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**Title:** Prevention and management of radiation-induced late gastrointestinal toxicity

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## **Abstract**

In the UK, about 90000 cancer survivors will suffer from pelvic radiation disease (PRD) due to their curative treatment including radiotherapy. The National Cancer Survivorship Initiative aims to improve the understanding and management of PRD by the oncology community. This overview covers the prevention, investigation and treatment for late radiation-induced gastrointestinal (GI) symptoms in PRD.

Multiple pharmacological and nutritional interventions have been studied, as prophylaxis for acute GI toxicity (aiming to prevent late consequential effects) though predominantly only small RCTs have been conducted. These have produced mixed results, though promising signals for some agents have been observed. Evidence for the pharmacological prevention of late GI toxicity is scarce. Even fewer RCTs have investigated the late GI toxicity profile of advanced radiotherapy technologies.

There are nationally agreed algorithms for the investigation and management of PRD, but a lack of awareness means patients still do not get referred appropriately. This article outlines the management of radiation proctopathy and diarrhoea, and signposts other accessible resources.

Finally, we provide recommendations for the management of late GI symptoms in PRD, and research in this field especially the need for high quality clinical trials.

## **Keywords**

Radiotherapy, Cancer, Bowel toxicity, Pelvic Radiation Disease, Prevention, Management, Review

## **Search Strategy**

A systematic search of the PubMed, EMBASE, MEDLINE and the Cochrane Library databases was performed. Keywords include: “radiotherapy”, “chemoradiotherapy”, “cancer”, “neoplasm”, “pelvic radiation disease”, “radiation enteropathy”, “radiation injuries”, “toxicity”, “morbidity”, “enteritis”, “prevention”, “radiomodulation” and “disease management”. Specific therapeutic names were also searched such as “intensity-modulated radiotherapy”, “amifostine”, “aminosalicylates” and “hyperbaric oxygen”.

## **Introduction**

In the United Kingdom, two million people live with or have survived cancer, of whom at least half had abdominal or pelvic cancer(1-3). About 90,000 cancer survivors will suffer from pelvic radiation disease(PRD) as a consequence of receiving either definitive or adjuvant radiotherapy(4, 5). Half of them are estimated to suffer from chronic gastrointestinal(GI) symptoms sufficient to inhibit daily living(5-8). These estimates, based on patient reported outcomes, contrast with more conservative clinician estimates (up to 24%)(9). This discrepancy is due to the lack of recognition and under-reporting of patient symptoms by clinicians(10, 11).

The impact of advanced radiotherapy technology, such as intensity-modulated radiotherapy, on the prevalence of PRD is uncertain. Although these technologies reduce the normal tissue volume exposed to high radiation doses, a larger volume receives a low radiation dose and the consequences of this are unclear(12). PRD incidence may also increase with the use of this technology for dose-escalation with the intention of improving oncological outcomes(13-15), or with current interest in radiotherapy for organ preservation strategies in early rectal cancer(16-18).

The National Cancer Survivorship Initiative(NCSI)(1) aims to improve the understanding and treatment of PRD. This overview focuses on the prevention and management of late radiation-induced GI symptoms in PRD. Finally, we provide recommendations to aid the oncologist in managing this disease.

### *Pelvic radiation disease and gastrointestinal symptoms*

PRD is defined as the “transient or longer term problems, ranging from mild to very severe, arising in non-cancerous tissues resulting from radiotherapy treatment to a tumour located in the pelvis”(12). PRD can present with up to 22 simultaneous GI symptoms (Table 1)(19-22). Multiple diagnoses are frequently involved with patients commonly having at least two diagnoses contributing to their symptoms, of which one-third are not radiotherapy-related(20). Though potentially treatable, there is low recognition of PRD symptoms by clinical oncologists and lack of uptake of standardised screening questionnaires, resulting in low referral rates with a minority of symptomatic patients having further investigations or management(9).

### *Clinician toxicity grading versus patient reported outcomes*

Clinician reporting of symptom severity is based on the Common Terminology Criteria for Adverse Events(CTCAE) due to its familiarity and being the preferred reporting tool in clinical trials(23). However, clinicians predominantly focus on more serious toxicities(CTCAE grade  $\geq 3$ ) grouping symptoms around a presumed affected organ unit. The Quantitative Analysis of Normal Tissue Effects in the Clinic(QUANTEC) recommendations used to guide radiotherapy dose-volume constraints for rectal and small bowel toxicity are based on the risk of grade  $\geq 2$  and grade  $\geq 3$  toxicity respectively(24, 25).

Yet, “milder” toxicity, such as grade 1 and 2 diarrhoea or faecal urgency, can have a very significant impact on daily life. Clinician CTCAE grading is poorly

concordant with patient reported outcomes(PRO) for “degree of distress”, “problems” and quality of life(26, 27). PRO validated questionnaires, such as the LENT-SOMA and the cancer-specific CTCAE/LENT-SOMA questionnaires, are significantly associated with patient symptoms, toxicity and quality of life(21, 27-29). The increasing inclusion in clinical trials of PROs will hopefully increase its clinical familiarity and routine clinical use.

## **Prevention of late radiation gastrointestinal toxicity**

There is very limited evidence base for the prevention of radiation GI toxicity.

This review will focus on key examples and their impact on late toxicity.

### *Lifestyle modification*

In a retrospective survey of prostate cancer patients treated with radiotherapy, Thomas *et al*(30) demonstrated increased GI symptoms in smokers, overweight and physically inactive men. Prospective studies evaluating the role of lifestyle intervention in preventing PRD are awaited.

### *Pharmacological prevention*

Only a few pharmacological agents have been studied in the prevention of late radiation GI toxicity, based on free radical scavengers or modulation of the transforming growth factor beta(TGF $\beta$ ), Smad and Rho GTPase/Rho-associated protein kinase(ROCK) signalling pathways involved in radiation-induced fibrosis.

*Amifostine* is thought to confer radioprotection by acting as a free radical scavenger. In head and neck cancers, it significantly reduced xerostomia, mucositis and dysphagia with radiotherapy only but not chemoradiotherapy(31, 32). Conflicting results for the prevention of radiation pneumonitis have been reported(33, 34). In pelvic cancers, seven small, randomised controlled trials(RCTs) have investigated amifostine(N=596)(35-41). All seven trials reported significant reductions in acute GI toxicity but conflicting results in late toxicity - three trials no benefit(36-38), two trials

reduced toxicity(35, 39). No compromises in oncological outcomes have been reported(42). The lack of standardised toxicity endpoints(43) and adequately powered trials with amifostine are significant limitations in forming firm conclusions of its role in preventing PRD.

*Statins*, may downregulate the Rho/ROCK pathway by inhibiting HMG-CoA reductase(44), while *ACE-inhibitors* may reduce TGF $\beta$  expression(45). A single-centre prospective cohort treated with pelvic radiotherapy reported better PRO scores for 1-year GI symptoms in statin and/or ACE-inhibitor users(46). No RCTs have tested these agents and further research is warranted.

More studies have attempted to modulate acute GI toxicity, which could indirectly reduce consequential late effects. However, studies were predominantly negative with late GI toxicity frequently unreported.

- *5-aminosalicylate* anti-inflammatories have been evaluated in five small, RCTs(N=196) – three trials closed early due to increased GI toxicity(47-49). The remaining two trials(N=114) reported reduced proctopathy scores(50) and decreased diarrhoea(51).
- *Orgotein*, an antioxidant superoxide dismutase, binds to extracellular superoxide radicals with the aim of reducing cell membrane peroxidation, thus inflammation and fibrosis. Three RCTs(N=569) reported reductions in acute GI toxicity(52-54) with one RCT(N=100) reduced grade  $\geq 2$  late GI toxicity(52).

- *Misoprostol* is a prostaglandin-E<sub>1</sub> analogue previously used in the treatment and prophylaxis of gastric ulceration. Of three RCTs(N=216)(55-57), only the smallest trial(N=16)(57) using a non-validated toxicity grading scale reduced radiation proctitis.
- *Octreotide*, a somatostatin analogue, is used to treat radiation-induced acute diarrhoea(58, 59). However, two RCTs(N=340) found no benefit in preventing acute GI toxicity(60, 61).
- *Sucralfate*, a polyanionic sulphated sucrose, forms a protective barrier over damaged mucosa and promotes epithelial healing. Of six RCTs(N=773)(62-69), only one(N=70) reported any benefit(68).
- *Butyrate*, a short chain fatty acid, is the predominant oxidative fuel for colonic mucosa promoting proliferation and differentiation(70). Two RCTs(N=186) evaluated sodium butyrate enemas for preventing radiation proctitis(71, 72) with no benefit in the largest RCT(N=166)(71).
- *Glutamine*, an essential amino acid, is vital for supporting intestinal mucosal growth, and electrolyte and nutrient absorption. Three RCTs(N=210) have reported no benefit(73-75).
- *Probiotics* have been evaluated in a systematic review of 10 RCTs(N=1449)(76). Meta-analysis indicated a significant reduction in acute diarrhoea though issues were noted with trial statistical quality and heterogeneity.
- *Dietary interventions* - Two small RCTs have found no benefit with an elemental diet(77, 78). A Cochrane review of four RCTs modifying dietary fibre, lactose and/or fat demonstrated a significant reduction in acute

diarrhoea though substantial clinical and trial heterogeneity, and variation in outcome measures were noted(79).

There remains limited evidence for the pharmacological prevention of PRD. Very few high quality clinical trials have been performed.

### Advanced radiotherapy technology

Recent developments in radiotherapy technology with improved target delineation, on-treatment image guidance and dose conformality allows dose reductions to organs at risk thus reducing acute and late toxicity. Examples of these approaches are summarised below.

*Improving target volume delineation*, by using alternative imaging modalities or protocols, can reduce the high dose target volume and consequently, normal tissue irradiated. *MRI-based planning* with its greater soft tissue definition can reduce the clinical target volume(CTV) by approximately 20% compared to CT-based planning though no significant difference has been reported in late toxicity(80, 81). *Four-dimensional CT(4DCT)* planning allows patient-specific reduction of internal motion margins in the treatment of upper GI cancers and has enabled dose-escalation in pancreatic cancer with relatively low acute and late GI toxicities(82-84).

*Image-guided radiotherapy*, besides improving target accuracy, allows reduction in CTV to planning target volume margins thus reducing the volume of normal tissue receiving high radiation doses. In a small cohort study(N=25),

*prostate fiducial markers* reduced acute grade  $\geq 2$  rectal toxicity by approximately 4-fold(85, 86). Grade  $\geq 2$  late rectal toxicity rates of approximately 3-5% have been reported(87-89). Retrospective studies using *cone-beam CT(CBCT)* image-guidance for 3D-conformal radiotherapy in prostate cancer have reported grade  $\geq 2$  late rectal toxicity rates of 10-11% compared to 30% with portal imaging(90, 91). In a small retrospective cohort study, *ultrasound-guided radiotherapy* for prostate cancer compared to portal imaging resulted in lower acute and late GI toxicity(92).

*Intensity-modulated radiotherapy(IMRT)* provides superior dose-conformality over conventional 3D-conformal radiotherapy(3D-CRT) thus lower normal tissue doses(93). Retrospective and prospective cohort studies have reported lower GI toxicity with IMRT in pelvic cancers compared with historical data and retrospective 3D-CRT cohorts(94-100). RCTs comparing GI toxicities of 3D-CRT versus IMRT reported reductions in grade  $\geq 3$  acute and late GI toxicity in cervical(101) and prostate(102) cancer.

#### *Other measures / interventions to reduce normal tissue irradiation*

Small single centre studies have explored methods to physically distance normal bowel tissue from radiotherapy high dose regions to try to reduce GI toxicity. None have been tested in RCTs. In prostate cancer, *endorectal balloons* are inserted daily to immobilise the prostate allowing smaller internal margins while pushing the distal rectal wall away. Teh *et al* demonstrated up to a 60% rectal dose reduction with a grade  $\geq 3$  late rectal toxicity rate of 1.7%(103).

*Tissue expanders* exclude small bowel from the pelvis by using implanted intra-peritoneal saline-filled tissue expanders, or separate the prostate and anterior rectal wall by transperineal injection of hyaluronic acid or hydrogel into the perirectal fat(104-106). These small studies have reported dosimetric advantages, improvements in PRO quality of life scores, or lower grade  $\geq 3$  late rectal toxicity with these approaches. In three small studies pre-1996, surgical creation of a *small bowel sling* using either omentum(107) or an absorbable polyglycolic acid mesh(108, 109) resulted in lower late GI toxicities with orthogonal field radiotherapy. So far, the invasive nature of these interventions has limited further research and their benefits with current radiotherapy techniques is unclear. Non-invasive approaches such as immobilisation with a *belly-board device* can reduce the small bowel volume receiving isodoses  $\geq 60\%$  in planning studies though no late toxicity data have been reported(110, 111),

*Normal tissue complication probability(NTCP) modelling* has correlated with grade  $\geq 3$  late rectal toxicity and PRO quality of life in retrospective studies(112-114). Further validation in prospective studies could allow future application of NTCP modelling in radiotherapy plan optimisation.

Despite rapid advances in radiotherapy technology and technique to improve dose delivery and reduce late toxicity, there are no high quality RCTs to quantify its benefits. However, with the dosimetric advantages seen, it would

prove ethically difficult to justify such RCTs, highlighting the importance of detailed follow-up and outcome reporting using standardised reporting tools.

## **Management of late radiation gastrointestinal toxicity**

### *Current challenges*

Following publication of the British Society of Gastroenterology guidance on the management of cancer treatment-related acute and chronic GI problems(115), there is now increasing awareness of this issue. However, surveys of gastroenterologists and oncologists(9) suggest there remain significant deficiencies in the provision of rapid and effective treatments, despite available investigation and treatment algorithms.

One of the initial barriers for patients is referral to an appropriate gastroenterologist. This may be challenging when symptoms can mimic irritable bowel syndrome, often managed in general practice. This is reflected in approximately one-third of patients referred to a general gastroenterology clinic having a functional GI disorder(116). However a diagnosis of IBS alone, with no further treatable disease is rarely made in tertiary referral centres assessing patients with PRD, underlining the importance of systematic investigation and treatment(22).

A second challenge is the multitude of symptoms associated with PRD – the Royal Marsden Hospital(RMH) algorithm identifies 22 different GI symptoms (Table 1)(22), each of which needs investigation. Individual patients often have 3-5 different GI symptoms, even without considering associated urinary or psychosexual issues, which can affect a quarter of patients receiving pelvic radiotherapy(115). In addition, symptoms frequently have more than one

diagnosis(20). Without addressing the multitude of different organic disorders, therapy is likely to result in a partial response at best.

A third issue is the current lack of infrastructure to cope with the numbers of patients, even if all affected were referred appropriately. Currently, only 11% of gastroenterologists consider themselves 'confident with all cases' of PRD(9). The recent ORBIT trial from RMH lends support for the idea of a nurse-led service, utilising their published algorithm(22). Patients with PRD(N=218) were randomised to receive 'standard care' (booklets and information), nurse-led care using the RMH algorithm or care led by a consultant gastroenterologist (who wrote the algorithm). 'Standard care' patients had inferior outcomes to both other groups, but there was no significance difference in outcomes between the two groups with algorithm-led care(22).

This lends the possibility of a different model to current gastroenterology-led clinics with the potential to improve access. In terms of health economics, patients often need focused assessment and treatment over a short period and then can be discharged. However, this would still be a new service requiring funding, competing with many other priorities in a financially challenged NHS.

### Approach to management

The RMH algorithm is summarised in a recent Nature Review article (Figure 1)(117). An initial triage is suggested to assess whether GI symptoms need to

be the only focus, or whether there are other significant issues (including, but not exclusive to, gynaecological, urological or psychological problems). The next distinction is the probability of cancer recurrence and to perform appropriate imaging if required.

The remaining patients can then be divided into those with new GI symptoms (likely the result of cancer therapy) or those with longstanding GI symptoms (with exacerbations possibly due to cancer therapy). Both of these groups may need investigation. It is important to remember that although 50% of patients have longstanding alteration in their bowel habit(115), some of these may be fairly insignificant and only reassurance is required.

The degree of investigation required will depend on symptom severity. A useful screen is to determine the presence of nocturnal diarrhoea, urgency and incontinence or any GI symptoms that affect quality of life(115). All of these patients need thorough evaluation including dietary assessment, particularly if excess fibre is contributing to symptoms (e.g. eating significantly more than '5-a-day' in an attempt to be healthy), alcohol history and medication history, especially any supplements taken in excess(115).

### *Management of two common conditions*

#### *Rectal bleeding*

All patients need a flexible sigmoidoscopy to diagnose radiation proctopathy (rectal telangiectasia), but also to exclude other conditions such as haemorrhoids, solitary rectal ulcer syndrome, bleeding diverticular disease,

colorectal cancer and other causes. Once a diagnosis of radiation proctopathy is confirmed, an assessment of severity is required, as infrequent bleeding needs no therapy. For more significant symptoms, bowel habit should be optimised(115) and suggested first-line therapy is sucralfate enemas, 2g twice daily. There is no evidence to suggest any benefit for standard inflammatory bowel disease therapies such as steroid enemas(70). An alternative is a 4-week course of metronidazole, which in a small RCT(N=60), resulted in improvements in bleeding and mucosal ulceration at 4 weeks, sustained until the final evaluation at 12 months(118). Although this is the only trial of metronidazole alone, further supportive data comes from another RCT with metronidazole and formalin therapy(119).

For prolonged symptoms, particularly if patients are iron- or transfusion-dependent, options are hyperbaric oxygen therapy (HBOT), formalin therapy or argon plasma coagulation.

HBOT is time-consuming, requiring five approximately 90-minute sessions per week for up to 8 weeks. Patients breathe 100% oxygen at pressures between 200-300kPa. There is RCT evidence supporting its use(120) although many of the trials are small, therefore results of the HOT II trial are awaited. There are however, access problems with limited numbers of NHS chambers with variable funding, while alternative charity-run centres are not always able to achieve the oxygen pressures advised. Currently NHS England is conducting a consultation exercise including a focus on access.

Formalin therapy, a mixture of methanol and formaldehyde which causes chemical cauterisation, is administered by infusing formalin into the rectum, after protection of the surrounding skin with barrier creams. Various formalin concentrations and contact times have been used, with a mean of 1.1-3.4 treatments required(121). Although efficacy looks promising with relief of symptoms in 60-100%(121), the quality of studies is poor(122) and a formal RCT is required. In addition, formalin reduces rectal compliance and therefore should be used cautiously in patients with incontinence issues. In selected patients, it can be a very effective therapy.

Argon plasma coagulation(APC) is the simplest therapy to give as most endoscopy units have access to the technology. A probe is passed down the channel of a sigmoidoscope to enable rectal telangiectasia to be cauterised. It is a popular therapy, but RCT data is lacking. In addition, APC should be used with caution due to the risk of significant ulcers and reported incidence of fistulae, which may lead to more radical surgery(115). It should therefore be reserved for patients with a limited area disease.

### *Diarrhoea and associated symptoms*

A clear history is essential to clarify the extent of symptoms. This should include bowel frequency (and stool volume), stool consistency (using the Bristol scale) and differentiation between diarrhoea and steatorrhoea (fatty, foul smelling, pale coloured stool or oily film on stool). Patients will often not volunteer this information, so appropriate direct questions should be asked.

Incontinence questions are also key as this may be the predominant issue, rather than stool looseness and sometimes persists, even if diarrhoea is fully treated.

A full colonoscopy is recommended for anybody with a persistent change in bowel habit or diarrhoea(123). This may be challenging in patients with previous gynaecological malignancies treated with chemo-radiotherapy/surgery as they are at high risk of a fixed sigmoid colon, which is difficult to negotiate, requiring a skilled endoscopist. Colonoscopy is useful to exclude new neoplasms, but also to diagnose other conditions such as inflammatory bowel disease or microscopic colitis (normal mucosa to the naked eye, but inflammation on biopsies). The more common scenario, however, is that patients undergo multiple colonoscopies, but no other investigations, which means their symptoms are not investigated and treated adequately.

At the same time as requesting colonoscopy, other functional investigations should be performed, including:

- Coeliac serology
- Thyroid function tests
- Faecal elastase (to test for pancreatic insufficiency)
- Tests for small bowel bacterial overgrowth (duodenal aspirate or breath test, depending on local expertise)
- SeHCAT scan for bile acid diarrhoea

A formal dietitian's evaluation is invaluable, but needs to be completed by a dietitian familiar with radiation enteropathy.

Treatment will depend on the conditions identified, but the RMH algorithm(22) gives detailed management plans for each scenario. In the short-term, the most useful anti-diarrhoeal agent is loperamide. This slows GI transit and importantly, gives patients confidence to leave home if incontinence is a problem. Tablets should be taken 30 minutes before food to slow the gastro-colic reflex, but it is important for the dose to be built up gradually as high doses may lead to abdominal pain/cramps, leading to cessation of this useful drug.

For patients suffering from incontinence, a mixture of loperamide and stool bulking agents are often required. Another essential tool is pelvic floor exercises and biofeedback, often performed by colorectal specialist nurses or community teams. With these strategies, plus treating underlying causes of diarrhoea, the majority of patients receive significant symptomatic improvements.

### *Moving forward*

There is now comprehensive guidance on how best to manage patients with late radiation GI effects, although further research is needed(115). The main challenge is facilitating referral of all appropriate patients, which may be assisted by the 'New Living With and Beyond Cancer Programme' under the umbrella of the NCSI(1). The second challenge is to consider a model of nurse-led clinics, but ideally involving multiple specialties to enable holistic care.

## **Discussion**

This is the first review covering pharmacological intervention and advanced radiotherapy technology in the prevention of late GI toxicity in PRD. There remains a paucity of high quality RCTs and research evidence. Several prophylactic pharmacological and nutritional measures, such as amifostine, statins, ACE inhibitors and probiotics may warrant further investigation. Advanced radiotherapy technology with its dosimetric advantages hold great promise but with a lack of late toxicity data available, prospective auditing of outcomes is strongly encouraged.

### *Key recommendations for the management of late GI toxicity*

With the lack of prophylactic interventions, current priorities are to improve PRD recognition by implementation of good PRO reporting and ensure appropriate management of late GI symptoms. This review covers approaches to aid clinical oncologists in the investigation and management of radiation-induced late GI toxicity. There is a need to improve case identification by increasing patient and clinician awareness (especially oncologists, surgeons, gastroenterologists and general practitioners). This will allow recognition of PRD as a treatable entity.

Clinical oncologists, gastroenterologists and surgeons need to develop local pathways for the investigation of late GI toxicity especially the importance of simultaneous investigation for multiple pathologies. Particularly with the rising number of cancer survivors, there will be a demand to establish regional multi-disciplinary specialist radiation late-effects teams, for expert management of

these patients, but established algorithms for GI toxicity already provide comprehensive guidance.

### *Recommendations*

1. More research and high quality clinical trials are needed to identify effective interventions in the prevention and management of PRD.
2. Current validated objective toxicity grading and PRO reporting tools should be used routinely in the clinic at baseline and follow-up with results acted upon appropriately.
3. Prospective multicentre audits of advanced radiotherapy toxicity outcomes, such as the on-going Royal College of Radiologists UK wide audit of IMRT in anal cancer chemoradiotherapy(124), is important to understand the toxicity profiles of these new technologies.

### **Conclusion**

The incidence of PRD is increasing with improved cancer survivorship and expansion of radiotherapy availability. There is currently limited research in the prevention and management of this condition. National and international collaboration is needed for future research and consensus to advance the understanding and management of PRD. Nonetheless, significant improvements in patient symptoms and quality of life can already be achieved by improving clinician recognition, investigation and management of PRD.

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**Conflict of Interest**

None of the authors have any conflict of interests to declare.

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**Figure Legends:**

**Figure 1:** Algorithm depicting simplified principles of work - up and common approaches for managing patients with delayed gastrointestinal symptoms after radiation therapy used at the Royal Marsden Hospital, London, UK. Abbreviations: BAM, bile acid malabsorption; FFA, free fatty acid; GI, gastrointestinal; QOL, quality of life; SIBO, small intestinal bacterial overgrowth.(117)

**Table 1: Gastrointestinal symptoms in pelvic radiation disease(22).**

<b>Symptoms</b>	<b>Examples of possible diagnoses</b>
<i>Abdominal bloating and cramps</i>	Faecal loading Enteral bacterial overgrowth Pancreatic insufficiency
<i>Borborygmi</i>	Enteral bacterial overgrowth
<i>Constipation or difficult rectal evacuation</i>	Faecal loading Drug-induced Anastamotic stricture
<i>Diarrhoea or frequency/ urgency/ nocturnal defaecation</i>	Dietary fibre intake Drug-induced Coeliac disease Radiation proctopathy Enteral bacterial overgrowth
<i>Faecal incontinence</i>	Pelvic floor dysfunction Overflow diarrhoea Anal sphincter defect
<i>Flatulence</i>	
Oral (burping)	Enteral bacterial overgrowth
Rectal	Enteral bacterial overgrowth Constipation
<i>Loss of sensation</i>	Spinal pathology Related to radiotherapy or surgery
<i>Nausea and vomiting</i>	Metabolic abnormality Biliary pathology Bowel obstruction
<i>Pain</i>	
Abdominal	Faecal loading Inflammatory bowel disease Enteral bacterial overgrowth
Back	Bone-related Bowel obstruction
Peri-anal/rectal (proctalgia fugax)	Spasm of levator ani muscles
Peri-anal/rectal (on defaecation)	Haemorrhoids Anal fissure Anorectal fistula or abscess Radiation-induced ulcer
<i>Per-rectal mucus discharge</i>	Haemorrhoids Radiation-induced ulcer
<i>Pruritus (perianal)</i>	Radiotherapy-related skin changes Haemorrhoids
<i>Rectal bleeding</i>	
Bright red +/- clots	Radiation proctopathy Haemorrhoids Inflammatory bowel disease Neoplasia Diverticular bleeding

Dark bleeding	Radiation-induced telangiectasia in the terminal ileum or colon
<i>Steatorrhoea</i>	Coeliac disease Pancreatic insufficiency
<i>Tenesmus</i>	Radiation proctopathy Neoplasia
<i>Weight loss</i>	Endocrine disorder (thyrotoxicosis Addison's disease)