

Project Title

Combined super-resolution ultrasound and functional MRI for non-invasive monitoring of tumour blood delivery during breast cancer radiotherapy

About This PhD Project

Institute of Cancer Research

Supervised by Prof. Mengxing Tang, Dr Navita Somaiah and Dr Matthew Blackledge

The student will be registered at Imperial College, leading to the award of a PhD from Imperial College, London

Project Description

Proposal outline

Success of targeted radiotherapy (RT) is strongly related to oxygenation levels within tumour tissues. Poor oxygen status (hypoxia) is associated with resistance to RT¹, and is linked to the chaotic capillary architecture observed within tumours as they grow uncontrollably; such disordered angiogenesis is one of the key hallmarks of cancer². As RT technology has improved, highly conformal radiation delivery has become possible, and may allow increased healthy-tissue sparing and higher therapeutic ratios. However, in order to achieve maximum benefit from these technologies and novel radiosensitisers it is essential that accurate, non-invasive imaging biomarkers be developed that can (i) spatially map the biology of the tumour (including hypoxic status) in order to boost the dose to more aggressive regions, and (ii) quantify tumour response during treatment so that RT plans can be adapted appropriately.

Dynamic contrast-enhanced (DCE-) ³, and diffusion-weighted (DW-) ⁴ MRI provide non-invasive mapping of the properties of tumour vasculature and cellularity respectively. Both techniques have shown considerable power as response biomarkers for a wide variety of tumour types and therapeutic interventions^{5–7}, and there is increasing hope that these techniques might provide potent biomarkers of response for RT^{8,9}. Although MRI provides excellent anatomical coverage within a clinically feasible time-frame, it still suffers from (i) a relatively low spatial resolution (order of millimetres), (ii) increasing safety concerns on the use of Gadolinium contrast agents used in DCE studies¹⁰, and (iii) lack of validation of MR-derived biomarkers, which only act as surrogate measures of the underlying biology that occurs at much smaller length-scales.

The convergent solution

We propose to combine a new imaging technique, super-resolution ultrasound (SRUS) pioneered at ICL and Kings College London, with clinical MRI to monitor RT response at multiple spatial (~20 microns to tens of centimetres) and temporal (sub-millisecond to tens of seconds) scales, validating these images with histopathological findings in breast cancer. Contrast-enhanced ultrasound (CEUS) imaging employs intravenously administered microbubbles that enhance ultrasound signals by two or more orders of magnitude within blood vessels. By tracking the paths of individual microbubbles over time, SRUS allows us to characterise the structure and dynamics of the tumour microvascular system (Figure 1) with much higher spatial resolutions than available using clinical systems such as MRI^{11–13}.

Hypothesis

SRUS combined with clinical DCE-MRI and DW-MRI will deliver unprecedented quantification of microvessel structure and dynamics within primary breast tumours; these measures can be monitored during treatment to provide deeper understanding of vascular disruption and change following radiotherapy.

The clinical setting

The recently funded KORTUC randomised phase II trial, led by the ICR, is testing the efficacy of intra-tumoural hydrogen peroxide (H₂O₂) as a radiation sensitiser in patients with locally advanced breast cancer. The successfully completed phase I trial has confirmed that intra-tumoural H₂O₂ injection prior to RT delivers safe and effective doses. In the phase II trial due to start in November 2019, 184 patients will be randomised 1:1 to RT alone or RT + H₂O₂; all patients will be followed up at 0, 6, 12, and 24 months after treatment using US and MRI, and also at baseline before the start of RT. Tumour tissue specimens will be collected using image-guided biopsy along with serum measurements at baseline and end of treatment.

Work packages

This project is divided into a number of core work-packages (WP) to be delivered by the successful student (approximate durations provided in parentheses).

WP1: Development of a robust clinical SRUS imaging pipeline (2.25 years).

The student will expand the preclinical SRUS system built at ICL13 into a clinical system suitable for human breast SRUS. In order to generate 3D volumetric SRUS data, a computer-controlled platform will be developed to mechanically sweep a linear ultrasound probe powered by either of two ultrasound (US) imaging systems: (i) a research US system available at ICL, and (ii) a clinical US system available at the Royal Marsden. To compare the performance of both systems, the student will design a novel MRI/US-compatible test-object that will mimic flow within capillaries at different flow-rates. Existing processing algorithms will be refined to reconstruct CEUS/SRUS images from clinical scanners, and in turn these images will be used to quantify novel biomarkers of vascular structure/dynamics: (i) local vascular density, (ii) flow velocity, (iii) flow volume, (iv) vascular tortuosity, and (v) distribution of flow directions (orderly/chaotic flow).

WP2: Development of multimodal SRUS/MRI (1 year)

The challenge of spatial coregistration of SRUS with clinical MRI will be addressed by the student using large field-of-view B-mode reference US images (acquired sequentially after SRUS) and anatomical MRI studies of the same patient. State-of-the-art image processing software frameworks^{14,15} will be compared for this purpose. Radiologist-defined landmarks positioned within lesions on both image sets will provide an independent gold-standard for quantifying the success of coregistration by these techniques. They will use their designed test-object to compare measures of vascular flow measured using DCE/DW-MRI with SRUS.

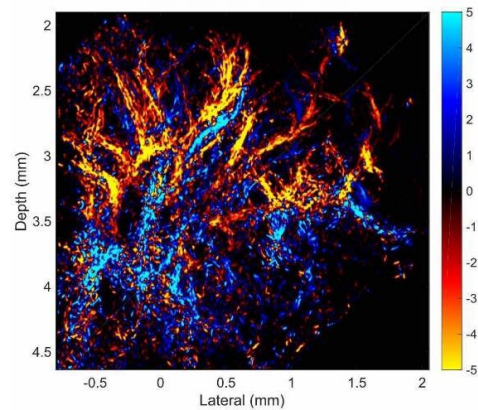
WP3: Combined mathematical modelling of tumour vasculature with SRUS and MRI (1 year)
Intra-voxel incoherent motion modelling (IVIM) of DW-MRI studies from the KORTUC trial will provide non-invasive surrogate measures of (i) extra-cellular diffusion coefficient, D , (ii) vascular pseudo diffusion coefficient, D^* , and (iii) vascular fraction, f . The latter of these will be correlated with SRUS measurements of the same parameter, defined here to be the gold standard. Furthermore, the student will also develop Bayesian analysis techniques to improve biomarker modelling of DCE/DW-MRI using SRUS measurements as prior information. This is particularly attractive for IVIM studies, where modelling can be highly sensitive to imaging noise^{16,17}.

WP4: Histopathological validation of vascular models (1 year) In all patients, tumour tissue samples will be collected via image-guided biopsy, at baseline and within 2 weeks after each imaging study. Slides will be stained for hematoxylin and eosin, CD31, Ki67 and HIF1 α /GLUT1 as markers of tumour cellularity (necrosis), endothelial cells (vascular density), cell proliferation and hypoxia, respectively. The student will explore how these histochemical markers correlate with the biomarkers they uncover using SRUS/MRI.

Expected scientific outcomes

1. A SRUS system for imaging primary breast tumours in a research setting.
2. A novel SRUS/MRI compatible test-object for quantifying microvessel flow.
3. An integrated SRUS/MRI imaging system, along with library of relevant image-processing routines.
4. Exploration of combined SRUS/MRI biomarkers of RT response (\pm hydrogen peroxide) in breast cancer.

Figure 1. Super-resolution ultrasound image of rabbit popliteal lymph node microvasculature covering a $\sim 5 \times 5 \times 1.7$ mm volume: Color indicates velocity and direction of blood flow within vessels



Keywords /Subject Areas

Quantitative Imaging Biomarkers
Super-Resolution Ultrasound
Breast Cancer Radiotherapy
Therapy Response Monitoring
Multi-Parametric MRI
Functional Image Modelling

Candidate profile

Candidates must have a first class or upper second class honours BSc Honours/MSc in Life Science, Chemistry, Physics or Engineering.

How to apply

Full details about these studentship projects, and the online application form, are available on our website, at: www.icr.ac.uk/phds Applications for all projects should be made online <https://apply.icr.ac.uk/> . Please ensure that you read and follow the application instructions carefully.