Region of Southern Denmark

DW-MRI as a decision making tool in the in-room MRI guided radiotherapy pipeline

Project description

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Abstract

In radiotherapy (RT), computed tomography (CT) is used for treatment planning and patient positioning, but suffers from poor soft-tissue contrast. Magnetic resonance imaging (MRI) provides excellent soft-tissue contrast and in addition, biological information. With the recent development of the so-called MR-linac, a fusion of an MR scanner and a linear accelerator, RT might be further individualized patients.

In conventional RT treatment planning, the gross tumour volume is homogeneously treated, neglecting any tumour heterogeneity. Diffusion weighted MRI (DW-MRI) may capture tumour sub-regions based on biological information. DW-MRI shows potential to define regions that need increased radiation dose, or to predict treatment response using DW-MRI derived metrics.

However, lack of standardization of DW-MRI data analysis complicates its use as a decision-making tool in the MR-linac treatment course. This PhD project aims at improving consistency in data analysis by: 1. proposing DW-MRI based segmentation tools for robust extraction of quantitative DW-MRI parameters, 2. demonstrating clinical feasibility of DW-MRI guided treatment adaptation in the MR-linac workflow, and 3. investigating the ability of the DW-MRI parameters to predict response. Fulfilment of the aims may increase chance of successful clinical implementation of DW-MRI aiming for higher cure rates and/or reduced toxicity in future RT patients.

Aim

The overall aim of this project is to investigate methods for integration of Diffusion-Weighted MRI in an in-room MR-guided radiotherapy workflow for potential treatment intervention. This includes DW-MRI based treatment plan adaptation during the course of RT, and response assessment for potential individualized treatment intervention.

Specifically, the project aims at

- Developing computer based segmentation tools for DW-MRI for improved consistency in parameter calculation.
- Demonstrating the technical and clinical feasibility of DW-MRI guided treatment adaptation using segmentation tools in the online MR-linac workflow.
- Clinical validation of standard model-based and a novel data driven method for response prediction using data from in-treatment DW-MRI measurements.

Introduction

In standard radiotherapy (RT), computed tomography (CT) provides the backbone of treatment planning for cancer patients, mainly because CT data can be used directly for calculation of the radiation dose distribution. In most cases however, other image modalities, especially positron emission tomography (PET) and magnetic resonance imaging (MRI), are needed in addition, to outline the extent of the disease. During the delivery of the RT course, which is divided into many treatment fractions and may extend to weeks, the patient is positioned with so-called cone beam CT (CBCT) imaging, an integrated CT device. CBCT has led to substantially improved precision of RT but suffers from poor soft-tissue contrast and gives no information about the tumour biology.

MRI provides exquisite soft tissue contrast allowing much easier differentiation between tumour and healthy tissue. For this reason, researchers and industry have worked together for almost two decades to fuse an MRI scanner and a clinical linear accelerator (linac) into one machine, the hybrid MRI linear accelerator (MR-linac). This was accomplished recently (2018), and OUH was the fifth center worldwide to go live with a high-field MR-linac[1] [2] [3], a strategic research investment worth 70 million DKK from the Region of Southern Denmark. Even today, the high-field MR-linac at OUH is the only of its kind in Denmark.

The MR-linac enables online MRI guidance at each treatment fraction. No extra appointment for dedicated MRI scan is needed, which is beneficial for both the patient and for the hospital from a cost perspective. Online MRI guidance allows adaptation of the treatment plan to match the “anatomy of the day”. In comparison to CBCT-based image guidance, MRI provides much higher anatomical details (Figure 1). However, the full clinical potential of the MR-linac is not limited to high quality anatomical images only, as it is also capable of providing information on tissue biology through advanced imaging methods.

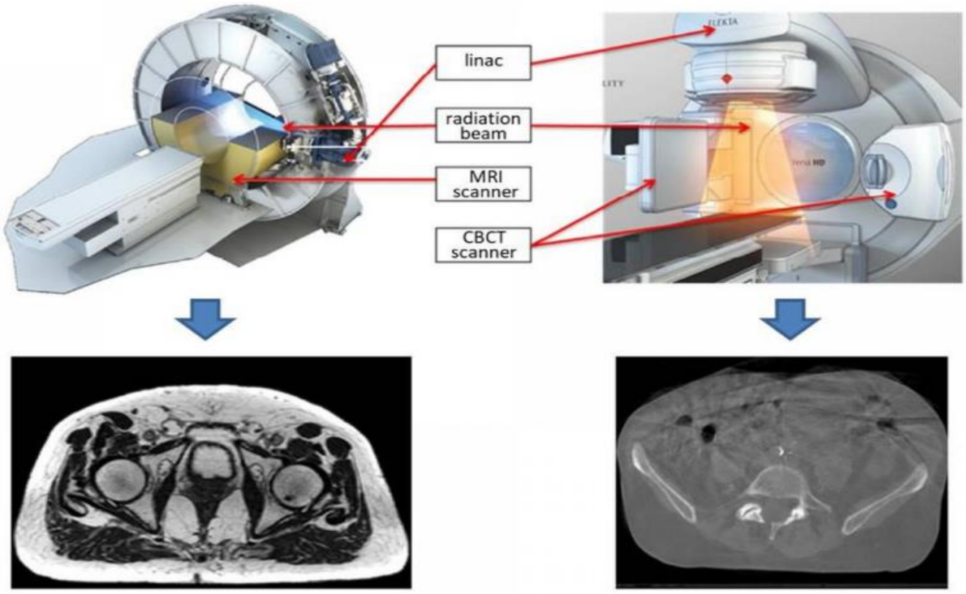

Figure 1: Schematic illustration of an MRI-linac (left) and a standard linac with CBCT imaging (right).

One such method is diffusion-weighted MRI (DW-MRI), which provides information on the water mobility in the tissue[4]. Low mobility of water is correlated to high cellularity within the tumour, typically indicative of higher cellular viability. Cellularity is quantifiable using DW-MRI derived metrics such as the apparent diffusion coefficient (ADC)[5]. Hence, DW-MRI enables quantitative detection of sub-regions of the tumour with increased viability. This holds great potential for individualising RT for the patients. The information provided by DW-MRI may for example be used in online adaption of the treatment plan by assigning a higher dose to regions of high cellular density[6] (dose painting), to increase the probability of tumour control. Furthermore, DW-MRI derived parameters within tumour during RT have shown potential for outcome prediction[7 8 9 10 11]. Hence, during an MR-linac treatment course, DW-MRI may aid in informed decision about alternative treatment options (including cessation) in patients with cancer that exhibits limited response to RT. The perspective is that these individualization strategies increase the probability of cure and/or minimize the risk of radiation induced toxicity in future patients.

However, to achieve a valid evaluation of the clinical potential of DW-MRI for the MR-linac workflow, it is critically important to secure consistency in the DW-MRI data analysis. This consists of two parts: outline of the region of interest (ROI) in the image (segmentation), and derivation of DW-MRI related parameters from the ROI. Manual segmentation of DW-MRI is time-consuming and requires a high level of expertise. On top of this, intra- and inter-observer variability of segmentations might lead to higher uncertainty of the derived parameters [12 13 14]. The parameter derivation process itself is also prone to uncertainty due to variations in methods. Typically, DW-MRI data analysis relies on mathematical models, however, the use of models might lead to biased parameters. Therefore, data driven methods may be preferred, since they allow extraction of unbiased parameters and may lead to more reliable prognostic information from DW-MRI.

In this project, these challenges are addressed in the following sub-studies:

Study 1: Development of computer based segmentation tools for DW-MRI for improved consistency in parameter calculation.

Study 2: Investigation of the technical and clinical feasibility of DW-MRI guided treatment adaptation using segmentation tools in the online MR-linac workflow

Study 3: Clinical investigation of the ability of a standard model-based and a novel data driven method for DW-MRI parameter derivation, to predict local control using repeated DW-MRI scans.

Project plan and methods

Study I: Automatic tumour segmentation on DW-MRI

Aim:

Development and validation of computer based tools to segment tumour sub-volumes based on DW-MRI with the intention of defining potential high-risk regions of the tumour volume.

Hypothesis/Outcome:

Semi-automatic and automatic segmentation tools for DW-MRI can be developed, and prove useful in the treatment preparation phase and in the on-line MRI guided RT workflow. The tools may perform comparable to the expert delineation and improve consistency.

Introduction:

MRI is often used as a supplementary image modality to delineate the gross tumour volume (GTV)[15] for treatment planning. The GTV is normally prescribed a uniform radiation dose, but is typically a heterogeneous region with several macroscopic sub-regions, that may best be targeted with a heterogeneous radiation dose. Increasing dose to the entire tumour (GTV), and at the same time keeping the dose to the surrounding normal tissues low, is often not technically achievable. Instead, the treatment plans may be modified to boost smaller regions within the GTV without compromising dose constraints of normal tissue.

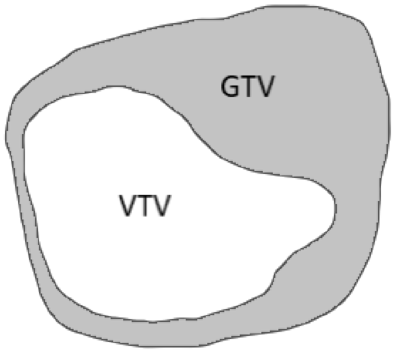

Figure 2: Illustration of the "viable tumour volume", VTV, captured by DW-MRI.

GTV heterogeneity can be captured with different imaging modalities, including DW-MRI, available on the MR-linac. Using the raw DW-MR images, regions with high tumour cellularity, referred to as the viable tumour volume (VTV), can be outlined[16] (Figure 2). The VTV is thus a potential region to assign a higher dose. In the current standard of care, the VTV is not outlined separately because current clinical evidence of its usefulness is weak. This is primarily because most pre MR-linac studies were exploratory, heterogeneous and with small patient cohorts due to the difficulty of acquiring repeated MRI on standalone scanners. However, the potential of VTV has been demonstrated in numerous pre MR-linac studies[6 11 16]. There is no golden standard for VTV segmentation, as the introduction of the VTV concept in research is still at its very beginning.

Tissue heterogeneity exist on a microscopic scale also. This means that each imaging voxel (3-dimensional volume element of an image) may contain a mix of different cell types that gives different diffusion environments. To disentangle the information from the DW-MRI voxels, mathematical decomposition can be applied to yield so-called mixture maps showing the content of the different DW-MRI environments within individual voxels of the GTV. The hope is that such mixture maps provide a more detailed information of the tumour heterogeneity.

Segmentation of GTV heterogeneity requires dedicated time of already heavily burdened radiologists and oncologists. Further, there might be considerable inter- and intra-observer variability, in the segmentations, as well as day-to-day variation in the MRI scans, which may translate into increased uncertainty in DW-MRI based studies. This limits both the validation of DW-MRI derived metrics as potential biomarkers for treatment response, and the potential identification of sub-regions within the GTV to which high dose (boost) may be given.

Method

a. Development of segmentation tools

Three approaches for tumour segmentation will be explored, of which the first two specifically aim for VTV segmentation and the third is exploratory (novel):

- *Method 1* is based on signal thresholding in DW-MRI and derived ADC-maps by Utso's method[17], and is implemented using the technical computing language Matlab (The MathWorks Inc., MA, USA). This approach is simple, easy to implement and does not require a priori input (learning).
- *Method 2* is an artificial intelligence based method (convolutional networks). It requires a larger set of learning data, but may potentially perform better. An already existing convolutional network design, developed for segmentation in medical images, will be applied to DW-MRI data.

- *Method 3* is an explorative approach based on thresholding in mixture maps obtained using a novel decomposition analysis suited for DW-MRI data. The decomposition analysis method has recently been developed and published by our group in collaboration with the Technical University of Denmark[19]

b. Performance of the segmentation tools

- Repeated DW-MRI (test-retest) from a cohort of 36 patients with rectal cancer are available for this study. Using method 1 and 2, VTV segmentation is performed on the repeated scans, and ADC values are extracted. The difference in ADC between repeated scans is measured and the ADC repeatability (limits of agreement) is determined using Bland Altman analysis[20]. The ADC repeatability is held up against the longitudinal change in ADC.
  As a reference, manual segmentation of GTV and VTV is performed by a radiologist on the repeated scans, and ADC values are extracted. The segmented regions and ADC repeatability is compared between the segmentation tools and the reference. The regions are compared using measures such as Dice similarity coefficient and Hausdorff distance.
- DW-MRI from three clinical cases are used in this study. Manual segmentation of GTV and VTV is performed at each of the MR-linac centers in the Elekta MR-linac consortium. Method 1 and 2 are used to perform segmentation on the same images. The inter-observer variability is compared between the manual segmentation and the segmentation tools.

c. Histological validation

- To validate that the segmented regions (VTVs) correspond to high tumour density regions, comparison to histology will be made in patients referred to MR-linac treatment where pre-treatment histological data from biopsies are available. The biopsies will be compared to corresponding DW-MRI of patients and agreement between VTV and localized biopsies will we estimated.
- Baseline Prostate Imaging-Reporting and Data System (PIRADS[18]) data from patients with prostate cancer is available for all patients with prostate cancer referred to MR-linac treatment. Agreement between PIRADS score and VTV will be evaluated.

Expected international peer-reviewed scientific publications

1. "*Semi-automatic segmentation tool for DW-MRI improves inter-observer variability compared to manual segmentation"*

Study 2: Feasibility of DW-MRI guided treatment adaptation using segmentation tools in the online MR-linac workflow

Aim

To demonstrate the feasibility of the online use of DW-MRI based plan adaptation and response evaluation in an MR-linac workflow.

Hypothesis/Outcome

It is feasible to implement a DW-MRI guided workflow on MR-linacs with semi-automatic segmentation for potential plan adaption and for response assessment.

Introduction

It has already been demonstrated that technically, DW-MRI can be acquired on MR-linacs with acceptable accuracy, repeatability and reproducibility in phantoms[24]. However, the feasibility of DW-MRI in a clinical setting remains to be demonstrated. Feasibility criteria include integration into the clinical treatment workflow: It should be possible within the normal treatment time, or with only a slight increase in the overall treatment time, to:

- acquire DW-MRI
- delineate VTV using the segmentation tools
- propagate the VTV to the online plan adaptation to perform potential GTV modification and dose modification (boost to VTV), without increasing dose to the surrounding tissue.
- extract parameters for response prediction.

Methods
Preliminary studies will be performed using phantoms to mimic the online workflow. Clinical test will be performed in patients for each of the following diagnosis: prostate, pancreas and liver cancer. The consistency of the VTV between fractions will be investigated to evaluate the general reliability and to identify the persistent VTV region. Local failure patterns may be compared to the VTV union and VTV intersections of all treatment fractions. Treatment plans with and without boost to the VTV will be simulated and compared to evaluate dose coverage of the target and compliance of dose constraints to normal tissue.

Expected international peer-reviewed scientific publications:
"Feasibility of DW-MRI only segmentation tool in an MR-linac workflow"

Study 3: Clinical investigation of the prognostic capacity of DW-MRI derived parameters from repeated in-treatment DW-MRI data

Aim:
To evaluate the ability of a standard model-based and a novel data driven frame framework to predict response using repeated DW-MRI data acquired during RT.

Hypothesis/Outcome
Repeated DW-MRI can be used as a tool for early prediction of local radiological response or biochemical response in patients treated with the MR-linac. The proposed frameworks will be tested on clinical data sets retrospectively to evaluate the prognostic value of DW-MRI derived parameters.

Introduction:
Extraction of DW-MRI parameters using mathematical models is common, but these models are unable to account for partial volume effects and might lead to biased parameters. The risk of biased parameters might be avoided using a data-driven (model-free) method. An example of such a method is the novel extension to the non-negative matrix factorization method (NMF), which has recently been developed and published by our group in collaboration with the Technical University of Denmark[19]. The novel method is named the monotonous slope NMF (msNMF), and is well suited for DW-MRI data.

Methods
DW-MRI parameters will be derived from regions of interest segmented using the three methods in study I. Method 1 and 2 yields a VTV and method 3 yields tumour features from mixing maps from the msNMF method. The derived parameters will be used as input (predictors) to a prediction framework. The methods will be tested using clinical datasets with known local radiological or biochemical response (volume reduction in follow-up scans for glioblastoma multiforme patients or PSA for prostate patients). Datasets will include longitudinal DW-MRI data from the MR-linac, from at least 50 patients with prostate cancer, and longitudinal DW-MRI data acquired with a diagnostic MR scanner during the RT course from at least 30 patients treated for glioblastoma multiforme.

Expected international peer-reviewed scientific publications:
"Outcome prediction from decomposition of repeated DW-MRI data acquired during treatment of prostate cancer with the hybrid MRI linear accelerator "

Statistical considerations
Overall study 1 and study 2 are technical aims which do not need bio-statistical power calculations. Phantom measurements will be repeated until sufficiently narrow confidence intervals are available. In study 2, the sample size is set to 3 patients in each site. This is clearly insufficient for any correlative efforts on clinical outcomes. However, the patient accrual is intended as a pilot project, which will serve to develop the workflow for adaptive planning with DW-MRI. Study 3 is a retrospective test in patients, in which the correlation between DW-MRI derived metrics and continuous response measures is determined. A Pearson correlation coefficient below 0.5 is found clinically irrelevant. Hence, in order to determine a Pearson correlation coefficient ≥ 0.5 on a significance level α = 0.05 and a power $(1-\beta)$= 80%, a sample size of 29 patients is required.

Ethics
This project will only include patients referred to MR-linac treatment or standard linac treatment, retrospectively, and will not influence patient treatment. No extra treatment time or disadvantage for the

patient is expected. In case any extra imaging is needed, the relevant permissions will be obtained, and the referring oncologist will inform the patient about possible extra imaging according to relevant authority regulations. All necessary regulatory approvals are already obtained as part of the project in accordance with Danish law and the Helsinki declaration.

Feasibility

The student will be enrolled at the University of Southern Denmark, and be a part of the research environment at the Department of Oncology, OUH. The Department of Oncology is experienced in MRI, and is equipped with an MR-linac (Elekta Instrument AB, Stockholm, Sweden) which is running clinically. OUH have access (and ethical approval) to PACS systems with image data identifiable through the Central Person Registry with 100% coverage. The departments have concurrent licenses to all necessary software packages. The student will work closely together with physicists and scientists with technical or basic science background, as well as radiologist and MRI radiographers, in order to address both technical and clinical questions. In-house developed phantoms will be used. The department has access to all necessary software packages.

Resources and collaborators

- MR-linac (Elekta Instrument AB, Stockholm, Sweden) at OUH.
- In house developed MR compatible end-to-end phantom with integrated dosimeter.
- A convolutional neural network algorithm for brain lesion segmentation on medical images is available on: https://biomedia.doc.ic.ac.uk/software/deepmedic/ [21], and will be used as a starting point in development of the AI model.
- The project “BRAIN”, currently running in the Department of Oncology, OUH, deals with segmentation of organs at risk using artificial intelligence.
- The novel monotonous slope non-negative matrix factorization method (msNMF) developed by collaborator Sofie Rahbek (ph.d. student at DTU), will be made available for this project with collaborators Lars Hanson , Department of Health Technology, DTU, and Kristoffer Madsen,Department of Applied Mathematics and Computer Science, DTU.
- OUH collaborates with other MR-linac centers through the Elekta MR-linac consortium[22] and is a member of the multi-institutional MOMENTUM study[23].
- Manual tumour segmentation is performed in collaboration with radiologists Frederik Severin Gråe Harbo and Maja Lynge Fransen at the Department of Radiology at OUH.
- Glioblastman multiforme data is made available by collaborator Rikke Hedegaard Dalhrot
- Biopsy and/or PIRADS correlation is studied in collaboration with oncologist Lars Dysager, Department of Oncology, OUH.
- A dataset of repeated DW-MRI from a cohort of 36 patients with rectal cancer is made available by physicist Henrik Dahl Nissen, Department of Oncology, Vejle Hospital.

Impact and relation to UN’s 17 sustainable Development Goals

In 2016, 71 percent of all deaths worldwide were related to one of the four main non-communicable diseases: cardiovascular disease, cancer, diabetes and chronic respiratory disease[25]. Improving cancer treatment is relevant in the greater perspective of ensuring healthy lives for all at all ages, as stated by the 3. of UN’s sustainable development goals[25]. This project aims at integrating DW-MRI into an MR-linac adaptive treatment workflow, which has the potential of improving treatment outcome for future cancer patients, as it might lead to optimized probability of cure and/or minimize the risk of toxicity.

Time Schedule

	2020		2021				2022				2023		
Quarter	3	4	1	2	3	4	1	2	3	4	1	2	3
Regulatory approvals													
PhD student employed													
Study 1													
Study 2													
Study 3													
Analyses and publications													

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