REVIEW

Managing gastrointestinal symptoms after cancer treatment: a practical approach for gastroenterologists

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ABSTRACT

The percentage of the population living with a diagnosis of cancer is rising. By 2030, there will be 4 million cancer survivors in the UK. One quarter of cancer survivors are left with physical symptoms, which affect their quality of life. Gastrointestinal (GI) symptoms are the most common of all chronic physical side-effects of cancer treatment and have the greatest impact on daily activity. Cancer therapies induce long-term changes in bowel function due to alterations to specific GI physiological functions. In addition, the psychological effect of a cancer diagnosis, new GI disease or pre-existing underlying conditions, may also contribute to new symptoms. Twenty-three upper GI symptoms have been identified as occurring after pelvic radiotherapy. After upper GI cancer treatment, the most troublesome symptoms include reflux, abdominal pain, indigestion, diarrhoea and fatigue. Often, several symptoms are present simultaneously and women experience more symptoms than men. The symptoms which patients rate as most difficult are urgency, wind, diarrhoea, incontinence, abdominal pain and rectal bleeding. Recent UK Guidance on managing GI symptoms suggests that these symptoms can be treated especially if gastroenterological advice is combined with dietetic and nursing input to optimise investigations and management. However, as different pathological processes can result in identical symptoms; a systematic, 'algorithmic' approach to assess and treat these symptoms is required. This paper aims to illustrate the value of such an approach to investigate and treat the most common GI symptoms that trouble patients. The algorithm allows clinicians to institute a comprehensive medical management plan.

BACKGROUND

The percentage of the population living with a diagnosis of cancer is rising.¹ The number of long-term survivors has tripled over the last three decades. The

current increase in numbers of survivors is 3% in the UK and 11% in the USA. It is estimated that there will be 4 million cancer survivors by 2030 in the UK.¹

The National Cancer Survivorship Initiative (NCSI) consequences of treatment work stream estimates that between one-fourth and one-fifth of people treated for cancer (up to 500 000 people in the UK as a whole) are currently experiencing a physical consequence of cancer treatment which has an adverse impact on the quality of their life.²⁻³ This number is expected to increase to 600 000 by 2020.³⁻⁴

Gastrointestinal (GI) symptoms are the most common of all chronic physical side-effects of cancer treatment and have the greatest impact on daily activity.⁵⁻⁶

The optimal management of these GI symptoms has been poorly researched but is best characterised in patients who have undergone radiotherapy for a pelvic cancer of whom 80% are left with chronic alteration in GI function and 50% state that these long-term GI symptoms affect their daily activity.⁷ Radiotherapy induces long-term changes in bowel function as a result of progressive endothelial and stem cell dysfunction which in turn induces ischaemia which in turn promotes fibrosis.⁸ Localised fibrosis affects specific GI physiological functions. These changes are mediated by a cytokine cascade and may worsen over decades. Cancer treatment frequently disturbs physiological function in more than one part of the GI tract. In addition, factors unrelated to treatment, such as the psychological effect of a cancer diagnosis and its treatment, new GI disease or pre-existing underlying conditions, may also result in GI symptoms.⁹

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Twenty-three GI symptoms (table 1) have been identified as occurring frequently after pelvic radiotherapy. Often, several symptoms are present simultaneously, more in women (median number of symptoms 11) than in men (median number of symptoms 6).¹⁰

Recent UK Guidance on managing GI symptoms has identified an additional 20 upper GI symptoms (table 2) in patients after cancer treatments. Increasing evidence suggests that these symptoms can also be treated especially if gastroenterologist advice is combined with dietetic and nursing input to optimise investigations and management.^{11 12}

However, different pathological processes can result in identical symptoms and the presence of a specific symptom or cluster of symptoms does not predict the underlying causes. Therefore, in these complex patients, a systematic, algorithmic approach to assess and treat the symptoms effectively is required.^{7 13} Just such an approach has recently been tested in a large randomised NIHR funded clinical trial, the ORBIT study (ISRCTN 22890916) and shown to produce significant benefit (unpublished data).

The most frequently troublesome symptoms after pelvic radiotherapy in patients referred to a specialist clinic were urgency (80–85%), flatulence (67–77%), diarrhoea (75%), abdominal pain (65%), faecal leakage (45–57%) and rectal bleeding (42%).¹⁴ After treatment for upper GI cancer, the most troublesome symptoms include reflux, abdominal pain, indigestion, diarrhoea and fatigue.¹⁵

The aim of this paper is to illustrate the value of an ‘algorithmic’ approach to investigate and treat the most common GI symptoms that trouble patients. The algorithm allows clinicians to institute a comprehensive medical management plan. The approach used in the algorithm is based on the following concepts:

- accurate identification of troublesome symptoms is essential
- patients usually have multiple symptoms
- symptoms are often multi-causal
- simple investigations used in normal GI practice can identify the causes
- simple treatment approaches ameliorate or resolve the underlying causes

Table 1 23 lower gastrointestinal symptoms

Bleeding	Nausea
Bloating	Nocturnal defaecation
Borborygmi	Pain (abdomen)
Change in bowel habit	Pain (back)
Constipation	Pain (anal, perianal, rectal)
Diarrhoea/loose stool	Perianal pruritus
Evacuation difficulty	Steatorrhoea
Flatulence (rectal)	Tenesmus
Frequency of defaecation	Urgency
Incontinence/soiling/leakage	Vomiting
Loss of rectal sensation	Weight loss
Mucus excess	

Table 2 20 upper gastrointestinal symptoms

Anorexia	Heartburn/indigestion
Acid reflux/bile reflux/water brash	Jaundice
Burping/belching	Nausea
Dysphagia with solids or liquids	Odynophagia
Dry painful mouth/teeth	Pain (back)
Early satiety	Pain (chest)
Flatulence (oral)	Pain (epigastric)
Gastric stasis	Regurgitation of food
Halitosis	Vomiting
Hypersalivation	Weight loss

The algorithm determines the choice of investigations according to the symptoms which the patient wants treated and provides a clinical management plan once a diagnosis has been confirmed. Blood tests defined by the algorithm include a blood screen to exclude systemic pathology (full blood count, urea and electrolytes, liver function tests and infection/inflammatory markers (C-reactive protein (CRP), ESR) and additional blood screening for coeliac disease: tissue transglutaminase (TTG) (IgA); Vitamin B12, fat soluble vitamins (A-D-E), trace elements (selenium and zinc), red cell folate, iron studies, corrected calcium and thyroid function. International Normalised Ratio (INR) is requested when a patient reports heavy bleeding, abnormal liver function and as a surrogate measure of vitamin K levels in patients with malabsorption. If liver function tests are abnormal, a full liver screen and a liver ultrasound will be requested.

Other relevant investigations are listed in the algorithm which can be accessed on the NCSI website via the following link: <http://www.ncsi.org.uk/wp-content/uploads/RMH-Bowel-Algorithm-v7-20111.pdf>.

AN APPROACH TO URGENCY AND FAECAL LEAKAGE

Urgency and faecal leakage are the most troublesome and common symptoms in patients who have undergone pelvic radiotherapy, colonic or rectal surgery.^{10 14} This may be due to changes in rectal compliance or reduction in rectal volume or damage especially to the internal anal sphincter complex. In addition, cancer treatments which increase the speed of transit through the GI tract, or alter the consistency of stool may precipitate urgency of defaecation with or without faecal leakage or soiling. These symptoms often occur in conjunction with urinary and sexual problems and have a severe impact on quality of life. The algorithm suggests a number of investigations to exclude the possibility of local or systemic pathology contributing to these symptoms.

CASE STUDY 1: URGENCY AND FAECAL LEAKAGE

Patient

Mrs A, 53, diagnosed with a Dukes A (T2N0M0) rectal cancer, 9 cm from the anal margin. Treated with

endoscopic resection followed by low anterior resection with ileostomy, stoma reversal 4 months later.

Symptoms on referral (10 months after stoma reversal)

- Bowel frequency: 4–6×/day
- Stool consistency: type 4–5 (Bristol Stool Chart)
- Daily urgency
- Faecal leakage and incontinence
- Urinary frequency and leakage
- Sexual problems
- Social isolation and low mood

Differential diagnoses include:

- Anterior resection syndrome
- Systemic disease (eg, thyrotoxicosis)
- Tumour recurrence
- Causes unrelated to the cancer diagnosis (eg, new or pre-existing underlying GI disease, such as inflammatory bowel disease)

The investigations required by the algorithm include:

- A blood screen to exclude systemic pathology
- Endoscopic assessment to exclude colonic pathology
- Assessment to exclude local recurrence
- Anorectal physiology to assess possible local causes

Test results

Laboratory tests:

- All results within normal range

Physical and anorectal physiology examination:

- Weak sphincter muscle tone
- Reduced rectal compliance

Endoanal US:

- Minor damage to internal anal sphincter
- External anal sphincter intact

Flexible sigmoidoscopy:

- No local organic cause

Imaging/radiology

- No recurrent disease

Treatment

1. Pelvic floor exercises to improve sphincter tone
2. Toileting exercises to help deal with urgency
3. Regular sterculia (Normacol) 7 g once daily/twice daily as a non-fermented fibre bulking agent taken with plenty of fluid ± glycerine suppositories after a meal to aid complete evacuation of larger more formed stool
4. Loperamide 2 mg 30–60 min once daily before her evening meal if required to ensure stool is firm enough to facilitate complete defaecation
5. Referral to a specialist sexual counsellor

Outcome after three visits to the clinic

- Bowel frequency: 1–2×/day
- Stool consistency: type 4 (Bristol Stool Chart)
- Daily urgency resolved
- Faecal leakage and incontinence resolved
- Urinary frequency and leakage improved
- Sexual concerns resolved after six sessions
- Social isolation resolved as able to return to work
- Overall improvement in mood

AN APPROACH TO FLATULENCE AND MUCUS DISCHARGE

Excessive flatulence occurs in 30–70% of patients after cancer treatment.^{10 14 16} Excessive flatulence is often paired with faecal leakage particularly of fluid which can be very distressing.⁹ Excessive, uncontrollable flatulence in itself can cause embarrassment, anxiety and reduction in social activity.¹⁴ Wind is natural and is caused by the fermentation of dietary fibre in the colon with the gas produced, primarily hydrogen, being excreted in breath or as flatus. The gut flora influence the odour of the stool.

Up to 40% of patients previously treated with pelvic radiation report troublesome mucus discharge.^{10 14} Stool normally contains a small amount of mucus which is produced to lubricate the passage of stool and is rarely visible. Rectal mucus discharge arises when the mucosal production is excessive. Causes include local anal irritation caused by prolapse or haemorrhoids, excess use of liquid paraffin, irritable bowel syndrome, inflammatory processes or bacterial infections. Rarely, large polyps secrete mucus. Giardiasis and bile acid malabsorption (BAM) are also occasional causes.^{17–19}

After pelvic radiotherapy, excessive rectal mucus discharge is not uncommon for several months but usually has disappeared by 1 year. It may be helpful to check that patients are not consuming an excessively high intake of dietary fibre.¹² The mean UK average consumption of non-starch polysaccharides for healthy adults (aged 19–64 years) is 14.9 g/day for men and 12.8 g/day for women.²⁰ The current dietary recommended daily intake for fibre—18 g non-starch polysaccharides per day—is based on the effect that total dietary fibre has on stool weight. The rationale for this is that daily stool output of <100 g/day is associated with a non-starch polysaccharides intake of below 12 g/day and with an increased risk of bowel disease. In healthy populations, increasing non-starch polysaccharides intake from 13 to 18 g/day is associated with a 25% increase in stool weight. Some patients after pelvic radiotherapy cannot tolerate as much fibre as guidelines suggest they should.^{16 21}

CASE STUDY 2: FLATULENCE AND MUCUS DISCHARGE

Patient

Mr B, 58, diagnosed with cancer of the prostate. Treated with a short course of hormone treatment, radical radiotherapy and ongoing luteinising hormone-releasing hormone (LHRH) agonist.

Symptoms on referral (2 years after treatment):

- Bowel frequency: 4–5×/day
- Stool consistency: type 5–6 (Bristol Stool Chart)
- Daily urgency of defaecation
- Excessive flatulence (lasting >20 s)
- Mucus discharge
- Faecal leakage with daily soiling
- ‘Wet wind’

Differential diagnoses include:

- Local pathology
- Systemic disease unrelated to previous radiotherapy
- Dietary indiscretion

The investigations required by the algorithm include:

- A blood screen to exclude systemic pathology
- Physical examination and flexible sigmoidoscopy
- Abdominal x-ray to exclude faecal loading with overflow diarrhoea
- Dietary assessment

Test results

Laboratory tests:

- All results within normal range

Physical and anorectal physiology examination:

- Weak sphincter muscle tone
- Reduced rectal compliance

Flexible sigmoidoscopy:

- No local organic cause

Abdominal x-ray:

- No evidence of obstruction
- No marked faecal loading

7 day food diary:

- High fibre intake in excess of 20 g fibre per day

Treatment

1. Reduction of high fibre intake with substitution of food with high fibre content to food groups with lower fibre content aiming for 12–14g daily.
2. Toileting and pelvic floor exercises to improve sphincter musculature and increase bowel control. Toileting exercises may take a month or so to start to work and patients need to be persuaded to persist with them.

Outcome after three visits to the clinic

- Bowel frequency: 1×/day
- Stool consistency: type 4 (Bristol Stool Chart)
- Daily urgency resolved
- Faecal leakage and constant soiling ‘wet wind’ resolved
- Flatulence reduced significantly
- Mucus discharge resolved

AN APPROACH TO CHRONIC DIARRHOEA/LOOSE STOOL

Loose stool is a frequent problem during cancer treatments and is a chronic problem in many cancer survivors. The causes may be directly related to cancer treatments but are surprisingly often unrelated, being due instead to endocrine and especially thyroid problems, related to side-effects of prescribed medication and dietary issues particularly excessive or inadequate fibre intake.¹²

Pelvic radiotherapy has a direct, probably permanent, effect on small bowel motility.^{22–23} This change predisposes patients to small bowel bacterial overgrowth which can cause symptoms ranging from pseudo-obstruction to constipation to diarrhoea⁷ and may be the commonest missed diagnosis in the cancer

patient. The diagnosis of small bowel bacterial overgrowth can be difficult. A glucose/hydrogen methane breath test is a non-invasive test indicating presence of organisms. Direct culture of duodenal contents, if yielding a coliform, allows accurate targeting of antibiotic therapy to which the organism is sensitive.^{24–25} Box 1 describes a method of obtaining a duodenal aspirate at endoscopy.

Data (unpublished) suggest that ciprofloxacin and doxycycline (which has a useful anti-anaerobic spectrum of activity) are each effective in two-thirds of patients. Other antibiotics which sometimes may help but cause more side-effects are clarithromycin and metronidazole. The length of treatment varies in different studies, however, in our clinic patients are generally treated for 1 week. If small bowel bacterial overgrowth recurs rapidly, some patients need long-term, low dose antibiotic treatment. Long-term antibiotics are not routinely rotated but the same antibiotic in the lowest effective dose is used continually. Metronidazole cannot be used long-term because of the risk of irreversible neuropathy.

Although bile acid malabsorption (BAM) may not be the most common cause of diarrhoea after radiotherapy (1–85% prevalence in published studies),⁷ it deserves the necessary consideration and investigation. Patients with mild to moderate BAM present with erratic loose stool (they may be relatively constipated between bouts) while those with severe malabsorption may also have steatorrhoea.¹⁹ Two major types of BAM have been identified: ileal dysfunction whereby the ability to absorb bile acids in the terminal ileum is impaired and secondly, hepatic overproduction which overwhelms terminal ileal absorption capacity.^{26–28} More rapid small bowel transit results in a reduced time in the ileum to allow absorption.¹⁹ Increased hepatic bile acid production, saturation of the uptake mechanism, altered enterohepatic cycling and reduced storage capacity can all account for bile acid spilling over in the colon resulting in watery diarrhoea.^{26–29}

Carbohydrate malabsorption may occur *de novo* during cancer therapies, presumably due to damage to brush border enzymes and in some patients persists long-term. The best characterised is the development of lactose intolerance in up to 10% patients during cancer chemotherapy,^{30–31} and is the cause of diarrhoea in up to 15% patients during pelvic radiotherapy.²⁴ It has been suggested as the cause for chronic diarrhoea in up to 5% of affected patients.²²

Box 1 Taking a duodenal aspirate at endoscopy

- ▶ 100 ml of sterile saline is flushed into the duodenum, followed by 20 ml of air to ensure no saline remains in the endoscope channel.
- ▶ The suction is turned down.
- ▶ After leaving the fluid to equilibrate with the duodenal contents for 10–20 s, 20 ml is aspirated into a sterile trap and sent directly to microbiology.

CASE STUDY 3: CHRONIC DIARRHOEA

Patient

Mrs C, 38, diagnosed with carcinoma of the cervix. Treated with radical surgery. Diagnosed with pelvic and para-aortic lymph node relapse and small bowel obstruction 18 months later. Subsequently treated with a 35cm terminal ileum resection, chemotherapy and pelvic and para-aortic lymph node irradiation.

Symptoms on referral (3 years after initial diagnosis):

- Bowel frequency: 3–6×/day
- Stool consistency: type 1–7 Bristol Stool Chart
- Daily urgency of defaecation
- Faecal leakage weekly
- Nocturnal defaecation ×3 per week
- Severe abdominal pain daily
- Frequent painful bloating
- Steatorrhoea ×2 per week

Differential diagnoses include:

- Development of small bowel bacterial overgrowth
- BAM
- Pancreatic insufficiency
- Underlying GI disease unrelated to previous cancer or radiotherapy (ie, coeliac disease, new onset IBD, carbohydrate malabsorption)
- Dietary inadequacy (ie, excessive fibre intake)
- Recurrent pelvic malignancy
- Damaged anal sphincters from previous childbirth

The investigations required by the algorithm include:

- A blood screen to exclude systemic pathology
- Investigations to exclude small intestinal bacterial overgrowth (box 1)
- Nuclear medicine 23-seleno-25-homo-tauro-cholic acid (SeHCAT) scan to exclude BAM
- Endoscopic assessment to exclude colonic pathology
- Anorectal physiology
- Assessment to exclude local recurrence
- Dietary assessment: 7 day food diary

Test results

Laboratory tests:

- Raised CRP (14) and low vitamin B12 (157 pg/ml)

Glucose/hydrogen methane breath test:

- Positive for both methane and hydrogen after 40 min

Upper GI endoscopy with duodenal aspirate and biopsies:

- Positive for E. Coli and streptococci both sensitive to ciprofloxacin

Flexible sigmoidoscopy:

- No organic cause for symptoms
- Weak sphincter muscle tone

SeHCAT scan:

- 7 day retention of 3.2% indicating severe BAM

Physical and anorectal physiology examination:

- Incomplete anterior internal sphincter trauma confirmed with endoanal ultrasound
- Anorectal manometry: reduced squeeze pressure, decreased rectal compliance

CT abdo pelvis:

- No recurrent disease
- No gall bladder disease

7 day food diary

- Fibre intake: 15 g/day
- Fat intake: 80 g/day

Trial of a lactose-free diet:

- No benefit

Treatment

1. Course of ciprofloxacin to treat small intestine bacterial overgrowth. A moderately low vitamin B12 level (150–180 pg/ml) is often associated with small bowel bacterial overgrowth and resolves spontaneously after treatment with antibiotics.^{32 25} A marginally elevated CRP (>10 and <20) is sometimes also seen. As the patient remains at risk of recurrent small bowel bacterial overgrowth, she may need repeat treatment with antibiotics.
2. Management of BAM with colesvelam two tablets three times a day and referral to a registered dietitian for a dietary assessment and reduced fat diet (50g/day).^{26 33}
3. Recheck vitamin B12 and CRP levels annually in addition to serum fat soluble vitamin levels trace elements and serum triglyceride levels²⁶

Outcome after five visits to the clinic

- Bowel frequency: 2×/day
- Stool consistency: type 4-5 (Bristol Stool Chart)
- Daily urgency resolved
- Faecal leakage resolved
- No nocturnal defaecation
- No abdominal pain
- Bloating resolved
- Steatorrhoea resolved

AN APPROACH TO ABDOMINAL PAIN

Some degree of abdominal or rectal pain affects up to 30% of all patients after radiotherapy.³⁴ This pain affects daily living in about 10% of patients.¹⁶ Lower abdominal pain may have many causes and warrants thorough history taking and examination. Pain is an uncommon symptom arising from luminal GI disease although it sometimes is seen in inflammatory bowel disease but more commonly, pain occurs as a result of bowel spasm (cramps), faecal loading, small bowel obstruction or extraluminal malignant disease. Bacterial overgrowth can mimic symptoms of subacute bowel obstruction or cause recurrent pain and wind.⁷ Severe, sharp pain during defaecation suggests the presence of anal pathology such as an anal fissure or perianal abscess.⁷ Other causes of abdominal pain such as urinary or pelvic sepsis or bone disease need to be considered.

Proctalgia fugax is a severe anorectal and sacrococcygeal pain which can last for seconds or minutes. It is caused by spasm of the levator ani muscles. It often occurs at night and is aggravated by defaecation or sitting.³⁵

CASE STUDY 4: ABDOMINAL PAIN AND PROCTALGIA FUGAX

Patient

Mr D, 47, diagnosed with cancer of the recto-sigmoid junction. Treated with a long course of chemoradiation, anterior resection with covering ileostomy followed by adjuvant chemoradiation and reversal of the stoma.

Symptoms on referral (18 months after treatment and 1 year after stoma closure):

- Bowel frequency: 1×/every other day
- Stool consistency: type 1 (Bristol Stool Chart)
- Urgency but unable to open bowels
- Many attempts on the toilet
- Straining
- Tenesmus
- Abdominal and lower back pain
- Anorectal pain
- Fatigue

Differential diagnoses include:

- Systemic disease (eg, hypothyroidism)
- Local organic disease (eg, recurrence of cancer, stricture formation)
- Slow transit time and constipation
- Pelvic floor dysfunction
- Small bowel bacterial overgrowth with methane producing organisms

The investigations required by the algorithm include:

- A blood screen to exclude systemic pathology
- Investigations to exclude small bowel bacterial overgrowth
- Endoscopic assessment to exclude colonic pathology
- Anorectal physiology to assess sphincter muscle squeeze, the function of nerve supply to the sphincter and sphincter sensitivity to rectal distension
- Anorectal US to assess for possible damage to the internal sphincter musculature
- Assessment to exclude local recurrence with CT abdomen pelvis and MRI

Test results

Laboratory tests:

- All results within normal range

Physical abdominal exam:

- Faecal loading on the right side
- No palpable masses noted
- Weak sphincter muscle tone

Anorectal physiology exam:

- Anal resting pressure: 26 mm Hg (normal: 40–80 mm Hg)
- Sphincter muscle squeeze: 62 mm Hg (normal: 80–160 mm Hg)
- 15 s squeeze: 15 mm Hg
- Normal pudendal nerve terminal motor latency 2.0 ± 0.2 ms (SD): 1.5 ms (normal: less than 2 ms)
- Sphincter sensitivity to rectal distension: 40 ml (normal: 10 ml)

Anorectal ultrasound (US):

- Sphincter muscle rings intact
- No organic cause

Flexible sigmoidoscopy:

- No recurrent disease

Imaging:

- Faecal loading on the right side of the colon

Treatment

1. Pelvic floor and toileting exercises and biofeedback³⁵
2. Regular sterculia (Normacol) 7 g OD/BD as a non-fermented fibre bulking agent with plenty of fluid
3. Glycerine suppositories, used after a meal as needed to promote complete bowel emptying
4. Low dose antidepressant to reduce anorectal pain.^{7 35}
If the stool consistency is firm, a selective serotonin reuptake inhibitor (SSRI) such as citalopram 10–20 mg is recommended to avoid worsening constipation. If the stool is loose, tricyclic antidepressants may have a useful constipating effect (eg, dothiepin 50–75 mg). Antidepressants frequently can be discontinued after 4–6 months without recurrence of the symptoms.

Outcome after four visits to the clinic

- Bowel frequency: 1×/day, on occasion 1×/every other day
- Stool consistency: type 3–4 (Bristol Stool Chart)
- Daily urgency resolved
- 1 daily attempt to open bowels
- No straining but using biofeedback techniques
- Tenesmus resolved
- No abdominal or lower back pain
- Anorectal pain (proctalgia fugax) resolved
- Fatigue improving as sleeping pattern more regular

AN APPROACH TO RECTAL BLEEDING

Microscopic changes of damage to the vascular endothelial cells after radiotherapy may progress to destruction of those epithelial cells in the rectal mucosa and can result in ulceration and fibrosis.^{12 36} The resultant local ischaemia promotes fragile new vessel formation (telangiectasia) on the bowel surface, which often causes recurrent haemorrhage.³⁷ Progressive chronic ischaemia caused by vascular damage also accelerates long-term complications or consequences of radiotherapy such as ulceration, strictures or fistulation.³⁸

Rectal bleeding occurs in up to 50% of patients who previously received pelvic radiotherapy,^{39–42} but requires therapeutic intervention in fewer than 6%^{13 16} with 1–5% becoming transfusion dependent.⁹ Rectal bleeding typically starts about 1 year after conformal radiotherapy for prostate cancer and is at its worst at 3 years before improving spontaneously over 5–10 years.³⁷ The natural history of rectal bleeding after radiotherapy for gynaecological cancer is less well characterised. The risk of bleeding is directly

related to the dose of radiotherapy delivered to the anterior rectal wall.^{13 43} Patients who do not develop anaemia and in whom the bleeding does not affect quality of life, do not require treatment.¹²

Suggested treatments for radiation induced rectal bleeding include sucralfate enemas, pentosan polysulphate, rectally administered steroids, thermal coagulation therapy, endoscopic application of formalin, metronidazole, vitamin A, thalidomide and hyperbaric oxygen therapy.^{12 41} There is virtually no evidence as to the true effectiveness of any of these therapies.^{37 44}

CASE STUDY 5: RECTAL BLEEDING AFTER PELVIC RADIATION

Patient

Mr E, 74, diagnosed with cancer of the prostate. Received hormone treatment and radical radiotherapy to the prostate and seminal vessels. He also takes clopidogrel for two coronary artery stents placed 2 years previously.

Symptoms on referral (18 months after treatment):

- Gradual deterioration in bowel function 6 months after treatment
- Bowel frequency: 3–4×/day
- Stool consistency: type 4–5–6 (Bristol Stool Chart)
- Urgency
- Increased rectal flatulence
- Rectal bleeding (daily fresh red blood on the toilet paper, into the pan, associated with clots and leakage onto his clothing once or twice/week)
- Fatigue

Differential diagnoses:

- Systemic disease
- Radiotherapy induced telangiectasia
- Local pathology
- Small bowel bacterial overgrowth
- BAM

The investigations required by the algorithm include:

- A blood screen to exclude systemic pathology
- Glucose/hydrogen methane breath test ± duodenal aspirate to exclude small intestinal bacterial overgrowth
- Nuclear imaging with SeHCAT scan to exclude BAM
- Endoscopic assessment to exclude colonic pathology

Test results

Laboratory tests:

- Low Hb (8.9 g/dl) and Iron deficiency (2 umol/L, normal: 9–30 umol/L; low TIBC)

Glucose/hydrogen methane breath test:

- Negative

SeHCAT scan:

- 7 day retention of 41% excluding BAM

Upper GI endoscopy duodenal biopsies and aspirate and colonoscopy:

- No other cause seen apart from grade 3 telangiectasia (Wachter classification) on the anterior and lateral rectal wall with copious spontaneous bleeding

Treatment

1. Blood transfusion and recheck Hb
2. Start ferrous sulphate 200 mg three times a day
3. Regular sterculia (Normacol) 7 g OD/BD as a non-fermented fibre bulking agent with plenty of fluid.
4. 3× treatment with endoscopically applied 5% Formalin (box 2), 6–8 weeks apart, and concomitant sucralfate enemas.⁴⁵

Before endoscopic application of formalin, the bowel is prepared as for colonoscopy with bowel cleansing agents (phosphate enemas induce too much bleeding and often the preparation is inadequate) and the use of a gastroscope not a colonoscope is recommended. 30–35 ml of 5% formalin is usually sufficient to cover the telangiectasia.

As the majority of patients tolerate intrarectal formalin very well, the procedure is performed without sedation. Patients usually require 1–3 treatments, 6–8 weeks apart. Formalin is contraindicated if there is rectal mucosal ulceration.

Outcome after six visits to the clinic

- Bowel frequency: 1–2×/day
- Stool consistency: type 4 (Bristol Stool Chart)
- Urgency resolved
- Rectal bleeding mostly resolved: seeing minor specs of blood on the toilet paper on occasion
- Hb 14 g/dl
- Fatigue improving

Comment

Mr. E's bleeding was heavy and affecting his quality of life. Modifying his bowel function alone was not sufficient to improve the degree of the bleeding which was probably being worsened by the clopidogrel he was taking. Therefore, he required definitive treatment for his bleeding. There were three options:

- A. An 8 week course of daily hyperbaric oxygen therapy which may also reverse changes caused by radiotherapy at other sites such as in the bladder.⁴⁶ His local centre was too far away and he would not consider this treatment.

Box 2 Method of formalin application via endoscopy

- ▶ The rectum is intubated with a gastroscope
- ▶ 5% Formalin is instilled through a catheter into the rectum with the patient positioned prone and wet cloths and steady hand pressure are applied to the perianal area to prevent leakage of fluid during the procedure.
- ▶ The gastroscope is not removed but after intrarectal instillation of formalin most of the air is aspirated out of the rectum.
- ▶ The formalin is left in the rectum for 3 minutes exactly and then removed with copious washes of water.
- ▶ The perianal pressure and clothes are not removed until all the formalin has been washed out.

- B. Argon plasma coagulation: we advise our patients that this carries up to a 26% serious complication risk⁹ and has unproven efficacy in heavy bleeding.
- C. Formalin therapy: we use 5% formalin⁴⁵ and prefer to reserve its use for older patients. We advise them that up to three treatments will be required and outcomes seem to be good although long term follow-up data are not available.

The frequency and severity of his rectal bleeding improved after three treatments with endoscopically applied formalin and regulation of his bowel habit with Normacol.

AN APPROACH TO NAUSEA AND VOMITING

Chronic nausea and vomiting are not uncommon in the general population and a careful history and examination are required to eliminate common medical causes. In the cancer patient, disease recurrence must be considered. Small bowel bacterial overgrowth, gastric bile reflux or acid reflux are frequent benign causes of nausea, vomiting and retching after cancer treatment.¹³ Metabolic causes such as hyperglycaemia, hypercalcaemia, renal impairment, and Addison's disease need to be excluded. Gastroparesis and slow upper GI transit can exacerbate symptoms. Oesophageal motility disorders such as diffuse oesophageal spasm or ineffective motility can develop. Oesophageal strictures are another important cause.¹²

After oesophagectomy with gastric tube reconstruction, symptoms of reflux and nausea are often accompanied by early satiety, absence of hunger, inhibited passage of food due to high viscosity and impaired gastric emptying and postprandial dumping.^{47 48} The surgical procedure itself can still influence nutritional aspects and lead to altered stool frequency for prolonged periods after surgery, so patients frequently struggle to maintain their body weight.⁴⁸

Dumping syndrome is often associated with nausea and vomiting and should be considered after oesophageal surgery. It can be divided into early and late forms depending on the occurrence of symptoms in relation to the time elapsed after a meal. It may also be associated with early satiety, cramps, (explosive) diarrhoea and vasomotor symptoms such as sweating, flushing, palpitations and dizziness. Early dumping is more frequent (75%) with both GI and vasomotor symptoms occurring 10–30 min after eating. Late dumping (25%) occurs 1–3 h after eating and is characterised by mainly systemic, vasomotor symptoms.⁴⁹

Assessment of these patients needs to be shared with specialist dietitians. The management of dumping includes adapting meal size, eating frequent small meals and restricting fluid intake during meals to avoid early satiety. Complex carbohydrates—such as porridge, pasta, rice, potatoes and starchy vegetables—are preferred. Simple sugars and refined carbohydrates are usually less well tolerated. Protein, fat and starchy carbohydrate intake should be increased

to meet daily energy needs in a meal pattern that is tolerated.⁴⁹ Loperamide, guar gum or pectin to slow gastric emptying may be helpful. For late dumping, acarbose occasionally helps. Octreotide or lanreotide may be helpful in the short term but trials suggest the benefits are not maintained long term.⁴⁹

CASE STUDY 6: NAUSEA AND VOMITING

Patient

Mr F, 64, diagnosed with squamous cell carcinoma of the mid oesophagus. Initial treatment consisted of chemoradiation. On biopsy at 3 months, local residual disease was detected and treated with a salvage Ivor-Lewis oesophagectomy. Mr F had undergone endoscopic dilation of the oesophago-gastric anastomosis twice with little clinical benefit previously. He received ongoing treatment with cyclizine 50 mg three times a day and omeprazole 20 mg BD.

Symptoms on referral (18 months after treatment):

- Constant nausea
- Intermittent vomiting and regurgitation
- Belching
- Progressive retrosternal pain when eating
- Early satiety
- Bowel frequency: 2–3×/day
- Stool consistency: type 4 (Bristol Stool Chart)
- Weight loss

Differential diagnoses:

- Tumour recurrence
- Bile or acid reflux
- Small bowel bacterial overgrowth
- Delayed gastric emptying of the solid phase of the meal

The investigations required by the algorithm include:

- A blood screen
- Upper GI endoscopic assessment to exclude oesophageal and gastric pathology
- Glucose/hydrogen methane breath test ± and endoscopic small bowel aspirate
- Contrast barium swallow to assess motility
- CT scan to exclude recurrent disease
- Nutritional assessment

Test results:

Laboratory tests:

- All test results within normal range

Upper GI endoscopy and duodenal aspirate:

- Minor stricture at the anastomosis but easily passable with a gastroscope. Large volume bile secretions noted in the gastric remnant together with food debris from a meal eating more than 20 hours previously and marked gastric mucosal inflammation.
- No growth from jejunal aspirate

Glucose hydrogen, methane breath test:

- Negative

Oesophageal manometry:

- Normal

CT scan:

- No evidence of recurrence or metastatic disease

Treatment

1. Sucralfate suspension 1G four times a day
2. Proton pump inhibitor
3. Promotility regime with domperidone suppository 30 mg three times a day, erythromycin syrup 250 mg BD, 30 min before food and paroxetine syrup 20 mg OD.
4. Dietary assessment of symptoms related to intake of food and fluid. Dietary advice on food consumption, increasing energy intake and meal pattern.

In patients who experience nausea and vomiting due to delayed gastric emptying, often, prokinetic antiemetics are used. Prolonged use (>3 months) of promotility medications can result in tachyphylaxis and rotation of metoclopramide with domperidone may be helpful to restore the original response.⁵⁰ Using domperidone rectally assures efficient absorption. Treatment with low dose erythromycin (eg, 250 mg BD), which acts as a motilin receptor agonist to promote upper GI transit, may also be considered to improve gastric motility if the patient tolerates this well. Other agents which in some studies have been suggested to have useful gastric promotility activity include paroxetine, naloxone, 5-hydroxytryptamine receptor 4 (5-HT₄) agonists (eg, prucalopride) muscarinic receptor antagonists (eg, bethanechol), anti-cholinesterase inhibitors (eg, physostigmine or nizatidine and α adenoceptor receptor agonists (eg, clonidine).⁵⁰ However, how they should be used optimally is not clear. When a patient with delayed gastric emptying has also developed symptoms of dumping syndrome, prokinetic antiemetics can exacerbate the symptoms and alternatives such as cyclizine may be more appropriate. Prokinetic antiemetics should be used with caution in those on antimuscarinic medications (eg, anti-Parkinsons medications, antispasmodics used for irritable bowel syndrome or to treat an over-active bladder) as the prokinetic effect is reduced or lost although the central antiemetic effect will be maintained.⁵⁰

Outcome after five visits to the clinic

- Nausea resolved with promotility regimen and the use of intermittent sucralfate suspension.
- Vomiting now infrequent
- No retrosternal pain when eating
- Early satiety managed with smaller, more frequent meals
- Bowel frequency: 1–2×/day
- Symptoms of early dumping only occurring when eating larger meal portions (usually when going out)
- Weight increasing

EXCLUDING OTHER CAUSES OF GI SYMPTOMS AFTER CANCER TREATMENT

Different pathological processes can produce identical symptoms, for example diarrhoea has at least 13 different mechanisms.¹³ As demonstrated in the above case studies, GI symptoms after cancer treatment are complex and within a specialist setting, less frequently

occurring diagnoses are made more commonly. However, other causes of GI symptoms and factors unrelated to cancer treatment, such as the psychological effect of a cancer diagnosis and its treatment, changes in diet, new GI disease or pre-existing underlying conditions, may also result in GI symptoms.^{7 9}

CASE STUDY 7: TWO PATIENTS WITH SIMILAR DIAGNOSES, TREATMENT MODALITIES AND GI SYMPTOMS BUT DIFFERENT CAUSES

Patients

Mr H, 76, diagnosed with cancer of the prostate. Treated with hormone treatment, followed by conformal radiotherapy.

Mr I, 54, diagnosed with cancer of the prostate. Treated with hormone treatment, followed by intensity modulated radiotherapy (IMRT).

Symptoms on referral (1 year after radiotherapy):

Mr H:

- Bowel frequency: 3–6×/day
- Urgency
- Often loose stool
- Faecal incontinence 2×/month
- Tenesmus
- Perianal soreness

Mr I:

- Bowel frequency: 4–6×/day
- Urgency
- Often loose stool
- Faecal incontinence 3×/month
- Tenesmus
- Perianal soreness

Differential diagnoses include:

- Systemic disease (eg, thyrotoxicosis)
- Tumour recurrence
- Causes unrelated to the cancer diagnosis (eg, new or pre-existing underlying GI disease (IBD))
- Dietary factors (eg, excessive fibre intake, excessive alcohol intake)
- BAM
- Small intestinal bacterial overgrowth with hydrogen producing organisms
- Pancreatic insufficiency
- Sphincter damage/weak sphincter tone

The investigations required by the algorithm for both include:

- A blood screen to exclude systemic pathology
- Endoscopic assessment to exclude colonic pathology
- Assessment to exclude local recurrence
- Anorectal physiology to assess possible local causes
- 7 day food diary and history taking to assess dietary factors
- SeHCAT scan to assess possibility of BAM
- Stool sample for faecal elastase to assess possible pancreatic insufficiency
- Stool sample to assess for infective causes
- Investigations to exclude small intestinal bacterial overgrowth

Test results

Laboratory tests:

- All results within normal range
- Physical and anorectal physiology examination:*
- Normal sphincter muscle tone
- Glucose/hydrogen methane breath test:*
- Negative
- Upper GI endoscopy with duodenal aspirate:*
- No abnormality of the upper GI tract
- No growth in aspirate
- Flexible sigmoidoscopy with biopsies:*
- Mr.H :
- 2 cm sigmoid polyp
- Duodenal biopsies show Giardia
- Mr. I;
- Normal
- Imaging/radiology:*
- No recurrent disease
- SeHCAT scan:*
- Mr H: 7 day retention of 68%Mr I: 7 day retention of 36%
- Stool sample: faecal elastase*
- >500 µg/g stool
- Stool sample: culture*
- Mr I:
- Normal
- 7 day food diary:*
- Mr. H:
- No excessive use of alcohol or fibre
- Mr. I:
- No excessive use of alcohol
- >25 g fibre of fibre/day

Treatment

Mr H:

1. Treatment of Giardia infection with metronidazole
2. Polypectomy at colonoscopy

Mr. I:

1. Reduction of excessive fibre intake

Outcome at next clinic appointment

Mr H:

- Bowel frequency: 1–2×/day
- Stool consistency: type 4 (Bristol Stool Chart)
- Daily urgency resolved
- Faecal incontinence resolved
- Tenesmus resolved
- Perianal soreness resolved

Mr I:

- Bowel frequency: 1–2×/day
- Stool consistency: type 4 (Bristol Stool Chart)
- Daily urgency resolved
- Faecal incontinence resolved
- Tenesmus resolved
- Perianal soreness resolved

In other words, identical symptoms require identical investigations but have a quite unpredictable outcome and quite different treatments are needed which could not have been guessed.

DISCUSSION AND CONCLUSION

Whilst the oncologist's priority is to get the patient through their treatment with survival as their goal and looking for possible signs of disease recurrence during follow-up after treatment, patients are often left with long-term consequences of their cancer treatment which are neglected. GI symptoms have the most impact on quality of life but are not exclusive. Patients often experience fatigue in addition to nutritional, urinary, sexual, financial or psychosocial problems as a result of a cancer diagnosis and the treatment they received. Incorporation of the management of those problems is part of holistic care and wellbeing. The focus in this article was on GI symptoms as these can be managed by gastroenterologists alongside other health care professionals following a systematic approach as suggested in the algorithm.

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