Title

Older prostate cancer survivors: health status, quality of life and function after radical treatment.

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Protocol dated: September 22, 2020
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Full title: Older Prostate cancer Survivors (OPS): health status, quality of life and function after radical treatment

Short title: The OPS study

The study emerges from Innlandet Hospital Trust and is conducted in co-operation with the Norwegian University of Science and Technology (NTNU).

The study is cross-sectional and has three parts, part I, part IIA and part IIB. Part I and IIA is registered jointly at ClinicalTrials.gov as NCT04863352, whereas part IIB has a separate ID: NCT05200039

This protocol covers the overarching design of all parts.

Funding

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Older prostate cancer survivors: health status, quality of life and function after radical treatment.

Introduction

In this study, addressing older prostate cancer survivors, i.e. men who received potentially curative (radical) treatment two to six years ago at the age of ≥ 70 years, we will investigate if older age at time of treatment is a detrimental factor with respect to long-term quality of life (Qol), health, and function. We will also compare QoL, health and function between the older survivors and matched population based cohorts, and thereby provide realistic information on the long-term impact of radical prostate cancer treatment in older age. As cancer specific survival after such treatment is good,[1] evidence for the outcomes addressed in this study, is of major importance to guide treatment decisions for older men with prostate cancer, who reportedly are undertreated.[2,3]

Background: Prostate cancer is the most common cancer among Norwegian men with about 5000 new cases each year. Median age at diagnosis is 70 years, and in 2018, 1330 (27%) new cases were diagnosed in men who were 75 years or older.[1] This implies that at least half of those diagnosed with prostate cancer are "older". There is no definite age limit to define this term, but aging is inevitable followed by a gradual reduction of functional reserves, and comorbidities and geriatric syndromes become more prevalent.[4] Thus, compared to their younger counterparts, men ≥70 years with prostate cancer are in general more vulnerable, and more susceptible to adverse treatment effects including functional decline.[5]

By the time of diagnosis, about 65-70% of men with prostate cancer will have local or locally advanced disease.[1] In this situation, the overall 10-year cancer specific survival is good (>90%), but varies with risk group (low, intermediate and high risk) decided according to histological aggressiveness, extent of local tumor growth, and prostate specific antigen (PSA) level.[1] Curative treatment options are radical surgery or radiotherapy (RT) with active surveillance as an alternative. The latter aims to avoid unnecessary treatment in men not needing immediate treatment, and to achieve correct timing for curative intervention in those who eventually do.[6] There is no definitive evidence of either radical surgery or RT being superior to the other,[7,8] but RT tends to be most frequently used in the older population. About 27-53% of men will have a biochemical recurrence (increasing PSA only),[6,9] but only a minority (10-20%) will develop metastases within 10 years.[7,9,10] Survival benefits are mainly detectable after 10 years and/or in patients with intermediate/high risk cancer.[9-11] Thus, men with shorter life expectancy and/or low risk disease, may be managed with a conservative observational approach.[12]

Radical surgery, removing the overall prostatic gland, is performed by open-, laparoscopic- or robot-assisted (RARP) surgery. Presently, RARP using the da Vinci Surgical System (2002) is the preferred minimal-invasive approach.[6] In Norway, radical RT is usually delivered as external photon beam RT, aiming at a high dose to the cancer site while sparing normal tissue. To increase precision, techniques have evolved from 3-dimensional (3-D) conformal techniques to intensity-modulated RT (IMRT).[6] Conventional dose is 74-80 gray (Gy) in 2 Gy fractions, 5 days/week. More recently, schedules of fewer fractions and higher fraction-doses have been introduced for selected patients.[6] For intermediate and high risk disease, external RT is combined with anti-androgen therapy for 4-6 months and 2-3 years, respectively.[6] External RT to the "prostate bed" is used for patients with persistent or increasing PSA after radical surgery (salvage RT)

Both radical surgery and RT are frequently followed by late adverse effects (occurring or persisting ≥ 12 months after therapy) that may have a severe and long lasting impact on men's daily life and well-being.[13-16] These effects can either be local, i.e. functional disturbances and symptoms from organs close to the prostate gland,[8,14,15] or general, i.e. affecting physical function and overall QoL.[17] Local effects tend to differ between treatment modalities. Urinary incontinence and erectile dysfunction are more prevalent after surgery, whereas bowel symptoms more often occur after RT.[8,14,15] For general aspects such as global QoL, physical and mental health, no difference has

been found.[13,14] Androgen therapy, frequently added to RT, may, however, negatively affect overall health and contribute to treatment related morbidity.[18]

Decisions to offer radical treatment for localized/locally advanced prostate cancer are based on tumor- and patient characteristics, and patients' preferences, and require an evaluation of potential adverse effects against benefits in terms of cancer control and survival. With older age, more men have high risk cancer and suffer from cancer-related symptoms.[3,19] Despite this, increasing age seems to be the major determinant for omitting curative treatment.[2,19,20] Older men are also underrepresented in clinical studies, [9-11] and studies specifically addressing older men are scarce.[21] Consequently, knowledge on the long-term outcomes in older prostate cancer survivors is limited. There is some evidence that older men may tolerate and benefit from curative treatment as well as their younger counterparts, but other reports indicate that adverse effects are more common.[3,21,22] A recent review on patient reported symptoms and QoL following radical treatment, concluded that the studies were of insufficient quality "to permit precise guidance to men about the risks to these aspects of their lives."[23] Furthermore, few studies evaluated general QoL aspects, physical function included, and the majority targeted men aged 56-70 years.[23]

Needs description

To select the best treatment for individual patients, actively involving them in decision-making, and providing health care that sustains their overall health, sound evidence on long-term health, function and QoL following cancer treatment is a pre-requisite. This is particularly important for older men with localized/locally advanced prostate cancer since ten years cancer specific survival is high, and maintenance of QoL, function and independence are highly prioritized outcomes.[24] However, for this large group of men with prostate cancer, information on these crucial outcomes is largely missing. This may substantially hamper treatment decisions and shared decision-making, and lead to suboptimal treatment caused by unfounded fear of adverse effects in a vulnerable population.

The present study will fill the existing knowledge gaps. We will provide evidence whether older age at time of treatment has a negative impact on prostate cancer survivors' health, function, and QoL. More importantly, through cooperation with The Trøndelag Health Survey 4 (HUNT4)[25] and the corresponding sub-survey including adults ≥ 70 years (HUNT4 70+), we have a unique opportunity to evaluate how prostate cancer survivors may differ from the general male population of the same age. Health conditions may rapidly change after the age of 70, and local late effects of prostate cancer treatment, i.e. urinary incontinence, erectile dysfunction and bowel problems, are frequent in older men without prostate cancer. Hence, comparison to population-based data is crucial.

To capture the patients' voice, we will use well-validated patient reported outcome measures (PROMs) to assess the older prostate cancer survivor's potential problems and needs. Additionally, we will assess physical performance, physical- and sedentary activity using established tests and electronic devices and compare the results to identical assessments in the general male population of the same age. To the best of our knowledge, no such comparison has formerly been performed.

Our study will provide new evidence of the late effects of modern radical treatment in older prostate cancer survivors and may thereby contribute to reduce current risks of unfounded under-treatment. The study will increase the knowledge base needed for patients to choose treatment according to their preferences, and provide a new, excellent basis for subsequent development of supportive rehabilitation measures that may minimize potentially negative impacts of radical treatment.

Aims and objective

The overarching aim is to investigate the long-term impact of radical treatment on older (≥70 years by the time of treatment) prostate cancer survivors' QoL, health, physical function and activity with comparisons to their younger counterparts and a general male population of the same age.

The objectives for the present PhD project are to investigate:

1. if older age at the time of radical treatment has a negative impact on self-reported QoL, function and local late treatment effects in prostate cancer survivors
2. if health status, health problems and use of health care services in older prostate cancer survivors differ from a general male population of the same age
3. if objectively assessed physical performance, physical and sedentary activity in older prostate cancer survivors differ from a general male population of the same age

Additional/secondary objectives: focusing on older prostate cancer survivors: a) investigate how objectively assessed physical performance is associated with self-reported health, QoL, and physical function; b) investigate how local late effects may influence self-reported health, QoL and physical function; c) describe the course of local effects of surgery (from pre-surgery and onward) by joining data from the present study with data from the existing quality database at the Urological Surgery Unit (USU), Hamar Hospital, SI.[26]

The pre-defined secondary objectives are subjects for additional research based on the data collected through the present project. Thus, these objectives are not further addressed in this protocol.

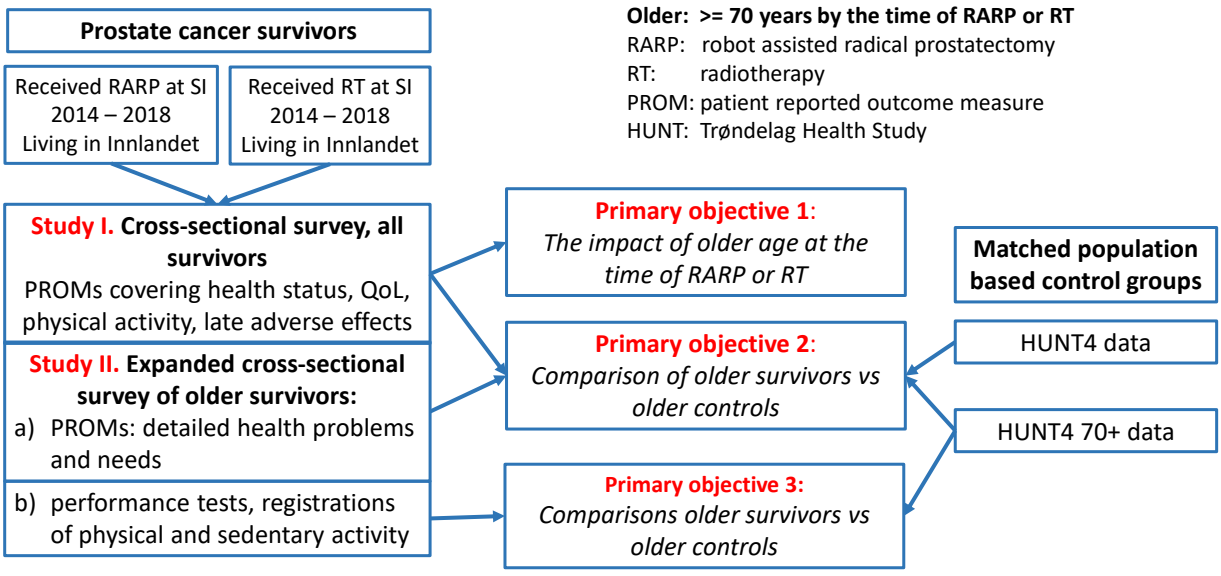
Project methodology

The project emerges from Innlandet Hospital Trust (SI) and will be conducted in close co-operation with researchers from the HUNT4 study. Two centers will contribute to participant enrolment: the Radiotherapy Unit (RTU), Gjøvik Hospital, and the USU, Hamar Hospital. Jointly they serve all patients with localized/locally advanced prostate cancer in Innlandet, annually about 280 patients. About 40% are ≥70 years, 2/3 undergo radical surgery, and 1/3 receive RT. Our target group are patients treated with radical RT or RARP from 2014 to 2018.

Both the RTU and USU have complete, easily accessible registries of their patients.[26] Since 2014, the RTU has provided radical RT using modern, high dose RT in accordance with official guidelines.[6] From 2014 to 2016, RT was given as 3-D conformal external RT, thereafter IMRT techniques have been used. RARP using the da Vinci Surgical System® has been the only approach for radical surgery at the USU.

The project is designed as two cross-sectional studies with matched control groups drawn from the HUNT4 and HUNT4 70+ surveys. Figure 1 below gives an overview

Figure 1: Overview – study design



Study I: PROMs survey targeting all patients from Innlandet having received radical treatment for localized/locally advanced prostate cancer at SI from 2014 to 2018 (Study I)

Study II: targeting older participants from Study I who were ≥70 years at time of treatment: expanded PROMs survey (**Study IIa**), performance tests and activity registrations (**Study IIb**).

For Study I, we will use validated PROMs to retrieve information on several aspects of prostate cancer survivors' QoL and health, including local late treatment effects, and investigate the association between older age and these outcomes, taking relevant confounders into account (e.g. treatment modality, cancer status, civil status, education, comorbidity) (Objective 1). Study I will also include PROMs used in HUNT4 to allow for comparison to matched population-based controls (Objective 2). For a broader evaluation of older prostate cancer survivors, Study II will include an additional set of PROMs which was used in HUNT4 70+ (Study IIa), and objective physical performance tests and activity registrations performed in a randomly drawn sub-group (Study IIb). Data will be compared to matched control groups from the HUNT4 70+ survey, which has performed identical assessments (Objective 2 and 3). All PROMs (Study I and II) will be administered as questionnaires to be filled in by the patients.

The data collection is broad and will provide basis for more than one PhD project (see secondary objectives). However, being cross-sectional collections of PROMs, neither Study I, nor Study IIa are time- or resource consuming. Based on former experience, we expect compliance to be good. Study IIb is the main challenge, but we have performed similar tests in other cohorts, and with the established co-operation with HUNT4/HUNT4 70+, we expect the tests to be successfully performed provided that funding for a project nurse is granted from SI as applied for.

Project arrangements, method selection and analyses

Subjects

Main eligibility criteria

Study I:

- received radical RT or RARP at SI between 01.01.2014 and 31.12.2018
- alive and living in Innlandet County
- fluent in Norwegian (orally and in writing)
- written informed consent

Study IIa) the subgroup of participants in Study I who were ≥ 70 years by the time of treatment.
Study IIb) a random sub-sample from Study IIb, excluding survivors with clinically significant relapse (verified metastases/local progression and/or start of lifelong antiandrogen therapy)

Clinically significant cancer relapse, occurring in approximately 10-20%, may affect all outcomes. Reliable information on this aspect cannot be retrieved before consent to participation, and as outcomes for the overall cohorts are of interest, all eligible and consenting survivors will be enrolled, and recurrence taken into account in the analyses. The exception is the subsample drawn for performance tests in Study II b (as explained above).

Control groups: For comparison with a general population, a control group of males matched on age and education will be drawn from the HUNT4/HUNT4 70+ surveys performed in 2017-2019, targeting all inhabitants and inhabitants ≥70 years in Trøndelag County, respectively.[25] Jointly these surveys include broad health assessments using questionnaires, physical examinations and tests.

Outcomes (overview Table 1, page 7)

Predefined primary outcomes are:

- Global QoL as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (QLQ-C30) (Objective 1: assessing the impact of age).[27]

- Overall health - self-reported, item one from HUNT4[28](Objective 2: assessing differences between older prostate cancer survivors and matched controls).
- Short Physical Performance Battery (SPPB) score (Objective 3, physical performance in older prostate cancer survivors vs controls).[29]

The QLQ-C30 is a widely used and validated 30-item questionnaire designed for cancer patients. National and international norm data from general populations are available.[30] In addition to global QoL, the QLQ-C30 comprises physical function (PF), emotional-, role- and cognitive function, and nine symptoms that are frequent in patients with cancer.[27]

The SPPB tests balance and mobility, and is a validated screening tool for physical performance in older people.[29]

Table 1: Overview over pre-defined primary and secondary outcome measures:

Study I (all participants)	Study II Expanded assessment (older participants ≥ 70 years by the time of treatment)
PROMs	**PROMs (all older participants)**
Global QoL (subscale QLQ-C30)[1]	Activities of daily living (as in HUNT4 70+)
Local late effects (EPIC-score)[2]	**Tests (subgroup of older participants)** (as in HUNT4 70+)
Overall health status (as in HUNT4)	SPPB[3] – physical performance including mobility and balance
Self-report physical function (sub-scale QLQ-C30)	Hand grip strength using the Jamar digital hand dynamometer
	One legged balance test (Flamingo test)
	Physical activity and sedentary activity, objectively measure by counts/readings from 7 days wearing accelerometer **Axivity AX3**.
[1] QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of life Questionnaire-C30 [2] Expanded Prostate Cancer Index Composite Instrument for Clinical Practice (EPIC-CP); [3] Short physical performance battery	

Predefined secondary outcomes are:

- Physical function (PF) (measured by the QLQ-C30) (objective 1).
- Local late effects (measured with the Expanded Prostate Composite Instrument for Clinical Practice (EPIC-CP) (objective 1)
- Activities of daily living (as in HUNT4 70+)[31] (objective 2)
- Objectively measured physical and sedentary activity (accelerometer counts from seven consecutive days), handgrip strength, and one-legged balance (objective 3).

Expanded Prostate Cancer Index Composite for Clinical Practice, EPIC-CP is a 16-item, widely used questionnaire designed for prostate cancer patients, comprising items on urinary, bowel and sexual disturbances.[32] It is currently in routine use in the quality database at USU, Hamar.[26]

Objective registrations of physical- and sedentary activity will be performed using the accelerometer Axivity AX3, which assesses time spent sitting, lying, standing, walking, running etc. Participants will wear two devices on all waking hours for seven days, one attached to their hip and one to their back. The registrations will be transferred to a designated software for analysis.

Other assessments

These data will be used for description, for adjustment in outcome analyses and/or for comparison to corresponding data on the matched control groups from HUNT4/HUNT4 70+.

Study I: **Patient reported**: major demographics including social status and education, cancer status, emotional-, role and cognitive function and common symptoms (QLQ-C30) and daily life, comorbidity, medications, use of health care services and physical activity (as in HUNT4). **From medical records**: comorbidity and prostate cancer details (e.g. risk group, RT regimen, treatment for relapse if present)

Study II a): health problems (including problems gastrointestinal/urinary tract, sexuality and urinary leakage, fatigue, falls) and use of health care services (patient reported as in HUNT4 70+).

Study IIb): test of cognitive function using the Montreal Cognitive Assessment (MoCA).[33]

Study conduct

Eligible subjects will be identified through the RT registry at the RTU, Gjøvik, and the quality database at the USU, Hamar,[26] respectively. Each unit will contact their former patients to ask for consent to participation. Study information (Study I and II), consent form (consent to both studies for older participant) and questionnaire for Study I will be administered by post. Consenting participant will be asked to mail the signed consent form and the completed questionnaire to the research center using pre-paid envelops. If no reply is received, one reminder will be mailed. Subsequently, consenting older participants will receive the questionnaires for Study II, and a random sub-sample of this group will be invited to performance tests and activity registration.

Testing will take place at present and former SI locations, and will be arranged for groups of about 12 at the time. Each participant's tests will take about 30-45 min. The PhD student and a project nurse will perform the testing, instruct the participants how to wear the accelerometers, and to return the devices in a pre-paid envelope. Consenting participants, unable to meet at the arranged occasions, will be tested locally/at home by community cancer nurses/physiotherapists trained through other studies by our group.

Strategy for analyses and sample size

Available and expected number of participants: About 400 men with prostate cancer received curative RT at SI from 2014 to 2018, about 250 of these were older (≥70 years) by time of treatment. In the same period about 1000 men underwent RARP, about 1/3 (330) being older. Thus, our target population includes about 1400 men of all ages, and about 580 older men. Estimating a response rate of 60%, our overall sample will include about 840 men of all ages (about 240 and 600 men having undergone RT and RARP, respectively), and about 350 older men (about 150 and 200 receiving RT and RARP, respectively). Matched controls will be drawn from the HUNT4 and HUNT4 70+ surveys, distribution 1:3 (cancer survivors : controls).

General statistical approach[1]: Simple descriptive statistics will be used to describe our cohorts. Comparison between groups will be made using parametric and non-parametric statistics as appropriate. To assess the impact of age, treatment regimen and relevant confounding factors on outcomes, multiple regression models will be estimated.

Objective 1. Statistical approach: To investigate if global QoL (scores 1-100) (primary outcome) is associated to age at the time of treatment, we will estimate a linear regression model, allowing us to assess possibly non-linear association between global QoL and age. Since several factors may influence QoL, we will adjust the analysis for potential confounders in a multiple linear regression model. The confounders to be included are treatment modality (surgery, RT and surgery followed by RT), cancer characteristic (low/intermediate/high risk), clinical relapse (yes/no), androgen therapy (yes/no), time from treatment, social status (living alone/with partner), education (four categories), and comorbidity score. To avoid uncertainties related to any cancer relapse, we will estimate a similar regression model for patients with no biochemical and clinical relapse as sensitivity analysis. **Sample size:** For the multiple linear regression analyses, sample size according to Green's rule of thumb should at least be 50+8*m, where m is the number of variables in the model. Due to categorical nature of some of the confounders, the number of variables in the model will be 13, requiring at least 154 participants. The size of the enrolled cohort of approximately 840 participants is clearly sufficient to perform the analysis with enough power.

Objective 2. Statistical approach: We will compare health status (a four-category primary outcome) between all older prostate cancer survivors and their matched controls by ordinal

[1] Detailed plan for analyses in separate document «statistical analysis plan»

regression model (nominal if proportional odds assumption is violated). The results will be adjusted for potential pre-defined confounder (social status, comorbidity scores, and relapse), and matching variables (age and education) to avoid residual confounding in a multiple regression model. As sensitivity analysis, the same analysis will be performed excluding survivors with clinical cancer relapse. **Sample size**: For regression model with categorical outcome to yield stable estimates, it is required at least 10 cases in the smallest outcome category per variable in the model. As the model includes 8 variables, at least 80 cases in the smallest category is required, which should be unproblematic given the expected number of older survivors (350) and thrice as many controls.

Objective 3. Statistical approach: We will compare SPPB scores (primary outcome) between the older prostate cancer survivors and their matched controls by bivariate linear regression model, and adjust the results for potential pre-defined confounders (social status, comorbidity scores and health status) and matching variables (age and education) to avoid the residual confounding in a multiple linear regression model. **Sample size**: According to Greens's rule of thumb, with 10 variables in the multiple model we will need at least 130 participants to obtain valid estimates. To cover for possible registration failures for some participants, we will include a random sample of 150 from the older participant group and thrice as many matched controls for these analyses.

Secondary outcomes will be assessed in the same way as the primary ones for each objective. The same confounders will be included into the multiple models. The type of regression model will be considered based on the nature of each outcome analysed

Participants, organization and collaborations

Participants/scientific project group

Project leader is *Marit Slaaen* (professor, MD, oncologist), the Cancer Unit, Hamar and the Research Centre for Age-related Functional Decline and Disease (AFS), SI and Institute of Clinical Medicine (ICM), University of Oslo (UiO).

The scientific project group consists of the following members: Reidun Sletten (MD), PhD student, resident physician at the RTU, Gjøvik SI. *Øyvind Kirkevold*, (professor, ass. research director), Faculty of Health, Care and Nursing, NTNU Gjøvik and AFS SI; *Sverre Bergh* (MD, PhD, leader of research), AFS, SI; *Ola Christiansen* (MD, urologist, PhD-student, former Head of Dept), Unit of Urologic Surgery, Hamar hospital, and AFS, SI; *Bjørn Henning Grønberg* (professor, MD, oncologist), Department of Cancer Research and Molecular Medicine, NTNU and the Cancer Clinic, St Olav Hospital (SOH); *Asta Bye* (associated professor, PhD, nutritionist), Oslo Metropolitan University; *Line Merethe Oldervoll* (professor, rehabilitation medicine), Department of Public Health and Nursing (ISM), NTNU and Norwegian Heart and Lung Patient Organization; *Siri Rostoft* (professor, MD, geriatric oncology), Dept. Geriatric Medicine, OUS and ICM, UiO; *Håvard Skjellegrind* (associated professor, specialist in Family Medicine, project leader HUNT 70+), ISM, NTNU and Steinkjer Municipality; *Jūratė Šaltytė Benth* (PhD, statistician), SI and UiO; *Lennart Åstrøm* (MD, PhD, uro-oncology), Dept of Immunology, Genetics and Pathology, Uppsala University and Dept of Oncology, Uppsala University Hospital, and *Paul Jarle Mork* (PhD, professor), ISM, NTNU.

Organization and collaboration

This project emerges from AFS, SI, and will be performed as a joint effort with the Radiotherapy unit at Gjøvik Hospital, SI and the Unit of Urologic Surgery at Hamar Hospital, SI, and with an. active collaboration with HUNT survey researchers. The study is organized with a project leader and a multiprofessional scientific project group as explained above. This scientific group works with input from a group of three user representatives.

User involvement

A group of three user representatives from The Norwegian Prostate Cancer Society was established in December 2019. Meetings have been arranged to discuss study design and focus to ensure that issues of importance to prostate cancer survivors are addressed by the assessments. The user representatives will further participate in all parts of the study conduct, including evaluation of assessment procedures and the information and consent form, and interpretation and dissemination of results to the public, patients and relatives. Furthermore, through their society, the user representatives will provide an important contribution by motivating their members to participate.

Ethical considerations

Approval for all parts of the project has been granted from the Regional Committee for Medical Research Ethics, Health Region South-East (REK HSØ) (ID 183868 and 266644) and the Data Protection Official for Research, SI. The study is performed according to the rules of the Helsinki-declaration and registered at ClinTrials.gov. Participation does not inflict upon the participants´ medical treatment and does not imply any health risks or deviation from good clinical practice. All participants provide written informed consent.

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Amendment

Changes to the original protocol

All changes affecting participants in any way (measurements, choice of instruments etc.) were approved by Regional Ethics Committee prior to enrolment of subjects in the research project.

- Predefined secondary outcome, page 7 [Local late effects (measured with the Expanded Prostate Composite Instrument for Clinical Practice (EPIC-CP) (objective 1)]. Instrument was changed from EPIC-CP to EPIC-26 (1). Approved by the Regional Ethics Committee (REC) March 10, 2021.
- Study IIB: Objective registrations of physical- and sedentary activity performed using the accelerometer Axivity AX3, page 7. The location of the accelerator was changed to subjects' back and right thigh, not hip and back as originally stated. Moreover, the participants would wear the accelerators continuously for seven days, not restricted to waking hours. Approved by the REC, January 19, 2022.
- Study IIB, page 8**:** test of cognitive function using the Montreal Cognitive Assessment (MoCA) was omitted from the project. Approved by the REC, November 30, 2021.
- Study IIB: the following registrations were added to those described in the protocol: Height, weight, waist circumference and resting heart rate. Approved by the REC, November 30, 2021.

(1) Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology. 2010;76(5):1245-50