CLINICAL STUDY PROTOCOL
(the intervention studied is not a drug substance)

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Study No:	
Study title:	Imaging for Prostate Cancer Metastasis Detection– Traditional Imaging (bone scan and CT) versus PSMA-PET, SPECT-CT, and Whole-Body MRI
Short title:	PROSTAGE
Scintigraphy and PET ligand(s):	^{99m}Tc-HMDP ^{18F}-PSMA-1007
Principal investigator:	Peter J. Boström, MD, PhD
Institute:	Department of Urology, Department of Diagnostic Radiology, Department of Surgery, University of Turku and Turku University Hospital, PET
Address:	P.O.BOX 52 FIN-20521 Turku, Finland

SIGNATURES

Principal investigator: _____ Date: ___/___/_____

LIST OF MAIN INVESTIGATORS IN ALPHABETICAL ORDER

Mikael Anttinen, MD
Researcher
Department of Urology, Turku University Hospital, Finland

Hannu Aronen, MD, PhD
Professor (radiology)
Department of Diagnostic Radiology, University of Turku, Finland

Roberto Blanco, MD, PhD
Adjunct Professor (radiology)
Department of Diagnostic Radiology, University of Turku, Finland

Peter J. Boström, MD, PhD
Adjunct Professor (urology)
Department Urology, Turku University Hospital, Finland

Otto Ettala, MD, PhD
Researcher
Department Urology, Turku University Hospital, Finland

Ivan Jambor, MD
Researcher (radiology)
Department of Diagnostic Radiology, University of Turku, Finland

Tuula Janatuinen, MD
Physician (nuclear medicine)
Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital
The Turku PET Centre, Turku, Finland

Tommi Kokki, MD
Physician (nuclear medicine)
Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital
The Turku PET Centre, Turku, Finland

Maija Mäki, MD
Physician (nuclear medicine)
Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital
The Turku PET Centre, Turku, Finland

Tommi Noponen, M. Sc., PhD
Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital
The Turku PET Centre, Turku, Finland

Jukka Kemppainen, MD, PhD
Adjunct professor (nuclear medicine),
Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital,
Turku PET Centre, Turku, Finland

Pietari Mäkelä, MD
Physician (radiology)
Medical Imaging Centre of Southwest Finland, Turku University Hospital, Turku, Finland

Pekka Taimen, MD, PhD
Adjunct Professor
Department of Pathology
University of Turku and Turku University Hospital, Turku, Finland

Antti Salminen, MD
Physician (urology)
Department Urology, Turku University Hospital, Finland

Minna Sandell, MD
Physician (radiology)
Medical Imaging Centre of Southwest Finland, Turku University Hospital, Turku, Finland

Jani Saunavaara, PhD
Physicist (MRI)
Medical Imaging Centre of Southwest Finland, Turku University Hospital, Turku, Finland

Jukka Schildt, MD

Marko Seppänen, MD, PhD
Adjunct professor (nuclear medicine)
Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital
The Turku PET Centre, Turku, Finland

Kari Syvänen, M.D, PhD.
Physician (urology)
Department Urology, Turku University Hospital, Finland

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1 Introduction

Prostate cancer (PC) is the most common cancer among men. The incidence of PC has increased dramatically in Finland since 1980´s and lately approximately 4.500 new PC cases have been diagnosed annually in Finland.[1]

About one quarter of diagnosed PC are metastatic at the time of diagnosis.[2] Accurate staging is extremely important, as the stage is single most important factor when treatment decisions are made and stage is the single most important prognostic factor. Localized PC is treated with active surveillance (low risk cases), or with treatment modalities with curative intent (radical prostatectomy or radiotherapy).[3] Although recently radical treatments have been suggested to play a role in low volume metastatic disease, the standard treatment of metastatic disease is castration therapy.[3]

In PC staging the most important anatomic locations to be imaged are i) bone, ii) lymph nodes (especially pelvic lymph nodes), and iii) extranodal soft tissues.

Detection of tumor bone metastases is commonly performed by bone scintigraphy (BS).[4] However, the results of recent studies have raised many doubts whether BS is as effective for confirming or excluding metastatic bone disease.[5] Moreover, the sensitivity for ^{99m}Tc-methylene diphosphonate bone scintigraphy (^{99m}Tc-MDP BS) is only 50-70%.[6] The detection of bone metastases in patients with high-risk PC is significantly improved by SPECT compared to planar BS.[7,8] Other imaging modalities with potentially improved accuracy to detect bone metastases in PC include PET-scan and whole body MRI.

The value of positron emission tomography (PET) imaging depends on the suitability of used isotope tracer to identify lesions of the imaged tumor type. When bone is imaged with PET, ^{18}F-fluoride has been the most commonly used tracer.[5] Other commonly used PET tracers in PC include ^{18}F-FDG, and ^{18}F/^{11}C-choline, but both have been late more or less replaced by PSMA-PET. Prostate-specific membrane antigen (PSMA) is a trans-membrane protein with an increased expression on cell membranes of PC cells.[9] ^{68}Ga-PSMA HBED-CC (Glu-NH-CO-NH-Lys- (Ahx)-[^{68}Ga(HBED-CC)]) was designed as an extracellular PSMA inhibitor for PET imaging and has been shown to demonstrate high specificity for PSMA-expressing tumor cell.[10] PSMA-PET results have been reported in several studies, but only in three prospective, one including 20-30 patients.[11-14] Of those studies only study by Fendler and coworkers investigated overall staging, the other two focused on intraprostatic tumor

detection or nodal metastases (van Leuwen).[12-14] Nevertheless, the ^{68}Ga-PSMA is a promising imaging modality both for soft tissues and bone. Recently ^{68}Ga-PSMA was reported to outperform ^{99m}Tc-DPD-SPECT in detection of bone metastases in PC.[15]

Recently, the novel PET tracer ^{18}F-PSMA-1007 has been developed as a promising PSMA ligand to compete and even outperform ^{68}Ga-PSMA-PET in overall staging. ^{18}F-PSMA-1007 have some advantages in comparison to ^{68}Ga-PSMA-PET including primary elimination of ^{18}F-PSMA-1007 via the hepatobiliary excretion route leading to less bladder isotope activity. Consequently, ^{18}F-PSMA-1007 might lead to better local staging because of its favorable pharmacokinetics and tumor-specific uptake. ^{18}F-PSMA-1007-PET combined with CT or even MRI could truly offer a 1-stop solution for both metastatic screening and local staging, but more prospective studies are needed to confirm this hypothesis.

Whole-body T1-weighted MRI is an effective method for bone imaging and is superior when compared to ^{99m}Tc-MDP BS.[16,17] If combined with soft tissue imaging, bone and nodal imaging may be performed in single imaging session.[18] Diffusion-weighted imaging (DWI) as a part of routine MRI examination is a promising tool for detection of an early intramedullary malignant lesion before cortical destruction or reactive processes due to bone marrow metastasis. DWI performs high contrast resolution between tumor and normal tissue. Individual variability of the mean apparent diffusion coefficient (ADC) values, as the result of DWI, may decrease the diagnostic accuracy of DWI.[19] Diagnostic accuracy of DWI for detection of malignant lesion is better than 18–fluoro-deoxy-glucose (FDG) and for detection of bone metastasis is comparable to ^{11}C-choline.[19,20] However, it is unclear if it is superior compared to the standard T1-weighted imaging or STIR fat suppression technique.[21] Currently there is not sufficient data comparing MRI and ^{68}Ga-PSMA and/or^{18}F-PSMA accuracy on bone imaging in PC.

In addition to bone, the possible tumor spread to soft tissues, especially pelvic lymph node is common in PC staging. Traditionally contrast enhanced abdomen and pelvic CT or MRI are used but the sensitivity of these imaging modalities is very limited.[22] Diffusion-weighted MRI may improve the diagnostic accuracy when normal sized lymph nodes are evaluated.[23] Still, different PET-tracers and recently especially ^{68}Ga-PSMA and novel ^{18}F-PSMA have both been considered as the most promising modalities for pelvic lymph node metastasis detection in PC and preliminary results suggest superior diagnostic accuracy of PSMA-PET compared to other modalities.[11]

We have previously investigated different imaging modalities for detection of bone metastases in prospective setting (Skeleta-trial).[24] According to that study, ^{18}F-NaF PET-CT and whole-body MRI are superior when compared to ^{99m}Tc-MDP SPECT-CT or ^{99m}Tc-MDP planar bone scan. Nevertheless, that study needs validation and further investigations as it was limited by low number (n=27) of PC patients, and PSMA-PET was not included in the study.

2 Rationale for the study

Clinicians face challenges when choosing optimal imaging modality/modalities for individual patient. Guidelines do not support any imaging in low risk cases.[3] For intermediate risk cases, and also for high-risk cases, if local treatment is planned, accurate staging of pelvic lymph node is important. In contrary, in very high-risk cases the knowledge of distant (bone) metastases is the single most important staging data. Optimally for clinicians most appropriate imaging technique would be chosen based on patient related risk factors or a single imaging modality would offer all aspects of needed staging information. The rationale for the present study is to find the most appropriate staging modality in high-risk PC at the time of initial staging.

3 Objectives of the study

The specific aims of the study are as follows:

i) To compare the diagnostic accuracy of ^{18}F-PSMA-1007 to ^{99m}Tc-MDP planar bone scintigraphy in pessimistic, patient-based analysis for diagnosis of bone metastases in the initial staging of patients with PC.

Secondary objectives

i) To compare the diagnostic accuracy of novel imaging modalities (^{18}F-PSMA-1007, whole-body MRI including DWI, ^{99m}Tc-HMDP SPECT-CT) to traditional imaging modalities (^{99m}Tc-HMDP planar bone scintigraphy, and contract enhanced CT of the thorax/abdomen/pelvis) for diagnosis of bone metastases in the initial staging of patients with PC.

ii) To compare the diagnostic accuracy of novel imaging modalities (^{18}F-PSMA-1007 PET/CT, whole-body MRI including DWI, ^{99m}Tc-HMDP SPECT-CT) to traditional imaging modalities

(contract enhanced CT of the thorax/abdomen/pelvis) for diagnosis of soft tissue metastases in the initial staging of patients with PC.

iii) To compare the effect of staging results of novel imaging modalities (^{18}F-PSMA-1007 PET/CT, whole-body MRI including DWI, ^{99m}Tc-HMDP SPECT-CT) to staging achieved with traditional imaging modalities (^{99m}Tc-HMDP planar bone scintigraphy, and contract enhanced CT of the thorax/abdomen/pelvis) in terms of the effect of staging on clinical treatment decision.

4 Patient selection

Following criteria are applied when patients are selected for the current study.

4.1 Inclusion criteria

1. Age > 18 years
2. Histologically confirmed PC without previous PC treatment
3. High-risk PC defined with one or more of the following criteria: Gleason ≥4+3, PSA ≥20, cT≥3a
4. Adequate physical status defined (by treating clinician) as capability to undergo some form of active treatment for the PC and the physical status allowing the patient to undergo all study imaging modalities
5. Signed informed consent

4.2 Exclusion criteria

1. Previous PC treatment. Short-term androgen deprivation therapy is permitted if necessary for symptomatic and/or very high-risk PC patients
2. Contraindications for MRI (cardiac pacemaker, intracranial clips etc.)
3. Claustrophobia

5 Study design

This is a non-randomized prospective single-institutional study comparing the diagnostic accuracy of novel imaging modalities (^{18}F-PSMA-1007 PET/CT, whole-body MRI including DWI, ^{99m}Tc-HMDP SPECT-CT) to traditional imaging modalities (^{99m}Tc-HMDP planar bone scintigraphy, and contract enhanced CT of the thorax/abdomen/pelvis).

6 Study endpoints, statistical considerations, and sample size

6.1 Study endpoints

The primary endpoint of the study is

1. Comparison of AUC values of ^{18}F-PSMA-1007 to ^{99m}Tc-HMDP in pessimistic, patient-based analysis detecting of bone metastases in the initial staging of high-risk PC patients.

The secondary end-points include

1. The sensitivity, specificity, accuracy and AUC value of ^{18}F-PSMA-1007, whole-body MRI including DWI, ^{99m}Tc-HMDP SPECT-CT, ^{99m}Tc-HMDP planar bone scintigraphy and contract enhanced CT detecting bone metastases in the initial staging of high-risk PC patients.
2. The sensitivity, specificity, accuracy and AUC value of ^{18}F-PSMA-1007, whole-body MRI including DWI, ^{99m}Tc-HMDP SPECT-CT, ^{99m}Tc-MDP planar bone scintigraphy and contract enhanced CT detecting lymph node metastases in the initial staging of high-risk PC patients
3. The sensitivity, specificity, accuracy and AUC value of ^{18}F-PSMA-1007, whole-body MRI including DWI, ^{99m}Tc-HMDP SPECT-CT, ^{99m}Tc-HMDP planar bone scintigraphy and contract enhanced CT detecting soft tissue metastases (excluding pelvic lymph node metastases) in the initial staging of high-risk PC patients
4. The effect of staging on clinical treatment-decisions

As in some cases the definition of a metastatic lesion is not confirmed with absolute certainty (e.g. with histological diagnosis) the final diagnosis concerning the metastatic status will be determined during follow up consisting of appropriate imaging modality and follow-up information from other parameters, especially PSA levels.

6.2 Statistical considerations and sample size

The power calculations are made according to our primary endpoint and on the basis of previously published work, the SKELETA trial. To be able to detect the 19% difference using a two-tailed test with a power of 80% at a significance level of 0.05 in a 2:1 ratio of sample sizes in negative/positive groups, 48 cases and 24 positive cases are required. Together 72 patients will be the sample size and taking into account possible dropouts, permission for 80 patients will be applied for Ethical Committee.

Equivocal findings of the imaging modalities will be classified either as suggestive for metastases ("pessimistic analysis") or suggestive for non-metastatic origin ("optimistic analysis"). Sensitivity and specificity values of patient-, region- and lesion-based analyses will be compared using McNemar test and two-sided p-values will be calculated. In region-based analysis, diagnostic accuracy values for the detection of bone metastases (sensitivity, specificity, accuracy and AUC) will be calculated from all ROIs which will be pooled into one group. Moreover, receiver operation characteristic curves (ROC) analysis will be performed using 60 000 bootstraps to account for within-patient correlations. Area under the curve (AUC) values will be calculated using the trapezoid rule and compared using a method described by Hanley and McNeil two-sided p-values will be calculated (28). Bootstrap samples will be constructed by stratifying patients based on overall cancer level (cancer present or not) and drawing patients as the independent units with replacement from these groups (cancer present or not). P-values smaller than 0.05 will be considered statistically significant.

7 Study execution

7.1 Patient identification and consenting

Patients are identified in the Department of Urology, Turku University Hospital. If the patient meets inclusion criteria, he will be informed of the study verbally and with the written information.

After adequate consideration of time, if the patients agree to participate in the study, signed informed consent is obtained. After this imaging studies are arranged within 2 weeks.

7.2 Laboratory sampling

In addition to imaging studies, besides routine clinical blood samples, an extra blood and urine sample are collected simultaneously for future molecular genetic studies exploring possible prognostic biomarkers for disseminated/metastasized PC.

7.3 Planar bone scintigraphy

Planar bone scintigraphy will be performed as a part of routine clinical evaluation protocol. The subjects will be positioned supine on a Discovery NM/CT 670 CZT, a digital SPECT/CT scanner (General Electric Healthcare). The scanner includes a dual-detector, free-geometry integrated nuclear imaging camera with the advanced digital CZT detector technology combined with the high-performance Optima CT540 subsystem. Whole-body planar images will be scanned from the anterior and posterior views three hours after the intravenous injection of 670 MBq of ^{99m}Tc-HMDP. A wide-energy high-resolution (WEHR) collimator, a scan speed of 13 cm/min, a zoom of 1.0 and a matrix size of 256 x 1024 are used in the scintigraphy.

7.4 Computer tomography

Computed tomography of the thorax, abdomen and pelvis will be performed as a part of routine clinical evaluation protocol. The imaging will be done with contrast agent if there are no clinical contraindications for the use of contrast agent.

7.5 SPECT-CT

SPECT/CT imaging will be carried out after acquisition of the planar images with the same scanner. Three bed positions of SPECT data will be acquired from the top of the head to mid femoral level using WEHR collimators. A non-circular orbit, 60 views with 15-s scanning time per view will be acquired during 180 degrees of rotation. A 128 x 128 matrix size, a zoom of 1.0 and 15% photopeak and lower scatter energy windows are used. After SPECT a CT topogram and a low-dose tomogram with a modulated mAs (noise index ~ 70), 120 kVp, a pitch of 1.35 and a 2.5-mm slice thickness are scanned. The co-registration of SPECT and CT data is verified after which

the SPECT images are reconstructed using modern iterative ordered subsets expectation (OSEM) reconstruction algorithm from General Electric or Hermes Medical Solutions, which includes, e.g., 10 iterations and 5 subsets and attenuation, collimator and scatter corrections.

7.6 MRI

Magnetic resonance imaging examination will be performed using a 1.5T (Philips 1.5T Ingenia, Best, Netherlands and/or Siemens 1.5T Aera/Avant, Erlangen, Germany) or 3T (Philips 3T Ingenia, Best, Netherlands and/or Siemens 3T Skyra fit, Erlangen, German) MR system. The body matrix coil in combination with a spinal coil will be used for image acquisition. T1-weighted anatomic imaging, STIR fat suppressed images and DWI will be performed in axial and coronal directions. DWI will be obtained with single-shot 2D spin-echo echo-planar imaging. The total scan time will be approximately 25-35 minutes.

7.7 PSMA-PET

^{18}F-PSMA-1007 tracer is manufactured by MAP Medical Technologies Oy (Helsinki, Finland). This radiolabeled tracer is targeting the prostate specific membrane antigen (PSMA). The solution is developed DKFZ and ABX companies and it is used for imaging studies with positron emission tomography (PET) (29.)

18F -PSMA-1007 is produced by radiolabelling with fluorine-18 (T1/2= 109,77 min) produced by irradiating oxygen-18. Administration of the formulated solution is done shortly (<10h) after production after quality control and release of the drug product by a Qualified Person. The process has been tested in three consecutive validation runs, showing consistent results. The results show that the solution met the requirements for sterility and bacterial endotoxins according to the European pharmacopoeia, confirming an acceptable manufacturing process from a microbiological point of view. Process verification and tests for microbiological purity is performed for all new batches of precursors and synthesis equipment before the manufacture

The PET/CT studies are carried out with digital PET/CT scanner: Discovery MI (General Electric Medical Systems, Milwaukee, WI, USA). It has combined PET/CT-scanners with a 128-slice CT and a 3D PET imaging capability. The PET imaging field of view (FOV) is 70 cm in diameter and 15.7 cm in axial length. To obtain attenuation correction for 511 keV photon distribution,

transmission scan is performed using a low-dose (noise index 25, automatic 3D current modulation, max 64 mAs and 120 kVp) CT protocol.

The patients receive intravenous injection of approximately 200-300MBq (3 MB/kg) of ^{18}F-PSMA-1007 diluted in 3-5 ml of saline as a 60-sec bolus which will be promptly flushed with saline. Before data acquisition patients will be asked to void. A static emission scan will be acquired 60-min from tracer injection over whole body. The sinogram data will be corrected for deadtime, decay and photon attenuation and reconstructed in a 256x256 matrix. Image reconstruction follows a fully 3D maximum likelihood ordered subsets expectation maximization (ML-OSEM) algorithm incorporating random and scatter correction with two iterations and 28 subsets. The final in-plane FWHM (full-width half-maximum) of the systems is < 6 mm.

7.8 Definition and recording of imaging findings

Imaging modalities will be read blindly without the knowledge of results of the other imaging modalities. Readers will only know that a patient has prostate cancer with high risk for metastases. All imaging data will be analyzed visually with classifying lesions as normal, equivocal or metastatic. Number and type of lesion will be recorded for each of following body parts: head, upper extremity, spine, rib and sternum, pelvis, lower extremity.

Lesions will be graded as highly suspicious for being metastases, equivocal or benign. On bone scans, lesions will be categorized as benign when they were located around joints, hot osteophytes, vertically involving several ribs (suggesting fracture), H-shaped pelvic abnormal, bursitis, avulsion injury, tendinitis.[5,25] The vertebral lesions were considered as highly suspicious when they involved posterior aspect, pedicle or the whole vertebral body. A lesion will be considered as highly suspicious on MRI if a focal or diffusion low signal intensity (SI) was present on T1wi with the corresponding intermediate or high SI on STIR and/or restricted diffusion on DWI. Typical benign lesions and/or sclerosis will be interpreted according to previously published criteria.[26,27] Trace images (geometric mean of 3 diffusion directions) will be evaluated visually in conjunction with anatomical T1wi and STIR. No quantitative cut-off values were used for DWI.

Anatomical localization of the potential tumor deposits will be confirmed by aligning the whole-body PET images with the corresponding CT images using Volumetrix™ hybrid imaging

software of the General Electric AWTM workstation where all visual and quantitative analyses of tracer uptake will be performed. Concurrent diagnostic evaluation of CT scans is made with Advantage Workstation version 4.6 for advanced processing. The findings on PET/CT whole-body images will be related to all previous clinical and imaging data and any new information likely to change patient's further treatment will be confirmed by other methods such as additional imaging studies.

Regions of interests (ROIs) will placed in the suspicious tumor lesion as seen in the co-registered CT. Tracer accumulation is measured as Standardized Uptake Value (SUV), which is the ratio of measured radioactivity concentration to the estimated body tracer concentration, assuming a uniform distribution throughout the entire body volume.

The bone, nodal and extra nodal findings will be compared on patient-, region- and lesion-level. In the region-based analysis for bone metastasis, the skeleton was divided into five regions: head, thorax and ribs, spine, pelvis and limbs. In the lesion-based analysis, only lesions which were highly suspicious or equivocal on at least one imaging modality were included. In addition, maximum of 5 lesions with the highest agreement between modalities per anatomical location (5 locations as defined in the region-based analysis) were included in the lesion-based analysis.

A detailed data collection sheet is applied prospectively for recording separately each individual imaging study results of equivocal, benign and malignant lesion/s.

8 Duration of the study

Enrollment of the patients to the study will start as soon as the Research Ethics Approval has been obtained and hospital permissions is available. The enrollment is estimated to spring 2018. The accrual period will end as the accrual target is fulfilled. This is estimated to take 18 months. For individual patients the study is concluded after the imagine studies with conclusive findings are

available. In the case of inconclusive imaging findings, follow-up is arranged for appropriate time period until the imaging lesion status is confirmed.

9 Administrative considerations

The trial will be conducted in compliance with the "Principles of Good Clinical Practice" (ICH-GCP). The investigator is responsible that the trial is carried out in accordance with the Declaration of Helsinki in the revised version of Somerset West, South Africa 1996 and the “Principles of Good Clinical Practice “(ICH-GCP), 1997.

9.1 Ethical review

The Principal Investigator (PI) is responsible for obtaining approval of the EC for the study protocol including its appendices. The PI shall file all correspondence with the EC in the Investigator`s Study File.

9.2 Information of the study subject

Every patient will be informed about the study details in accordance with the enclosed patient information sheet. The patient is informed both in writing information sheet and verbally by the physician. The patient must have the opportunity to decide whether or not to participate in the clinical trial and this decision will not affect the clinical treatment. Both the informing physician and the patient must sign a declaration of consent. The patient will retain a copy of the declaration. The declarations of consent are part of the patient file and will be retained with this.

10 Quality assurance

10.1 Study personnel and training

The clinical investigators and research staff (research coordinator and research nurse) at Department of Urology are experienced in conducting various types of clinical trials including imaging studies in uro-oncology. This team will take care of study subject identification, information and consenting as well as clinical treatment of the individuals. The technical and other supporting personnel of Department of Clinical Physiology and Nuclear Medicine, and Department of Diagnostic

Radiology is well experienced in performing ^{99m}Tc-MDP BS, CT, and MRI studies. In the beginning of the study all investigators will be informed on the practical implementation of the protocol in a separate meeting. They will be informed on the rationale of the study and possible clinical implications as well.

10.2 Protocol amendments

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 Ethical Committee.

11 Insurance

The study patients are insured during the imaging examinations by the "Insurance against medicine-related injuries" (In Finnish: "Lääkevahinkovakuutus") under regulations currently in effect in Turku University Hospital

12 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.

12.1 Archiving

The principal investigator 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 Ethics Committee approvals and amendments, all source documents and case report copies and patient informed consent forms are kept in a locked room at the Department of Urology, Turku University Hospital for a minimum of 15 years. Imaging studies will be stored at hospital PACS systems.

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