Addition of focal boost to primary radiotherapy for prostate cancer in 12 or 20 fractions: A large DAPROCA randomised trial.

Fast and Focal

Version 1, 07.07.2025

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Study protocol

Addition of focal boost to primary radiotherapy for prostate cancer in 12 or 20 fractions: A large DAPROCA randomised trial.

Purpose

The DAPROCA multidisciplinary group is planning a large trial to answer two pertinent questions of how to improve radiotherapy for high - and intermediate risk prostate cancer:

1. Will increasing dose to intra-prostatic cancer lesions improve outcomes with respect to prostate cancer without increasing toxicity?
2. Is it possible to shorten the treatment without increased toxicity?

The success of both increased dose to intra-prostatic cancer lesions and shortening of treatment, which means treatment with fewer treatment fractions with higher dose per fraction, is most likely dependent on high quality, high precision radiotherapy (RT) planning and delivery. A French randomised trial in prostate cancer demonstrated improved rectal toxicity scores (p=<0.03) and biochemical control with image guidance, and the MIRAGE randomised trial demonstrated improvements with smaller margins and more precise delivery (1-3). Many European clinics, including the Danish RT-clinics are able to provide high quality RT to all patients as per national consensus guidelines and in this study, we aim to further develop and implement this high quality opportunities in order to deliver hypofractionated RT and to boost the dose to intraprostatic lesions in all participating centers.

Background

Prostate cancer (PCa) is the second most common malignancy in men worldwide (4), and the most common cancer in Denmark (*5*). The incidence of PCa has been increasing in most countries and varies between countries. In Denmark, the incidence is now 124/100.000 men per year (5), and the median age for men diagnosed with PCa is 72 years (6). In the public, PCa is considered to have a good prognosis, but the fact is that the mortality is high with 1323 Danish men annually dying from PCa, exceeding the age-standardised breast cancer mortality (nordcan,https://nordcan.iarc.fr/en). The prognosis and the treatment of PCa depends on patient factors, as well as the histology grade, the prostate specific antigen (PSA) level, and the extent of disease (7).

This trial focuses on the group of patients with intermediate and high risk PCa, who have a risk of relapse of 25 - 60% (8,9) and a risk of getting metastatic disease of up to 20 % after 5 - 8 years (10-12).

Large, randomised trials have shown improved oncological outcomes, including overall survival, and disease specific survival for RT combined with androgen deprivation therapy (ADT) compared to ADT

only (9,13,14). In addition, large, randomised trials have shown a benefit with RT and ADT compared to RT only (15,16). In 2023 in Denmark, 463 high risk patients and 144 intermediate risk patients received definitive RT with 36+ fractions (17). The RT is delivered with intensity modulated RT (IMRT) and with prostate implanted fiducial markers for image guidance (IGRT) (17). The RT clinics follow national guidelines securing the quality of treatment.

Endocrine treatment

Endocrine treatment in combination with definitive RT has been standard of care for many years. The addition of 6-36 months of ADT has been shown to significantly improve overall survival (OS) in high risk and selected intermediate risk patients. Recent results revealed that two years of abiraterone acetate plus 3 years of ADT further improved the OS in patients with lymph node involvement or in high risk patients patients with two of three risk factors (>=cT3a, PSA ≧ 40, ISUP>=4) (12).

Elective pelvic lymph node radiotherapy

Elective pelvic lymph node radiotherapy (PLNRT) is offered in Denmark as a standard of care to PCa patients referred to definitive RT with either pelvic lymph node metastases or patients with a risk of lymph node metastases above 5- 7%. Risk of lymph node metastases can be estimated using different nomograms e.g. the Roach Formula, the Briganti nomogram 2012, Briganti nomogram 2019, and the Briganti nomogram 2023 (18-21). Risk estimation can be based on imaging with PSMA PET/CT, mpMRI, PSA level, ISUP grade, T stage, tumour size, and the percentage of systematic prostate core biopsies with cancer. The benefit of elective pelvic lymph node irradiation is dependent on the risk of lymph node involvement, the higher the risk of lymph node involvement the more likely the patient is to benefit. Trials indicate improvement of outcome and pelvic nodes can be included safely with contemporary radiotherapy techniques with tolerable risks of gastro-intestinal toxicity and edema (22-27).

Increased dose to intra-prostatic cancer lesions

A strategy to improve outcome is dose escalation to the cancer lesions in the prostate. The FLAME randomised trial (NCT01168479) demonstrated improved biochemical control, reduced local failure (LF) and reduced regional + distant metastatic failure (8,28). Toxicity is the limiting factor, and the boost dose was strictly limited depending on organ at risk exposure (OAR) in the FLAME trial. A dose response analysis for biochemical control indicated that patients with higher achieved boost doses experienced better tumour control (29). At the same time, the data suggested reduced toxicity as a result of further consideration of radiation dose to OARs and improved urethral sparing in particular (30). The question is therefore whether the addition of a focal boost can be established as standard of care.

A study larger than FLAME is needed in order to confirm effectiveness with freedom from distant metastases (FFDM) as an improved primary endpoint, compared to biochemical control which was used as primary endpoint in FLAME. However, while endpoints based on biochemical relapse free

survival are not surrogate for overall survival in localised prostate cancer, FFDM is now shown to be a valid surrogate endpoint for OS in trials of localised prostate cancer (31-33). Biochemical control is used as a secondary endpoint in the current study to confirm the FLAME results and study heterogeneity of treatment effects as detailed in the statistics section.

Shortening of treatment duration

In recent years, different approaches have been taken to decrease the number of fractions of prostate RT. These schedules reduce the number of hospital visits for patient convenience and cost-efficiency improvements. The large randomised CHHiP trial has shown good results with a 20-fraction schedule, albeit excluding the very high-risk patients (34). One study compared 78 Gy in 39 fractions with 60 Gy in 20 fractions and shortening treatment was not inferior regarding biochemical disease-free survival or toxicity (35). One phase III study in locally advanced disease showed more acute, but similar long-term gastro-intestinal toxicity with the same tumour control in patients treated with 64.6 Gy / 19 fractions than with 78 Gy/39 fractions (10,36). Early results of a high-risk patient only trial including 329 patients were published in May 2023, showing that moderate hypo-fractionation RT is well-tolerated, similar to standard fractionation RT at 2 years (37). These findings are in agreement with a large meta-analysis concerning moderate hypofractionation for high-risk PCa patients who also received pelvic lymph node irradiation, with the conclusion that moderate hypofractionation could be considered an alternative to standard fractionated RT (38).

Ultra-hypofractionation trials show promising results but are currently not conclusive enough to be considered standard of care (39,40). The second research question is therefore to ultimately investigate if a shorter treatment of patients with intermediate and high-risk PCa, including treatment to pelvic lymph nodes, can be introduced.

In our study, the dose to elective lymph nodes is either 45 Gy in 20 fractions (2.25 Gy per fraction) or 37 Gy in 12 fractions (3.08 Gy per fraction). The table below provides an overview of selected studies in which fractionations between 2 – 5 Gy have been used for pelvic lymph node radiotherapy.

Trials in which fractionations between 2.2 – 5 Gy have been used for pelvic lymph node radiotherapy	N	Dose (Gy) and fraction (f)	Dose per fraction (Gy) to pelvic lymph nodes
Faria S, 2020 [41]	105	44 Gy/ 20 f to pelvic lymph nodes 60 Gy/20 f to the prostate	2.2 Gy
Pollak A, 2013 (Phase III) [42]	303 (104)	50–52 Gy/ 26 f to pelvic lymph nodes 70.2 Gy /26 f to the prostate	1,92-2 Gy
Phuong C, 2022 [43]	22	41.25 Gy/ 15 f to pelvic lymph nodes Either HDR BT (1 f of 15 Gy) or SBRT (19 Gy in 2 f) to the prostate	2.75 Gy
Nanos C, 2022 (phase II) [44]	22	37.8 Gy/ 14 f to pelvic lymph nodes 51.38 Gy/ 14 f to the prostate	2.7 Gy
Murthy V, 2021 (phase III) [23]	224	50 Gy/25 f to pelvic lymph nodes 68 Gy/25 f to the prostate	2 Gy
Adkison JB, 2009 (phase I) [45]	53	56 Gy/ 25 f to pelvic lymph nodes 70 Gy/28 f to the prostate	2.24 Gy
Maulik S, 2022 [46]	120	44 Gy/20 f to pelvic lymph nodes 60 Gy/ 20 f to the prostate	2.2 Gy
Magli A, 2018 (phase II) [47]	41	50 Gy/25 f to pelvic lymph nodes 67.5 Gy/25 f to the prostate	2.0 Gy
Bauman G, 2015 (phase I/II) [48]	15	25 Gy/5 f to pelvic lymph nodes 40 Gy/5 f to the prostate	5.0 Gy
Glicksman RM, 2021 (phase I/II) [49]	165	25 Gy/5 f to pelvic lymph nodes 40 Gy/5 f to the prostate	5.0 Gy
Hannan R, 2022, (phase I) [50]	55	22.5 -25 Gy/ 5 f to pelvic lymph nodes 47.5 Gy/ 5 f to the prostate + intraprostatic boost, 50Gy -52.5 Gy -55 Gy	4.5 – 5 Gy
Houlihan OA, 2023, (feasibility) [51]	15	25 Gy/5 f to pelvic lymph nodes 36.25-40 Gy/ 5 f to the prostate, + intraprostatic boost, 45-50Gy	5.0 Gy
Murthy V, 2022, (Comparative study from prospective data) [52]	102	25 Gy/5 f to pelvic lymph nodes 35-37.5 Gy/5 f to the prostate	5.0 Gy
Pinitpatcharalert A, 2019 (Retrospective analysis) [53]	23	25 Gy/5 f to pelvic lymph nodes 35-37.5 Gy/5 f to the prostate	5.0 Gy
Poon DMC, 2022 (Prospective trial) [54]	42	25 Gy/5 f to pelvic lymph nodes 40 Gy/5 f to the prostate	5.0 Gy
Meta-analyses; Viani GA [38] and Mohamad O [55]			

Imaging

During the recent two decades, imaging procedures have shown to improve accuracy of staging in prostate cancer (7). T stage is still strictly based on digital rectal examination, however multiparametric MRI is now standard staging procedure in order to predict extra prostatic extension, seminal vesicle involvement, T-staging and to guide biopsies (56). Recently, PET using radioactive ligands binding to the prostate-specific membrane antigen (PSMA) combined with CT (PSMA-PET/CT) has shown higher accuracy for N and M staging (57) and PSMA-PET/CT is now according to international guidelines the recommended staging procedure N and M stage (7) even though the prognosis and ideal management of patients diagnosed as metastatic by these more sensitive tests is unknown (7).

MRI has been shown to improve accuracy of prostate delineation (58) and to correlate with histology and definition of intra-prostatic lesions with MRI has shown a high accuracy (59). Recently, the combination of PSMA-PET and MRI has demonstrated even higher accuracy (57).

Based on the randomised trials showing benefit of radiotherapy with combined hormone- and radiotherapy compared to hormone therapy only (9,13,14), 3 months pre-irradiation castration is standard for high-risk patients in many institutions (7). Studies have addressed weakening MRI signals and PSMA PET-uptake after castration (60,61). However, there is not enough data to guide us to the optimal imaging to define intra-prostatic lesions in patients who are treated with a combination

of medical castration and radiotherapy. Currently this topic is being investigated in a phase 2 study (Danish Ethical Committee 2303938), conducted by the research group to prepare for the present study.

Additional improvements in delivery, such as MRI based image guidance, improved CT based image guidance, or adaption of the daily dose plan to the anatomy of the day etc. may improve outcomes further (58,62). If participating centers implement follow local adaptive strategies for adaptation due to anatomical changes, the center must document the procedures.

Study design

Statistical considerations

The reference schedule is 20 fractions, 5 fractions per week, without boost. For this reference schedule we assume the following outcomes of relevance to the statistical sample size calculation:

- 5-year biochemical control: 87%
- 5-year freedom from distant metastasis: 90% with sensitivity analysis 85%-90% 5 year OS: 82%.
- Prevalence of grade 2 or worse gastrointestinal(GI) toxicity: 10% at ~1 year
- Prevalence of grade 2 or worse genitourinary(GU) events: 20% at ~1 year

Dropout is assumed to be dominated by death from other causes. The expected OS of 82% yields a dropout rate of eta=0.039 when assessing endpoints where death is a competing event (Such as freedom from distant metastasis). We account for this dropout in the calculations below.

Table showing overall design

		Fractionation trial Trial tests for non-inferiority of short fractionation	
		12 fractions	**20 fractions**
Boost trial Trial tests for superiority of focal boost	**Boost**	Boost: 60 Gy/12 fractions (EQD2=110 Gy) Prostate: 50 Gy/12 fractions (EQD2=80 Gy) Pelvic: 37 Gy/12 fractions (EQD2=48 Gy)	Boost: 75 Gy/20 fractions (EQD2=110 Gy) Prostate: 60 Gy/20 fractions (EQD2=77 Gy) Pelvic: 45 Gy/20 fractions (EQD2=48 Gy)
	No boost	Prostate: 50 Gy/12 fractions (EQD2=80 Gy) Pelvic: 37 Gy/12 fractions (EQD2=48 Gy)	Prostate: 60 Gy/20 fractions (EQD2=77 Gy) Pelvic: 45 Gy/20 fractions (EQD2=48 Gy)

Primary endpoints and dimensioning

Superiority trial: Effect of focal boost

Primary endpoint will be freedom from distant metastasis (FFDM), which is concluded to be a strong surrogate of OS in localised PCa (32). The reference level for FFDM is a challenging parameter to address as it should be expected to improve with recent advances in the adjuvant systemic treatments. However, the population of this study is the highest risk RT patients, and we should therefore expect a distant metastasis (DM) rate that is on average higher than in other trial populations. The FLAME trial reported a DM rate of approximately 11% at 78 Gy dose to the primary target (Data supplement in FLAME). The current trial has a higher risk profile in patient uptake. We thus assume a 10% DM rate (90% FFDM) as a conservative reference level at 5 years, but with sensitivity analysis down to 85% FFDM. Furthermore, a single sided alpha of 5% is used to assess the alternative hypothesis that the boost arms have a FFDM rate at five years of 95% or better. We will assume 5 years uniform accrual plus 1-year additional follow-up (32). This primary sample size assessment yields the need for 254 patients in each of the four arms for a total of 1,016 patients to reach a power of 80% for the one-sided test for superiority on FFDM. The power after an additional 4 years of follow-up under the same assumptions increases to 96%.

Sensitivity analyses for the less conservative power calculations assume 85% FFDM and yield a power of 91% after 5+1 years and 99% after 5+5 years with the same number of patients and relative risk.

Non-inferiority of short fractionation

Defining boundaries of non-inferiority at 15% for GI events and 27% of GU events we have >80% power to detect inferiority with 1,016 patients on both endpoints.

Conclusion

In conclusion, 4x254 patients is a realistic sample size from a recruitment perspective. It is also sufficient to have an impact on guidelines for future patients if the trial is successful.

Secondary endpoints with formal power assessment

Prior data including the FLAME trial (8) show improvement in biochemical control, but meta analyses have criticised this endpoint. The Meta-Analysis of Randomised Trials in Cancer of the Prostate (MARCAP) investigators conclude that “Overall, these results strongly suggest that biochemical recurrence based endpoints should not be the primary end point of any randomised trial in localised PCa” (63). The proposed trial here is thus needed to investigate the clinical relevance of intraprostatic boosting with modern RT techniques using a more strict endpoint.

Nevertheless, biochemical control remains a commonly used endpoint and correlates heavily with the clinically relevant endpoint of onset of salvage hormonal therapy (63). It has also been repeatedly shown to correlate with radiation dose (64) and can thus be valuable for testing heterogeneity of treatment effect between techniques used in the involved clinical sites. We therefore perform a full power assessment of this important secondary endpoint.

The effect size for focal boost under the alternative hypothesis is assumed to be HR=0.45 for biochemical control (the estimate from 8) leading to greater than 90% power on a two-sided test for superiority with 1,016 patients.

The factorial design performs best when there is no interaction between the interventions. A test for interaction can be made by a within-the-table comparison as supplement to the main analysis at the margins (65, 66). These tests will be performed with biochemical control as the endpoint to optimise power.

In addition, tests for heterogeneity of treatment effects across the technological approaches to subvolume boosting (e.g. MR-linac based versus CT based versus proton therapy) will be performed on the endpoint of biochemical control for optimal power.

Further secondary endpoints

- Time to next treatment for prostate cancer.

- Regional relapse-free survival (rRFS)
- Overall survival (OS)
- Self-reported quality of life (QoL)

Pre-planned analyses during accrual

A number of pre-planned analyses will be conducted during the trial accrual period. Influence on the primary outcome p-values is avoided by 1) refraining from analysing efficacy endpoints before trial completion and 2) blinding the analysis of radiation dose response to trial arm in the planned dose response study. Therefore, no adjustment for multiplicity of tests is made on the primary endpoints.

Acute toxicity after 400 patients

This is a safety metric and a planned publication is made comparing all four arms with approximately 100 patients each.

Late GI and GU toxicity dose-response

A pre-planned dose response analysis is made after 600 patients accrued. 3D dose matrices and organ segmentations will be exported, and the dose converted to equivalent dose in 2 Gy fractions (EQD2) to avoid bias from the trial arm. This part of the analysis can be fully automated (67) and the trial arm will not be disclosed to the investigators. Subsequently, a dose-response relationship can be derived for rectum, bladder, urethra and bowel (68). A Novo Nordic funded data science infrastructure, DESIRE, can be used to collect the relevant data from the referring institutions and computationally time-dose-fractionation considerations. The open source model TotalSegmentator, which is being made available in the DESIRE infrastructure and for individual institutions, may greatly improve our ability to perform the dose response-analyses without relying on time-consuming human annotations (69-71).

Heterogeneity of treatment effect

Pre-planned heterogeneity of treatment effect will be performed on both the fractionation trial and the boost trial for the below mentioned covariables and outcomes. Heterogeneity of treatment effect will be assessed using appropriate statistical methods, such as interaction terms in the regression modelling.

With regards to superiority of focal boost we will test for heterogeneity for age effect of HR for FFDM and test for age and treatment modality for HR of biochemical control.

With regards to non-inferiority of short fractionation, we will test for age effect on HR for GI and GU toxicity and test for treatment modality effect on HR for GI and GU toxicity.

Further details of these pre-planned tests will be designed in the cancer society funded phase of the trial in the first half of 2025. A statistical analysis plan will be published prior to initiating data analysis.

Risks and contingency plans

A pre-planned trial assessment after 3 years with an expectation of 600 patients is planned (see section “Timeline”). Here, the data monitoring committee and the trial steering group will assess both the feasibility and progress of the trial in relation to the accrual plan and statistical sample size. In addition the assessment will involve scouting the recent literature and active trials and discuss possible needs for adjustments based on emerging evidence.

Communication with external partners, including the SPCG network, are planned if necessary to increase accrual through wider collaboration.

A prerequisite of the trial is that all Danish radiotherapy (RT) centres are able to join with most patients with locally or locally advanced disease offered inclusion (72, 73). The impact of an unexpected heterogeneity according to the individual department’s equipment will be minimised by performing the randomisation with stratification on the centre. In addition, the dosimetric performance of each center’s technical implementation will be vetted during the trial as described the RT-QA program, cf. Appendix A.

Patients

Inclusion criteria:

- Patients with biopsy verified PCa with no distant metastases with either
- Intermediate- or high-risk PCa, defined as at least one of the following risk criteria:
    - Clinical stage cT2c-T3b (UICC TNM 8th edition)
    - Imaging stage, T3a or T3b
    - ≥ Gleason score 4+3, (ISUP Grade groups 3,4 or 5)
    - Regional lymph node metastases N1
- Age > 18
- WHO score 0-1
- Intraprostatic lesion visible on MRI
- Suitable for focal boost
- Ability to give written informed consent and willingness to return for follow-up

Exclusion Criteria:

- WHO performance status ≥ 2
- If, for any patient related reason, an MRI cannot be performed
- T4
- International prostate symptom score (IPSS) ≧ 20

- If fiducial markers cannot be inserted
- TURP within 3 months from start of treatment
- Previous pelvic irradiation
- If the patient is judged by the physician to be unable to adhere to trial activities
- History of chronic inflammatory bowel disease (CIBD)

Treatment related procedures

- Neoadjuvant and adjuvant endocrine treatment according to Danish national guidelines, which currently includes 3 months LHRH agonist or antagonist before the start of RT. Abiraterone treatment for 2 years is allowed for participants with either N1 disease or two or three of the following criteria: Gleason score 8 – 10, PSA > 40 ng/ml, T3-4.
- MRI prostate and PSMA-PET/CT or PSMA-PET/MRI before the start of endocrine treatment.
- Planning with fiducial markers according to institutional protocol, MRI and PSMA-PET/ CT according to imaging guidelines in this protocol.
- Bladder and rectum according to institutional protocol
- Contouring and target definition according to guidelines in this protocol: boost, prostate, seminal vesicles, pelvic lymph nodes.
- Dose constraints for organs at risk are kept according to guidelines in this protocol
- Guidelines for IGRT according to institutional protocol.
- Treatment is delivered with institutional protocols that fulfil the goals and constraints given in this protocol (appendix B).

Radiotherapy

Radiotherapy planning:

Modern RT planning is wholly dependent on high level computing. This allows for creation of highly personalised dose plans with several different dose levels within the same plan. Additionally, these plans exhibit sharp dose gradients towards critical organs at risk (OAR). Depending on treatment modality plans will either use a simultaneously integrated or sequential boost. In the former case the treatment session delivers a boost to the intraprostatic lesion (if randomised for boost) in addition to the prescribed doses to prostate and elective targets. In the latter case prescribed doses to prostate and elective targets are delivered in the same treatment sessions whereas a boost will be delivered in separate sessions using specialised equipment e.g. an MR-Linac. In either case the dose planning will seek to minimise the trade-off between sufficient target coverage - usually between 95% and 107% of the prescribed target doses - and reducing as much as possible the doses to OAR. It is not uncommon that requirements for target and OAR doses are mutually exclusive. The order in which every dose requirement should be prioritised is detailed in Appendix B as well as specific

requirements to target coverage. To ensure that the dose planning of all participating centres will be vetted as part of the comprehensive RT-QA program described in Appendix A.

Rectal and bladder preparation protocol:

Patients should be treated with a comfortably filled bladder and an empty rectum/bowel according to local protocol. Use of Image Guided Radiotherapy (IGRT) is mandatory to ensure the elective target coverage and to assess bladder- and rectal filling. Application of a bladder-filling protocol in an attempt to decrease the volume of bladder irradiated is recommended using IGRT to check the target positioning.

Target volume definition, dose and fractionation:

Delineation of the targets are performed on the treatment planning MRI, guided by both the diagnostic multiparametric MRI (mpMRI) and PSMA-PET CT scan. Organs at risk (OARs) are delineated on the planning CT scan.

Fractionation:

- 20 fractions, no boost: Prostate and seminal vesicles: 60 Gy/ 20 fractions. Pelvic: 45 Gy /20 fractions.
- 20 fractions, boost: Boost 75 Gy/20 fractions, prostate and seminal vesicles: 60 Gy/ 20 fractions. Pelvic: 45 Gy /20 fractions.
    - If a boost is delivered on special equipment, such as an MR accelerator, it is allowed to give the boost in fewer fractions with same equivalent dose and maintaining same overall treatment time
- 12 fractions, no boost: Prostate and seminal vesicles: 50 Gy/ 12 fractions, Pelvic: 37 Gy /12 fractions.
- 12 fractions, boost: Boost 60 Gy/12 fractions, prostate and seminal vesicles: 50 Gy/12 fractions, Pelvic: 37 Gy /12 fractions.
    - If a boost is delivered on special equipment, such as an MR accelerator, it is allowed to give the boost in fewer fractions with same equivalent dose and maintaining same overall treatment time

All treatments with 5 fractions per week

Intraprostatic lesion(s): If a boost is to be performed, the most dominant lesion(s) are contoured as GTVp_FB_post with the prefix 1, 2 etc. according to the number of lesions with the use of information from the planning MRI and PSMA-PET/CT used as guidance. As the lesions and the prostate gland normally decrease in size with neoadjuvant ADT, a CTVp_FB_final should be created. This volume should not only include the GTVp_FB_post but also account for the potential initial tumor volume (GTVp_FB_pre) as observed on the diagnostic MRI performed prior to initiating ADT. The three sequences used from mpMRI are:

1) T2 weighted image, where the tumour lesions appear in grey
2) DWI (Diffusion Weighted Imaging), where the tumour lesions appear as white areas
3) ADC (Apparent Diffusion Coefficient), where the tumour lesions appear as black areas

CTVp_FB should be included in the CTVp or CTVp_SV. No margin is used for intraprostatic lesions.

For radiation target nomenclature, see appendix C

Prostate: MRI is used to contour the CTVp volume as the whole gland with any visible extracapsular extension of disease included.

Elective pelvic lymph nodes: If N1, elective lymph nodes should be delineated according to NRG Oncology Updated International Consensus Atlas on Pelvic Lymph Node Volumes for Intact and Postoperative Prostate Cancer, 2021 (74). Elective pelvic lymph node area is named CTVn_E. Any clinically suspicious lymph nodes should be included in the CTVn_E. PTV is derived by adding a 5-10mm margin to CTVp, CTVp_SV and CTVn_E. See appendix D

Seminal Vesicles (SV): If T3b disease, the entire seminal vesicle volume bilateral should be included in the CTVp_SV and treated to a high dose. If ≤ T3a, only the proximal 2 cm of the seminal vesicle bilateral should be included in the CTVp_SV and treated to an elective dose. See appendix E

Organ at risk (OAR): will be contoured according to national guidelines.

Organs at risk

The prostate is situated adjacent to both the rectum and urinary system which risks gastro-intestinal (GI) and genitourinary (GI) adverse effects. The FLAME trial showed that long term side effects of conventional prostate RT even when combined with a mildly fractionated intra-prostatic boost are generally modest in frequency and severity (28). However, the addition of an extremely hypofractionated boost close to organs at risk approaches the realm of brachytherapy where very high point doses directly adjacent or even in the organ can lead to very severe adverse effects. The HypoFLAME trial (75) demonstrated that such an approach leads to only low frequencies of grade 2 side effects and very rarely grade 3. The results rely on the treatment being isotoxic i.e. maintaining pre-existing dose constraints of equivalent dose in the specific hypofractionated scheme. Table 1 in appendix B details the isotoxic dose constraints for the relevant organs at risk for each trial arm while Table 2 details the requirements for target coverage.

Study procedures

Identification and information of eligible patients

Eligible patients will be identified and discussed by doctors at the regional multidisciplinary team conference (MDT). Data from the medical record for eligibility screening are handed over to the researcher (name and CPR number of patients to receive radiotherapy, and diagnosis, i.e. cancer of the prostate/DC61.9). Other study relevant data are retrieved only after written consent. All patients

referred for RT who meet the inclusion criteria will be recorded on a screening list. Neoadjuvant and adjuvant ADT will follow Danish national guidelines, which currently include 3 months LHRH agonist or antagonist prior to the start of radiotherapy

The patients are enrolled on the basis of oral and written information about the study. At the first doctor's appointment, the doctor informs about the study and the patient receives the written information. At the next appointment, any questions can be answered and the patient has the basis for giving written consent to participating in the study.

The information will include the purpose of the study, the risks, benefits and disadvantages. The patients will be offered at least 24 hours to consider participation and be informed that they can withdraw their consent at any time. The conversation takes place in a suitable, quiet room, and sufficient time for the patient to ask questions is provided. The patient has the right to an assessor or observer. Informed consent will be obtained prior to any study related procedure. The signed and dated consent form will be kept in a locked room and be available for audit and inspection at any time.

The patient consent allows sponsor, sponsor representatives, investigators and relevant authorities to access health information directly in the electronic medical record necessary for trial conduct and control purposes. Data regarding trial subjects are handled according to the Data Protection Act and the General Data Protection Regulation.

Each participating center has a written agreement delegating the information procedure to the treating physicians.

Patients who do not want to participate in the study are treated with standard radiotherapy according to institutional guidelines.

Randomisation

After eligibility screening has been completed, a computer randomisation procedure will be performed centrally stratified by participating centres.

Follow-up and Data Collection

Data from the medical record include: age, date of cancer diagnosis (biopsy date), tumor stage (TNM), PSA, Gleason score, performance status (PS), length of ADT, imaging results, date of radiotherapy treatment, dose plan parameters, prescribed dose and fractionation, gross tumor volume, side effects, QoL and PRO data, progression and survival data.

Subjects will accordingly to standard practice be followed for 10 years with a blood sample (PSA) monitoring disease control, whereas toxicity and quality of life (QoL) will be followed for 5 years. Testosterone is measured accordingly to local practice. Survival will be followed for up to 20 years. Additional visits beyond those established by the protocol will follow local guidelines. Protocol visits can be conducted by phone or video meeting, if preferred.

Data will be collected at follow-up visits as shown in the figure below

	Department of Urology 1. ADT	Department of Oncology Baseline Inclusion	Radiotherapy 20 fx 12 fx	3 months after start of RT 2. ADT	1 year 4. ADT	2 years 6. ADT	3 years	4 years	5 years	6-10 years
Months	-3	-1	0	3	15	27	39	51	63	75, 87,99, 111,123
Psysical exam		x								
PSA	x	x		x	x	x	x	x	x	x
Testosterone*		(x)		(x)	(x)	(x)	(x)			
Biomarkers		x		x						
CTCAE		x		x	x	x			x	
PRO´s and QoL		x		x	x	x			x	

* Recommended, but can be according to local practice

Toxicity registration

Gastrointestinal (GI) and genitourinary (GU) toxicities will be assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Acute toxicity is defined as adverse effects occurring within 90 days of the first radiation treatment, while late toxicity is defined as effects occurring 90 days or more after the first treatment. Toxicities will be analyzed in relation to dose-volume histograms (DVHs) for organs at risk (OARs), including the bladder, urethra, and rectum, as well as target structures, such as the gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV).

Patient-reported outcome measures (PROM) will include EORTC QLQ-PR25 and QLQ-C30.

PROM questionnaires will be sent to the patient's digital mailbox at predefined dates and to ensure a high response rate, the system will be configured to send automated reminders in case of missing responses. Data will be filed and stored using eCRFs in a REDCap database.

The data management system ensures compliance with current legislation and regulations on data handling and data safety. Sponsor, sponsor's representatives, investigators and controlling authorities have direct access to the above mentioned data including access to electronic patient records in order to ensure data quality and to monitor data quality.

Adverse Events (AEs) and Serious Adverse Events (SAEs)

The side effects of ADT are well documented and an integral part of daily clinical practice in the treatment of PCa patients. The expected side effects of ADT will be documented via the PROM questionnaires filled in by the patients at each follow-up visit. They will not be recorded continuously as adverse events (AE).

Boost to prostate and the hypofractionation schedule in the protocol are the new parameters being examined in the study and any AE and serious adverse events (SAE) will be reported continuously.

The local investigator is responsible for assessing the causality of all AE and SAE in relation to the trial therapy.

Adverse Event (AE)

Any unfavourable and unintended (acute or chronic) symptom related to the organs in the pelvic and abdomen and caused by radiotherapy:

Urogenital: urinary incontinence, urinary retention, urgency, increased urinary frequency, irritative urinary symptoms, bladder spasm, pain, hematuria, urinary tract obstruction, urinary fistula.

Gastrointestinal: Incontinence for gas/liquid or solid stool, diarrhea, inability to defer defecation, increased number of daily defecation, abdominal pain, rectal bleeding, rectal fistula.

Any condition that exists when the patient is included in the study will be recorded as Medical History. However, it must be reported as an AE if the condition deteriorates during the trial.

AEs are recorded in the eCRF.

Serious Adverse Event (SAE)

A SAE is a radiotherapy related serious event, which may be caused by radiotherapy, occurring during radiotherapy and in the follow-up, which results in any of the following: death, a life-threatening experience that requires hospitalization or requires intervention to prevent permanent impairment/damage.

SAEs are recorded in the SAE eCRF

A detailed description of the AE and SAE will be collected and include the time of onset, grade and severity, management and treatment of the side effect, the outcome, the time to resolution or stabilization and consequence for the RT treatment. All AEs and SAEs occurring during the study must be systematically documented, irrespective of their causal relationship to the treatment

The AEs and SAEs will be followed until resolved or considered stable or until it has been established that participation in the study was not the cause. They will be evaluated by the local site investigator and reported to the trial management committee.

During follow-up after radiotherapy (up to 60 months), all radiation-induced SAE will be reported and followed.

Due to the severity of the disease in this study, the following situations are excluded from expedited notification on a SAE form and should instead be reported in the Case Report Form (CRF) follow-up form.

- Elective hospitalisation to simplify treatment or procedures
- Elective hospitalisation for pre-existing conditions that, in the investigator’s opinion, have not been exacerbated by trial treatment

- Disease progression
- Death as a result of disease progression

All SAE must be reported to sponsor within 1 working day.

Sponsor reports all SUSARs (Suspected Unexpected Serious Adverse Reactions) to the Ethics Committee within 7 days, if life threatening or fatal, and within 15 days, if not life threatening. Sponsor will annually report all SAEs to the Ethics Committee.

Endpoints

Primary endpoint

- Freedom from distant metastasis (FFDM)

Secondary endpoints

- Freedom from biochemical relapse
- Time to salvage hormonal therapy
- Regional relapse-free survival (rRFS)
- Local relapse-free survival (rRFS)
- Overall survival (OS)
- Prostate cancer specific survival
- Self-reported quality of life (QoL)
- Toxicity as CTCAE

Disease related endpoints are calculated from randomisation to event.

Recommended work-up at suspected recurrence

Diagnostic workup on suspicion of recurrence takes place according to national guidelines as described below.

PSMA PET/CT is recommended:

- If a recurrence is suspected biochemically according to the Phoenix criteria
- If a recurrence is suspected clinically, e.g: Bone pain, anemia, urinary symptoms
- If recurrence is suspected by radiographic test

If PSMA PET/CT shows no sign of regional or distant metastases, a diagnostic mpMRI of the prostate is recommended. Local recurrence after definitive radiotherapy should be confirmed by biopsy from the site of suspected recurrence if the result has implication for the treatment.

Cancer related endpoints

Events are: occurrence of distant metastases, castration resistance, biochemical relapse as defined by Phoenix criteria (PSA nadir + 2) (76), start of endocrine treatment, local recurrence, regional recurrence, and death.

Distant metastasis

The event distant metastasis can be detected radiographically as PSMA PET/CT is recommended at suspicion of relapse. Biopsy is also accepted and MRI, CT, bone scintigraphy, NAF-PET, ultrasound or clinical examination may also be accepted with further confirmation, e.g. biopsy or laboratory tests. If the event “distant metastasis” is based on tests without biopsy or PSMA positivity the event shall be confirmed at MDT.

Biochemical relapse

Phoenix criteria are used for definition of the event biochemical relapse, defined as a PSA increase of 2 ug/l from nadir. The date of recurrence is the first date with a PSA level of nadir + 2. The PSA level must be confirmed by a second PSA measurement performed at minimum two weeks later.

Local recurrence

The event local recurrence is defined as a local PSMA positive lesion. Local recurrence after definitive radiotherapy should be confirmed by biopsy from the site of suspected recurrence if the result has implication for the treatment. MRI, CT, ultrasound or clinical examination may also be accepted with further confirmation, e.g. biopsy.

Regional relapse

The event regional recurrence is defined as at least one regional PSMA positive lesion. Biopsy is also accepted and MRI, CT, ultrasound or clinical examination may also be accepted with further confirmation, e.g. biopsy or laboratory tests. If the event “distant metastasis” is based on tests without biopsy or PSMA positivity the event shall be confirmed at MDT.

Death

Cause and time of death is collected from electronic patient charts for up to 20 years. If no information is available, data will be retrieved from the national death register.

Endpoints related to toxicity

Self-reported quality of life (QoL)

Qol is registered as described in the paragraph “Follow-up and Data Collection” using EORTC QLQ-PR25 and QLQ-C30.

CTCA registered toxicity

Toxicity is registered using CTCAE v 5.0 as described in the paragraph “Follow-up and Data Collection”

Radiotherapy Quality Assurance (QA)

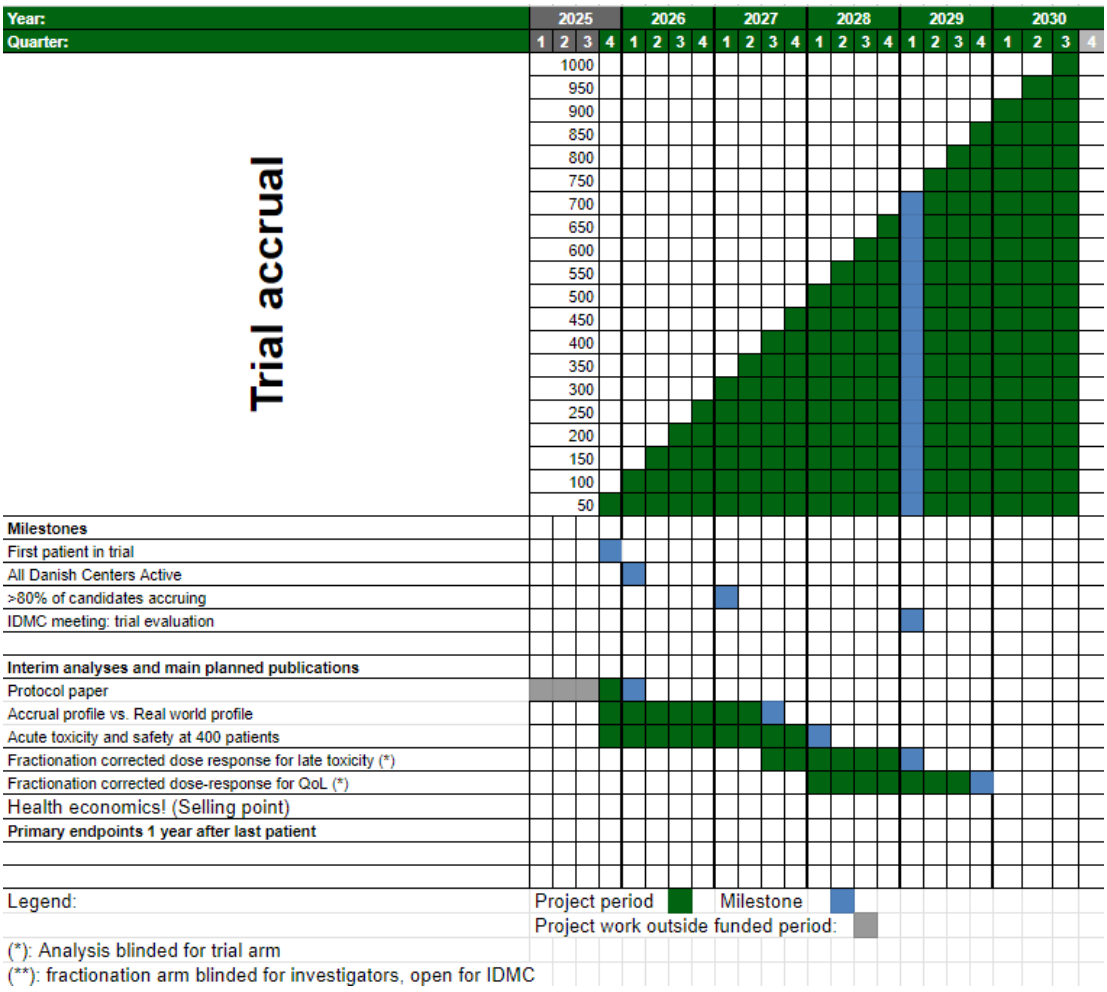
The radiotherapy (RT) approach in this study is a highly advanced treatment combining several modalities. Tumour targets are identified by multi-parametric MRI, PET and CT. The individualised dose-plans are optimised for tumour dose while minimising doses to healthy critical tissue. The treatment is delivered by linear accelerators using daily on-line imaging and treatment adaptation.

A comprehensive quality assurance (QA) program is essential to ensure reliability and reproducibility in RT trials in general. This is especially the case in multi-center trials with different local routines and equipment. Past trials have shown significant variability in various parts of the treatment planning process, underscoring the need for QA, as seen in the CHHiP and PEACE V-STORM trials (77,78). The QA program needs to cover all aspects of the treatment chain: imaging, delineation, treatment planning, treatment delivery, and dosimetry.

The study aims to develop and standardise procedures across centres by utilising modern imaging data, collected with strict protocols. The data will be used to create a strategy compatible with routine RT practices. Workshops regarding treatment planning and plan quality will be conducted using established national imaging and planning archives (DcmCollab). The consensus plans will serve as a benchmark for the plan complexity that the treatment delivery machines must be able to reproduce. This in turn will form the basis of the QA-program across participating institutions described in detail in Appendix A.

Timeline

Figure: Gantt chart



Organisation

The study is led by the core group consisting of oncologists and medical physicists based in three regions of Denmark. A trial management group and a data management group will also be established.

Core Group

The core group consists of Simon Buus, Steffen Bjerre Hokland, Christine Vestergaard Madsen, Peter Meidahl Petersen, Bjarke Mortensen, Rebecca Jean Tobin and Ivan Vogelius. The group has substantial experience in prostate cancer research on an international level. The core group is responsible for the scientific content of the trial, funding of the trial and establishing the infrastructure of the trial. The core group has regular online and onsite meetings.

Sponsor

The sponsor is the head of the department of Oncology, Rigshospitalet, Professor Ulrik Lassen. A letter of support is enclosed in the appendices section.

Trial Management Group

The Trial Management Group (TMG) includes investigators from all participating centres and the members of the core group. The TMG will be responsible for the day-to-day running and management of the trial and will meet regularly by teleconference or at meetings.

Data Monitoring Committee

The group will be led by Professor Søren Bentsen. The group will secure the completeness of the data, quality of data, monitor the progression of the trial and make the data available for the IDMC.

Independent data monitoring

An independent data monitoring committee (IDMC) will also be established. The Independent Data Monitoring Committee (IDMC) is the only group who sees the confidential, accumulating data from the trial. Reports to the IDMC will be produced by the Data Monitoring Committee.

Work Packages

To manage the study's technical issues during planning and running the trial, we have defined the following work packages:

- Imaging: leaders Rebecca Jean Tobin and Helle Zacho
- Radiotherapy dose planning: leader Steffen Bjerre Hokland
- Radiation treatment delivery: leader Bjarke Mortensen
- Patient data and toxicity registration: leader Christine Vestergaard Madsen

We have agreements from physicians and physicists to establish the listed work packages. The groups represent the Danish centres broadly.

The aim of a work package is overall to ensure the highest possible level of reproducibility and quality in real-world settings across the participating institutions within the different project tasks.

Patient involvement

The trial has been presented to two patient representatives with a history of PCa; Jesper Thorsen and Per Baltzersen Knudsen. Both representatives have reviewed and provided insightful feedback on the project, and have also consented to being mentioned in funding applications. Both found the scientific questions asked in the trial of high relevance for PCa patients. Patient engagement and collaboration within the trial management group remain ongoing.

Ethical consideration

The trial will follow the current Helsinki Declaration (2013). The trial can only start when approved by the Ethical Committee.

The trial consists of one standard arm and three arms with experimental therapy. At every participating centre, there is an investigator, responsible for the trial, who assures that every patient is informed, orally and in writing, about the trial with respect to the content of the trial and the detailed follow up before the patient can enter the trial. This includes benefits and risks from participating in the trial. All patients receive a trial specific patient information booklet, which follows the Danish guidelines for patient information.

Potential benefits for the patient

The potential advantages for a patient participating in the trial is to have fewer fractions in the experimental arms (12 fractions versus the standard arm of 20 fractions), and to reduce the risk of distant metastases by increasing the dose to the intraprostatic tumor lesion.

Potential risks for the patient

The potential disadvantage for the patient is an increased risk of late side effects from the lower urinary tract and rectum and bowel.

The side effects and risks of curatively intended combined LHRH-treatment, and radiotherapy for prostate cancer is well described and the patients will be informed about the risks before treatment.

We cannot exclude an increased risk of urinary and/or genito-urinary toxicity in the short treatment arm as the primary endpoint is non-inferiority for increased toxicity. A careful collection of recorded toxicity is therefore an important part of the study. An independent data monitoring committee will oversee the data during the study (see paragraph on independent data monitoring committee).

The concept of the study is to test if increased dose to intra prostatic lesions without increased dose to the surrounding organs improves tumour control. For the patients in the boost arm, we will also ensure that dose to urethra is kept the same dose level as the non-boost arm. However, we cannot completely exclude a higher risk of urinary toxicity.

Withdrawal of consent

The participant can withdraw from the trial at any time, and he does not have to give a reason for withdrawal. If he chooses to have standard therapy, this will be external beam radiotherapy according to the current DAPROCA guidelines.

Patients, who for some reason do not receive the allocated therapy, are to be treated at the doctor's discretion. The analysis of data will be according to the intention-to-treat principle. Unless the patient

does not accept it, he is followed as all other patients in the trial regarding the primary and secondary endpoints.

For patients not receiving the allocated therapy or withdrawing from the trial at a later point of time, the date of exit from the trial is registered as also the reason if possible. The patient is informed about the burden of follow up before randomization to minimize withdrawal from the trial. The patient can withdraw from the trial without telling a reason at any time.

Possible benefits for society

If successful, the societal impact of the trial will be significant, resulting in improved treatment outcomes at a lower cost. The current diagnosis-related cost for a fraction of radiotherapy (DRG takst) is set at 2,709 DKK. Reducing the number of fractions from the current standard of 39 to 12 is projected to decrease the annual DRG cost of radiotherapy by approximately 25 million DKK (approximately 3.4 million EUR), assuming 350 patients per year. However, the actual reduction may be slightly less due to the increased complexity of the fractions.

Additionally, there is potential for savings in subsequent salvage therapy if the disease control is superior. A health economics task is outlined in the Gantt chart in section “Timeline”. A comprehensive procedure list can be extracted from the Danish registries on the randomised patients to facilitate a high-quality assessment of health economics. An external partner with domain knowledge will be involved once the data is mature for this analysis.

The healthcare sector is globally responsible for 5% of greenhouse gas emissions (79,80). Chuter et al. found that 226.9 kg of CO_2 equivalents were emitted during a 20-fraction RT course for a patient with prostate cancer (81). More than 80% of these CO_2 emissions were related to transportation. Therefore, the environmental impact of RT will also be substantially reduced if the trial successfully decreases the number of fractions from the current standard of 39 to the emerging standard of 20, and further down to 12 fractions in the experimental arm.

Economic issues

This trial protocol is initiated and developed by the DAPROCA10 Core Group, and the trial will be nationwide in Denmark. Radiation therapy is standard to all patients included in this trial, so there will be no additional costs regarding the radiation therapy for the participating departments. The reduction of the number of treatments may reduce the costs for the participating centers.

The individual radiation therapy department participating in the trial will cover the costs related to follow up. The principal investigator and the trial responsible staff have no economic interests in the trial.

Further funding will be applied for to cover the study procedures. The project has received 2 million DKK from Danish Cancer Foundation (KB) which has no influence on the planning and conduct of the

study or the interpretation of results. Additional funding will be applied for, and the ethics committee will be informed if such funding is achieved. The participant information document will be updated accordingly.

The participants will not have extra costs and no compensation will be given to participants.

Funding

Peter Meidahl Petersen has a 3-month grant from Rigshospitalet to develop the focal boost technique up to the grant start date. Furthermore, we have funding for 1 year research assistant time for Christina Jakobsen, MD, to facilitate the imaging study and data analysis of the studies preparing for this national trial.

A grant of 2,000,000 DKK from the Danish Cancer Society has been secured for preparing the randomised national trial, implementing imaging, and training physicians in defining intraprostatic targets to optimise radiotherapy planning and treatment.

A grant of 200.000 DKK from DCCC has recently been given to the group for supporting the completion of the trial protocol, grant application and meeting activities.

Insurance

The participants in the study are covered by the Patient Compensation Association.

Publication

The results from this trial will be published irrespective of them being positive, negative, or inconclusive. After approval by the Ethical Committee, the trial will be registered at www.clinicaltrials.gov. Co-authorship follows the Vancouver guidelines.

The Trial Management Group (TMG) will form the basis of the Writing Committee and will advise on the nature of all publications. The TMG will decide on authorship and co-authorships, however, for the paper on primary end points, co-authorship will likely be assigned to the one representative from each center with >5% of the accrued patients and two co-authors from centres recruiting 30% or more of eligible patients in the trial. Investigators who contribute to designing, collection, validation and analysis or in other ways contribute significantly to the trial may also earn authorship.

Any publication, that is not pre-planned, on the primary and secondary endpoints cannot be accepted until the primary and secondary endpoints from the entire study have been published. Other information from the trial (e.g. local quality assurance on radiation therapy or of the morbidity evaluations) can be published with approval from TMG.

Projects defined at a later point of time using results/data from this trial, can be conducted and published with approval from TMG.

All publications from this trial must be on behalf of the DAPROCA10 TMG and either ”DAPROCA10” must be in the title or stated ”on behalf of the DAPROCA10 TMG”. Relevant funding e.g. DCCC and the Danish Cancer Society must be mentioned and acknowledged when results are published (contact the principal investigator or the DAPROCA for more details).

Appendices

Addition of focal boost to primary radiotherapy for prostate cancer in 12 or 20 fractions: A large DAPROCA randomised trial.

Appendix A: Radiotherapy Quality Assurance

An internal Quality Assurance (QA) group will be established, consisting of at least two medical physicists and two oncologists selected from the Core Group or Work Packages.

The QA group will review the first patient treated with a focal boost in each fractionation regimen at each center, totaling two patients. The group will evaluate and provide feedback on the delineation of the focal boost, targets, and organs at risk, in accordance with the established consensus guidelines. Additionally, dose planning for these two patients will be reviewed by the QA group prior to the initiation of the first treatment, with detailed feedback provided.

Each participating center is also required to submit its daily imaging and adaptive strategies to the QA group for evaluation and subsequent feedback.

Image data include prospective trial data collection from Rigshospitalet (Ethical approval, VMK case nr. 2303938 approved 21/06-2023). We expect 10 patients to be available with multiparametric or PSMA PET/MRI before the start of hormone treatment and at the start of RT, 3 months later. Image acquisitions will be optimal for comparison of response using the same sequences in the two acquisitions and optimised for RT planning.

The data will be made available for a consensus workshop on target delineation following the model used by other multidisciplinary groups in Denmark using the available infrastructure (82-85). The inter- and intraobserver variability in delineation will be assessed, and guidelines written based on these results and consensus at the workshop.

Finally, a small dataset of 10 patients with weekly MRI during RT (Ethical approval number nr. 91936), available at Rigshospitalet can be used for documenting the delivery precision in the simulated treatments accounting for anatomical variations. Workshops regarding treatment planning and plan quality will be conducted using established national imaging and planning archive (DcmCollab). The consensus plans will serve as a benchmark for the plan complexity that the treatment delivery machines must be able to reproduce. This in turn will form the basis of the QA-program across participating institutions.

Imaging quality assurance

The imaging protocol will consist of sequences recommended by the European society of urogenital radiology (ESUR) and their prostate imaging reporting and data system (PI-RADS v. 2.1 (https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PIRADS-V2-1.pdf)) assessment (86,87). Minor adaptations specific to radiotherapy planning, such as axial sequences without tilting, will be decided by the imaging group, with the insights gained from the FLAME trial and capabilities of each centre taken into consideration (88). To ensure the proper sequences are taken and optimised to the highest quality on each centre's MR or PET/MR scanner, the MR physicist will visit each site to set-up the MR protocol. The images will be optimised after the priorities set within the imaging working group, between the MR specialised radiologists and MR physicist. Once the optimization is complete, the images will be sent for review and approval of the MR radiologists and adjusted accordingly until met with unanimous approval.

The geometric stability of the MR scanners at all radiotherapy sites in Denmark has been investigated and evaluated by the national interdisciplinary network for quality assurance of MR images in radiotherapy (NIMBUS) (89). Further measurements will be performed to minimise and quantify the size of the artefacts around the implanted gold markers, which are required for RT treatment. The results will be shared with the physicists for consideration in choice of PTV margins and with physicians for consideration in delineation uncertainty of the intraprostatic tumour.

PSMA-PET/CT is an implemented procedure in Denmark and Danish Centers more than fulfil the requirements of the EARL PET/CT Accreditation User Manual (https://earl.eanm.org/wp-content/uploads/2023/05/EARL_Manual_4.2.pdf). PSMA-PET/CT is done as a part of the standard procedures in the participating patients, but not a tested procedure in this study, therefore no additional QA is done regarding this procedure.

PSMA-PET/MRI is an add-on procedure in this study and the use of PSMA-PET/CT will be developed in this trial.

Delineation and dose planning quality assurance

In order to assure the greatest level of consistency across participating institutions a workshop will be held January 2025 to establish and train consensus guidelines for target and OAR delineation. The workshop will use data from the prospective trial at Rigshospitalet (Ethical approval: VMK case nr. 2303938 approved 21/06-2023) including multiparametric or PSMA PET/MRI before the start of hormone treatment and at the start of RT and 3 months later. The consensus workshop will follow the model used by other multidisciplinary groups in Denmark using the available infrastructure (82,84,85,90). The inter- and intraobserver variability in delineation will be assessed, and guidelines written based on these results and consensus at the workshop.

Image guidance and adaptive strategies

When applying a normo-fractionated RT schedule daily variations in e.g. rectal or bladder filling are often negligible due to the sheer number of treatments. However, in a hypo-fractionated regime - especially when combined with a boost volume - these variations have much greater impact. Hence, daily imaging is a necessary requirement to monitor such changes. This also means that in addition to a thorough patient specific QA program all participating centers must have a comprehensive and well documented program for adaptation to systematic anatomical changes. Procedures must be in place to monitor variations on a daily basis and identify cases that pose a potential risk of too high doses to organs at risk and/or low doses to target volumes. Furthermore, the procedures must include methods to evaluate the dosimetric impact of the anatomical variations and finally methods to mitigate unacceptable instances. Each participating center must submit its daily imaging and adaptive strategies to the QA group for evaluation and feedback.

AQA group as described above will evaluate the contouring of the focal boost contouring and dose planning before starting the patient's first treatment.

Plan delivery quality assurance

Before enrolling patients in the protocol, each participating centre must complete a validation "dummy run" to verify the accuracy of the delivered dose. This validation requires dose planning on a test case with a delineation of a focal boost, along with patient-specific QA measurements for the delivered dose. Centres may use their standard patient-specific QA devices for these measurements, which involve two evaluations: (a) a general assessment of the total dose delivered and (b) a precise evaluation of the dose delivered specifically to the prostate area, including the focal boost, with stereotactic accuracy (91).

QA measurements should follow AAPM Task Group 218 methodologies (92), such as:

- Conducting IMRT QA measurements using True Composite (TC) or Perpendicular Field-by-Field (PFF) if TC is unsuitable,
- Analysing dose measurements against the corresponding dose plan doses in absolute dose mode, using a threshold for excluding low-dose areas,
- Variations of the detector response as well as of the accelerator output should be factored out of the analysis.

To pass the dummy run, QA analysis must achieve:

- A ≥95% pass rate for $\gamma_{3\%;2mm}$ with a 10% dose threshold for overall dose evaluation,
- A ≥95% pass rate for $\gamma_{3\%;1mm}$ with a 10% dose threshold specifically for the prostate area including the focal boost (stereotactic accuracy).

Different QA approaches may be used for these two evaluations, and each centre must submit a documentation of its QA procedure as well as a detailed evaluation of the test case to the QA group.

Appendix B: Dose constraints

Table 1 below shows isotoxic dose constraints to organs at risk. The Equivalent Dose at 2 Gy fractions known from the conventional 39-fraction treatment regime have been converted to equivalent doses for the two hypo-fractionated schemes using an α/β-value of 3. Requirements for target coverage for the two hypo-fractionated schemes are listed in table 2. Both tables include priorities designating in which order specific constraints should be fulfilled in case of conflicts between target and OAR. CTVs and certain OARs both have priority 1. This should not lead to conflicts since there are no overlaps between the two.

Table 1

OAR	Normo-fractionated DVH constraint	EQD2 of physical dose	Isotoxic dose: 20 fractions (α/β = 3)	Isotoxic dose: 12 fractions (α/β = 3)	Priority
Rectum	V_{75Gy}<2cm^3	74 Gy	60 Gy	50 Gy	1
	V_{70Gy}<10%	67 Gy	55 Gy	46 Gy	3
	V_{50Gy}<60%	43 Gy	46 Gy	31 Gy	3
Urethra	$D_{0.1ccm}$ < 85Gy	88 Gy	71 Gy	59 Gy	1
	D_{1ccm} < 80Gy	81 Gy	65 Gy	54 Gy	1
Bowel Bag	D_{max} < 78Gy	78 Gy	63 Gy	53 Gy	1
Bowel Bag - PTV_5mm	V_{30Gy}<450cm^3	23 Gy	20 Gy	18 Gy	3
	V_{45Gy}<195cm^3	37 Gy	32 Gy	28 Gy	3
Bladder	D_{mean}<62Gy	57 Gy	47 Gy	40 Gy	3
	V_{80Gy}<15%	81 Gy	65 Gy	54 Gy	3
	V_{70Gy}<35%	67 Gy	55 Gy	46 Gy	3
Femoral Heads	$D_{2\%}$<55Gy	48 Gy	41 Gy	35 Gy	3
Body (outside PTVs)	$D_{2\%}$<83Gy	85 Gy	67 Gy	56 Gy	3

Table 2

Target volume (X denoting specific dose scheme)	DVH constraint		Priority
	20 fractions	12 fractions	
GTVp_FB_post_X	D_{mean} = 75 Gy (±1%)	D_{mean} = 60 Gy (±1%)	2
GTVp_FB_post_X	$V_{71.25Gy}$ >99.5%	V_{57Gy}>99.5%	2
CTVp_FB_final_X	$V_{71.25Gy}$ >95%	V_{57Gy}>95%	3
CTVp_FB_final_X	$D_{0.1ccm}$ >80.25Gy	$D_{0.1ccm}$ >64.2 Gy	3
CTVp_X	V_{57Gy}>99.5%	$V_{47.5Gy}$>99.5%	1
CTVp_SV_X (T3b)	V_{57Gy}>99.5%	$V_{47.5Gy}$>99.5%	1
CTVp_SV_X (≤T3a)	$V_{42.75Gy}$>99.5%	$V_{35.15Gy}$>99.5%	1
CTVn_E_X	$V_{42.75Gy}$>99.5%	$V_{35.15Gy}$>99.5%	1
PTVp_X	V_{57Gy}>98%	$V_{47.5Gy}$>98%	2
PTV_SV_X (T3b)	V_{57Gy}>98%	$V_{47.5Gy}$>98%	2
PTVn_E_X	$V_{42.75Gy}$>98%	$V_{35.15Gy}$>98%	2

Appendix C: Radiation target nomenclature

Target	Delineation	GTV nomenclature	CTV nomenclature	PTV According to local guidelines	Doses	Number of fractions
Intraprostatic lesion(s) if boost is performed (prior to initiating ADT)	Based on MRI +/- PSMA-PET CT signals	GTVp1_FB_pre* GTVp2_FB_pre* etc.	N/A	N/A	N/A	N/A
Intraprostatic lesion(s) if boost is performed (post initiating ADT)	Based on MRI +/- PSMA-PET CT signals	GTVp1_FB_post_ 75 GTVp2_FB_post _75 etc. GTVp1_FB_ post_60 GTVp2_FB _post_60 etc.	CTVp1_FB_final_75 CTVp2_FB_final_75 etc. CTVp1_FB_final_60 CTVp2_FB_final_60 etc.	N/A	75 Gy 60 Gy	20 fx 12 fx
Prostate	MRI used for volume definition		CTVp_60 CTVp_50	PTVp_60 PTVp_50	60 Gy 50 Gy	20 fx 12 fx
Seminal Vesicles - if invasion (T3b) Seminal Vesicles - no invasion (≤ T3a)	Based on the MRI and adjusted according to location on the CT scan The proximal 2 cm of vesicles		CTVp_SV_60 CTVp_SV_50 CTVp_SV_45 CTVp_SV_37	PTVp_SV_60 CTVp_SV_50 PTVp_SV_45 PTVp_SV_37	60 Gy 50 Gy 45 Gy 37 Gy	20 fx 12 fx 20 fx 12 fx
Elective pelvic lymph nodes	According to NRG Oncology Updated International Consensus Atlas on Pelvic Lymph Node Volumes		CTVn_E _45 CTVn_E _37	PTVn_E_45 PTVn_E_37	45 Gy 37 Gy	20 fx 12 fx

Abbreviations: GTV: Gross Tumour Volume; CTV: Clinical Target Volume; PTV: Planning Target Volume; Gy: Gray; fx: Fractions
* There are no dose constraints for the GTV(s) defined prior to initiating ADT. This/these volume(s) should be included in the CTV(s) for the intraprostatic lesion(s).

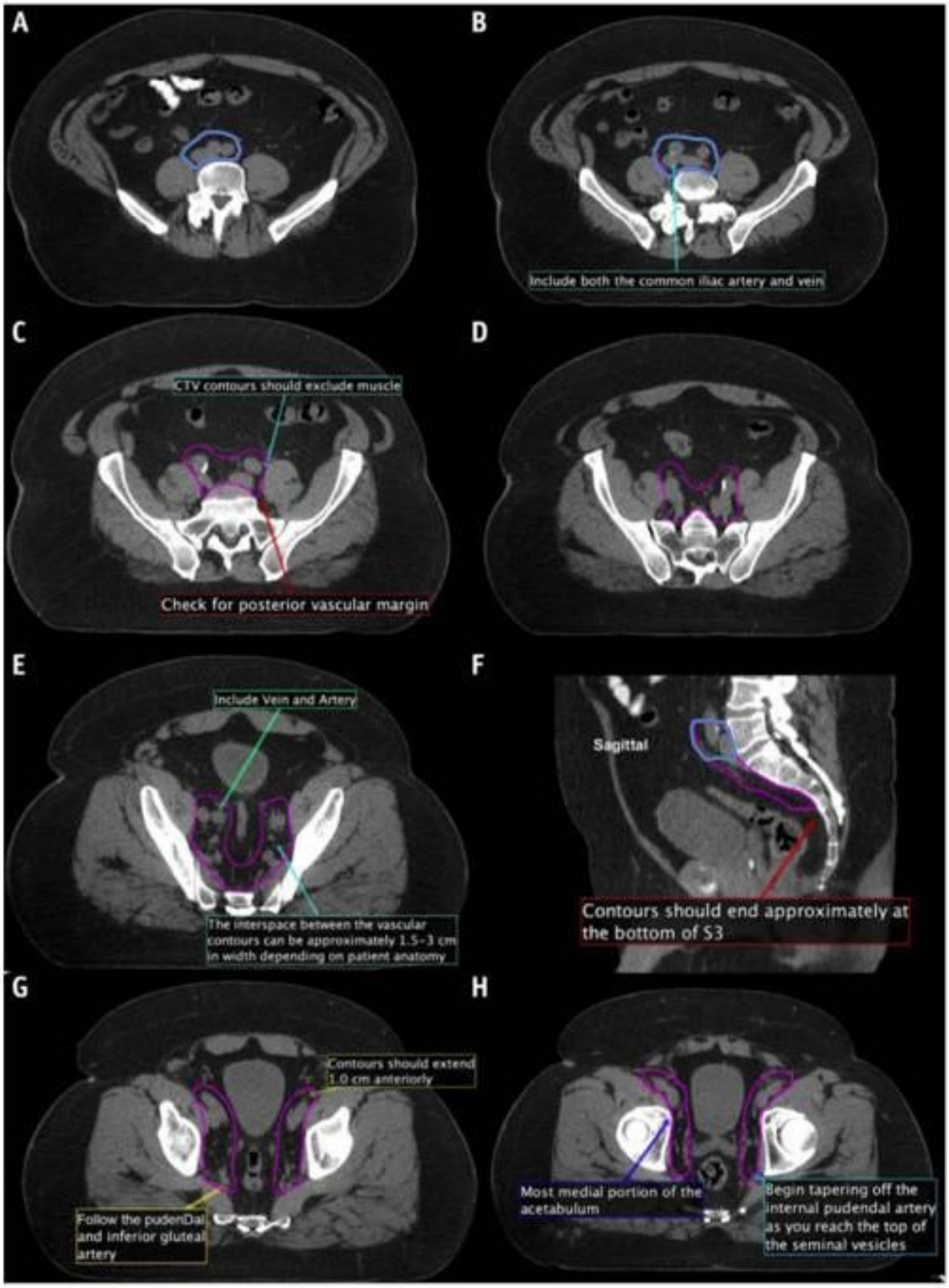
Appendix D: Guideline for elective pelvic lymph node radiotherapy

DAPROCA 10 core group encourages all investigators to have a clear strategy for elective pelvic lymph node irradiation and to adhere to this strategy consistently during the trial. Below are the core groups´ suggestions for a strategy for elective pelvic lymph node radiation. The indication for lymph is based on the risk group of the patient and the available imaging used for detection of lymph node metastases with either conventional imaging (CT and bone scan) or PSMA PET/CT. The below guidelines are divided in two sections based on either conventional imaging or PSMA PET/CT.

The indication for pelvic lymph node radiotherapy are in accordance with the current DAPROCA guidelines and are based on the BRIGANTI 2019 nomogram and the BRIGANTI 2023 nomogram for estimating the risk of lymph node involvement (LNI). Both nomograms are depicted in the figures below illustrating the suggested cut-offs of either 7% or 5% (18,19).

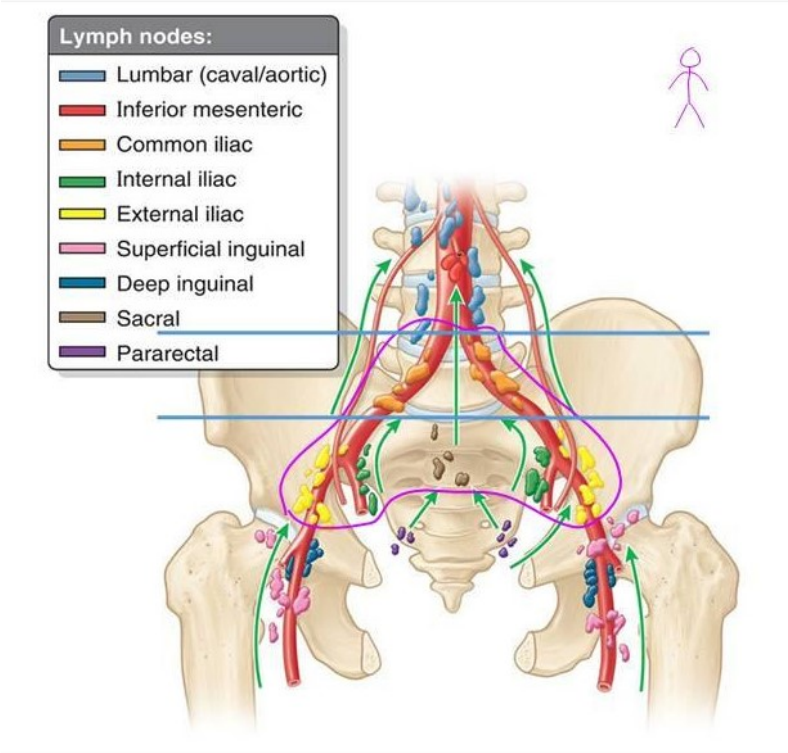
The guideline introduces the term “true pelvis”, which includes the pelvic lymph nodes up to the L5/S1 junction and the “pelvis” which is the “true pelvis” plus the common iliac nodes. The figure below is copied and modified from the study of Lawton et al (74) showing the consensus contours. The “true pelvis” is in cyan and the “pelvis” includes both the cyan and blue volumes.

The “pelvis” with the inclusion of common iliac lymph nodes should only be used if the patient has N1 disease as the common iliac lymph nodes are a secondary drainage area that is rarely involved without lymph node metastases in the “true pelvis”.


A
B
Include both the common iliac artery and vein
C
CTV contours should exclude muscle
Check for posterior vascular margin
D
E
Include Vein and Artery
The interspace between the vascular contours can be approximately 1.5-3 cm in width depending on patient anatomy
F
Sagittal
Contours should end approximately at the bottom of S3
G
Contours should extend 1.0 cm anteriorly
Follow the pudenDal and inferior gluteal artery
H
Most medial portion of the acetabulum
Begin tapering off the internal pudendal artery as you reach the top of the seminal vesicles


i
External Iliac nodes should end approximately as the external iliac/inguinal vessels cross the most medial point of the acetabulum, or enter the inguinal canal on coronal views
j
Coronal
External iliacs terminate at entry to inguinal canal
k
Anteriorly extend approximately 1 cm anterior to the anterior edge of the obturator internus muscle
Posterior edge following the obturator internus muscle
l
m
End the obturator fossa contours when the seminal vesicles join the top of the prostate gland or the disappearence of the fat plane between the obturator internus muscle and the prostate gland, whichever is more superior

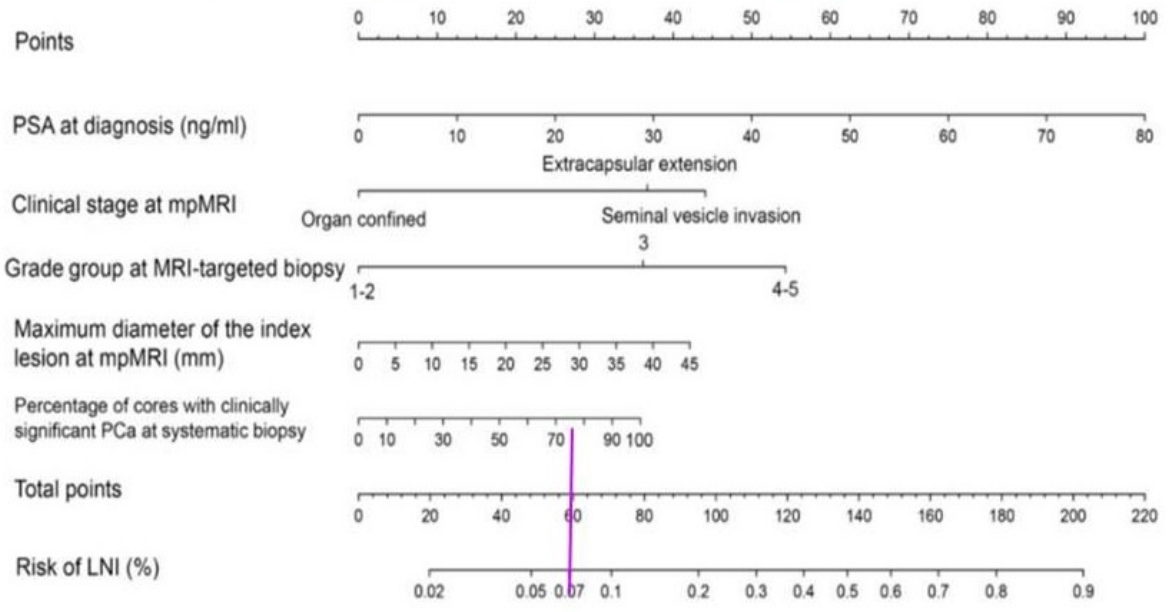
DAPROCA 10 GUIDELINE - CONVENTIONAL IMAGING FOR LN MET



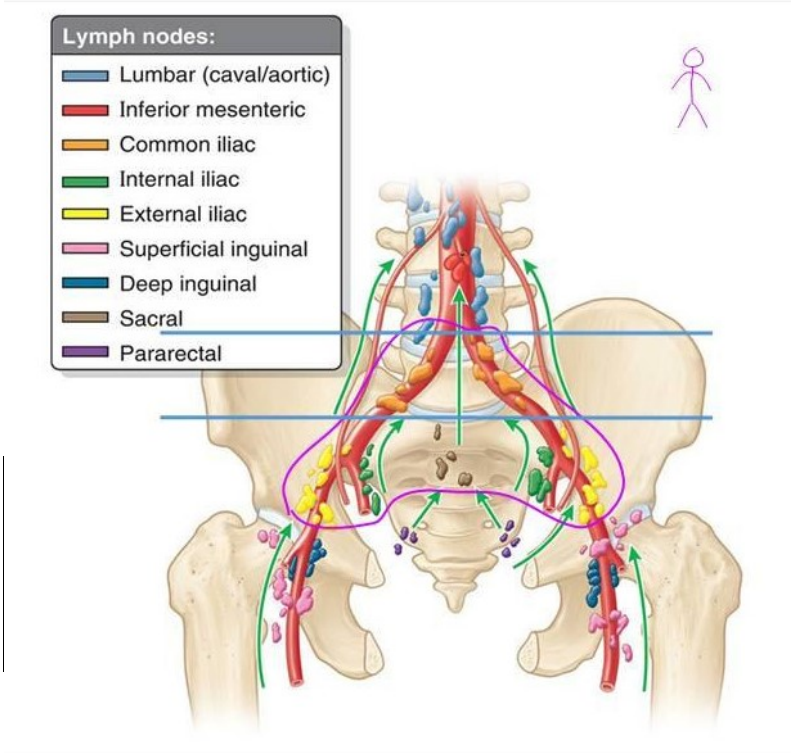
"True pelvis" (sacral, internal iliac, external iliac, and obturator nodes)
- Intermediate risk LNI risk >= 7%
- High risk

Pelvis (including common iliac LN)
- N1 disease

BRIGANTI 2019 nomogram conventional imaging for LN metastases



DAPROCA 10 GUIDELINE - PSMA PET/CT FOR LN MET

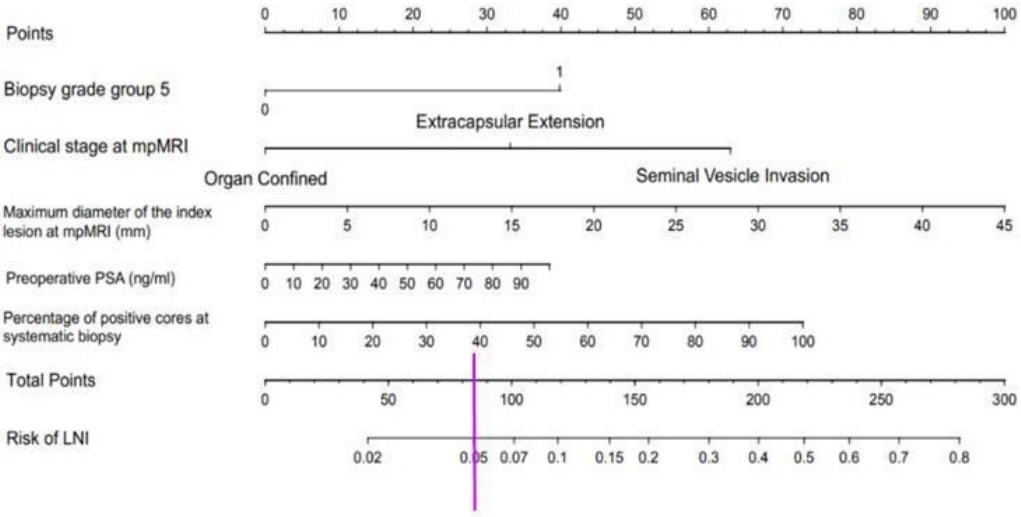


No elective pelvic lymph node target
- Intermediate risk LNI risk < 5%
- High risk LNI risk < 5%

“True pelvis” (sacral, internal iliac, external iliac, and obturator nodes)
- Intermediate risk LNI risk >= 5%
- High risk LNI risk >= 5%

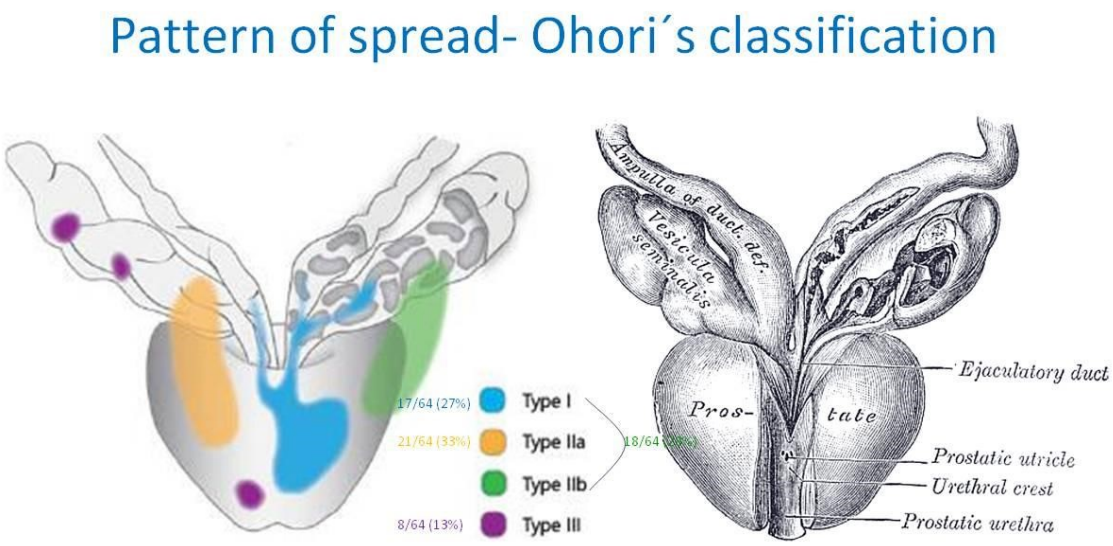
Pelvis (including common iliac LN)
- N1 disease

BRIGANTI 2023 nomogram for patients N0 on PSMA PET/CT



Appendix E: Guideline for seminal vesicle radiotherapy

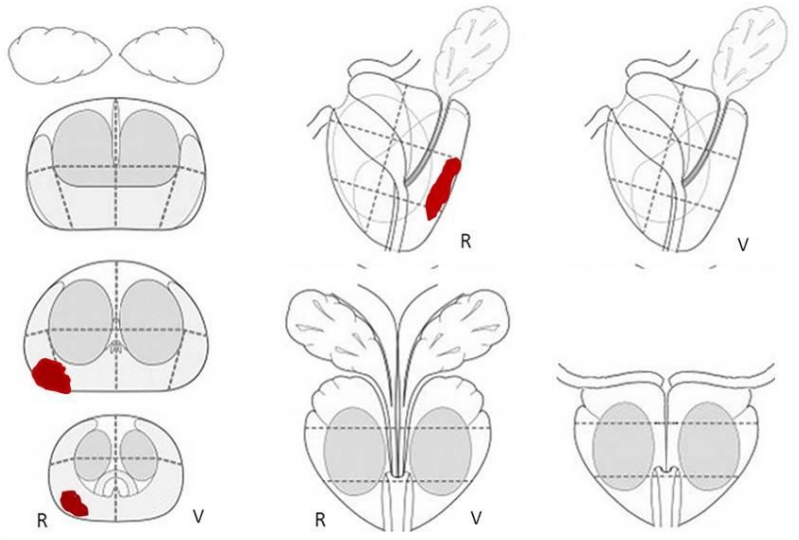
Radiotherapy to the seminal vesicles are being performed quite differently throughout Denmark. The DAPROCA10 core group suggests the below strategy to be used in the trial for consistency and improved outcomes of the trial, where precision of the radiotherapy is a key factor. Imaging of seminal vesicle involvement (SVI) is optimally performed with a combination of multiparametric MRI and PSMA PET/CT and the proposed strategy is dependent on the use of contemporary prostate cancer imaging. SVI rarely occurs without the involvement of the “midbase” of the prostate gland, as the cancer spreads along the ejaculatory ducts or as extraprostatic extension into the seminal vesicles. In a study of prostate cancer specimens, the percentage of seminal vesicle invasion with and without “midbase” invasion was 78% and 0.7%, respectively (93,94).



In an often referred publication from Kestin et al the median length of SVI was 1 cm with a 90% percentile of 2 cm, forming the basis for including the proximal 2 cm of the seminal vesicles as an elective target (95).

Below are three examples illustrating when and how the seminal vesicles are to be included as a target.

No elective irradiation of seminal vesicles

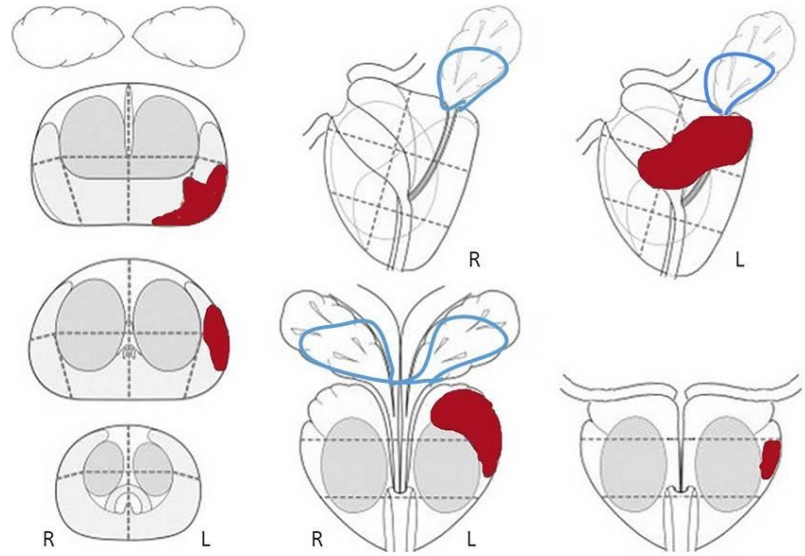


Tumour does not involve base of prostate gland

Little risk of SVI

No elective SV volume

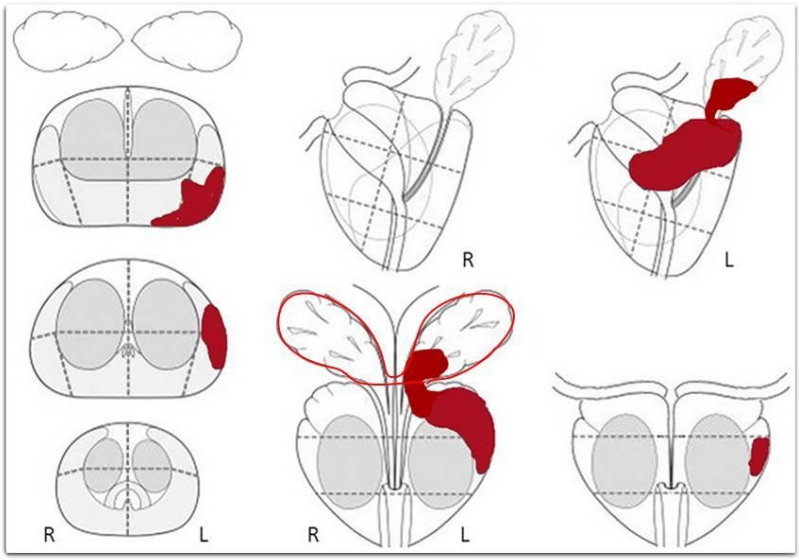
Elective irradiation of seminal vesicles



Tumour involves base of prostate gland

Include proximal 2 cm of seminal vesicles bilaterally as elective target

Irradiation of seminal vesicles



Tumour involves left SV on MRI/PET

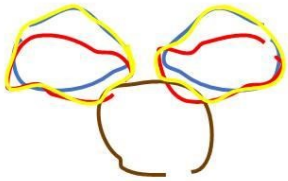
Include GTV of involved seminal vesicle in focal boost volume if randomised for boost

The remaining SV volume included in 50 or 60 Gy volume

Contouring of seminal vesicles

Delineate CTV SV on both planning CT (blue) and MRI (red)

Create ITV SV from the sum of both volumes (yellow) and subtract the part of the ITV SV extending into rectum (brown)



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