REGION SYDDANMARK

A national investigation of the safety of dose delivery in a daily treatment adaption workflow in MR-Linacs

Project description

13-03-2020

PhD-student: Signe Winther Hasler, Msc, Department of Oncology, Odense University Hospital

Main supervisor: Faisal Mahmood, PhD, Department of Clinical Research, University of Southern Denmark. Department of Oncology, Odense University Hospital

Co-supervisor: Uffe Bernchou, PhD, Department of Clinical Research, University of Southern Denamark. Department of Oncology, Odense University Hospital

Co-supervisor: Claus F. Behrens, Physicist, PhD, Radiotherapy Research Unit, Department of Oncology, Division of Radiotherapy, Herlev Hospital, University of Copenhagen

Co-supervisor: Ivan Richter Vogelius, PhD, DMSc, Professor, Department of Oncology, Rigshospitalet & Faulty of Health & Medical Sciences, University of Copenhagen, Denmark. Adjunct Professor, Dept. of Epidemiology and Public Health, University of Maryland – Baltimore, School of Medicine.

ABSTRACT
MRI excel by providing high soft-tissue contrast, high resolution and reasonably fast imaging options. For this reason standalone MRI machines have over the last about 10 years been installed in modern radiotherapy departments. The vast clinical potential of MRI in radiotherapy has recently led to the commercialization of a hybrid system, integrating an MRI scanner and radiotherapy delivery machine (linear accelerator), a so-called MR-Linac [2]. The main goal of the MR-Linac is to improve treatment of cancer patients by more precise identification of both tumor and surrounding normal tissue through live imaging with superior soft tissue contrast during daily treatment fractions. To unleash the full potential of such techniques, however, it would be required to take action on the live imaging by either beam stop (gating) or/and daily adaptation of the treatment plan. In either case, it is necessary to develop and maintain a rigorous system to ensure that dose accumulation based on the daily MR images is accurate and not affected by MR image distortion, which will be investigated in this PhD project through three subprojects:

1. Geometrical distortion and its dosimetric impact in MRI-guided treatment delivery
2. Evaluation of dosimetric safety in daily treatment adaptation
3. Clinical feasibility of daily adapted MR-Linac treatments

AIM
The overall aim of the current project is twofold:

1. To ensure that the MR-Linac safely delivers the prescribed dose to the target.
2. Establish a common and solid technical foundation for a collaborative setup between the MR-Linac centers in Denmark (Odense University Hospital, Rigshospitalet and Herlev Hospital), enabling safe referral of patients between centers and allow comparison of multicenter study data for stronger clinical research conclusions.

INTRODUCTION
Imaging is central in the standard of care for cancer patients. For diagnosis and staging Computed Tomography (CT), Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) are indispensable imaging modalities.

MRI excel by providing high soft-tissue contrast, high resolution and reasonably fast imaging options. For this reason standalone MRI machines have over the last about 10 years been installed in modern radiotherapy departments and used routinely in treatment planning for a large number of indications. Besides structural imaging MRI also provides functional and biological information, which holds promise as early biomarker for treatment response [1].

The vast clinical potential of MRI in radiotherapy has recently led to the commercialization of a hybrid system, integrating an MRI scanner and radiotherapy delivery machine (linear accelerator), a so-called MR-Linac [2]. This is a substantial technological achievement as MR imaging is highly sensitive to noise from moving metals in the linac (gantry rotation), and the linac is very sensitive to the magnetic field of the scanner. The main goal of the MR-Linac is to improve treatment of cancer patients by more precise

identification of both tumor and surrounding normal tissue through live imaging with superior soft tissue contrast during daily treatment fractions. To unleash the full potential of such techniques, however, it would be required to take action on the live imaging by either beam stop (gating) or/and daily adaptation of the treatment plan. In either case, it is necessary to develop and maintain a rigorous system to ensure that dose accumulation based on the daily MR images is accurate and not affected by MR image distortion. For the question of daily adaptation, this is a substantial challenge to handle at reasonable personnel resources and adequate safety of targeting. Odense University Hospital (OUH), Rigshospitalet (RH) and Herlev Hospital (HH) are among the first centers worldwide to purchase each an MR-Linac. The first patient treatment in Denmark with an MR-Linac was recently performed successfully at OUH, while MR-Linacs installations are being finalized at RH and HH, and treatments are expected soon. The MR-Linac centers in Denmark are initiating what is hoped to become a long term collaboration including common clinical trials on selected cancer diagnoses and support through possibility to transfer patients across institutions. A different type of MR-Linacs are being installed at OUH (Unity by Elekta) and RH/HH (MRIdian by Viewray) respectively, emphasizing the need for a common technical foundation. Regardless of vendor similarities or dissimilarities, however, safe delivery of the dose to the target requires an investigation on the individual MR-Linacs with full documentation of the chain of uncertainties and developments of methods to ensure dose verification at clinical levels within the time limits of such an approach. We propose that such an effort is substantially better if implemented in a national collaboration, which will also benefit future adopters of MR-Linacs in Denmark. Specifically, we will look into the impact of geometric distortions of MR images on the precision of dose delivery and benchmark daily treatment adaptation procedures of the MR-Linacs against standard adaptation techniques. Further, feasibility and potential clinical benefit of daily dose adaptation with MR-Linac will be investigated in patients.

PROJECT PLAN AND METHODS

This project will be carried out in collaboration between OUH, RH and HH. It consists of three subprojects that will each be carried out at all three MR-Linacs centers.

Subproject 1: Geometrical distortion and its dosimetric impact in MRI-guided treatment delivery – Adaption based on

Aim: *To estimate the level of inaccuracy in dose delivery as a result of geometrical distortion of MRI in MR-Linac treatments.*

Hypothesis/outcome: *A common method for independent verification of spatial integrity and dosimetric impact thereof can be developed across vendors and sites. Unified documentation of spatial integrity made available as technical documentation for national clinical trials.*

Distortion in MRI imaging is a problem uniquely relevant to radiotherapy and further emphasized if dose accumulation and plan adaptation is considered for clinical use. The distortion is partly object/patient related and partly system related and also depends on the choice of imaging sequence. It is unique that we have three high level centers with different machine setups that collaborate on a much needed quantification of the impact on dose accumulation as such measures across institutions are lacking. Further, this project will provide essential support to clinical trials aiming at demonstrating clinical benefit of treatments on MR-Linacs, including trials of oligo-metastatic disease and stereotactic radiotherapy of liver metastases.

Specialized phantoms with different sizes and materials will be used to simulate different conditions inside the scanner (MR-Linac). A procedure for evaluation of MR sequences will be established. MRI images will be evaluated by comparison to the known geometrical form of the phantoms [5] and by field mapping [10] using patient imaging. The calculated distortion information will be used to 'undistort' images of the disease sites mentioned in Subproject 3. The dosimetric impact of the distortion will be evaluated by recalculating the original treatment plan using the undistorted images.

Resources:

- Distortion measurement phantoms: QUASAR MRID-3D (Modus QA, USA), ACR MRI Phantom, MagPhan RT 1230 (The Phantom Laboratory, USA), in-house made phantom being developed at OUH.
- Deformation vector field is acquired using Monaco (Elekta Instrument AB Stockholm) and MRIdian Treatment Planning and Delivery Software (TPDS) supplemented by Elastix.
- Treatment plan generation and recalculation is done using Monaco (TPS) and MRIdian TPDS. It will be the responsibility of the PhD student to travel to the three sites and perform the measurements in collaboration with the on-site clinical physics team. Likewise, it will be the responsibility of the PhD student to analyze the data and write scientific report as well as suggest an online updatable whitepaper to support future multi institutional clinical trials.

Subproject 2: Evaluation of dosimetric safety in daily treatment adaptation
Aim: *To compare MR-Linac based dose adaptation strategies with standard methods.*

Hypothesis: *It is possible to define limits of perturbations such that accumulated dose uncertainties in MR guided dose adaptation are sufficiently small to be without clinical relevance.*

To evaluate the complete dosimetric impact of the MR-Linac workflow with daily adaptation an end-to-end (E2E) phantom currently being developed at OUH will be used. This phantom will be designed to be visible in both CT scans and MR scans and will simulate the patient in the treatment flow of a standard treatment and an MR-Linac treatment, respectively. Clinically relevant treatments will be planned for the E2E phantom ('patient'). Three treatment plans representative of the disease sites mentioned in Subproject 3 will be used. A random setup variation in a clinically relevant range in 10 simulated treatment fractions will be applied in both treatment arms. After online realignment of the phantom based on standard and MR-Linac methods, respectively, the planned treatment will be delivered and the total treatment dose will be collected by an in-phantom dosimeter.

Resources, roles and responsibilities:

- End-to-end (E2E) phantom: An E2E phantom currently being developed at OUH will be made available for the current project. For dose measurements radiochromic film will be used (GAFchromic) and the OUH setup for film dosimetry will be applied.
- Treatment plans for standard treatment will be generated using Pinnacle (Philips Healthcare) at OUH and with Eclipse (Varian Medical Systems) at RH/HH. MR-Linac treatment plans will be generated with Monaco at OUH and with MRIdian TPDS at RH/HH.
- An independent MR to electron density algorithm will be used to distinguish the source of possible dose deviations from the MR image processing (electron density map), distortions (Subproject 1) and dose calculation inaccuracies (remainder).
- For comparison of total accumulated dose distribution of the standard accelerator and the MR-Linac treatments gamma analysis will be performed using 3 %/3 mm and 95 % passing rate criteria.

In addition, target coverage metrics (dose volume histograms) as well as full 3D dose assessment in the treatment planning systems will be used.

All measurements will be performed at all institutions with roles and responsibilities as in Subproject 1. Differences between sites/implementations will be discussed at national meetings on MR guided radiotherapy (a sequence of meeting has already been established with approximate frequency of one per quarter). A paper on the sub distribution of dose accumulation uncertainty will be published.

Subproject 3: Clinical feasibility of daily adapted MR-Linac treatments
Aim: *To clinically validate the daily dose adaptation strategy in MR-Linac treatment in three different disease sites.*

Hypothesis: *On-line dose adaptation is possible and off-line dose verification using the uncertainty estimation procedures of aim 1 and 2 confirms that uncertainties are well within clinical acceptability.*

Clinical validation will be performed as a feasibility trial focusing on the ability and potential benefit from on-line dose adaptation (re-planning) in 3 patients in each of the following 3 disease sites: Head and neck cancer, prostate only, gynecological cancer with regional lymph node irradiation with possible addition of further sites as experience with the modality grows. Patients will be scanned on the MR-Linac and an online dose re-planning will be made for at least 3 fractions during the course of radiotherapy. In each MR-Linac based fraction, the dosimetric benefit from the on-line adaptation will be assessed. MR on-line monitoring will be performed throughout the entire process to account for these in the overall efficacy analysis. Extrapolation to estimate the patient level benefit will be made by bioeffect modelling – a documented strength of both RH and OUH groups. The potential benefit from using full adaptation versus a library of plans will be compared, taking the organ motion during adaptation/plan selection into account.

Resources and detailed plan:

- Sequences applied will follow the (evolving) clinical protocols at all three sites, but an on-line CINE MRI sequence will be required.
- Dose re-planning will be based on the 'image of the day' using deformable image registration of the baseline MRI and outlined organs at risk and the tumor, to the MRI scan of the day.
- Hounsfield Units are propagated as a uniform average bulk assignment to the individual structures and in addition an independent MR to electron density map will be applied if necessary based on the results of aim 2.
- Modeling of expected effect of dose adaptation and biological effect of procedure-related uncertainties will be performed using normal tissue complication probability models with accumulated radiation dose as covariable and clinical risk factors as potential risk modulators. The effect on tumor control is more challenging as the biological consequence of partial dose compromises is essentially unknown. A sensitivity analysis will be made using a model based on the mean dose to target and a model based on a generalized mean following the gEUD (generalized Equivalent Uniform Dose) formulation of Niemierko et al. [6] where relevant, composite endpoints of tumor control and toxicity will be used [7].

Time plan:

	2020				2021				2022			
Quarter	1	2	3	4	1	2	3	4	1	2	3	4

Regulatory approvals												
PhD student employed												
Subproject 1												
Subproject 2												
Subproject 3												
Analyses and publications												

PROJECT FEASIBILITY

The PhD student will be enrolled in Odense (co-supervised by RH and HH) and will need to travel to all MR-Linac centers and work closely with the local physics team. The investigational team consists of physicians and scientist with technical or basic science background to address both the clinical and technical investigational questions, and to allow assessment of the clinical feasibility. Department of Oncology at OUH is equipped with an MR-Linac from Elekta and running clinically, RH is equipped with an MR-Linac from Viewray also running clinically, while HH is current completing their installation and expect to start clinically soon. All departments are experienced in MRI with dedicated MRI scanners and MRI radiographers. Specialized phantoms will be crafted by in-house workshop at OUH. OUH, RH and HH have access 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.

COLLABORATORS

On national level the key collaborators are OUH, RH and HH, Departments of Oncology, in particular Faisal Mahmood (OUH), Ivan Richter Vogelius (RH), Claus Behrens (HH). This team holds a strong track record and leading position within the multi-disciplinary field, in particular within image-guided RT, MR in RT, dosimetry and biostatistics.

Internationally, OUH is a member of the Elekta MR-Linac consortium which consists of all leading MR-Linac (Unity) sites. Strong bonds are established to the founding MR-Linac sites University Medical Center Utrecht, Utrecht and The Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Amsterdam. Elekta Instrument AB and Philips Healthcare provide technical support and can provide research access if needed. RH and HH are in the process of initiating a research contract with ViewRay and participate in the ViewRay research consortium of early adopters. In addition, RH and HH have direct collaborations with Heidelberg and Amsterdam MR-Linac centers.

CLINICAL AND NATIONAL PERSPECTIVES

Treatment with the MR-Linac enables visualization of the cancer and the normal tissue surrounding it. This may facilitate new or re-emerging treatments in high risk settings including soft tissue oligometastatic disease, pancreatic cancers and liver or prostate treatments without prior marker implantation procedures. The complexity of the MR-Linac treatment requires an investigation to establish a common technical baseline across Danish MR-Linac types and centers. This is clinically important in order to allow referral of patients between centers, and in order to evaluate the potential clinical benefit of MR-Linac treatments locally and in national multicenter trials. The current research proposal will involve all three MR-Linac centers in Denmark equally and future Danish MR-Linac centers will be invited to implement the transferrable investigational methods developed during the project period.

ETHICAL CONSIDERATIONS

Regulatory approvals will be obtained as part of the project in accordance with Danish law and the Helsinki declaration. Application work has begun and formal submissions are expected soon. No issues are anticipated formally and with regard to the time plan.

REFERENCES

[1] Faisal Mahmood, Helle H Johannesen, Poul Geertsen, Rasmus H Hansen. Repeated diffusion MRI reveals earliest time point for stratification of radiotherapy response in brain metastases. Phys. Med. Biol. 62 : 2990-3002, 2017.

[2] Jan J W. Lagendijk, Bas W. Raaymakers, Alexander J E. Raaijmakers, Johan Overweg, Kevin J. Brown, Ellen M. Kerkhof, Richard W. van der Put, Björn Hårdemark, Marco van Vulpen, and Uulke A. van der Heide. Mri/linac integration. Radiother Oncol, 86(1):25–29, Jan 2008.

[3] Søren M Bentzen, Louis S Constine, Joseph O Deasy, Avi Eisbruch, Andrew Jackson, Lawrence B Marks, Randall K Ten Haken, and Ellen D Yorke. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys, 76(3 Suppl):S3–S9, Mar 2010.

[4] Alan E Nahum, Beatriz Sanchez-Nieto. Tumor control probability modeling: basic principles and applications in treatment planning. Phys Medica 2001;17:13-23.

[5] Lesley N Baldwin, Keith Wachowicz, Steven D Thomas, Ryan Rivest, Gino Fallone. Characterization, prediction, and correction of geometric distortion in 3 T MR images. Med. Phys. 34 (2), February 2007.

[6] Niemierko A. Reporting and analyzing dose distributions: a concept of equivalent uniform dose. Med Phys. 1997 Jan;24(1):103-10.

[7] Stick LB, et al. Joint estimation of cardiac toxicity and recurrence risks after comprehensive nodal photon versus proton therapy for breast cancer. Int J Radiat Oncol Biol Phys 2017;97:754-761.

[8] Dirk Verellen, Mark De Ridder, Nadine Linthout, Koen Tournel, Guy Soete, Guy Storme. Nat Rev Cancer. 2007 Dec;7(12):949-60. Review. Erratum in: Nat Rev Cancer. 2008 Jan;8(1):71.

[9] Dow-Mu Koh and David J. Collins. Diffusion-Weighted MRI in the Body: Applications and Challenges in Oncology, American Journal of Roentgenology, 188(6):1622-1635, june 2007.

[10] Jezzard, P., & Balaban, R. S. (1995). Correction for geometric distortion in echo planar images from B0 field variations. Magnetic Resonance in Medicine, 34(1), 65–73.