Biomarkers of Anastomotic Leakage

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Intestinal resection and anastomosis is a commonly performed abdominal procedure used in the treatment of colorectal cancers. Unfortunately, ~7% of all patients will develop an anastomotic leak (AL) following surgery. This situation occurs when the anastomotic site fails to heal correctly leading to contamination of the abdominal cavity with intestinal contents and the development of septic peritonitis. Patients often require revision surgery and intensive care, both of which are associated with significantly longer hospitalisation stays and increased economic costs. Patients also have higher morbidity and mortality rates and poorer oncological prognosis. Predicting which patients are at high-risk of developing an AL or diagnosing an AL early in the post-operative period is essential to optimise patient care and improve outcome. Unfortunately, predicting and diagnosing an AL following surgery for colorectal cancers is extremely difficult. Patients can present with a range of clinical symptoms and have non-specific findings on routine bloodwork. Diagnosis currently relies heavily on abdominal imaging with CT scans and contrast studies. Unfortunately, these techniques suffer from variable sensitivity and specificity and may delay diagnosis. To overcome these issues, pre-clinical and clinical research is continuing to identify diagnostic and predictive AL biomarkers.

Keywords: colorectal cancer ; intestinal anastomosis ; anastomotic leak ; biomarkers ; precision medicine

1. Introduction

Development of an anastomotic leak (AL) following intestinal surgery for the treatment of colorectal cancers is a life-threatening complication. Failure of the anastomosis to heal correctly can lead to contamination of the abdomen with intestinal contents and the development of peritonitis. The additional care that these patients require is associated with longer hospitalisation stays and increased economic costs. Patients also have higher morbidity and mortality rates and poorer oncological prognosis. Unfortunately, current practices for AL diagnosis are non-specific, which may delay diagnosis and have a negative impact on patient outcome. To overcome these issues, research is continuing to identify AL diagnostic or predictive biomarkers. In this review, we highlight promising candidate biomarkers including ischaemic metabolites, inflammatory markers and bacteria. Although research has focused on the use of blood or peritoneal fluid samples, we describe the use of implantable medical devices that have been designed to measure biomarkers in peri-anastomotic tissue. Biomarkers that can be used in conjunction with clinical status, routine haematological and biochemical analysis and imaging have the potential to help to deliver a precision medicine package that could significantly enhance a patient's post-operative care and improve outcomes. Although no AL biomarker has yet been validated in large-scale clinical trials, there is confidence that personalised medicine, through biomarker analysis, could be realised for colorectal cancer intestinal resection and anastomosis patients in the years to come.

2. Biomarkers of Ischaemia

- Lactate/Pyruvate Ratio
- pH
- Tissue Oxygenation

3. Biomarkers of Inflammation

- C-reactive Protein
- Albumin
- Procalcitonin
- Cytokines

- Tumour Necrosis Factor-α
- Growth Factors
- Leukocytes
- Neutrophils
- Intestinal Damage Markers
- Macrophage Biomarkers
- Hyponatraemia

4. Biomarkers of Tissue Repair

- Matrix metalloprotease
- Tissue inhibitors of metalloproteinase

The Intestinal Microbiome and Bacterial Contamination

- Bacterial Load

5. Conclusions

In the field of colorectal cancer research, significant advancements have been made in the identification of diagnostic and predictive biomarkers of AL. This research is driven by the clinical need to identify patients at high-risk of developing an AL and to diagnose AL earlier than current protocols allow. The ideal biomarker would allow for rapid, cost-effective and reliable prediction or detection of an AL in a time frame that allows clinicians to instigate interventions that minimise patient morbidity and mortality. Here we have highlighted the current most promising potential candidate biomarkers including ischaemic metabolites, inflammatory markers and bacterial components. Although none of these biomarkers have yet to be validated in large scale clinical trials, with none in routine clinical use, ongoing biomarker research in the field of intestinal surgery holds much promise. The incorporation of such biomarkers outlined in our review with other techniques, such as clinical status, routine haematological and biochemical analysis and imaging, has the potential to deliver an overall precision medicine package that could significantly enhance the effectiveness of a patient's post-operative care. There is a need, now more than ever, to utilise our knowledge of these biomarkers in carefully designed prospective, multicentre studies. These trials should be designed to investigate whether proactive post-operative patient management based on predictive biomarkers levels can be used to reduce AL rates. There is confidence within the scientific community that precision medicine, through the incorporation of biomarker analysis, will finally be realised for intestinal resection and anastomosis patients in the decades to come.
