PhD Project Proposal

Funder details

Studentship funded by:	NIHR BRC at RMH/ICR

Project details

Project title:	**Advancing clinical elastography for early, non-invasive imaging assessment of normal tissue toxicity and tumour response**

Supervisory team

Primary Supervisor:	Jessica Winfield
Associate Supervisor(s):	Joshua Shur Simon Robinson Jeff Bamber (IRS Partner)
Secondary Supervisor:	Emma Harris

Divisional affiliation

Primary Division:	Radiotherapy and Imaging
Primary Team:	Applied Physics in Clinical MRI
Site:	Sutton

Project background

This project will provide direct benefits to patients by enabling non-invasive, earlier identification of treatment-related toxicities in systemic therapies and response assessment in immunotherapies, both of which are required to deliver smarter, kinder treatments.

Recent pre-clinical and clinical evidence suggests that biomechanical properties of tissues indicate disease status, for example liver disease (Xiao 2017) and tumour fibrosis and treatment response (Li 2019). Aberrant stiffness is a hallmark of solid tumours, linked to metastasis and progression (Swaminathan 2011).

Elastography uses magnetic resonance imaging (MR-Elastography) or ultrasound (US-Elastography) to measure biomechanical properties (e.g. stiffness, wave-speed) offering potential to fulfil two unmet needs: (i) quantitative assessment of liver toxicity, (ii) quantitative immunotherapy response assessment.

Systemic anticancer therapies are associated with liver toxicities. Liver toxicity can reproduce virtually any pattern of injury (King 2001) with steatosis, steatohepatitis, nodular regenerative hyperplasia and sinusoidal obstruction/microvascular congestion encountered. Hepatic dysfunction may require dose-reduction or discontinuation of therapy, and early changes of toxicity may not be apparent clinically, or progress rapidly to fulminant liver failure. Liver stiffness from US-Elastography is a marker for fibrosis and cirrhosis (Mueller 2010) and is correlated with venous pressure (present during congestion). Advanced MR-Elastography measures properties beyond standard stiffness measurements, which may discriminate between patterns of liver injury (Yin 2017). MR-Elastography and US-Elastography may detect early toxicity-related changes to guide treatment.

Immunotherapy treatment-response patterns differ from conventional agents, necessitating immunotherapy-specific criteria (iRECIST) (Seymour 2017, 2019). Identification of patterns such as pseudo-progression are clinically

relevant, requiring continuation of treatment despite initial tumour growth. Preliminary MR-Elastography studies in patients with liver metastases treated with immunotherapy reported initial increase in tumour stiffness and later decrease in patients who responded to treatment, and correlation with intra-tumour T-lymphocytes (Qayyum 2019). Tumour stiffness may better identify responders at early time-points, improving treatment selection, compared with current size-based assessments.

Project aims

- Implement and evaluate advanced MR-Elastography measurements, which use the full information about the mechanical properties. (Advanced MR-Elastography measurements will use the complex shear modulus, which includes real and imaginary parts for calculation of separate elastic and viscous components of the modulus, whereas standard MR-Elastography used currently in liver fibrosis assessments employs a simpler readout using only the magnitude data, which may obscure valuable information such as fat content or changes associated with vascular damage.) Assess the ability of advanced MR-Elastography to discriminate between different patterns of liver injury or detect changes in tumours in response to treatment and evaluate against the standard magnitude measurements.

- Implement and evaluate whole-liver MR-Elastography methods to assess treatment-related toxicity in patients with secondary breast cancer and patients with colorectal cancer treated with systemic therapies who frequently encounter hepatic toxicity impacting on clinical management. Combine MR-Elastography and US-Elastography with other quantitative MR techniques to understand changes in tissue properties and develop early biomarkers of toxicity.

- Evaluate MR-Elastography methods to assess changes in tumours and normal liver in patients treated with immunotherapy. Combine MR-Elastography and US-Elastography with other routinely-acquired quantitative MR techniques to improve understanding of temporal and spatial changes in tumour properties and develop early biomarkers of response to treatment.

Research proposal

There is an unmet clinical need for early detection and characterisation of liver toxicity in patients treated with systemic therapies, and for early assessment of response to treatment in immunotherapies. This study will address these needs using elastography, building on synergistic information from MR-Elastography and US-Elastography for assessment of liver toxicity in patients with colorectal cancer or secondary breast cancer treated with systemic therapies, and monitoring response to immunotherapy, to provide early biomarkers of toxicity or tumour response.

This project aligns with three BRC themes: Imaging and Data Science, evaluating elastography as a next-generation imaging tool providing novel biomarkers in oncology; Immunotherapeutics, evaluating elastography for early non-invasive assessment of treatment response; and Cancer Treatment Effects, evaluating elastography for early recognition and characterisation of liver toxicity.

MR-Elastography and US-Elastography are non-invasive with no ionising radiation, making them more acceptable to patients than invasive sampling and enabling longitudinal assessments. MR-Elastography and US-Elastography offer complementary assessments of tumours and normal organs and may probe different aspects of the biomechanical properties of tissues. Furthermore, MR-Elastography and US-Elastography each have different advantages in clinical studies. US-Elastography is faster and more accessible, providing scope for more frequent assessments, while MR-Elastography provides large field-of-view assessment, with scope to assess spatial heterogeneity. Combination with other quantitative MRI-derived parameters enables a multi-parametric assessment of tumour/tissue properties. Unlike pre-clinical MR-Elastography, clinical MR-Elastography currently uses only the magnitude of the complex shear modulus, which may be less sensitive to discriminate between different patterns of liver injury or changes in tumours in response to treatment compared with the complex shear modulus (real and imaginary parts); addressing these limitations will enable greater use of MR-Elastography in oncology.

This project will be divided into three work packages (WP):

- **WP1.** Assess the value of using the complex shear modulus (real and imaginary parts) to distinguish between different tissue properties e.g. inflammation versus fibrosis versus fatty liver occurring in liver injury, or changes in vascular properties. Phantoms will be constructed based on phantom-building expertise in MR/US at ICR/RMH. Phantom experiments will assess MR-Elastography and US-Elastography methods, including sensitivity to material properties and spatial resolution. MR-Elastography methods will be assessed further in healthy volunteers and patients.

Outcome: Assessment of whether the complex shear modulus (real and imaginary parts) provides improved ability to distinguish between different patterns of liver injury versus the performance of standard clinical elastography (magnitude of the complex shear modulus).

- **WP2.** Elastogram analysis methods will be developed for extraction of imaging biomarkers to assess liver toxicity in patients with secondary breast cancer and patients with colorectal cancer treated with systemic therapies. The work will build on methodological developments from WP1 to provide assessments of the complex shear modulus using MR-Elastography. The study will test the hypothesis that there is an early increase in liver stiffness measured using elastography in patients who develop liver toxicities during or after systemic therapies. The study will build on a current pilot study using MR-Elastography for liver toxicity assessment in patients at RMH (Figure 1; White 2022). Advanced MR-Elastography methods, which measure properties beyond standard stiffness measurements, will be assessed in patients with different patterns of liver injury to determine the imaging changes arising from injury to hepatocytes (hepatitis) separately from drug-induced vascular changes (e.g. sinusoidal obstruction syndrome), alongside multi-parametric quantitative MRI measures such as fat quantification to distinguish altered lipid metabolism. These studies will extend the ability of MR-Elastography to probe these different disease processes.

MR-Elastography and US-Elastography will be assessed together in conjunction with established quantitative MRI-derived parameters including apparent diffusion coefficient (ADC) from diffusion-weighted MRI, relaxation times, and magnetisation transfer, which inform on different aspects of tissue micro-structure and have been shown to relate to viscoelasticity in pre-clinical MRI studies (Reeves 2023), and MRI-based fat quantification. These measurements will be used to understand changes in tissue properties, and the dynamic range of each of the measurements will be investigated to determine the most sensitive method for toxicity assessment. The study will assess whether frequent US-Elastography to inform less frequent MR-Elastography can be a suitable paradigm for toxicity monitoring.

Outcome: Method for early non-invasive assessment of abdominal organ toxicity in patients treated with systemic therapies.
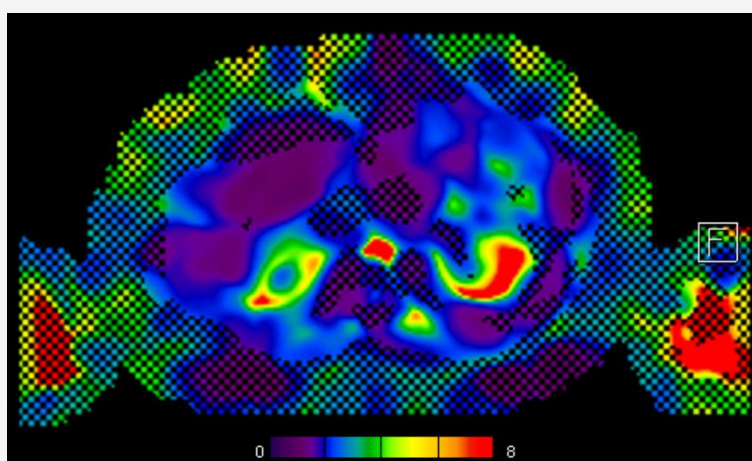

Figure 1: Stiffness map of the liver in a healthy volunteer acquired using MR-Elastography at RMH (White 2022). Scalebar indicates stiffness (magnitude of complex shear modulus) in kPa.

WP3. Elastography methods will be evaluated to assess response to treatment in patients treated with immunotherapy. The study will consist of two parts: the first part will test the hypothesis that there is an early increase in tumour stiffness associated with T-cell infiltration followed by later decrease in responding tumours relating to cell death; the second part will test the hypothesis that there is a change in the stiffness of the spleen in patients who respond to immunotherapy. US-Elastography measurements will be acquired more frequently

alongside less frequent MR-Elastography measurements to understand the time-course of tissue changes in response to immunotherapy, which will inform the most appropriate methods for assessment and the appropriate time-points for MR-Elastography. Other quantitative MRI-derived parameters will be combined with MR-Elastography measurements to improve understanding of response mechanisms.

<u>Outcome:</u> Method for early non-invasive assessment of response in patients treated with immunotherapies and improved understanding of temporal and spatial changes at early time-points.

Collaborators: Professor Ian Chau, Consultant Medical Oncologist in Gastrointestinal and Lymphoma Units, RMH; Reader at ICR. Professor Chau will assist in prioritising clinical questions in gastrointestinal cancers and facilitate recruitment of patients for clinical studies.

Research ethics approval is in place for evaluation of new MR techniques in patients and healthy volunteers (CCR5359, clinicaltrials.gov NCT05118555). RMH has recently acquired hardware for clinical studies in MR-Elastography and US-Elastography. The first part of WP1 will be conducted in phantoms and volunteers, which is lower risk as the work is methodological development and does not rely on patient recruitment. Patient studies in WP1 and initial work in WP2-3 will recruit clinical patients under existing ethical approval, which is lower risk as the project does not rely on timing of clinical trials or recruitment to trials. Research ethics committee approval will be applied for to conduct combined MR/US studies in WP2-3. This project will create opportunities to embed elastography in future clinical trials of novel agents.

This project will provide training in multi-disciplinary clinical research, working with scientists, clinicians and other healthcare professionals to translate scientific developments for patient benefit. The student will develop expertise in MR-Elastography and US-Elastography, including data acquisition and analysis. The student to develop a deep understanding of the biomechanical properties of tumours and normal tissues, linking these underlying properties with quantitative imaging measurements. Clinical studies will enable the student to develop their understanding of current challenges in oncology and apply scientific skills in novel imaging methods for patient benefit.

The project will be based in MR Physics and the clinical MRI Unit at RMH (Jessica Winfield, Josh Shur), working closely with Ultrasound Physics at ICR/RMH (Emma Harris, Jeff Bamber), who have extensive experience of developing and commercialising US-Elastography. Simon Robinson will advise on translation from pre-clinical to clinical MRI. No animal experiments will be undertaken, but the student will have opportunities to observe existing pre-clinical studies, providing additional translational value. This project builds links across the Division of Radiotherapy and Imaging, and between ICR and RMH, drawing together expertise at ICR in US-Elastography, with RMH/ICR expertise in quantitative MRI, and will enhance translation of elastography techniques from pre-clinical to clinical MRI.

Literature references

KING, P. D. & PERRY, M. C. 2001. Hepatotoxicity of chemotherapy. *The oncologist,* 6**,** 162-176.

LI, J., ZORMPAS-PETRIDIS, K., BOULT, J. K., REEVES, E. L., HEINDL, A., VINCI, M., LOPES, F., CUMMINGS, C., SPRINGER, C. J., CHESLER, L., JONES, C., BAMBER, J. C., YINYIN, Y., SINKUS, R., JAMIN, Y. & ROBINSON, S. P. 2019. Investigating the Contribution of Collagen to the Tumor Biomechanical Phenotype with Noninvasive Magnetic Resonance Elastography Imaging Tumor Viscoelasticity with MR Elastography. *Cancer Research,* 79**,** 5874-5883.

MUELLER, S. & SANDRIN, L. 2010. Liver stiffness: a novel parameter for the diagnosis of liver disease. *Hepatic medicine: evidence and research,* 2**,** 49.

QAYYUM, A., HWANG, K.-P., STAFFORD, J., VERMA, A., MARU, D. M., SANDESH, S., SUN, J., PESTANA, R. C., AVRITSCHER, R. & HASSAN, M. M. 2019. Immunotherapy response evaluation with magnetic resonance elastography (MRE) in advanced HCC. *Journal for immunotherapy of cancer,* 7**,** 1-6.

REEVES, E. L., LI, J., ZORMPAS-PETRIDIS, K., BOULT, J. K. R., SULLIVAN, J., CUMMINGS, C., BLOUW, B., KANG, D., SINKUS, R., BAMBER, J. C., JAMIN, Y. & ROBINSON, S. P. 2023. Investigating the contribution of hyaluronan to the breast tumour microenvironment using multiparametric MRI and MR elastography. *Mol Oncol,* 17**,** 1076-1092.

SEYMOUR, L., BOGAERTS, J., PERRONE, A., FORD, R., SCHWARTZ, L. H., MANDREKAR, S., LIN, N. U., LITIÈRE, S., DANCEY, J. & CHEN, A. 2017. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *The Lancet Oncology,* 18**,** e143-e152. 2019. Correction to Lancet Oncol 2017; 18: e143-52. *Lancet Oncol,* 20**,** e242.

SWAMINATHAN, V., MYTHREYE, K., O'BRIEN, E. T., BERCHUCK, A., BLOBE, G. C. & SUPERFINE, R. 2011. Mechanical Stiffness Grades Metastatic Potential in Patient Tumor Cells and in Cancer Cell Lines Mechanical Stiffness of Cells Dictates Cancer Cell Invasion. *Cancer research,* 71**,** 5075-5080.

WHITE, O., SCURR, E., ORTON, M., WINFIELD, J. & KOH, D.-M. Repeatability and relationships between pixel-matched MR Elastography, T1, T2, and ADC measurements in the liver. ISMRM workshop on MR Elastography, 2022 Berlin.

XIAO, G., ZHU, S., XIAO, X., YAN, L., YANG, J. & WU, G. 2017. Comparison of laboratory tests, ultrasound, or magnetic resonance elastography to detect fibrosis in patients with nonalcoholic fatty liver disease: a meta-analysis. *Hepatology,* 66**,** 1486-1501.

YIN, M., GLASER, K. J., MANDUCA, A., MOUNAJJED, T., MALHI, H., SIMONETTO, D. A., WANG, R. S., YANG, L., MAO, S. A., GLORIOSO, J. M., ELGILANI, F. M., WARD, C. J., HARRIS, P. C., NYBERG, S. L., SHAH, V. H. & EHMAN, R. L. 2017. Distinguishing between Hepatic Inflammation and Fibrosis with MR Elastography. *Radiology,* 284**,** 694-705.

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: BSc or equivalent in physics or engineering

Intended learning outcomes:

- Expertise in magnetic resonance and ultrasound data acquisition and analysis.
- Development of image processing and data analysis techniques.
- Expertise in clinical research in oncology.
- A deep understanding of the properties of tumours and normal tissues, effects of treatment, and interaction of these properties with imaging.
- Develop excellent written and oral presentation skills through presentations at seminars and national/international conferences, and publications.
- Experience of conducting research in a multi-disciplinary team, including scientific and clinical collaborators.
- Training within a stimulating research environment, including a wide range of imaging and analysis methods.

Advertising details

Project suitable for a student with a background in:

- ☐ Biological Sciences
- ☒ Physics or Engineering
- ☐ Chemistry
- ☐ Maths, Statistics or Epidemiology
- ☐ Computer Science