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Proton therapy planning and image-guidance strategies within a randomized controlled trial for high-risk prostate cancer

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ABSTRACT

The Danish Prostate Cancer Group is launching the randomized trial, PROstate PROTON Trial 1 (NCT05350475), that compares photons and protons to the prostate and pelvic lymph nodes in treatment of high-risk prostate cancer. The aim of the work described in this paper was, in preparation of this trial, to establish a strategy for conventionally fractionated proton therapy of prostate and elective pelvic lymph nodes that is feasible and robust. Proton treatments are image-guided based on gold fiducial markers and on-board imaging systems in line with current practice. Our established proton beam configuration consists of four coplanar fields; two posterior oblique fields and two lateral oblique fields, chosen to minimize range uncertainties associated with penetrating a varying amount of material from both treatment couch and patient body. Proton plans are robustly optimized to ensure target coverage while keeping normal tissue doses as low as is reasonably achievable throughout the course of treatment. Specific focus is on dose to the bowel as a reduction in gastrointestinal toxicity is the primary endpoint of the trial. Strategies have been established using previously treated patients and will be further investigated and evaluated through the ongoing pilot phase of the trial.

1. Introduction

Prostate cancer is the second most common cancer diagnosed in men worldwide [1,2]. Patients with high-risk prostate cancer are susceptible to metastatic disease spread to the pelvic lymph nodes and hence according to national guidelines it is an accepted practice to include the prostate, the seminal vesicles and the lymph nodes in the treated volume in radiotherapy of high-risk prostate cancer [3]. In a recent randomized study, patients receiving radiotherapy including also the pelvic lymph nodes had superior biochemical failure-free and disease-free survival compared to those receiving prostate only radiotherapy [4]. However, additional radiotherapy of elective volumes of the pelvis may be associated with an increased risk of late morbidities [5,6].

Radiotherapy-related morbidities have traditionally been assessed using physician-reported scores, however, there is an increasing tendency to record patient-reported outcomes (PROs) [7]. It has been shown that physician-reported scoring tends to underestimate the adversity of morbidities compared to PRO measures [8,9]. Since the adversity of morbidities is closely linked to quality of life for the patients [10], PROs are considered a central source for quality of life assessment. A phase II study revealed that PROs related to late morbidities and in particular gastrointestinal (GI) morbidities remained elevated as long as 60 months after whole pelvic radiotherapy for high-risk prostate cancer [8]. It is likely that reduced radiation exposure to the bowel by applying more conformal radiotherapy techniques such as proton therapy will lead to fever side-effects and improved quality of life.

The primary dose deposition from a proton beam is at the Bragg peak, hence proton radiotherapy has a large potential for organ sparing [11–14]. The clinical experience with proton therapy for high-risk prostate cancer, however, is so far limited to single arm protocols

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[15–19] with only two reports on late effects [18,19]. In 2018, Chuong et al. were the first to publish physician reported GI and genitourinary (GU) toxicities following whole-pelvis irradiation with protons for prostate cancer [15]. Recently, Hasan et al. reported from a prospectively collected multicenter registry with 605 high-risk prostate cancer patients, where 58% also received pelvic lymph node irradiation, showing GI grade 2 events in 5% of patients and no grade 3 events [18]. Similarly, they reported late grade 2 and late grade 3 GU toxicity in 6% and 2% of patients respectively. Choo et al. reported late 3-year morbidities from the Mayo clinic study on moderately hypofractionated proton therapy for prostate and pelvic lymph nodes: GI effects of grade ⩾2 were seen in 7% of cases, grade ⩾3 in 2% [19]. There were substantially more GU effects, with grade ⩾2 in 29% of cases although there were no grade ⩾3 morbidities.

Currently, seven clinical trials with whole pelvic proton therapy for prostate cancer are active according to ClinicalTrials.gov, however, none of these are randomized, comparative studies of radiotherapy treatment modalities for primary disease (Table 1). To formally and objectively investigate the expected clinical benefit of whole pelvic proton therapy for patients with high-risk prostate cancer, there is therefore a need for a randomized controlled trial for this patient group (See Table 2).

The depth of the Bragg peak is dependent on tissue density in the proton beam path and hence inter- and intra-fractional organ variations will influence the delivered dose [20,21]. When treating the pelvic lymph nodes in high-risk prostate cancer patients, the combined target volume extends further cranio-caudally than for prostate-only irradiation and hence the treatment is more sensitive towards organ motion and set-up uncertainties. Internal organ motion should be handled through robust treatment planning and image-guidance to ensure robust dose delivery and sufficient target coverage with protons [22–28].

Table 2
Inclusion criteria in PRO-PROTON 1.[1]

Stage	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.
Histology	Adenocarcinoma (mixed histology allowed as long as the adenocarcinoma component comprise more than 50%) Indication for elective lymph node irradiation
PSA	< 100 ng/mL
Age	⩾18 years
Performance status	0–1
Life expectancy	⩾10 years

[1] In addition to the inclusion criteria listed in Table 2, patients should be able to understand and comply with the treatment protocol and have no evidence of inflammatory bowel disease. Patients should be able to adhere to procedures for study and follow-up and they have to sign informed consent to participate in the study - including acceptance of blood samples, that treatment plans and scans will be stored in a dose plan bank, and the remaining data stored in a central database.

Clinically feasible beam angles should be selected such that the penetration of critical normal tissue before the target is minimal, and such that the patient positioning uncertainties are as inconsequential as possible [29,30].

To evaluate the value of protons in treatment of high-risk prostate cancer, we have launched a national, multicenter randomized trial between protons and photons. The primary endpoint of this trial is PROs related to GI morbidities. This paper describes the trial protocol, with a special focus on treatment planning and image-guidance strategies and considerations within the proton therapy arm.

Table 1
Clinical proton therapy trials with whole-pelvis irradiation for prostate cancer. From ClinicalTrials.gov with the search string '"proton" AND "prostate" AND ("high-risk" OR "nodal" OR "pelvic") |Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation, Unknown status Studies |Interventional Studies'. Studies were excluded if they were not about prostate cancer, did not investigate radiotherapy, or did not include radiotherapy to the pelvic lymph nodes. Search performed on March 29, 2023.

NCT No.	Title	Status	Radiation	First posted	Locations
05106699	Carbon Ion Followed by Proton Radiotherapy for Prostate Cancer With Pelvic Lymph Nodes Metastases	Recruiting	• Proton plus carbon ion radiation	Nov 4, 2021	• Shanghai Proton and Heavy Ion Center, Shanghai, China
04725903	Proton Radiation Therapy for the Treatment of Patients With High Risk Prostate Cancer	Recruiting	• High-dose rate brachy-therapy • Proton beam radiation therapy	Jan 27, 2021	• Emory University Hospital/ Winship Cancer Institute Atlanta, Georgia, United States
04486755	Hypofractionated Accelerated Pelvic Nodal Radiotherapy (GCC 2048)	Recruiting	• Hypofractionated radiation therapy	Jul 27, 2020	• Maryland Proton Treatment Center, Baltimore, Maryland, United States
04190446	Radiation Therapy (Hypofractionated Proton Beam Therapy or IMRT) for the Treatment of Recurrent, Oligometastatic Prostate Cancer Following Primary Localized Treatment	Active, not recruiting	• Intensity-modulated radiation therapy • Proton beam radiation therapy	Dec 9, 2019	• Mayo Clinic in Rochester, Rochester, Minnesota, United States
03624660	Dose-Escalated Proton Radiation Therapy for High-Risk Prostate Cancer	Recuiting	• Proton beam radiation therapy	Aug 10, 2018	• University of Florida Health Proton Therapy Institute, Jacksonville, Florida, United States
02874014	Prospective Evaluation of Hypofractionation Proton Beam Therapy With Concurrent Treatment of the Prostate and Pelvic Nodes for Clinically Localized, High Risk or Unfavorable Intermediate Risk Prostate Cancer	Active, not recruiting	• Hypofractionated proton beam therapy with concurrent treatment of the prostate and pelvic nodes	Aug 22, 2016	• Mayo Clinic in Arizona, Scottsdale, Arizona, United States • Mayo Clinic in Rochester, Rochester, Minnesota, United States
01040624	Docetaxel, Androgen Deprivation and Proton Therapy for High Risk Prostate Cancer	Active, not recruiting	• Proton beam radiation therapy	Dec 29, 2009	• University of Florida Proton Therapy Institute, Jacksonville, Florida, United States

2. Materials and methods

2.1. Patients

The PROstate PROTON trial 1 (PRO-PROTON 1, NCT05350475) [31] consists of a pilot phase with 40 patients, followed by a randomized phase with 400 patients randomized 1:1 between protons or photons stratified with respect to tumor stage and treatment center. The patients in the proton arm are referred to the Danish Center for Particle Therapy (DCPT) while the patients in the photon arm will receive treatment at their local cancer centers. The trial is expected to complete patient inclusion within three years. Inclusion criteria are described in Table 1.

2.2. Target volumes and constraints

All patients in either arm of the trial are subject to the same delineation and treatment planning objectives. Target volumes are separated into a high-dose and low-dose clinical target volume (CTV) depending on T-stage: The high-dose (primary) target, CTVp, contains the prostate or a combined volume of the prostate and the seminal vesicles, the low-dose (elective) target, CTVe, contains the pelvic lymph nodes and the remaining seminal vesicles. In accordance with Danish national guidelines, the primary target volume is treated to 78 Gy in 39 fractions with a concomitant dose of 56 Gy in the 39 fraction to the elective volume using a simultaneously integrated boost technique.

For treatment planning purposes in the proton therapy arm, the high-dose CTV is expanded into an internal target volume (ITV) with margins of 2 mm in the anterior, posterior and lateral directions and 4 mm in the superior and inferior directions. The ITV is subsequently cropped so that any parts extending inside the rectum are omitted from the resulting ITV. For all patients, organs at risk (OARs) are delineated according to national consensus guidelines. Dose constraints are the same for all patients in the trial. Target coverage has the highest priority and we require a dose constraint of $V\ 95\% > 98\%$ to be met. Next, we aim at sparing the OARs as much as possible with the rectum constraints at highest priority followed by anal canal, bowel cavity, penile bulb and bladder. See supplementary material for the full list of dose constraints (Supplementary material p. 21).

2.3. Pre-treatment imaging

The patients are instructed to empty their bladder and subsequently drink 300 ml of fluid 30–45 min before acquisition of a scan, or commencing of a treatment session. The bladder should be comfortably filled with a volume ideally between 150 cm^3 and 350 cm^3 during image acquisition or treatment.

We also aim at minimizing the amount of air cavities in the rectum for the planning CT (pCT) scan and treatment. If the diameter of the rectum is more than 4 cm in a transversal slice of the CT or pre-treatment cone beam CT (CBCT), this is noted by the personnel and attempts to remove the air are made either by a catheter or laxatives. Afterwards, the patient is rescanned. If the air cavities persist in the pCT, we overwrite the air cavities in the pCT with CT numbers corresponding to water or the surrounding tissue. This will be more robust through the whole course of treatment as the air cavities will differ between treatment fractions. After treatment planning the dose is recalculated on the original pCT with air cavities to assess if the target coverage is robust.

2.4. Markers

Patients in both treatment arms have fiducial markers (Gold Anchor, Naslund Medical AB, Huddinge, Sweden) for image-guidance implanted in the prostate at their local urology departments before they are included in the PRO-PROTON 1 trial. Gold fiducial markers are used for set-up of prostate cancer patients in all radiotherapy facilities in Denmark. The compatibility of Gold Anchor fiducial markers with proton therapy was determined based on visibility and contrast in the imaging modalities shown in Fig. 1 as well as the absence of shadowing effects and dose degradations downstream of the implanted markers in the relevant clinical beam configuration [32].

2.5. Proton treatment planning - beam angle configuration

The clinically implemented proton treatment planning strategy builds upon previous in-house studies as well as clinical experiences from other sites [11,29]. Two posterior oblique beams from 170° and 190° cover the entire target volume; the combination of the high-dose ITV and the elective target. These posterior beams are angled 5–10° away from directly posterior to spare the rectum. Furthermore, two posterior beams instead of one smear out the effect of any range uncertainties. Additionally, two lateral oblique fields at 100° and 260° are aimed at the combined volume of the high-dose ITV and the lateral proximal half of the elective target, respectively; denoted CTV_L (left) and CTV_R (right). CTV_L and CTV_R overlap with 1 cm medially to secure a smooth joining between the dose distributions from the lateral beams. Depending on individual anatomy and positioning of the patient, the lateral beams may be angled ±5° relative to the specified values. This is to avoid going directly through the femoral heads that may shift due to inter-fractional positioning uncertainties.

An example of beam angles from the clinical treatment plan for a patient in the pilot study are shown in Fig. 2.

2.6. Robust treatment planning and evaluation for proton therapy

The PTV margins used in the photon centers are mirrored by robust optimization in the proton setup at DCPT. The plan uncertainty parameters used for the robust optimization on the CTVs and ITV are thus 5 mm for the isocenter shift and 3.5% for the distal edge uncertainty. The plans are optimized on the pCT using a spot scanning algorithm and multifield optimisation.

A robust evaluation (RE) is performed on the resulting treatment plan with the same robustness parameters as described above for robust optimization. The target coverage constraint for both CTVs and ITV is $V\ 95\% > 98\%$ in the worst-case scenario. If the high-dose rectum constraint $V\ 75\ Gy < 3\%$ is not fulfilled, $V\ 95\% > 95\%$ to the ITV may be accepted. An example of a dose distribution from the clinical treatment plan of a patient in the pilot study is shown in Fig. 3 and the corresponding dose-volume histogram is shown in Fig. 4.

2.7. Image-guidance and off-line dose review

The image-guidance strategy used in the proton arm of the randomized trial mirrors the image-guidance technique of the photon standard treatment. The patient is thus positioned using CBCT. The daily CBCT scan is matched to the pCT with a 6D[1] match on bony anatomy allowing tolerances of 5 mm translational and 1.5° rotational error, followed by a 3D[2] match on fiducial markers.

Dose monitoring in the pilot phase of the trial is based on both daily CBCTs and weekly control CT scans (cCTs). The patient's anatomy is evaluated using the daily CBCTs both with standardized measures at the acquisition time and off-line by a clinician. If large systematic deviations are observed in prostate position, rectum diameter, bladder volume, surface contour or femur position, the patient will be re-scanned and re-planned, otherwise, the treatment is continued.

Weekly cCTs are performed for the ten first patients in the pilot phase of the trial, while the subsequent 30 pilot patients will have two repeat cCTs during the course of the treatment. For off-line quantitative dose

[1] Six degrees of freedom; translational movement in three dimensions and rotations around all three axes.

[2] Three degrees of freedom; translational movement in three dimensions.

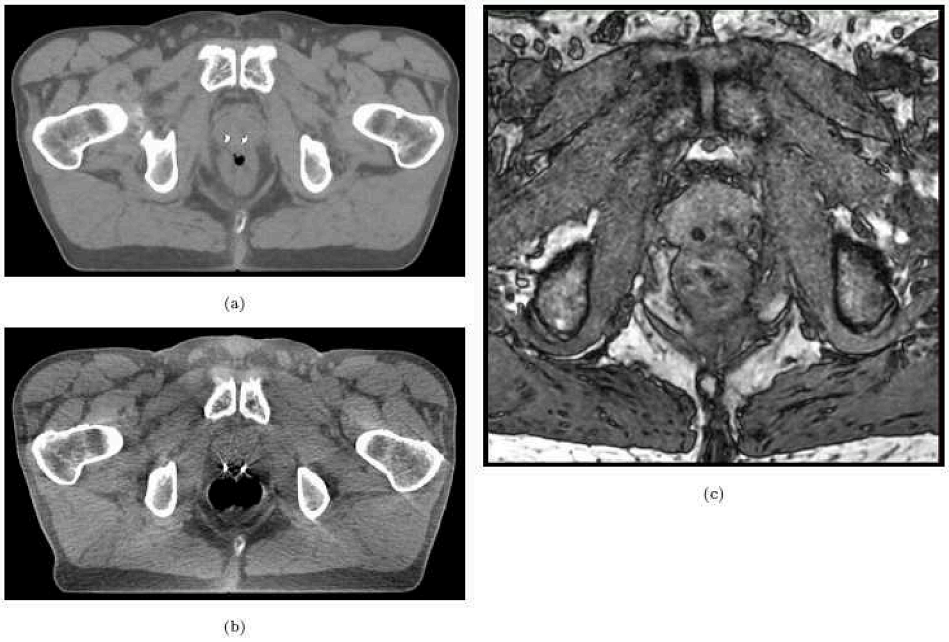

Fig. 1. Clinical case from one of the patients treated in the pilot phase of PRO-PROTON 1. The patient has Gold Anchor GA200–10B (Naslund Medical AB, 10 mm long and 0.4 mm in diameter) implanted. The markers are visualized on (a) CT, (b) CBCT and (c) MR.

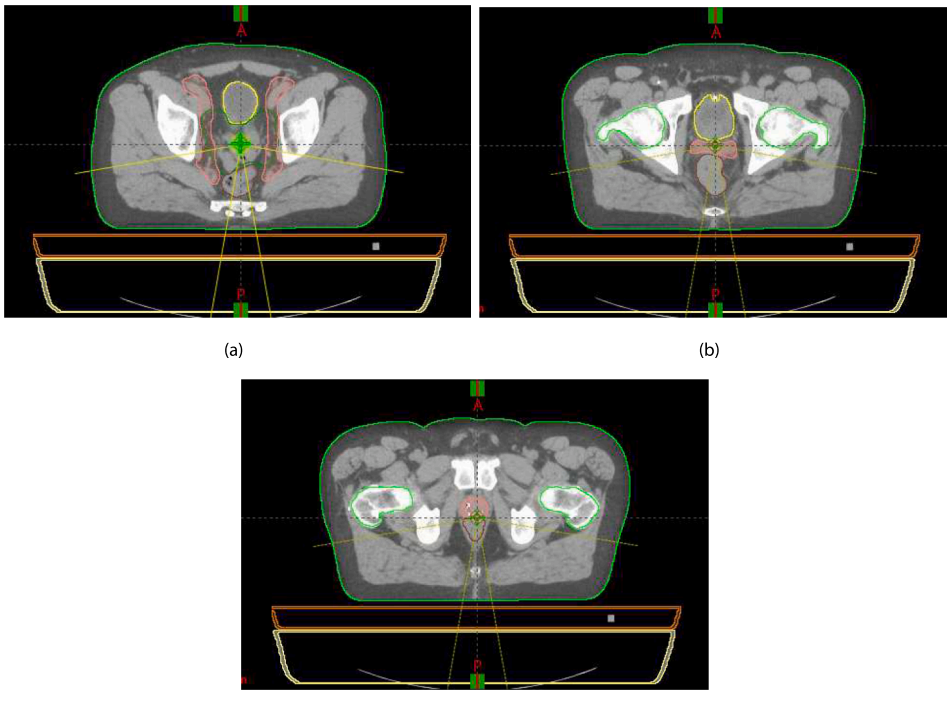

Fig. 2. Clinical case with treatment fields from $170°, 100°, 260°$ and $190°$. Views at the level of (a) elective lymph nodes, (b) seminal vesicles and (c) prostate. Delineations of clinical target volumes in pink, bladder in yellow, rectum in brown, bowel bag in dark green, femurs in light green, body outline in light green, couch structures in orange and yellow. Treatment beams through the edge of the couch are avoided since the amount of material the beam will traverse varies considerably even with small displacements at the edge of the couch.

monitoring, the original treatment plan is recalculated on each cCT including a RE with range uncertainties. It is verified that the dose distribution covers the target structures robustly with the same constraints as the original plan. We expect 90% of the actual treatment scenarios reflected by the cCTs to be within the span of the original RE scenarios. The cCTs are compared qualitatively to the daily CBCTs to evaluate how representative the cCTs are for the actual treatment situation, and this is also taken into consideration in the evaluation.

2.8. Endpoints

The primary endpoint of the trial is the change (delta score) in patient-reported late GI toxicity at two years compared to baseline using EPIC-26 bowel score [33]. A comparison of delta scores for patient-reported GI toxicity between photon and proton therapy will be performed. The secondary endpoints are late GU, sexual and GI toxicity as well as acute GI and GU toxicity. The secondary endpoints also include general health related quality of life, biochemical progression free survival, non-biochemical progression free survival and overall survival.

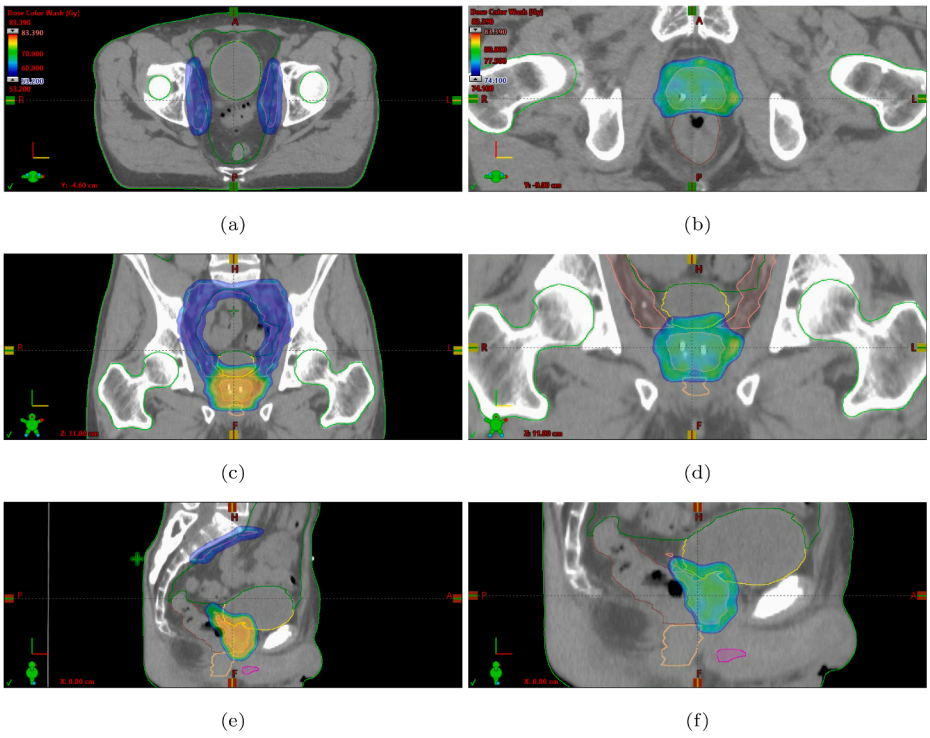

Fig. 3. Transversal (top row), frontal (middle row) and sagittal (bottom row) views of the clinical treatment plan of a patient in the pilot study. The dose distribution is shown in dose color wash with lower limit of 53.2 Gy in the left column and 74.1 Gy in the right column; corresponding to 95% of the dose to the elective and the primary target respectively. Delineations of clinical target volumes in pink, bladder in yellow, rectum in brown, anal canal in beige, penile bulb in magenta, bowel bag in dark green, femurs in light green, body outline in light green.

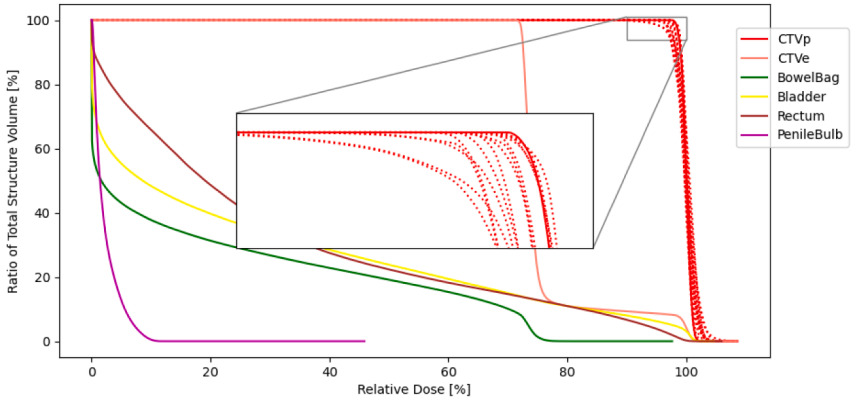

Fig. 4. Dose-volume histograms including robustness scenarios for the high-dose (primary) clinical target volume (CTVp). The elective target is referred to as CTVe. Data from the clinical treatment plan of a patient in the pilot study.

2.9. Follow-up

Patients will be scored with Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) [34], PROs and quality of life (QoL) scores as well as prostate specific antigen (PSA) level and blood samples at baseline. At the end of radiotherapy, at four weeks after and then at years 1, 2, 3, 4, 5, 8 and 10 after completing radiotherapy, PROs, QoL and CTCAE will be collected. Moreover, PSA and relevant blood samples are collected at different time points according to the protocol guidelines [31]. If patients are diagnosed with biochemical progression, loco-regional progression or distant metastases they are excluded from further follow-up within the protocol regime and referred to their local urology clinics for treatment.

2.10. Statistics

The sample-size estimation of the trial has been performed based on the primary endpoint. The clinical relevance of the primary endpoint has been defined on the basis of a minimally important difference (MID) study [35]. The sample-size required to show this five-point reduction in delta EPIC-26 score is a result of a power calculation with the following assumptions: The calculation is based on a two-sample t-test assuming that delta EPIC-26 scores follow a normal distribution. There will be a 1:1 randomization and an assumption of 10% loss. We aim at 80% power in the study and a two-sided type one error of 5%.

3. Discussion

The present randomized trial aims to exploit the potentially favorable morbidity profile of proton therapy in patients with high-risk prostate cancer, and specifically reduce GI toxicity. With the work leading up to this trial, we have established treatment planning and delivery strategies toward reaching these primary aims of the trial. As described in this paper, this included all technical steps from the choice of marker and initial scanning, through delineation and treatment plan optimization to image-guidance and dose monitoring.

Choosing beam angles avoiding as much of the femoral heads as possible will keep the range uncertainty associated with penetrating though a varying amount of bone in the femoral heads at a minimum [30]. The same considerations apply to the choice of posterior beam angles: As none of the treatment beams are to go through the edge of the treatment couch, there is a limited interval of lateral and posterior beam angles that are clinically feasible. Furthermore, beams through the anterior part of the patient are avoided since the anterior part of the patient will have larger inter-fractional variations than the posterior part when the patients are in a supine position.

Following the example of an ongoing trial conducted at the Danish Center for Particle Therapy; DAHANCA 35 [36], weekly cCTs are performed in the pilot phase of the trial for treatment quality assurance and verification. When further practical knowledge about the practical treatment delivery is acquired, this extra safety measure may be relaxed and treatment verification will rely on daily positioning imaging.

To reasonably compare the treatments in either arm of the trial, we aim at the same prioritization between target coverage and doses to normal tissues in both arms. After fulfilling the target constraints, we follow the ALARA (as low as is reasonably achievable) principle [37] for all normal tissue and specific OARs. Most OAR constraints in conventional prostate radiotherapy focus on limiting high doses in the organs [38], but with this trial we specifically aim at also reducing low doses to all tissue surrounding the target structures. Limiting the volume receiving a so-called low dose bath is one of the main advantages of proton therapy and this might translate into improved outcome in terms of reduced morbidities [10].

The patients in this trial are randomized between proton treatment in one national proton treatment center and photon treatment in their respective local photon facilities of which we have seven in Denmark. This set-up challenges the comparison between proton and photon treatment as the latter will vary with different practices in the different facilities. There are uncertainties associated with both target and normal tissue delineations, treatment planning system and technique as well as during-treatment imaging and re-scanning action levels. We are addressing these challenges in the radiotherapy network under DaProCa, the prostate-specific Danish Multidisciplinary Cancer Group. Within this network, workshops and treatment planning comparisons are being conducted in order to minimize these differences.

The present trial will add to the accumulating evidence for proton therapy for prostate cancer overall. Also for localized disease, several clinical trials are ongoing (Table 3) that will contribute to the clinical evidence. However, the morbidity profile is less severe in localized disease and hence a reduction in morbidity might be harder to demonstrate. The present trial, on the other hand, is concerned with high-risk prostate cancer and the primary endpoint is a reduction of five points in delta EPIC-26 bowel score – defined on the basis of a minimally important difference study [35]. Our assumption is that this reduction is clinically significant for this patient group.

The proton treatment strategies established for this trial are utilized to keep the doses to normal tissues as low as possible and thereby potentially reduce morbidities. However, the level of evidence in favor of proton therapy is still low and only randomized trials can provide the evidence necessary for establishing proton therapy as standard of care in

Table 3
Clinical proton therapy trials for irradiation of the prostate. From ClinicalTrials.gov with search string 'Proton AND ("photon" OR "IMRT" OR "external beam radiotherapy" OR "radiotherapy") |Recruiting, Not yet recruiting Studies |Interventional Studies |Prostate Cancer'. Studies were excluded if they were not related to prostate cancer, involved pelvic lymph node irradiation (included in Table 1), or did not primarily investigate proton therapy. Search performed on March 29, 2023.

NCT No.	Title	Status	Radiation	First posted	Locations
05313191	Prospective Evaluation of Pencil Beam Scanning Proton Therapy for Previously Irradiated Tumors	Recruiting	• Pencil Beam Scanning Proton Therapy	Apr 6, 2022	• The New York Proton Center New York, New York, United States
04842890	Phase II Study of Pencil Beam Scanning Proton Stereotactic Body Radiation Therapy for Prostate Cancer	Recruiting	• Pencil Beam Scanning Proton SBRT	Apr 13, 2021	• The New York Proton Center, New York, New York, United States
04083937	Prostate Cancer Patients Treated With Alternative Radiation Oncology Strategies (PAROS)	Recruiting	• Hypofractionated radiotherapy with photons • Hypofractionated radiotherapy with protons • Normofractionated radiotherapy with photons	Sep 10, 2019	• University Hospital Heidelberg, Heidelberg, Germany
03740191	Spot-Scanning Based Hypofractionated Proton Therapy for Low and Intermediate Risk Prostate Cancer	Recruiting	• Hypofractionated proton therapy	Nov 14, 2018	• EBG MedAustron GmbH, Wiener Neustadt, Niederösterreich, Austria
02766686	Preference-based Comparative Study on Definitive Radiotherapy of Prostate Cancer With Protons (ProtoChoice-P)	Recruiting	• Radiotherapy with protons • Radiotherapy with photons	May 10, 2016	• University Hospital Carl Gustav Carus, Department of Radiotherapy and Radiation Oncology, Dresden, Germany • Klinikum rechts der Isar, Technische Universität München, Munich, Germany • Universitätsklinik für Radioonkologie, Universitätsklinikum Tübingen, Tubingen, Germany
02040610	Hypofractionated Image Guided Proton Therapy for Low and Intermediate Risk Prostate Cancer	Recruiting	• Hypofractionated Proton Therapy	Jan 20, 2014	• Provision Cares Proton Therapy Center Knoxville Knoxville, Tennessee, United States • Provision Cares Proton Therapy Center Nashville Nashville, Tennessee, United States
00969111	Postoperative or Salvage Radiotherapy (RT) for Node Negative Prostate Cancer Following Radical Prostatectomy	Recruiting	• IMRT to 45 Gy; prostate bed proton boost of 21.6 CGE • Proton (prostate bed) to 70.2 CGE • IMRT to 45 Gy; proton boost to prostate bed to 25.2 CGE • Proton to 66.6 CGE	Aug 31, 2009	• University of Florida Proton Therapy Institute, Jacksonville, Florida, United States • Northwestern Medicine Chicago Proton Center, Warrenville, Illinois, United States • Inova Schar Cancer Institute, Fairfax, Virginia, United States

high-risk prostate cancer. As such, the PRO-PROTON 1 trial has the potential to change current treatment practice and improve the quality of life for a large patient group.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, athttps://doi.org/10.1016/j.ctro.2023.100632.

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