The Institute of Cancer Research

PHD STUDENTSHIP PROJECT PROPOSAL:

PROJECT DETAILS	
Project Title:	Developing methods for automated response characterisation of soft-tissue sarcoma following pre-operative radiotherapy: How artificial intelligence can improve our knowledge of heterogeneous change.
Short Project Title:	Artificial intelligence (AI) for monitoring heterogeneous radiotherapy response in soft-tissue sarcoma imaging.

SUPERVISORY TEAM	
Primary Supervisor:	Matthew Blackledge
Other members of the supervisory team:	Paul Huang, Christina Messiou, Simon Robinson and Uwe Oelfke

DIVISIONAL AFFILIATION	
Primary Division:	Radiotherapy and Imaging
Primary Team:	Computational Imaging in Radiotherapy
Other Team (if applicable)):	Protein Networks

PROJECT PROPOSAL

BACKGROUND TO THE PROJECT

Soft-tissue sarcoma (STS) is a rare form of cancer that develops in connective tissues. Approximately 3,300 new cases are diagnosed every year and only 50% of patients are expected to live for five years or more[1]. STS tumours often consist of different components including fatty, cystic, cellular and haemorrhagic tissues; these tumours are considered highly 'heterogeneous'. In patients undergoing radiotherapy, conventional imaging methods for assessing treatment response are limited as responding tumours may not change in size, or may even grow (progress) after treatment[2–4]. Therefore, more effective methods for assessing the success of radiotherapy in treating these tumours, and which also account for the high degree of tumour heterogeneity, are highly desired.

Magnetic resonance imaging (MRI) is widely used in soft-tissue sarcoma, owing to its excellent soft-tissue contrast and the lack of ionising radiation associated with other imaging techniques such as computed tomography (CT) and positron emission tomography (PET). Quantitative MRI (qMRI) techniques also provide non-invasive information about the biological properties throughout the entire tumour volume, including (i) cellularity from diffusion-weighted imaging[5] (DWI), (ii) vasculature by dynamic contrast-enhanced MRI[6] (DCE-MRI), and (iii) fat content with Dixon imaging[7]. However, evaluation of these quantitative metrics for response assessment is made difficult by the heterogeneous nature of STS. In addition, the best approach for combining such imaging metrics with other blood- or tissue-based measurements is not known.

The primary aims of this studentship are to investigate and develop new artificial intelligence techniques (including deep learning) to establish methods for quantifying MRI-derived heterogeneous tissue response following radiotherapy in STS, and validate these methods with regional molecular profiling.

PROJECT AIMS

- Develop multi-parametric, quantitative MRI protocols for investigating STS *in vivo*
- Investigate deep-learning methods for automatic identification of STS sub-compartments from qMRI
- Correlate imaging response markers in STS sub-compartments with regional molecular profiling, in collaboration with the ICR tumour profiling unit
- Identify whether imaging characteristics of surrounding healthy tissues are predictive of radiotoxicity following radiotherapy.

RESEARCH PROPOSAL

Within this multidisciplinary PhD studentship, the successful candidate will develop and explore a number of core scientific themes including (i) design of quantitative clinical MR-imaging methods, (ii) application of cutting-edge artificial intelligence techniques to meaningful problems in medical imaging, and (iii) innovation of synergistic approaches to combined image-based and genomic analysis for improving patient healthcare. The successful candidate will join a recently established Computational Imaging Team, within the division of Radiotherapy and Imaging, whose core aim is to develop new computational approaches for radiotherapy response assessment and prediction. Leveraging the close partnership with the imaging team at the Royal Marsden Hospital (RMH), the student will have access to state-of-the-art imaging and radiotherapy equipment, and also the most up-to-date computing architecture. They will also work in close collaboration with the Protein Networks team at the ICR to develop the skills and understanding necessary to explore combined imaging-/tissue-markers of treatment response and prediction for radiotherapy assessment.

A reduction in the amount of oxygen reaching tissues with tumours (hypoxia) is associated with an increase in the chances of cancer spread (metastasis), and is much harder to treat with radiotherapy (radioresistance). Therefore, a methodology that can measure this phenomenon non-invasively is highly desirable. In addition to the aforementioned qMRI methods, the student will develop a clinical protocol for an emerging MR-imaging technique established at the ICR, called oxygen-enhanced (OE-) MRI[8], to provide maps of hypoxic subvolumes within soft-tissue sarcomas.

These methods will be developed into dedicated clinical study at the RMH, with support from the student, that will provide the datasets required to deliver the aspects of this work. This will provide them with core understanding and experience in clinical trials, including data governance and anonymization. The key **hypotheses** of this trial and studentship are:

1. Intra-tumoural heterogeneity of STS can be evaluated using multi-parametric QI, and mpQI depicts the changes occurring to the underlying biology following radiotherapy.
2. Radiosensitivity of STS sub-compartments can be assessed using QI, and baseline measurement of radiosensitivity can predict the response of STS to radiotherapy.

An additional exploratory hypothesis is that changes in the imaging phenotype of surrounding healthy tissues during radiotherapy, measured through an approach known as radiomics[9], is predictive of radiotoxicity in STS.

Project Plan

Year 1: Protocol development and biomarker validation will be performed using test-object experiments, and then enhanced through volunteer studies at the RMH. OE-MRI will be developed, in combination with the other MR-imaging techniques (DWI, DCE-MRI and Dixon methods), for both 1.5T and 3.0T MRI systems. The quality of

spatial alignment between different qMRI images will be assessed, with methods for improving of this alignment developed where required. Quantitative modelling of MR-imaging biomarker maps will be established, including the development of statistical models for reducing the influence of imaging noise on derived imaging biomarkers. These methods will be developed into a set of software tools for use throughout project.

Year 2: Methods for spatial co-localisation of imaging with post-surgical tissue samples will be investigated. This will include an initial assessment of the accuracy of localisation, and where necessary additional techniques will be explored, such as 3D-printed moulds from in-vivo MR-images for the spatial alignment of imaging and excised tissue specimens[10]. Following attendance at relevant courses, the student will begin investigation into deep-learning techniques for (i) automatic segmentation of STS tumours from multi-parametric MRI, and (ii) characterisation of the intra-tumoural sub-compartments. Expert defined regions-of-interest will be used as a gold standard, comparing the inter-observer variability between automatic and manual delineation methods.

Year 3: Techniques for correlating imaging-derived metrics of tumour response with genomic analysis from tissue samples in the clinical study will be investigated. These methods will be used to corroborate the changes observed on imaging throughout the course of radiotherapy, and provide biological validation of the interpretation behind response assessments made through qMRI. In addition, the student will develop techniques for monitoring changes in radiomic features throughout the course of radiotherapy in both the tumour and surrounding healthy tissues, to explore the potential of using imaging as (i) a response biomarker and (ii) a predictive marker of radiotoxicity in STS.

Year 4: The student will finish processing all imaging results from the study to test the primary hypotheses outlined in this proposal. In the final 6-8 months, they will draft their final thesis and publish trial and methodological results in high-impact peer-reviewed articles.

Expected Outcomes

Following the conclusion of their studentship, the successful candidate should have

1. Optimised a clinical MRI protocol for longitudinal imaging of soft-tissue sarcoma throughout pre-operative radiotherapy.
2. Developed novel artificial intelligence networks for (i) automatic STS delineation and (ii) segmentation of STS tumour tissue sub-compartments.
3. Established methodologies for combining imaging biomarkers with tissue and blood samples for combined response/predictive biomarkers in radiotherapy of STS.
4. Published their work in high-impact relevant journals and presented results in international conferences.

LITERATURE REFERENCES

1. Cancer Research UK: Soft tissue sarcoma statistics. http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/soft-tissue-sarcoma.
2. Messiou C, Bonvalot S, Gronchi A, et al. Evaluation of response after pre-operative radiotherapy in soft tissue sarcomas; The European Organisation for Research and Treatment of Cancer - Soft Tissue and Bone Sarcoma Group (EORTC - STBSG) and Imaging Group recommendations for radiological examina. *Eur J Cancer*. 2016;56:37-44. doi:10.1016/j.ejca.2015.12.008.
3. Roberge D, Skamene T, Nahal A, Turcotte RE, Powell T, Freeman C. Radiological and pathological response following pre-operative radiotherapy for soft-tissue sarcoma. *Radiother Oncol*. 2010;97(3):404-407.

doi:10.1016/j.radonc.2010.10.007.

4. Canter RJ, Martinez SR, Tamurian RM, et al. Radiographic and histologic response to neoadjuvant radiotherapy in patients with soft tissue sarcoma. *Ann Surg Oncol*. 2010;17(10):2578-2584. doi:10.1245/s10434-010-1156-3.
5. Koh DM, Collins DJ. Diffusion-weighted MRI in the body: Applications and challenges in oncology. *Am J Roentgenol*. 2007;188(6):1622-1635. doi:10.2214/AJR.06.1403.
6. Messiou C, Orton M, Ang JE, et al. Advanced Solid Tumors Treated with Cediranib: Comparison of Dynamic Contrast-enhanced MR Imaging and CT as Markers of Vascular Activity. *Radiology*. 2012;265(2):426-436. doi:10.1148/radiol.12112565.
7. Ma J. Dixon techniques for water and fat imaging. *J Magn Reson Imaging*. 2008;28(3):543-558. doi:10.1002/jmri.21492.
8. O'Connor JPB, Boult JKR, Jamin Y, et al. Oxygen-enhanced MRI accurately identifies, quantifies, and maps tumor hypoxia in preclinical cancer models. *Cancer Res*. 2016;76(4):787-795. doi:10.1158/0008-5472.CAN-15-2062.
9. Aerts HJWL, Velazquez ER, Leijenaar RTH, et al. imaging using a quantitative radiomics approach. *Nat Commun*. 2014. doi:10.1038/ncomms5006.
10. Bourne RM, Bailey C, Johnston EW, et al. Apparatus for Histological Validation of In Vivo and Ex Vivo Magnetic Resonance Imaging of the Human Prostate. *Front Oncol*. 2017;7. doi:10.3389/fonc.2017.00047.

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 class undergraduate honours degree in Physics, mathematics or computational science. In interest in medical application of these subjects is essential.
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.	• MR-image protocol development and optimisation, with fundamental knowledge of MR-physics. • Establish expertise in state-of-the-art artificial intelligence methods and their application to medical imaging. • In-depth knowledge of image processing algorithms and their use in healthcare. • Develop core understanding of radiotherapy physics and its applications in oncology. • Proficiency in integrative data-science for combined imaging- and biological-biomarker discovery in radiotherapy. • Experience in clinical research design and data governance, including drafting of peer-reviewed publications.