

# One Thing at a Time... Timeliness of Rehabilitation for Sexual Problems in Men With Prostate Cancer

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## Research note

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# Abstract

## Objective

**The randomised clinical trial ProCaRe (Prostate Cancer Rehabilitation)** aimed to test the effect of sexual pre-habilitation in prostate cancer patients treated with radiotherapy concomitant with androgen deprivation therapy.

We planned recruitment of 92 participants. The complex intervention designed with previously treated patients and partners included sexual counselling, penile rehabilitation and supervised exercise in groups. The primary outcome was sexual functioning measured by the International Index of Erectile Function Score (IIEF-5). The secondary outcomes included a reduction in irritative urinary problems and improvement in quality of life.

## Results

**We identified eight eligible patients among nine screened between January 22<sup>th</sup> and June 1<sup>st</sup>, 2018.** Among these patients, three accepted study enrollment but one withdrew because of a lack of energy. The study was closed because of slow recruitment, i.e. a low number of eligible patients and low participation rate (38%) according to the timeframe and intervention planned.

The study had a strong design but was not sufficiently pilot-tested because the study site had too few eligible patients. Furthermore, at this early time of the disease trajectory, sexual rehabilitation was not perceived relevant to the patients or prioritised. Future studies should be co-designed with patients more representative for the target group.

## Introduction

Patients with prostate cancer (PC) treated with radiotherapy and concomitant androgen deprivation therapy often have several adverse effects, including problems with sexuality (1, 2). Sexual problems may be irreversible as radiotherapy might impact the neurovascular bundle. Furthermore, androgen deprivation therapy blocks testosterone levels and leads to loss of libido and erectile dysfunction (ED) in the majority of patients (2, 3). In a Danish randomised clinical trial (n = 161), 44% had moderate-severe sexual dysfunction after three months of neoadjuvant androgen deprivation therapy. The sexual impairment exacerbated to 61% one month after completion of radiotherapy (4) and did not improve during the following three years. Also, the partner is affected as sexual adverse effects influence intimacy, sexuality, and partner relations (5).

The key components in most intervention studies regarding penile rehabilitation is oral phosphodiesterase type 5 inhibitor (PDE5), injection therapy or different medical devices, often with positive results (6–8). However, most studies include patients after prostatectomy and do not target the often complex multi-factorial aetiology of sexual impairment (2). Interventions have not been tested

systematically in patients with PC treated with radiotherapy and androgen deprivation therapy. White et al. recommended an intervention targeting both penile rehabilitation, management of physical problems and lifestyle changes (2), which is supported by a randomised trial showing that physical activity in addition to PDE5 is more effective than PDE5 alone in a mixed population (9).

Although recommendations underline that rehabilitation should start at the time of diagnosis, most studies have been executed after completion of treatment. Thus, taking advantage of the waiting time before initiation of radiotherapy, pre-habilitation may be effective in preparing patients and caregivers for treatment, inform about likely adverse effects, and to build up health (10). In this study, we hypothesised that a multimodal and multidisciplinary early intervention might reduce sexual decline, result in better physical and mental well-being after radiotherapy, and prevent chronic sexual impairment. We, therefore, designed a randomised clinical trial to test our hypothesis. This paper report the enrolment phase as part of the process evaluation (11).

## Main Text

## Materials And Methods

We used a two-arm randomised non-blinded design. Patients were recruited at Odense University Hospital (OUH). Each morning a study nurse screened patients for eligibility for the ProCaRe (**Prostate Cancer Rehabilitation**) study before a medical consultation at the Department of Urology after diagnosis of PC, and eligible patients were invited into ProCaRe by the physician.

Inclusion criteria were a) Danish speaking men  $\geq 18$  years, b) biopsy documented T1-T3 adenocarcinoma of the prostate, c) referred to curatively intended radiotherapy, d) accepted treatment with neo-adjuvant and concomitant androgen deprivation therapy, e) sexual active before the diagnosis.

## ProCaRe Intervention

The primary aim of ProCaRe was to examine if pre-habilitation and early rehabilitation, as described below, could:

- reduce sexual adverse effects in patients with PC treated with radiotherapy and androgen deprivation therapy

The secondary aims were to investigate if pre-habilitation and early rehabilitation could:

- reduce irritative urinary problems
- improve several aspects of quality of life including physical and mental functioning

The development of the intervention was based on a literature search and the intervention developed through discussions with clinicians (urologists and nurse specialists) and after a focus group with  $n = 5$

former patients and n = 4 partners from the Danish prostate cancer patients' association.

The intervention targeted multi-factorial sexual impairment and included sexual counselling of the patient (with or without a partner) in combination with supervised and home-based physical exercises, pelvic exercises and peer support. The intervention lasted 20 weeks and began three months before radiotherapy when androgen deprivation therapy was initiated. The control group received standard care. It included information about the risk of adverse effects, but rehabilitation was not offered systematically.

The intervention group was offered (details in Table 1):

Table 1

Overview of the elements and professionals involved in the 5-hour ProCaRe pre-habilitation program including test program (in green boxes)

Session number	Elements
Time	
Place	
Duration	
Professional	
Baseline PRO Questionnaires	IIEF-5, EPIC-26, SF-12, Godin, EQ5D, Relationship ladder step 0–10 Demographic questions about self-reported sexual activity, smoking, alcohol, co-morbidity, civil status
Baseline Tests Three months before radiotherapy Study nurse	Blood pressure, heart rate, Blood tests: (Hga1c, PSA, lipids), height, weight, BMI, waist measure Handgrip strength, 30-s chair stand test
Session no. 1 Before radiotherapy Clinic of Sexology 60 minutes (Nurse Specialist)	Patient with partner • Sexual Counselling incl. penile rehabilitation with Vacuum Erection Device (VED). • Guidance toward sustained intimacy Training Logs Letter to GP
Session no. 2 Before radiotherapy 90 minutes (Physiotherapist + Nurse specialist)	Exercises for patients: • Group session • Supervised Group Pelvic floor exercises and physical exercises and guidance for non-supervised home exercises • Peer support Training Logs Letter to municipality

White: Intervention, Dark green: Patient-Reported Outcomes (PRO) and tests, Light green: Follow-up PRO

IIEF-5, EPIC-26, SF-12, Godin, EQ5D, Hga1c, Prostate-Specific Antigen, Body Mass Index

<b>Session number</b>	<b>Elements</b>
<b>Time</b>	
<b>Place</b>	
<b>Duration</b>	
<b>Professional</b>	
Session no. 3	Exercises for patients:
During radiotherapy	• Follow-up - Group session for patients
90 minutes	• Supervised Group Pelvic floor exercises and guidance for non-supervised home exercises
(Physiotherapist + Nurse specialist)	• Peer support
	Training Logs
Session no. 4	Individual follow-up sessions for patients with a partner
Two months after radiotherapy	• Compliance with the use of the vacuum device.
Clinic of Sexology	• Guidance on sustained intimacy
60 minutes	Training Logs
(Nurse Specialist)	
Evaluation PRO	IIEF-5, EPIC-26, SF-12, Godin, EQ5D, Relationship ladder step 0–10
Three months after radiotherapy	Questions about what was most helpful
Evaluation Tests	Blood pressure, heart rate, Blood tests: (Hga1c, PSA, lipids), height, weight, BMI, waist measure
Three months after radiotherapy	Handgrip strength, 30-s chair stand test
Follow-up PRO	IIEF-5, EPIC-26, SF-12, Godin, EQ5D, Relationship ladder step 0–10, self-reported weight
Six months after radiotherapy	Questions about what was most helpful
Follow-up PRO	IIEF-5, EPIC-26, SF-12, Godin, EQ5D, Relationship ladder step 0–10, self-reported weight
12 month after radiotherapy	Questions about what was most helpful
White: Intervention, Dark green: Patient-Reported Outcomes (PRO) and tests, Light green: Follow-up PRO	
IIEF-5, EPIC-26, SF-12, Godin, EQ5D, Hga1c, Prostate-Specific Antigen, Body Mass Index	

- Two visits at the Clinic of Sexology, OUH with individual sexual counselling, with or without a partner. The first visit included assessment of sexual problems, information, and guidance about sexual adverse effects due to treatment with androgen deprivation therapy and radiotherapy, and instructions in the daily training of the pelvic floor and use of a vacuum erection device (VED) (7, 8). The importance of sustaining intimacy was underlined, and training logs of the actual use of VED were provided. (3, 5). Following consent, the general practitioner was informed by letter. The second visit two months after the end of radiotherapy primarily targeted future compliance.
- Two supervised exercise sessions in groups with other patients (no partners): These sessions were led by an experienced physiotherapist and included instructions of home exercises covering daily pelvic floor exercises and general physical training at least 3 hours per week (12). Furthermore, exercises containing 10 min. warm-up, 20 min. interval aerobic exercises, 20 min. Resistance exercises for major muscle groups (quadriceps femoris, gluteus maximus and biceps) (13–15), and 10 min. pelvic floor exercises were included (4). The pelvic floor exercises were performed in concordance to the regime described by Dorey et al. (16). Instructions in daily training logs covering home exercises were given. The second session primarily aimed to ensure compliance. Following consent, the municipality was informed about the programme. In line with national programs, health care professionals at the highly specialised hospital are responsible for specialised rehabilitation, and for a referral to external partners like the GP and the municipality (17, 18).

A minimum of one visit at the Clinic of Sexology and one exercise session was accepted as a ProCare intervention. All health care professionals were trained to deliver the different elements of the intervention.

## Assessments

Patient-reported and objective outcomes were used (Table 1). The primary effect parameter was sexual functioning three months after radiotherapy evaluated with the International Index of Erectile Function score (IIEF-5).

## Sample Size Calculation

Studies using VED after prostatectomy have shown positive results with an increase in erectile functioning from 65–90% (8). Our estimated increase in primary outcome three months after radiotherapy was based on a randomised trial (19). The power calculation was based on a two-sided test of the difference between groups in the primary effect parameter. An expected mean in the intervention group of 9 (SD 9.4), compared to a decline in the usual care group to 1.8 (SD 9.4). A significance level of 5% and power of 90% was applied, and the study needed data from 37 patients in each group. The sample size of 46 patients in each group was expected to take into account a maximal drop-out rate of 20% (4). P values < 0.05 were considered statistically significant.

The expected timeframe for the inclusion period was two years which was considered feasible for the departments, and the intervention was planned to be executed by clinical staff (Fig. 1).

# Ethical considerations

The study was performed following the Helsinki II declaration and the principles of Good Clinical Practice. Verbal and written informed consent to participate was obtained. The Danish Data Protection Agency registered the study (journal no. 17/15967) and approved by the Local Ethical Committee (journal no. S-20170080).

## Results

This study was prematurely closed after five months due to very slow recruitment, which was far behind our scheduled recruitment plan (Fig. 1). Of nine patients screened with PC for five months, eight patients were eligible for inclusion. One patient was ineligible due to ten years of impotence. Five patients had no interest in the intervention offered and declined to participate. Several of them reported that sexual problems were not on their agenda at the moment.

We recruited three patients with PC aged 55–69 years which resulted in a recruitment rate of 38%. Two patients were randomised to the intervention group, and one patient to the control group. One patient from the intervention group withdrew after session no. 2 due to lack of energy to make the penile and physical exercises. We decided to offer the one patient left in the intervention group individually supervised exercise. This procedure was not in line with the protocol because the supervised exercise session should have been based on group dynamics and peer support. He completed two sessions, and then we closed the study and stopped data collection. The few patients in the study did not offer any useful information, so no further data apply to the present.

## Discussion And Conclusion

No matter the best intentions of early intervention for this vulnerable group, we found it impossible to recruit the number of newly diagnosed patients with PC referred to radiotherapy and androgen deprivation therapy as planned. The inclusion rate of 38% was not lower than other randomised trials targeting sexual problems (20, 21), but patients available in this single study site were too few according to the time frame and intervention planned. The inclusion period was defined based on expectations of recruitment of at least four patients every month (Fig. 1). Based on five months of inclusion, we learned that a multi-centre study was needed. However, multi-centre studies require expertise in many centres and a much larger resource allocation.

Major obstacles for recruitment was patients' not being sexually active or that they declined participation for other reasons, i.e. logistical challenges, before receiving the thorough written and oral information on the study. As such, they did not even appear on the screening list. Another major obstacle for recruitment was the concurrent inclusion of patients in the multicenter Scandinavian SPCG-15 trial randomising patients with locally advanced PC to radiotherapy or prostatectomy (22). This was prioritised over the ProCaRe trial, and therefore patients were primarily screened for the SPCG-15 trial. Inclusion in ProCaRe

could potentially affect the quality of life measurements of the SPCG-15 trial study; therefore, inclusion in both trials was not feasible. On the other hand, patients planned for radiotherapy after declining participation in the SPCG trial were offered inclusion in ProCaRe. However, at the initial visit patients' and partners' only concern was the treatment of cancer. They did not have any mental surplus concerning sexuality, aligned with a recent study showing that the most preferable time for sexual rehabilitation is three months past treatment (23).

We involved patients and partners of the target group when co-designing the intervention using a focus group with five former patients with PC and four female partners. They were excited about the intervention, and as one man said: *"I would have hoped that I had this opportunity"*. However, they may have forgotten own prioritizations and thereby introduced recall bias.

We expected ProCaRe to study the effects of a health care model combining sexual advice, VED, and physical exercising on improving sexual well-being. However, sufficient study enrollment was not feasible, and the study was closed. This finding was in line with Karlsen et al., who had a recruitment rate as low as 14% in a population of prostate patients and partners offered sexual rehabilitation after prostatectomy (21). A more thorough pilot phase of the study might have resulted in critical knowledge and sufficient redesign of the study. We hypothesise that the primary problem of the program was timing, not the combination of the different elements: sexual advice, VED, and physical exercises in groups and at home.

In conclusion, sexual rehabilitation for patients with PC referred to radiotherapy and androgen deprivation therapy was not feasible as pre-habilitation, because patients were too impervious for dealing with sexuality so close to diagnosis, and the study was not prioritised. Sexual rehabilitation has to be timely delivered when the prostate cancer patient and partner are ready for intervention, and patients and partners in the co-design have to be representative of the target group. We believe that a later intervention in the cancer trajectory may be more appropriate.

## Limitations

This randomised controlled trial was limited by insufficient pilot-testing and of being second priority at the study site during the inclusion period. The co-design of the intervention with patients with PC and partners should have been with patients more representative from the target population, meaning patients newly diagnosed. As such, the randomised design should have been preceded by a feasibility study investigating intervention delivery, timeliness, and acceptance of test and questionnaires. Furthermore, our experiences underline the importance of alignment of study activities at study sites

## List Of Abbreviations

PC Prostate Cancer

PDE5 phosphodiesterase type 5 inhibitor

ProCaRe Prostate Cancer Rehabilitation

VED vacuum erection device

GP general practitioner

IIEF-5 International Index of Erectile Function score

## Declarations

### *Ethics approval and consent to participate*

The study was following the Helsinki II declaration and the principles of Good Clinical Practice (GCP). Verbal and written informed consent to participate was obtained. The study was registered by the Danish Data Protection Agency with journal no. 17/15967, and approved by the Region of Southern Denmark ethical committee journal no. S-20170080.

### *Consent for publication*

Our paper is not under consideration for publication elsewhere, and will not be submitted or published elsewhere while acceptance for BMC Research Note is under consideration.

### *Availability of data and materials*

The first author has all the available data.

### *Competing interest*

All authors have nothing to declare regarding any financial interest or competing interest related to the work described in this paper

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### *Authors`contributions*

All authors contributed in planning the protocol. KD, LL and MAM executed the inclusion. KD analysed and interpreted the patient data. All authors participated in drafting, revision and approval of the final version of the manuscript as submitted.

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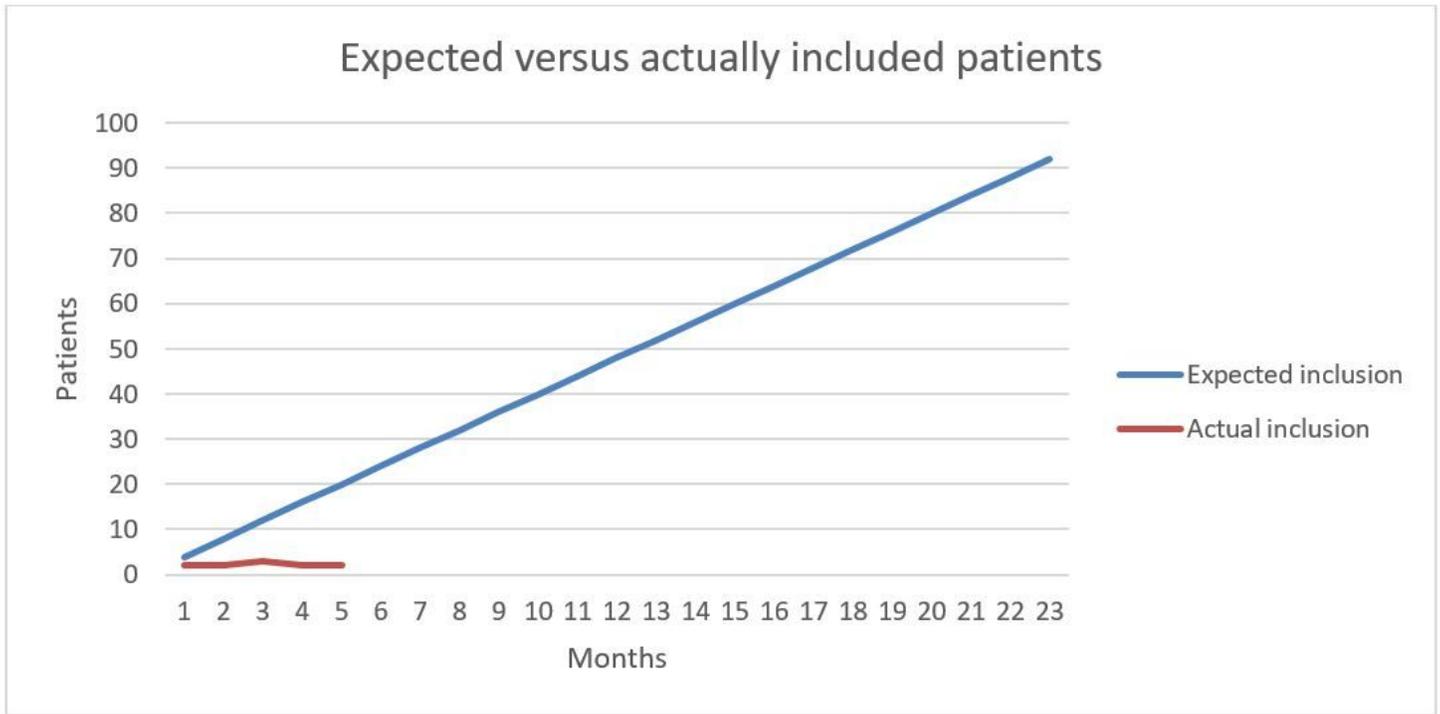
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## Figures



**Figure 1**

Expected versus actually included patients