BJS Open, 2022, zrac009
https://doi.org/10.1093/bjsopen/zrac009
Research Letter

Prognostic significance of the microbiome–adipose tissue axis in rectal cancer: protocol of a prospective observational study

Pere Planellas[1,2,3,*], Lídia Cornejo[2], Ramon Farrés[1,2,3], Anna Pigem[1,2], Ander Timoteo[1,2], Nuria Ortega[1,2], Gianluca Pellino[4], José-Ignacio Rodríguez-Hermosa[5], Eugeni López-Bonet[6], José Manuel Fernández-Real[2,3,7] and Antoni Codina-Cazador[1,2,3]

[1]Colorectal Surgery Unit, Department of General and Digestive Surgery, University Hospital of Girona Dr. Josep Trueta, Girona, Spain
[2]Girona Biomedical Research Institute (IDIBGI), Girona, Spain
[3]Department of Medical Sciences, Faculty of Medicine, University of Girona, Girona, Spain
[4]Colorectal Surgery, Vall d'Hebron University Hospital, Barcelona, Spain
[5]Endocrine Surgery Unit, Department of General and Digestive Surgery, University Hospital of Girona Dr. Josep Trueta, Girona, Spain
[6]Department of Anatomical Pathology, University Hospital of Girona Dr. Josep Trueta, Girona, Spain
[7]Department of Endocrinology, Diabetes and Nutrition, University Hospital of Girona Dr. Josep Trueta, Girona, Spain

*Correspondence to: Pere Planellas, Colorectal Surgery Unit, Department of General and Digestive Surgery, University Hospital of Girona, Avinguda de França s/n, 17007, Girona, Spain (e-mail: pplanellas.girona.ics@gencat.cat)

Dear Editor

Colorectal cancer is the second-leading oncological cause of death worldwide[1]. Despite advances in treatment, there is still a risk of local and distant recurrence, which impacts on long-term outcomes.

The influence of the tumour microenvironment in rectal cancer progression is gaining significant attention. Investigations into the role of peritumoral fatty tissue in the pathogenesis of oncological disease such as rectal, oesophageal, and breast cancer have shown tissue remodelling, which contribute to the generation of a pro-inflammatory, hypoxic, neoangiogenic environment[2].

Another component of the tumour microenvironment analysed in rectal cancer is the gut microbiome. Previous studies have described rectal mucosa dysbiosis and the association of micro-organisms with the progression of carcinogenesis[3].

These findings suggest there might be an interaction between microbiome and adipose tissue due to disruption of the intestinal barrier by pathogenic micro-organisms[4,5].

To understand how the tumour microenvironment could modulate short- and long-term outcomes, it is essential explore the complex relationship between the microbiome and adipose tissue dysfunction. The aim of this study is to analyse the microbiome–adipose tissue axis in patients with rectal cancer and determine the impact of the microbiome present in adipose tissue for predicting tumour progression and surgical outcomes.

The BIORECTUM study is a prospective observational study conducted at a high-volume tertiary referral colorectal surgical unit at a university hospital. All consecutive patients with a resectable, histologically confirmed rectal adenocarcinoma who are scheduled for surgery will be invited to participate. Participants will be required to sign an informed consent form before inclusion in the study.

Initially, the study aims to enrol at least 100 consecutive patients with rectal cancer per year, from April 2021 to April 2023. Patients are expected to participate from the first preoperative surgical outpatient visit (after giving verbal and written consent to participate) to the final follow-up visit, 5 years after oncological surgery. Participation in this study does not modify the standard treatment pathway.

To evaluate the microbiome–adipose tissue axis, the following samples will be collected: subcutaneous, visceral, and mesorectal adipose tissue; and faecal and rectal mucosa specimens. *Fig. 1* shows the timeline for the collection of samples.

The microbiome in visceral, subcutaneous, and mesorectal adipose tissue will be characterized with 16s rDNA metagenomic analysis and shotgun metagenomics. Adipose tissue dysfunctionality, inflammation, and angiogenesis will be assessed with standard histological techniques and with quantitative reverse transcriptase–polymerase chain reaction in fresh samples and formalin-fixed, paraffin-embedded blocks. Microbiome and gene expression data will be deposited in open-access repositories.

In addition to characterizing the microbiome–adipose tissue axis in patients with rectal cancer, analysis will be performed on the prognostic value for 3- and 5-year local recurrence, disease-free and overall survival, as well as its possible impact on surgical and pathological outcomes.

Data will be collected prospectively and will include demographics, preoperative, surgical, intraoperative, postoperative, pathology, and follow-up variables (local and distal recurrence, overall survival, cancer-specific survival, and disease-free survival).

The study has been approved by the hospital's ethics committee (no. 2021.028). The study protocol can be accessed

Received: December 07, 2021. **Revised:** January 14, 2022. **Accepted:** January 18, 2022

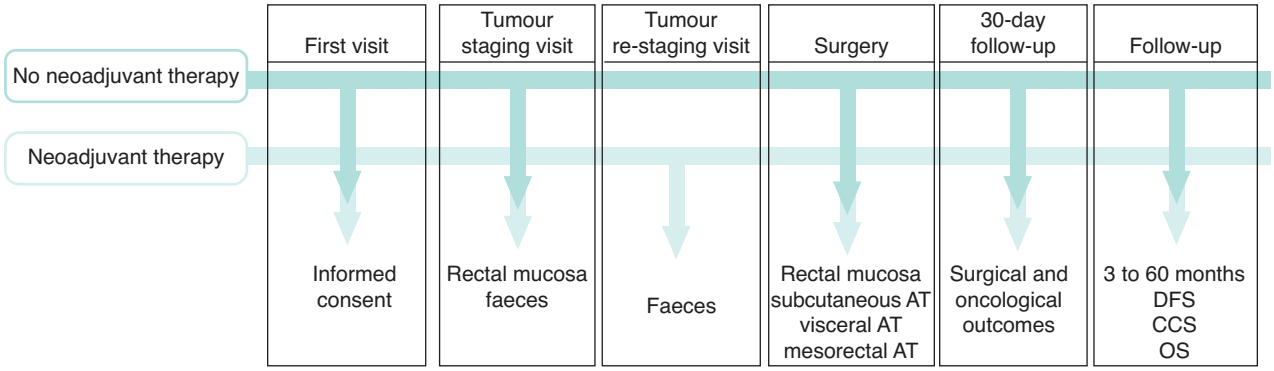

Fig. 1 Participant and sample collection timeline

AT, adipose tissue; DFS, disease-free survival; CSS, cancer-specific survival; OS, overall survival.

at http://www.clinicaltrials.gov (NCT04804956) and the Supplementary material.

The aim of this study is to gain a better understanding of how the tumour microenvironment could affect rectal cancer progression, which could help improve and develop therapeutic strategies.

Funding

This study was awarded a grant by the 'Asociación Española de Coloproctolgía' and 'Col·legi Oficial de Metges de Girona—Joan Bruguera Grant' in 2021.

Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;**71**:209–249
2. Rojas A, Araya P, Gonzalez I, Morales E. Tumor microenvironments in organs. *Adv Exp Med Biol* 2020;**1226**:23–36
3. Lu Y, Chen J, Zheng J, Hu G, Wang J, Huang C *et al.* Mucosal adherent bacterial dysbiosis in patients with colorectal adenomas. *Sci Rep* 2016;**6**:26337
4. Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, Han YW. Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA Adhesin. *Cell Host Microbe* 2013;**14**:195–206
5. Søby JH, Watt SK, Vogelsang RP, Servant F, Lelouvier B, Raskov H *et al.* Alterations in blood microbiota after colonic cancer surgery. *BJS Open* 2020;**4**:1227–1237