Clinical trials registration number: NCT01339780

Status: Study completed

1 SUMMARY

Prostate and breast cancer continues to be the most common cancer among men and women, respectively. The exact assessment of the cancer spread with detection of possible bone metastasis is crucial for treatment decision. In the current study 50 patients with prostate cancer and 50 patients with breast cancer at high risk for bone metastases or with know metastatic disease will be studied with multiple imaging modalities. Patients will be recruited from the Department of Oncology, Turku University Hospital. Planar bone scintigraphy (BS), single photon emission computed tomography combined with low-dose computed tomography (SPECT/CT), ^{18}F-fluoride positron emission tomography computed tomography (PET/CT) and magnetic resonance imaging (MRI) will be performed to all patients. The primary objective is to determine the diagnostic accuracy of the four imaging modalities. The secondary goal is to calculate the sensitivities and specificities of the four imaging modalities on a patient-to-patient and lesion-to-lesion basis. Based on the results of this study an optimal imaging protocol for detection of prostate and breast cancer bone metastasis will be developed and validated.

2 INTRODUCTION

Prostate and breast cancer continues to be the most common cancer among men and women (*1*). The incidence of both cancers in Finland has increased dramatically over the last few years. In 2007 the number of new prostate and breast cancer cases was 4183 and 4140, respectively (www.cancerregistry.fi).

Prostate cancer incidence increases worldwide, both as a result of population aging and because of better diagnostic methods. As the result of common prostate-specific antigen (PSA) screening, most prostate cancers are currently diagnosed at an early stage. Despite the commonness of the disease, there is currently no routine method of choice for treatment within the individual patient. Several clinical nomograms exist which are based mainly on the differentiation between the indolent and aggressive disease, with the Gleason score and serum level of PSA as the major indicator of tumor aggressiveness (*2*). Knowledge of tumor extent and possible bone metastasis is an important determinant in the choice of treatment. Although clinical nomograms partly facilitate the choice of treatment, there is a great demand for further individualization in order to limit the current practice of over-treatment of men with an intrinsic good prognosis (*3*).

The detection and diagnosis of breast cancer is based upon X-ray mammography, both for screening purposes and to assess. According to the Finnish guidelines the screening program is applicable for women between 50 - 69 years of age, with a 2-year interval, free of charge. The sensitivity of mammography varies according to technical standards, physician competence and measurement criteria, reported between 69% and 90% (*4*). Similar to prostate cancer, the knowledge of possible bone metastasis plays an important role on treatments decision making process.

Detection of tumor bone metastases is commonly performed by bone scintigraphy (BS). 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 just about 50-70% (*6,7*). The detection of bone metastases in patients with high-risk prostate cancer is significantly improved by SPECT compared to planar BS (*8*).

^{18}F-NaF is a positron emission tomography (PET) tracer used for detection bone metastasis (*9*). ^{18}F-Fluoride uptake is more sensitive than ^{99m}Tc-MDP BS mainly for the detection of lytic lesions accompanied with only minimal osteoblastic activity. Increased uptake of ^{18}F-fluoride and ^{99m}Tc-methylene diphosphonate (MDP) reflects the osteoblastic reaction of bone to the presence of tumor cells. Increased ^{99m}Tc-MDP or ^{18}F-Fluoride uptake is, however, not specific for tumoral bone involvement. Correlation with morphologic imaging such as computed tomography (CT) or MRI greatly improves diagnostic accuracy. Image fusion of ^{18}F-NaF PET and CT increased diagnostic performance and PET/CT obviates the use of a full-diagnostic CT (*10*). Studies comparing ^{18}F PET/CT with technetium-99m bone scintigraphy (*8*)or ^{18}F-choline PET/CT suggested that ^{18}F PET/CT is better imaging tool for bone metastasis that ^{99m}Tc-MDP BS and comparable to ^{18}F-choline PET/CT. ^{18}F-Fluoride PET/CT imaging is not a routine imaging modality for detecting malignant bone involvement due to its relatively high cost and low availability. Hybrid SPECT/CT scanners allow acquisition of the functional images (SPECT) and of the morphologic images (CT) without changing the patients´ positioning and generation of fused functional-anatomical data. With the use of iterative 3D reconstruction protocols multislice SPECT imaging combined with whole-body low-dose CT, imaging can be performed in a reasonable time. The diagnostic accuracy of such fusion imaging is unclear.

Basic T1-weighted MRI is superior in detection of bone metastasis compared to ^{99m}Tc-MDP BS (*6,7*). 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 variabilities of the mean apparent diffusion coefficient (ADC) values, as the result of DWI, may decrease the diagnostic accuracy of DWI (*11*). Diagnostic accuracy of DWI for detection of malignant lesion is better then 18–fluoro-deoxy-glucose (FDG) (*11*) and for detection of bone metastasis is comparable to ^{11}C-choline (*12*). However, it is unclear if it is superior compared to the standard T1-weighted imaging or STIR fat suppression technique (*13*).

To our knowledge there is no study comparing whole body MRI examination (including T1-weighted imaging, STIR, DWI) with ^{18}F-NaF PET/CT for detection of bone metastasis in patient with histological confirmed prostate and breast cancer so the clinical role of MRI and ^{18}F-NaF PET/CT for detection of bone metastasis remains questionable.

3 OBJECTIVES AND PURPOSE

Specific aims of the current study are:

i) To determine the sensitivity, specificity and accuracy of ^{99m}Tc-MDP BS, SPECT/CT, ^{18}F-NaF PET/CT, T1-weighted MRI, STIR- MRI, DWI alone and their combinations in the diagnosis of bone metastases in patients with breast cancer and prostate cancer

ii) To develop imaging guidelines which will become the standard protocol for prostate and breast cancer imaging at thee following institutions:

- Medical Imaging Centre of Southwest Finland (VSKK) / TYKS, Turku University Hospital Turku, Finland.
- Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland.
- The Turku PET Centre, Turku, Finland

iii) To evaluate cost-effectiveness of ^{99m}Tc-MDP BS, SPECT/CT, ^{18}F-NaF PET/CT and MRI

4 STUDY DESIGN

This is a non-randomized prospective study to determine the applicability of SPECT/CT, PET/CT and MRI for the diagnosis of prostate and breast cancer. The use of SPECT/CT, ^{18}F-NaF PET/CT leads to more accurate diagnosis compared to BS. We hypothesized that the addition of MRI shows more accurately heterogeneous distribution of bone metatstasis compared to ^{99m}Tc-MDP BS or SPECT/CT, ^{18}F-NaF PET/CT and enable early detection of metabolically active metastasis. If the hypothesis is proven, the use of MRI for detection of prostate and breast cancer bone metatstatsis may result in substantial decrease number of false negative findings and more

accurate staging of individual patients. Moreover, it would enable better monitoring of treatment response.

Images will be viewed by an experienced radiologist and nuclear medicine specialist. Lesions will be categorized separately on each of the four modalities as normal, benign, equivocal or malignant. Patient-based and lesion based analysis will be performed in order to assess sensitivity, specificity and diagnostic accuracy for the detection of metastatic spread. The final diagnosis for assessment of accuracy will be determined by clinical follow-up of at least 6 weeks.

5 PATIENT/SUBJECT SELECTION

5.1 Source population

Subjects will be recruited from the Department of Oncology, Turku University Hospital. Patients referred for ^{99m}Tc-MDP BS, SPECT, ^{18}F-NaF PET/CT, T1-weighted MRI, STIR- MRI, DWI examination live either in the Hospital Districts of Southwestern Finland, Satakunta, or Åland. The total population in these three hospital districts is approximately 714000.

5.2 Number of patients

This study will include 50 patients with histologically confirmed prostate cancer and 50 patients with histologically confirmed breast cancer.

5.3 Inclusion criteria for patients with prostate cancer and breast cancer

- Age: 40 to 80 years
- Language spoken: Finnish or Swedish
- Performance status: Karnofsky score 70 or better or WHO performance status 2 or better
- Diagnosis: Histologically confirmed prostate or breast cancer
- 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
- strong suspicion of first bone metastatic disease (already diagnosed metastase in other organs, elevated tumor markers, destruction of bone in plain x-ray or otherwise specified reasons
- adjuvant chemo- or endocrine therapy is allowed

5.4 Exclusion criteria for patients with prostate and breast cancer

- Ongoing treatment for metastatic disease
- Contraindications for MRI (cardiac pacemaker, intracranial clips etc.)
- Infections: Patient must not have an uncontrolled serious infection
- Claustrophobia

6 IMAGING MODALITIES

6.1 Pre-study evaluation

All patients will be seen by an oncologist who reviews patient's medical reports in order to meet the inclusion criteria of the current study. Routine clinically relevant bone marker blood samles (like AFOS, CTX) will be taken. ^{99m}Tc-MDP BS will be performed as a part of normal clinical practice. If the patient agrees to participate he/she will be scheduled for the SPECT/CT, ^{18}F-NaF PET/CT and MRI as described below. The time period between the SPECTCT, ^{18}F-NaF PET/CT and MRI examination will be a maximum of 2 weeks. For the study logistics of patients please see Appendix.

6.2 Planar bone scintigraphy

The subjects will be positioned supine on a Symbia T6, True Point SPECT-CT scanner (Siemens Healthcare). The system includes a six row ultrafast Ceramic (UFC™) CT detector and state-of-the-art dual-detector variable-angle SPECT camera. 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-MDP. A low-energy high-resolution (LEHR) 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.

6.3 SPECT/CT bone scintigraphy

SPECT/CT imaging will be scanned after acquisition of the planar images. Three bed positions of SPECT data will be acquired from the top of the head to mid femoral level using LEHR collimators. A non-circular orbit, 60 views with 20-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 an effective mAs of 10, 130 kVp, a pitch of 1.5 and a 3.0-mm slice thickness are scanned. The co-registration

of SPECT and CT data is verified after which the SPECT images are reconstructed using a Flash 3D Iterative reconstruction algorithm (Siemens Healthcare) with 10 iterations and 5 subsets or using an ordered subsets expectation (OSEM) algorithm of HybridRecon-Oncology (v1.0.15) software including attenuation, collimator and scatter corrections with 5 iterations and 20 subsets (Hermes Medical Solutions).

6.4 Synthesis of ^{18}F

The [^{18}F]Fluoride for injection is made in accordance with the quality system of Turku PET Centre Radiopharmaceutical chemistry laboratory. Fluorine-18 is produced via $^{18}O(p,n)^{18}F$ nuclear reaction by irradiating O-18 enriched water using 17 MeV protons from the MGC-20 cyclotron at Åbo Akademi, Accelerator Laboratory. The irradiated water (800 µl) containing the [^{18}F]F^- is passed through a Plus QMA light Sep-Pak to trap the fluoride. After trapping, the Sep-Pak is eluted with 10 ml ultra pure water, removing contaminants and traces of target water (irradiated water).

The purified [^{18}F]fluoride is eluted from the Sep-Pak into a lagenula with 1 ml 9 mg/ml NaCl-solution (physiological solution) thereafter 4 ml of the same NaCl-solution is added to the lagenula. The solution is filtered through a single use apyrogenic sterile filter (Supor Acrodisc 13) into a 10 ml sterile sealed lagenula.

6.5 ^{18}F-Fluoride PET/CT

The PET/CT studies are carried out with one of our PET/CT scanners: Discovery VCT or Discovery PET-CT 690 (General Electric Medical Systems, Milwaukee, WI, USA). Both devices are combined PET/CT-scanners with a 64-slice CT and a 3D PET imaging capability. The PET scanner part consists of 24 rings of bismuth germinate or lutetium based scintillator yielding 47 transverse slices spaced axially by 3.27 mm. In both systems 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 MBq of ^{18}F-NaF diluted in 3-5 ml of saline as a 60-sec bolus which will be promptly flushed with saline. A static emission scan will be acquired 60-min from tracer injection over whole body. After finishing data acquisition patients will be asked to void. 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.

6.6 MRI

MRI examination will be performed using a 1.5T Siemens system (Magnetom Avanto [76x32] Q-engine, Erlangen, Germany) or 3T Siemens system (Magnetom Verio 3T [76x18], Erlangen, Germany). The body matrix coil in combination with a spinal coil will be used for image acquisition. Glucagon (0.2 mg - 0.5 mg, GlucaGen, Novo Nordisk A/S) will be injected subcutaneously into lower abdomen immediately prior to beginning the MR imaging examination to reduce peristalsis as a part of the normal clinical routine. 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 3D spin-echo echo-planar imaging followed by gadolinium-enhanced T1-weighted imaging. The total scan time will be approximately 40 minutes. Imaging data will be analyzed using the Siemens "Leonardo" dedicated workstation.

6.7 Primary and secondary variables/end-points

The primary end point is the percentage of patients in whom the treatment strategy is changed according to a different imaging modality. The final diagnosis will be determined by clinical follow up. The secondary end points are the number of metastatic lesions detected by the four different imaging modalities and the calculated sensitivities and specificities of the four imaging modalities.

7 ADVERSE EVENTS

Emergencies may occur during SPECT/CT, PET/CT or MRI imaging. An experienced medical doctor will be present all the time. Vital function will be monitored, and material and drugs needed for first care are readily available. Since MRI is not based on ionizing radiation, the risk for adverse events in properly selected patients is associated only with administration of paramagnetic contrast agents. Only patients with physiological renal function will be included, resulting in substantial decreased in the risk associated with administration of paramagnetic contrast agents. Administration of paramagnetic contrast agent is generally accepted and in the routine clinical use at the Medical Imaging Centre of Southwest Finland. 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.

8 ETHICS

8.1 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 (59nd World Medical Association General Assembly, Soul, Korea, 2008). Prior to commencement of this investigation, the study protocol, patient information sheet and informed consent form will be submitted for approval to EC of the Hospital District of Southwest Finland.

The ^{99m}Tc-MDP BS, SPECT/CT, PET and CT studies will be performed using standard procedures. The duration of ^{99m}Tc-MDP BS, SPECT/CT imaging will be about 60 minutes. Radiation exposure associated with ^{99m}Tc-MDP BS is 3.8 mSv (ICRP 80,1997). The addition of a SPECT scan following whole-body imaging will not increase the radiation burden to the patient. Combining low-dose CT imaging into the study protocol will add 2.6 mSv of radiation exposure. The duration of ^{18}F-NaF PET/CT imaging will be about 30 minutes. Radiation exposure associated with injection of 200MBq of ^{18}F-NaF 4.8 mSv (ICRP 80,1997). The addition of a low-dose CT scan covering whole-body will add 7.1 mSv of radiation exposure.

8.2 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.

8.3 Subject information and informed consent

The patients will receive both oral and written information about the study procedure. They will be informed that they are free to withdraw from the study at any study stage without mentioning reason for withdrawal. The informed consent for the study will be obtained from every enrolled patient.

9 DATA COLLECTION AND MANAGEMENT

9.1 Case Report Forms

The major finding of the study will be classified separately for each of the four imaging modalities as normal, equivocal or metastatic. In addition, the number of lesions will the documented separately for each of the four imaging modalities.

9.2 Electronic data collection

Raw data of planar BS and SPECT/CT is stored in Hermes Gold archive. The BS, SPECT , CT and MRI images are also stored in the Hospital Carestream archive system.

9.3 Data management

After the data collection period (24 to 30 months) the personal identification numbers will be erased from the electronic data banks. The study material will not be sent through e-mail without sufficient encryption.

9.4 Study subject register

All involved investigators will have possibility to review patient's imaging data sets. For purpose of image presentation all the personal identification numbers will be deleted.

10 DATA ANALYSIS

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 or breast cancer with high risk for bone metastasis or know bone metastasis. 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.

10.1 Analysis of SPECT/CT bone scintigraphy

Images from planar and SPECT/CT bone scintigraphy and from ^{18}F-Fluoride PET/CT are compared using the Hermes Hybrid PDR v1.3 dedicated image fusion and analyzing software (Hermes Medical Solutions).

10.2 Analysis of PET-data

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 AW^{TM} 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 4.4 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.

10.3 Analysis of MRI data

Images will be analyzed using the Siemens "Leonardo" dedicated workstation. The present of cancer will be determined by T1-weighted anatomic images, STIR fat suppressed images and DWI alone and their combinations. ROI will be drawn around suspicious lesion. In every ROI pharmacokinetic parameters (ie. wash-in, time to peak, wash-out) and mean apparent diffusion coefficient (ADC) values, as the result of DWI, will be measured. This finding will be correlated with final diagnosis and other imaging modalities.

11 STATISTICS

11.1 Statistical plan

Statistical analysis will be performed by using SAS version 9.1 (SAS Institute, Inc., Cary, NC). Statistical analysis performed by receiver operating characteristic curve (ROC) analysis will be based on visual and semi-quantitative evaluation of imaging data sets. To determine a possible cut-

off value for SUV and ADC for detection of tumor tissue, ROC analysis and area under receiver operating characteristic curve (AUC) will be calculated. SUV and ADC values will expressed as mean values ± SDs.

12 QUALITY ASSURANCE

12.1 Information of study personnel and training

The technical and other supporting personnel of Department of Clinical Physiology and Nuclear Medicine, Turku PET Centre and Department of Diagnostic Radiology is well experienced in performing ^{99m}Tc-MDP BS, SPECT/CT , PET/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.

12.2 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.

13 STUDY SCHEDULE

The study will start in December 2010 and all mandatory authorizations will be obtained before the beginning of the study. All imaging studies are expected to be performed within 24 to 30 months. Preliminary analysis of all results will be available in October - November 2012 and reports are expected to be written during summer 2013.

14 FINANCING

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

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16 APPENDICES

16.1 Appendix 1

Sequence of events

Histologically confirmed prostate cancer/breast cancer

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Inform consent by patient

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^{99m}Tc-methylene diphosphonate bone scintigraphy

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SPECT/CT

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^{18}F-NaF PET/CT

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MRI examination

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Clinical follow up

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Imaging correlation