Clinical trials registration number: Not applicable

Status: Enrolment of healthy volunteers on-going

1 SUMMARY

Gliomas are the most common primary brain neoplasms. Unfortunately, grading of gliomas, which is of significant clinical importance, is challenging due to sampling errors With standard MRI sequence a reliable targeting of biopsy is often impossible. More advanced MRI techniques are urgently needed which could provide new means of characterizing and visualizing brain tissue. Non-invasive quantitative characterization is potentially a promising approach. Imaging of healthy volunteers is a pre-requisition to develop optimal imaging protocols and analyses methods for patients with brain tumors. Understanding of age related changes is crucial for quantitative analyses. The aim of our study is to develop novel imaging protocols suitable for the brain MRI and to detect age related changes by the means of rotating frame and diffusion weighted imaging.

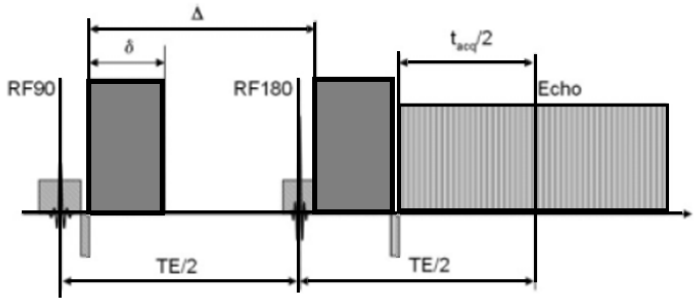
2 INTRODUCTION

Optimalization of imaging protocol involving healthy volunteers is necessary to achieve the highest diagnostic performance of brain MRI at 3T magnetic field for patients with suspected brain neoplasm. Gliomas are the most common primary brain neoplasms. They range from low grade to anaplastic and glioblastoma multiforme (GBM) which are also referred to as high grade gliomas. The current standard criterion for tumor grading is based on the histopathologic assessment of tumor specimen obtained during surgery. However, this may have severe limitations due to sampling errors especially when tumor-grade heterogeneity is presented within the same tumor specimen. These sampling errors could have profound consequences on the management of the disease and survival. Therefore, novel more accurate non-invasive imaging tools are needed that could predict cancer aggressiveness and thus complement the histopathologic grade. (1).

Anatomical MRI (T2-wighted sequences, fluid-attenuated inversion-recovery based sequences, ….) is unable to reliable differentiate low and high grade gliomas. Relaxation along a fictitious field (RAFF) is relatively very new MR imaging technique applying amplitude and frequency-modulated irradiation in a subadiabatic regime. The use of

radiofrequencypulse is based on sine and cosine amplitude and frequency modulations of equal amplitudes, which give rise to a stationary fictitious magnetic field in a doubly rotating frame. The RAFF relaxation time constant (T_{RAFF}) was found to differ from laboratory frame relaxation times (T_1 and T_2) and rotating frame relaxation times ($T_{1\rho}$ and $T_{2\rho}$) (2). Rotating frame relaxations ($T_{1\rho}$ and T_{RAFF}) have shown to be quantitative MRI markers to follow up disease progression, including brain and myocardial ischemia (3) and to follow up response to therapy(4). Moreover, T_{RAFF} has shown excellent correlation with cell density in a rat glioma model, which makes it a potential biomarker to follow up cancer therapy outcome (5).

In order to measure diffusion properties of tissue using MRI, the Stejskal–Tanner imaging sequence is used (Stejskal and Tanner, 1965). Information about proton diffusion is acquired by applying motion-encoding gradients, which cause phase shifts in moving protons. This phase shift depends on the quantity as well as direction of movement.



where γ denotes the gyromagnetic ratio, G the diffusion gradient amplitude, δ the diffusion gradient duration and Δ the time between the leading edges of the diffusion gradient pulses.

It was demonstrated that fractional anisotropy (FA) and apparent diffusion coefficient (ADC) correlate with glioma grade (6). In addition, DTI could reveal larger peritumoral abnormalities in gliomas, which are not apparent on conventional anatomical MRI (7).

3 OBJECTIVES AND PURPOSE

Specific aims of this project are as follows:

i) To measure quantitative MR relaxation values (T_{RAFF}, T_1, T_2, $T_{1\rho}$, $T_{2\rho}$) of normal gray and white matter

ii) To develop quantitative and qualitative methods for evaluation of advanced MRI techniques

iii) To determine age related changes in gray and white matter by the means of MR relaxation measurements (T_{RAFF}, T_1, T_2, $T_{1\rho}$, $T_{2\rho}$) and DWI

iv) To evaluate reliability and repeatability of novel MR imaging protocol suitable for brain MRI

4 STUDY DESIGN

This is an open prospective study to obtain information on applicability of rotating frame imaging and DWI methods for the purpose of non-invasive brain imaging. The use of rotating frame imaging and advanced DWI models could provide useful information concerning tissue structure. It is hypothesized that novel rotating frame imaging and DWI methods could provide new non-invasive tools to characterize brain tissue.

5 HEATHY VOLUNTEERS

5.1 Number of healthy volunteers

This study comprises of 5 sub-groups of different age: 20-30 years, 30-40 years, 40-50 years, 50-60 years, 60 years and more. Each sub-group will consist of 30 healthy volunteers resulting into the total number of 150 healthy volunteers. In order to evaluate repeatability of the novel MRI methods, 40 healthy volunteers will undergo two repeated MRI examinations performed within one week.

5.2 Inclusion criteria

- Age: 20 to 80 years old
- Language spoken: Finnish
- Mental status: Healthy volunteers must be able to understand the meaning of the study
- Informed consent: The patient must sign the appropriate Ethical Committee (EC) approved informed consent documents in the presence of the designated staff

5.3 Exclusion criteria

- Prior medical history: Healthy volunteers must have no history of serious cardiovascular, liver or kidney disease
- Any psychiatric condition that compromises the subject’s ability to participate in the study
- Infections: Healthy volunteers must not have an uncontrolled serious infection
- No contraindications for MRI (cardiac pacemaker, intracranial clips etc)

- Healthy volunteers must not have claustrophobia with serious symptoms
- Pregnant or lactating women

6 MULTIMODALITY IMAGING

6.1 Pre-study evaluation

All hearthy volunteers will be first evaluated by a member of the research group to find if they are suitable for the study. Typically they will be allowed 2-4 days to read the inform sheet before their consent to participate is requested.

7.2 MRI

MRI imaging of the brain will last approximately 35 minutes. The used MRI systems will 1.5T/3T Siemens system (Magnetom Aera 1.5T or Verio 3T, Erlangen, Germany) or 1.5T/3T Philips system (Philips Ingenia, Best, Netherlands) or 3T Philips PET/MR system (Philips Ingenuity, Best, Netherlands). Integrated RF coil will be used for excitation while dedicated 32 or 15 channel coil will be used for signal perception. Initially, data for attenuation correction will be obtained followed by anatomical sequences such as T_2-weighted turbo spin echo, FLAIR and T_1-weighted anatomic imaging in axial, sagittal and coronal directions followed by RAFF, continues wave $T_{1\rho}$, adiabatic $T_{1\rho}$, continues wave $T_{2\rho}$ and adiabatic $T_{2\rho}$. Diffusion weighted imaging will be obtained with single-shot 2D spin-echo echo-planar imaging. No gadolinium-enhanced T1-weighted imaging will be performed.

7 ADVERSE EVENTS

The risks for the hearthy volunteers inflicted by participation in the study are deemed minimal. Anatomical MRI and advanced MRI techniques are considered as safe techniques since no ionizing irradiation is used. In addition, no intravenous catheters are required since no paramagnetic contrast agents will be used. The presence of claustrophobia will be evaluated in the screening phase and patients with serious symptoms will be excluded from study.

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).

8.2 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.

8.3 Potential risks and benefits to study subjects

The risks for the hearthy volunteers inflicted by participation in the study are deemed minimal. Both standard MRI and advanced MRI are considered as safe techniques.

9 DATA ANALYSIS

9.1 Quantitative analysis of DWI data

Several b-values will be used in calculations. The following four mathematical models will be applied to the simulated curve:

1. Monoexponential:

$$\frac{S(b)}{S(b_0)} = S_0 e^{-bADC_{mono}} \qquad \text{[eg. 3]}$$

where b is the b-value, $S(b_o)$ is signal intensity at b-value of 0 s/mm^2, ADC_m is the diffusion coefficient. This is the simplest, one parameter DWI model which describes diffusion of pure water without any barriers.

2. Stretched exponential:

$$\frac{S(b)}{S(b_0)} = S_0 e^{-(bADC_{streched})^{\alpha}} \qquad \text{[eg. 4]}$$

where b is the b-value, $S(b_o)$ is signal intensity at b-value of 0 s/mm^2, ADC_s is the diffusion coefficient, α is the heterogeneity index/"anomalous exponent". Equation 4 is also known as Kohlrausch-Williams-Watts model (8, 9). The dimensionless α parameters, varies from 0 to 1, characterizes the deviation from the monoexponential decay. The stretched exponential model can be considered as a liner superposition of monoexponential decays (10) and not surprisingly has shown to be more robust than the biexponential model for DWI of PCa (9).

3. Kurtosis:

$$\frac{S(b)}{S(b_0)} = S_0 e^{(-bADC_{kurtosis} + \frac{1}{6} b^2 ADC_{kurtosis}^2 K)} \qquad \text{[eg. 5]}$$

where b is the b-value, S_0 is the signal intensity at b=0 s/mm^2, ADC_k is the diffusion coefficient, K is the kurtosis. Kurtosis model has been developed by Jensen at al. (11) to characterize deviation of DWI signal decay from monoexponential function. The dimensionless K parameter characterizes the deviation from the monoexpoenantial decay.

4. Biexponential:

$$\frac{S(b)}{S(b_0)} = S_0(1-f)e^{-bD_s} + fe^{-bD_f} \qquad \text{[eg. 6]}$$

where b is the b-value, $S(b_o)$ is signal intensity at b-values of 0 s/mm^2, f is the fraction of fast diffusion, Df is fast diffusion, Ds is slow diffusion. Biexponential model is two compartmental model but two distinct diffusion components do not correspond to the intra- and extracellular spaces. Poor correlations between volumes of intra- and extra-cellular spaces and parameters of the biexponential model have been shown (12, 13). Nevertheless, in formalin fixed prostate tissue Ds and Df values correlated with the partial volumes of stromal and epithelial compartments (14).

The intravoxel incoherent motion (IVIM) theory is an advanced method to separate diffusion and perfusion effects using DWI (15) 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.

9.2 Quantitative analysis of rotating frame imaging data sets

Mono-exponential function will used to fit signal decay of the rotating frame imaging data sets.

9.3 Statistical analysis

All analyses will be performed with SAS version 9.1 (SAS Institute, Inc., Cary, NC). A p-value of <0.05 will be considered to be statistically significant. In order to evaluate reliability and repeatability of all estimated parameters, interclass correction coefficient valeus (ICC 3,1) according to Shrout and Fleiss (16) will be caluated.

10 SAMPLE SIZE

This prospective feasibility study which evaluates the utility of advanced MRI techniques for detection and characterization of brain tissue will enroll 150 healthy volunteers. An interim analysis will be made after 30 healthy volunteers with emphasis on imaging characteristics and the study may be interrupted at the discretion of principal investigator after consulting other chief investigators.

11 QUALITY ASSURANCE

11.1 Training and information of study personnel

The technical and other supporting personnel of Turku PET Centre and Department of Diagnostic Radiology are well experienced in performing MRI studies. In the beginning of the study all involved personnel 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.

11.2 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.

12 STUDY SCHEDULE

The study will start in summer 2014 pending all mandatory authorizations have been obtained. All MRI studies are expected to be performed within two years. Analysis and modeling of the MRI data is feasible once 15-30 healthy volunteers have been imaged. Preliminary analysis of the results will be available in early 2015 and first reports are expected to be written during 2015.

13 FINANCING

The study will be financed in part by Finnish Governmental Special Funding (In Finnish: ’Erityisvaltionosuus, EVO’). Additional funding is sought through national non-profit organizations such as Sigrid Juselius Foundation and Cancer Foundations of Finland.

14 STUDY REPORT AND PUBLICATION(S)

Any formal presentation or publication of data collected within 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).

15 ARCHIVING

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, and patient informed consent forms are kept in a locked room at the Turku PET Centre of Turku University Hospital 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.

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