1 SUMMARY

Although most of the prostate cancers (PCas) are currently being diagnosed at early stage, at present, 30% of men are diagnosed with primarily metastatic disease. The need for better diagnostic methods is, therefore, warranted. Recent studies have shown that an alternative pathway using multiparametric (mpMRI) or biparametric (bpMRI) magnetic resonance imaging as a triage test reduces unnecessary biopsies, decreases the detection of clinically non-significant PCa (nonSPCa), and improves the detection of clinically significant PCa (SPCa) [2,3]. In addition, based on these trials, also EAU guideline was updated to recommend that all men should undergo pre-biopsy mpMRI. However, shortcoming of the approach is the recommendation to biopsy all men post-MRI even if there is no lesion seen in MRI, ie. risk of PCa is very low. Therefore, the primary objective of this randomised controlled trial is to compare if there is a difference between significant cancer detection rate in men undergoing prostate biopsies after MRI scan when compared to men undergoing prostate biopsies when MRI is followed with a shared decision-making regarding need of prostate biopsy based on risk estimation.

The trial will enrol 600 patients from four hostiptal disctricts: Varsinais-Suomi, Satakunta, Pirkanmaa and Keski-Suomi. Key inclusion criteria are suspicion of prostate cancer based on elevated PSA and/or abnormal digital rectal examination. Men with previous PCa diagnosis and contraindications for MRI are excluded. The primary outcome measure is the comparison of the proportion of men with CSPCa (Gleason 4+3 prostate cancer or higher) between the control and intervention arms at baseline.

Using PSA as strata, eligible men are randomised 1:1 in two groups. After randomisation MRI examination is performed and interpreted by one experienced uroradiologist using Likert and PI-RADS2.1 classifications. In control arm in all men prostate biopsies are performed after MRI whereas in intervention arm prostate biopsies are performed only after a shared decision-making between urologist and the patient and the discussion is based on risk estimation. Men with negative biopsies or with no biopsies performed are all assigned for five year follow-up with semiannual PSA. Long-term follow-up based on health records and national registries is performed for additional 15 years for all patients.

All mandatory authorizations will be obtained before the beginning of the study. The study will start in October 2019. Recruitment is estimated to be completed by the end of year 2021. The prospective follow-up will stop latest 2026. After this a retrospective follow-up will be initiated ending at 2039.

The study will be financed by Finnish Governmental Special Funding (In Finnish: ’Erityisvaltionosuus, EVO’) and public foundations supporting cancer research with academic research grants.

2 INTRODUCTION

The incidence of prostate cancer (PCa) continues to increase worldwide, mainly as a result of population aging, better diagnostic methods and potentially due to real increase in incidence. Although most of the prostate cancers are currently being diagnosed at early stage, at present 30% of men are diagnosed with primarily metastatic disease (Seikkula ref PMID 28406044). In addition, PCa continues to be the second leading cause of cancer death in men (4) calling for better diagnostic methods. Traditionally the diagnosis of prostate cancer is mostly based on the result of systematic transrectal ultrasonography (TRUS) guided biopsies. However, the accuracy of TRUS guided biopsies for prostate cancer detection is limited since in more than 85% of cases the cancer is multifocal and intermingled with normal tissue and about 30% of tumours are localized in central and transitional zone (10, 11). In addition, transrectal biopsies carries a risk of haemorrhagic and infectious complications (9). Therefore, more accurate non-invasive modalities are needed to improve the diagnostic pathway.

Two recent prospective trials have shown that an alternative pathway using multiparametric magnetic resonance imaging (mpMRI) with dynamic contrast enhancement as a triage test reduces unnecessary biopsies, decreases the detection of clinically non-significant PCa (non-SPCa), and improves the detection of clinically significant PCa (SPCa) [2,3]. In addition, based on these two trials, also EAU guideline was updated to recommend that all men should undergo pre-biopsy mpMRI in all setting, not only after negative primary systematic biopsies as previous recommendation stated. The shortcomings of this approach are the costs and the resources. Our previous studies (IMPROD, multi-IMPROD) have shown that biparametric MRI (bpMRI) has high diagnostic accuracy in pre-biopsy setting and this notion is supported by few other studies such as the BIDOC-trial and the trial by Barents et al. The advantages of bpMRI over mpMRI are the diminished costs and resources since leaving out contrast media decreases the acquisition time and makes the scanning non-invasive. Although bpMRI has meny documented advantages, still, having all men undergoing pre-biopsy MRI is a major challenge in economical perspective and may lead to overdiagnosis.

To address the issue, one should be able to use MRI to select men not needing to undergo biopsies at all. Although both mp- and bpMRI alone can rule clinically significant prostate cancer in high certainty, according to multi-IMPROD trial, 5-7% of men with negative MRI are diagnosed with SPCa in prostate biopsies. To improve this outcome, both the BIDOC- and multi-IMPROD-trials have demonstrated that, combining MRI findings with other clinical variables improves PCa risk estimation (ref). In addition to clinical variables, in modern clinical

practice, also the opinion, co-morbidities, life-expectancy and general expectations of the patient should be taken into an account. Especially, as it is known that prostate biopsies are uncomfortable, and they are associated with a significant risk of severe complications. Therefore, the concept of the study is to generate a risk calculator, based on MRI and clinical variables describing individual patient's risk of having SPCa and this risk-estimation is used as a basis for discussion of the benefits and potential harms of proceeding with the prostate biopsy.

The objective of this prospective, randomised, controlled trial is to compare if there is a difference between significant cancer detection rate in men undergoing prostate biopsies post-MRI and men undergoing prostate biopsies post-MRI only after a shared decision based on risk estimation

3 OBJECTIVES AND PURPOSE

3.1 Primary objective

i) To compare if there is a difference between significant cancer detection rate in men undergoing prostate biopsies after post-MRI and men undergoing prostate biopsies post-MRI only after a shared decision based on individualised risk estimation

3.2 Secondary objectives

i) To compare the detection rate of non-SPCa between the two study groups.

ii) To compare the detection rate if SPca during the five year of follow-up between the two study groups

iii) To study and compare anxiety related to the prostate cancer diagnosis pathway between the two study groups

4 STUDY DESIGN

This is a prospective, randomised, controlled multicenter trial to compare if there is a difference between significant cancer detection rate in men undergoing prostate biopsies after MRI and men undergoing prostate biopsies post-MRI only after a shared decision based on individualized risk estimation.

5 OUTCOME MEASURES

5.1 Primary outcome measure

i) The proportion of men with CSPCa (Gleason 4+3 prostate cancer or higher) in the control and intervention arms after primary diagnostic pathway

5.2 Secondary outcome measures

i) The proportion of men with non-CSPCa (Gleason 3+4 prostate cancer or lower) in the control and intervention arms after primary diagnostic pathway

ii) The proportion of men with CSPCa (Gleason 4+3 prostate cancer or higher) in the control and intervention arms during the five years of follow-up

iii) Anxiety at six and 12 months

6 STUDY PROCEDURES

Study design is depicted in Appendix 1.

6.1 Pre-screening (visit 0)

After patient referral to participating centres, all patients are evaluated for inclusion and exclusion criteria. If eligible, the patient will receive an information sheet of the study, the information sheet of shared decision-making process, and the time for the screening visit.

6.2 Screening visit (visit 1)

During the screening visit at the urology out-patient clinic the study design is discussed again in detail. If willing to participate, patient will sign the informed consent. After consenting, patients will complete baseline questionnaires, and baseline blood and urine samples are taken.

6.3 MRI scan (visit 2)

MRI scan is performed according the guidelines in each centre. However, for study related requirements please refer to chapter 8.1.

6.4 Randomisation

Randomisation is performed before the TRUS-visit. Patients are randomised into two arms: the control arm, and the intervention arm. Randomisation will be stratified by baseline PSA: <4 ng / mL, 4-9.9 ng / mL, ≥10 ng / mL.

6.5 TRUS-visit (visit 3)

The visit follows a protocol used in normal outpatient clinic. MRI results are discussed with the patient. In the control arm all men will undergo TRUS-biopsies. In the intervention arm the probability of SPCa is estimated using the risk calculator. Based on risk calculation and the information sheet of shared decision, potential benefits and harms of a prostate biopsy are discussed and a shared decision is made between the urologist and the patient whether to perform the biopsies.

6.6 Biopsy results (visit 4)

According to clinical guidelines in each centre, either a telephone conference or a visit, patient is contacted to discuss the results of the biopsies. If biopsies were not taken, patients are informed about follow-up procedures.

6.7 Treatment

If diagnosed with prostate cancer, the patient and the treating urologist will decide the treatment modality according to local, national and international guidelines.

6.8 Follow-up

6.8.1 Men with benign biopsies or no biopsies performed

PSA is measured according to local guidelines in each centre but should be performed at least as follows:

Years 1-2: every six months

Years 3-5: every 12 months

Thereafter, follow-up is performed according to clinical guidelines in every centre.

6.8.2 Trigger for new intervention

If suspicion of Pca persists after initial benign biopsies or in men with no biopsies taken, the decision to perform biopsies and/or MRI is according to local guidelines in each centre and/ or treating urologist. However, if no such suspicion, new intervention (discussion and consideration of MRI and/ or biopsies), should be performed at least as follows:

1. PSA increases over 20
2. PSA is doubled during the follow-up

6.8.3 Men with malignant biopsies

Men with malignant biopsies are treated according to clinical guidelines in every centre and followed up until biochemical relapse, metastatic disease, or death.

6.8.4 Long-term follow-up

A long-term follow-up of all patients will be performed from medical charts, Finnish national registries and if needed, contacting the patient, up to 20 years in order to have a comprehensive data concerning incident prostate cancer in men without a diagnosis of prostate cancer and clinical end points (biochemical relapse, metastasis, death) in men with diagnosed prostate cancer.

7 PATIENT SELECTION

7.1 Source population

All patients with clinical suspicion of prostate cancer living in the Hospital Districts of Southwest Finland, Satakunta, Keski-Suomi, and Pirkanmaa are potentially eligible.

7.2 Number of patients

The study will enrol 300 patients in two groups. Potentially eligible patients include all patients referred to Turku University Hospital, Tampre University Hospital, Satakunta central hospital, Keski-Suomi central hospital because of clinical suspicion of prostate cancer. There are approx. 1000 patients diagnosed with prostate cancer in each year in these regions and at least twice as much biopsies taken due to suspicion of prostate cancer.

7.3 Inclusion criteria

- Age: 18 years or older
- Language spoken: Finnish
- Clinical suspicion of prostate cancer, based on: serum level of PSA from 2,5 ng/ml to 20 ng/ml and/or abnormal digital rectal examination according to the referral physician
- Mental status: Patients must be able to understand the meaning of the study
- Informed consent: The patient must sign the appropriate Ethics Committee (EC) approved informed consent documents in the presence of the designated staff

7.4 Exclusion criteria

- previous diagnosis of prostate cancer
- any contraindications for MRI
- any other conditions that might compromise patient’s safety, based on the clinical judgment of the responsible urologist
- bilateral hip prosthesis?

8 STUDY INSTRUMENTS

8.1 MRI

Patient scheduled for the MRI examination will receive natriumpikosulphate drops (Laxoberon, Boehringer Ingelheim GmbH) and a Bisacodyl enema (Toilax, Orion Pharma Ltd) for bowel preparation. Prostate MRI examinations prostate will be performed using a 1.5T or 3T MR scanner. Body array coils will be used for image data acquisition. No endorectal coil will be used. Glucagon (0.2 mg - 0.5 mg, GlucaGen, Novo Nordisk A/S) will be injected subcutaneously into lower abdomen immediately prior to the beginning of the MR imaging examination to reduce peristalsis as a part of the normal clinical routine. T2-weighted anatomic imaging will be performed in axial and sagittal plane. Single-shot spin-echo echo-planar imaging will be used for DWI. The total scan time will be approximately fifteen minutes.

8.1.1 PI-RADS v2.0 and Likert scores

MRI will be interpreted using a Likert scoring system follows: 1, significant cancer is highly unlikely to be present; 2, significant cancer is unlikely to be present; 3, significant cancer is equivocal; 4, significant cancer is likely to be present; 5, significant cancer is highly likely to be present. The calculator and clinical judgement are based on Likert scoring system. An additional classification of MRI lesions is performed using modified PI-RADS2.1 system.

8.1.2 MRI reporting

A standardised form to report the MRI is used (Appendix 2). All MRI images will be interpreted by one experienced radiologist to ensure integrity of the reporting. Also, a later analysis of inter-reader variability is performed.

8.1.3 Time intervals

To evaluate the time elapsed during the different steps of MRI protocol a timer is given to radiologists performing the MRI interpretation and reporting, and to nurses performing the MRI. The time intervals to be recorded:

MRI protocol

1. Preparation of the patient: interval between patient coming to MRI unit to start of the MRI
2. MRI acquisition: interval between start and stop of MRI
3. Post MRI preparation: interval between stop of MRI to patient leaving the unit

MRI interpretation

1. The total time elapsed to perform the interpretation and generating the report.

8.2 TRUS and prostate biopsies

The time period between the MRI examination and TRUS biopsy will be a maximum of 4 weeks. Prophylactic antibiotic treatment is given according to institutional guidelines, and the regimen used is recorded. Systematic TRUS-guided 12-core biopsies are performed and if suspicious MRI-lesions are present, targeted biopsies are performed. Targeting is performed either with cognitive- or MRI-fusion according to clinical guidelines in each centre. The maximum of two cores will be taken from each MRI suspicious lesion. If more than two suspicions lesions are observed only two of most suspicious ones are targeted. Therefore, four targeted biopsies at maximum are performed. A post-hoc analysis on inter-operator variability will be performed.

Control arm.
In men with Likert scores of 1-2, TRUS guided systematic biopsies are performed. In men with Likert 3-5 score, in addition to systematic biopsies, two targeted biopsies are taken from each lesion (up to two lesions).

Intervention arm.
According to shared decision-making by the treating urologist and the patient biopsies are performed. If biopsies are to be performed, in men with likert scores of 1-2, TRUS guided systematic biopsies are performed and in men with Likert 3-5 score lesions systematic biopsies are performed and two targeted biopsies are taken from each lesion (up to two lesions). If biopsies are not performed, men are referred for a PSA follow-up.

8.3 The risk estimation

The calculator is constructed as previously described (Ankerst Eur URol 2018). In brief, a multinomial logistic model will be created to estimate risks of SPCa versus nonSPCa with predictors MRI risk estimation (5-tiered Likert scale), age, PSA (logarithmically transformed), prostate volume, and prior negative biopsy history. The calculator will provide an *individualized* risk estimation of detecting clinically significant PCa in prostate biopsies.

8.4 Description of shared decision

8.4.1 Information sheet

All consented patients will be provided an information sheet about the concept of shared decision. The sheet will describe the biopsy pathway and the risks and benefits related to the biopsies. Also, the risk calculator and its usefulness the rule out significant prostate cancer is described. At the end of the sheet there will be questions related to patient's values of life, especially related to risk of prostate cancer, its treatment, and treatment related side effects. (Appendix 3)

8.4.2 Execution of shared decision at the TRUS-visit (visit 3)

If the patient is randomized to the intervention arm, the information sheet is used to aid the discussion. The risk of clinically significant cancer is calculated and a shared decision with the patient whether to perform biopsies or not is made.

8.4.3 Informing the investigators

In addition to the details of the protocol and execution of the trial, the concept of shared decision-making is discussed with all the investigators during the investigator meeting before the start of the trial. Also the concept of the calculator is discussed and the use of calculator is demonstrated.

8.5 Laboratory evaluation

As a part of routine clinical practice blood tests including serum PSA, free-to-total PSA ratio, standard blood counts, S-AFOS, S-Ca, and serum testosterone are collected.

8.6 Serum and urine biomarkers

Selected biomarkers will be analysed from the anticoagulated EDTA plasma (10 ml) and urine (min. 10 ml). The blood and urine are drawn before the TRUS-visit. Patients give their written consent to the sampling.

8.7 Histopathologic evaluation of tissue samples

All histopathological biopsies were reported separately (core length, cancer length, Gleason grade) at each centre by expert pathologists, each with at least five years of experience in genitourinary pathology at the beginning of the trial, using the 2014 International Society of Urological Pathology Modified Gleason Grading System [20]. The biopsy specimen are analysed so that pathologists are aware that patients are part of the study.

However, they are not aware of the exact details of the study protocol, and they are blinded to the sequence of individual biopsy cores.

8.7.1 Definition of overall Gleason grade and clinically significant prostate cancer

CSPCa is defined as Gleason 4+3 or higher in overall Gleason grade which is defined for each patient as the combination of the most frequent Gleason grade and the highest Gleason grade.

8.8 Questionnaires

8.8.1 Prostate cancer related anxiety

Prostate cancer related anxiety is measured with Memorial Anxiety Score for Prostate Cancer anxiety score (MAX-PC).
The questionnaire will be collected at baseline, at six, and 12 months.

8.8.2 Prostate cancer specific quality of life

The quality of life will be measured by the EPIC-26 questionnaire, which is translated and cross-culturally validated in Finnish. It consists of 26 questions which are calculated either as a total score or as five different domain scores; obstructive/ irritative urinary symptoms, incontinence, bowel function, sexual function, and hormonal function. All subscales and the total score are graded from 0 to 100, zero score denoting the worst and 100 the best functional score.
The questionnaire will be collected at baseline, at six, and 12 months.

8.8.3 Health-related quality of life

The health-related quality of life is measured by SF-36 at baseline, six, and 12 months.

9 ADVERSE EVENTS

9.1 MRI related adverse events

Since anatomical MRI and DWI are not based on ionizing radiation, the risk for adverse events in properly selected patients is considered minimal if any. Claustrofobic patients will be excluded from the study. Commonly no side-effects are associated with administration of Glucagon (0.2 mg - 0.5 mg, GlucaGen, Novo Nordisk A/S) but it is recommended for patients to eat (sugar containing food) after MRI examination to prevent mild nausea. Commonly no side-effects or only mild side-effects are associated with taking of natriumpikosulphate drops (Laxoberon, Boehringer Ingelheim GmbH) or Bisacodyl enema (Toilax, Orion Pharma Ltd) for bowel preparation but it is recommended for patients to maintain their water balance with increased water intake. No MRI contrast agents will be given to the patients.

The type and the severity of the adverse events will be defined during the MRI-visit by using the CTCAE4.0 classification.

9.2 TRUS and biopsy related adverse events

TRUS guided biopsies are associated with risk of complications, the most important being serious infections (0.5%) and bleeding (4%) complications.

Adverse events related to TRUS and prostate biopsies are recorded for 14 days after the biopsies. The type and the severity of the complication are defined and recorded. The severity will be defined by using the Clavien-Dindo classification.

10 ETHICS

10.1 Ethical considerations

The study will be conducted in compliance with the current revision of Declaration of Helsinki guiding physicians and medical research involving human subjects (64th WMA General Assembly, Fortaleza, Brazil, October 2013).

10.2 Ethical Review

Prior to commencement of this investigation, the study protocol, patient information sheet and informed consent form will be submitted for approval to ethics committee of the Hospital District of Southwest Finland. The Principal Investigator (PI) is responsible for obtaining approval of the ethics committee for the study protocol including its appendices. The PI shall file all correspondence with the ethics committee in the Investigator`s Study File.

10.3 Potential risks and benefits to study subjects

The risks for the patients inflicted by participation in study are deemed minimal. Anatomical MRI and DWI are considered as safe techniques. TRUS guided biopsies potentially pose patients to serious infections (0.5 %) and bleeding (4%) complications. However, in normal clinical practice every man with suspicion of prostate cancer undergoes TRUS guided biopsies. Since it is estimate that in intervention arm, 35% of men will avoid biopsies, in the respect of the whole cohort, these complications will occur seldom than in normal clinical practice. There is robust scientific evidence that the risk of PCa can be accurately estimated based on individual MRI and clinical characteristics and therefore we estimate that potential risks related to the risk calculation and shared-decision making are minimal.

11 DATA HANDLING AND ANALYSIS

11.1 RedCap database

All survey and clinical data are collected using electric forms, which are located in electronic data capture tool software hosted at University of Turku (RedCap, University of Vanderbilt, Nashville, Tennessee, URL: https://projectredcap.org). For identification, the patient initials and randomization number are used.

11.2 Qualitative analysis of MRI data

The prostate gland will be divided according to zonal anatomy into 6 regions of interests (ROIs) (covering the whole organ) in the same fashion as biopsy samples are taken. The base is defined as the upper third, which extended from the vesical margin of the prostate; the mid-region is defined as the central third; the apex is defined as the inferior remaining third. Each third will be further divide into right and left side. Prostate cancer in the peripheral zone appears as round or ill-defined, low-signal-intensity foci on T2-weighted images while central gland tumors appear as homogeneous low signal intensity lesions with irregular margins and without a capsule. Invasion of the pseudocapsule with lenticular extension into the urethra or anterior fibromuscular zone is commonly seen on T2-weighted images of central gland tumors (25). The central zone prostate cancers tend to have higher Gleason scores compared with cancers located in peripheral zone (26). Moreover, the central zone prostate cancers were shown to have higher pathological stage (higher rate of extracapsular extension and seminal vesicle invasion) as well higher Gleason score (26).

11.3 Quantitative analysis of DWI

The signal intensity of DWI will be fitting using monoexponetial fit.

Monoexponential calculation of apparent diffusion coefficient (ADC) is described by the following equation (eq.1):

$$ADC = -\ln\left(\frac{SI(b_2)}{SI(b_1)}\right)$$

(eq. 1)

where $SI(b_2)$ and $SI(b_1)$ denotes the signal intensity at higher (b_2) and at b = 0 mm^2/s (b_1).

12 STATISTICAL ANALYSIS PLAN

12.1 Sample size considerations

We aim to accrue 600 men equally in the two arms. With this sample size, the lower bound of a one-sided 95% C.I. for the difference of two proportions close will be -6% for proportions close to 35% (number of clinically significant Pca found) and -8% for proportions close to 25% (number of clinically non-significant Pca found). Assuming that the biopsy rate in the experimental group is close to 50%, the 95% C.I. around the reduction in biopsy rate related to use of the prediction model will be ± 5%.

12.2 Analysis plan

The primary analysis is the proportion of men with clinically significant cancer in each group. Analysis will be by logistic regression, with randomization strata as covariate. The odds ratio and confidence interval between groups will be applied to the risk in the control group in order to calculate a risk difference and confidence interval. A one-sided 95% confidence interval will be used to place a bound on the maximum reduction in detection rates associated with the experimental arm. A similar approach will be used for proportion of men with clinically non-significant Pca, biopsy rate, and biopsy-related complications. For the patient reported outcome of biopsy-related anxiety, analysis will be by ANCOVA, with randomization strata as covariate. In this case, a two-sided 95% C.I. will be calculated.

To evaluate the rate of significant Pca during follow-up, we will use time-to-event methods, with patients censored at the time of their last biopsy or curative treatment (if received for non-significant Pca). Cox proportional hazards will be used to compare between groups, with randomization strata as covariate.

As a descriptive analysis, we will evaluate how biopsy rates in the experimental arm vary by predicted risk produced by the model. We will first divide patients into low (<7.5%), intermediate (7.5- 19.9%) and high (≥20%) predicted risk of high-grade disease and report the rate of biopsy in each category. We will then calculate the probability of biopsy by the predicted risk of high-grade cancer using locally weighted scatterplot smoothing (lowess).

We will conduct two additional exploratory analyses. First, we will evaluate the hypothetical results in the control group had biopsy been restricted to those meeting different biopsy criteria - including PI-RADS 3 or higher; PI-RADS 4 or higher; PI-RADS 3 or higher or PSA density > 0.2 ng / mL / mm^3 – reporting the number of biopsies that would have been conducted and the number of clinically-significant cancers found for each strategy in comparison to the observed strategy of biopsying all men. The results of these analyses will be

standardized per 1000 men presenting with elevated PSA. In the second exploratory analysis, we will report the calibration of the prediction model in the control group.

13 QUALITY ASSURANCE

13.1 Information of study personnel and training

The technical and other supporting personnel of all participating centers are well experienced. In the beginning of the study all investigators will be informed on the practical implementation of the protocol in a separate institutional meeting. They will be informed on the rationale of the study and possible clinical implications as well.

13.2 Protocol amendments

According to Finnish national regulations, protocol amendments can be made if all investigators agree. They are presented in a written form and dated as applicable. They include the original chapter of the study protocol and the amended chapter, with an explanation to this change. Important protocol amendments are reviewed by the local ethics committee.

14 STUDY SCHEDULE

All mandatory authorizations will be obtained before the beginning of the study. The study will start in Sep 2019. All the patients are recruited until the end of year 2021. The prospective follow-up will stop latest 2026. After this a retrospective follow-up will be initiated ending at 2035.

15 FINANCING

The study will be financed by Finnish Governmental Special Funding (In Finnish: ’Erityisvaltionosuus, EVO’) and Finnish Cancer Society.

16 INSURANCE

The study patients are insured during the MRI procedure by the “Insurance against medicine-related injuries” (In Finnish: “Lääkevahinkovakuutus”) under regulations currently in effect in Turku University Central Hospital.

17 STUDY REPORT AND PUBLICATION(S)

Any formal presentation or publication of data collected from this research protocol will be considered as a joint publication by the investigator(s) and other appropriate persons deemed to have a significant academic output in the implementation of the study. Full reports of this study will be submitted to peer-reviewed journals in concerned fields (mainly radiology and oncology).

18 ARCHIVING

18.1 Paper documents

The PI retains a list of all patients and their identifying codes for at least 15 years after completion or discontinuation of the study. All patient files, including ethical approvals and amendments, all source documents and case report copies, and patient's informed consent forms are kept in a locked room at the Medical Imaging Centre of Southwest Finland for a minimum of 15 years.

18.2 RedCap database

All clinical and sample data are stored pseudoanonymised in RedCap database. Please see chapter 12.1.

18.3 Department of Biotechnology

A part of urine and blood samples, which are obtained for research purposes, will be frozen and stored for possible future research at the Department of Biotechnology, University of Turku.

18.4 Medical Imaging Centre of Southwest Finland

All MRI studies including reconstructed images are stored up on the hospital PACS system of the Medical Imaging Centre of Southwest Finland similarly to the routine clinical data.

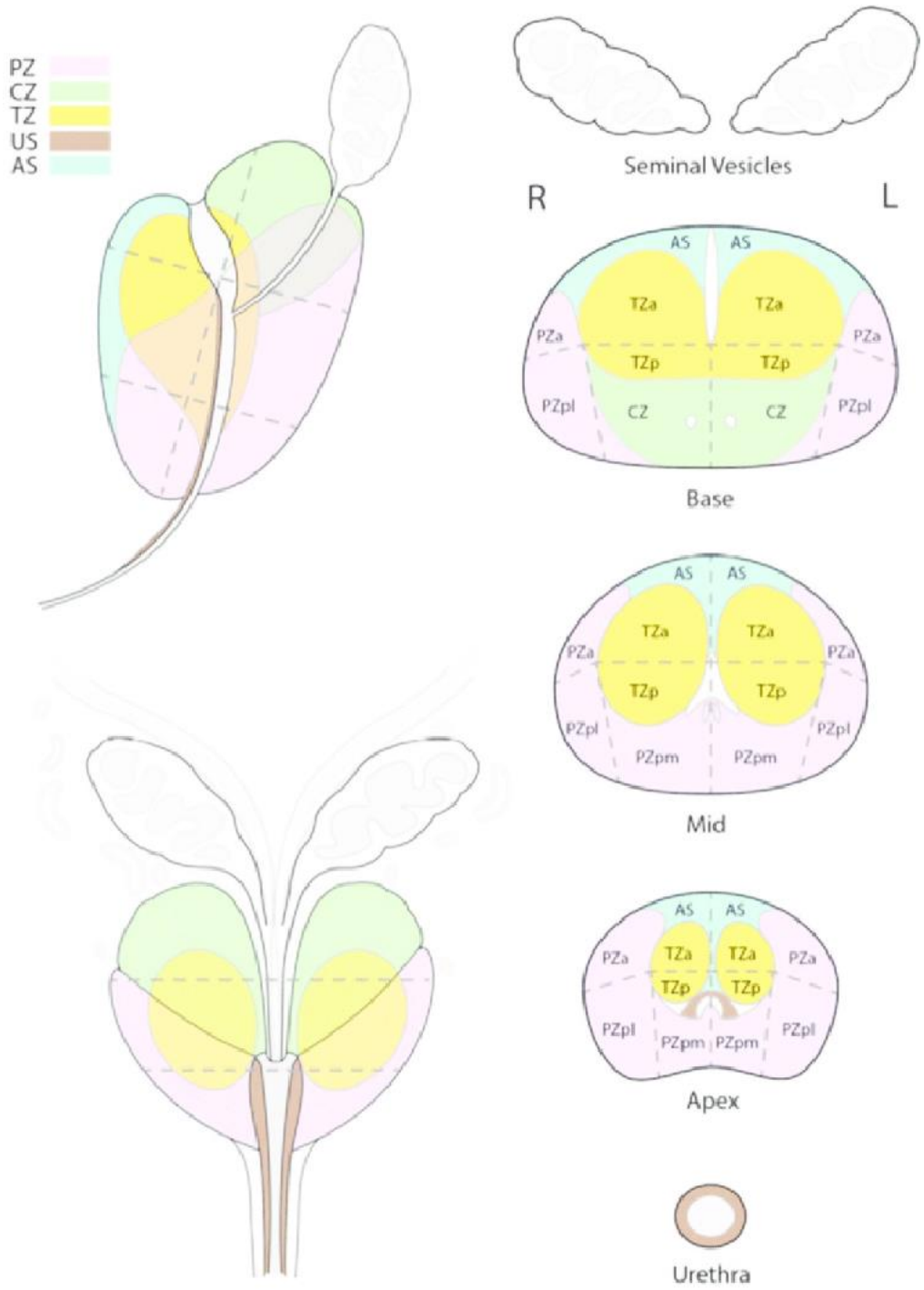
19 Appendices

19.1 Appendix 1. Study design, procedures and instruments.

	Visit 1	Visit 2	Visit 3	Visit 4	Follow-up	Follow-up	Follow-up 6mo intervals until 2 years	Follow-up 12mo intervals until 5 years	Follow-up Long term
Time	-50days	-30days	0	+14days	6mo	12mo			
PSA	x				x	x	x	x	
Laboratory*	x								
Biomarkers	x								
MAX-PC	x				x	x			
EPIC-26	x				x	x			
SF-36	x				x	x			
MRI		x							
Adverse events**		x							
TRUS			x						
Biopsies			x						
Complications***				x					
Medical charts, national registries									x

PSA, prostate spesific antigen (serum PSA and free-to-total PSA ratio); MAX-PC, the Memorial Anxiety Score for Prostate Cancer anxiety score; EPIC-26, Expanded Prostate Cancer Index Composite short form; MRI, magnetic resonance imaging; TRUS, transrectal ultrasound.
* standard blood count, S-AFOS, S-Ca, S-testo. ** Adverse events related to MRI visit according to CTCAE4.0 classification. *** Compliations related to biopsies according to Clavien Dindo classification.

19.2 Appendix 2. MRI reporting form, the prostate sector map.



19.3 Appendix 3. Shared decision information sheet provided to the patients.

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