 82) | Refusers (n = 48) |
|---|-----------------------------|------------------------|----------------------|
| Socio demographic characteristics | | | |
| Age at first radiotherapy date (years), mean (s.d.) | 68.2 (4.8) | 69.0 (5.2) | 68.7 (6.4) |
| Weight (kilo) reported at pre-intervention mean (s.d.) | 84.7 (12.7) | 86.3 (14.8) | 85.9 (15.6) |
| Unknown | 1 | 3 | 7 |
| Body mass index (BMI) kg m ⁻² mean (s.d.) | 27.1 (3.6) | 27.4 (4.1) | 27.2 (4.6) |
| Unknown | 1 | 3 | 7 |
| Social status reported at pre-intervention | | | |
| Living alone | 10 (13%) | 12 (15%) | 8 (19%) |
| Living with a spouse | 68 (87%) | 67 (85%) | 33 (81%) |
| Unknown | 1 | 3 | 7 |
| Education (years) | | | |
| 9–10 | 31 (40%) | 36 (46%) | 21 (52%) |
| 12–13 | 24 (31%) | 23 (29%) | 12 (30%) |
| 13–16 | 18 (23%) | 18 (23%) | 6 (15%) |
| 18–20 | 5 (6%) | 2 (2%) | 1 (3%) |
| Unknown | 1 | 3 | 8 |
| Smoking status at pre-intervention | | | |
| Never smoker | 33 (42%) | 32 (41%) | 12 (29%) |
| Past smoker | 30 (39%) | 35 (44%) | 20 (49%) |
| Current smoker | 15 (19%) | 12 (15%) | 9 (22%) |
| Unknown | 1 | 3 | 7 |
| Medical characteristics | | | |
| PSA pre-treatment serum mean ng ml ⁻¹ (s.d.) | 21.5 (17.7) | 19.8 (16.8) | 21.6 (18.4) |
| Gleason score | | | |
| ≤ 7 | 10 (13%) | 17 (21%) | 10 (21%) |
| 7 | 47 (59%) | 44 (54%) | 25 (52%) |
| > 7 | 22 (28%) | 21 (25%) | 13 (27%) |
| Degree of malignancy | | | |
| T1 | 8 (10%) | 9 (11%) | 6 (12%) |
| T2 | 34 (44%) | 35 (43%) | 23 (48%) |
| T3 | 36 (46%) | 38 (46%) | 19 (40%) |
| Unknown | 1 | | |
| Risk group | | | |
| Low | 1 (1%) | 3 (4%) | 6 (12%) ^a |
| Intermediate | 19 (24%) | 13 (16%) | 8 (17%) |
| High | 59 (75%) | 65 (80%) | 34 (71%) |
| Unknown | | 1 | |
| Hormone therapy | | | |
| No | 3 (4%) | 2 (3%) | 5 (11%) ^b |
| Androgen deprivation therapy (ADT) | 76 (96%) | 79 (97%) | 42 (89%) |
| Unknown | | 1 | 1 |
| Patient-reported comorbidity at pre-intervention | | | |
| Charlson index score 1 | 20 (25%) | 19 (23%) | 13 (27%) |
| Score 2 | 4 (5%) | 5 (6%) | 1 (2%) |
| Score 3 | 0 | 0 | 0 |
| Score 6 | 0 | 0 | 0 |

Abbreviation: PSA prostate specific antigen values.

^aFisher's exact test *P* = 0.028^bFisher's exact test *P* = 0.049

Multiple linear regression adjusted for pre-intervention scores showed that PCa patients in the intervention group benefitted significantly with regard to urinary irritative symptoms with 5.8 point, Cohen's $d = 0.40$; $P = 0.011$ (Tables 2 and 3 and Figure 3). No significant interactions between groups and pre-intervention scores were seen. Covariates (age, body mass index, risk group, prostate-specific antigen values, education, smoking, and marital status) showed no significant correlation with the urinary irritative sum-score.

Physical Component Summary and Mental Component Summary correlated with improved urinary irritative sum-score, $r = 0.55$; $P = 0.015$ and $r = 0.58$; $P < 0.001$, respectively.

Subanalysis showed that the improvement of the urinary sum-score was most pronounced in patients living alone (12.0 point, $d = 0.83$; $P = 0.021$), that pre-intervention urinary bother (score > 3) indicating moderate-to-severe problems gained (13.1 point, $d = 0.90$; $P = 0.034$), and a pre-intervention urinary irritative sum-score below the study mean value of 68 point predicted a higher intervention effect with (10.1 point, $d = 0.70$; $P = 0.031$). Urinary sum-score, hormonal sum-score, and physical QoL (Physical Component Summary) improved significantly in the intervention group compared with controls, whereas pelvic floor muscle strength measured by digital evaluation (Modified Oxford Scale 0–6) did not change significantly during the study period at post intervention in the intervention and the control groups, Table 4. Muscle strength measured by EMG declined

Table 2. Mean changes in QoL scores among 161 Danish prostate cancer survivors included in a randomised rehabilitation study, Odense, Denmark

| | Effect (coefficient) ^a | CI (95%) | P ^b |
|--|-----------------------------------|-----------|----------------|
| Intervention group vs control group | | | |
| SF-12 | | | |
| Physical QoL (PCS) | 3.6 | 1.3; 5.8 | 0.002 |
| Mental QoL (MCS) | 0.7 | -1.6; 3.0 | 0.549 |
| EPIC domains | | | |
| Urinary | 4.5 | 0.6; 8.4 | 0.023 |
| Incontinence | 2.6 | -1.8; 6.9 | 0.242 |
| Irritative | 5.8 ^c | 1.4; 10.3 | 0.011 |
| Bowel | 3.0 | -1.9; 8.0 | 0.224 |
| Sexual | 3.6 | -0.9; 8.0 | 0.117 |
| Hormonal | 4.8 | 0.8; 8.8 | 0.018 |

Abbreviations: CI 95% confidence interval; EPIC Expanded Prostate Cancer Index Composite; MCS Mental Component Summary; PCS Physical Component Summary; QoL quality of life.

^aMultiple linear regression analysis adjusted for pre intervention scores.

^bReported P values are two sided and $P < 0.05$ was considered statistically significant.

^cExample: if the patient is in the intervention group, his mean QoL score (0–100 scale) regarding urinary irritative sum score increases with 5.8 point compared with the controls.

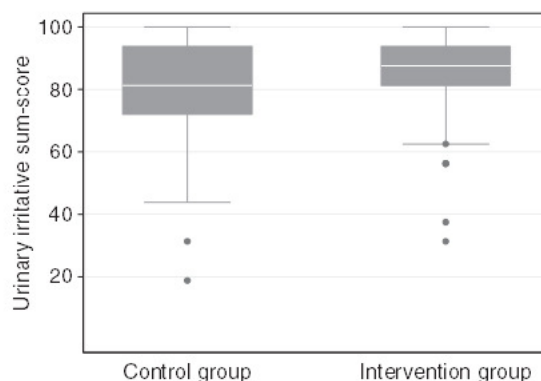


Figure 3. Box-plot median urinary irritative sum-score post intervention in a randomised rehabilitation study with 161 participants with PCa, Odense, Denmark. The whiskers show the lower/upper adjacent value and the box shows 25th–75th percentile. The dots show outliers.

Table 3. Pre-intervention level and changes in disease-specific QoL scores (EPIC), and general QoL scores (SF-12) in intervention and control groups at 4 weeks (pre-intervention) and 24 weeks after radiotherapy (post intervention) among 161 survivors with primary prostate cancer included in (RePCa) a prospective randomised rehabilitation study, 2010–2012 Odense, Denmark

| QoL | EPIC and SF-12 mean QoL (score 0–100) ^a | | | | Cohen's d ^b |
|----------------------|--|--|----------------------------|--|--------------------------|
| | Intervention group, $n = 79$ | | Control group, $n = 82$ | | |
| | Pre-intervention | Difference at 6 months | Pre-intervention | Difference at 6 months | |
| Mean (s.d.) | 4 Weeks after radiotherapy | Between follow-up and pre-intervention | 4 Weeks after radiotherapy | Between follow-up and pre-intervention | |
| EPIC domain | | | | | |
| Urinary irritative | 67.7 (18.7) | 17.6 (18.1) | 68.1 (18.7) | 11.6 (16.5) | 0.40 |
| Urinary incontinence | 82.5 (17.5) | 7.3 (14.9) | 82.2 (21.7) | 4.9 (15.8) | |
| Urinary sum-score | 73.5 (14.5) | 13.3 (13.9) | 73.1 (17.4) | 9.0 (12.9) | 0.34 |
| Bowel sum-score | 77.6 (19.9) | 9.7 (20.3) | 77.0 (20.0) | 7.6 (16.4) | |
| Sexual sum-score | 15.0 (19.5) | -1.3 (13.7) | 14.0 (20.1) | -4.1 (16.4) | |
| Hormonal sum-score | 71.6 (18.8) | 2.3 (13.2) | 72.8 (18.9) | -2.8 (12.8) | 0.19 |
| SF-12 domain | | | | | |
| PCS | 47.4 (8.3) | 1.9 (6.7) | 47.5 (9.0) | -1.7 (7.9) | 0.35 |
| MCS | 53.0 (8.7) | 2.3 (7.1) | 51.7 (9.6) | 2.3 (8.9) | |

Abbreviations: EPIC Expanded Prostate Cancer Index Composite; MCS Mental Component Summary; PCS Physical Component Summary; QoL quality of life; SF 12 Short form 12.

^aHigher scores indicating better QoL. Note: SF 12 is standardised to the population normative values of the United States of America, with a mean score of 50 and a s.d. of 10.

^bCohen's d effect size group mean differences at patients post intervention divided by mean s.d.

Table 4. Pelvic floor muscle strength in prostate cancer patients treated with radiotherapy in RePCa: a randomised controlled rehabilitation study

| Pelvic floor muscle strength | | Intervention group, n = 79 | | Control group, n = 82 | | P-value ^a |
|--|--------------------------------|----------------------------|-------------------|-----------------------|-------------------|----------------------|
| Mean (95%CI) | Study population pre-radiation | Pre-intervention | Post intervention | Pre-intervention | Post intervention | |
| No. of participants | n = 156 | n = 73 | n = 68 | n = 75 | n = 71 | |
| Digital evaluation ^b | 4.0 (3.8;4.1) | 3.8 (3.5;4.0) | 3.9 (3.6;4.1) | 3.8 (3.6;4.1) | 3.7 (3.5;4.0) | NS |
| Static strength no. of seconds to hold one contraction | 34.4 (31.1;37.7) | 35.2 (30.2;40.2) | 36.1 (31.0;41.2) | 31.6 (26.6;36.6) | 32.9 (28.0;37.8) | NS |
| Dynamic strength no. of contractions during 60 s | 22.2 (19.9;24.5) | 21.2 (17.7;24.7) | 22.7 (18.9;26.5) | 19.1 (15.9;22.3) | 19.2 (15.9;22.6) | NS |
| No. of participants | n = 156 | n = 72 | n = 66 | n = 71 | n = 71 | |
| EMG average activity (µV) | 38.2 (34.8;41.6) | 31.3 (27.9;34.8) | 24.7 (21.7;27.7) | 31.6 (27.3;35.9) | 23.3 (20.4;26.2) | NS |
| EMG average rest (µV) | 6.8 (6.2;7.5) | 5.8 (5.0;6.6) | 4.8 (4.0;5.5) | 5.5 (4.9;6.1) | 4.9 (3.6;6.2) | NS |

Abbreviations: CI class interval; EMG electromyography.
^aPost intervention differences between groups. Wilcoxon Sign rank test. Reported P values are two sided and P<0.05 was considered statistically significant.
^bMeasured by Modified Oxford Scale 0–6.

concurrently ($P=0.001$), 31.3–24.7 mV in the intervention group and 31.6–23.3 mV in the control group, with no significant differences between the two groups. At post intervention in the overall population, a significant correlation was found between muscle strength measured by digital evaluation and EMG ($r=0.5698$, $P<0.001$).

In the intervention group compared with the control group, the urinary irritative sum-score improved in patients with impaired ≤ 5 pelvic floor strength at pre-intervention Modified Oxford Scale, (7.4 point, $d=0.51$; $P=0.012$) as did the urinary irritative sum-score in patients with low EMG at pre-intervention, ≤ 21 mV (9.2 point, $d=0.63$; $P=0.012$).

In the digital evaluation, inter-rater reliability among the three assessors had Kappa values of 0.72, 0.83, and 0.84.

The time used for the intervention for each patient was estimated to 4 h including time for documentation.

DISCUSSION

We found that the multidisciplinary rehabilitation had a significant effect compared with usual care on the primary outcome: urinary irritative symptoms, among a large sample of irradiated PCa patients. As secondary outcomes, we observed benefits of the intervention in improvement in overall urinary and hormonal symptoms, and physical QoL. Our intervention improved urinary irritative symptoms by > 5 points on a 0–100 scale compared with a control group, which is considered clinically significant (Osoba *et al*, 1998). The clinical meaningfulness was furthermore confirmed by the patients as they experienced the intervention useful in everyday life, as stated in focus groups (Dieperink *et al*, 2013).

Consistent with our finding, Faithfull *et al* (2011) in a small phase II trial including 22 irradiated patients observed significant improvements, with a median score change of 5, on lower urinary tract symptoms following an intervention consisting of a programme almost the same as used in this study (self-management programme comprising pelvic floor exercises, bladder training, patient education, and problem solving). However, Faithfull *et al* (2011) included only patients with moderate-to-severe symptoms, and their pelvic floor exercises were conducted

as group sessions, whereas we included all patients with an individualised intervention aiming at the targeted and exact need of each individual patient. Our results are parallel to those from two randomised studies ($N=102$ and 300) among PCa patients treated with prostatectomy using a single component pelvic floor exercise programme to improve incontinence (Van Kampen *et al*, 2000; Filocamo *et al*, 2005). Ribeiro *et al* (2010) found in a controlled study in prostatectomy patients a positive effect of pelvic floor muscle training and biofeedback. They concluded that training improved not only recovery of urinary incontinence but also voiding symptoms and pelvic floor muscle strength. Ribeiro *et al* (2010) also included an extensive review and discussion of the available studies on prostatectomy patients. They described how a more precise comparison of the studies was difficult because of methodological differences among these. As the two treatments of PCa, prostatectomy, or radiotherapy have different adverse effects, a direct comparison with our data is even more difficult.

Pelvic floor function is closely related to bladder capacity or voiding dysfunction.

Previous research has examined pelvic floor muscle strength in men treated with prostatectomy, but there is no gold standard of measurement (Messelink *et al*, 2005). The pelvic floor strength measured by digital evaluation was stable during the period, but as measured by EMG, the pelvic floor strength declined significantly. Thus, EMG may be more sensitive in detecting changes in muscle strength, although the signals from the surface EMG must be made with caution owing to the risk of cross talk from other muscles (Herrington, 1996). Furthermore, studies show that ADT may cause a decline in large muscle groups (Williams *et al*, 2005; Alibhai *et al*, 2010), and perhaps this includes the muscles of the pelvic floor. Hence, the self-reported urinary improvements were in some contradiction to the clinical measurements of the pelvic floor, as the pelvic floor strength was stable as judged by repeated digital evaluation and declined as judged by EMG. Therefore, no clearcut causal relationship between the subjective dimensions of QoL and the objective measurements of the pelvic floor were seen. Pelvic floor muscle strength must be of some importance for the urinary irritative sum-score, as the intervention improved urinary irritative sum-score especially in patients with impaired muscle strength after radiotherapy. However, the exact relationship between the pelvic floor function and urinary irritative symptoms are still to be investigated. As this is the first study that investigates

the pelvic floor in PCa patients treated with radiotherapy, it remains to be seen whether the finding can be reproduced in future studies.

The patients in the control group met the blinded assessors only when being tested. However, patients were able to obtain information from the internet or elsewhere, and this may, in theory, have watered down the intervention. Pelvic floor exercises are difficult to learn without instructions (Messelink *et al*, 2005), and consequently, we offered the intervention group meticulous instructions in order to give the best opportunity to counteract adverse effects, which may have been superior to information from other sources, for example, the internet.

Our recently published cross-sectional survey including 317 PCa patients (Dieperink *et al*, 2012) showed that risk factors (for example, smoking, severe obesity BMI >30, and the condition of living alone) were associated with increased risk of late adverse effects after radiotherapy. The present study showed that patients living alone had a better outcome after intervention. These results imply a need for integration of not only the adverse effects but also personal factors as lifestyle and life conditions during intervention.

Screening before intervention may identify patients with a potential for improvement and the motivation to make an effort. The present study showed that patients with pre-intervention objective (i.e., digital evaluation ≤ 5 or EMGO 21) or subjective (i.e., EPIC irritative sum-score below 68 points) impairment improved the most. Therefore, screening with these measures may be considered in future rehabilitation intervention studies.

This study has a number of advantages. The accrual procedures made it possible to obtain information about the majority of the patients who denied participation, as 41 out of 48 filled out questionnaires before radiotherapy. This group of patients differed from patients included in the randomisation by having a statistically significant, but marginally lower D'Amico risk. We find it unlikely that it was related with not joining the study. In addition, this group included more patients living alone, and they had a lower but not significant level of education and higher incidence of smoking than did the randomised patients. Taken together, these factors should be taken into account if the intervention tested in this study is used as a standard of care (Holm *et al*, 2013), and health care professionals should make special efforts to include these groups in rehabilitation studies. Internal validity was maintained because of the randomisation and the homogeneity of the groups. The study provided good feasibility with a high inclusion rate and few drop-outs, although one important limitation was that we did not monitor the patients' compliance to the recommended self-training home exercises. In future studies, monitoring has to be considered at least with patient-reported outcomes, for example, exercise logbooks. Although we have the calculated time consumption used for the intervention, we did not make an exact cost-effectiveness analysis, but this could be recommended in future studies. Another limitation was that the design including psychosocial support and physical instructions do not allow blinding as a possibility. Instead, a trusting relation between patients and professionals is considered as an important motivation and may influence patient-reported outcome. Owing to concerns about the impact of radiotherapy on the pelvic floor muscles, the intervention started 1 month after radiotherapy, although we are aware of the recommendation that rehabilitation is started at diagnosis. Some of the patients complained of rectal tenderness when pelvic floor strength was tested, and this indicates that this was a correct decision. However, the intervention did not have any negative effects on the outcomes measured, and only few patients dropped out. The relative unrestricted inclusion and exclusion criteria, the uniform treatment protocol, and the fact that men who attended the study were living in cities as well as in rural areas in Denmark, allow generalisation of the results because the study sample was

representative of a population of irradiated PCa patients. However, only one patient included in the study was not an ethnic Dane, and this limits the generalisation from the findings into a broader context. Furthermore, the design permits only causal conclusions about the combined programme of nursing and physical therapy counselling and not about the components separately.

Based on the results of this study, it can be recommended that patients treated with radiotherapy of the prostate may be offered a combined nurse-physiotherapist intervention programme, especially patients with impairments within urinary irritative function. Timing, duration, and more focus on the empowerment aspects of this intervention need further study.

ACKNOWLEDGEMENTS

We owe special thanks to the cancer patients who participated in the study for their valuable contributions. We are indebted to all colleagues who took part in the study. The study was supported by the Odense University Hospital (OUH) Research Foundation, the University of Southern Denmark, the Danish Cancer Society, CIRRO – the Lundbeck Foundation Center for Interventional Research in Radiation Oncology, the Department of Oncology, OUH, the Mette Hede Nielsen Foundation, the Danish Nurses Organization Research Foundation, and the Propa Vita Foundation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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