Editorial Commentary

Gut microbiota modulation: the key to improving outcomes after colorectal cancer surgery?

Jack A. Helliwell^, David G. Jayne

Leeds Institute of Medical Research at St. James's, University of Leeds, Leeds, UK

Correspondence to: Jack A. Helliwell, MBChB, MRes, MRCS. Leeds Institute of Medical Research at St. James's, University of Leeds, Beckett Street, Leeds LS9 7TF, UK. Email: J.A.Helliwell@leeds.ac.uk.

Comment on: Hajjar R, Oliero M, Fragoso G, *et al.* Modulating Gut Microbiota Prevents Anastomotic Leak to Reduce Local Implantation and Dissemination of Colorectal Cancer Cells after Surgery. Clin Cancer Res 2024;30:616-28.

Keywords: Microbiome; colorectal cancer; surgery

Submitted Apr 18, 2024. Accepted for publication Jul 05, 2024. Published online Aug 15, 2024.
doi: 10.21037/jgo-24-289
View this article at: https://dx.doi.org/10.21037/jgo-24-289

Anastomotic leak is the most feared complication after colorectal surgery, carrying significant clinical implications including abscess formation, faecal peritonitis, sepsis, and multi-organ failure. It extends average in-patient stay from 7 to 19 days and increases in-hospital morbidity and mortality (1). Anastomotic leak also has a long-term impact, and several studies have shown that it is associated with increased local cancer recurrence and reduced disease-free survival (2,3).

In their study, Hajjar *et al.* (4) began by conducting a retrospective review of cases at their own institution, revealing poorer oncological outcomes in patients who experienced anastomotic leak. While these observations could potentially stem from a delay in initiating adjuvant therapy, various alternative hypotheses are of note, including one suggesting the implantation of exfoliated tumour cells onto the anastomotic site (5). Using a murine model, Hajjar *et al.* (4) created an anastomosis following caecal colotomy and administered a rectal enema containing CT26 colorectal cancer cells. Their findings revealed that mice with impaired anastomotic healing developed larger anastomotic tumours (suggesting greater implantation of cancer cells in the anastomotic wound), as well as increased haemorrhagic ascites and peritoneal tumours (indicating greater extraintestinal dissemination).

Next, the authors explored the potential involvement of the gut microbiota in this process, building upon previous research showing differences in the microbiome between patients with and without anastomotic leak (6,7). Utilising a murine model, they found that the microbiome of patients with anastomotic leak led to reduced activation of the peroxisome proliferator-activated receptor gamma (PPAR-γ) pathway, which is known for its anti-inflammatory effects (8) and its inhibition of colorectal cancer cell proliferation (9).

Finally, Hajjar *et al.* (4) investigated the therapeutic potential of modulating the microbiome through dietary supplementation with inulin or 5-aminosalicylate (5-ASA). Inulin, a dietary fibre fermented by gut bacteria to produce butyrate, and 5-ASA, a PPAR-γ activator used in inflammatory bowel disease treatment, were administered to mice prior to caecal colotomy and sutured anastomosis. These interventions resulted in smaller local anastomotic tumours, reduced peritoneal disease dissemination, and reduced splenic bacterial levels.

While these findings highlight promising avenues for microbiome-based interventions, they warrant careful interpretation due to the challenges of using animal models to replicate mechanisms of anastomotic leak seen in human patients. First, the animal model used in the study, involved sutured closure of a caecal colotomy with six sutures (instead of the standard eight), suggesting a mechanical rather than bacterial-mediated mechanism underpinning

^ ORCID: 0000-0002-3579-0183.

poor anastomotic healing. Second, the microbiomes of humans and mice differ substantially, with variations in the abundance of key phyla and presence of several unique genera (10). Evaluating inulin and 5-ASA in a non-humanised microbiome model raises questions about the translatability of these findings to human patients.

Despite this, these findings add to a growing body of evidence indicating that the microbiome holds considerable promise in preventing anastomotic leakage and, in turn, lowering the likelihood of disease recurrence. Various other perioperative interventions, such as low-fat/high-fibre dietary prehabilitation (11), pre- and pro-biotic supplementation (12), and phosphate supplementation (13), have demonstrated promising effects on the microbiome and anastomotic healing in experimental animal studies. However, the safety and efficacy of these interventions in reducing anastomotic leak remains to be established through rigorous evaluation in clinical trials. As interest in this area grows, there is pressing need for translational research to ascertain whether encouraging pre-clinical data on the microbiome can be replicated in patients undergoing colorectal surgery.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*. The article has undergone external peer review.

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-289/prf

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-289/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Boccola MA, Buettner PG, Rozen WM, et al. Risk factors and outcomes for anastomotic leakage in colorectal surgery: a single-institution analysis of 1576 patients. World J Surg 2011;35:186-95.
2. Mirnezami A, Mirnezami R, Chandrakumaran K, et al. Increased local recurrence and reduced survival from colorectal cancer following anastomotic leak: systematic review and meta-analysis. Ann Surg 2011;253:890-9.
3. Goto S, Hasegawa S, Hida K, et al. Multicenter analysis of impact of anastomotic leakage on long-term oncologic outcomes after curative resection of colon cancer. Surgery 2017;162:317-24.
4. Hajjar R, Oliero M, Fragoso G, et al. Modulating Gut Microbiota Prevents Anastomotic Leak to Reduce Local Implantation and Dissemination of Colorectal Cancer Cells after Surgery. Clin Cancer Res 2024;30:616-28.
5. Umpleby HC, Fermor B, Symes MO, et al. Viability of exfoliated colorectal carcinoma cells. Br J Surg 1984;71:659-63.
6. Hajjar R, Gonzalez E, Fragoso G, et al. Gut microbiota influence anastomotic healing in colorectal cancer surgery through modulation of mucosal proinflammatory cytokines. Gut 2023;72:1143-54.
7. Hajjar R, Fragoso G, Oliero M, et al. Basal levels of microbiota-driven subclinical inflammation are associated with anastomotic leak in patients with colorectal cancer. Gut 2024;73:1031-3.
8. Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature 1998;391:82-6.
9. Motawi TK, Shaker OG, Ismail MF, et al. Peroxisome Proliferator-Activated Receptor Gamma in Obesity and Colorectal Cancer: the Role of Epigenetics. Sci Rep 2017;7:10714.
10. Park JC, Im SH. Of men in mice: the development and application of a humanized gnotobiotic mouse model for microbiome therapeutics. Exp Mol Med 2020;52:1383-96.
11. Hyoju SK, Adriaansens C, Wienholts K, et al. Low-fat/

high-fibre diet prehabilitation improves anastomotic healing via the microbiome: an experimental model. Br J Surg 2020;107:743-55.
12. Mocanu V, Park H, Dang J, et al. Timing of Tributyrin Supplementation Differentially Modulates Gastrointestinal Inflammation and Gut Microbial Recolonization Following Murine Ileocecal Resection. Nutrients 2021;13:2069.
13. Wiegerinck M, Hyoju SK, Mao J, et al. Novel de novo synthesized phosphate carrier compound ABA-PEG20k-Pi20 suppresses collagenase production in Enterococcus faecalis and prevents colonic anastomotic leak in an experimental model. Br J Surg 2018;105:1368-76.

Cite this article as: Helliwell JA, Jayne DG. Gut microbiota modulation: the key to improving outcomes after colorectal cancer surgery? J Gastrointest Oncol 2024;15(4):1993-1995. doi: 10.21037/jgo-24-289

