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Study Protocols

Protocol of a randomised, controlled trial comparing immediate curative therapy with conservative treatment in men aged ≥75 years with non-metastatic high-risk prostate cancer (SPCG 19/GRand-P)

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Background

Older men (aged ≥75 years) with high risk, non-metastatic prostate cancer (PCa) are increasingly treated with curative therapy (surgery or radiotherapy). However, it is unclear if curative therapy prolongs life and improves health-related quality of life (HRQoL) in this age group compared to conservative therapy, which has evolved considerably during the last decade.

Study Design

The Scandinavian Prostate Cancer Group (SPCG) 19/Norwegian Get-Randomized Research Group-Prostate (GRand-P) is a randomised, two-armed, controlled, multicentre, phase III trial carried out at study centres in Norway, Denmark, Finland, and Sweden.

Endpoints

The primary endpoints are overall survival and HRQoL (burden of disease scale, European Organisation for the Research and Treatment of Cancer [EORTC] Elderly Cancer patients). Secondary endpoints are PCa-specific survival, metastasis-free survival, role-functioning scale (EORTC quality of life questionnaire 30-item core), urinary irritative/obstructive scale (26-item Expanded Prostate Cancer Index Composite [EPIC-26]), bowel scale (EPIC-26), intervention-free survival, PCa morbidity, use of secondary and tertiary systemic therapies, mean quality-adjusted life-years (QALYs), and mean total healthcare costs.

Patients and Methods

A total of 980 men (aged ≥75 years) with non-metastatic, high-risk PCa will initially be screened with Geriatric 8 (G8) health status screening tool and Mini-COG© brief cognitive test. Participants identified by G8 as 'fit' or 'frail' will be

randomised (ratio 1:1) to either immediate curative therapy (radiotherapy or prostatectomy) or conservative therapy (endocrine therapy or observation). Participants who are unable or unwilling to participate in randomisation will be enrolled in a separate observation group. Randomised patients will be followed for 10 years.

Trial Registration

Ethics approval has been granted in Norway (457593), Denmark (H-22051998), Finland (R23043) and Sweden (Dnr 2023-05296-01). The trial is registered on Clinicaltrials.org (NCT05448547).

Keywords

clinical trial, prostate cancer, elderly patients, geriatric oncology, curative treatment

Background

Prostate cancer (PCa) is a major cause of cancer-related mortality and morbidity in older Scandinavian men [1–3]. Almost 80% of patients who die from PCa in Norway are aged ≥75 years with a median age of 83 years at death [4]. Mirroring the advanced age at death, the majority of patients with lethal PCa are aged >70 years at diagnosis. In a retrospective study from Vestfold County, Norway, the median age at diagnosis was 72.5 years for patients with non-metastatic (M0) disease who later died from PCa [5], corresponding with increasing risk of developing high-risk PCa with increasing age [3,6–8]. With increasing life-expectancy in developed countries, PCa morbidity and mortality may increase in the older male population.

Despite this, older men with PCa are less likely to receive curative treatment [9,10]. Data from the US National Cancer Database (NCDB) showed that increasing age was significantly associated with a decreased likelihood of receiving curative treatment in patients with intermediate- and high-risk PCa. However, the same study showed that most patients aged >80 years with high-risk PCa received curative radiotherapy (RT) [11]. In contrast, in Scandinavia, curative treatment was until recently reserved for patients aged <75 years and was rarely offered to octogenarians [1,12,13]. Despite a clear trend towards more aggressive treatment in older patients [4,14], it is still uncertain whether the benefits of curative treatment seen in younger patients can be achieved in their older counterparts [15,16]. This is particularly relevant in the light of novel, life-prolonging medical treatments, that are generally well tolerated by older patients, and which have significantly increased the efficacy of conservative treatment [17,18].

The reluctance to offer immediate curative treatment to older patients is also motivated by concerns about its toxicity and the balance between efficacy and side-effects. These are still valid concerns, particularly in the oldest patients who appear to value functional independence [19] and are less concerned with survival gains [20,21]. Thus, health-related quality of life (HRQoL) is an equally important outcome in older patients [22].

A systematic review of the literature was performed identifying randomised, controlled clinical trials that investigated curative treatment (surgery or RT) [15,16,23–26]. Recruitment of older patients (aged ≥75 years) in these trials was mapped. Only two of the trials [25,26] recruited patients between the ages of 75 and 80 years (~25% of the study population). No subgroup analysis for this age group was provided. None of the trials included patients aged >80 years and only one of the trials that recruited patients aged 75–80 years reported HRQoL data [25] also without a subgroup analysis for older patients.

Here, we introduce a randomised, controlled, multicentre, phase III trial to investigate whether immediate curative treatment can prolong life and improve HRQoL in older patients (aged ≥75 years) with high-risk, non-metastatic PCa compared with a more conservative approach, which aims to reduce overtreatment while treating disease-related progression and morbidity when necessary.

The trial was initiated by the Norwegian Get-Randomized (GRand) Research Group and is conducted by the Scandinavian Prostate Cancer Group (SPCG). Results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Aims and Objectives

The overall aim of the study is to demonstrate that immediate tumour-directed therapy in older patients with non-metastatic, high-risk PCa prolongs life and improves HRQoL.

The specific objectives of the study are:

- To demonstrate that immediate tumour-directed therapy in older patients with non-metastatic, high-risk PCa improves overall survival (OS).
- To demonstrate that immediate tumour-directed therapy in older patients with non-metastatic, high-risk PCa improves short-term and long-term HRQoL.

- To demonstrate that immediate tumour-directed therapy in older patients with non-metastatic, high-risk PCa improves PCa-specific survival.
- To demonstrate that immediate tumour-directed therapy in older patients with non-metastatic, high-risk PCa is cost-effective.
- To demonstrate that immediate tumour-directed therapy in older patients with non-metastatic, high-risk PCa reduces morbidity caused by PCa progression/treatment.
- To demonstrate that immediate tumour-directed therapy in older patients with non-metastatic, high-risk PCa preserves functional status.

Study Design

The SPCG 19/GRand-Prostate (-P) is a phase III, randomised, controlled, prospective, open-label, parallel group (two-arm), multicentre, interventional trial. The recruitment target is 980 patients (490 per arm).

Patients aged ≥75 years with high-risk PCa are eligible for participation. High-risk PCa in the context of this study is defined as either locally advanced PCa (T3 or T4 on DRE or MRI) with Gleason Grade 7–10 (International Society of Urological Pathology [ISUP] 2–5) or localised PCa (T1/ T2 on DRE and MRI) with Gleason Grade 8–10 (ISUP 4–5). Gleason 6 (ISUP 1) is not permitted due to its often indolent course and low potential for metastasis.

Eligible participants will sign an informed consent form and are screened using the geriatric 8 (G8) health status screening tool and Mini-COG© brief cognitive test. Patients with a G8 score of ≤14 will undergo a simplified geriatric evaluation (Cumulative Illness Rating Scale-Geriatric [CIRS-G], activities of daily living [ADL], and malnutrition) to establish if their problems can be considered reversible. Patients with reversible problems are categorised as 'frail' [27]. Participants identified by G8 as 'fit' or 'frail' will be randomised (ratio 1:1) to either immediate curative therapy or conservative treatment.

Participants in the intervention arm will receive immediate curative treatment (surgery or RT) within the first 6 months following randomisation. Participants in the control arm will be managed conservatively (initial observation or immediate endocrine therapy). Participants in both arms will be followed for at least 10 years with follow-up visits every 6 months for the first 3 years and yearly thereafter (13 follow-up visits, on-site or remotely).

Participants who cannot participate in the study due to failing G8/Mini-COG© testing (G8 score of ≤14 and not reversible or/and failed Mini-COG©) or because they are considered too healthy or fit to be treated with initial conservative treatment, will be asked to sign a separate informed consent form. This allows for registration of basic patient, tumour and survival data. These patients will constitute a separate 'observation group'. For the study overview, see Fig. 1.

An independent Data Monitoring Committee (DMC) will be appointed by the Trial Steering Committee to aid in the assessment of the safety and well-being of the participants, and to oversee the trial conduct. A DMC charter will detail the provisions of the committee.

The study sponsor is Vestfold Hospital Trust, Tønsberg, Norway. Ethics approval has been obtained in Norway, Denmark, Finland, and Sweden. Recruitment of patients was initiated on 8 November 2022.

Endpoints

Primary Endpoints

The co-primary endpoints of this trial are OS and the change in HRQoL defined by the EORTC QLQ-ELD14 'burden of illness' scale between baseline and 36 months after the initiation of the treatment. There are two possible ways to show superiority of the immediate, tumour-directed therapy in comparison to conservative treatment in older men with high-risk, non-metastatic PCa: either prolongation of OS or better HRQoL, or both in the intervention group.

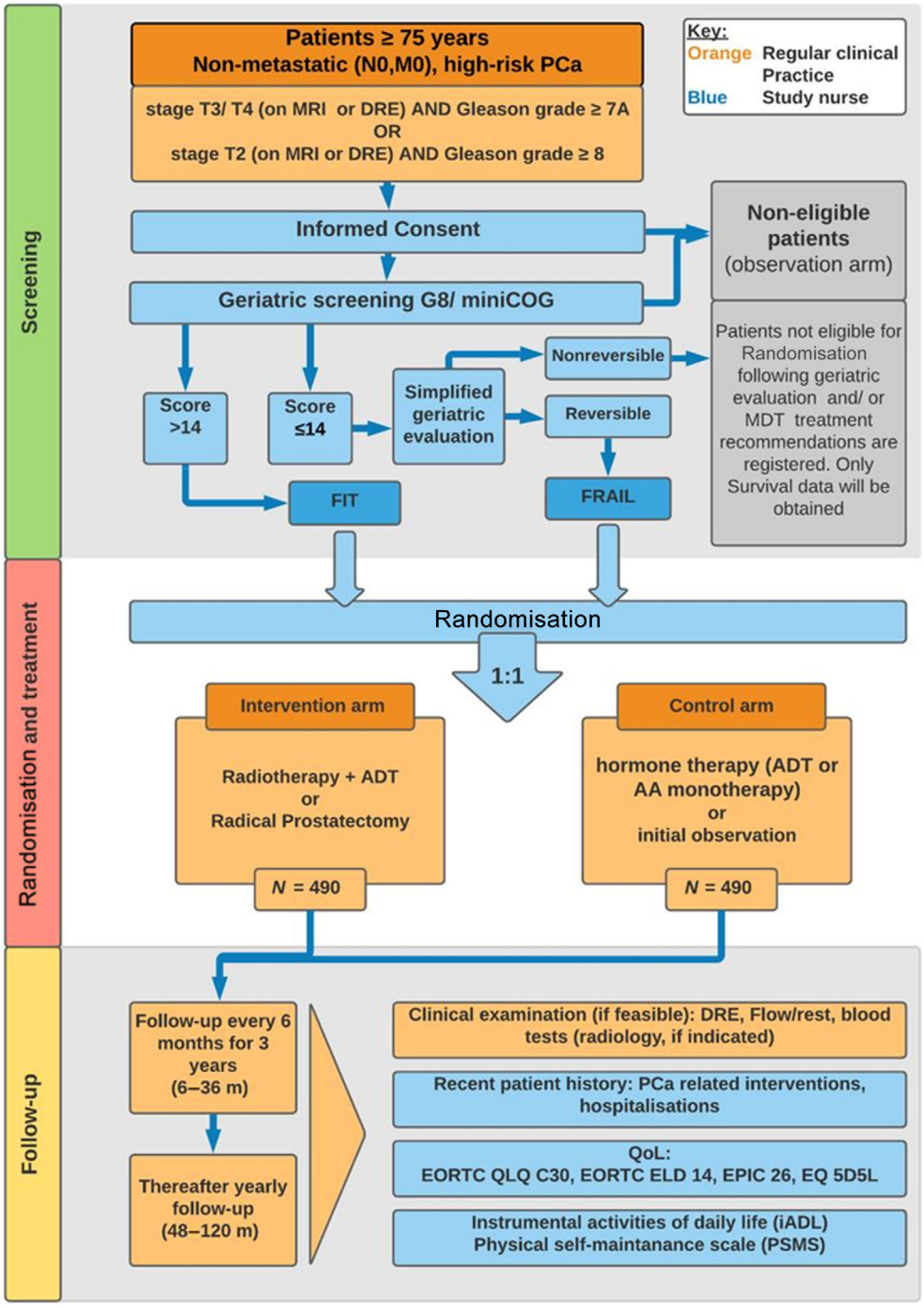
Secondary Endpoints

- PCa-specific survival (cause of death determined by cause of death committee).
- Metastasis-free survival.
- Role-functioning scale (EORTC QLQ-C30).
- Urinary irritative/obstructive scale (EPIC-26).
- Bowel scale (EPIC-26).
- Intervention-free survival.
- Hospitalisations, interventions, complications due to local progression or systemic progression.
- Use of secondary and tertiary systemic therapies (chemotherapy, second-generation antiandrogens, radioisotope treatments, poly-[ADP-ribose]-polymerase [PARP] inhibitors or other treatment of castration-resistant PCa).
- Mean quality-adjusted life-years (QALYs) in each treatment arm.
- Mean total healthcare costs in each treatment arm.

Tertiary (Exploratory) Endpoints

- HRQoL scales measured by EORTC QLQ-C30, EORTC ELD14, EPIC-26, EuroQoL five Dimensions five Levels (EQ-5D-5L).

Fig. 1 Study flow-chart with description of screening, randomisation/treatment and follow-up.



- Lawton and Brody personal ADL (pADL) and instrumental ADL (iADL).
- Need for nursing home care.
- Need for home care.

Eligibility Criteria

The inclusion and exclusion criteria are listed in Table 1.

Methods

Interventions

Intervention Arm

- Curative RT to the prostate is the preferred treatment for older patients. Combined androgen-deprivation therapy

Table 1 Inclusion and exclusion criteria.

Inclusion criteria	
Age	≥75 years at time of informed consent.
Health status	Fit: G8 test score >14 and Mini-COG© score >3 Frail: G8 test score ≤14, reversible problems on SGA and Mini-COG© score >3
PCa properties	High-risk PCa defined as: T2 (on DRE and MRI) with Gleason Grade 8–10 (ISUP 4–5); broad capsular contact of tumour on MRI is categorised as localised disease, T2, in the context of this study T3 (on DRE or MRI) with Gleason Grade 7–10 (ISUP 2–5)
Other	Capable of giving signed informed consent Able to read, understand and complete HRQoL questionnaires (PROM)
Exclusion criteria	
Medical conditions	Dementia
Prior/concomitant therapy	Prior RT to the pelvis Initiation of hormone therapy >3 months prior to randomisation
PCa properties	Gleason Grade 6 (ISUP 1) Radiographic evidence of lymph node metastasis (cN1) on MRI, CT, or PSMA-PET CT (equivocal findings = cN0). Distant metastasis (M1) on MRI, CT, bone scan or PSMA-PET CT (equivocal bone scan findings need to be confirmed with MRI or CT).
Other	Disabled or severe comorbidity (identified by G8 screening) Unable to read, understand or complete HRQoL questionnaires (PROM) Mini-COG© score ≤3

PROM, patient-reported outcome measures, PSMA-PET, prostate-specific membrane antigen positron emission tomography; SGA, simplified geriatric evaluation.

(ADT) is mandatory and should be given according to clinical practice/ national guidelines.

For men with very high-risk disease according to Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) criteria [28] (at least two of the following: T stage T3/4, ISUP ≥4, PSA level ≥40 ng/mL), abiraterone/ prednisolone in combination with ADT is permitted.

Elective RT of the pelvic nodes is permitted according to physician's choice in the absence of contraindications.

Details and minimum standards are defined in the RT appendix of the study protocol.

- Radical prostatectomy is permitted for patients who are unwilling or unable to undergo RT and who have localised high-risk PCa (cT2/radT2). Surgery of limited T3 disease is permitted where national guidelines allow for this treatment approach.

Control Arm

- Immediate or delayed endocrine therapy is administered at the discretion of the treating physician. ADT, antiandrogen monotherapy and total androgen blockade are permitted. Hormone therapy can be given intermittently.
- Initial observation is permitted at the discretion of the treating physician.

Sample Size Determination

The aim of this trial is to demonstrate that immediate curative therapy in the intervention group is superior in comparison to the control group in terms of overall mortality (OM) and/or burden of illness.

The co-primary endpoints of this trial are OS and the change in HRQoL defined by the EORTC QLQ-ELD14 'burden of illness' scale from baseline to 36 months after treatment initiation. As there are two possible ways to 'succeed' (one of the two or both endpoints show an effect), the use of co-primary endpoints creates a problem of multiple comparisons. Here, a simple and conservative Bonferroni method is applied and each of the two hypotheses are tested at a significance level of $P < 0.025$. The required sample size is calculated so that the test of the co-primary endpoints upon which it is most difficult to demonstrate an effect, has a power of 80%. Consequently, the other endpoint may have power >80%. Below, we derive the required sample sizes for each of the endpoints separately, and the final sample size will be the larger of the two.

A total of 466 events (deaths from any cause) are expected to achieve a power of 80% ($P < 0.025$, two-sided) of detecting a 25% reduction in OM in the intervention group (corresponding to hazard ratio of 0.75). Assuming an OM across the groups at the end of study (after 10 years) of ~50%, it can be expected that the number of required events would be reached in 10 years, if a total of 932 patients (466 in each arm) are followed. Assuming a drop-out rate of 5%, ~980 patients will be recruited.

The second co-primary endpoint, change in HRQoL between baseline and 36 months, is based on EORTC QLQ-ELD14 scale 'burden of illness', which is a continuous score of values ranging from 0 to 100, with a high score representing a

Table 2 Data collection tools/sources and measures.

Data source/Tool	Measure
Geriatric assessment tools	
G8	Frailty
Mini-COG™	Cognitive status
Cumulative Illness Rating Scale-Geriatric (CIRS-G)	Comorbidities
pADL	Basic capacity of persons to care for themselves
iADL	Capacity for more complex activities
Patient-reported outcome measures	
EORTC QLQ-C30	HRQoL in all cancer patients
EORTC QLQ-ELD14	HRQoL in elderly cancer patients
EPIC-26-SF (short form)	Patient function and bother following PCa treatment
EQ-5D-5L	HRQoL
Patient records/anamnestic information	
Hospital admissions	PCa and treatment morbidity
Surgical/other invasive interventions	
Complications due to cancer progression	
Complications due to cancer treatment	
Palliative RT	Secondary/tertiary cancer treatment
Palliative surgery	
Second-generation hormone therapy	
Systemic medical therapy (e.g. chemotherapy, targeted therapy, radioisotopes)	
Need for nursing home/mobile care	Independence
Cause of death	PCSM

higher burden of illness. It can be assumed that at the time of the evaluation at 36 months, there are negligible treatment-related mortality differences between the arms, and thus any missing values in HRQoL scores caused by death are equally distributed across the arms. A recent article by Aghdam et al. [29] reported trends in self-reported burden (ELD14) in a sample of 111 patients aged >70 years with PCa treated with stereotactic body RT between start of the treatment and 24 months. During this time period, they observed an average change of −5.6 units in a total ELD-14 burden score (burden of treatment and illness). It can be assumed, that the change between baseline and 36 months could be of similar magnitude, or higher. The variance of the score was 73.28 at baseline (SD = 8.56) and 62.44 at 24 months (SD = 7.9). To get an estimate of the variation of the 'change', the time points are assumed to be independent (conservative assumption), following that the variance of the difference between the time points is the sum of the variances at each time point. Thus, an estimate of the variance for the change is 135.72 (SD = 11.65). Assuming that the burden score in the control group would either stay the same or increase over time, the reported change of 5.6 for the patients receiving RT can also be regarded as the treatment effect size. Thus, to detect a change of at least 5.6 units in the burden score between the two arms when assuming a SD of 11.65, would require 168 patients (84 in each arm) to achieve a power of 80% ($P < 0.025$, two-sided).

In summary, a total of 980 patients (490 in each group) are required to show a 25% decrease in mortality in the immediate curative therapy group with a significance level of 2.5% and power of 80%. This sample size is also enough to detect a difference of at least 5.6 points in the 'burden of illness' score at 2.5% significance level and with 80% power.

Data Collection

Data are collected by means of patient history, electronic health records, and HRQoL and other questionnaires (Table 2). Study data are registered in a Viedoc™-based database and stored on a research server at the Clinical Trials Unit, Oslo University Hospital, Oslo, Norway.

Analysis Plan

The statistical analysis plan will be finalised prior to database lock and it will include a more technical and detailed description of the statistical analyses.

Primary Endpoint(s)

The efficacy endpoints will be summarised and analysed both in the Full Analysis Set (FAS, all randomised participants, regardless of protocol adherence, who are exposed to study intervention, i.e., have data after randomisation) and Per Protocol Set (PPS, all randomised participants who sufficiently comply with the protocol and who did not refuse or withdraw consent). As a superiority trial, the FAS will be used for the primary analysis, while the PPS will be used for sensitivity analysis.

The first co-primary efficacy endpoint, time from randomisation to death from any cause, as well as all time-to-event secondary endpoints will be analysed using a stratified

log-rank test accounting for the stratification factor (study centre), and the treatment effect will be estimated using the Cox proportional hazards regression model stratified by study centre.

As exploratory analyses, these endpoints will also be analysed using stratified Cox proportional hazards models adjusted for other baseline covariates considered to be of potential prognostic value such as type of immediate curative therapy (RT/surgical), tumour type (localised/advanced) and patient age.

All time-to-event endpoints will be summarised using Kaplan–Meier/Nelson-Aalen plots, estimates of median, 25th and 75th percentiles and hazard ratios.

The second co-primary endpoint, change from baseline HRQoL, is assessed seven times, at baseline and then every 6 months until 36 months, and will be analysed using a linear mixed model accounting for the correlations between repeated measurements within each participant by random intercept. The intervention group, stratification factor (study centre), and intervention × time interaction will be treated as fixed effects in the model. In addition, the model will be adjusted for the baseline value of the HRQoL score. The primary effect measure is the marginal estimate for the change from baseline at 36 months.

Secondary Endpoint(s)

The time-to-event secondary endpoints (PCa-free survival, metastasis-free survival, intervention-free survival) will be analysed similarly to the primary endpoints, as described above.

The continuous secondary HRQoL endpoints will be measured repeatedly over the follow-up period and analysed using linear mixed models similarly to the co-primary HRQoL endpoint.

Between group comparisons for the continuous secondary endpoints, number of hospitalisation days and number of (any) interventions will be analysed using a linear regression model with the intervention group as a factor and adjusted for the study centre.

Between group comparisons for the binary secondary endpoints, complications due to local progression ('yes/no'), complications due to systemic progression ('yes/no'), will be analysed using logistic regression model with the intervention group as a factor and adjusted for the study centre.

Tertiary/Exploratory Endpoint(s)

Exploratory analyses will be described in the statistical analysis plan finalised before database lock.

Safety Analysis

All safety analyses will be presented on the Safety Population. No formal statistical analysis of safety endpoints will be performed.

Safety data will include a summary of perioperative mortality with the number and percentage of patients dying, regardless of the cause, within 30 days after surgery in or out of the hospital.

Observation Group

The observation group will be registered and receive treatment and follow-up according to local procedures. Only the deaths in this group will be observed, and the OS (time from screening to death from any cause) function will be estimated. This serves as a reference for assessing selection based on patient's age and frailty.

Interim Analysis

No interim analysis on the efficacy of the study intervention will be performed.

Health Economic Analysis

The cost-effectiveness of immediate curative therapy and standard care for older patients with non-metastatic, high-risk PCa will be determined from a *de novo* Markov model. Cost will be estimated from healthcare sector resource use, retrospectively collected from patient journals. The analysis' health benefit will be QALYs, estimated from the collected EQ-5D-5L and survival data. The results of the economic evaluation will be expressed as incremental cost effectiveness ratio (ICER), i.e., cost per QALYs gained. In addition to validating the Markov model, sensitivity analyses on the assumptions and parameters used in the simulation will be performed.

Subgroup Analyses

Subgroup analyses will be performed by including an interaction term between the group variable in question and the dichotomous intervention variable in the model for the primary outcome. The following subgroup analyses for the primary outcome will be performed:

- Age (<80 vs ≥80 years).
- T stage (T2 vs >T2).
- Gleason Grade (7 vs >7).

Discussion

In the Nordic countries, age has until recently been a major factor in determining eligibility for curative PCa treatment.

The case for age limits was based on the following arguments: first, there is scant level 1 evidence that immediate curative treatment offers a survival benefit in men aged ≥75 years. However, the randomised PCa trials that documented survival benefits included none [15,16,24,30] or few patients aged ≥75 years [26,31]. Patients aged >80 years were not represented at all. This highlights a general problem in clinical intervention trials in which older patients are under-represented [32]. Second, there is the widespread notion that endocrine therapy alone confers adequate control of high-risk PCa in older patients. However, several register-based studies have demonstrated a high PCa-specific mortality (PCSM) in the older age group [1,3,10], questioning the long-term efficacy of stand-alone endocrine therapy in older patients. Third, there is a general understanding that octogenarians have few remaining life years because life expectancy for men in Western countries is ~80 years (Norway 2019: 81 years, Denmark: 80 years, Finland: 79 years, Sweden: 80 years; source: Statistics Norway/Denmark/Finland/Sweden). However, these numbers describe life expectancy at birth. In clinical practice, remaining life years for specific ages have greater clinical significance. Older Norwegian, Danish, and Finnish men have long average life expectancies (Table 3). Studies have demonstrated that both urologists and oncologists are not sufficiently aware of this and routinely underestimate life expectancy in patients with PCa [33,34].

The strongest arguments in support of immediate curative treatment in older patients quote register-based evidence indicating improvements in PCSM. A Swedish, nationwide study showed that RT had the potential of improving PCSM in older patients [10]. A Surveillance, Epidemiology and End Results (SEER) database study found a positive impact on PCSM in older American patients. However, the benefit was only seen in patients with cT3b/4 tumours, Gleason score 8–10, negative lymph nodes or PSA level >10 ng/mL [35], suggesting that treatment benefits may only be observed in selected patients. An Australian study showed that immediate curative treatment reduced the risk of PCSM even in patients aged >80 years [36]. A Norwegian study based on Norwegian Cancer Registry data showed that in patients with high-risk PCa, curative treatment was associated with reduced PCSM and OM in both younger and older patients [1]. However, these results are based on information from death certificates, which are an unreliable source of cause of death in older patients with PCa [5].

Table 3 Average remaining life years for men at specific ages in the four participating Nordic countries for 2018–2022 (Source: Statistics Norway/Denmark/Finland/Sweden).

Age, years	Average remaining life years			
	Norway	Denmark	Finland	Sweden
At 75	12	11	11	12
At 80	8	8	8	9
At 82	7	7	7	7
At 85	6	5	5	6

Furthermore, the Scandinavian landmark studies (SPCG 4/SPCG 7), that demonstrated OS benefits of curative treatment in younger men did not achieve statistical significance until ~10 years [15,16]. It is unclear if these long-term benefits in OS can be achieved in older patients.

Furthermore, conservative treatments have evolved considerably. In randomised clinical trials that documented OS benefits of immediate curative treatment, the control arm was either watchful waiting or endocrine therapy, mostly ADT. Patients who failed ADT had no further therapeutic options. Novel therapeutics such as abiraterone, enzalutamide, docetaxel and other agents have changed this landscape considerably [37]. The improved survival achieved by these agents may offset some of the effects of curative treatment.

Furthermore, the impact of immediate curative treatment on HRQoL in older men is not well documented. HRQoL has been recognised as the second key outcome of cancer treatment by the European Society of Medical Oncology (ESMO) [22] and the American Society of Clinical Oncology (ASCO) [38]. There is convincing evidence that HRQoL and other patient-reported outcomes are independent prognostic factors for survival in randomised clinical trials [39]. For older patients in particular there is an emerging consensus that HRQoL considerations should be a fundamental component in cancer management [40]. Older patients with cancer tend to perceive HRQoL as more important than improved survival compared to younger patients [20,21]. However, lack of tumour control could increase symptom burden and require surgical and medical interventions [2]; thus, immediate tumour-directed treatment, could confer long-term HRQoL benefits.

The obvious limitations of chronological age as a guide for treatment decisions raise the question of how to identify older patients who may benefit from immediate curative treatment. The International Society of Geriatric Oncology (SIOG) published its recommendations for evaluation and treatment of older patients with PCa for the first time in 2010 [41] and an update has recently been published [27]. The SIOG Prostate Cancer Task Force recommends that older men with PCa should be managed according to their individual health status and not by chronological age. The SIOG recommendations have been adapted by the European Association of Urology (EAU) and are today referred to as the EAU/European Society for Radiotherapy and Oncology (ESTRO)/SIOG guidelines [42,43]. To evaluate health status, SIOG recommends a stepwise process: initial screening of patients by using the G8 and Mini-COG©. Both tests are little time-consuming (~5 min each) and can be performed by a trained nurse/study nurse. Patients with a normal G8 and Mini-COG© should receive the same treatment as

younger patients according to guidelines. For the first time, this recommendation will be tested in this randomised clinical trial.

This study will provide a better understanding of the benefits and harms of immediate curative treatment vs conservative treatment in this large and increasing patient population.

In contrast to previous trials, this study will not only document long-term survival data and HRQoL but also map treatment- and cancer-related morbidity and patient functional status in detail. Furthermore, it will provide important insights into the feasibility of randomised clinical trials in an older patient population.

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Disclosure of Interests

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Abbreviations: (i)(p)ADL, (instrumental) (personal) activities of daily living; ADT, androgen-deprivation therapy; DMC, Data Monitoring Committee; EAU, European Association of Urology; ELD14, Elderly 14-item; EORTC, European Organisation for the Research and Treatment of Cancer; EPIC-26, 26-item Expanded Prostate cancer Index Composite; EQ-5D-5L, EuroQoL five Dimensions five Levels; ESTRO, European Society for Radiotherapy and Oncology; FAS, Full Analysis Set; G8, geriatric 8 questionnaire; Grand(-P), Norwegian Get-Randomized Research Group (-Prostate); HRQoL, health-related quality of life; ISUP, International Society of Urological Pathology; Mini-COG©, cognitive function test; OM, overall mortality; OS, overall survival; PCa, prostate cancer; PCSM, prostate cancer-specific mortality; PPS, Per Protocol Set; QALY, quality-adjusted life-year; QLQ (-C30), quality of life questionnaire (30-item core); RT, radiotherapy; SIOG, International Society of Geriatric Oncology; SPCG, Scandinavian Prostate Cancer Group.