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British Society of Gastroenterology practice guidance on the management of acute and chronic gastrointestinal symptoms and complications as a result of treatment for cancer

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ABSTRACT

Background Survival rates after a diagnosis of cancer are improving. Poorly managed gastrointestinal (GI) side effects can interfere with delivery of curative cancer treatment. Long-term physical side effects of cancer therapy impinge on quality of life in up to 25% of those treated for cancer, and GI side effects are the most common and troublesome.

Aim To provide comprehensive, practical guidance on the management of acute and chronic luminal gastrointestinal symptoms arising during and after treatment for cancer

Methods A multidisciplinary expert group including patients treated for cancer, divided into working parties to identify, and synthesise recommendations for the optimal assessment, diagnosis and appropriate interventions for luminal GI side effects of systemic and local cancer therapies. Recommendations were developed using the principles of the BMJ AGREE II reporting.

Results 103 recommendations were agreed. The importance of the patient perspective and what can be done to support patients are emphasised. Key physiological principles underlying the development of GI toxicity arising from cancer therapy are outlined. Individual symptoms or symptom clusters are poor at distinguishing the underlying cause(s), and investigations are required if empirical therapy does not lead rapidly to significant benefits. Patients frequently have multiple GI causes for symptoms; all need to be diagnosed and optimally treated to achieve resolution. Investigations and management approaches now known to be ineffective or of questionable benefit are highlighted.

Conclusions The physical, emotional and financial costs to individuals, their families and society from cancer therapy can be considerable. Identifying and signposting affected patients who require specialist services is the role of all clinicians. Progress in the treatment of cancer increasingly means that patients require expert, multidisciplinary supportive care providing effective and safe treatment at every stage of the cancer journey. Development of such expertise should be prioritised as should the education of health professionals and the public in what, when and how acute and chronic gastrointestinal symptoms and complications should be managed.

EXECUTIVE SUMMARY

This guidance document is intended for health professionals who see patients who have gastrointestinal issues during and after treatment for cancer which could be affecting their quality of life or potentially interfering with the effective delivery of their treatment for cancer. In a rapidly evolving area, it also touches on future perspectives. There is little definitive evidence so recommendations are largely based on expert opinion. Areas addressed and key points include:

Patient perspectives

- All patients should be informed about possible future side effects and how to access appropriate help at the end of their cancer treatment using a personalised care and support plan.
- Continued holistic assessment is recommended in all patients before and after treatment for cancer to ensure understanding of the ongoing issues.
- All clinicians seeing patients after cancer therapies have responsibility for identifying unmet needs, listening to their concerns and signposting patients to appropriate services.

Pathophysiology: overview

- Optimal symptom management requires the identification of the physiological deficits which have developed as a result of cancer treatment, with appropriate testing.
- The majority of patients developing GI symptoms after cancer treatment have more than one cause for their symptoms.

GI symptoms and patient-centred assessment

- Clinicians are encouraged to use validated symptom questionnaires (eg, the gastrointestinal symptom rating scale) or patient-reported outcome measures (PROMs), routinely completed by the patients when they attend clinics to help ensure accurate comprehensive assessment.
- In those patients who underwent curatively intended treatment pathways, recurrence needs to be considered and ruled out.
- Investigations for conditions not associated with the cancer or its treatment need to be considered.

Diagnostic tests

- Clinical acumen, specific individual symptoms or patterns of symptoms are not reliable in diagnosing the underlying cause(s) for those symptoms in patients treated for cancer. Therefore, comprehensive investigation is required at an early stage if troublesome symptoms do not respond fully to simple, empirical intervention.
- A wide variety of cancer treatments cause the same treatable physiological changes, which frequently include bile acid diarrhoea (BAD), carbohydrate intolerance, pancreatic exocrine insufficiency (PEI), small intestinal bacterial overgrowth (SIBO), and after immunosuppressive treatment, bacterial or viral infection.
- Investigating acutely during chemotherapy/radiotherapy in symptomatic patients is feasible and beneficial if symptoms are impacting on treatment.
- With ongoing or severe toxicity, early advice from a gastroenterologist, ideally with an interest in managing side effects of cancer treatment, should be sought.

Commonly occurring conditions during and after cancer therapy: diagnostic and treatment approaches

- In patients on restrictive diets, consider daily supplementation with long-term trace elements and multivitamin supplements until dietitian review.
- If long-term dietary interventions are recommended, dietetic review should be arranged to ensure nutritional adequacy.
- A 10-day trial with pancreatic enzyme replacement therapy at adequate dose after education of the patient is usually sufficient to assess efficacy.
- If multiple diagnoses have been reached, treatments should usually be introduced one at a time with a documented symptom response before introducing the next treatment.

Pain

- Chronic pain after abdominal surgery and/or radiotherapy may be caused by stricture formation, adhesions or fibrosis and the resulting obstruction. However, faecal loading and SIBO are under-appreciated causes.
- With new onset or unexplained pain, tumour recurrence should be considered.
- Signs of complete intestinal obstruction and severe abdominal pain require emergency surgical assessment (eg, small bowel obstruction, ischaemic bowel).
- In general, a multidisciplinary approach is required to manage these patients, including input from gastroenterology, surgery, pain management and nutrition teams.

Cytotoxic chemotherapy

- Frequent physiological disorders resulting from cytotoxic chemotherapy include lactose intolerance, SIBO, BAD and PEI.
- Investigations to determine the cause for new-onset symptoms during treatment are feasible and beneficial.
- In patients developing acute diarrhoea, stool analysis for infection should be performed; however, it is generally safe to start loperamide while awaiting the results. Reassess the patient regularly to exclude the development of toxic dilatation of the colon.
- Potentially aggravating oral anticancer drugs in patients with moderate to severe diarrhoea should be temporarily paused until they have been reviewed by an oncologist.
- Patients presenting with severe capecitabine/5-fluorouracil (5FU) GI toxicity, require an urgent CT scan to exclude enterocolitis which, if present, requires rapid, intensive intervention.

Small molecules/targeted therapy

- PEI is a common cause for GI symptoms in patients treated with sorafenib.
- BAD is a common cause for GI symptoms in patients treated with lenalidomide.

Acute radiotherapy effects

- Smoking and low body mass index both increase the risk of toxicity and should be addressed if possible before radiotherapy is given.
- Dietary counselling and/or protein supplementation may be helpful.
- Lactobacilli±bifidobacteria containing probiotics may reduce acute radiotherapy (RT)-related diarrhoea.
- A high-fibre diet may reduce the risk of toxicity during pelvic radiotherapy.

Acute upper GI symptoms

- Exclude herpes simplex virus, cytomegalovirus and extensive candidiasis in those with persistent painful mucositis.
- Symptomatic treatment should follow the modified WHO analgesia ladder.
- Early referral to the nutrition team should be considered in people at risk of malnutrition.
- Mouth washes, topical analgesics, coating agents or anti-inflammatories may help.
- Upper GI dilatation of potentially malignant strictures should not be performed until recurrent cancer has been excluded or the multidisciplinary team (MDT) have approved this approach.
- If dilatation is required, British Society of Gastroenterology (BSG) and National Institute for Health and Care Excellence (NICE) guidelines should be followed.
- High oesophageal stents which impinge on the cricopharyngeus are poorly tolerated and should be avoided.

Late effects after upper GI cancer treatment

- Symptoms are often related to the mechanical reconfiguration of the upper GI tract and the resulting physiological changes.
- Extensive investigation of symptoms within 3 months of surgery is generally unnecessary, as symptoms often settle over time.

- A history of presurgery, GI symptoms is important to determine if symptoms represent an exacerbation of a pre-existing condition or are new onset as a result of surgery.
- For an anastomotic stricture, endoscopic dilatation is the preferred treatment, with triamcinolone or a needle knife stricturoplasty reserved for recurrent strictures.
- Acid reflux should be treated with proton pump inhibitors; the addition of prokinetics for up to 6 weeks may help.
- Oral sucralfate suspension may be useful for recurrent bile reflux.
- Postprandial pain after upper GI surgery is commonly due to eating too much at one sitting.
- After upper GI surgery, bowel dysfunction with steatorrhoea is commonly due to PEI, SIBO and/or severe BAD; as these conditions often coexist, diagnostic testing and targeted treatment is recommended over empirical treatment.
- Symptoms should not be attributed to irritable bowel syndrome until comprehensive investigation/trials of treatment have excluded organic causes.

Late effects after pelvic cancer treatment

Radiation-induced rectal bleeding

- Appropriate endoscopic or radiological investigation of the bowel should be arranged as it cannot be assumed that rectal bleeding after radiotherapy is caused by radiation-induced telangiectasia.
- Diagnosis of radiation proctopathy should be made based on the typical appearance; biopsy confirmation should not be performed.
- Radiation-induced bleeding is an ischaemic problem, interventions in ischaemic tissue may not heal and may lead to necrosis and perforation.
- Interventions to stop significant bleeding should be performed only after patients have been informed of the risks and benefits of the intervention and have provided signed informed consent.
- If bleeding is not affecting quality of life and assessment has excluded underlying malignancy, the patient should be reassured and the natural history of radiation-induced bleeding explained; intervention is not required.
- If radiation-induced telangiectasia is the source of bleeding affecting quality of life or causing anaemia, optimising irregular bowel function will often reduce bleeding to a level which no longer affects quality of life.
- Stopping anticoagulants/antiplatelet agents if possible will often reduce bleeding to a level which no longer affects quality of life.
- Sucralfate enemas can be useful as a temporary treatment until definitive disease-modifying therapy in patients with heavy bleeding becomes effective or for long-term use in those with problematic bleeding unsuitable for disease-modifying therapy.

Lower GI functional symptoms

- Post-pelvic cancer symptoms need to be actively identified and managed.
- The extent of surgery and position of the anastomosis (or stoma) has direct influence on symptoms and quality of life.
- Multimodal treatment has a higher risk for long-term complaints and complications.
- Interventions include bowel habit training, toilet positioning, advice on raising abdominal pressure for evacuation without straining, modifying stool consistency via diet and fluid adjustments, loperamide or fibre supplements, following a stepwise algorithm.
- A large bowel transit study may help distinguish between slow transit constipation and evacuation difficulty.
- Biofeedback for incontinence or evacuation difficulties, transanal irrigation or use of suppositories or mini-enemas are sometimes needed, but evidence for efficacy is lacking.
- A stoma should be discussed in patients with poorly controlled symptoms and severely impaired quality of life, when other treatments have failed.
- Prophylactic use of laxatives is recommended when opioids are prescribed.
- Evidence that a defaecating proctogram, endoanal ultrasound or anorectal physiological assessment change clinical practice is lacking so should be reserved for specialist practice or research.

Low anterior resection syndrome (LARS)

- The risk of LARS should be assessed using a formal scoring tool and discussed with patients before surgery.
- Supported self-management interventions to expedite an improvement in their bowel function should be offered to all patients undergoing anterior resection.
- Objective testing is not required to make the diagnosis of LARS.
- If symptoms persist beyond 3 months and supported self-management interventions have failed, a referral to specialist services should be made.
- Other conditions may worsen LARS and should be excluded particularly BAD, PEI and SIBO.
- Pelvic floor exercises may improve functional outcome.
- Bulking agents may reduce clustering and improve stool consistency.
- Transanal irrigation can be helpful.
- Stoma formation can be helpful.

Haematopoietic stem cell transplant

- GI toxicity predicts post-transplant complications.
- A multidisciplinary approach to care, including input from haematologists, dietitian, gastroenterologists and specialist symptom control team, is helpful.
- Endoscopic tests with small bowel aspiration and biopsies are helpful in patients with diarrhoea after stem cell transplantation for differentiating between small bowel bacterial or fungal overgrowth, enteric infections (especially with *C. difficile* or cytomegalovirus) and graft versus host disease (GvHD).
- Upper GI endoscopy with small intestinal aspirate and biopsies combined with flexible sigmoidoscopy is significantly safer than colonoscopy in patients with lower GI symptoms and is similarly effective at reaching a diagnosis.
- Wireless capsule endoscopy is not recommended to make the diagnosis of GvHD.
- In patients with typical symptoms of GvHD, treatment should not be delayed while waiting for biopsy results.

Neuroendocrine neoplasms (NENs)

- The majority of GI symptoms in patients who have NENs, do not result from excess production of hormones.
- Gastroenterologists should be involved in the NEN MDT.
- Surgery and systemic treatments for NENs, particularly somatostatin analogues, frequently cause abnormal GI symptoms.

- Common causes of GI symptoms include PEI, BAD and SIBO.
- Starting pancreatic enzyme replacement therapy (PERT) is appropriate without faecal elastase measurement in those with steatorrhoea starting after treatment with a somatostatin analogue.
- Prophylactic cholecystectomy should be considered when undertaking initial surgery for NENs to prevent recurrent or chronic pancreatitis.
- In an existing non-functioning NEN, new GI symptoms should prompt investigation to exclude a change in hormone secretion.
- If a NEN directly contributes to GI symptoms, either from pressure effects or from hormonal secretion, debulking surgery or systemic therapies should be considered.
- Surgical management of mesenteric fibrosis should be considered, even in a metastatic setting, if quality of life is impaired significantly (and if there is a reasonable prognosis from the NEN).
- Dietetics and multidisciplinary nutrition teams should be involved in patient care, especially in those at risk of short bowel syndrome from either mesenteric fibrosis or its surgical management.
- NENs are associated with an increased risk of developing other cancers so new unexplained symptoms should prompt investigations for other GI cancers.

Mesenteric fibrosis

- Abdominal pain can be difficult to manage and requires a close collaboration with pain and palliative care teams and dietitians.
- Early and sustained dietetic input is needed to optimise nutritional status and prevent malnutrition.
- Resection of fibrotic tissue or of involved bowel segments may offer symptomatic relief but risks short bowel syndrome.
- Despite stage IV disease, surgery may be an option but must be agreed in a NEN MDT.
- Long-term home parenteral nutrition is a valid alternative to surgery if the risks of surgery are considered too high.

Palliative and end of life care

- Focus on remote monitoring of patient-reported outcome measures.
- Provide treatment to optimise symptoms and quality of life.
- Consider referral to palliative care when there is ≥70% risk of death within 1 year.
- Prioritise minimising pain and avoiding opioid-induced constipation.
- For diarrhoea/bloating consider an empirical trial of rifaximin for 1 week/a bile acid sequestrant for 10 days/PERT for 10 days.
- Consider early adjunctive iron support including parenteral iron in patients with bleeding.
- For malignant bowel obstruction consider corticosteroids and octreotide. Only insert a nasogastric tube if the patient wants to try this and other measures to relieve obstructive symptoms have failed.
- Palliative venting gastrostomy can relieve symptoms and improve quality of life in the absence of extensive peritoneal or gastric serosal disease.

INTRODUCTION

Up to 25% of cancer survivors report a decline in quality of life resulting from physical consequences of their treatment.[1] Of all cancer treatment-related side effects, gastrointestinal (GI) symptoms experienced during, soon after or many years after treatment are the most common and have the greatest impact on quality of life. Diarrhoea occurs in 20–95% of patients receiving cytotoxic treatments and in 30% of cases requires hospitalisation.[2] During radiotherapy for a pelvic cancer, up to 80% develop acute GI toxicity and depending on the tumour site irradiated, between 20% and 50% have long-term bowel dysfunction affecting daily activities.[3] After often multimodality treatment for colorectal cancer, 16% of those without a stoma have no control of their bowels and large numbers have ongoing moderate GI, urinary and/or sexual issues.[4] The burden on patients is often substantial:

> Just get through the tiredness and diarrhoea… then everything will be normal again. But, it's never been the same ……On a good day uncomfortable, using pads, and planning carefully every time I went out … On a bad day, I'd rather not eat than embarrass myself in front of family and friends and I sleep in a separate room…[5]

This practice guidance is relevant to the management of patients experiencing luminal GI symptoms resulting from single or multimodality treatment given for local tumour control as well as systemic anticancer therapy (SACT). Associated relevant guidelines are available, that address SACT-induced nausea and vomiting, mucositis and GI symptoms resulting from immunotherapy or those effects on specific organs such as liver and pancreas, as are guidelines from patient-facing charities (table 1).

This practice guidance aims to inform all clinicians seeing patients who could be experiencing cancer therapy-induced GI side effects. It provides a brief introduction to the pathophysiology of commonly encountered symptoms arising from specific treatments and emphasises the role of patient-facing assessment, diagnosis and treatment approach. It includes recommendations for investigation and management. Future perspectives on clinical management are also briefly explored. The term 'toxicity' used throughout the text describes the unwanted side effects of cancer therapy.

METHODOLOGY

The last BSG practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer was published in 2012.[6] This update was commissioned by the BSG.

The development of this guidance adhered to the principles of the BMJ AGREE II reporting guidelines.[7] This document covers a very broad spectrum of topics. There is significant heterogeneity regarding the level of evidence available for the different sections. The authors were assigned to six working groups covering each topic and performed a structured literature search. Most of the recommendations are based on retrospective cohort studies, case series, clinical experience and, as a result, often expert consensus. We therefore did not attempt to list the totality of evidence or grade the level of evidence for each statement, but where relevant, provide an overview of the key literature. Clinical practice guidance statements relevant to each clinical domain were defined and subsequently voted on by all contributing authors using 'agree'; 'disagree' or 'abstain' options. Statements were discussed individually, refined where there was disagreement, and two further rounds of voting took place. Clinical practice guidance statements were included only if they reached 90% or more agreement (excluding abstentions).

Table 1 Relevant additional guidelines

From professional organisations			
Originating organisation	**Year of publication**	**Guideline title Most recent publication**	**Coverage Patient group and indication**
ESMO	2015	Management of oral and gastrointestinal mucosal injury: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up[153]	Management of oral and gastrointestinal mucositis occurring in response to CT+/-RT and HSCT, including review of evidence for management of mucosal injury in patients receiving targeted therapy agents
MASCC/ESMO	2016	2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in patients with advanced cancer[154]	Prevention of acute and delayed nausea and vomiting induced by CT with high and low emetic potential. Prevention of RT-induced nausea and vomiting. Prevention of anticipatory nausea and vomiting in patient receiving CT. Use of antiemetics in patients with advanced cancer
ENETS	2016–2023	ENETS guidance paper for non-functioning pancreatic neuroendocrine tumours[155] ENETS guidance paper for functioning pancreatic neuroendocrine tumour syndromes[156] ENETS guidance paper for carcinoid syndrome and carcinoid heart disease[157] ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms and neuroendocrine neoplasms of Unknown Primary Site[158]	Diagnosis, treatment and follow-up of patients with functioning and non-functioning gastroenteropancreatic neuroendocrine neoplasms
AGIHO/DGHO	2017	Diagnosis and empirical treatment of fever of unknown origin (FUO) in adult neutropenic patients: guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO)[159]	Risk-adapted diagnostic procedures and empirical antimicrobial treatment of neutropenia in patients with cancer with fever of unknown origin
BSG	2018	UK guidelines on oesophageal dilatation in clinical practice[100]	
BSG	2018	Guidelines for the investigation of chronic diarrhoea in adults[25]	Diagnosis of patients with diarrhoea in primary or secondary care
AGIHO/DGHO	2019	Management of sepsis in patients with neutropenia in cancer: 2018 guidelines from the Infectious Diseases Working Party (AGIHO) and Intensive Care Working Party (iCHOP) of the German Society of Haematology and Medical Oncology (DGHO)[160]	Screening, diagnosis and management of sepsis occurring in patients with haematologic malignancies or solid tumours undergoing intensive cytotoxic CT
BSG	2020	British Society of Gastroenterology endorsed guidance for the management of immune checkpoint inhibitor-induced enterocolitis[58]	Management of GI and liver immune-related adverse events (irAEs) in patients with cancer receiving treatment with immune checkpoint inhibitors (ICI)
MASCC/ISOO	2020	MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy[84]	Management of oral and gastrointestinal mucositis secondary to radiotherapy (RT), chemotherapy (CT), chemo-radiotherapy (CT-RT) and haematopoietic stem cell transplantation (HSCT)
SITC	2021	Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events[161]	Management of immune-related adverse events (irAEs) in patients with cancer receiving treatment with immune checkpoint inhibitors (ICI)
AGIHO/DGHO	2021	Prophylaxis, diagnosis and therapy of infections in patients undergoing high-dose chemotherapy and autologous haematopoietic stem cell transplantation. 2020 update of the recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Haematology and Medical Oncology (DGHO)[162]	Infectious complications following high-dose chemotherapy and autologous stem cell transplantation (ASCT)
MASCC/ESMO	2023	Updated MASCC/ESMO Consensus Recommendations: prevention of radiotherapy- and chemoradiotherapy-induced nausea and vomiting[163]	Use of antiemetic prophylaxis agents in patients with cancer receiving RT and CT-RT
From charities providing support for people diagnosed with a gastrointestinal cancer			
Charity name	**Website**	**Helpline**	**Information and support offered to:**
Action Against Heartburn	https://www.actionagainstheartburn.org.uk/	heartburn17@outlook.com	Promoting earlier diagnosis of stomach and gullet (oesophageal) cancer
Bowel Cancer UK	https://www.bowelcanceruk.org.uk/	020 7940 1760 admin@bowelcanceruk.org.uk	For everyone affected by bowel cancer in the UK
DiCE (Digestive Cancers Europe)	https://digestivecancers.eu/	info@digestivecancers.eu	European umbrella organisation representing patients with digestive cancer colorectal, gastric, liver, oesophageal, pancreatic and rare cancers
GIST Cancer UK (Gastrointestinal Stromal Tumour)	https://www.gistcancer.org.uk/	0300 400 0000 admin@gistcancer.org.uk	Supporting patients living with GIST cancer
GUTS UK	https://gutscharity.org.uk/	info@gutscharity.org.uk	Funding research into the digestive system
Heart Burn Cancer UK	https://heartburncanceruk.org/	01256 338668 info@heartburncanceruk.org	Everyone living with persistent heartburn, Barrett's oesophagus or oesophageal cancer
Macmillan Cancer Support	https://www.macmillan.org.uk/	0808 239 9397	Any adult diagnosed with cancer, UK-wide
Neuroendocrine Cancer UK (NCUK)	https://www.neuroendocrinecancer.org.uk/	0800 434 6476	Providing patient information and support groups for patients with neuroendocrine neoplasms
The Oesophageal Patients Association (OPA)	www.opa.org.uk	0121 704 9860 enquiries@opa.org.uk	People affected by oesophageal and gastric cancers
Pelvic Radiation Disease Association (PRDA)	www.prda.org.uk	info@prda.org.uk	For people with symptoms that start or continue for 3 months or more, after the end of radiotherapy for a pelvic cancer

aDGHO, German Society of Haematology and Medical Oncology; AGIHO, Infectious Diseases Working Party of DGHO; BSG, British Society of Gastroenterology; ENETS, European Neuroendocrine Tumour Society; ESMO, The European Society of Medical Oncology; HSCT, Haematopoietic Stem Cell Transplantation ; iCHOP, Intensive Care Working Party of DGHO; ISOO, International Society for Oral Oncology; MASCC, Multinational Association of Supportive Care in Cancer; SITC, Society for Immunotherapy of Cancer.

Patient perspectives

Clinical practice guidance

1. *All patients should be informed about possible future side effects and how to access appropriate help at the end of their cancer treatment using a personalised care and support plan.*
2. *Continued holistic assessment is recommended in all patients before and after treatment for cancer to ensure understanding of the ongoing issues.*
3. *All clinicians seeing patients after cancer therapies have responsibility for identifying unmet needs, listening to their concerns and signposting patients to appropriate services.*

The complexity and success of modern multimodality cancer treatments and the speed with which they have been introduced into clinical practice has meant that health professionals have sometimes not been able to appreciate the impact that treatment-induced side effects can have on the patient and their environment (box 1, table 2). This is especially problematic when patients feel their specific needs are not adequately addressed in both the acute and chronic settings. Inadequate evidence, lack of clinical leadership or clinical 'ownership' of the issues and the fact that supportive care is not a priority, make it very difficult to know how to address unmet needs despite the efforts of charities.

To gain understanding of the psychosocial impact of living with cancer treatment toxicity it is vital to listen to the patients. Ongoing, often unacknowledged, symptoms have a negative impact on their lives.[4 8 9]

Box 1 Quotes from patients with lived experience who have contributed to this document illustrating a collation of holistic concerns and the broad impact on quality of life and future concerns during and after cancer treatment.

⇒ Medical professionals need to understand that it doesn't just end with the cancer treatment.
⇒ Once the issue had been raised, medical professionals tried to help, but they just didn't have the knowledge – they didn't know where to signpost me.
⇒ My bowel issues are the first thing I think about in the morning and the last thing I think about at night.
⇒ Trying to get help has been a battle every step of the way and 3 years down the line, I'm still fighting that battle. It's exhausting.
⇒ It took 4 years for my bile acid malabsorption to be diagnosed and even then, it was just luck.
⇒ Post-cancer treatment is a very lonely place; trying to deal with long-term side effects which seriously impact on your quality of life alone and without support, further heightens that feeling.
⇒ There's a high threshold before a patient will ask for help – we're conscious that we're lucky to be alive and so prepared to accept a lot as just being the 'new normal'.

The use of a holistic needs assessment, including the emotional, social, occupational and financial impact at the time of a cancer diagnosis, on completion of treatment and repeatedly during follow-up can be helpful in highlighting problems (figure 1), which would not otherwise be addressed in a consultation.[10]

Simple questions that any health professional can ask to identify patients who should be offered a gastroenterology referral are shown in box 2.

Pathophysiology: overview

Clinical practice guidance

4. *Optimal symptom management requires the identification of the physiological deficits which have developed as a result of cancer treatment with appropriate testing.*
5. *The majority of patients developing GI symptoms after cancer treatment have more than one cause for their symptoms*

Cancer treatments frequently cause multiple GI symptoms. Different treatments often cause the same symptoms, although identical symptoms may be triggered by damage to different physiological mechanisms. Abnormal symptoms arise after pathological insults if that leads to change in physiological processes within the GI tract (figure 2).

Cytotoxic chemotherapy agents have a direct effect on rapidly proliferating GI tissues, particularly the mucosal barrier function and enzyme systems, through inflammation, oedema and cell death. They may additionally damage the GI tract indirectly—for example, by microvascular damage or damage to the visceral nervous system.

Agents targeting receptors critical to cancer growth and metastasis are increasingly widely used. These include receptors regulating vascular endothelial growth factor, epidermal growth factor, tyrosine kinases, mammalian target of rapamycin, cyclin-dependent kinase 4/6 and poly(adenosine diphosphate-ribose) polymerase. These receptors are also found in normal tissues within the GI tract. Therefore, GI toxicity, particularly diarrhoea, occurs in 18–95% of treated patients,[2] presumably through these pathways, although almost no research into the mechanisms of toxicity has been performed.

Table 2 Issues most frequently concerning patients, illustrated by data from 18 000 patients with upper and lower GI cancer collected in 2020-2022 from Macmillan Cancer Support electronic-holistic needs assessment data (unpublished, personal communication Dr Minton)

Issues raised by holistic needs assessment in order of frequency raised	Issues raised by holistic needs assessment in order of frequency raised
Lower GI cancer	**Upper GI cancer**
I have questions about my diagnosis, treatments or effects	I have questions about my diagnosis, treatments or effects
Thinking about the future	Partner
Partner	Uncertainty
Uncertainty	Thinking about the future
Person who I look after	Person who I look after
Children	Children
Housing	Person who looks after me
Taking care of others	Taking care of others
Person who looks after me	Worry, fear or anxiety
Money or finance	Housing
Hopelessness	Tired, exhausted or fatigued
Worry, fear or anxiety	Loss of interest in activities
Independence	Independence
Unable to express feelings	Hopelessness
Anger or frustration	Eating, appetite or taste
Loss of interest in activities	Sleep problems
Sadness or depression	Anger or frustration
Other relatives or friends	Sadness or depression
Work or education	Money or finance
Loneliness or isolation	Pain or discomfort

Radiotherapy causes mucosal changes, initially characterised by inflammation and oedema and a subsequent, persistent cytokine activation. This happens predominantly in the intestinal submucosa and leads to ischaemia, fibrosis, atrophy and loss of stem cells.[11] Radiation damage to the GI tract manifests in different ways: physiological dysfunction, bleeding, stricture formation, obstruction or fistulation[12 13] and may be progressive.[11]

Resectional GI surgery may cause important GI physiological changes as a result of denervation or reconfiguration. Examples include nerve resection such as vagotomy, disconnection of the duodenal pacemaker, loss of gastric or rectal reservoirs, mechanical shortening of the GI tract, creation of blind loops and altered secretion of enzymes, hormones, bile or other fluids.

The known physiological abnormalities caused by cancer therapies are described in table 3.

GI symptoms and patient-centred assessment

Clinical practice guidance

6. *Clinicians are encouraged to use validated symptom questionnaires (e.g., the gastrointestinal symptom rating scale) or patient-reported outcome measures (PROMs), routinely completed by the patients when they attend clinics to help ensure accurate comprehensive assessment.*
7. *In those patients who underwent treatment pathways with curative intention, recurrence needs to be considered and ruled out.*
8. *Investigations for conditions not associated with the cancer or its treatment need to be considered.*

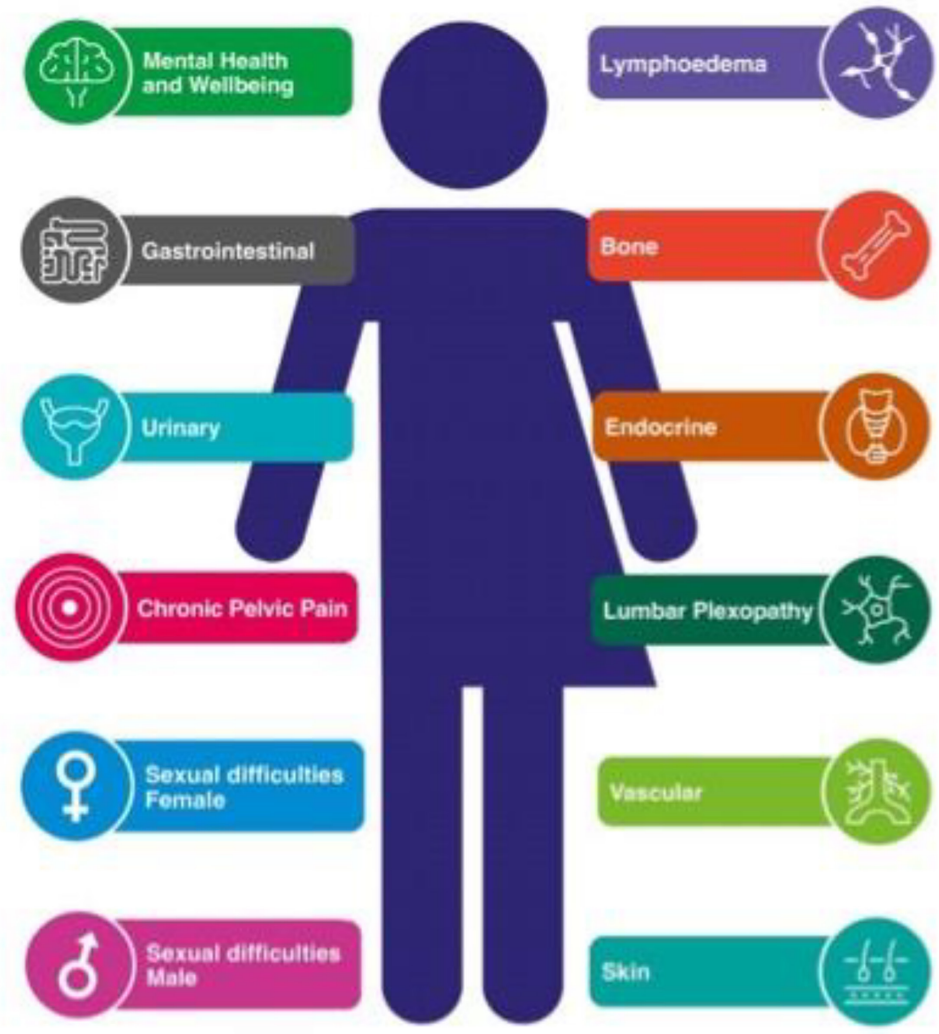

Figure 1 Extent of the holistic issues which may arise even after targeted therapy and should be considered in all patients after cancer treatment (adapted from the Pelvic Radiation Disease Association best practice pathway)[164]

More than 30 different GI symptoms may develop after cancer treatment (table 4). Ample data show that in the acute and chronic settings, individual symptoms and clusters of symptoms do not delineate reliably the underlying cause(s) of the symptoms because different physiological disorders may cause similar symptoms (table 5).[14 15] Most patients present with multiple GI symptoms after cancer treatment and while clinicians are often more concerned by some symptoms than others (e.g., rectal bleeding), even specialists predict poorly which symptoms affect individuals most severely. So, it is important to work with the patient to identify all the symptoms that cause distress.[16] To assess symptoms optimally in a way that ensures the patient's perspective is captured, there are useful questionnaires which should be considered for routine use in clinics—for example, the gastrointestinal symptom rating scale, validated PROMs, which can be disease-specific (eg, European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ) CR29 or general (eg, PRO-CTCAE). Visual aids, such as visual analogue scales or the Bristol stool chart, may provide significant support in the clinical decision-making process and gives confidence to patients that the clinician understands that the patient is best placed to describe how they actually feel.[17 18]

Box 2 Trigger questions to identify patients in need of a gastroenterological assessment; answering 'Yes' to any should lead to an offer of referral[165 166]

1. Do you have frequent loose stools?
2. Do you wake up at night needing to poo?
3. Do you have leakage from your bottom?
4. Do you have blood in your stools/rectal bleeding?
5. Is your quality of life reduced owing to your bowel function?
6. Has your mental health been affected by your bowel function?

Diagnostic tests

Clinical practice guidance

9. *Clinical acumen, specific individual symptoms or patterns of symptoms are not reliable in diagnosing the underlying cause(s) for those symptoms in patients treated for cancer. Therefore, comprehensive investigation is required at an early stage if troublesome symptoms do not respond fully to simple, empirical intervention.*

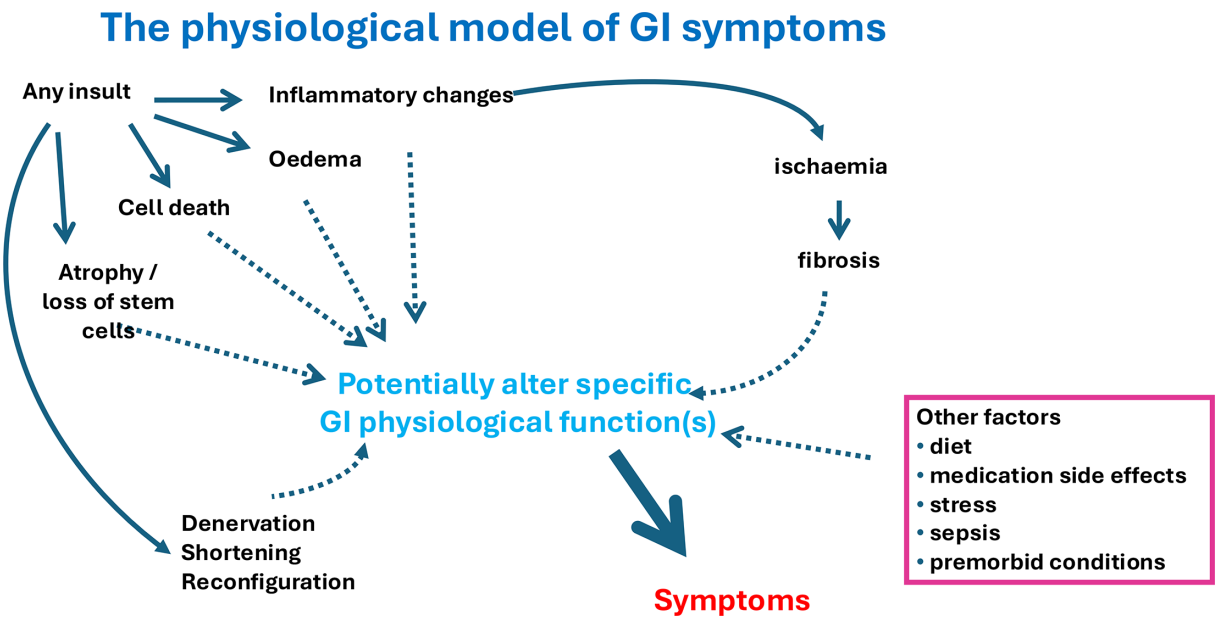

Figure 2 Abnormal GI symptoms develop as a result of changes to GI physiology.

10. *A wide variety of cancer treatments cause the same treatable physiological changes, which frequently include bile acid diarrhoea, carbohydrate intolerance, pancreatic exocrine insufficiency, small intestinal bacterial overgrowth, and after immunosuppressive treatment, bacterial or viral infection.*
11. *Investigating acutely during chemotherapy/radiotherapy in symptomatic patients is feasible and beneficial if symptoms are impacting on treatment.*
12. *With ongoing or severe toxicity, early advice from a gastroenterologist, ideally with an interest in managing side effects of cancer treatment, should be sought.*

Comprehensive, systematic approaches (table 6) to investigate, diagnose and treat symptoms, arising after upper GI cancer therapy and pelvic radiotherapy have been published[19 20] and are free to download from the Macmillan Cancer Support website. The approach used for symptoms after upper GI cancers and pelvic radiotherapy has also be usefully applied to patients treated for other cancers.[21] Randomised trials have shown that this type of systematic approach is beneficial in the acute setting[22] and in patients with chronic symptoms after pelvic radiotherapy.[23] Investigations are important as they aid management and allow targeted treatment to be given. In benign disorders, trials of empirical treatment are often recommended. However, when patients have multiple causes for their symptoms, an apparent lack of response to empirical treatment can be confusing as it could be due to (a) absence of that condition, (b) lack of patient engagement or compliance, (c) inadequate dosing of the treatment, (d) side effects from the intervention or (e) improvement being masked by other conditions causing the same symptoms. The establishment of clear diagnoses made after comprehensive diagnostic tests helps both the clinician and the patient to define appropriate treatment and assists compliance with interventions.

Commonly occurring conditions during and after cancer therapy: diagnostic and treatment approaches

Clinical practice guidance

13. *In patients on restrictive diets, consider daily supplementation with long-term trace elements and multivitamin supplements until dietitian review.*
14. *If long-term dietary interventions are recommended, dietetic review should be arranged to ensure nutritional adequacy.*

Table 3 Physiological abnormalities caused by cancer therapies

Physiological abnormalities	During chemotherapy	During biological therapy	During radiotherapy	After radiotherapy	After upper GI surgery
Lactose intolerance	5–10%	?	50%	5–7%	No
Malabsorption of other disaccharides	Yes	?	?	Yes	Yes
Bile acid malabsorption	Yes	Yes	50%	1–83%	Yes
Small bowel bacterial overgrowth	Yes	Yes	25%	8–45%	Yes
Pancreatic insufficiency	Yes	Yes	?	Yes	Yes
Rapid transit	?	?	100%	100%	Yes
Viral infection	Yes	Yes	?	?	?
C. difficile	Yes	Yes	?	?	Yes
Drug-related (non chemotherapy)	Yes	Yes	10%	5%	Yes
Other	Yes	?	>10%	24–55%	?

'Yes' indicates it happens based on case reports or clinical experience, but the frequency is unknown. Percentage frequency when shown is derived from published case series.[22 42 43 167–170] '?' indicates that there are no published data and no clinical experience of whether these physiological abnormalities are happening.

Table 4 Multiple symptoms can occur during and after cancer treatment; the range of symptoms can be broadly divided into those arising from the upper GI tract and those arising from the lower GI tract. Most patients would like all abnormal symptoms addressed

Upper GI tract symptoms	Lower GI tract symptoms
Altered taste and smell	Accidents/incontinence/inability to control the bowel
Bad breath	Bleeding from the bottom
Belching/burping	Constipation
Bloating	Cramps
Decreased appetite	Diarrhoea
Difficulty swallowing liquids	Excessive mucus in the stool
Difficulty swallowing solids	Farting - excessive wind/incontinence of wind
Easily full on eating	Grumbling/noisy belly
Greasy stool	Incomplete emptying of the bowel
Heartburn	Itching around the bottom
Hiccoughs	Lower abdominal pain
Nausea	Rectal pain
Painful swallowing	Rushing to have the bowels open
Regurgitation	Straining to have the bowels open
Upper abdominal pain	Trapped wind
Vomiting/retching	Waking from sleep to have the bowels open

15. *A 10 day trial with pancreatic enzyme replacement therapy at adequate dose after education of the patient is usually sufficient to assess efficacy.*
16. *If multiple diagnoses have been reached, treatments should usually be introduced one at a time with symptom response documented before introducing the next treatment.*

Bile acid diarrhoea/malabsorption (BAD/BAM)

BAD (excessive hepatic production of bile) and BAM (malabsorption of bile in the terminal ileum) are common after many different oncological treatments.[24] A definitive diagnosis should be made using a SeHCAT scan which can help guide treatment.[25 26] In those with borderline or mild BAD/BAM (SeHCAT 7-day retention 10–20%), a long-term low-fat diet may be a treatment option. Bile is produced in response to the dietary intake of fat. Low-fat diets are well tolerated and effective with high compliance in symptomatic patients.[26 27]

Patients with moderate BAD/BAM (SeHCAT 7-day retention 5–10%) or those inadequately responding to dietary adjustments, require a bile sequestrant and, if severe BAD/BAM (SeHCAT 7-day retention 0-5%), a sequestrant in combination with a low-fat diet. There are no licensed treatments for BAD/BAM. Currently available sequestrants include anion-binding resin powders colestyramine, colestipol or colesevelam, a non-absorbed hydrogel in large tablet form. Colestyramine is cheaper but often poorly tolerated owing to unpalatability or side effects.[28] Colesevelam is more effective, better tolerated and has fewer interactions.[29] Additional symptomatic treatment with antidiarrhoeal agents may be required, but they are not adequate by themselves for most of the symptoms experienced.[30] Clinical experience suggests that tolerance is improved by starting sequestrants at a low dose (eg, ¼ sachet of colestyramine), taking it at mealtimes not on an empty stomach and slowly increasing the dose over a few days to titrate to symptoms. Vitamin D deficiency occurs in 20% of patients taking bile acid sequestrants,[21] who can also rarely develop significant hypertriglyceridaemia and/or vitamin A, E and K deficiency.[31]

Small intestinal bacterial overgrowth (SIBO)

SIBO occurs very commonly during and after cancer treatment.[32] SIBO can be difficult to diagnose and suggested approaches to its diagnosis, how to undertake a breath testing and how to interpret the results differ significantly between authorities.[25 33 34]

BSG guidance previously has suggested that in patients with chronic diarrhoea, if suspected, empirical therapy should be used.[25] Lack of response to empirical antibiotics may be due to resistant organisms, SIBO not being present or because other disorders causing similar symptoms are also present. To avoid this potential issue in a patient group where multiple diagnoses often coincide, and to help with antibiotic stewardship, we recommend that testing rather than empirical treatment should be used whenever possible to help establish the cause for symptoms.

Glucose or lactulose breath tests can be helpful, although not always accurate. When clearly positive, they point to the presence of SIBO. The use of methane breath analysis in addition to hydrogen breath analysis increases the accuracy of breath testing.[35] Quantitative small bowel aspiration can help make the diagnosis,[34] but it is time consuming. Qualitative assessment for SIBO on the contrary is much easier to carry out (box 3)[20]; before it is undertaken, agreement on the appropriate processing and reporting of samples by local microbiology services should be obtained.

Table 5 Different or '-' conditions may present with very similar symptoms. Symptoms associated with four conditions frequently identified after cancer treatment. Not all symptoms may be found in any one individual with the same condition

Symptoms	Conditions			
	Bile acid malabsorption	Carbohydrate malabsorption	Exocrine pancreatic insufficiency	Small intestinal bacterial overgrowth
Abdominal pain	yes	yes	yes	yes
Belching	–	yes	yes	yes
Bloating	yes	yes	yes	yes
Borborygmi	yes	yes	yes	yes
Constipation	–	–	–	yes
Diarrhoea	yes	yes	yes	yes
Flatulence	yes	yes	yes	yes
Gastric stasis	–	–	–	yes
Mucus discharge	–	–	–	yes
Nausea/vomiting	–	–	–	yes
Nocturnal defaecation	yes	yes	yes	yes
Steatorrhoea	yes	–	yes	yes

Table 6 Suggestions for symptom-specific tests

Symptom	Lifestyle contributors	Test 1	If abnormal	Test 2	If abnormal	Test 3	If abnormal	Second-line tests to consider
Steatorrhoea	Orlistat	Faecal elastase	PERT	SeHCAT study	Sequestrant+/-low fat diet+/-loperamide	Glucose hydrogen methane breath test */SI aspiration	Antibiotics	OGD with biopsy SI MRI scan/capsule endoscopy/ Fasting gut hormones 9am cortisol/TFTs
Diarrhoea (±urgency)	High or low fibre intake or high insoluble fibre High alcohol intake High caffeine intake Carbohydrate malabsorption Medication—for example, metformin/lansoprazole/ SSRIs	Faecal elastase Faecal calprotectin FIT Stool microbiology Sigmoidoscopy† + biopsies	PERT Colonoscopy/MRE Treat infection Treat microscopic colitis	Transit study SeHCAT study	Fluids±laxatives Sequestrant+/-low fat diet+/-loperamide -rifaximin	Glucose hydrogen methane breath test/ SI aspiration	Antibiotics	Plain AXR -overflow/ colitis? Fasting gut hormones Carbohydrate exclusions
Constipation	Low dietary fibre intake Drug-induced Anal fissure Hypothyroidism Hypercalcaemia	FIT AXR - impaction/obstruction Transit study	Colonoscopy Full bowel clearance for example, Picolax, Klean Prep Maintenance Laxative/ softeners/prucalopride/ linaclotide Correct positioning on lavatory (toileting exercises)	CT colonography	Depends on results			
Upper abdominal pain	Drug-induced Excess portion size after oesophagectomy/ gastrectomy	*H. pylori* test Glucose hydrogen methane breath test OGD+aspirate Biliary US	Eradicate H. pylori Treat PUD/SIBO Further tests	CT - to exclude recurrence/mesenteric ischaemia/faecal loading				MRI- SI
Lower abdominal pain		Hydrogen methane breath test OGD+aspirate Pelvic US	Antibiotics	CT/MRI	Depends on results			
Anorectal pain	Anal fissure	Flexible sigmoidoscopy		MRI pelvis – to exclude recurrence/pelvic insufficiency fracture/ abscess/fistula				
Bloating/flatulence/ belching	High or low fibre intake or high insoluble fibre intake Inadequate fluids High sorbitol intake High caffeine intake Carbohydrate malabsorption Drug-induced	Faecal calprotectin FIT Faecal elastase Glucose hydrogen methane breath test/SI aspiration	Flexible sigmoidoscopy/ colonoscopy PERT Antibiotics	Transit study	Fluids±laxatives			Carbohydrate challenge US biliary tree MRI SI to exclude stricture
Nausea/vomiting/ indigestion/reflux	High alcohol intake High caffeine intake	*H. pylori* test ±OGD	Eradicate Depends on results	Barium swallow Gastric emptying study	Further tests Change in meal regimen+/- prokinetics			

Continued

Table 6 Continued

Symptom	Lifestyle contributors	Test 1	If abnormal	Test 2	If abnormal	Test 3	If abnormal	Second-line tests to consider
Rectal mucus discharge (wet wind)	High or low fibre intake Haemorrhoids	Flexible sigmoidoscopy	Treat IBD/polyps/anal pathology	Glucose hydrogen methane breath test/SI aspiration	Antibiotics			
PR bleeding	See table 7	–						
Faecal incontinence		Assessment of anal tone Assessment for diarrhoea as above if present Sigmoidoscopy†		Abdominal X-ray	Depends on results			

*If testing for SIBO, hydrogen combined with methane breath testing is more effective at identifying SIBO than hydrogen testing alone.
†Consider complete colonoscopy if altered PR bleeding and/or if patient has never undergone complete colon assessment. Breath test where available, or endoscopic aspiration (see box 1); empiric treatment could be considered if no test available.
AXR, abdominal X ray; FIT, faecal immunochemical test; IBD, inflammatory bowel disease; MRE, magnetic resonance enterography; OGD, oesophagogastroduodenoscopy; PERT, pancreatic exocrine replacement therapy ; PR, pelvic radiation; PUD, peptic ulcer disease; SI, small intestine; SIBO, small intestinal bacterial overgrowth ; SSRI, selective seretonin reuptake inhibitor; TFT, thyroid function test; US, ultrasound.

Box 3 How to take a small bowel aspirate for qualitative assessment of small intestinal bacterial overgrowth at upper GI endoscopy

⇒ On intubation, avoid aspirating.
⇒ Flush 100 mL of sterile saline into the duodenum.
⇒ Flush channel with 10 mL of air.
⇒ Turn down the suction.
⇒ Leave the fluid for a few seconds.
⇒ Aspirate ≥10 mL into a sterile trap.
⇒ Send the aspirate to microbiology.
⇒ Positive aspirates will grow colonic bacteria.

The most investigated treatment is rifaximin for 1–2 weeks, 550 mg twice a day, which is effective in approximately 60–80% of patients with proven SIBO.[36] Other equally effective antibiotics include doxycycline, ciprofloxacin or amoxicillin–clavulanic acid and cefoxitin. Metronidazole is less effective.[37] Antibiotics which are not absorbed from the GI tract may be preferable to absorbed antibiotics to reduce the risk of systemic resistance. In patients with reversible cause for SIBO—for example, immunosuppression during chemotherapy, usually one course of antibiotics is all that is required. In patients with recurrent SIBO a variety of approaches are used, which include low-dose, long-term antibiotics, cyclical antibiotics or recurrent short course of antibiotics.[32]

Pancreatic exocrine insufficiency (PEI)

PEI is best diagnosed after measurement of faecal elastase-1. A faecal elastase level <500 µg/g may indicate PEI, untreated coeliac disease, SIBO or a watery stool sample submitted for analysis.[38–40]

PEI is common in patients with pancreatic cancer and after pancreatico-duodenal resection. PEI also frequently develops soon after initiation of somatostatin analogue therapy for neuroendocrine neoplasms. It can occur after surgery involving diversion/bypass surgery, where faecal elastase levels are normal, but there is suboptimal timing of release of pancreatic enzymes.[41] Routine testing in those situations is not required and patients should be offered a trial of treatment with PERT, which should be at a dose equivalent of 50 000 units of lipase with meals and 25 000 with snacks, increasing the dose if abnormal symptoms persist, failure to maintain weight and micronutrient deficiency.[40] Clinical experience suggests that if PERT is not tolerated, this often indicates underlying SIBO. Once the SIBO has been eradicated, then PERT is tolerated.

Carbohydrate intolerance

Lactose intolerance may be induced by chemotherapy and or radiotherapy and may resolve within a few weeks after the end of treatment.[22 42] If present, it requires dietary modifications by eliminating only lactose-containing products rather than a complete dairy-free diet. Lactose-containing foods are an important source of calories, protein and calcium and if removed from the diet, this risks weight and muscle loss and compromises bone health.

It is likely that metabolism and absorption of other monosaccharides and disaccharides may contribute to GI symptoms—for example, fructose intolerance sometimes develops during chemotherapy, although the frequency of this is unknown.[43]

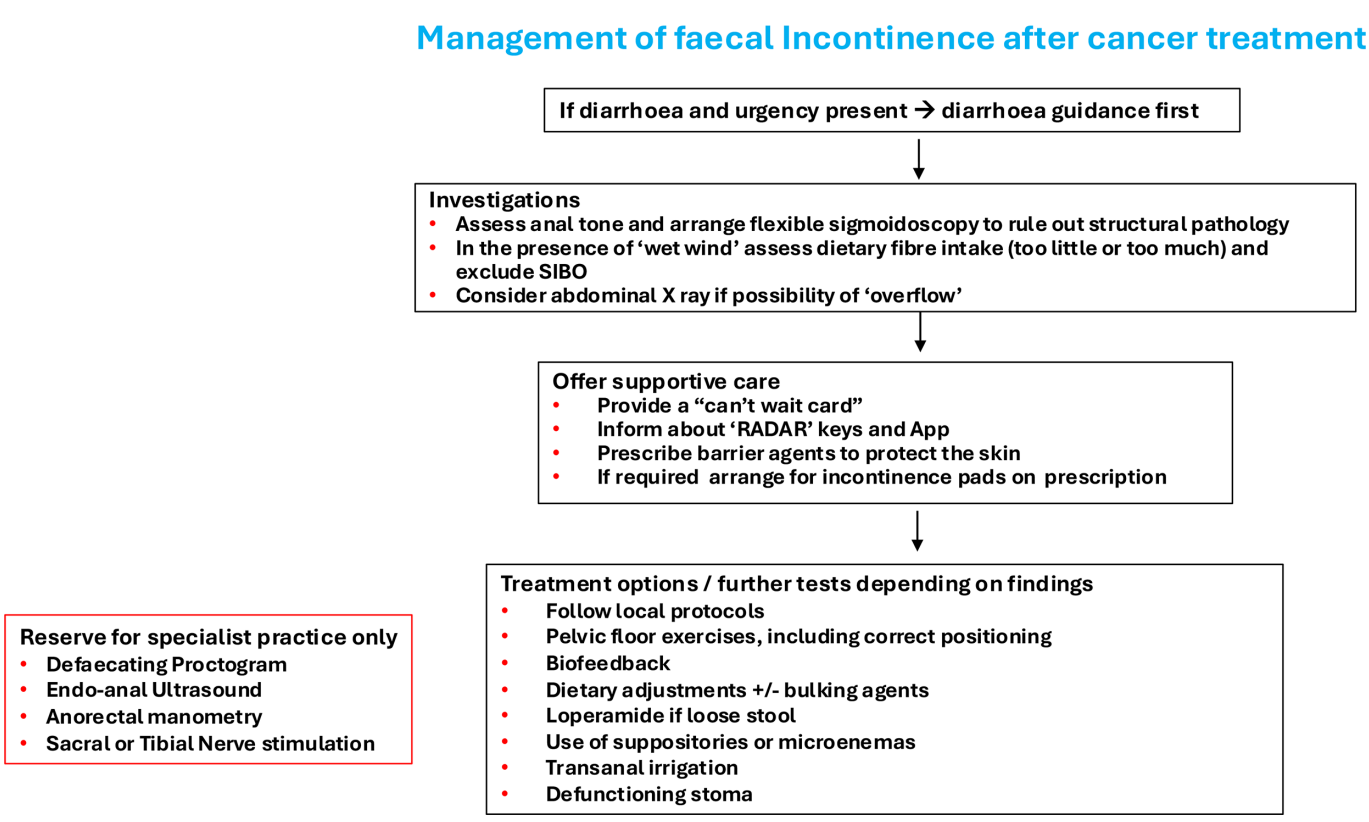

Figure 3 A management approach to patients with faecal incontinence. SIBO, small intestinal bacterial overgrowth.

Pelvic floor dysfunction

Evidence for interventions is poor, but usually include bowel habit training, toilet positioning, advice on raising abdominal pressure for evacuation without straining, modifying stool consistency via diet and fluid adjustments or fibre supplements, possibly following a stepwise algorithm.[44 45] Faecal incontinence may respond to pelvic floor muscle training, urge resistance training or firming the stool if loose—for example, with loperamide, titrated to individual response (figure 3).

On the other hand, constipation can be very problematic and distressing for patients (figure 4), affecting 40–90% with advanced cancer or those taking opioids. Prevention by prophylactic use of laxatives when opioids are prescribed is

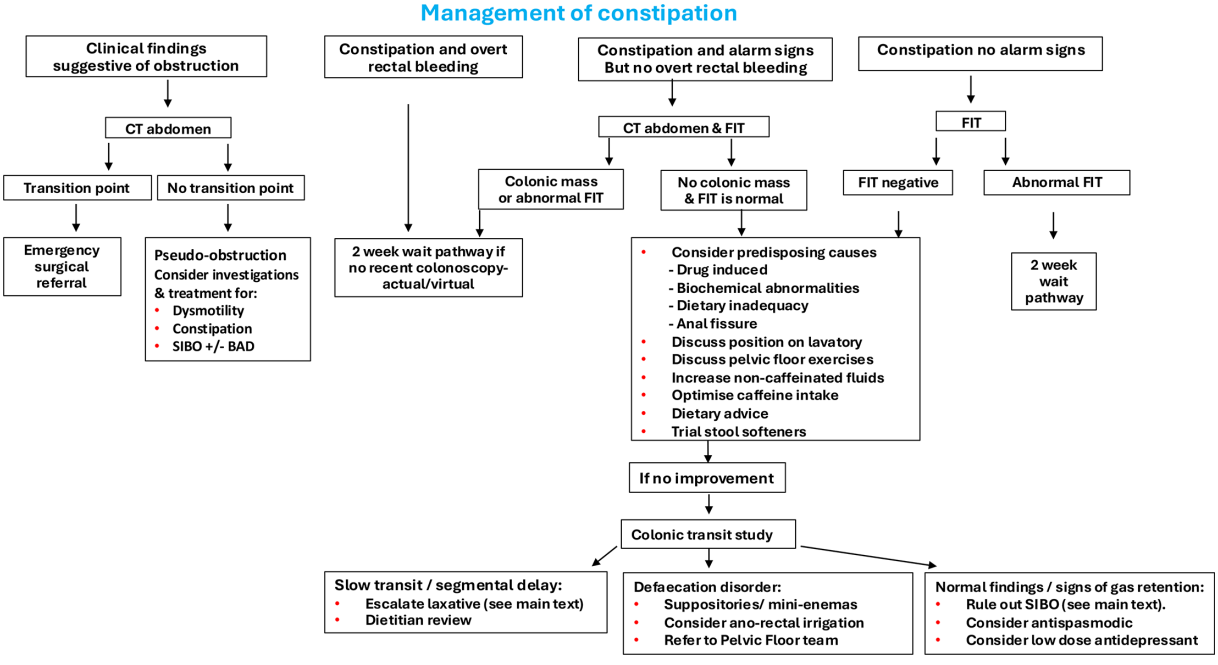

Figure 4 A management approach to those with constipation developing during or after cancer therapies. BAD, bile acid diarrhoea; FIT, faecal immunochemical test; RT, radiotherapy; SIBO, small intestinal bacterial overgrowth.

recommended.[46] There is a growing body of evidence for the use of PAMORAs (peripherally acting mu opioid receptor antagonists), but conventional laxatives may also be effective for many and are recommended as first line.[47] Prucalopride is sometimes recommended. However, its mode of action is upstream and does not directly affect the mu opioid receptor. Faecal impaction and overflow should be considered as a possible cause of apparent diarrhoea in this group and is usually managed by suppositories or enemas initially.[46] SIBO may contribute to constipation, especially with methane-producing organisms, but data as to its importance are sparse. PEI and BAD may be masked in patients on constipating drugs and occasionally contribute to significant pain in patients with constipation. Transanal irrigation can be effective when other treatments have failed, especially in those with passive incontinence, severe constipation and anterior resection syndrome.[48]

GI infection

Bacterial

GI tract bacterial infection may be increased in immunosuppressed patients. Loperamide may be given safely in patients with diarrhoea before the results of microbiology tests to exclude infection are available.[49] However, there are theoretical risks that high-dose loperamide may predispose to toxic dilatation especially in neutropenic patients with *C. difficile* infection, and repeated assessment for this should be considered. Pseudomembrane formation (in *C. difficile* infection) requires neutrophils so might not be seen if the patient is neutropenic. Endoscopic biopsy can diagnose *C. difficile* colitis in this context and in patients with *C. difficile* toxin negative colitis.

Viral

Multiple ulcers seen in the GI tract during and after cancer treatment, especially when associated with diarrhoea or bleeding, should raise the possibility of cytomegalovirus (CMV) or Herpes simplex infection (HSV). CMV IgM antibodies often do not develop acutely; however, if suspected, immunocytochemistry and PCR of biopsy samples taken from ulcerated areas may be helpful in identifying CMV. Blood-based PCR tests for CMV are insensitive.[50]

Fungal

The frequency and significance of fungal overgrowth in the bowel has been barely studied but is identified intermittently in patients during or after cancer treatment when small bowel aspiration is performed. It may be related to ongoing GI symptoms and has been associated with an increased risk of bowel perforation.[51] Clinical experience suggests that fungal small bowel overgrowth can also cause symptoms akin to SIBO, and oral treatment with antifungal agents may improve symptoms.

Pain

Clinical practice guidance

17. *Chronic pain after abdominal surgery and/or radiotherapy may be caused by stricture formation, adhesions or fibrosis and the resulting obstruction. However, colonic faecal loading and SIBO are under-appreciated causes.*
18. *With new onset or unexplained pain, tumour recurrence should be considered.*
19. *Signs of complete intestinal obstruction and severe abdominal pain require emergency surgical assessment (eg, small bowel obstruction, ischaemic bowel).*
20. *In general, a multidisciplinary approach is required to manage these patients, including input from gastroenterology, surgery, pain management and nutrition teams.*

Chronic pain following surgery and/or radiotherapy can be caused by mechanical obstruction of the bowel due to stricturing, adhesion formation, fibrosis or mass obstruction from recurrence of the cancer or enlarged lymph nodes. The resulting pain is often colicky and is worse after oral intake. It may be associated with vomiting. Incomplete bowel obstruction may cause intermittent symptoms. If the obstruction is complete, the patient will vomit regularly or have absolute constipation with a distended abdomen. This is a surgical emergency. Early CT imaging is required to understand the anatomy of the obstruction and exclude cancer recurrence.

Pseudo-obstruction is present when there are symptoms suggestive of obstruction, but a point of obstruction cannot be defined after appropriate cross-sectional imaging. It generally presents as a result of factors which can include an area of dysmotility in the bowel, sometimes related to myenteric plexus damage, constipation, exacerbated by SIBO, especially when the patient has concurrent BAD. Careful diagnosis and management of the predisposing causes by an experienced gastroenterologist can prevent surgery.

Radiotherapy can also cause neuropathic pain. Radiotherapy increases the risk of chronic pain after breast cancer surgery, independently of other variables; however, this is a poorly understood condition, possibly caused by tissue fibrosis and arteriolar endarteritis leading to nerve entrapment.[52–54]

The possibility that pain is caused by localised sepsis, tumour recurrence or bone insufficiency fracture (sometimes only identified after MRI imaging) always needs to be considered.

GI TOXICITY FROM SPECIFIC THERAPIES

Cytotoxic chemotherapy

Clinical practice guidance

21. *Frequent physiological disorders resulting from cytotoxic chemotherapy include lactose intolerance, SIBO, BAD and PEI.*
22. *Investigations to determine the cause for new-onset symptoms during treatment are feasible and beneficial.*
23. *In patients developing acute diarrhoea, stool analysis for infection should be performed; however, it is generally safe to start loperamide while awaiting the results. Reassess the patient regularly to exclude the development of toxic dilatation of the colon.*
24. *Potentially aggravating oral anti-cancer drugs in patients with moderate to severe diarrhoea should be temporarily paused until they have been reviewed by their oncologist.*
25. *Patients presenting with severe capecitabine/5FU GI toxicity, require an urgent CT scan to exclude enterocolitis which, if present requires rapid, intensive intervention.*

Cancer chemotherapy causes symptoms through direct injury to tissues, which then leads potentially to metabolic derangement, dehydration, nutritional depletion and emotional distress.[55 56] Supportive medication given to reduce specific toxicities may cause other side effects—for example, some antiemetics cause constipation. The toxicity of modern systemic chemotherapy continues to lead to a mortality rate of 1–5% in randomised trials, largely due to sepsis or multiorgan failure with diarrhoea. The Common Terminology Criteria for Adverse Events provides

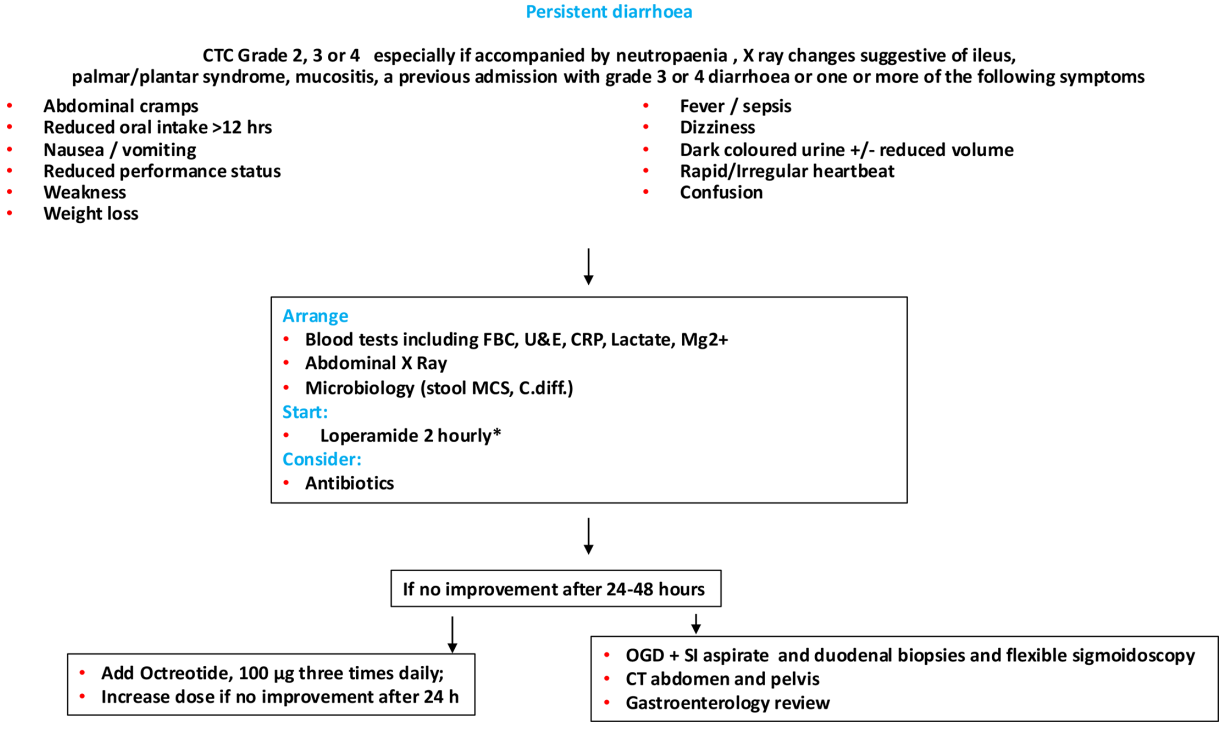

Figure 5 A recommended management approach to patients with acute, severe diarrhoea developing during chemotherapy. In patients with chronic symptoms consider whether any of the physiological abnormalities described as occurring during chemotherapy (table 3) have developed. CRP, C-reactive protein; FBC, full blood count; Mg, magnesium; MCS, microscopy, culture & sensitivity; OGD, oesophagogastroduodenoscopy; SI, small intestine; U&E, urea and electrolytes.

the descriptive terminology for adverse event reporting for patients receiving treatment. The lowest grades, grades 1 and 2, are viewed as mild or moderate and, usually, patients can manage this toxicity at home. However, the experience of opening their bowels more than 4–6 times a day above baseline will have a significant impact on the patient's experience of care. If not recognised and managed correctly mild toxicity can progress to severe toxicity requiring hospitalisation.

Recent studies have demonstrated that the root cause of chemotherapy-induced symptoms can be diagnosed accurately, treated acutely and may improve outcomes. Frequent diagnoses made following new chemotherapy-induced GI symptoms include the development of lactose intolerance, SIBO, BAD and PEI.[22 42 43] Currently, only symptomatic treatment and dose modification is usually offered and this approach should be reconsidered

A suggested approach to the development of acute severe diarrhoea is shown in figure 5. However, clinicians should consider the possibility of the rare syndrome of capecitabine/5FU-induced enterocolitis. Partial or complete dihydropyrimidine dehydrogenase (DPD) deficiency, found in 3–5% of the population may lead to potentially life-threatening bone marrow suppression and enterocolitis after the administration of capecitabine or 5FU. Patients may also present with hair loss and mucositis, which are usually uncommon side effects outside of this syndrome. If a heterozygous DPD mutation is present, 50% dose reductions are recommended for the first cycle of capecitabine or 5FU, which may then be increased as tolerated. In those with a homozygous mutation, consideration must be made about the safety of administering any capecitabine or 5FU. Patients with no DPD mutation found may also rarely present in this way. In this syndrome, cross-sectional imaging usually suggests an inflammatory enterocolitis and endoscopic biopsies typically show ischaemic changes, with lymphocytic and eosinophilic infiltration. Intensive intervention with immediate cessation of capecitabine/5FU, intravenous fluids, antibiotics and early consideration of parenteral nutrition are required. Octreotide or corticosteroids are also sometimes advocated, but their benefits are controversial. If capecitabine is reintroduced after symptoms resolve, this carries a high risk of recurrent inflammation and death.[57]

Immunotherapy

Diarrhoea is common after treatment with checkpoint inhibitors and may occur at any time after treatment is initiated.[58 59] Figure 6 outlines management both in those with evidence of gastrointestinal inflammation and those without. Mild symptoms can be managed initially without diagnostic tests, but more severe diarrhoea (increase of more than six stools per day over baseline/severe abdominal pain) usually requires admission, intravenous (IV) corticosteroids and urgent investigation. If there is endoscopic evidence of an enterocolitis and no response to IV corticosteroids within 2-3 days, second-line treatment, infliximab or vedolizumab should be started—they are equally efficacious,[60] and expert advice sought. In patients with refractory enterocolitis not responding to second-line therapy, third-line options include tofacitinib[61] (however, JAK inhibition may increase the risk of cancer progression and thrombosis), tocilizumab, an IL6 inhibitor (which has potentially useful antitumour effects[62] but possibly carries a small increased risk of intestinal perforation) and ustekinumab.[63] More detailed BSG-endorsed guidance is available.[58 64] Authoritative guidance to help

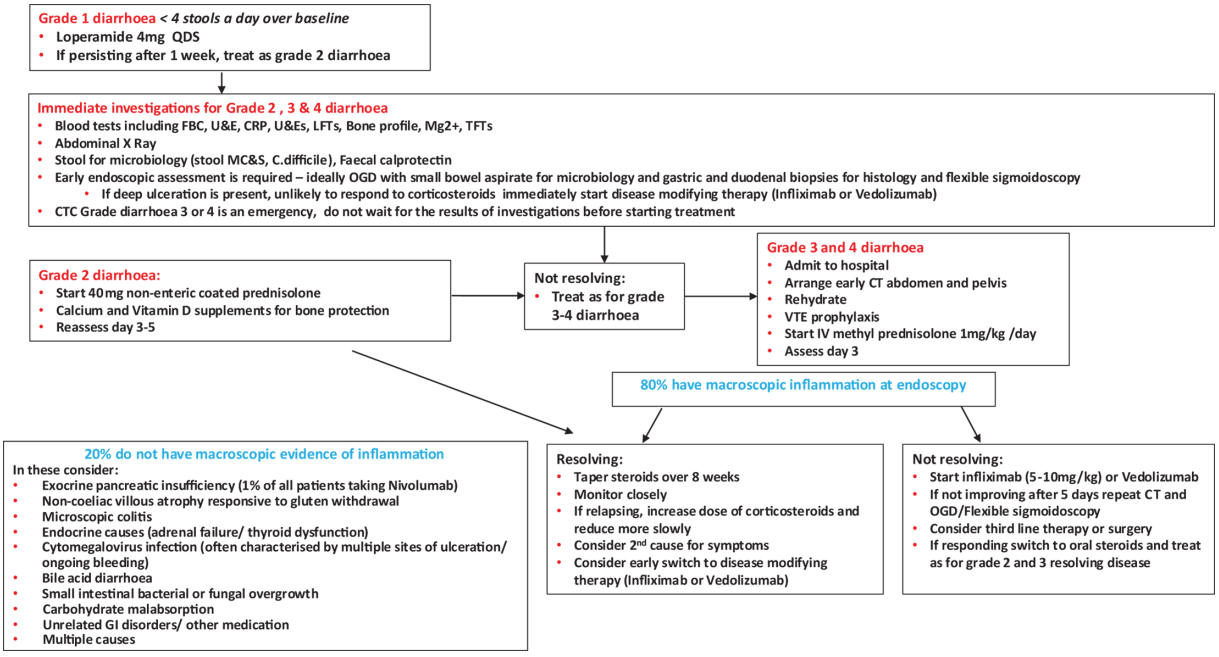

Figure 6 A management approach for those developing diarrhoea during or after checkpoint inhibitor therapy. CRP, C-reactive protein; CTC, common toxicity criteria; FBC, full blood count; LFT, liver function test; MC&S, microscopy, culture & sensitivity ; OGD, oesophagogastroduodenoscopy; TFT, thyroid function test; U&E, urea and electrolytes; VTE, venous thromboembolism.

manage immunotherapy-induced hepatotoxicity is also available elsewhere.[65]

Small molecules/targeted agents

Clinical practice guidance

26. *Pancreatic insufficiency is a common cause for GI symptoms in patients treated with sorafenib*
27. *Bile acid diarrhoea is a common cause for GI symptoms for patients treated with lenalidomide.*

Biological agents are increasingly used long-term both in the curative and the palliative setting. Diarrhoea occurs in up to 95% of treated patients. Small molecules from the same class cause diarrhoea with a very variable frequency. Little research has been done into the downstream physiological changes caused by small molecule targeted therapy. The two agents characterised in better detail are lenalidomide and sorafenib. Lenalidomide causes BAD in 20% of patients a median of 4 months after being prescribed. Accurate diagnosis and treatment generally allows patients to continue with their lenalidomide long-term.[66] Sorafenib causes PEI in more than 10% of patients a median of 6 months after starting treatment.[67]

One small series and clinical experience concurs that PEI, BAD or SIBO can often be diagnosed in those developing abnormal symptoms after initiation of small molecule therapies, and appropriate treatment leads to resolution of symptoms.[68]

Large molecule targeted treatment-induced diarrhoea with or without SACT

Cytotoxic drugs at higher risk of inducing chemotherapy-induced diarrhoea include 5FU, capecitabine and irinotecan. Specifically, irinotecan can induce diarrhoea very soon after infusion due to the inhibition of acetylcholinesterase activity, which can be effectively treated with atropine. Many anticancer regimens now combine a large molecule such as an anti-epidermal growth factor antibody with a cytotoxic doublet or triple spine. Many of these large molecule targeted treatments also induce diarrhoea, which means that the risk of chemotherapy-induced diarrhoea is higher for these combination regimens and toxicity more severe. 5FU or capecitabine is commonly used in association with pelvic radiotherapy to treat lower GI cancers and this combination also increases the risk of toxicity.

Hormonal therapy

Hormonal agents are used for the treatment of breast, prostate and endometrial cancer. Both older agents, such as gonadotropin-releasing hormone agonists, anti-androgens and anti-oestrogens and newer agents cause diarrhoea in 4–21% of patients.[2]Nausea may also sometimes be a problem. While there are no systematic studies looking at the cause for diarrhoea in these patients, clinical experience shows that new onset BAD and PEI is diagnosed in these patients more often than might be expected.

Radiotherapy

Clinical practice guidance

28. *Smoking and low body mass index both increase the risk of toxicity and should be addressed if possible before radiotherapy is given.*

The dose and frequency of radiotherapy delivery is limited by the tolerance of acutely reacting normal tissues and subsequent or 'consequential' late damage.[69] Critical to these processes is the breakdown of surface epithelial function.[70] This has been best studied after pelvic radiotherapy, where it has been shown that mechanisms independent of the radiotherapy dose contribute to the development of toxicity.[71] This suggests that future developments in radiotherapy techniques are unlikely to abolish toxicity completely. Smoking and low BMI (less than 18.5 kg/m^2) predict worse toxicity acutely.[72] The gut microbiota appears to be important.[73] Predicting late toxicity accurately in the individual patient is still not possible.[8] As the severity of acute toxicity predisposes to late toxicity, reduction of acute toxicity should be prioritised.

Despite major advances in the delivery of some forms of localised radiotherapy with very low toxicity achieved[74] there remains

a high prevalence of gastrointestinal symptoms (tables 3 and 5) developing in many patients receiving long-course pelvic radiotherapy (ie, daily treatment sessions delivered over 4–5 weeks) for some urological, colorectal and gynaecological cancers.[3 75]

Late reactions may occur months or years after treatment, ranging from mild and treatable to irreversible and severe. Serious issues include transfusion-dependent bleeding, fistula formation, perforation and bowel obstruction. Late onset bone (insufficiency) fracture may be picked up incidentally on follow-up imaging or cause pain, which sometimes is misinterpreted as being of bowel origin. Evaluation and treatment of underlying osteoporosis is the key preventative step. There is a risk of secondary cancer affecting the GI tract. As radiation techniques change, the focus has been on reducing acute toxicity not on measuring and reducing late toxicity, which is poorly defined and quantified.[76–78]

Acute RT-induced toxicity prevention

Clinical practice guidance

29. *Dietary counselling and/or protein supplementation may reduce the risk of toxicity during pelvic radiotherapy.*
30. *Lactobacilli±bifidobacteria containing probiotics may reduce acute RT-related diarrhoea.*
31. *A high-fibre diet may reduce the risk of toxicity during pelvic radiotherapy*.

Non-pharmacological strategies to reduce GI toxicity include nutritional interventions and bowel preparation regimens. Probiotics, prebiotics and faecal microbiota transplantation have been trialled. Nutritional intervention strategies include dietary supplementation, counselling and dietary modification. Dietary modifications trialled include partial or complete replacement of normal nutritional intake with elemental (pre-hydrolysed liquid) diet, modified fat (including reduced fat intake and replacement of long-chain with medium-chain triglycerides), low lactose diets and modified fibre intake.[79] High fibre diets may be beneficial possibly by enhancing production of anti-inflammatory short chain fatty acids.[80] There is sound scientific rationale for many of these interventions, but there are inadequate data to say which of them make a useful difference. They are all potentially burdensome and should not be used outside the context of clinical trials.[81]

New approaches aimed at limiting toxicity through attempting to exclude the GI tract from the radiation field (endorectal spacers, balloons, rectal emptying) have not improved GI outcomes.[81] Synchronising bowel evacuation with treatment delivery showed that rectal gas is commonly responsible for rectal dimensional change.[82] The aetiology of rectal gas is difficult to identify, control and eliminate. The benefit of daily enemas to control gas through the radiotherapy treatment pathway is unproven.

The introduction of daily adapted radiotherapy delivery techniques such as MR-guided radiotherapy may improve toxicity in patients, especially those prone to daily shifts in rectal positioning and dimension or with critical organs at risk abutting target volumes.[83]multinational

Neither Cochrane review nor recentMultinational Association of Supportive Care in Cancer/International Society for Oral Oncology guidelines were able to i dentify effective toxicity prevention by pharmacological agents.[81 84] Pharmacological agents with potentially preventative effect for acute and late GI toxicity include aminosalicylates,[85] corticosteroids with clodronate,[86] superoxide dismutase,[87] amifostine,[88] magnesium oxide,[89] misoprostol,[90] octreotide,[91] pentoxifylline,[92] selenium,[93] sodium butyrate,[94] sucralfate,[95] tocotrienols,[96] vitamin A[97] and vitamin C and E.[98] The studies are few, small and often contradictory so these agents should not be used except in clinical trials. Some agents (eg, mesalazine given during radiotherapy) may worsen symptoms.[95] Data are now clear that glutamine supplementation does not prevent RT-induced diarrhoea.

Acute mucositis: oral and oesophageal

Clinical practice guidance

32. *Exclude HSV, CMV and extensive candidiasis in those with persistent painful mucositis.*
33. *Symptomatic treatment should follow the modified WHO analgesia ladder.*
34. *Early referral to the nutrition team should be considered in people at risk of malnutrition.*
35. *Mouth washes, topical analgesics, coating agents or anti-inflammatories may help.*

Mucositis is common during radiation to the upper GI tract and ideally should be managed without interrupting therapy. Severe mucositis may result in fever, rarely, sepsis or even, oesophageal perforation. Baseline observations and investigations should include temperature, blood pressure and heart rate and full blood count, biochemical profile and C-reactive protein. Repeated assessment of hydration, weight, oral intake and nutrition as well as oropharyngeal visualisation is required. If HSV or CMV is suspected, swabs or occasionally, endoscopic evaluation are required.

Analgesia is best provided in soluble or liquid form. Useful mouth washes, topical analgesics, coating agents or anti-inflammatories include benzydamine hydrochloride, Gelclair gel (glycyrrhetinic acid, povidone, sodium hyaluronate), carboxymethylcellulose suspension and sucralfate.

Nutritional management

Patients with oral or upper GI cancer are already at high risk of malnutrition due to disease-specific symptoms, such as obstructive dysphagia, odynophagia, early satiety and gastric outlet obstruction. Dietary assessment should be provided by a specialist team to ensure appropriate intervention with close follow-up. Dietary advice relating to texture modification and food fortification can mitigate some acute symptoms such as odynophagia, inflammatory dysphagia, loss of appetite and taste changes. Interventions may also include texture modification, oral nutritional supplements and multivitamins with trace elements. Enteral feeding tubes or rarely parenteral nutrition should be considered when other measures fail to maintain weight and hydration. Inadequate evidence around the optimal route and timing of adjunctive nutrition support has led to a wide variety of clinical practice.

Upper GI tract strictures

Clinical practice guidance

36. *Upper GI dilatation of potentially malignant strictures should not be performed until recurrent cancer has been excluded or the MDT have approved this approach.*
37. *If dilatation is required, BSG and NICE guidelines should be followed.*
38. *High oesophageal stents which impinge on cricopharyngeus are poorly tolerated and should be avoided.*

In a preoperative setting, stenting of the oesophagus or stomach should only be considered after discussion in a MDT. The presence of the stent may make surgical resection more difficult, compromise surgical resection margins or impact radiotherapy planning and delivery.

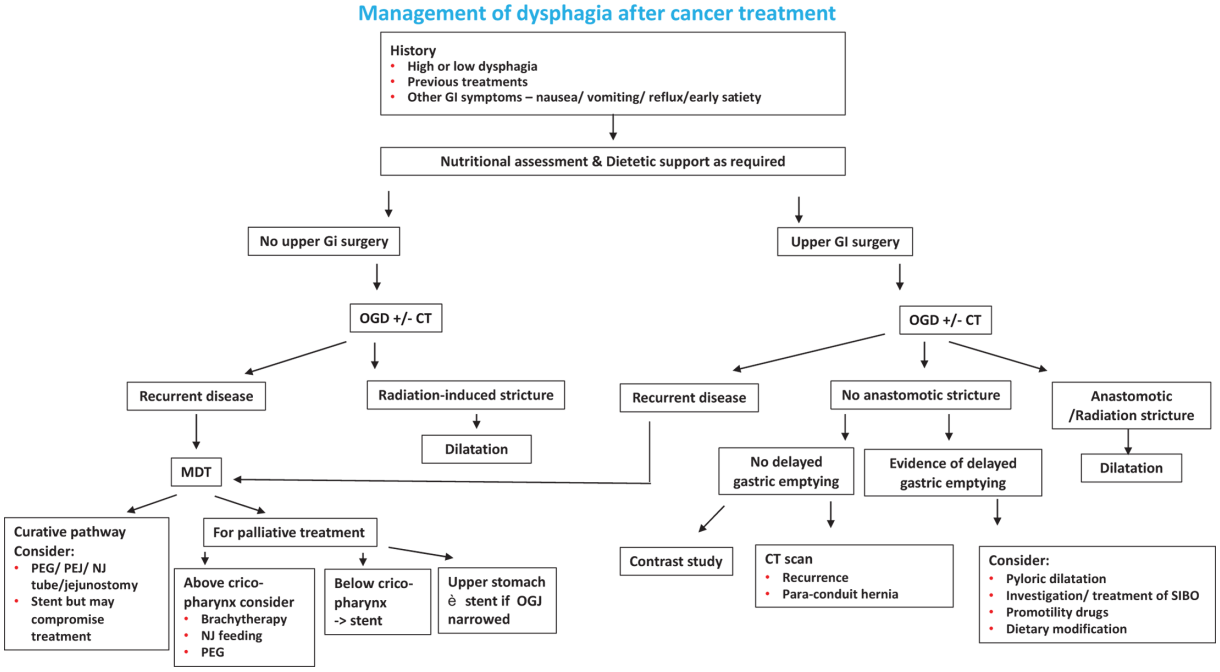

Figure 7 A management approach to dysphagia after treatment for upper GI cancer. MDT, multidisciplinary team; NJ, nasojejunal; OGD, OGD, oesophagogastroduodenoscopy; OGJ, oesophago-gastric junction; PEG, percutaneous endoscopic gastrostomy; PEJ, percutaneous endoscopic jejunostomy; SIBO, small intestinal bacterial overgrowth .

Oesophageal strictures are most common after definitive treatment for oesophageal cancer but may occur after radiotherapy for lung and oropharyngeal cancers. Fibrotic strictures occur in approximately 30% of patients after radiotherapy for oesophageal cancer.[99] Dysphagia after radiotherapy requires early endoscopic evaluation (figure 7). Where there is a clinically significant fibrotic stricture following chemoradiation and no evidence of malignancy, careful dilatation can be performed by cautiously increasing the size of dilators over a number of procedures. However, there is a risk of perforation and fistula formation.[100] Success is typically achieved in >80% manifesting as an improvement in dysphagia after an average of two dilatations.[101] Expandable metal stents should be avoided except if there is a fistula or in the palliative setting. Biodegradable or removable stents are preferred.[102] Intramucosal steroids are sometimes helpful but a careful, individualised approach should be taken.[103] Endoscopic needle knife stricturoplasty is newer option for resistant strictures but, to date, prospective trials demonstrating significant benefit are lacking.

Acute lower GI chemotherapy/radiotherapy-induced symptoms

Acute GI symptoms usually begin in the second week after starting radiotherapy, tend to peak in the last week of treatment and continue for at least 1–2 weeks after completion. Treatment with hypofractionated regimens means that acute symptoms may not start before treatment is completed.[104] Changes in radiotherapy techniques may lead to new patterns of toxicity.[104] The management of toxicity remains empirical as evidence is lacking.[81] For mild symptoms, supportive measures such as antidiarrhoeal or antispasmodic drugs may help. For radiation dermatitis topical agents such as hydroactive colloid gels for mild symptoms to wound healing agents or dressings for moderate to severe symptoms are used. Severe symptoms occasionally indicate localised perforation. Skin irritation from incontinence may be helped by barrier agents. Incontinence pads may need to be supplied. Overlapping toxicity from concurrent chemotherapy may further complicate management. Grade 3 or 4 diarrhoea mandates chemotherapy to be stopped with subsequent dose reduction if restarted. Clinical experience suggests that it is prudent to investigate rectal bleeding occurring during radiotherapy 6 weeks after treatment completion with flexible sigmoidoscopy if no recent lower GI endoscopic or virtual colonoscopy has been performed.

A recent feasibility, single centre randomised controlled trial showed promise in using a personalised approach to toxicity. In this study, a MDT embedded in the oncology unit arranged rapid investigations to exclude lactose intolerance, SIBO and BAD for symptomatic patients during their chemoradiotherapy. Appropriate treatment was provided when these conditions were diagnosed, in addition to personalised dietary support for all patients. This led to improved outcomes.[22]

Chronic issues: after upper GI surgery

Clinical practice guidance

39. *Symptoms are often related to the mechanical reconfiguration of the upper GI tract and the resulting physiological changes.*
40. *Extensive investigation of symptoms within 3 months of surgery is generally unnecessary, as symptoms often settle over time.*
41. *A history of presurgery, GI symptoms is important to determine if symptoms represent an exacerbation of a pre-existing condition or are new onset as a result of surgery.*
42. *For an anastomotic stricture, endoscopic dilatation is the preferred treatment with triamcinolone or a needle knife stricturoplasty reserved for recurrent strictures.*
43. *Acid reflux should be treated with proton pump inhibitors, the addition of pro-kinetics for up to 6 weeks may help.*
44. *Oral sucralfate suspension may be useful for recurrent bile reflux.*

45. *Postprandial pain after upper GI surgery is commonly due to eating too much at one sitting.*
46. *After upper GI surgery, bowel dysfunction with steatorrhoea is commonly due to PEI, SIBO and/or severe BAD; as these conditions often coexist, diagnostic testing and targeted treatment is recommended over empirical treatment.*
47. *Symptoms should not be attributed to irritable bowel syndrome (IBS) until comprehensive investigation/trials of treatment have excluded organic causes.*

Symptoms occurring in the first 2–3 months after surgery often settle spontaneously and do not usually require extensive investigation. Persistent symptoms, or those that develop at a later stage, require investigation and are a source of significant anxiety for patients. Recurrence is most likely to be detected 6 months to 3 years after surgery.

The type of surgery (oesophagectomy/total gastrectomy/partial gastrectomy) is important in understanding symptoms. These may be subdivided into those of clearly upper gastrointestinal origin, those of clearly lower GI origin and those which originate from either location or the small intestine (table 4). The differential diagnosis for most upper GI symptoms include an anastomotic stricture (usually dysphagia) or delayed gastric emptying (usually regurgitation, vomiting, early satiety) with significant overlap of symptoms between the two. Mechanical issues such as paraconduit herniation or conduit failure may also occur (figure 7).

Postprandial pain which starts soon after eating and lasts for an hour or so, often requiring people to take to their bed, may indicate that the person is trying to eat too much at one sitting. Rarely, it indicates mesenteric ischaemia. Postprandial dizziness, light-headedness, nausea, bloating, abdominal cramps and diarrhoea may suggest dumping syndrome or reactive hypoglycaemia but are also symptoms commonly caused by SIBO.

Significant weight loss is common after upper GI surgery. It may be a consequence of the catabolic state from surgery, radiotherapy, or systemic therapies or cancer recurrence or an imbalance between calorific requirements and dietary intake. Poorly controlled GI symptoms also contribute. Weight loss, although easy to record, may not be as important as changes to body composition or sarcopenia.

Non-specific symptoms are common in this patient group and inadequate investigation risks missing treatable causes. If IBS was not present before surgery, it is unreasonable to attribute them to IBS afterwards. Nocturnal waking to defaecate and steatorrhoea are never features of IBS. A systematic investigative approach[20] can be very effective to diagnose the potential multiple coexisting diagnoses including BAD, PEI, SIBO, overflow diarrhoea, jejunostomy feed related diarrhoea, malabsorption syndromes and late dumping syndrome. Further contributing factors may include alimentary and lifestyle issues, such as too much or too little fibre, excessive alcohol, excessive caffeine, excess consumption of drinks containing artificial sweeteners or side effects of prescribed medication. Lower GI symptoms are common after upper GI surgery and should be investigated systematically (table 6).

To identify patients who need appropriate assessment requires patients and clinicians to be vigilant and to understand that the development of chronic symptoms is not 'normal' and that dietetic support usually needs to be supplemented by an appropriate systematic investigation so that the underlying cause(s) can be correctly diagnosed and treated.[20] It is of note that contrast studies and/or gastric emptying studies for the diagnosis of delayed gastric emptying are compromised by a lack of standard normal range values in this specific patient group and if undertaken, should be interpreted with caution.

Chronic issues: functional symptoms after lower GI surgery

Clinical practice guidance

48. *Post-pelvic cancer symptoms need to be actively identified and managed.*
49. *The extent of surgery and position of the anastomosis (or stoma) has direct influence on symptoms and quality of life.*
50. *Multimodal treatment has a higher risk for long-term complaints and complications.*
51. *Interventions include bowel habit training, toilet positioning, advice on raising abdominal pressure for evacuation without straining, modifying stool consistency via diet and fluid adjustments, loperamide or fibre supplements, following a stepwise algorithm.*
52. *A large bowel transit study may help distinguish between slow transit constipation and evacuation difficulty.*
53. *Biofeedback for incontinence or evacuation difficulties, transanal irrigation or use of suppositories or mini-enemas are sometimes needed, but evidence for efficacy is lacking.*
54. *A stoma should be discussed in patients with poorly controlled symptoms and severely impaired quality of life, when other treatment options have failed.*
55. *Prophylactic use of laxatives is recommended when opioids are prescribed.*
56. *Evidence that a defaecating proctogram, endoanal ultrasound or ano-rectal physiological assessment change clinical practice is lacking so should be reserved for specialist practice or research.*

Key factors which impact on long-term symptoms and complications are the type of operation (eg, diarrhoea being more common after right than left hemicolectomy) and the length of bowel segment removed (segmental vs complete), especially in the case of rectal surgery or resections of the terminal ileum. The position of the anastomosis is important, with fewer symptoms if placed more proximally.[105 106] Resection of even very short segments of ileum (>5 cm) increases the risk of bile acid malabsorption.[107] Transit time is dysregulated in the absence of the so-called 'ileal brake', and bile acids can directly affect intestinal motility. The role of the sigmoid in regulating bowel function and the loss of function that occurs after resection (and irradiation) is also underappreciated.[108] Multimodal treatment (eg, neoadjuvant radiotherapy or adjuvant chemotherapy) further aggravates symptoms. SIBO affects approximately a third of patients after bowel surgery.[32] Some evidence suggests that hydrogen-positive SIBO predisposes to diarrhoea, whereas methane-positive SIBO predisposes to constipation.

Older studies report that symptoms may improve within the first year of surgery, but more recent data suggest that spontaneous improvement is rare after 3 months and that early active case finding of those with disordered bowel function affecting quality of life is required.[109–111]

Urgency, which may or may not result in faecal incontinence (and the restrictions caused are often similar) is often considered by patients as the most troublesome symptom.[112] Loose stool, particularly if combined with fibrosed sphincters or immobility makes incontinence more common. Patients describe 'living in limbo' because of symptoms such as incontinence.[113] Constipation and evacuation difficulties, including related symptoms of straining, incomplete or prolonged evacuation, tenesmus, bloating, borborygmi, and flatulence may be exacerbated by poor diet, inadequate fluid intake, visceral neuropathy and

medication. GI symptoms should be investigated systematically as described in table 6.

The impact of loss of bowel volume is well demonstrated by LARS, which significantly impacts on quality of life in 60–90% of patients.[114]

Low anterior resection syndrome (LARS)

Clinical practice guidance

57. *The risk of LARS should be assessed using a formal scoring tool and discussed with patients before surgery.*
58. *Supported self-management interventions to expedite an improvement in their bowel function should be offered to all patients undergoing anterior resection.*
59. *Objective testing is not required to make the diagnosis of LARS.*
60. *If symptoms persist beyond 3 months and supported self-management interventions have failed, a referral to specialist services should be made.*
61. *Other conditions may worsen LARS and should be excluded, particularly BAD, PEI and SIBO.*
62. *Pelvic floor exercises may improve functional outcome.*
63. *Bulking agents may reduce clustering and improve stool consistency.*
64. *Transanal irrigation can be helpful.*
65. *Stoma formation can be helpful.*

LARS is defined by at least one of eight bowel symptoms including variable, unpredictable bowel function, urgency, frequency and emptying difficulties resulting reduced quality of life.[115] Causes are treatment-related and often multifactorial.[116]

With intervention, improvements may occur within 3 to 4 months.[117] Without intervention, bowel symptoms may take years or may never improve.[118 119]

Symptom-led intervention pathways are likely to be helpful in planning individualised care. Possible management approaches are comprehensively reviewed by the Danish MANUEL Project Working Group.[114] Further research is required to define the precise role of tibial nerve and sacral nerve stimulation in clinical practice. A suggested approach to management is described in Box 4.

Box 4 Suggested staged treatment algorithm for low anterior resection syndrome

Level 1
⇒ Correct positioning on the lavatory
⇒ Pelvic floor exercises
⇒ Diet bulking agent
⇒ Loperamide
⇒ Enema/suppository to aid defaec

Level 2
⇒ Exclude bile acid diarrhoea/pancreatic exocrine insufficiency/small intestinal bacterial overgrowth
⇒ Exclude overflow diarrhoea

Level 3
⇒ Biofeedback
⇒ Rectal irrigation
⇒ Stoma formation

Short bowel syndrome

Short bowel syndrome is a condition where high output leads to water, sodium and often magnesium depletion. It occurs with a small bowel stoma, or fistula when output is greater than 1.5 litres over 24 hours.[120] Detailed management is outside the remit of this document but involves looking for and treating other contributory factors to explain the high output. Management then includes use of oral rehydration solution, restriction of hypotonic fluids, use of loperamide and codeine to slow bowel transit, proton pump inhibitors (PPIs) to reduce gastric secretions and bile sequestrants if the colon is in continuity. PERT and antibiotics to treat SIBO are also sometimes useful. It is a rare entity, often managed suboptimally, so nutrition-focused gastroenterologists and specialist dietitians should be involved.

CHRONIC ISSUES AFTER PELVIC RADIOTHERAPY

Radiation-induced rectal bleeding

Clinical practice guidance

66. *Appropriate endoscopic or radiological investigation of the bowel should be arranged as it cannot be assumed that rectal bleeding after radiotherapy is caused by radiation-induced telangiectasia.*
67. *Diagnosis of radiation proctopathy should be based on the typical appearance; biopsy confirmation should not be performed.*
68. *Radiation-induced bleeding is an ischaemic problem, interventions in ischaemic tissue may not heal and may lead to necrosis and perforation.*
69. *Interventions to stop significant bleeding should be performed only after patients have been informed of the risks and benefits of the intervention and have provided signed informed consent.*
70. *If bleeding is not affecting quality of life and assessment has excluded underlying malignancy, the patient should be reassured and the natural history of radiation-induced bleeding explained; intervention is not required.*
71. *If radiation-induced telangiectasia is the source of bleeding affecting quality of life or causing anaemia, optimising irregular bowel function will often reduce bleeding to a level which no longer affects quality of life.*
72. *Stopping anticoagulants/antiplatelet agents if possible will often reduce bleeding to a level which no longer affects quality of life.*
73. *Sucralfate enemas can be useful as a temporary treatment until definitive disease-modifying therapy in patients with heavy bleeding is effective or for long-term use in those with problematic bleeding unsuitable for disease-modifying therapy (Box 5).*

Rectal bleeding occurs in up to half of all patients treated with radiotherapy for a pelvic tumour. It is often occasional and minor. Severe bleeding which affects about 1% of patients after radical pelvic irradiation may result in repeated need for hospitalisation, transfusion and severely affects quality of life. People usually start to notice intermittent bleeding a few months after the end of radiotherapy. It usually reaches a peak within 3 years, sometimes then persisting for 10 or more years.[121–123] The risk of bleeding is directly related to the dose of radiotherapy delivered to the bowel wall. Increased risks may occur in patients treated with contact brachytherapy for early rectal cancers or brachytherapy for prostate cancer.[124] Brachytherapy for cervix and endometrial cancers may move the site of maximum damage from the rectum to the sigmoid, or rarely, the small bowel.

Box 5 How to make and give a sucralfate enema

Sucralfate enemas

⇒ 2 g sucralfate suspension
⇒ Add to 30–50 mL tap water
⇒ Draw up in a bladder syringe
⇒ Fit a soft Foley catheter to the syringe
⇒ Lubricate the catheter and pass into the rectum
⇒ Inject the sucralfate mixed with water into the rectum
⇒ Encourage the patient to roll through 360 degrees to coat the entire rectal surface
⇒ Lying prone then best covers anterior wall rectal telangiectasia, the usual area of greatest bleeding
⇒ Retain the enema for as long as possible or 20 minutes
⇒ Use twice daily initially, but if symptoms stabilise, long-term maintenance treatment once daily may be adequate
⇒ When treatment is stopped, bleeding is likely to recur.

The underlying pathological process is driven by radiotherapy-induced ischaemia in the bowel wall which promotes the development of new vessels on the luminal surface.

In up to half of the patients presenting with rectal bleeding after radiotherapy, the bleeding is not caused by the radiotherapy so no assumptions as to the cause of the bleeding should be made. All patients should be assessed with digital rectal examination and either flexible sigmoidoscopy (if the bleeding is bright red) or colonoscopy. Virtual CT colonoscopy is less helpful for assessing bleeding unless there is a high suspicion of a neoplasm within the bowel.

Endoscopy frequently reveals telangiectasia after pelvic radiotherapy. These can be categorised in different ways,[125] but the correlation between the endoscopic appearance and the risk of bleeding is poor. Biopsy of irradiated mucosa does not contribute usefully to making a diagnosis of radiation damage and carries a risk of fistula development or necrosis.[126] Biopsies should be carried out cautiously if neoplastic or inflammatory processes seem likely.

Treatment approaches to radiation-induced bleeding

Many treatment options for people with bleeding interfering with their life have been described, but there is no agreed optimal approach.[6 81] All treatments used historically for radiation-induced bleeding carry a significant risk of serious complications.[127] Treatment is only required if symptoms demand it (eg, faecal incontinence with blood, rectal bleeding interfering with daily life, transfusion-dependent bleeding or recurrent anaemia). Reassurance and explanation of the natural history of radiation bleeding are often all that is necessary. Where anaemia or troublesome symptoms are present, a number of strategies exist, a recommended approach to management is described in figure 8.

Argon plasma coagulation is widely used for bleeding radiation proctopathy. However, it carries a serious complication rate of up to 26%, including stricture formation, rectal pain, perforation and fistula formation.[128] Its use is absolutely contraindicated on the anterior rectal wall after prostate brachytherapy because of the high risk of fistula formation, which invariably then requires diversion of the bowel.

Any thermal therapy risks causing deep, progressive or non-healing injury, because radiation proctopathy is an ischaemic condition. Theoretically, the least risk is from the use of radiofrequency ablation. Initial data suggested a good response rate and no significant complications, but no new data have been published using radiofrequency ablation for this context since 2015.[129] Non-contact diode laser treatment deemed safe and effective, with 88% response in a 24 patient case series, is a novel thermal therapy described.[130] In another study, endoscopic band ligation was said to be effective and safe but again risks non-healing or progressive ulceration.[131]

A meta-analysis and a separate Cochrane review suggest significant benefit of treatment with hyperbaric oxygen (HBO).[132 133] Data from randomised trials are contradictory. The underpowered HOT2 study showed no statistically significant benefit (p=0.09) compared with sham treatment in rectal bleeding, while the HORTIS IV study, demonstrated greater healing in patients receiving HBO versus sham therapy.[134] Clinical experience suggests that little benefit is seen until patients have

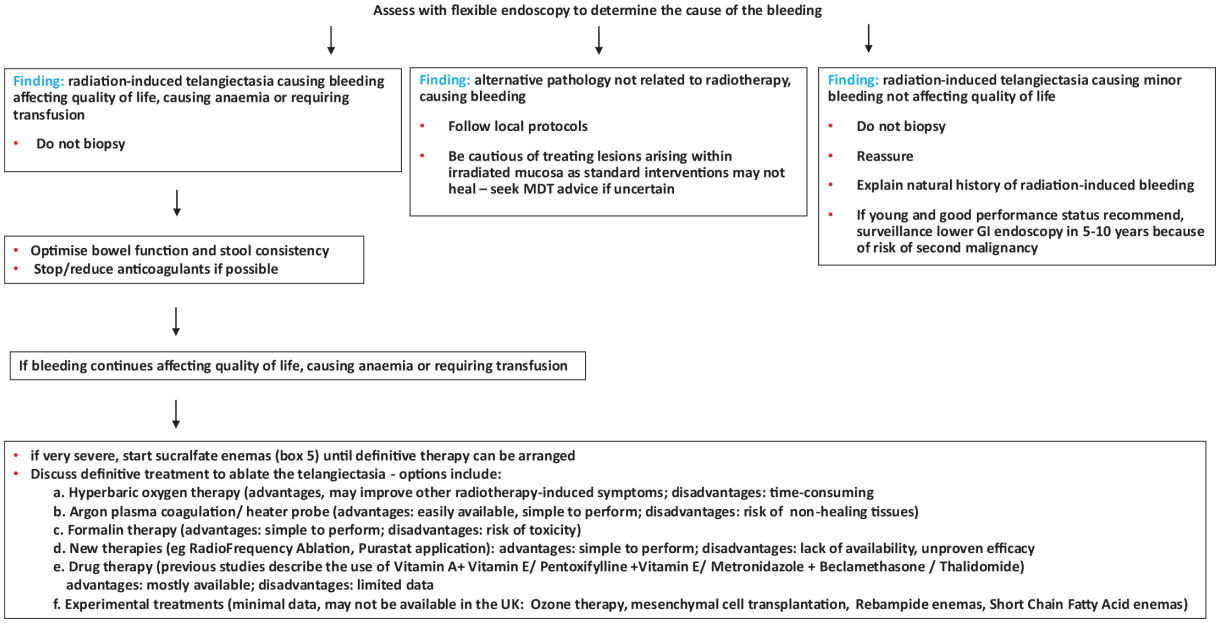

Figure 8 A management approach to patients with rectal bleeding developing after pelvic radiotherapy for a cancer in the pelvis. MDT, multidisciplinary team.

completed at least 30 sessions of HBO. Lower-pressure HBO as used in chambers treating people with multiple sclerosis is probably ineffective to treat radiation-induced injury.

Formalin has been used in many observational single-arm studies and retrospective series with apparent effect. However, there are few long-term data, no placebo-controlled randomised trials and a variety of techniques, including instillation at different concentrations (3.6–15%), for varying lengths of time or using a gauze or dab spotting approach.[128] Complications include colitis, which can be prolonged and severe especially if formalin enters the submucosa, stricturing, perforation and pain.

Purastat is a haemostatic self-assembling peptide that forms a molecular mesh in contact with blood. It is licensed to treat bleeding radiation proctopathy, is simple to apply and has no recorded side effects. In a 21 patient prospective study, the only published data, Purastat led to significantly reduced bleeding in three-quarters of patients at 1 year.[135]

Fistulae

Gastrointestinal fistulae are a relatively rare complication of radiotherapy and their incidence is probably decreasing owing to changes in its delivery. They may occur in any part of the GI tract from oro-tracheal to recto-vaginal fistulae. They can present acutely or many years later.

The presence of a fistula can often be made on history taking and examination. Once there is a clinical suspicion of a fistula it is crucial to rule out disease recurrence before assuming that it is secondary to radiation injury. Treatment needs a multidisciplinary approach, ideally by a regionally based team, as numbers are small. Detailed diagnosis and management are beyond the scope of this document; however, the principles include the following: (a) sepsis should be actively managed with radiological/surgical drainage and antimicrobial agents, (b) clear understanding of the anatomy of the fistula—that is, which parts of the bowel and other viscera are involved is required before any definitive treatment is planned, (c) the nutritional status of the patient must be optimised before any corrective surgery is attempted, (d) corrective surgery aims to restore normal anatomy by disconnecting the fistula and restoring intestinal integrity with minimum loss of bowel length.

Multiple operations and the judicious use of stomas may be required. The use of normal, non-irradiated tissue to fashion repairs helps to ensure an adequate blood supply. These often complex operations, require multidisciplinary surgical expertise and carry a high risk of prolonged morbidity. Rarely, there may be a role for non-operative therapies such as hyperbaric oxygen therapy or for non-radiotherapy-related fistulae in the distal bowel, treatments based on short bowel regimens.

Surveillance for second cancer

There is an increased risk of a radiation-induced gastrointestinal tract cancer in patients, starting 5–10 years after pelvic radiotherapy. Patients should be encouraged to take part in screening programmes, if fit enough, every 5 years after their radiotherapy.

Haematopoietic stem cell transplantation

Clinical practice guidance

74. *GI toxicity predicts post-transplant complications.*
75. *A multidisciplinary approach to care including input from haematologists, dietitian, gastroenterologists and specialist symptom control team is helpful.*
76. *Endoscopic tests with small bowel aspiration and biopsies are helpful in patients with diarrhoea after stem cell transplantation for differentiating between small bowel bacterial or fungal overgrowth, enteric infections (especially with C. difficile or cytomegalovirus) and GvHD.*
77. *Oesophagogastroduodenoscopy with small intestinal aspirate and biopsies combined with flexible sigmoidoscopy is significantly safer than colonoscopy in patients with lower GI symptoms and is similarly effective at reaching a diagnosis.*
78. *Wireless capsule endoscopy is not recommended to make the diagnosis of GvHD.*
79. *In patients with typical symptoms of GvHD, treatment should not be delayed while waiting for biopsy results.*

GI toxicity after a haematopoietic stem cell transplant relates to complications from preconditioning of the bone marrow secondary to SACT and GvHD after allogeneic stem cell transplants.[136] Mucositis in common following both autologous and allogeneic stem cell transplants, and pain is usually managed with soluble paracetamol and oral morphine. In addition, mouthwashes and coating agents can be helpful as described in the oral mucositis section above. In more severe cases, a subcutaneous infusion of morphine and antiemetics is required. Expert advice from the palliative care team can be sought if symptoms are severe.

Regular review by a dietitian is necessary for all patients undergoing stem cell transplantation. Many patients tolerate nutritional supplements, but those with more severe symptoms will require interventional nutritional support. When possible, a nasogastric tube should be used, but parenteral nutrition is often required owing to malabsorptive symptoms and inability to tolerate a feeding tube.[136]

Nausea, vomiting, anorexia, abdominal pain and diarrhoea are very common following a haematopoietic stem cell transplant. In patients undergoing autologous transplantation these symptoms are related to the SACT and are managed with antiemetics and antidiarrhoeal agents. Stool cultures should be obtained to exclude *C. difficile* infection before institution of antidiarrhoeal medications. Diarrhoea is commonly due to medication, GvHD, malabsorptive syndromes as a result of mucosal damage, SIBO, fungal overgrowth and viral enteritides. It is common for several causes to coexist.

There is a wider differential diagnosis for these symptoms in patients undergoing allogeneic stem cell transplantation and includes mucositis secondary to conditioning therapy, atypical infection, typhlitis, side effects of other drugs and GvHD. In the early post-transplant period before engraftment has occurred these symptoms usually relate to the conditioning regimen. Typhlitis is usually managed conservatively in the neutropenic patient and surgery should be reserved for patients with abdominal perforation. Acute GvHD can occur following engraftment of the donor cells and targets the skin, liver and GI tract. It usually occurs in the first 3 months following the transplant although later onset is possible.[137]

Biomarkers are not widely used in clinical practice. Endoscopic investigations with biopsies can be helpful. Upper GI endoscopy with small bowel aspiration for microbiological analysis and biopsy should be considered in those with predominantly upper GI symptoms. Although the yield of diagnostic accuracy is slightly higher with a colonoscopy, a flexible sigmoidoscopy is significantly safer in this patient group.[138] Small bowel capsule endoscopy is not specific for acute GvHD.[138] Biopsies can be difficult to interpret in GvHD and a detailed clinical history as well as review by an expert histopathologist together with the haematologist and gastroenterologist is required.

Chronic GvHD is characterised by distinctive and diagnostic features and can include oral and oesophageal involvement. The diagnosis of oesophageal involvement includes oesophageal web or strictures seen on endoscopy or barium studies.[139]

Treatment of both acute and chronic GvHD is determined by the severity of the disease and includes supportive measures as well as corticosteroids and other immunosuppressive drugs. Recent European guidelines provide an overview of specific treatment options.[140] Patients with severe acute GvHD are likely to need nutritional support with parenteral nutrition. If there is a delay in obtaining biopsy samples and results then corticosteroids should be started based on clinical assessment of the patient.

Patients are at higher risk of second cancers following a stem cell transplant and should be encouraged to participate in national bowel cancer screening programmes.[141] There should be a low threshold for investigating new GI symptoms in order to exclude secondary malignancy.

Neuroendocrine neoplasms (NENs)

Clinical practice guidance

80. *The majority of GI symptoms in patients who have NENs, do not result from excess production of hormones.*
81. *Gastroenterologists should be involved in the NEN MDT.*
82. *Surgery and systemic treatments for NENs, particularly somatostatin analogues, frequently cause abnormal GI symptoms.*
83. *Common causes of GI symptoms include pancreatic exocrine insufficiency, bile acid diarrhoea and small intestinal bacterial overgrowth.*
84. *Starting PERT is appropriate without faecal elastase measurement in those with steatorrhoea starting after treatment with a somatostatin analogue.*
85. *Prophylactic cholecystectomy should be considered when undertaking initial surgery for NENs to prevent recurrent or chronic pancreatitis.*
86. *In an existing non-functioning NEN, new GI symptoms should prompt investigation to exclude a change in hormone secretion.*
87. *If a NEN directly contributes to GI symptoms, either from pressure effects or from hormonal secretion, debulking surgery or systemic therapies should be considered.*
88. *Surgical management of mesenteric fibrosis should be considered, even in a metastatic setting, if quality of life is impaired significantly (and if there is a reasonable prognosis from the NEN).*
89. *Dietetics and multidisciplinary nutrition teams should be involved in patient care, especially in those at risk of short bowel syndrome from either mesenteric fibrosis or its surgical management.*
90. *NENs are associated with an increased risk of developing other cancers, so new unexplained symptoms should prompt investigations for other GI cancers.*

NENs encompass relatively indolent well-differentiated neuroendocrine tumours and more aggressive neuroendocrine carcincomas. GI symptoms associated with NENs arise from a combination of factors, including hormones produced by secretory/functional tumours, tumour-induced alterations in GI physiology/anatomy, surgical interventions or from systemic treatments that are used to target tumour control or hormone secretion.

PATIENT PERSPECTIVE AND OUTCOMES

Some patients with NENs live for many years with persistent and troublesome GI symptoms, and optimal management requires the combined expertise of gastroenterology, dietetics, specialist nurses and psychological support. As the disease progresses, palliative care support can also be helpful. Early investigation (tables 6 and 7) to identify reversible causes for new symptoms is important.

FUNCTIONING NENS AND SPECIFIC SYNDROMES

The majority of NENs are non-functional. Suppression of hormone and peptide secretion in those with functional syndromes is fundamental to patient management (table 7). The presence of carcinoid syndrome is typically associated with metastatic small intestinal NENs but can also occur in lung, pancreatic, and ovarian NENs. 'Curative' resection of the NEN and metastases will alleviate GI symptoms from hormone hypersecretion. If resection is not possible, suppression of hormone secretion using somatostatin analogues is needed (table 7).

Due to the heterogeneity of NENs, some systemic therapy options overlap with the treatment of other cancers. GI symptoms in those receiving cytotoxic chemotherapy or TKIs should be managed as previously detailed in this guidance.

Mesenteric fibrosis

Clinical practice guidance

91. *Abdominal pain can be difficult to manage and requires a close collaboration between pain and palliative care teams and dietitians.*
92. *Early and sustained dietetic input is needed to optimise nutritional status and prevent malnutrition.*
93. *Resection of fibrotic tissue or of involved bowel segments may offer symptomatic relief, but risks short bowel syndrome.*
94. *Despite stage IV disease, surgery may be an option but must be agreed in a NEN MDT.*
95. *Long-term home parenteral nutrition is a valid alternative to surgery if the risks of surgery are considered too high.*

The development of mesenteric fibrosis (desmoplasia) is difficult to predict; there is no specific blood marker and imaging may not identify subtle fibrosis.

Fibrosis causes shrinkage and fixation of the mesentery and mesenteric root to the retroperitoneum, potentially causing small bowel obstruction. Entrapped small and large mesenteric blood vessels may lead to arterial and venous ischaemia. Compromised absorption secondary to obstructive or ischaemic processes can lead to malnutrition and rarely short bowel syndrome. While the underlying NEN often remains indolent, fibrosis may affect anticancer treatment options. For example, peptide receptor radionuclide therapy can exacerbate obstruction in 22–30% of patient, requiring steroids and surgery. It is unclear whether stenting of the superior mesenteric vein affects symptoms and quality of life.

The impact of somatostatin analogue therapy on fibrotic processes in patients remains unclear. Corticosteroids may have a role and there are promising preclinical studies using terguride (5-HT2A/B antagonist) and tamoxifen. There is an unmet need for therapy targeting mesenteric fibrosis.

Resection of fibrotic tissue or involved bowel segments may offer symptomatic relief, but home parenteral nutrition may help improve nutrition and reduce the oral intake which induces pain. Its use in NENs often extends significantly longer than in other cancers, with low catheter-related complications. It is vital not to forget the role home can play when surgical resection is deemed too risky.

Table 7 Functioning neuroendocrine tumours and their syndromes affecting the GI tract

	Site of primary NET	Hormone secreted	Biochemical test	Consequences and symptoms	Initial treatment (If curative resection not undertaken)	Treatment of refractory symptoms
Carcinoid syndrome	Jejunoileum with liver metastases, or lung, or pancreas (rare), or ovary (rare)	Serotonin, kallikrein, tachykinins, prostaglandins	Serotonin or 5-HIAA (plasma or urinary)	Secretory diarrhoea, abdominal discomfort, faecal urgency, which continues even during fasting Upper body flushing (dry) Fibrosis of cardiac valves causing carcinoid syndrome Mesenteric fibrosis causing small bowel ischaemia and obstruction	Long-acting SSAs (octreotide LAR up to 30 mg, or Lanreotide Ipsen up to 120 mg) every 28 days	Short-acting SSAs for example, octreotide 100–500 µg every 6–8 hours Telotristat (tryptophan hydroxylase inhibitor) Liver resection/debulking TAE PRRT
VIPoma	Pancreas or duodenum	VIP	Plasma VIP	Profound watery diarrhoea, persisting during fasting Dehydration, hypokalaemia, and acidosis	Fluid and electrolyte replacement Long-acting SSAs	Glucocorticoids Parenteral fluids/ electrolytes Resection/debulking surgery TAE PRRT Chemotherapy TKIs
Gastrinoma	Duodenum or pancreas (often multiple)	Gastrin	Plasma gastrin and gastric fluid pH ≤2	Zollinger-Ellison Syndrome (ZES) – Upper GI Bleeding, perforation, or strictures. Abdominal pain, gastro-oesophageal reflux, diarrhoea, significant peptic ulceration	High dose PPIs for example, 60–120 mg omeprazole or equivalent	SSAs Resection/debulking surgery TAE PRRT
Somatostatinoma	Duodenum or pancreas	Somatostatin Often associated with neurofibromatosis one or MEN-1	Plasma somatostatin	Abdominal pain, weight loss, diarrhoea, steatorrhoea, and jaundice Gallstones (suppression of CCK) Diabetes (suppression of insulin)	Pancreatic enzyme replacement therapy Loperamide Long-acting SSAs	Resection/debulking surgery TAE PRRT Chemotherapy Everolimus Sunitinib
Glucagonoma	Pancreas	Glucagon	Plasma glucagon	Diarrhoea, glossitis, weight loss, and abdominal pain Diabetes, deep vein thrombosis rash (necrolytic migratory erythema)	Long-acting SSAs	Resection/debulking surgery TAE PRRT Chemotherapy Sunitinib
Medullary thyroid cancer	Thyroid	Calcitonin Frequently associated with MEN-2 (suspect in patients with diarrhoea and phaeochromocytoma and/or parathyroid) adenoma)	Plasma calcitonin	Secretory diarrhoea (40%)	Long-acting SSAs	Resection/debulking surgery TKIs PRRT

CCK, cholecystokinin; 5- HIAA, 5-hydroxyindoleacetic acid; LAR, long-acting-repeatable octreotide; MEN, multiple endocrine neoplasia; PPI, proton pump inhibitors; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analogues; TAE, transhepatic arterial embolisation; TKI, tyrosine kinase inhibitors; VIP, vasoactive intestinal peptide.

Palliative and end of life care

Clinical practice guidance

96. *Focus on remote monitoring of patient-reported outcome measures.*
97. *Provide treatment to optimise symptoms and quality of life.*
98. *Consider referral to palliative care when there is ≥70% risk of death within 1 year.*
99. *Prioritise minimising pain and avoiding opioid-induced constipation.*
100. *For diarrhoea/bloating consider an empirical trial of rifaximin for 1 week/a bile acid sequestrant for 10 day/ PERT for 10 days.*
101. *Consider early adjunctive iron support including parenteral iron in patients with bleeding.*
102. *For malignant bowel obstruction consider corticosteroids and octreotide. Only insert a nasogastric tube if the patient wants to try this and other measures to relieve obstructive symptoms have failed.*
103. *Palliative venting gastrostomy can relieve symptoms and improve quality of life in the absence of extensive peritoneal or gastric serosal disease.*

It can be difficult to determine when someone is in their last year of life and when to adopt a more pragmatic approach to their care, managing symptoms and using interventions which focus only on improving quality of life. However, within this uncertainty, sensible guidance around common problems and symptoms, and links to helpful resources, are useful. An early referral to palliative care services for additional support to maintain quality of life and advocate further interventions is beneficial. Acute admission to hospital should be considered as a trigger for referral.[142] An important aim of palliative care should be to avoid unnecessary attendance at hospital as it is commonly reported that patients in the last phase of their life have poor experiences in hospital and frequently have no clear benefits from their attendance.

Macmillan Cancer Support have multiple resources for education of patients and carers, including ideas for managing symptoms as well as general management strategies.[143]

Bowel obstruction

Decision-making for partial or complete bowel obstruction is complex so specialist advice is required. There is a potential

useful role for venting gastrostomy and parenteral nutrition.[144] If the patient has good performance status and parenteral nutrition is a possibility, the advice of a gastroenterologist-led nutrition team should be sought at the earliest opportunity. The role of colonic stenting is controversial.[145 146] The majority will not be suitable for surgery. However, if the patient is not actively dying, it should be considered if the patient has good functional status (ASA grade <3) and for whom the reversal of enteral failure might make therapeutic options available.[147]

Management of bleeding tumours

Bleeding in people with advanced malignancy is often assumed to be from the tumour. However, in a series of patients with cancer with an upper GI bleed more than one-third were bleeding from non-malignant treatable causes, such as varices, peptic ulcer disease, angioectasia and Mallory-Weiss tears.[148] Embolisation or radiotherapy may be helpful if a bleeding point can be identified. In those with a short prognosis, a pragmatic approach to supporting patients with recurrent transfusions and/or the use of tranexamic acid may be appropriate, although this carries an increased risk of thrombosis. Regular endoscopic debulking of the tumour using a YAG laser can be effective but is increasingly unavailable.

Future developments

Technological change

There will be continuing technological developments in oncology bringing advances in treatment delivery. Radiotherapy is becoming increasingly conformal with enhanced accuracy despite target organ motion. Liver transplantation for metastatic disease will be increasingly used. More patients will remain on long-term anticancer treatment. Furthermore, new cellular therapies will have effects on GI mucosal behaviour and molecular pathways as will other multimodality systemic therapies. So, optimal management of toxicity will become essential.

While the GI tract will be less prone to high-dose radiation exposure, the long-term effects of lower-dose radiation exposure to extensive areas of the GI tract are unknown. Therapies to reduce radiation-induced ischaemia and fibrosis will become available. Stem cell therapy will aid repair of damaged tissues. Novel treatments for toxicity may bring their own concerns.

Artificial intelligence may be able to analyse and provide first-line advice. While improved software has a vital role to play in this process, some patients preference for face-to-face consultation or completion of paper questionnaires should not be ignored. Similarly, monitoring of prescription adherence (eg, via on-line Apps) or better feedback on the frequency/severity of symptoms should alert teams treating patients to situations requiring early or urgent intervention and help to prevent chronic problems.

Wide use of validated PROMs encompassing both GI and non-GI symptoms will result in improved quality of life for patients and better understanding among clinicians of the severity and frequency of symptoms.

Regionally, more centres are developing specialist teams that can deal with management of significant symptoms. However, the introduction and use of technological aids will require trained staff to evaluate responses and effect interventions within appropriate timeframes.

Improved awareness/education

Patients

Patients will get better access to support groups and will increasingly be aware not to accept unmanaged or non-resolving GI symptoms as the price to pay for cancer treatment. The Montgomery ruling has made this increasingly important from a medicolegal perspective.[149] They will receive balanced information on self-help, when to seek specialist help, therapeutic options available and signs of cancer recurrence. The expert patient support programme will be expanded by the proliferation of patient support groups, and those that have been successfully operating for decades can continue to do more if they secure the funding they need.

Professionals

Routine referral pathways for those with complex toxicities to appropriate multidisciplinary specialist services will need to be available within each region and centres offering new anticancer technologies must be encouraged to invest also in appropriate and expert supportive care services. It is not reasonable to expect non-experts to manage complex issues arising from novel therapies. However, when they see people affected by toxicity related to treatment, all clinicians will need to know what questions to ask, the minimal basic assessment to perform, first-line management, when and who to refer to, and how to conduct patient-focused, holistic assessment. Urgent changes need to be embedded in to training programmes for key specialities, particularly dermatology, gastroenterology, GI surgery, gynaecology, oncology, primary care, psychological medicine and urology, to ensure that this becomes possible.

Research priorities

A great deal of effort has been expended to define strategic research priorities in those living with cancer[150 151] but despite this, the required expertise, number of centres with a critical mass patients and funding have been lacking. Studies using preventative approaches have struggled in the absence of clearly defined groups of patients at particularly high risk and the absence of objective biomarkers of toxicity, so defining these remains an important priority. Interventional studies to reduce or treat toxicity traditionally have failed to recruit adequately, mainly because most centres do not have individuals who have ownership in this field and the pharmaceutical industry has not been incentivised to drive studies where the primary end points are other than progression-free survival and overall survival. This paper describes many areas where pioneers have suggested likely benefit from intervention and it now time for the oncology community to embrace the obvious benefits that supportive care in cancer brings to healthcare and patients and invest in these services, which in turn will drive further research.

As anticancer therapies evolve, it will not be enough to monitor only what happens during, and for a short time after, treatment, and standardised programmes of long-term surveillance for toxicity must be instituted. The acute annual costs of treatment for cancer in the UK are currently £3.4 billion. The costs of cancer-induced morbidity are poorly defined, but enormous.[152] To bring down these costs to patients, society and the exchequer, national improvements will require a fundamental change in mindset. Improving survival must be integrated with strategies to reduce toxicity and enhance quality of life.

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