CLINICAL STUDY PROTOCOL

(The intervention studied is not a drug substance)

Date:	March 20, 2015
Version:	1.0
Study No:	
Study title:	Development and validation of novel MRI methods for the detection of prostate cancer aggressiveness
Short title:	PROAG
Principal Investigator:	Hannu Aronen, MD, PhD, radiologist
Contact address:	Department of Diagnostic Radiology, Turku University Central Hospital Kiinamyllynkatu 4-8 P.O.BOX 52 FIN-20521 Turku, Finland tel: +358 3133896 email: hannu.aronen@utu.fi
Institute:	Department of Radiology, Turku University
Address:	P.O.BOX 52 FIN-20521 Turku, Finland

SIGNATURES

Principal investigator: _____ Date: 20/03/2015
Hannu Aronen

LIST OF MAIN INVESTIGATORS IN ALPHABETICAL ORDER

Hannu Aronen, M.D., Ph.D.
Professor (radiology)
Principal Investigator
Department of Diagnostic Radiology, University of Turku, Finland

Peter Boström, M.D., Ph.D.
Adjunct Professor (urology)
Department of Urology, University of Turku, Finland

Ivan Jambor, M.D.
Researcher (radiology)
Department of Diagnostic Radiology, University of Turku, Finland

Otto Ettala, M.D.
Physician (urology)
Department of Surgery, Division of Urology, Turku University Hospital, Finland

Markku Kallajoki, M.D., Ph.D.
Adjunct Professor (pathology)
Department of Pathology, University of Turku, Finland

Aida Kiviniemi, M.D.,
Radiologist (oncology)
Department of Diagnostic Radiology, University of Turku, Finland

Pekka Taimen, M.D., Ph.D.
Adjunct Professor (radiology)
Department of Urology, University of Turku, Finland

Marko Pesola, M. Sc., Ph.D.
Physicist (MRI)
Department of Diagnostic Radiology, University of Turku, Finland

CONTACT INFORMATION

Names, titles, and e-mail addresses of signatories.

Principal investigator: Hannu Aronen, M.D., Ph.D.
Department of Radiology, Turku University Central Hospital
Kiinamyllynkatu 4-8 P.O.BOX 52 FIN-20521
Turku, Finland
email: hannu.aronen@utu.fi
tel: +358 3133896

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1 SUMMARY

Prostate cancer has been the most common neoplastic disease in men in Finland over the last ten years. Prostate specific antigen (PSA) has only a limited role in the diagnosis and characterization of prostate cancer (1). The diagnosis of prostate cancer is done by transrectal ultrasonography (TRUS) guided biopsy. However, TRUS guided biopsy carries a risk of increase in complications. There is an increasing interest in developing more accurate non-invasive imaging modalities which could potentially detect prostate cancer aggressiveness.

Diffusion weighted imaging (DWI) and rotating frame relaxation measurements have shown to be particularly promising in prostate cancer detection and characterization. This study focuses on further development and validation of DWI and novel rotating frame relaxation measurements will enroll 200 men with histological diagnosed prostate cancer who will undergo MRI examination before prostatectomy. Anatomical magnetic resonance imaging (MRI) and novel acquisition methods focusing on DWI and rotating frame relaxation measurements will be performed using surface coils to non-invasively detect and characterize prostate cancer.

2 INTRODUCTION

Prostate cancer continues to be the most common cancer in elderly men and the second leading cause of cancer death in men (2). As the result of common prostate-specific antigen (PSA) screening, most prostate cancers are currently diagnosed at an early stage. At detection most of prostate cancers are still localized within the gland with an incidence of local lymph node metastasis <10% (3).

Traditionally the diagnosis of prostate cancer is mostly based on the result of systematic ultrasonography (US) guided biopsies. Transrectal biopsy carries a risk of hemorrhagic and infectious complications (4) and the accuracy for prostate cancer detection is limited because in more than 85% of cases the cancer is multifocal and intermingled with normal tissue and about 30% of tumors are localized in central and transitional zone (5, 6). Therefore, more accurate noninvasive imaging modalities are needed to improved diagnosis and avoid unnecessary biopsies.

Diffusion weighted imaging has shown to be particularly promising in prostate cancer (7, 8). Due to restricted diffusion, prostate cancer has lower apparent diffusion coefficient (ADC) values than normal prostate tissue. However, some less aggressive tumors remain undetected

on ADC maps calculated using the monoexponential fit of DWI signal decay. Several studies have shown the correlation of ADC values, calculated using monoexponential model, and Gleason score (9-14). Moreover, Gleason scores based on biopsy samples from DWI guided MRI biopsies were shown to better predict the final Gleason score, based on prostatectomy, compared to the Gleason scores based on biopsy samples taken with TRUS guided systematic biopsies (15). Diagnostic performance of DWI in the transitional zone (TZ) and central zone (CZ) of prostate is less than that in the peripheral zone (PZ). This is due to the presence of BPH causing changes in the tissue structure which in turn has an effect on the properties of water diffusion. These changes can lead to false positive findings on DWI (16). Currently, there is no consensus with regard to the optimal number, range and distribution of b-values used for DWI of prostate cancer. Further research is needed to assess the potential additional value of biexponential DWI for cancer detection and characterization of cancer aggressiveness. Animal models have shown different responses of fast and slow diffusion components to cancer therapy (17), implying a potential for these non-invasive biomarkers in monitoring cancer therapy response. Currently, there is no consensus considering the optimal imaging parameters and mathematical model for prostate DWI.

Several previous studies demonstrated correlation of apparent diffusion coefficient (ADC_m), applying the monoexponential model to diffusion weighted imaging (DWI) data sets, with Gleason score based on prostatectomy sections (11, 18-22) and biopsy cores (10, 12, 23). However, there is still a need for development and validation of novel non-invasive method for prostate cancer characterization.

Recently, a novel method called **r**elaxation **a**long a **f**ictitious **f**ield (RAFF) has been developed (24-26). Rotating frame relaxation measurements utilizing RAFF method are done under sub-adiabatic condition with approximately 40 % less radiofrequency power deposition (SAR) than a continuous wave rotating frame relaxation time $T_{1\rho}$ radiofrequency pulse with the same peak power and duration (27, 28). In a pre-clinical glioma gene therapy study (29), relaxation values using RAFF method (T_{RAFF}) were the only parameter having significant association with cell density in all tumor parts of glioma rat model, outperforming DWI. We have already demonstrated that T_{RAFF} values significantly ($p < 0.01$) differ between prostate cancer lesion with Gleason score of 3+3 version >3+4 (30). However, our initial study consisted of only 36 patients and RAFF was performed using voxel size of 2.47 x 3.08 x 5.00 mm^3. No comparison with DWI derived parameters was performed. Thus, the purpose of the current study is to futher evaluate association of T_{RAFF}, DWI derived parameters, T_2 relaxation time values with Gleason score.

3 OBJECTIVES AND PURPOSE

Specific aims of the current study are as follows:

i) To determine the sensitivity, specificity, and accuracy of different DWI sequences, DWI models and rotating frame relaxation measurements for the detection and characterization of prostate cancer in correlation with whole mount prostatectomy samples

ii) To develop and validate novel acquisition methods for DWI and rotating frame relaxation measurements

4 STUDY DESIGN

This is a non-randomized prospective study to determine the applicability MRI, including DWI and rotating frame relaxation measurements for the characterization and detection of prostate cancer in patients with histologically confirmed prostate cancer scheduled for radical prostatectomy. We hypothesized that advanced novel DWI modeling and rotating frame relaxation measurements would allow more precise prostate cancer characterization.

If the hypothesis is proven, the use of MRI, including DWI and rotating frame relaxation measurements, would allow selecting patients who need prostate biopsy. This would result into substantially decreased number of biopsies and biopsy-related complications.

5 PATIENT SELECTION

5.1 Source population

All diagnosed patients with prostate cancer living in referral areas to Turku University Hospital living either in the Hospital Districts of Southwest Finland, Satakunta, or Åland islands are potentially eligible. The total population in these three hospital districts is approximately 724000.

5.2 Number of patients

This study will include 200 patients with histological confirmed prostate cancer scheduled for radical prostatectomy. All patients will undergo MRI examinations performed before prostatectomy. The imaging datasets will be analyzed after each imaging session and

before radical prostatectomy in order to benefit from MR findings concerning possible cancer localization.

5.3 Inclusion criteria

- Age: 35 to 85 years
- Language spoken: Finnish
- Performance status: Karnofsky score 70 or better or WHO performance status 2 or better
- Diagnosis: Histologically confirmed adenocarcinoma of prostate
- No previous surgical, radiation or endocrine treatment for prostate carcinoma
- Clinical stage T1c-T3aN0 based on transrectal ultrasound, pelvic CT and bone scintigraphy
- Time period between the last biopsy and scheduled radical prostatectomy less than 8 months
- 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

5.4 Exclusion criteria

- previous prostate surgeries, e.g. TURP (transurethral prostatic resection)
- symptomatic acute prostatitis
- contraindications for MRI (cardiac pacemaker, intracranial clips etc)
- uncontrolled serious infection
- claustrophobia

6 SCREENING MODALITIES

6.1 Pre-study evaluation

If a patient scheduled for radical prostatectomy fulfill the inclusion criteria and agrees to participate in the study he will be scheduled to the MRI examination after obtaining inform consent. The time period between MRI and radical prostatectomy will be less the 1 month. Patient scheduled for the MRI examination (as described below) will receive natriumpikosulphate drops (Laxoberon, Boehringer Ingelheim GmbH) for bowel preparation**.**

6.2 MRI

MR imaging of the prostate will be performed on using a 1.5T or 3T Siemens system (Magnetom Aera 1.5T or Verio 3T, Erlangen, Germany) or 3T Philips system (Philips Ingenia, Best, Netherlands) or 3T Philips PET/MRI system (Philips Ingenuity, Best, Netherlands). No PET imaging will be performed. The body matrix coil in combination with a spine coil will be used for image data 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. T2-weighted anatomic imaging will be performed in axial and sagittal plane. Single-shot spin-echo echo-planar imaging as well as different turbo spin-echo based sequence will be used for DWI. Rotating frame relaxation measurements will be performed without specific absorption rate limits. The total scan time will be approximately 40 minutes for each MRI examination. No MRI contrast agent will be given.

7 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) 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.

7.1 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).

7.2 Ethical Review

Prior to commencement of this investigation, the study protocol, patient information sheet and informed consent form will be submitted for approval to EC of the Hospital District of Southwest Finland. 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.

7.3 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. Participating patients potentially benefit of a more exact diagnosis.

8 DATA ANALYSIS

8.1 Qualitative analysis of MRI data

The prostate gland will be divided according to zonal anatomy into 26 regions of interests (ROIs) (covering the whole organ). 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 remaining inferior third. The peripheral zone in each part of prostate (the base, mid-region and apex) will be divided into 6 ROIs so 18 ROIs will contain the peripheral zone. The central and transitional zone which is just in the base and mid-gland will be divided in each part of prostate into 4 ROIs so 8 ROIs will contain central and transitional zone tissue. In each ROI the present of cancer will be determined by anatomical MRI, and difference DWI sequences alone and their combinations.

8.2 Quantitative analysis of DWI

8.2.1. Monoexponential quantification of DWI

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

$$ADC = -\ln\left(\frac{SI(b_2)}{SI(b_1)}\right) \qquad \text{(eq. 1)}$$

where SI(b_2) and SI(b_1) denotes the signal intensity at higher (b_2) and lower b-value (b_1).

8.2.2. Biexponential quantification of DWI using high b-values

It has been shown that when using high b-values, up to 3000 s/mm^2, the signal decay is better described by a biexponential fit rather than a monoexponential fit in healthy prostate tissue (31) and prostate cancer (32).

In that case the following biexponential function (eq. 2) can be used to describe signal decay:

$$\frac{S(b)}{S(0)} = (1-f)\cdot\exp(-b\cdot Ds) + f\cdot\exp(-b\cdot Df), \qquad \text{(eq. 2)}$$

where *f* is the fraction of fast diffusion, *Ds* represents the slow components of diffusion and *Df* represents the fast components of diffusion.

8.2.3. Biexponential quantification of DWI using low b-values

The intravoxel incoherent motion (IVIM) theory is an advanced method to separate diffusion and perfusion effects using DWI (33) at low b-values. The IVIM theory states that the blood flow in the capillaries causes a dephasing of the blood magnetization when motion-encoding gradients are applied. This means that the motion of water molecules due to microcirculation of blood in the capillary network (perfusion) has a similar impact on of resulting MRI signal as their motion due to molecular diffusion.

IVIM can be expressed by the following biexponential equation (eq. 3):

$$\frac{S(b)}{S(0)} = f\cdot\exp(-b\cdot D^*) + (1-f)\cdot\exp(-b\cdot D), \qquad \text{(eq. 3)}$$

where *f* is the perfusion fraction, D^* is the perfusion components of diffusion and *D* represents the fast components of diffusion.

A high variation of the perfusion fraction and perfusion coefficient in normal prostate and prostate cancer has been reported (34) suggesting that the removal of the perfusion component from calculation of diffusion properties might increase diagnostic performance of DWI. In addition, ADC maps calculated using monoexponetial fit, provided better diagnostic performance for tumor detection compared to parametric maps based on IVIM theory (35).

9 SAMPLE SIZE

This prospective feasibility study which assesses the utility of difference models and DWI sequences for the diagnosis and characterization of prostate cancer in patients with histologically confirmed prostate cancer scheduled for radical prostatectomy will enroll 200 patients. Imaging data analysis will be performed after every patient with emphasis on reporting the suspected location of possible tumor within the prostate gland. The study may be interrupted at the discretion of principal investigator after consulting other chief investigators.

10 QUALITY ASSURANCE

10.1 Information of study personnel and training

The technical and other supporting personnel of Medical Imaging Centre of Southwest Finland, Department of Urology and Department of Radiology, University of Turku, Finland is 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.

10.2 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 Ethical Committee.

11 STUDY SCHEDULE

The study will start in spring 2015 and all mandatory authorizations will be obtained before the beginning of the study. All MRI studies are expected to be performed within 24 to 30 months. Preliminary analysis of all results will be available in autumn 2016 and reports are expected to be written during autumn 2018.

12 FINANCING

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

13 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.

14 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).

15 ARCHIVING

15.1 Medical Imaging Centre of Southwest Finland

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 EC approvals and amendments, all source documents and case report copies, MRI raw data, 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. All MRI studies including reconstructed images are stored up on PACS system at the Medical Imaging Centre of Southwest Finland as other routine clinical imaging data.

16 Appendix

16.1 Appendix 1

SEQUENCE OF EVENTS

Event

Diagnosis of prostate cancer

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Inform consent by patient

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Referral to MRI examination

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MRI examination

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Prostatectomy

↓

Pathologic evaluation

↓

Final diagnosis

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Imaging and pathology corrections

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