**The Institute of Cancer Research**

## PHD STUDENTSHIP PROJECT PROPOSAL:

| **PROJECT DETAILS** | |
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| **Project Title:** | Leveraging state-of-the-art methods in Artificial Intelligence and medical imaging for automated response evaluation and prediction of soft-tissue sarcomas to systemic treatment. |
| **Short Project Title:** | **Automated response evaluation and prediction of soft-tissue sarcomas using Artificial Intelligence and Imaging** |

| **SUPERVISORY TEAM** | |
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| **Primary Supervisor(s):** | Matthew Blackledge |
| **Associate Supervisor(s):** | Christina Messiou |
| **IRS Partner :** | Paul Huang |
| **Lead contact person for the project:** | Matthew Blackledge |

| **DIVISIONAL AFFILIATION** | |
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| **Primary Division:** | Radiotherapy and Imaging |
| **Primary Team:** | Computational Imaging |

**PROJECT PROPOSAL**

**BACKGROUND TO THE PROJECT**

Soft tissue sarcomas (STSs) are a group of rare cancers for which surgery is the standard treatment. Approximately 50% of patients will relapse following surgery developing both local tumour re-growth and distant metastatic disease, which significantly reduce patient survival. In addition to this, many surgeries are highly invasive leading to poor patient quality of life and functional impairment.

Radiotherapy and/or systemic chemotherapy can be used before or after surgery in an effort to reduce the risk of relapse. However, there is still little consensus on how these treatment options should be stratified across the patient population, meaning that many centres employ their own treatment strategies for STS. Treatment is further complicated by the fact that STS tumours are highly heterogeneous; different regions within the same tumour can behave very differently to the same treatment (intra-tumoural heterogeneity), and there are approximately 100 different sub-types of STS (inter-tumoural heterogeneity). In addition, the location and grade of STS tumours must be carefully considered before adequate treatment pathways can be designed for individual patients.

Diagnosis and treatment is conventionally monitored through multidisciplinary teams at select specialist STS services throughout the UK, and involves the use of multiple clinical investigations

such as imaging, multi-core biopsies, histopathology and molecular profiling. Post-surgical follow-up protocols are currently ad-hoc, and consist of imaging and patient/clinician reported outcomes (PROs/CROs).

The aim of this project is to develop novel analysis tools, using state-of-the-art artificial intelligence (AI), that can make sense of the complex data acquired during STS treatment in an effort to help improve and standardise the patient pathway for STS.

**PROJECT AIMS**

- Develop new analysis pipelines for integrating imaging and patient demographic data in soft-tissue sarcoma (STS).
- Innovate techniques for assessing imaging data acquired at multiple institutions with diverse imaging protocols and modalities.
- Identify new multi-omic biomarkers of STS response prediction and tumour grading using cutting-edge Artificial Intelligence (AI).
- Integrate research into a software prototype for use within future clinical trials and further clinical implementation.

**RESEARCH PROPOSAL**

In this PhD project, the student will focus on the development of new AI methodologies for response assessment of STS using multi-centre imaging data. Imaging provides perhaps the only non-invasive approach for monitoring how heterogeneous regions within STS tumours change during the course of treatment, but analysis methods for accurately tracking these changes are still in their infancy. Furthermore, given the paucity of robust imaging guidelines for evaluating STS tumours during treatment, the student will develop novel approaches for (i) integrating imaging data with the other patient-related information (including age, family history, blood markers etc.), and (ii) combining disparate imaging datasets from multiple institutions. The developed techniques will be integrated into a software framework with an aim to provide a robust prototype for further integration into clinical practise and improvement in patient outcome.

In this project, the student will leverage imaging and other multiomic data to develop data-driven AI models of (i) image-based STS tumour grading, (ii) heterogeneous tumour response, and (iii) prediction of local recurrence, treatment toxicity and patient survival. They will integrate these developments into a robust research software framework, with an aim for clinical dissemination of these tools into the healthcare sector.

i) **Image-based tumour grading**
MRI is typically performed prior to surgery for STS diagnosis, along with multi-core biopsy for tumour grading[1]. Whilst the latter technique offers excellent specificity, it suffers from sample bias in spatially heterogeneous STS tumours. Imaging provides visualisation of whole extent of disease and can take tumoural heterogeneity into account (**Figure 1**). The student will

utilise the evolving field of radiomics[3,4] to extract high-order features from MRI and CT images (e.g. tumour shape and texture), and determine image-based models of tumour grade. Recorded STS grades identified using histopathology will be used as gold-standard in this objective.

ii) **Automated detection of heterogeneous STS environments through imaging**
Conventional radiological measures of tumour size using CT or MRI fail as response biomarkers due to the large inter-tumoural heterogeneity encountered in STS [2]. We have demonstrated preliminary evidence that AI can be used to detect heterogeneous sub-compartments from multi-parametric MRI in response to neoadjuvant radiotherapy (**Figure 1**). The student will further test and refine this methodology in the context of neoadjuvant chemotherapy response, and validate the technique by correlating findings with digital histopathology using in-silico methods previously established by our team[5]. Realising that X-ray CT imaging is also a popular approach (though with weaker soft-tissue contrast), we will train U-Net models [6] for detecting STS heterogeneity within CT, using MRI as gold-standard.

**iii) Multi-omic prediction biomarkers in STS**
Investigators have demonstrated utility for predictive models of patient prognosis based on patient demographic information and STS tumour descriptors such as size and location[7] – these descriptors cannot account for spatial tumour heterogeneity in the way imaging can. To our knowledge no such models have been defined for disease recurrence or therapeutic toxicities. We will develop a novel AI toolkit using wide-and-deep learning (WDL)[8] that can combine imaging data with patient demographic information to determine new predictive models of local recurrence, treatment toxicity, and eventually, patient survival. The improved accuracy of the combined imaging/demographic features will be compared to existing models, or to models developed using demographics alone using a cross-validation approach.

**Expected Outcomes**

- Novel AI methodologies for integrating imaging data with patient demographic information and histological grading within STS.
- A radiomic features extraction pipeline for STS.
- New analysis methodologies for combining imaging data from multiple institutions, comprising of different imaging modalities and protocols.
- A prototype software library for multi-omic analysis of STS datasets, including image analysis pipelines.
- Discovery of potential multi-omic, predictive biomarkers of STS tumour response to neoadjuvant chemotherapy.
- Validation of discovered biomarkers using available histopathology data.

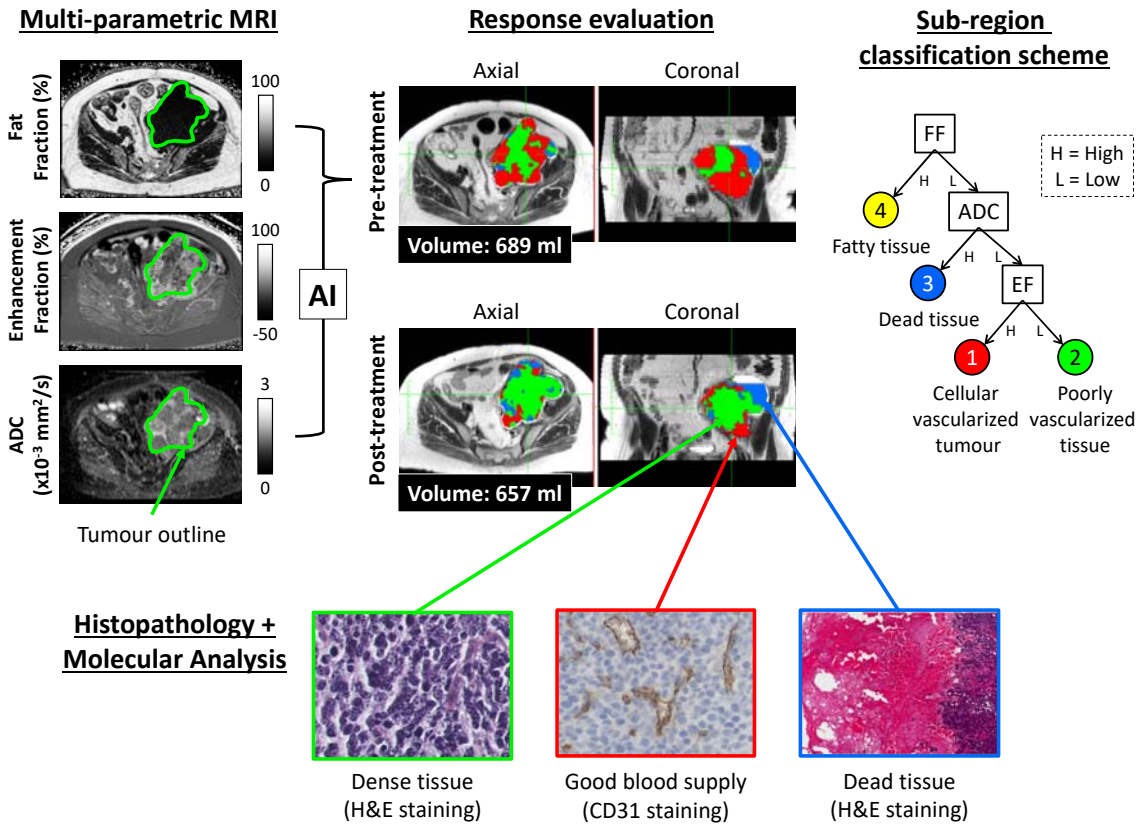


**Figure 1.** AI classification a patient with soft-tissue- sarcoma (liposarcoma). **Top-left**: Multi-parametric MRI images are combined using artificial-intelligence (AI) to categorize regions into one of four possible tissue groups (defined in **top-right** illustration). **Middle-top**: This classification scheme is also applied following radiotherapy to assess for changes in the volume of each compartment. A heterogeneous pattern is identified before treatment, with the majority of the tumour consisting of highly vascular regions (in red). Following radiotherapy, despite no marked change in overall tumour volume, the proportion of poorly vascularised tissue (in green) increases, possibly indicating a disruption in the blood supply to the tumour (some aggressive regions remain). **Middle-bottom**: Using our collective data archive, we will study the biological underpinning of these regions, and develop response/prognostic models that combine imaging phenotypes with regional histopathology and molecular profiling of tissues (histology data displayed for illustration purposes only).

**LITERATURE REFERENCES**


1. Dangoor, A. *et al.* UK guidelines for the management of soft tissue sarcomas. *Clin. Sarcoma Res.* (2016). doi:10.1186/s13569-016-0060-4
2. Messiou, C. *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* **56,** 37–44 (2016).
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radiomics approach. *Nat. Commun.* **5,** (2014).
4. Sala, E. *et al.* Unravelling tumour heterogeneity using next-generation imaging: radiomics, radiogenomics, and habitat imaging. *Clinical Radiology* **72,** 3–10 (2017).
5. Hill, D. K. *et al.* Non-invasive prostate cancer characterization with diffusion-weighted MRI: Insight from in silico studies of a transgenic mouse model. *Front. Oncol.* **7,** (2017).
6. Ronneberger, O., Fischer, P. & Brox, T. U-Net: Convolutional Networks for Biomedical Image Segmentation. *Miccai* 234–241 (2015). doi:10.1007/978-3-319-24574-4_28
7. Grobmyer, S. R. & Brennan, M. F. Predictive variables detailing the recurrence rate of soft tissue sarcomas. *Current Opinion in Oncology* **15,** 319–326 (2003).
8. Cheng, H.-T. *et al.* Wide & Deep Learning for Recommender Systems. in *Proceedings of the 1st Workshop on Deep Learning for Recommender Systems - DLRS 2016* 7–10 (2016). doi:10.1145/2988450.2988454

| **CANDIDATE PROFILE** | |
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| 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 specific subject areas (Physics, Engineering, Mathematics, or Computer Science) |
| **Intended learning outcomes:** | • Establish expertise in state-of-the-art artificial intelligence methods and their application to medical imaging.<br>• In-depth knowledge of image processing algorithms and their use in healthcare.<br>• Develop core understanding of soft-tissue sarcoma and treatment approaches.<br>• Proficiency in integrative data-science for combined imaging- and biological-biomarker discovery.<br>• Experience in clinical research design and data governance, including drafting of peer-reviewed publications. |
| **ADVERTISING DETAILS** | |
| **Project suitable for a student with a background in:** | ☐ Biological Sciences<br>**X** Physics or Engineering<br>☐ Chemistry<br>**X** Maths, Statistics or Epidemiology<br>**X** Computer Science<br>☐ Other (provide details) |
| | **1.** Magnetic Resonance Imaging |

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| **Keywords:** | **2.** Aritifical Intelligence |
| | **3.** Soft-Tissue Sarcoma |
| | **4.** Habitat Imaging |
| | **5.** Image Analysis |
| | **6.** |