Project title: Understanding microenvironmental responses to radiation in gastrointestinal cancers

Project Summary: Radiation is used in many gastrointestinal (GI) cancers but cure with (chemo)radiotherapy is rare. Most GI cancers have also not benefited from the immunotherapy revolution. Radiotherapy is known to modulate the tumour microenvironment, but the effects are not well understood. Focusing on immune-cold pancreatic, rectal and oesophageal tumours, this project will analyse human samples to identify (i) potential new radiation combination targets in the tumour microenvironment, and (ii) baseline and dynamic microenvironmental characteristics of tumours predicting response to therapy.

Initially focusing on pancreatic cancer, cohorts of samples from patients who received neoadjuvant chemoradiotherapy or chemotherapy alone will be analysed by spatial transcriptomics to identify differences between these groups. Longitudinal sample analysis will include blood (ctDNA, immunophenotyping), tissue (diagnostic biopsy and surgical specimen). Other available sample cohorts include rectal cancer and oesophageal cancer, which can be individually analysed or used as a validation cohort for pan-tumour radiotherapy effects. Skills in spatial analysis will be developed: multiplex immunofluorescence (in collaboration with the Integrated Pathology Unit) will be used to analyse the large volume clinical trial sample sets, and correlated with spatial transcriptomic and bulk sequencing data. The possibility to develop assays on fresh tissues including live tissue slices, organoids, and patient-derived immune cells and fibroblasts will be explored, which could allow the assessment of radiation responses *ex vivo*, potentially developing techniques which can screen multiple drug-radiation conditions from patient samples and assess for immune activation and tumour control.

There will be opportunity to correlate with functional imaging data from the MR-Linac. The medium-term aim of this work is to bring promising candidates into phase I clinical trials in combination with radiotherapy.

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Clinical specialties

Clinical oncology; medical oncology or surgery can be considered, but clinical component will not include MR-Linac.