CHIEF SCIENTIST OFFICE

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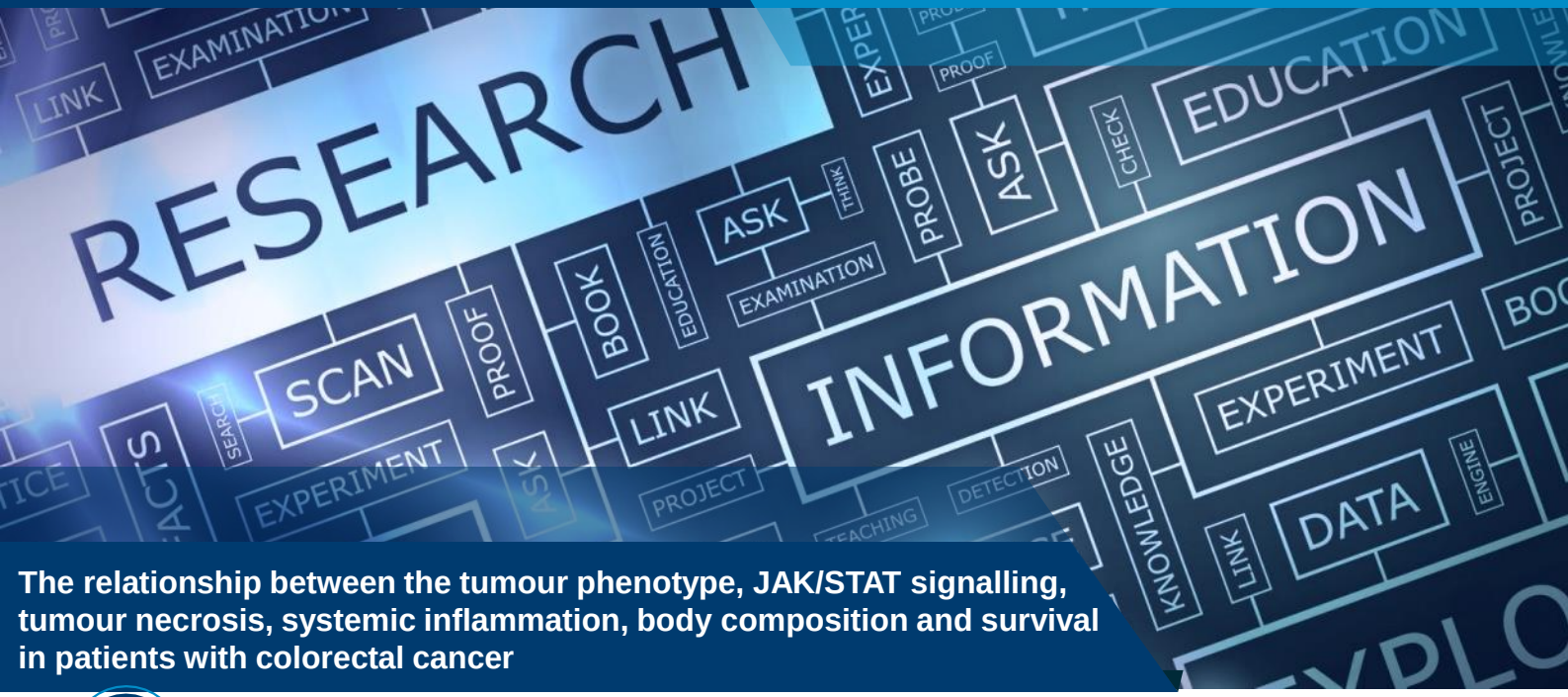
RESEARCH PROJECT BRIEFING



The relationship between the tumour phenotype, JAK/STAT signalling, tumour necrosis, systemic inflammation, body composition and survival in patients with colorectal cancer

AIMS

1. To examine the relationship between the systemic inflammatory response (SIR), body composition, phenotypic subtypes, tumour necrosis levels, inflammatory signalling and survival in patients with colorectal cancer.
2. To examine the strength of the above relationships and to look for other histopathological tumour characteristics that influence that loss of muscle mass, phenotype subtyping and survival in patients with colorectal cancer.
3. To identify potential therapeutic targets for future therapy in patients with cancer cachexia a multifactorial condition leading to loss of skeletal muscle and adipose tissue producing a deterioration in physical function in patients with cancer.

KEY FINDINGS

- Tumour Necrosis was associated with the SIR and in turn Computer Tomography (CT) derived body composition in patients with colorectal cancer
- Interleukin-6/Janus Kinase/Signal Transducer and activator of transcription protein (IL-6/JAK/STAT) signalling within the tumour was associated with the SIR but not body composition
- Nuclear factor kappa light chain enhancer of activated B cells (NFκB) signalling within the tumour was associated with the SIR but not body composition
- This suggests a more complex tumour/host interaction with the level of dead decaying cells within the tumour (tumour necrosis) playing a part in driving systemic inflammation which in turn drives cachexia.
- Further work on the signal pathways underpinning the relationship between tumour necrosis and systemic inflammation is warranted and could provide new therapeutic targets for the treatment of cancer cachexia.

WHAT DID THE STUDY INVOLVE?

This study was carried out in a retrospective manner in 677 patients with colorectal cancer. Systemic inflammation was assessed using the systemic inflammatory grade (SIG) a cumulative inflammatory score running from 0 to 4 which uses inflammatory proteins (CRP and albumin) and components of the differential blood cell counts. Body composition was assessed with CT based muscle analysis focusing on height adjusted skeletal muscle area (SMI) and skeletal muscle density (SMD). Tumour subtyping was assessed using immunohistochemical staining for proliferation, inflammatory infiltrate, stromal invasion and necrosis. The activation of the JAK/STAT and NFκB pathways was assessed with immunohistochemical staining of previously resected tissue. This was a dual site project with all patient characteristics and body composition analysis taking place at Glasgow Royal Infirmary and all tumour subtyping taking place at the Institute of Cancer Sciences.

WHAT WERE THE RESULTS AND WHAT DO THEY MEAN?

677 patients were included in the study. Two-thirds of patients were over 65, 56% were male and 54% had an American Society of Anaesthesiologists physical status classification (ASA) grade of 1 or 2. Pathological examination showed that the majority of patients had a T3 (57%) or a T4 (27%) cancer and 73% had evidence of tumour necrosis. A SIG score of 0 or 1 was present in 62% of patients. Low SMI was present in 54% and low SMD was present in 59% of patients.

Tumour necrosis was associated with age ($p<0.01$), tumour location ($p<0.01$), T-stage ($p<0.001$), SIG ($p<0.001$), low SMI ($p<0.01$), IL6 ($p<0.05$) and STAT1 ($p<0.05$). IL-6 levels association T-stage (<0.001), N-stage (<0.05), margin involvement ($p<0.01$) and SIG ($p=0.001$). NFκB markers association with Adjuvant therapy ($p<0.01$), margin involvement ($p<0.01$) and SIG ($p<0.01$). SIG was associated with BMI (<0.001), Low SMI ($p<0.001$) and Low SMD ($p<0.001$).

This suggests that tumour necrosis with the associated activation of inflammatory pathways within the tumour drives systemic inflammation; which in turn drives cachexia. Further work on the specific signal pathways underpinning the relationship between tumour necrosis and systemic inflammation is needed to provide potential new therapeutic targets in patients with cancer cachexia.

Figure 1: Assessment of tumor inflammatory cell infiltrate and TSP on H&E-stained sections. A: high KM grade. B: low KM grade. C: low TSP. D: high TSP. E: Low Ki67 and F: High Ki6720.

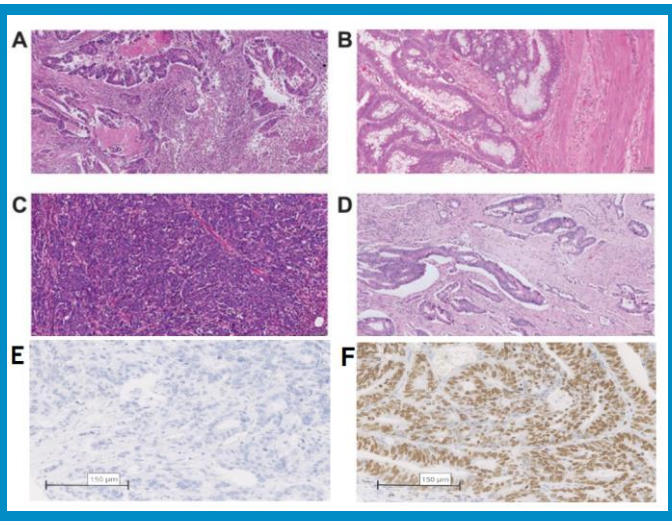
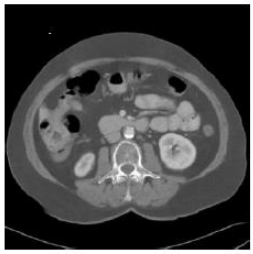
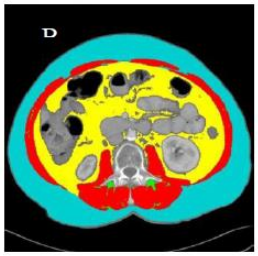


Figure 2: CT derived body composition using SliceOMatic 2023.





WHAT IMPACT COULD THE FINDINGS HAVE?

- Patients: The results of this study suggest that new therapeutic targets focused on modulation of the SIR in patients with colorectal cancer could have a positive impact of patient care as part of a multimodal treatment strategy in patients with cancer cachexia.
- Policy: Following on from recent phase one trials in the US using multimodal interventions, integrated cachexia care and patient phenotyping should form part of any future policies.
- Practice: Healthcare practice for patients with cachexia should now focus on integrated care involving pharmacological, nutritional and targeted exercise programs in patients with cancer cachexia.

HOW WILL THE OUTCOMES BE DISSEMINATED?

- The results of this study have already been presented internationally at the 6th Cancer Cachexia Conference in Edinburgh and at the ASCO GI conference in San Francisco
- The initial results of our necrosis work have been published in BJC Reports (DOI: 10.1038/s44276-024-00119-w)
- Currently further analysis in 600 patients is being carried out in order to reach the initial study goal of 1000 patients. Following this the results will be published.
- Collaborations with other centres within the UK and US have already started to look at targeting the inflammatory response as a treatment strategy in patients with cancer cachexia.

CONCLUSION

- Tumour necrosis and inflammatory pathways within the tumour impact upon systemic inflammation.
- This in turn has a strong association with the CT derived body composition, function and outcomes in patients with colorectal cancer
- Therefore, any treatment strategies for cancer cachexia will require a multimodal treatment strategy including pharmacological manipulation of systemic inflammation, nutritional support and targeted exercise strategies

RESEARCH TEAM & CONTACT

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Additional Information

This project is ongoing

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