DAPROCA

Danish Prostate Cancer Group

PROstate PROTON Trial 1
(PRO-PROTON 1)

Lymph node radiation therapy with integrated boost to prostate for high-risk prostate cancer

A randomized phase 3 trial comparing photons vs. protons

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Number 1-10-72-290-21 Ethical Committee

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1 Protocol organization: Daproca

Principal Investigators and Steering Committee

Lise Bentzen, Jimmi Søndergaard, Ludvig Muren, Morten Høyer, Stine Elleberg Petersen

The steering committee will be in charge of the study and will be responsible for assigning tasks, discuss propagation of the study and secure that authorships are according to the Vancouver Declaration concerning publishing medical science. Since this is a long-term study, we will expect new investigators are participating during the study and others leaving.

Clinical medical co-investigators

One co-investigator from each participating center – if a center has a principal investigator; it is allowed to have a co-investigator

Clinical medical physicists

One co-investigator from each participating center

Medical physics co-investigators DCPT

Co-investigators are the clinical responsible physicist at DCPT

Scientific personnel (such as Ph.D. students, bachelor students, post docs.) attached to the design, planning phase of the study etc.

Medical co-investigators DCPT

Stine Elleberg Petersen

Participation Departments

Dept. Oncology Aalborg Universitetshospital – Afsnit Syd Hobrovej 99 9100 Aalborg	Jimmi Søndergaard Mette Moe
Dept. Oncology Aarhus University Hospital Palle Juul-Jensens Boulevard 99 8200 Aarhus N	Anders Schwartz Vittrup Simon Buus
Dept. Oncology Vejle Sygehus Kabbeltoft 25 7100 Vejle	Christine Vestergaard Madsen Lise Bentzen (National primary investigator)
Dept. Oncology Odense Universitetshospital Sdr. Boulevard 29 5000 Odense C	Steinbjørn Hansen
Dept. Oncology Herlev Ringvej 75 2730 Herlev	Henriette Lindberg
Rigshospitalet Dept. Oncology Blegdamsvej 9 København	Peter Meidahl Petersen
Dept. Oncology Næstved Sygehus Ringstedgade 61 4700 Næstved	Marko Bebek
Danish Centre for Particle Therapy, Palle Juul-Jensens Boulevard 99 8200 Aarhus N	Stine Elleberg Petersen (National primary co-investigator Morten Høyer Ludvig Muren
Protocol organisation DAPROCA	Michael Borre
Statistical calculations	BIOS, Aarhus University

2 Purpose

Background

Prostate cancer (PC) is the most common malignancy among men, worldwide[1] as well as in Denmark (DK)[2]. In addition, the incidence of PC is increasing[1]. Based on the annual rapport from The Danish Multidisciplinary Cancer Group (Daproca) database[3], 4263 men were diagnosed with prostate cancer in 2020. The incidence per 100.000 for PC is approximately 185 and the prevalence for PC in the male population was more than 42000 men. Prostate cancer incidence and mortality rates are strongly related to age with the highest incidence in elderly men[1]. In Denmark, the median age for diagnosis was 72 years[3] in 2020.

The 5-year survival rate in the western part of the world is high[1]. Low risk and low intermediate risk patients are primarily offered active surveillance with intent for curative treatment if the cancer progresses. Patients with higher risk but localised disease are offered curative treatment. Thus, the number of patients surviving and having to live with adverse effects of cancer treatment is also increasing. It is of outmost importance to continue to improve treatment outcomes both in terms of survival but also aim at reducing adverse effect and improving quality of life (QoL).

From 2015–2019, more than 22000 Danish men were diagnosed and registered with prostate cancer in The Danish Prostate Cancer Registry[3]. Patient-reported outcome (PRO) measures were routinely collected at diagnosis, at 1-year, and at 3-year follow-up from 2011 to 2016. Nguyen-Nielsen et al. published data on a sub-set of this patient cohort (more than 15 000 patients)[4]. The PRO scoring was a short form of Expanded Prostate Cancer Index Composite, a health-related QoL instrument developed to assess patient function and symptom bother after treatment of prostate cancer[5]. Data showed that there was a clinically significant decline in mean scores across all symptom domains at 1-year follow up. Thereafter, mean scores for all symptom domains improved marginally and remained relatively unchanged at 3-year follow-up. Similarly, in a proton study Mishra et al. found a 9-point decline with a SD of 17 in the EPIC-26 bowel score at one year[6]. However, in this cohort the patients were treated to the prostate only.

PC patients staged without lymph node (LN) metastasis but with a significant risk of lymph node involvement can be successfully treated surgically with extended LN adenectomy before radiation therapy or combined with prostatectomy. In 2011, Bentzen et al. initiated a national multicentre phase 1/2 trial (Propel) to explore the possibility to treat these patients with radiation therapy (RT) combining treating the prostate gland to a high dose and the LNs to a lower dose[7]. The study was a nation-wide study anchored within Daproca and carried out at all radiotherapy clinics in Denmark. The proposed treatment to the lymph nodes became standard treatment in DK. Data from the study showed that prevalence of late gastro-intestinal morbidity and its impact on QoL, scored by PROs, was significantly higher at 60 months' follow-up compared to baseline. In comparison, no significant differences were found on grade2+ gastro-intestinal at 60 months' follow-up compared to baseline using the physician administered Common Toxicity Criteria for Adverse Events (CTC_AE vers.4.0) (manuscript submitted for publication). Currently in Denmark, approximately 300 patients are every year treated with prostate combined with lymph node irradiation. This treatment is combined with androgen deprivation therapy (ADT) either short-course 6 months (mos.) intermediate-risk with high risk of LN metastases or long course 36 months for high-risk pts.

Studies exploring morbidity after radiation for PC have used a variety of different toxicity scoring systems and even within one study. Gulliford et al. published a paper examining normo-fractionated RT vs. hypo-fractionated RT with toxicity scoring by multiple scoring systems: RTOG, Lent-Soma and a local system. In the same study they used PRO (EPIC-26). A review regarding PROs after proton therapy (PT), covering genito-urinary (GU), gastro-intestinal (GI), and sexual toxicity, concluded that for prostate cancer the benefit of PT was modest for localised PC and PRO's used varied[8]. Conclusively, this study endorsed more focus on QoL data in future PT trials. Direct comparison of toxicity data from different studies is often difficult. Preferentially, the clinical trials need to have the same endpoints and grading systems.

The promise of improved outcome in terms of reduced toxicity following proton therapy (PT) lies in the physical properties of the proton beam. The proton beam will deposit most of its energy in the so-called Bragg-peak (BP), which will be in the tumour target and almost no dose after the BP. In comparison, the photon beam will deposit entrance dose before reaching the target as well as a substantial dose beyond the target. With the use of multiple proton fields, the treatment plan achieves high dose conformity, with rapid dose fall off to eliminate high doses, where it is not wanted i.e., organs at risk (OAR).

PT for PC is used at various cancer centres worldwide, but mainly for patients receiving RT of the prostate only. However, one PT study explored acute toxicity in patients treated with prostate and LN. The study compared data to other published papers and found that patients receiving pelvic irradiation using PT compared to photon therapy experienced less acute toxicity[9]. The number of registered randomised trials at clinicaltrials.gov for PC and PT is very few with only 3 trials with primary RT and randomisation between photon therapy and proton therapy. At present, no randomised trial (level I evidence) has published significant difference between IMRT and PT regarding survival or toxicity. One study randomises directly between primary RT and PT for low and intermediate risk PC, to the prostate alone, data are awaited[10]. The primary endpoint of this trial is bowel toxicity at 24 mos. measured by a clinically significant reduction in mean EPIC-26 bowel score[11]. A recent study showed the main results of several treatment planning studies comparing proton to photon treatment plans of PC[12]. The studies demonstrated consistently, that the prostate was covered with both IMRT and PT, but with lower dose to OAR using PT. In lack of data from prospective randomized trials, the authors reviewed clinical trials, presenting toxicity for photon and proton studies. In the prospective trials, no significant difference was found in toxicity for the domains gastro-intestinal toxicity (GI), genito-urinary toxicity (GU) and sexual toxicity in general.

The Danish Centre for Particle Therapy (DCPT) is a national facility, with frontline proton therapy planning and delivery equipment, being in clinical operation since January 2019. DCPT has sufficient treatment capacity to enable and support clinical trials in a number of tumour sites, where the outcome of current RT could be improved. DCPT is also part of a European Network for Particle Therapy (ENPT). This proposed study is part of the Danish Comprehensive Cancer Centre (DCCC) Prostate cancer WP13.

In DK, standard photon-based RT is delivered at a very high technical level, using so-called intensity modulated radiotherapy (IMRT) with prostate implanted fiducial markers for image guidance (IGRT). The treating radiotherapy clinics follow national guidelines securing the quality of treatment. With contemporary IMRT, it is possible to reduce treatment toxicity for bladder and bowel, but patients are still

experiencing toxicity grade 2 or more as shown in our phase 1/2 study[7]. The aim of this study is therefore to reduce the toxicity experienced by this large patient group, using proton therapy.

Hypothesis, endpoints and rational

We propose a phase III randomized controlled trial (RCT) of PT versus IMRT of the prostate including the regional elective LNs for localised/locally advanced PC patients eligible for LN irradiation including standard of care concomitant treatment according to national guidelines. The radiation dose to the clinical target will be 78 Gy in 39 fractions for prostate target and 56 Gy in 39 fractions for LN target. Both RT and PT will be delivered 5 fractions per week. ***We aim*** at reducing gastrointestinal toxicity more than 5 points, measured by mean EPIC-26 bowel scores and improve HRQOL.

We hypothesise that the dosimetry advantage of PT with sparing of large parts of the bowel will result in clinically relevant reduced gastrointestinal toxicity compared to IMRT. This patient population might benefit from PT, but this has never been tested in a randomised trial. This patient population is underrepresented in the PT literature. In the Danish PC patient population, these patients account for approximately 50% of the patients treated with curative RT. We propose a national study with participation from all oncology departments treating prostate cancer pts. We have shown previously that we are able to conduct a nation-wide trial within Daproca. We expect to be able to recruit the required number of patients within the Danish population.

Primary endpoint: The change (delta score) in patient reported late gastro-intestinal (GI) toxicity at year 2 compared to baseline using EPIC-26 bowel score.

Secondary endpoints include morbidity and survival data up to 10 years after treatment:

- Late GU and sexual toxicity ≥ 2 grade at year 2 and 5 compared to baseline (CTC_AE 5.0)
- Late GU and sexual toxicity at year 2, 5 and 10 compared to baseline (EPIC-26)
- Late GI toxicity at year 2 and 5 compared to baseline (EPIC-26 (year 5) and selected items from the RT-ARD score)
- Acute GI and GU toxicity at start, at the end of therapy and week 12 compared to baseline (EPIC-26, selected items from the RT-ARD score and CTC_AE v.5.0)
- General health related quality of life (QoL) at year 2, 5 and 10 compared to baseline (EORTC QLQ-C30)
- Biochemical progression free survival (BCR), (Phoenix criteria)
- Non-biochemical progression free survival (by imaging and confirmed by biopsy)
- Overall survival (OS)

No data analysis may be performed before a final statistical analysis plan is completed.

EPIC-26 is a commonly used PRO tool and is the primary outcome measurement in an ongoing clinical trial of low and intermediate prostate cancer comparing protons to photons[10]. Skolarus et al. showed the threshold for a minimal important difference (MID), representing the smallest change in EPIC score considered clinically relevant, for the bowel, urinary and sexual was 4-6, 5-9 and 10-12 points, respectively[11]. The primary outcome for the current study will compare the mean decline in bowel EPIC-

26 at two years of follow-up for the proton and photon therapy, respectively. A reduction in the EPIC-26 bowel score of 5 points will be considered clinically relevant.

CTC_AE: To allow comparison with earlier studies of radiotherapy of PC the acute and late toxicity will be evaluated by the CTC_AE 5.0 physician reported scoring system.

EORTC QLQ-C30: This is a 30-item questionnaire covering functional, physical and global health issues.

Biochemical recurrence (BCR): BCR of the PSA according to the RTOG-ASTRO phoenix guidelines is a rise in PSA by 2 ng/mL or more above the nadir PSA after EBRT with ADT[13].

Overall survival (OS): Time from randomization to death from any cause.

For the proton study and translational study 1 and 2 we will use data from the patients charts and data stored in our database:
1. Prostate cancer TNM stage
2. Pathological grade (Gleason/ISUP)
3. Imaging at diagnosis and if any suspicion of recurrence
4. Prostate specific antigen (PSA) measurements according to the protocol
5. Morbidity scores (CTCAE), including sexual morbidity, genitourinary morbidity and gastro-intestinal morbidity. Will be recorded according to the protocol
6. Patient reported outcomes (PROs) including quality of life measurements (EORTC C30)
7. Medication including medical castration treatment which is standard treatment for high risk prostate cancer
8. Measurement of testosterone at the end of medical castration treatment
9. Dose plans

Translational studies

PT is a new and relatively expensive treatment modality with a rapid increase in indications. There may be significant differences in the radiobiological mechanisms between protons and photons both for anti-cancer effects and for normal tissue toxicities. It is also important to develop predictive factors for optimal selection of patients for PT, and a well-controlled clinical trial is a valuable resource to address such questions. Therefore, this study is obligated to perform translational studies. Currently the following studies are part of the current the trial. Others are likely to come in the future.

Translational study 1: Organ motion management through advanced IGRT for locally advanced prostate cancer

Since radiotherapy with protons is more sensitive to density variations than a corresponding treatment with photons, the choice of image guidance technique needs to be a subject of special consideration. We will establish and test an image guidance strategy to position parts of the total target in separate procedures according to their independent motion: Prostate positioned using implanted markers and

lymph node target positioned with a match to bony structures. The success of this approach is evaluated through dose/volume measures in a cohort of previously treated patients, which we have access to, as well as through the pilot phase of the trial. Further, we will use early normal tissue outcome data from each arm of the trial to assess whether the available models can predict which patients has the largest benefit of protons, and whether our ability to identify these patients improves when accounting for the actually received doses [15]. Finally, we will analyze in detail both dose/volume-based and clinical outcomes for all patients treated in the trial within the time frame of this translational study with a focus on normal tissue sparing and GI and GU symptoms in particular. All treatment plans for patients treated in this protocol must be submitted to the Danish national dose plan bank (DCMcollab) for quality assurance and detailed research.

We will study the dose plans and compare given doses to normal tissue with morbidity data (physician reported toxicity and patient reported outcome data). As stated above we plan to store all dose plans in the above mentioned Danish national dose plan bank.

Translational study 2: Proton therapy specific normal tissue dose response models

The difference in response between photons and protons is referred to as the so-called relative biologically effectiveness (RBE). In current clinical practice it is assumed that protons are uniformly 10% more effective, i.e. that the RBE is equal to 1.1, for all tumor entities, and for all normal tissues. However, there are indications of increased cell damage towards the end of the proton range, where the RBE has been found to range up to 1.7. The region with elevated RBE correlates with elevations in what is called linear energy transfer (LET), and LET has been found as one of the main reasons for the increase in RBE. When comparing the effectiveness of different treatment plans, one can use normal tissue complication probability (NTCP) models. Current proton therapy (PT) based NTCP models, however, do not consider LET or RBE changes. Hence, we will enable incorporation of LET calculations in NTCP models, quantifying the effects of LET in PT of prostate cancer.

This will allow for new treatment planning strategies within PT that minimizes the risk of normal tissue complications in patients.

We will examine the dose plans and use those for studying the radiobiology and the RBE as mentioned above. Again we wish to further explore whether it is correct to state that the RBE is equal to 1.1. for all tumours and normal tissues.

Translational study 3: Health economics of PT

Proton therapy is associated with higher treatment costs when comparing to conventional radiotherapy, and still its impact on patients' outcome is unclear relative to cost. Therefore, it is essential to study the magnitude of the clinical benefits for the patients, for which patients it is cost-effective, and what is the expected impact on the health care budget[14]. For all patients enrolled in the randomized trial, we plan to collect and analyse the relevant health economic parameters, including type, number and cost of equipment and personnel, patient population and treatment indications, time requirements, use of health related resources, disutility of care, return to work life etc.[14] Data will compose the basis of a cost accounting model, which together with the outcome data (morbidity, quality of life, biochemical free survival and overall survival) will be used to assess the cost-effectiveness of protons vs. photons in

radiotherapy for prostate cancer. The study will be planned and conducted in collaboration with leading health economists in Denmark and Europe through the European Particle Therapy Network (EPTN).

For translational study 3 there will be no data concerning the economics for the individual patient. For the outcome data, data from the patients charts and data stored in our database will be used.

When entering the trial, the patients will be asked if they want to deliver one whole-blood sample of 30 ml. The blood sample is collected in the Danish Cancer Biobank under the auspices of Danish Cancer Biobank ((DCB)/Regionernes Bio- og genombank (RBGB)) and stored in this clinical biobank. The blood sample is extra material that will be used for future non-specific research and it is not part of the trial. The patients will receive a separate patient information and sign a separate written consent regarding the blood sample.

3 Methods

Study design

We plan to perform a phase III randomized controlled trial (RCT) of PT versus IMRT of the prostate including the regional elective LNs for localised/locally advanced PC patients eligible for LN irradiation including standard of care concomitant treatment according to national guidelines. The radiation dose to the clinical target will be 78 Gy in 39 fractions for prostate target and 56 Gy in 39 fractions for LN target. Both RT and PT will be delivered 5 fractions per week.

Registration and randomisation

Eligible patients will be identified at the regional multidisciplinary team conference (MDT). The oncologist will approach them about possible trial enrolment at the first visit at the department of oncology. At this planned visit the patient will be seen by a medical doctor and/or a nurse in a consultation room without disturbances. The patient may bring a relative or another person as the patient wishes. All patients are introduced to the trial by written information and a consultation elaborating on the material. The patients will have at least 24 hours' notice before signing the informed consent. After signing the informed consent, the patients can be registered into the trial before or after commencement of ADT. The patients will be randomised in a one-to-one ratio and stratified by tumour stage[15] as the most important prognostic factor and also for treatment centre to insure a balanced distribution between the treatment arms. The study will thus be open-label for the patient and the treating physician. Randomisation will be performed centrally, using an online 24-hour system maintained by the Clinical Trial Office in DCPT, at Aarhus University Hospital, Denmark. Centres will able to access the randomisation form when eligibility screening has been completed. We plan to include a total of 400 patients 1:1 over a period of three years.

Radiotherapy Planning and Treatment

Following randomisation, the patient should start radiotherapy treatment three months after initiating the hormonal therapy.

Planning CT and MRI scan

For planning purposes, patients will have a CT scan and a MRI-scan performed on the same day before the commencement of radiotherapy. It is accepted that MRI only RT clinics for prostate use MRI only.

Pre-imaging and treatment preparation

The patients should have and empty rectum and a comfortably filled bladder during planning CT/MRI and radiotherapy treatment. Please refer to the appendix.

Target volume definition

For all patients, the clinical target volume (CTV) and organ at risk (OAR) volumes must be defined on the planning CT scan using the protocol nomenclature / treatment planning system naming (TPS name).

TPS name	Description
CVT1_78Gy/39fx	The prostate only, delineated on the MRI co-registered to the treatment planning CT based on the fiducial markers
CTV2_56Gy/39fx	The prostate including the proximal 2 cm of un-involved vesicles (≤cT3) delineated on the MRI scan
CTV3_78Gy/39Fx	The prostate and entire vesicles on both sides. Only delineated if the prostate tumor involves the vesicles i.e., T3b
CTV4_56Gy/39fx	Elective lymph nodes delineated according to the RTOG guidelines[16,17]

For photon therapy, to account for treatment uncertainties a minimal margin of 5-7 mm should be added to the CTV1-4 to create the planned target volume PTV1-4, with respect to local guidelines.

For proton therapy, the PTV will be replaced by robust optimization where the parameters are defined by the centre specific setup uncertainty and stopping power range uncertainty.

Organ at risk (OAR) definition

Delineation of the OAR will be performed following national guidelines as defined by in the appendix.

Dose and fractionation

Prescribed mean doses are 78 Gy to the CTV1 and CTV3 and 56 Gy to the CTV2 and CTV4 in 39 fractions 5 fractions per week using simultaneous integrated boost. The CTV1 must be covered with 95%-107% of the prescribed dose. For proton therapy, the PTV will be replaced by robust optimization where the parameters are defined by the centre specific setup uncertainty and stopping power range uncertainty. Proton therapy will be delivered assuming RBE=1.1.

Target dose and OAR constraints

See appendix.

Radiotherapy planning

The photon and the proton dose plans will be planned calculated using the same prioritization of target structures and OARs. The constraints to the targets must be fulfilled whereas the constraints to the OAR should be fulfilled, and in case one or more constraint cannot be achieved this must be reported. The treatment planning priorities in order of decreasing importance: CTV(1-4), AnoRectum, PTV(1-4), AnalCanal, Bladder, BowelBag, PenileBulb, Femoral head L/R.

Planning CT and MRI scans will be performed either locally or at the DCPT depending on the treatment randomization. The photon dose plans will be calculated locally, and the proton dose plans will be conducted at the DCPT.

Photon (standard arm)

Inverse-optimized intensity modulated radiotherapy (IMRT) will be used. Plans will be optimized in order to fulfil constraints in OAR.

Proton (experimental arm)

Dose, fractionation and boost will follow the national guidelines, using a fixed RBE of 1.1.
At the current time much work is ongoing regarding the details of the proton treatment. The field arrangement is most likely going to be lateral fields; however, the exact strategy will depend on a treatment protocol, which is expected to be modified as more experience is gained.

Target coverage and normal tissue sparing are secured through robust optimization as defined by DCPT.

To ensure optimal robustness, a weekly control CT scan is necessary at least in the initial phase of the trial. The need for a weekly control CT scan will be evaluated during the trial and it may be ceased if found not necessary. The requirement for extra CT scans will follow the DCPT guidelines.

Treatment verification

- Daily image-guide treatment
- Position of the fiducial markers in the prostate and required corrections (not rotational) is based on electronic kV or cone-beam CT.
- After setup corrections treatment should start as soon as possible.

Dose prescription and reporting

- According to ICRU 83, see appendix.
- The following dose values should be reported, prescription dose, CTV D2%, CTV D98%, target mean dose.

Quality assurance

Before start of the randomized trial all participating departments will be informed about the trial protocol. Principal investigator is responsible for that.
All proton and photon therapy plans from patients treated as part of the trial must be submitted to the Danish national dose plan bank and detailed quality (QA) assurance based on protocol for QA will be

performed based on these plans. The first five dose plans from each treatment centre including DCPT have to send in dose plans for QA both for planning and delineation of target and organs at risk.

Pilot phase

To ensure feasibility and workflow to a maximum of 40 patients with locally advanced PC needs to have been treated in a pilot study before the randomised study can be initiated. Patients enrolled in the pilot study will be treated with protons at the DCPT. The pilot study resembles the proton arm in the DAPROCA Proton Trial regarding baseline investigations, treatment delivery and follow-up program. Except for the planning phase, where the patients will have up to two extra consecutive planning CTs performed (max. three planning CTs in total). This is to identify patients with large organ motion and to ensure robust treatment planning in these type of patients in our phase III clinical study.

RT Quality assurance

In clinical RT trials, quality assurance (QA) is of pivotal importance, and there will be an extensive reporting and evaluation of aspects such as target volume definition and dose distribution in targets and organs at risk. The pelvic region is characterised by a considerable degree of internal organ motion. Particular attention will be paid to ensure safe delivery of treatment, through advanced image-guidance during treatment delivery, for both protons and photons. In the proton arm of the trial, dedicated treatment planning and delivery strategies will be applied in order to efficiently account for organ motion. These strategies include methods for individualised 'robust' treatment planning as well as daily monitoring of the actually delivered range of the protons inside the patients. This will ensure that the hypothesised normal tissue sparing potential of proton therapy achieved at the planning stage is also maintained during the course of therapy. Image-guidance strategies are essential for accurate delivery also for photon-based RT. We will ensure that the normal tissue dose/volume and clinical outcomes of the patients randomized to photons are as good as possible and uniform across the different including centres. Proton therapy will be delivered according to DCPT guidelines and photon therapy will be delivered according to national and local guidelines. If other QA methods becomes available during the study, it will of course be evaluated if these methods should be used.

National dose plan bank

All treatment plans for patients treated in this protocol must be submitted to the Danish national dose plan bank (DCMcollab) for quality assurance and detailed research. The first five dose plans from each centre will be evaluated before start of treatment. As part of later planned research studies more detailed volumes for example of the bowel will be delineated. It is of utmost importance that the delineated structures are named according to the nomenclature used in the national guidelines. All details about the treatment planning will be collected through the dose plan bank, thus there will be no reporting of doses to organs at risk outside the dose plan bank. The randomisation number will serve a patient identifier.

The submission must take place prospectively with max 2 months' intervals. This is to assure access to plans for quality assurance. All images related to planning and treatment verification is also collected in the bank.

Feasibility

The trial setup is simple and feasible since IMRT for prostate cancer is a routine treatment within the Danish Radiotherapy Clinics. Proton therapy will be delivered and administered at DCPT. We plan to initiate

the study in 2021. The 400 patients recruited in Denmark are expected to be enrolled within the study period finishing in 2024. We plan to recruit approximately 150 pts. a year.

Timetable
August 2021: Development of the online QA platform. QA dummy runs to ensure compliance and cohesion of the individual treatment centres. In this period the first PC patients will be treated in the pilot phase of the trial to confirm treatment delivery, logistics and set-up.

December/January 2021/22: Pilot phase

February 2022: Start of the randomized trial.

2025: Estimated end of recruitment.

2027: Primary endpoint assessment.

Independent Data Monitoring Committee (IDMC)
An IDMC will be established to audit patient safety and treatment efficacy during the trial period. The IDMC will include oncologists and a statistician. If any grade four (CTCAE) or five serious adverse events occurs quality assurance will immediately.

Follow-up
Patients will be followed for 10 years after randomization at the local radiotherapy clinics/local research units regarding registration of protocol related endpoints. Telephone/video conferences can be used to register adverse events.

		Follow-up after radiotherapy							
	Inclusion (Baseline, local dept.)	End of treatment (Week 8)	4 weeks after treatment (Week 12)	1y	2y	3y	5y	8y	10y
PSA	x		x	x	x	x	x	x	x
Testosteron							x		
Kolesterol, triglycerid, p-glucose, D vitamin,ioniseret Ca, kreatinin, Hgb, or according to local guidelines			X	X	X	X	X	X	x
CTC-AE	x	x	x	x	x	x	x	x	x
PROs	x	x	x	x	x	x	x	x	x
QoL	x	x	x	x	x	x	x	x	x

Patients with BCR will be offered diagnostic work-up according to local guidelines. Additional interim visits and diagnostic interventions should be performed when necessary. Date of non-BCR recurrence will be defined as the date an imaging modality suspects a relapse, verified by biopsy or determined as radiological or nuclear medicine defined relapse. If a suspected relapse is later rejected; the date of relapse is cancelled. Patients diagnosed with distant metastases, loco-regional progression or BCR are referred the local Urology Clinic for further treatment and censored for CTCAE, QoL and PRO's. Patients diagnosed with a different cancer (except for basal cell carcinoma) during treatment or follow-up should also be terminated from the study.

Data analysis

Data will be analyzed according to intention to treat including all pts. enrolled in the study with completed PRO data. Two years after the last patient have finished irradiation the primary endpoint will be analyzed by comparing the mean decrease in EPIC-26 summary scores from baseline to 24 months after treatment by a two-sample t test. Time to occurrence of any grade 2+ toxicity (CTCAE v.5.0) will be analyzed using the Kaplan-Meier method and using the log-rank test for comparison. Moreover, 2x2 contingency tables of year 2 and 5 incidences will be performed using Fischer's exact test for difference. The reported mean change in the general HRQOL (EORTC-C30QLQ) score from baseline will be compared by two-sample t test.

Biochemical progression-free survival and overall survival at year five and ten will be reported. Cox proportional hazards regression models will be used for multivariable analyses of overall survival and biochemical free survival. Significance testing will be two-sided and at the 5% level. Missing data will be handled by multiple imputation strategy.

4 Statistical considerations

Power calculation

This is a phase III RCT comparing the rate of late toxicity at year 2 after PT or IMRT. Toxicity levels have been reported in prospective RT trials. Regarding PT, most prospective and retrospective data are obtained in cohorts treating local PC without LN irradiation. We have data available [7] for patients treated in a national clinical phase 1/2 trial for locally advanced PC and followed prospectively.

The power calculation is based on the primary endpoint. We consider a reduction in delta EPIC-26 bowel score of 5 points as clinically significant [11]. In the proposed study, irradiating the prostate and the pelvic LN we expect that the mean change from baseline to year 2 in bowel EPIC-26 score will be reduced by 5 points from the proton arm to the photon arm. The required sample size for a 1:1 randomization, 80% power, two-sided type one error of 5% and 10% loss for primary endpoint assessment is 400 patients in total. The sample size calculation is based on a two-sample t-test assuming normal distribution of the mean difference between baseline and 24 months EPIC-26 bowel score.

In the current trial, it is difficult to do an interim analysis based on efficacy (biochemical failure or other). This is due to the fact that all participating patients receive ADT. In the rare situation a case of biochemical failure or other occurs before end of ADT it will be recorded.

5 Patient selection

Inclusion criteria

- Histologically verified localized/locally advanced prostate cancer T1-3bN0M0 (TNM 8th edition). A clinical T4 is allowed if it is because of invasion into the bladder neck.
- Adenocarcinoma (mixed histology allowed as long as the adenocarcinoma component comprise more than 50%)
- Indication for elective lymph node irradiation
- ADT started before randomization
- PSA < 100 ng/mL
- Age ≥18 years
- Performance status 0-1
- Life expectancy ≥ 10 years
- Able to understand and comply with the treatment protocol
- No evidence of inflammatory bowel disease

Ability to adhere to procedures for study and follow-up
- Signed informed consent to participate in the study, including acceptance of treatment plans and scans will be stored in a dose plan bank, and the remaining data stored in a central database

Exclusion criteria

- No previous treatment for prostate cancer
- Hip-prostheses
- Other metal devices in the pelvic region (except fiducials)
- Implanted cardiac pacemaker
- Previous major abdominal/rectal surgery
- Any other malignancy the last five years except for basal or squamous cell skin cancer
- Unable to understand patient information or comply with treatment and safety instructions
- Unable to read and understand patient information due to cognitive disabilities or language (Danish).

6 Risks to the patient and side effects

Risk to the patient

Patients included in the randomised trial do not receive more radiation than they would otherwise. It is, however expected that patients treated with proton therapy will receive a lower dose to organs at risk. The biologically effective dose (BED) calculated for proton therapy is based on the photon therapy, and the proton therapy will provide the same dose as photon therapy. All patients treated with protons will have daily cone beam CT (CBCT) for set-up verification. Most Danish departments already use CBCT for daily set-up of all irradiated PC patients. If daily CBCT is not used for daily set-up, kV and MV are usually used for set-up verification, which also give a small radiation dose to the patient. The purpose of the CBCT is to ensure that the patient position is optimal, and it provides the best possibility to detect, if unanticipated anatomical changes have occurred.

The patients receiving proton therapy will also have additional weekly pelvic CT scans performed during therapy, at least in the beginning of the study. And the patients enrolled in the pilot study will have up to two extra planning CT's performed. The pelvic CT scans will expose the patient to approximately 10 mSv per scan, compared to the approximately 78.000 mSv they receive from the radiotherapy. However, since the low dose area in proton therapy is considerably lower compared to photon therapy, proton treated patients will in total receive less radiation, even with the extra CT scans.

The discomfort during therapy is expected identical, except many patients living far from DCPT will need to stay at a hotel during the weeks of treatment. The cost for the stay at the hotel is covered by the Danish Health Authorities.

Side effects

Photon radiotherapy is the standard treatment in Denmark, and information is given in accordance with the normal procedure for these patients. The range of acute side-effects of photon and proton treatment during and after radiation therapy is assumed equal. The severity of late effects, especially gastro-intestinal side-effects, is expected to be lower after proton therapy.

Side-effects during or after PC radiation in general can be acute or chronic (short or long term) and may include:

Gastro-intestinal:

- Incontinence for gas/liquid or solid stool (acute/chronic)
- Diarrhoea (acute/chronic)
- Inability to defer defecation (acute/chronic)
- Increased number of daily defecation (acute/chronic)
- Abdominal pain (acute/chronic)
- Rectal bleeding (acute/chronic)
- Mucus discharge (acute/chronic)

Uro-genital:

- Urinary incontinence (acute/chronic)
- Nocturia (acute/chronic)
- Irritative urinary symptoms with pain and inability to defer urination (acute/chronic)
- Haematuria (acute/chronic)

Sexual:

- Impotence (chronic but with ADT acute)
- Loss of libido (acute/chronic with ADT)

General: (most of the general side effects are due to ADT treatment)

- Fatigue (acute/chronic) (ADT)
- Loss of muscle tissue (sarcopenia)(chronic) (ADT)
- Risk of stroke and acute myocardial infarct (ADT)
- Weight gain (chronic) (ADT)
- Hypercholesterolemia (ADT)

Rare complications include: fistulas to the surrounding tissue.

Serious Adverse Events

A serious adverse event (SAE) is an adverse event or adverse reaction that fulfills any of the following criteria:
• Results in death
• Is life-threatening
• Requires hospitalization or prolonging of existing hospitalization
• Results in persistent or significant disability or incapacity Apart from assessing chronic side effects in the quality-of-life questionnaire.
We will report serious adverse events during the treatment phase and the follow-up of the study by recording any adverse event possibly associated with per-protocol treatment requiring hospitalization in the online database (RedCap).

7 Data collection and management

Data management plan

The randomisation and the study database will be anchored at the Danish Centre for Particle Therapy, AUH. The protocol data including CRF, PRO and outcome registrations will be online entered into the database by the investigator or an individual authorized by the investigators. The data will be stored and available following Danish Data Protection Agency, The Act on Processing of Personal Data and the National Research Ethics Committee. The trial will be conducted according to the principles and Good Clinical Practice. The final analysis of the primary endpoint will be two years after the end of the inclusion period. All proton and photon treatment plans must be centrally stored in the Danish national plan database (DcmCollab) for quality assurance and analysis of radiotherapy dose and volume parameters. The data will be archived 15 years after the inclusion of the last patient. The anonymised data will be made available through the Zenodo open data repository after completion of the trial.
All data will be handled confidentially, and each recruiting centre is responsible of managing the data safe and in compliance with the Danish Data Protection Agency.

Personal data collection

A central database (RedCap) will be used for data collection at all centres. Data handling will comply with the data protection act and the data protection regulation. The study is registrered at Den Interne Fortegnelse at The Central Denmark Region (Sagsnr.: 1-16-02-338-21).
To conduct and monitor the project, data from the electronical patient record will be registered in the database after written informed consent. Information on demographics, general health, treatments (current and previous), side-effects, scans and biochemistry will be obtained.
The written informed consent allows the principal investigator, appointed health personnel and control authorities direct access to obtain information in electronical patient records, to conduct the research protocol and to ensure necessary control, quality insurance and monitoring.

8 Financial plans

In the planning phase of this study funding to cover salary of a physician (post doc.) and a physicist (Ph.D.) was available. For initiating this study, we received funding from DCCC including network meetings for initiating the study at the Danish radiotherapy clinics. There are no financial benefits for the departments or the investigators relating to the trial. No health professionals involved in the study have any financial disclosures or conflicts of interest related to the project.

The study has been supported from The Danish Cancer Society with 1.320.000 DKK. The grant will be effective if The Danish Cancer Society reach its goals with the upcoming "Knæk Cancer" collections. Furthermore, DCCC has supported the project for initiating the study with 196.000 DKK.

All Danish parties will co-finance the project with in-kind use of facilities and staff. Most notably, the cost of the experimental treatment (proton beam therapy) will be completely covered by the Danish Regions as part of the public health care budget. The incremental cost of a complete proton treatment course compared to standard radiotherapy is for this study estimated to be 20.000 DKK per patient, corresponding to 4 mill. DKK for the 200 Danish patients randomized to protons in this trial. The expected co-financing of

staff is set to an additional 2.2 mill. DKK, as it is estimated that at least five senior clinicians, trial unit staff and scientists from the project group are dedicating 5-20% FTE for the activities in five years.

9 Reimbursements to the patients

No payment or reimbursement will be made to enrolled patients. However, extra expenses associated with the stay in Aarhus (for patients in the PT arm) will be covered by the patient's home region/the Danish Health Authorities. No economical compensation will be provided from the Danish Centre for Particle Therapy or DAPROCA.

All patients included in the trial will by law by covered by the general insurance for patients treated in the health care system at the different study locations.

10 Recruitment of patients and written informed consent

Eligible patients will be identified at the regional multidisciplinary conference (MDT). The oncologist will approach them about possible trial enrolment at the first visit. All patients are introduced to the trial by written information and a consultation elaborating on the material. Again, the patient can bring a relative or friend. The consultation will be in a closed room without disturbances. After signing the informed consent, the patients can be registered into the trial before or after commencement of ADT. After enrolment the patient is informed about the result of the randomization.

1. Randomisation to the photon arm
    a. Planning CT and/or MR scans at local clinic
    b. Start of photon treatment at the local clinic (standard arm)
    c. Follow-up at local clinic at the end of treatment

2. Randomisation to the proton arm
    a. Referral to DCPT
    b. Planning CT and MR scans at DCPT
    c. Start of proton treatment at DCPT (experimental arm)
    d. Follow-up at local clinic at the end of proton therapy

If the patient regrets his consent to the study, he can withdraw the consent at any time; he will then be treated according to the standard DAPROCA/national guidelines. He will be informed orally and written about this during the first information about the study. If a patient withdraws the consent during radiation therapy, he will be treated with photons at the local clinic for the rest of the therapy; the number of fractions will depend on how dose was already received.

11 Publication and announcement

The study will be registered on ClinicalTrials.gov. The main clinical results of the study linked to the primary and secondary endpoints of the trial will be sought published in international peer review journals irrespective them being positive, negative or inconclusive. Authorship of publications to these main publications is assigned the principal investigators and the steering committee; the local investigators (one

from each site that has included patients), as well as other personnel that has contributed significantly to conduction and/or evaluation of the study protocol. The primary author for the publication in question will be responsible for preparation of the first draft of the manuscript and this draft must be discussed with the co-authors.

Other data and results that may be collected from the study (i.e. locally performed translational studies, or imaging, treatment planning and/or quality assurance focused studies) may be published from the institute/institutions where the work is conducted, however, the principal investigators and the steering committee of this protocol must be informed about such plans and should approve the final publication before submission. Co-authorship regarding such translational/imaging/treatment planning/quality studies will be assigned the scientists/personnel that has conducted the studies including the (local) investigator of the translational study in question. The principal investigators and the steering committee of this protocol as well as one person from each site that has contributed with material/data for the study (oncologist or e.g. physicist, as appropriate) can be considered as co-authors, given that they have taken part in the study fulfilling established author criteria (e.g. in the Vancouver Declaration). However, this may be overruled if an involved personnel is not active in the study anymore or if another personnel is becoming involved in the study at a later point. This is to ensure that all involved partners will be accommodated. Projects defined at a later point that may use data/materiel from this study protocol, may be published by the involved partners only after agreement with the principal investigators and the steering committee. All publications from this study protocol must be anchored in Daproca or be "on behalf of Daproca". Any relevant financial support must be mentioned and thanked in publications. This is a Daproca initiated and controlled trial protocol.

12 Ethical accounts

One of the standard treatments for locally advanced PC is photon radiotherapy. This treatment is effective but associated with a certain degree of short- and long-term side effects, among this incontinence for stool and diarrhoea. In theoretical studies and a few clinical studies proton therapy seems to provide a safe treatment with less toxicity. There are no randomised trials comparing photon to proton radiation treatment in patients with locally advanced PC, the proposed national study will therefore provide very important evidence to whether or not these patients will benefit from proton radiotherapy. All included patients in the randomized study will be treated according to the randomization key and followed as described in the protocol. The study will be conducted according to current legislation and the Helsinki Declaration.

13 Appendix

Organ at risk (OAR) definition

A national consensus guideline for the delineation of the OAR in the pelvic area is under development. Adherence to the nomenclature and delineation guideline is mandatory, however supplementary structures for planning optimization are accepted.
The structures should be delineated based the CT anatomy guided by the MRI. For hollow organs the structure includes wall and content.

TPS name	Description
AnoRectum	Outlined from the anal verge to the recto-sigmoid transition.
AnalCanal	Outlined from the anal verge to the superior extent of the puborectal muscle.
BowelBag	Outlined as the whole the bowel cavity excluding the vessels, AnoRectum and the Bladder, to the most inferior axial image that includes large or small bowel.
PenileBulb	Outlined as the oval-shaped proximal part of the corpus spongiosum bounded by the crura of the corpus cavernosum laterally, the levator ani posterior and the narrow part of the corpus spongiosum anteriorly.
Bladder	Outlined inferiorly from the prostate, not overlapping with the CTV, to the dome of the bladder.
FemoralHead_L/R	Outlined as two separate structures, left and right FemoralHead, from the femoral head to the inferior part of the trochanter minor.

Target dose constraints

	Target	Dose constraints
1	CTV1, CTV2, CTV3, CTV4	V95%≥98%
	Photon RT	
3	PTV1, PTV2, PTV3, PTV4	V95%≥95%
9	PTV4 (PTV2 or PTV3 plus a 5mm margin subtracted)	Dmax≤107%
	Proton RT	Robust optimization will be used for proton planning where the PTV is suspended

OAR dose constraints

	Structure	TPS name	Constraints	Reference
2	AnalCanal and Rectum	AnoRectum	V75Gy≤3% V70Gy≤15% V65Gy≤30% V50Gy≤60%	[18]

			V40Gy≤70% V30Gy≤80%	
4	Anal canal	AnalCanal	Dmean≤40Gy	[19]
5	Bowel cavity	BowelBag	V35Gy <= 40% Optimal V45Gy≤195cm3	[20]
7	Penile bulb	PenileBulb	V50Gy<2% Dmean≤20Gy	[21]
6	Bladder	Bladder	V80Gy≤15% V70Gy≤35% V65Gy≤50%	[22]
8	Femoral Head	FemoralHead_L/R	V50Gy≤5%	RTOG consensus

Treatment preparations

Pre-imaging and treatment preparation

The patients should have and empty rectum and a comfortably filled bladder during planning CT/MRI and radiotherapy treatment.

- The maximum diameter of the rectum at the level of the prostate is 4 cm. For some patients a rectal enema or daily laxative should be considered.
- The patient should empty the bladder approximately 30-45 minutes before planning CT and then drink 300 ml of fluid. The goal is a bladder filling between 150 cm3 and 350 cm3. This drinking protocol or a drinking protocol according to local guidelines should be repeated before every treatment fraction[23].

Patient positioning

- Supine position using a knee support and a feet-holding-device.

Image acquisition

- Flat table top.
- From lower part of L3 to just below the trochanter minor.
- Maximum 3 mm slice thickness according to the institution standard.
- Intravenous or oral contrast is not mandatory.

Co-registration between planning CT and MRI is based on the fiducial markers in the prostate.

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