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NEW STUDY

A randomized trial of early detection of clinically significant prostate cancer (ProScreen): study design and rationale

Anssi Auvinen[1] · Antti Rannikko[2] · Kimmo Taari[2] · Paula Kujala[3] · Tuomas Mirtti[4] · Anu Kenttämies[5] · Irina Rinta-Kiikka[6] · Terho Lehtimäki[7] · Niku Oksala[8] · Kim Pettersson[9] · Teuvo L. Tammela[10]

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Abstract The current evidence of PSA-based prostate cancer screening shows a reduction in cause-specific mortality, but with substantial overdiagnosis. Recently, new developments in detection of clinically relevant prostate cancer include multiple kallikreins as biomarkers besides PSA, and multiparametric magnetic resonance imaging (mpMRI) for biopsy decision. They offer opportunities for improving the outcomes in screening, particularly reduction in overdiagnosis and higher specificity for potentially lethal cancer. A population-based randomized screening trial will be started, with 67,000 men aged 55–67 years at entry. A quarter of the men will be allocated to the intervention arm, and invited to screening. The control arm will receive no intervention. All men in the screening arm will be offered a serum PSA determination. Those with PSA of 3 ng/ml or higher will have an additional multi-kallikrein panel and those with indications of increased risk of clinically relevant prostate cancer will undergo mpMRI. Men with a malignancy-suspect finding in MRI are referred to targeted biopsies. Screening interval is 6 years for men with baseline PSA < 1.5 ng/ml, 4 years with PSA 1.5–3.0 and 2 years if initial PSA > 3. The main outcome of the trial is prostate cancer mortality, with analysis at 10 and 15 years. The statistical power is sufficient for detecting a 28% reduction at 10 years and 22% at 15 years. The proposed study has the potential to provide the evidence to justify screening as a public health policy if mortality benefit can be sustained with substantially reduced overdiagnosis.

Keywords Prostate neoplasm · Screening · Randomized trial · Mortality

✉ Anssi Auvinen
anssi.auvinen@uta.fi

[1] Faculty of Social Sciences, University of Tampere, Arvo B335, Box 100, 33014 Tampere, Finland

[2] Department of Urology, Faculty of Medicine, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

[3] Fimlab Laboratories, Department of Pathology, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

[4] Department of Pathology, Faculty of Medicine, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

[5] HUS Medical Imaging Center, Helsinki University Hospital, Helsinki, Finland

[6] Department of Radiology, Faculty of Medicine and Life Sciences, Tampere University Hospital, University of Tampere, Tampere, Finland

[7] Fimlab Laboratories, Department of Clinical Chemistry, Faculty of Medicine and Life Sciences, University of Tampere, Tampere, Finland

[8] Department of Surgery, Faculty of Medicine and Life Sciences, Tampere University Hospital, University of Tampere, Tampere, Finland

[9] Division of Biotechnology, Department of Biochemistry, University of Turku, Turku, Finland

[10] Department of Urology, Faculty of Medicine and Life Sciences, Tampere University Hospital, University of Tampere, Tampere, Finland

Introduction

Prostate cancer is one of the key medical and public health challenges at the moment: It is the most common cancer among men in Western countries, and the second most common cause of cancer death in men in Finland and third in Europe [1]. The prostate cancer epidemic is, however, largely iatrogenic, as the increase in incidence is attributable predominantly to increased serum prostate-specific antigen (PSA) testing. A substantial proportion of the cases detected at an asymptomatic stage represent overdiagnosis, as relative survival from localized prostate cancer at 5 years approaches—or in some studies exceeds—100% [2–4] Hence, not all cases benefit from active curative management. Overdiagnosis is defined as detection of disease that would not have caused any harm during a man's lifetime, i.e. unnecessary detection of latent disease of dubious clinical relevance. It involves adverse effects of treatment (e.g. erectile dysfunction and urinary incontinence) without therapeutic benefit to the patient. Overdiagnosis is more extensive in prostate cancer screening than other cancer screening programs—modelling studies have estimated that it amounts to 40% of the screen-detected case [5], or three excess cases per 100 men invited to screening [6].

Screening frequency is an important determinant of overdiagnosis [7]. Etzioni et al. [8] estimated that 27% of overdiagnosis could be reduced by using longer screening intervals in men with low PSA. Overdiagnosis is most common in the oldest age groups, which is one of the reasons why conservative policy should be adopted for men older than 70 years [7, 8]. Comparable results were also found in the Finnish screening trial (FinRSPC) [6].

Screening can potentially offer a means for reducing prostate cancer mortality. The PSA-based European randomised screening trial (ERSPC) showed a 20% reduction in prostate cancer mortality at 13 years of follow-up [9]. The absolute screening effect has increased with follow-up (781 men needed to invite to avert one prostate cancer death at 13 years) and it is comparable to the well-established cancer screening modalities (number needed to screen for preventing a cancer death in the range 800–1000 in mammography screening for breast cancer and fecal occult blood testing for colorectal cancer) [10, 11].

Modelling studies have shown varying estimates of overall quality of life impact and cost-effectiveness for prostate cancer screening [12–14]. The frequent adverse effects have so far tipped the balance against prostate cancer screening, and therefore we will focus on employing the best available means for reducing them.

What is the optimal screening test?

Even though PSA is one of the best cancer biomarkers developed, it has turned out to be insufficient as a stand-alone test for prostate cancer screening, due to low specificity for clinically relevant cancer. The best option for improving performance of PSA as a screening test is to combine it with other biochemical indicators. A panel of four kallikreins (total PSA, free PSA, intact PSA and human kallikrein-related peptidase-2, hK2), known as the 4Kscore has been developed to indicate the probability of an aggressive prostate cancer [15]. In four studies, it reduced the number of biopsies by 25–43%, while detecting 89–97% of GS $\geq$ 7 cases with AUC 0.78–0.84 [15–18]. Yet, it has never been applied as a screening tool in a randomized trial.

The Prostate Health Index (PHI) is another multicomponent biochemical risk indicator (with total, free and pro-PSA) with reasonably similar performance as 4Kscore, but its characteristics have not been equally well documented [19, 20].

Optimizing the diagnostic process for clinically relevant cancer

Major developments have been made with magnetic resonance imaging of the prostate during the past years. An endorectal coil has been replaced by a pelvic coil, and imaging sequences have been substantially improved. Targeted biopsies guided by multiparametric MRI (mpMRI) has been shown to decrease the frequency of biopsied men by 20–54% compared to systematic transrectal ultrasound-guided biopsies, with a substantial reduction in detection of GS < 7 cancer (20–54%). Nevertheless, MRI-guided biopsies retain a very high sensitivity (90–93%) for Gleason 7+ prostate cancer in previously non-biopsied men [21–23] The positive predictive value in such biopsies among men with elevated PSA has ranged 38–66% [22]. The recent PROMIS trial using the latest technique and procedures with 576 men showed a sensitivity of 93%, with a positive predictive value of 51% and a negative predictive value of 89% [23]. Hence, MRI can reduce both the number of biopsied men and the number of cores per man by focusing only lesions visualized through MRI, thought to reveal neoplastic tissue with Gleason pattern 4–5 suggestive of potentially aggressive cancer, but not pattern <4 indicating low-risk disease. Use of directed biopsies has the additional benefit of decreasing biopsy complications. Further, targeting the suspect lesion can decrease the proportion of cancers missed—estimated around 25% for systematic 10–12 core biopsy (mainly in the anterior, apex and midline of the

prostate) [24]. Superior sensitivity for MRI-based targeted biopsy than TRUS-based systematic biopsy for Gleason 7+ cancer has been shown in several studies [21]. Hence, mpMRI complements the biomarkers in screening as the final step in selection of high-risk men for biopsy.

The main objective of the ProScreen trial is to assess the impact of early detection through screening on prostate cancer mortality, when the main adverse effect, i.e. overdiagnosis is minimized using the best potential methods for avoiding it: a kallikrein panel, multiparametric MRI and a flexible screening interval (Fig. 1). Each of the methods has been shown to reduce the detection of Gleason <7 prostate cancer by at least a third, while missing only 10–15% of the more aggressive cases. Their combined effect has not, however, been studied.

The challenge is in maintaining the mortality benefit, i.e. decreasing detection of non-progressive disease without missing the clinically relevant cases. Ideally, a screening regimen specific for aggressive disease would eliminate the need for active surveillance, as it is used for low-risk cancers only. Reducing overdiagnosis is a key to improving the balance of benefits and harms, but reduction in prostate cancer mortality is required to justify screening.

The rationale of the ProScreen trial is to optimize the outcomes by refining the screening process through three layers of risk assessment to identify men at elevated risk of potentially lethal cancer. The early risk stratification stage is assessed in terms of diagnostic accuracy (specificity and sensitivity as well as receiver operating characteristic, ROC for clinically relevant cancer) as an interim end-point. In addition, novel screening methods are evaluated besides those used for decision making and subsequently analysis of effectiveness (mortality effect). The latter analyses are not based on randomization, but observational comparison of alternative tests. This will increase the frequency of referrals, as evaluation of the more experimental methods used as ancillary tests also requires diagnostic assessment of men with negative results in PSA, kallikrein panel and/or mpMRI.

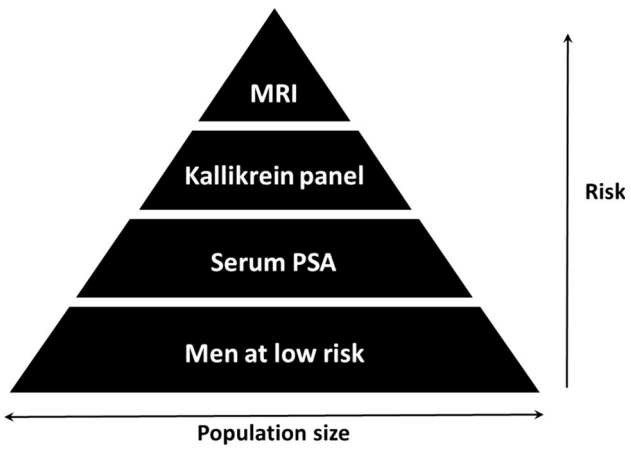

Fig. 1 A schematic representation of the risk stratification algorithm in the ProScreen trial (risk pyramid)

Methods

Trial population

We will identify all 67,000 men aged 55–67 years and residing in Tampere or Helsinki, and randomize them into two trial arms with 1:3 allocation. Men with prevalent prostate cancer will be identified through the Finnish Cancer Registry and excluded (expected number is 200, based on prevalence 0.3% at entry to our previous FinRSPC trial).

Screening procedure

A 30 ml blood sample will be drawn to an EDTA tube, with plasma and serum separated and frozen. The extensive network of >100 local hubs in the region is essential, enabling easy access for all men, as well as efficient sample processing and transportation. The blood and urine will be analysed within 4 weeks of the sample to allow timely screening decision-making based on the risk stratification results. PSA determination will be performed using WHO calibration and continuous quality assurance programs with certified performance.

Additional analyses of biomarkers will be conducted for men with PSA $\geq$ 3 ng/ml (expected number 1520 men in the first round) to determine who are screen-positive. A multi-kallikrein panel will be used to identify men at increased risk of an aggressive prostate cancer (out of those with PSA > 3). They will be regarded as screen-positive and referred to diagnostic examination at the local University Hospital urology clinic. Men with PSA density >0.15 will also be referred to biopsy to improve sensitivity. The expected frequency of screen-positive men referred to MRI is 912 men in the first round (60% of the men with PSA $\geq$ 3).

The screen-positive men will undergo a multiparametric MRI using 3T equipment with 32-channel pelvic phased-array coil. T2-weighted, diffusion-weighted and dynamic contrast-enhanced imaging is employed in accordance with the European Society for Urogenital Radiology guideline ("Appendix") [25]. The findings will be classified according to the Prostate Imaging Reporting and Data System (PIRADS-2), which is a 5-point scale to combine the MRI findings and indicate the likelihood of a significant cancer [26]. MP-MRI scans are evaluated by specialized urologic radiologists with substantial experience in prostate imaging. In centralized training, a sample of cases will be

first reviewed individually, scored, and then reviewed as a group. Further training will be arranged during the trial. To assess inter-observer agreement, a sample of patient scans will re-evaluated in a blinded fashion.

Prostate biopsies are processed in pathology laboratories in Helsinki (HUSLAB) and Tampere (Fimlab Laboratories). Both are accredited testing laboratories according to the standard SFS-EN ISO 15,189:2013. The biopsies are evaluated by experienced uropathologists at both hospitals using standardized procedures [27], with amount of malignant tissue and Gleason pattern evaluated separately for each biopsy core. Standardization and quality control of clinical chemistry, radiology and pathology is ensured before the launch of the trial.

The expected number of screen-detected cases in the first round is 365. A flowchart of the trial with the expected numbers of men is shown in Fig. 2. The expected numbers were obtained from previous research (the Finnish results of the ERSPC trial for participation, PSA distribution [9, 28], Assel et al. (submitted) for 4Kscore distribution, and MRI results [21–23]).

Buffy coat will also be obtained for DNA extraction from all participants. Urine samples are obtained from all men in Tampere (a quarter of the population), as well as all screen-positive men referred to MRI for development of new markers of risk and prognosis.

Follow-up

Information on prostate cancer cases diagnosed in the entire study population will be obtained from the Finnish Cancer Registry. Detailed clinical information on Gleason score, PSA at diagnosis, treatment and other features will be abstracted from the medical records at each hospital. Follow-up for vital status and emigration is through Population Registry, and causes of death will be obtained from Statistics Finland. We have previously evaluated the accuracy of the official causes of death for prostate cancer and shown an excellent agreement with a blinded expert panel [28, 29].

The main outcome of the trial is mortality from prostate cancer. The analysis of the main end-point is based on the intention to screen principle, i.e. comparing groups defined by the random allocation, regardless of compliance. Based on the age-specific Finnish population rates, at 10 years of follow-up (allowing for mortality from other causes estimated from the current age-specific lifetables), we expect 475,000 person-years with 222 prostate cancer deaths in the control arm. Using these figures, the minimal detectable difference ($\alpha = 0.05$ two-sided and $1 - \beta = 0.8$) between the arms is 28% at 10 years ($RR \leq 0.72$). At 15 years, the predicted number of prostate cancer deaths in the control arm is 451, with sufficient statistical power to show a 22% reduction.

For the diagnostic accuracy studies of the main screening tests and the novel methods such as eNose and urine kallikreins, a sample size of 10,638 is needed to demonstrate a sensitivity of 0.9 with 5% margin of uncertainty, assuming binary results and the prevalence of clinically relevant prostate cancer of 1.3%. Not all men will be biopsied for diagnostic confirmation, but the analysis will rely on incidence method, with the true disease status being revealed with sufficient follow-up, say 5 years [30]. For ROC estimation, the expected number of

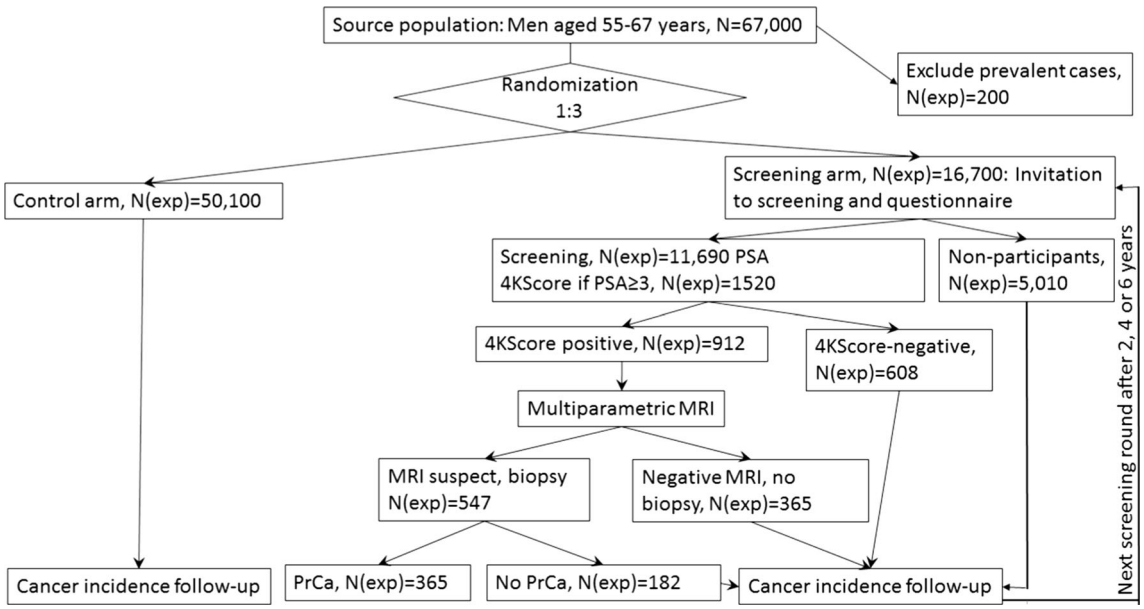

Fig. 2 A flow chart of the ProScreen trial. N(exp) stands for expected number

screened men with assumed 1.3% prevalence of clinically relevant cancer would provide roughly 9% confidence interval width for diagnostically relevant ROC values (0.7–0.8).

The recruitment will commence in 2018 (trial year 1). The target population will be identified and randomized at Population Registry, with invitations for the screening arm sent from early 2018. The first screening round will be completed in 2019 and screening-positive men will be re-invited after 2 years (2020–2021), and for the second time in 2022–23 (Table 1). For the screen-negative men, the second screening round will take place after this (4-year interval 2022–2023, 6-year 2024–2025), overlapping with the subsequent screening rounds for the screen-positive men at each round.

A data monitoring committee will be established, with the main adverse outcome defined as incidence of advanced prostate to ensure that a large fraction of cases are not missed in the intervention arm. The trial can be stopped early for benefit or harm, if evidence for difference between the arms is obtained. For assessment of harm from the intervention, biopsy and treatment complications will be analysed, as well as incidence of advanced cancer (as an indicator of cancers missed by screening) and Gleason <7 cancer (as indicator of overdiagnosis) by arm are performed annually for the data monitoring committee. Monitoring of the main end-point (prostate cancer mortality) is carried out by an external committee. Interim analyses are performed at 5 and 8 years in accordance with sequential analysis rules (total alpha spending 0.005 of the two interim analyses according O'Brien-Fleming).

Discussion

The trial investigates whether new developments in the diagnosis of clinically relevant prostate cancer, magnetic resonance imaging and combination of several kallikreins as biomarkers, can be translated into a screening program that would achieve reduction in prostate cancer mortality, while avoiding the major adverse effect of overdiagnosis hampering the PSA-based efforts. The large-scale, population-based effectiveness design ensures that the evidence obtained will be readily applicable in real-world clinical and public health decision-making.

The advantages of the study include a population-based design, with the target population identified from the comprehensive population center; a Zelen-type randomization further enhances the generalizability, as men in the control arm will not need to be contacted for inclusion in the follow-up.

The selection of the PSA cut-off requires consideration of the relative importance of sensitivity and specificity. PSA levels increase with age and strongly predict lethal prostate cancer well before clinical stage of the disease [31, 32]. An aggressive screening policy would use a lower threshold, with lower specificity and higher sensitivity. This would likely maximize the mortality reduction, but also increase the cost and adverse effects. PSA threshold of 3 ng/ml was used in the ERSPC trial [9], while 4 ng/ml was used in the PLCO [33].

Major challenges for the trial include maintaining a high adherence. In the earlier Finnish randomized prostate cancer screening trial, participation was 67%, and the ProScreen trial is expected to achieve similar compliance. Another concern is the extent of opportunistic PSA testing in the population. In the previous trial, PSA testing rates were high in the control arm particularly in the early 2000s [34]. However, prostate cancer incidence rates declined by a fifth from the peak levels in Finland (as in several other countries) during the past decade, likely indicating decrease in the opportunistic screening [35]. A continuing decline in population mortality rates may also decrease the predicted power of the trial. As for achieving a mortality impact, a delicate balance needs to be achieved in treatment, avoiding both overtreatment of non-aggressive cases to avoid adverse effects, while providing effective management of potentially progressive disease for reducing mortality. As prostate cancer has only a minor contribution to overall mortality (3% of all deaths in men), no reduction in overall mortality can be expected.

The target effect size of a reduction in prostate cancer mortality by approximately a quarter is ambitious. Reducing overdiagnosis and avoiding detection of cases of low malignancy will inevitably decrease the mortality impact to some extent. If both kallikrein panel and MRI

Table 1 Schedule of the study

	Trial years 1–2	Years 3–4	Years 5–6	Years 7–8	Years 9–10
All subjects	Recruitment				
All participants	1st screening				
Men with PSA > 3		2nd screen	3rd screen	4th screen	5th screen
Men with PSA 1.5–3			2nd screen		3rd screen
Men with PSA < 1.5				2nd screen	

have sensitivity of 90%, the reduction in detection of clinically relevant cancer may be 20% ($0.9 \times 0.9 = 0.81$, compared with PSA alone), with a corresponding loss of mortality benefit. Yet, using a 2-year screening interval in men with PSA 3 ng/ml or higher will likely counterbalance this and most aggressive cases will be detected at subsequent rounds, optimally still at organ-confined stage.

As a pragmatic trial, any developments in prostate cancer diagnostics will be implemented (to both trial arms), as they are adopted into clinical practice. For instance, MRI protocols are being refined and biparametric imaging may simplify the procedure and reduce the costs [36].

A randomized trial provides the most scientifically rigorous evidence, and our previous experience shows that it can yield material for extensive research utilization, spanning from molecular biology to biochemistry and cancer genetics, as well as clinical and public health research. Besides the pragmatic effectiveness study, the screening trial will be utilized for developing new methods for detecting early clinically relevant prostate cancer. As a novel approach, we will evaluate a sensitive artificial olfaction system ('eNose') [37, 38]. The method is based on ion mobility spectrometry, a differential mobility spectrometry and a field-asymmetric ion mobility spectrometry (ENVI-AMC, Environics Inc, Mikkeli, Finland; Owlstone Lonestar, Owlstone Nanotech Ltd, Cambridge, UK; Juno, Chemring Ltd, USA), capable of detecting a vast range of volatile organic compounds at particle per million-trillion (ppm-ppt) concentrations in a 5 ml sample. A semi-supervised machine learning algorithm is developed to recognize a typical multidimensional pattern of volatile compounds (mainly amines) characterizing prostate cancer. The current setup has a substantially improved sensitivity, while already the previous generation (with an order of magnitude lower detection capacity) showed AUC of 0.77, with sensitivity 0.78 and specificity of 0.67 in distinguishing prostate cancer patients from cancer-free subjects [37, 38].

Kallikrein glycovariants have shown promise as novel methods for detection of early, clinically relevant PrCa, Lectin-assisted target cancer-associated changes in the carbohydrate moiety at Asn-45 of PSA. The rationale is based on lectins (carbohydrate binding proteins having the unique specificities for glycan structures), which are covalently coupled to fluorescent nanoparticles and used to specifically detect cancer associated glycans on PSA. From a library of lectin nanoparticles established, the most promising lectins will be identified to preferentially detect PSA from men with PrCa, whereas urine or seminal plasma derived PSA of healthy individuals remains non-reactive. Early results demonstrate improved cancer specificity (improved discrimination of high grade PrCa from biopsy negative and Gleason score 6 patients) in urine using a plant lectin nanoparticle-aided PSA assay [39]. Observational studies of diagnostic accuracy of other tests will also be incorporated, though referral will be based on the primary tests.

In conclusion, we propose a population-based screening trial combining serum PSA and a multi-kallikrein panel as biomarkers, with MRI-imaging to guide targeted biopsies. A three-tiered risk stratification protocol is aimed at minimizing overdetection, while retaining most of the mortality benefit. The final analysis of the main end-point, prostate cancer mortality, will be at 15 years of follow-up. Side studies of novel tests for identifying clinically relevant disease will be carried out and a sample repository established for etiologic and prognostic research.

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Appendix: MRI protocol

The patient preparation includes the evacuation of the rectum and administration of antispasmolytic.

The mpMRI consists of T2WI, DWI with ADC maps and DCE performed by 3T scanners, using a protocol in accordance with PI-RADS v2 published by the American College of Radiology in 2015. Slice thickness is 3 mm for T2WI and DWI, and 4 mm for DCE. The T2WI are obtained with turbo-spin-echo (TSE) sequences covering the whole prostate gland and the seminal vesicles. The DWI utilize b-values up to 800 for calculating ADC-maps and b-values up to 2000 for tumor detection. High b-value images are obtained by calculating those images by extrapolation up to b1400 from the acquired lower b-value data. Pre-contrast enhancement T1W images with fat suppression are obtained to detect haemorrhages. The DCE imaging, T1WI is performed with intravenous administration of gadolinium-based contrast agent with the temporal resolution of 7 s and total observation time 2 min 30 s to detect possible early enhancement. The DCE data are visually assessed and further analyzed by using DynaCad software to produce signal intensity curves of each lesion detected.

All uroradiologists who read the prostate MRI scans have attended the European Society of Uroradiology two-day Prostate MRI course at least once, and most of them have more than 5 years of experience in interpreting prostate MRIs. Currently, each of them read at least 300 prostate MRIs annually.

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