The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL:

PROJECT DETAILS	
Project Title:	Synthetic 4D CT for adaptive MR-guided radiotherapy treatment on an MR-Linac
SUPERVISORY TEAM	
Primary Supervisor:	Dr. Andreas Wetscherek
Additional members of the supervisory team:	Prof. Uwe Oelfke
DIVISIONAL AFFILIATION	
Primary Division:	Radiotherapy and Imaging
Primary Team:	Magnetic Resonance Imaging in Radiotherapy

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

Every second cancer patient receives radiotherapy as part of their treatment. Its success is based on the higher radiosensitivity and lower repair capability of rapidly proliferating tissue, which applies to most tumours. Treatment is typically delivered using a linear accelerator (Linac) over the course of several days (fractions). The aim of radiotherapy treatment planning is to combine beams from different directions and with different beam shapes (achieved with multileaf collimators) to deliver the prescribed dose and minimise damage to healthy tissue.

To calculate the attenuation and deposition of the treatment, electron density information is required. In a conventional radiotherapy setting, this information comes from a planning computed tomography scan (CT). However, the planning CT might be acquired well before the start of radiotherapy and changes in the patient's anatomy during the weeks of treatment, such as weight loss or tumour shrinkage, are not reflected. Furthermore, soft tissue is difficult to differentiate on CT, which is why magnetic resonance imaging (MRI) is consulted during planning to facilitate target and organ-at-risk delineation (Schmidt & Payne, 2015).

The availability of combined devices is a paradigm shift for radiotherapy (Raaymakers et al., 2017). The ICR's Elekta Unity MR-Linac was the first of its kind in the UK and first patients were treated in September 2018. The possibility for anatomical imaging during treatment delivery enables tracking of the tumour with the treatment beam (Menten et al., 2016) and treatment response can be assessed with daily functional MRI (Jones et al., 2018). To unleash the MR-Linac's full potential, up-to-date synthetic CT calculated from the acquired MR images, is required to account for daily anatomical changes. Because respiratory and peristatic (bowel) motion varies, plan adaptation "online" (patient on the treatment couch) would benefit from synthetic 4D CT.

PROJECT AIMS

- Optimisation of MRI pulse sequences for synthetic 4D CT generation on the MR-Linac in phantom and volunteer experiments.
- Implementation of an "offline" 4D synthetic CT image reconstruction on high-performance computing hardware.

- Setting up an imaging protocol for a patient study in cooperation with our clinical partners at the Royal Marsden NHS Foundation Trust.
- Employ machine learning techniques to accelerate the 4D synthetic CT image reconstruction and make it suitable for “online” applications.

RESEARCH PROPOSAL

The overall aim of this PhD project is to develop and implement synthetic 4D CT generation on a 1.5 Tesla MR-Linac system. The availability of daily updated synthetic 4D CT imaging in the treatment position would lay the foundations for extending the concept of treatment adaptation from reacting to anatomical day-to-day variations, e.g. in the position of pelvic organs (Thörnqvist et al., 2016) to exploiting changes in respiratory and peristaltic motion patterns for treatment optimisation. The synthetic 4D CT could further be used for retrospective calculation of the dose delivered during a treatment fraction (offline dose reconstruction). Current approaches (Dolde et al., 2018), are still relying on deforming (warping) an actual static CT image, which was acquired on a previous day and on a different machine.

The main hypotheses of this PhD project are:

- The concepts of state-of-the-art 4D MR image reconstruction (Rank et al., 2017), such as self-gating and compressed sensing can be applied to an MRI pulse sequence for synthetic 4D CT generation on a 1.5 T MR-Linac system.
- The MR image acquisition and synthetic 4D CT reconstruction can be accelerated sufficiently (less than 10 min in total) to inform treatment delivery.

The main outcomes of this PhD project are:

- Up-to-date synthetic CT for treatment planning and reconstruction of the delivered dose on a hybrid MR-Linac system.
- Characterization of respiratory and peristaltic motion patterns to inform treatment planning and definition of margins to account for the motion.

The PhD student will be part of the Magnetic Resonance Imaging in Radiotherapy team within the division of Radiotherapy and Imaging at the Institute of Cancer Research, which aims at performing cutting-edge research in close collaboration with our clinical oncology partners at the Royal Marsden NHS Foundation Trust.

Project Plan:

Months 1-12: Implementation of an MRI pulse sequence for synthetic CT generation on the Elekta Unity MR-Linac system.

After acquiring basic knowledge in magnetic resonance imaging and receiving training to perform imaging experiments on the MRI scanner independently, the successful applicant will have the opportunity to work on basic MRI image reconstruction problems, before attending a course in pulse sequence development for the Philips MR Paradise platform. Using this knowledge, the applicant will implement an MR imaging sequence for synthetic 4D CT on the MR-Linac and test it in healthy volunteers and phantoms, such as the QUASAR^{TM} MRI^{4D} Motion Phantom. At the end of the first year, initial results should be submitted for presentation at the ISMRM 29th Annual Meeting & Exhibition in Vancouver.

Months 13-24: Implementation of an “offline” 4D synthetic CT image reconstruction on high-performance computing hardware.

The main task of year 2 will be the implementation of a compressed sensing based iterative image reconstruction algorithm on the team’s dedicated reconstruction server or on the ICR’s high performance computing system

"Davros". The student will be able to resort to the 4D MR image reconstruction expertise of the team (Rank et al., 2017; Freedman et al., 2018). To obtain synthetic 4D CT from the MR imaging data, a variety of methods have been suggested (Johnstone et al., 2018), with machine learning techniques representing the most appealing class of solutions.

In parallel, a patient volunteer imaging study needs to be set up to obtain ground truth 4D CT data against which the synthetic 4D CT data could be validated. This will be planned in close collaboration with the clinical oncology team at our partner institute, the Royal Marsden NHS Foundation Trust, and should ideally start recruiting before the end of the second year.

Months 25-42: Employ machine learning techniques to accelerate the 4D synthetic CT image reconstruction and make it suitable for "online" applications.

Equipped with the data to validate the synthetic CT, the student will be able to refine his methods and publish the results in a peer-reviewed high-impact factor journal. While it might be possible that the synthetic 4D CT reconstruction times on dedicated hardware are fast enough (Mickevicius & Paulson, 2017) to be used for online applications, it might be possible that further acceleration is required at this stage. One possibility would be to replace the 4D MR image reconstruction step by a trained convolutional neural network or apply the state-of-the-art machine learning techniques of 2022, respectively.

Month 43-48: Finishing experiments and writing of PhD thesis

LITERATURE REFERENCES

Dolde, K., Naumann, P., Dávid, C., Gnirs, R., Kachelrieß, M., Lomax, A., Saito, N., Weber, D., Pfaffenberger, A. and Zhang, Y. (2018). 4D dose calculation for pencil beam scanning proton therapy of pancreatic cancer using repeated 4D MRI datasets. *Physics in Medicine & Biology*, 63(16), p.165005.

Freedman, J., Collins, D., Gurney-Champion, O., McClelland, J., Nill, S., Oelfke, U., Leach, M. and Wetscherek, A. (2018). Super-resolution T2-weighted 4D MRI for image guided radiotherapy. *Radiotherapy and Oncology*.

Johnstone, E., Wyatt, J., Henry, A., Short, S., Sebag-Montefiore, D., Murray, L., Kelly, C., McCallum, H. and Speight, R. (2018). Systematic Review of Synthetic Computed Tomography Generation Methodologies for Use in Magnetic Resonance Imaging–Only Radiation Therapy. *International Journal of Radiation Oncology*Biology*Physics*, 100(1), pp.199-217.

Jones, K., Michel, K., Bankson, J., Fuller, C., Klopp, A. and Venkatesan, A. (2018). Emerging Magnetic Resonance Imaging Technologies for Radiation Therapy Planning and Response Assessment. *International Journal of Radiation Oncology*Biology*Physics*, 101(5), pp.1046-1056.

Menten, M., Fast, M., Nill, S., Kamerling, C., McDonald, F. and Oelfke, U. (2016). Lung stereotactic body radiotherapy with an MR-linac – Quantifying the impact of the magnetic field and real-time tumor tracking. *Radiotherapy and Oncology*, 119(3), pp.461-466.

Mickevicius, N. and Paulson, E. (2017). Investigation of undersampling and reconstruction algorithm dependence on respiratory correlated 4D-MRI for online MR-guided radiation therapy. *Physics in Medicine and Biology*, 62(8), pp.2910-2921.

Raaymakers, B., Jürgenliemk-Schulz, I., Bol, G., Glitzner, M., Kotte, A., van Asselen, B., de Boer, J., Bluemink, J., Hackett, S., et al. (2017). First patients treated with a 1.5 T MRI-Linac: clinical proof of concept of a high-precision, high-field MRI guided radiotherapy treatment. *Physics in Medicine & Biology*, 62(23), pp.L41-L50.

Rank, C., Heußer, T., Buzan, M., Wetscherek, A., Freitag, M., Dinkel, J. and Kachelrieß, M. (2017). 4D respiratory motion-compensated image reconstruction of free-breathing radial MR data with very high undersampling. *Magnetic Resonance in Medicine*, 77(3), pp.1170-1183.

Schmidt, M. and Payne, G. (2015). Radiotherapy planning using MRI. *Physics in Medicine & Biology*, 60(22), pp.R323-361.

Thörnqvist, S., Hysing, L., Tuomikoski, L., Vestergaard, A., Tanderup, K., Muren, L. and Heijmen, B. (2016).

Adaptive radiotherapy strategies for pelvic tumors – a systematic review of clinical implementations. *Acta Oncologica*, 55(8), pp.943-958.	
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: e.g. BSc or equivalent in specific subject area(s)	First or upper-second class honours degree (Bsc or Msci) in Physics, Mechanical Engineering, Bioengineering or Computational Physics. This project has a strong computational component.
Intended learning outcomes: Please provide a bullet point list (maximum of seven) of the knowledge and skills you expect the student to have attained on completion of the project.	• Theoretical and practical magnetic resonance imaging • Pulse programming in Philips MR Paradise (C++) • Basic radiotherapy treatment planning • Working with an Elekta Unity MR-Linac • MR Image reconstruction on high-performance computing architecture