CHIEF SCIENTIST OFFICE

CODE: SCAF/19/01

RESEARCH PROJECT BRIEFING

Development and evaluation of novel treatment strategies using immune-oncology agents in combination with radiotherapy in rectal cancer.

AIMS

- To support the development of new ways of treating rectal cancers to allow us to clear cancers more reliably, curing more patients and facilitate organ preserving approaches by avoiding major surgery.
- To conduct a study collecting serial samples at sigmoidoscopy from rectal cancer patients in undergoing radiotherapy treatment in the West of Scotland – this allowed us to understand how immune cell populations change in biopsies to understand how immunotherapies could be employed to better target rectal cancer.
- To conduct preclinical experiments of immunotherapy and radiotherapy in mouse models of rectal cancer to establish optimal combinations and timings of treatment and to identify mechanisms associated with therapeutic response and resistance.

KEY FINDINGS

- Different radiotherapy treatments and doses impact the presence of immune responses within tumours to varying degrees. In general, activation of immune responses early on in treatment is associated with improved treatment outcome (higher rates of complete response). These results are important in helping us plan clinical trials in patients.
- In preclinical models the addition of immunotherapy to radiotherapy improves treatment responses compared to radiotherapy alone. In these models, immunotherapy and radiotherapy combine to switch on anticancer immune responses in rectal cancers.
- Results suggest that other types of immune cells (called myeloid cells) may stop successful immunotherapy – radiotherapy treatment response.
- These findings from preclinical and clinical studies have implications for clinical trials of immunotherapy and radiotherapy in rectal cancer. These results support the testing of these combinations in larger trials with the aim of enhancing cure rates and facilitating higher rates of complete response and organ preservation in patients with rectal cancer.

WHAT DID THE STUDY INVOLVE?

The study involved working to refine a preclinical mouse model of rectal cancer correlating radiation related changes in mouse tumours to those seen in patients. In the preclinical setting these mice tumours were resistant to radiotherapy but when immunotherapy was added some tumours were cleared. Treated tumours were analysed showing presence of anticancer immune responses and molecular changes associated with a more immune cell permissive environment. When specifc experimental conditions were applied (a chemokine receptor knock out model) to limit the presence of a population of immune cells termed macrophages in tumours, higher rates of tumour regression/ response to immunotherapy-radiotherapy was observed (https://doi.org/10.1158/1557-3265.TARGETEDTHERAP-P022). Thes results suggest targetting these immune cell types in patients may further improve clinical outcomes.

Figure 1: Changes in molecular subtype to a more immune permissive type with radiotherapy (RT) and immunotherapy (PD-1) in preclinical mouse model of rectal cancer. The use of RT-PD-1 inhibition resulted in a change towards the CMS1 (immune rich) molecular phenotype.

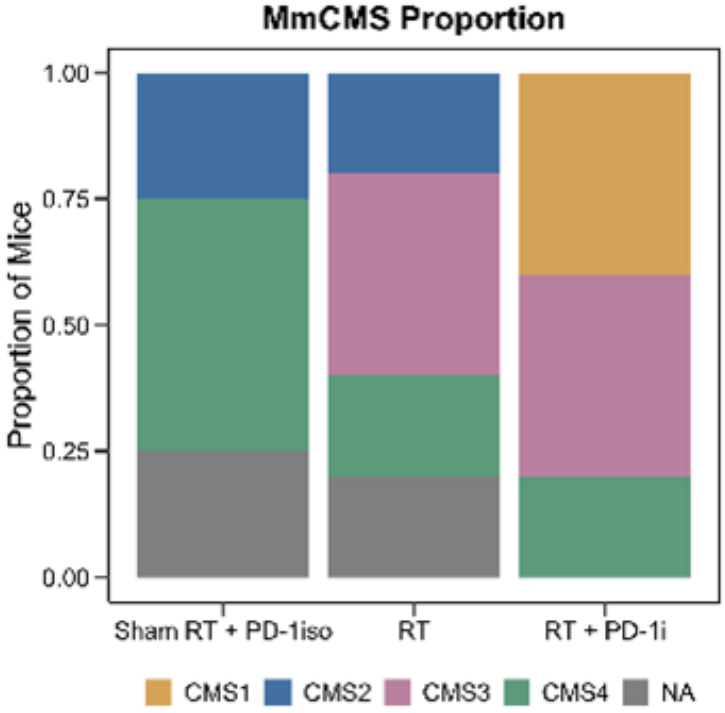
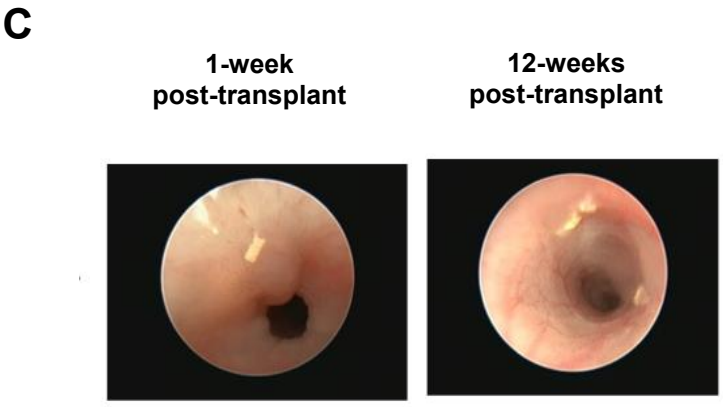
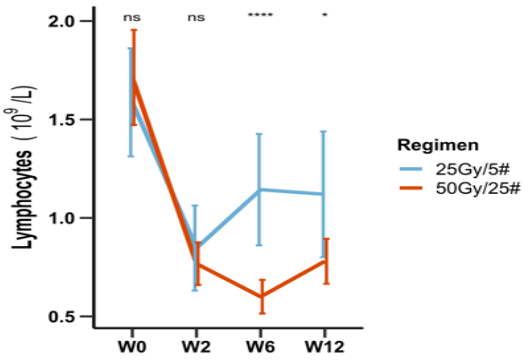


Figure 2: Complete tumour response to treatment with radiotherapy and immunotherapy in preclinical rectal cancer model. These views at mouse colonosocpy show complete regression of a previously established rectal cancer in a mouse model.

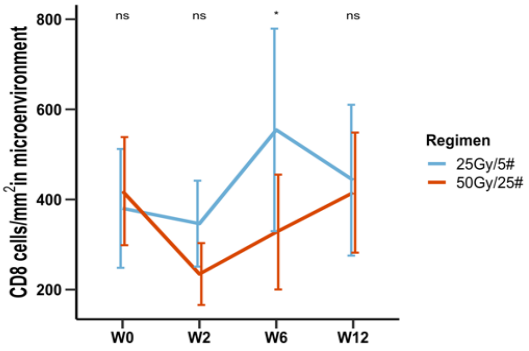


In the other research performed during my fellowship, a serial sample collection study was conducted to obtain tumour biopsies from consenting rectal cancer patients being treated with radiotherapy. Patient feedback and patient reported experience tools were used to confirm positive experiences in relation to research participation by study participants. In the tumour samples, we reported the different radiotherapy treatments and doses enhanced immune cell responses in tumours and circulating blood in different ways - short course radiotherapy was less immunosuppressive compared to long course radiotherapy (https://doi.org/10.1158/1078-0432.CCR-25-2733). We think these results in part explain the results seen in our clinical trial (called PRIME-RT) where rectal cancer patients had excellent responses to immunotherapy and radiotherapy with the best results seen with the 'short course' type of radiotherapy. (https://www.gla.ac.uk/news/archiveofnews/2025/may/headline_1174534_en.html)

Figure 3: Changes in (a) circulating lymphocytes and (b) intratumoural lymphocytes (CD8+ T cells) during treatment from week 0 through 2, 6 and 12 for both short course and long course radiotherapy schedules (Taken from Hillson LV et al, Clin Cancer Research 2026).



(A)



(B)

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

These results support the rationale for further clinical trials of immunotherapies and radiotherapy to improve outcomes for rectal cancer patients. These involve larger scale studies with longer term clinical endpoints to change clinical practice. In addition results from evaluation of clinical samples and the preclinical experiments support development of other strategies which could be added to immunotherapy to further improve outcomes. These include combinations of

immunotherapies and targeting other components of the immune system including myeloid cell types.

WHAT IMPACT COULD THE FINDINGS HAVE?

Colorectal cancer is the 3rd most common cancer and 2nd leading cause of cancer death in Scotland. I hope the research will continue to impact clinical outcomes for rectal cancer patients in the coming years. We will accomplish this through the delivery of (a) later phase clinical trials to move these strategies into routine clinical practice and (b) trials of more novel strategies to refine the improvements we have already reported. The aim is to improve responses in tumours so more cancers can be cleared completely and more patients can be offered an organ preserving management approach avoiding major life changing surgery. Better treatment responses and tumour clearance rates should mean fewer people suffering recurrence and ultimately dying from rectal cancer.

HOW WILL THE OUTCOMES BE DISSEMINATED?

Outcomes have been disseminated via presentations at national and international meetings, through publication in peer reviewed journals (including Clinical Cancer Research, PMID 41511399, and Diseases of Colon and Rectum, PMID 40071757). Other manuscripts are currently in preparation/under review. In addition, several press releases related to clinical trial outcomes and patient engagement have been dissemination through press and media. Patients recruited to the clinical studies and trials have participated in research engagement days and PPIE representatives have supported additional rectal cancer research in Glasgow and across the UK. Examples of patient engagement/ media:

https://www.scotsman.com/health/scotland-to-lead-new-ps55m-international-cancer-supergroup-5060094

https://www.oxfordmail.co.uk/news/23558338.oxford-grandad-praises-study-bowel-cancer-diagnosis/

https://www.christie.nhs.uk/about-us/news-at-the-christie/latest-news-stories/mum-of-3-cancer-free-after-clinical-trial-at-the-christie

https://ascopost.com/news/may-2025/five-major-advances-in-radiotherapy-for-anal-and-rectal-cancer-presented-at-estro-2025/

CONCLUSION

The preclinical and clinical research conducted during my fellowship support the use of immunotherapy and radiotherapy synergy to improve treatment responses in patients with rectal cancer. Further clinical trials are indicated to move these treatments towards routine practice. My research has identified several areas in which treatments could be refined or potentially improved with selection of radiation type and addition of other treatments.

RESEARCH TEAM & CONTACT

Professor Campbell Roxburgh

School of Cancer Sciences,
University of Glasgow

Campbell.Roxburgh@glasgow.ac.uk