The Institute of Cancer Research

The Institute of Cancer Research **PHD STUDENTSHIP PROJECT PROPOSAL**	
FUNDER DETAILS	
Studentship funded by:	CRUK Programme Grant: Adaptive Data Driven Radiation Oncology
PROJECT DETAILS	
Project title:	Development of a patient model for real-time MRI guided radiotherapy of pancreas and liver cancer
SUPERVISORY TEAM	
Primary Supervisor	Prof. Uwe Oelfke
Associate Supervisor(s)	Dr Jamie McClelland (UCL) Dr Simeon Nill Dr Andrea Wetscherek Dr Bjoern Eiben Dr Katherine Aitken
Secondary Supervisor	Dr Alison Tree
DIVISIONAL AFFILIATION	
Primary Division	Radiotherapy and Imaging
Primary Team	Radiotherapy Physical Modelling
Site	Sutton
BACKGROUND TO THE PROJECT	

Despite tremendous technical advances of RT within the past decades the clinical outcome of patients with pancreatic/liver cancer is poor. The suspected primary reason for treatment failure is the inability to accurately target the respective tumours with sufficiently high therapeutic doses in a continuously changing patient anatomy over the treatment course. Further dose escalations and accelerated hypo-fractionation are prohibited for these patients by severe toxicities of radiosensitive organs at risk (colon, healthy liver etc) located directly adjacent to tumour targets.

The new MR-Linac technology, clinically available since 2018 at RMH, offers opportunities to improve the clinical outcome of these patients by providing high contrast MR images of the patient anatomy (tumours and OARs) directly prior and even during treatment. The challenge is to exploit these images for an on-line adaption of the radiation beam to the observed patient anatomy.

This PhD project aims to address the central problem of analysing the acquired patient images in real-time to guide the radiation beam for an intelligent tumour tracking dose delivery process. The required ultra-fast image registration and auto-segmentation of tumours and OARs will need to be embedded in a dynamic motion model of the whole patient anatomy. The development of this model, based on prior and current 4D-MR image sets, will be performed in a collaboration between the Centre for Medical Image Computing (CMIC (McClelland), the Joint Department of Physics at ICR/RMH (Oelfke, Wetscherek, Nill, Eiben) and the team of RMH/ICR liver/pancreas consultants (Aitken).

The PhD position is fully funded by the CRUK programme grant ‘Data driven adapted RT’ (Oelfke, Tree).

PROJECT AIMS

- We hypothesize that an automated pipeline of AI-driven software tools, supervised by minimal human interaction, can facilitate an on-line adaptive workflow for pancreas patients treated at the MR-Linac facility at ICR/RMH.
- Development of an automated segmentation tool for radiation targets and OARs on MR-Linac-generated images based on deep learning strategies. Automatic generation, subsequent amendment, and approval of these contours by a clinical oncologist is aimed to be completed within clinically acceptable time scales.
- Development of volumetric deformable motion model of the patient anatomy suitable for dose accumulation
- Adaptation of automated inverse planning research tools and its commercial derivative (ELEKTA, AB)) to generate clinically acceptable treatment plans within clinical acceptable time scales
- Integration of these tools into the clinical workflow at the MRL facility at RMH/ICR allowing first clinical studies in year 4 of the project.

RESEARCH PROPOSAL

The aims outlined above are envisioned to be realized within a 4-year PhD project at ICR/RMH. The project will be organized in five work packages (WPs) within 44 months, while the last 4 months will be used for the PhD student to write their thesis. In the following we will briefly describe the WPs mapped to the given objectives.

The development of the complete real-time adapted motion model will be developed in a sequence of mutually dependent steps.

First, a consistent methodology of MR-image acquisition at the MR-Linac, reliable image registration to reference data and robust auto-contouring of OARs and radiation targets, will be developed for daily on-line adaptation of treatments, i.e., only inter-fraction anatomical variations can be accounted for. The developed software tools aim to facilitate an on-line adaptive workflow at the MR-linac for each treatment fraction, i.e., the process of image analysis and subsequent treatment planning needs to be robust and completed within time scales of a 5-15 mins.

The developed methodology and imaging data will form the basis of a fully dynamic patient model to be developed in step 2 of the PhD project. This model will employ all MRI data for an individual patient available prior to the actual treatment session. The dynamic real-time adaptive dose delivery, accounting for intra-fractional anatomical changes, will be enabled by a dynamic refinement of the patient model based on a limited number of 2D-MRI-Cine projections acquired with a repetition rate of approximately 5Hz.

Automated segmentation of MR images for pancreas and liver patients for daily treatment adaptations (Months 1 – 12)

The starting point of this WP are the results of an Oracle Cancer Trust-funded PhD project at ICR, recently finished by J. Kieselmann [1] and the 4D-motion models developed at CMIC [2,3,4]. Building on the existing software and a data base of MR images, which includes data from the MOMENTUM data base of the Elekta MR-Linac consortium [5,6], we will train AI networks on data for OARs and will attempt to generate a first estimate of the relevant target volumes. This work will be performed in a close collaboration of the MR image acquisition team of the MRL (Wetscherek), the image processing experts at CMIC/ICR (McClelland/Eiben) and the pancreas/liver consultants at RMH (Aitken). We are well aware that automated segmentation of radiation targets is an ambitious task and will likely need initial supervision and amendments by the clinical oncologist. However, we are confident that we can achieve the complete segmentation of an MRI data set can be completed within clinically acceptable time scales.

Integration of the automated segmentation/registration software into the RMH clinical workflow (Months 13-18)

The integration of the developed software modules into the RMH clinical workflow will be facilitated in close collaboration with the clinical physics team (Nill) responsible for operation of the MR-Linac at RMH. The work will include specifically an extended validation phase to improve the robustness of the image analysis tools assisted by RMH radiographers and clinical research fellows. The second focus will be the software-integration with the Elekta planning system (Monaco treatment planning system).

Development of a dynamic patient model for real-time motion management of pancreas/liver patients (Months 19 - 36)

Dynamic volumetric information of the patient anatomy during RT delivery is key to enabling the calculation of the actual delivered dose, and beyond this, could inform gating on unexpected target and/or OAR motion or even enable deformable tracking. While real-time MR imaging is possible before and during treatment, it does not provide fast dynamic information of the full 3D field of view. Surrogate driven, deformable motion models can be utilised to bridge the gap between spatial and temporal resolution, meaning that with a fitted model and a reconstructed image of the patient, a low-dimensional surrogate signal is sufficient to estimate the 3D patient motion for any given surrogate signal time point. This work package builds on the unified image registration and motion modelling framework proposed by McClelland et al. [2] which was tailored towards MR-guided lung RT by a recently completed PhD project [3 and PhD thesis due to be submitted 03/2022)]. The open-source software package SuPReMo [4] implements this framework and will be adapted by the PhD student to the specific requirements of this project, including the MR acquisition (e.g. fitting the model to dynamic 2d MR images or directly to k-space data and k-space sampling strategies), the generation of a suitable surrogate signal generation from the MR data, and a motion-compensated image reconstruction. Given the time constraints of the clinical workflow, investigating the variation in motion patters from one fraction to the next and developing strategies how to adapt a model built on data acquired during the previous fraction to the motion of the day will form another key component of the complete workflow.

Integration of the dynamic patient model within the intelligent tumour tracking platform (TrackAdapt) (Months 36 – 40)

TrackAdapt links the RT delivery system, the treatment planning system and the dose reconstruction with each other and is designed to feed information from the treatment delivery back into the planning procedure to inform adaptations for remaining beams. A key information required for replanning is the delivered dose, which in general will be different from the planned dose due, for instance, to motion which occurs during treatment. This work will integrate the developed patient model within the existing TrackAdapt framework. This will allow the combination of the dynamic treatment delivery parameters such as MLC shapes, beam angles, and monitor units and the dynamic patient model to compute an estimate of the delivered dose per segment. Different dose accumulation techniques will be evaluated to generate a time resolved 3D dose distribution which will be feed back into the existing optimisation algorithms in TrackAdapt. The accuracy, precision and clinical applicability will be evaluated for different motion patterns. The outcome of the investigation will help to guide the decision which approach should be translated into clinical practice.

Clinical workflow integration and validation (Months 36 – 44)

The final 8 months of the research work will be used to integrate the developed pipeline of software modules directly into the clinical workflow of the MR-Linac. This work will include the adaptation of interfaces to our commercial treatment planning software and validation through end-to-end testing for a group of typical pancreas/liver patients. After successful completion of this phase, we anticipate the start of first clinical studies in 2026.

LITERATURE REFERENCES

[1] J. Kieselmann. 'Novel Concepts for Automated Segmentation to Facilitate MRI-Guided Radiotherapy in Head and Neck Cancer', 2019. https://repository.icr.ac.uk/handle/internal/3414.

[2] J.R. McClelland, M. Modat, S. Arridge, H. Grimes, D. D'Souza, D. Thomas, D. O' Connell, et al. 'A Generalized Framework Unifying Image Registration and Respiratory Motion Models and Incorporating Image Reconstruction, for Partial Image Data or Full Images'. Physics in Medicine and Biology 62, no. 11 (2017): 4273–92. https://doi.org/10.1088/1361-6560/aa6070.

[3] E.H. Tran, B. Eiben, A. Wetscherek, U. Oelfke, G. Meedt, D.J. Hawkes, and J.R. McClelland. 'Evaluation of MRI-Derived Surrogate Signals to Model Respiratory Motion'. Biomedical Physics & Engineering Express 6, no. 4 (2020): 045015. https://doi.org/10.1088/2057-1976/ab944c. [4] B. Eiben. SuPReMo - Surrogate Parametrised Respiratory Motion Modelling. C++. 2020. University College London, 2021. https://github.com/UCL/SuPReMo. [5] LG.W. Kerkmeijer, C.D. Fuller, H. M. Verkooijen, M. Verheij, A. Choudhury, K.J. Harrington, C. Schultz, et al. 'The MRI-Linear Accelerator Consortium: Evidence-Based Clinical Introduction of an Innovation in Radiation Oncology Connecting Researchers, Methodology, Data Collection, Quality Assurance, and Technical Development'. Frontiers in Oncology 6 (2016). https://doi.org/10.3389/fonc.2016.00215. [6] S.R. de Mol van Otterloo, J.P. Christodouleas, E.L.A. Blezer, H. Akhiat, K. Brown, A. Choudhury, D. Eggert, et al. 'The MOMENTUM Study: An International Registry for the Evidence-Based Introduction of MR-Guided Adaptive Therapy'. Frontiers in Oncology 10 (2020). https://doi.org/10.3389/fonc.2020.01328.	
CANDIDATE PROFILE	
Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).	
Pre-requisite qualifications of applicants:	MSc or equivalent in Medical Physics, Medical Image Computing, Computer Science or a related field
Intended learning outcomes:	• Critical knowledge of adaptive, MR-guided radiotherapy and clinical workflows in the context of liver and pancreatic • In depth understanding of the interaction and integration of systems required for daily online treatment adaptation • Motion management, monitoring and mitigation strategies during radiotherapy with a focus on deformable motion models • Research software development and validation in the clinical research environment
ADVERTISING DETAILS	
Project suitable for a student with a background in:	☐ Biological Sciences ☒ Physics or Engineering ☐ Chemistry ☐ Maths, Statistics or Epidemiology ☒ Computer Science