



# Practice guidance on the management of acute and chronic gastrointestinal problems arising as a result of treatment for cancer

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## ABSTRACT

**Background** The number of patients with chronic gastrointestinal (GI) symptoms after cancer therapies which have a moderate or severe impact on quality of life is similar to the number diagnosed with inflammatory bowel disease annually. However, in contrast to patients with inflammatory bowel disease, most of these patients are not referred for gastroenterological assessment. Clinicians who do see these patients are often unaware of the benefits of targeted investigation (which differ from those required to exclude recurrent cancer), the range of available treatments and how the pathological processes underlying side effects of cancer treatment differ from those in benign GI disorders. This paper aims to help clinicians become aware of the problem and suggests ways in which the panoply of syndromes can be managed.

**Methods** A multidisciplinary literature review was performed to develop guidance to facilitate clinical management of GI side effects of cancer treatments.

**Results** Different pathological processes within the GI tract may produce identical symptoms. Optimal management requires appropriate investigations and coordinated multidisciplinary working. Lactose intolerance, small bowel bacterial overgrowth and bile acid malabsorption frequently develop during or after chemotherapy. Toxin-negative *Clostridium difficile* and cytomegalovirus infection may be fulminant in immunosuppressed patients and require rapid diagnosis and treatment. Hepatic side effects include reactivation of viral hepatitis, sinusoidal obstruction syndrome, steatosis and steatohepatitis. Anticancer biological agents have multiple interactions with conventional drugs. Colonoscopy is contraindicated in neutropenic enterocolitis but endoscopy may be life-saving in other patients with GI bleeding. After cancer treatment, simple questions can identify patients who need referral for specialist management of GI symptoms. Other troublesome pelvic problems (eg, urinary, sexual, nutritional) are frequent and may also require specialist input. The largest group of patients affected by chronic GI symptoms are those who have been treated with pelvic radiotherapy. Their complex symptoms, often caused by more than one diagnosis, need systematic investigation by gastroenterologists when empirical treatments fail. All endoscopic and surgical interventions after radiotherapy are potentially hazardous as radiotherapy may induce significant local ischaemia. The best current evidence for effective treatment of radiation-induced GI bleeding is with sucralfate enemas and hyperbaric oxygen therapy.

**Conclusions** All cancer units must develop simple methods to identify the many patients who need help

## Key facts

- ▶ There has been a threefold increase in the numbers of survivors of cancer in the last 30 years
- ▶ Chronic gastrointestinal side effects are a common cause of morbidity and reduced quality of life
- ▶ Side effects of treatment are frequently missed or overlooked because the current priority of cancer follow-up is to perform surveillance for recurrent cancer
- ▶ Individual GPs are unlikely to have many patients with complex problems after cancer therapy and so will require guidance if these patients are to be optimally managed
- ▶ Symptoms can often be alleviated or cured.

and establish routine referral pathways to specialist gastroenterologists where patients can receive safe and effective treatment. Early contact with oncologists and/or specialist surgeons with input from the patient's family and friends often helps the gastroenterologist to refine management strategies. Increased training in the late effects of cancer treatment is required.

## BACKGROUND

Improvements in the outcome for patients with cancer over the last 30 years have reflected earlier diagnosis and advances in multimodality treatments. There has been a threefold increase in survival and, although some patients are not cured, their cancer is controlled, often for very long periods. Others may be cured but suffer side effects of their otherwise successful therapies. The National Survivorship Initiative<sup>1</sup> has identified four key needs of cancer survivors:

1. a personalised 'survivorship' care plan formulated for each patient on completion of treatment;
2. support to self-manage their condition if appropriate;
3. provision of information on long-term effects of living with and beyond cancer;
4. access to specialist medical care for complications that occur after cancer.

Potentially serious complications are an inevitable consequence of radical therapies. Profound fatigue is not unusual; emotional and psychological difficulties are common. However, of the two million people currently living with or cured of cancer in the UK, 25% report chronic physical problems following treatment which impair their quality of life.<sup>1–3</sup>

Gastrointestinal (GI) symptoms are the most common of all the chronic physical side effects of cancer treatment and have the greatest impact on quality of life.<sup>4</sup> Fewer than 20% of affected patients are referred to a GI specialist<sup>5</sup> because clear management algorithms and routine referral pathways are not in place and the treatable aspects of the symptom complexes go unrecognised. When patients are referred, they usually meet a clinician who has had no formal training in the management of late effects of cancer treatment. Clinicians are further hampered by limited research into the range of problems or their optimal treatment,<sup>6,7</sup> and few gastroenterologists or GI surgeons feel confident in managing such patients.<sup>5</sup> As a result, these patients need—but fail to get—appropriate assessment.<sup>8</sup> Ineffective and potentially harmful treatments are prescribed,<sup>1,6,7,9</sup> and some patients may be forced unnecessarily to withdraw from work and society.<sup>10</sup> Sometimes continuing symptoms compromise or prevent ongoing anticancer treatment. In a few patients, chronic symptoms mask the early diagnosis of recurrent or second cancers.

This guidance has been designed to facilitate clinical practice. It focuses on the physical causes of symptoms rather than the psychological, because gastroenterologists are already very familiar with identifying psychological factors in GI disease. While these patients are exposed to a unique set of psychological stresses which in turn may produce GI symptoms, there are robust data that organic causes for symptoms are frequently missed. This guidance will therefore emphasise those areas where symptoms starting after cancer treatments can be considered in the same way as other GI diseases and when clinicians need to be wary. It defines principles of management where possible and outlines research priorities for the future. There is very little level A (randomised controlled trial) or level B (outcomes research) evidence to define optimal management of these patients or to produce definitive guidelines. In the absence of anything better, the recommendations presented in this guidance to inform practical approaches to treatment are largely based on level C (case series) and level D (expert opinion, physiological and laboratory studies) data.

## **PATHOPHYSIOLOGY OF SIDE EFFECTS OF CANCER THERAPIES**

### **Chemotherapy**

Cytotoxic chemotherapy agents have a direct effect on the GI mucosa causing inflammation,<sup>11–13</sup> oedema, ulceration and atrophy. Increased bowel permeability combined with the secondary effects of immunosuppression predispose to increased susceptibility to GI transmural infection potentially leading to septicaemia, shock, associated hypotension and secondary mucosal ischaemia.

New-onset lactose intolerance is the cause of diarrhoea and bloating during 5-fluorouracil chemotherapy in 10% of patients.<sup>14,15</sup> Clinical experience suggests that small bowel bacterial overgrowth, bile acid malabsorption and pancreatic insufficiency are three other important contributory factors to chemotherapy-induced GI symptoms.<sup>16</sup>

Hepatic side effects include reactivation of hepatitis B,<sup>17</sup> severe sinusoidal obstruction syndrome (especially oxalipatin-

based regimens)<sup>18</sup> and steatosis. Following treatment with irinotecan in particular, steatosis may progress to steatohepatitis.<sup>19</sup> This may be exacerbated by pre-existing conditions (eg, alcohol excess, diabetes and obesity). Both steatosis and steatohepatitis are potentially reversible after cessation of chemotherapy but occasionally contribute to morbidity and mortality.<sup>18–21</sup> The detailed management of these conditions is described elsewhere.<sup>22</sup>

Chronic GI side effects of chemotherapy have not been studied systematically or prospectively. Clinical experience suggests that a small proportion of patients do have ongoing GI problems with constipation, diarrhoea, flatulence, bloating and pain, and that small bowel bacterial overgrowth is a frequent cause of these symptoms. However, specific drugs, their cumulative dose, the degree of immunosuppression during treatment together with the degree of damage to the mucosa, submucosa and GI stem cells may also play a role in the development of chronic problems.<sup>16,23</sup> The interaction with other cancer treatments complicates the clinical picture further.

### **Biological agents**

Rapidly increasing numbers of biological agents are being introduced for cancer therapy. This includes both immunotherapy and inhibitors of specific molecular targets. The main categories of targeted therapies currently include tyrosine kinase inhibitors (eg, erlotinib, imatinib, gefitinib, sorafenib), proteasome inhibitors (eg, velcade) and anti-angiogenesis agents (eg, bevacizumab). The spectrum of GI toxicity with these agents and their causes are poorly defined. Biological agents have multiple interactions with conventional drugs and, when new drugs are prescribed, the potential for interactions must always be checked. It is particularly important for gastroenterologists to know that altering gastric pH in a patient taking a biological agent orally can markedly affect its bioavailability. In the emergency setting, if there is any possibility that the biological agent is the cause of severe symptoms, it is always acceptable that the agent should be stopped while waiting for urgent advice from the oncologist treating the patient. Acute severe GI symptoms should otherwise be managed normally.

### **Radiotherapy**

Radiotherapy initially causes mucosal changes characterised by inflammation or cell death, but subsequently persistent cytokine activation in the submucosa leads to progressive ischaemia, fibrosis and loss of stem cells.<sup>24</sup> These ischaemic and fibrotic changes potentially cause impairment of GI physiological function(s). Chemotherapy increases the sensitivity of non-cancerous tissues to damage from radiotherapy. Chronic GI dysfunction may follow without pause from acute symptoms induced by radiotherapy or may arise de novo months, years or even decades later. The time allowed for follow-up in most studies prevents the recognition of these late side effects, their frequency or severity.<sup>25</sup>

It is argued that introduction of new chemotherapy and biological agents and more targeted radiotherapy techniques over the last two decades will diminish toxicity rates,<sup>26,27</sup> but the long-term effects of these new cancer treatments are unknown.<sup>28</sup> For example, the technique of intensity-modulated radiotherapy (IMRT) has been introduced widely. One possibly important consequence of IMRT is that more organs are exposed to low-dose irradiation than was the case with conventional treatment. It will be some time before definitive evidence from clinical trials shows the true impact of this on

acute and chronic toxicity. Clinical experience suggests that IMRT simply changes the timing and spectrum of toxicity. There are virtually no data on the long-term effects of even newer techniques such as proton beam therapy and cyber knife treatment.

### Surgery

Radical resectional surgery may cause significant disruption of GI physiology. This includes disturbance in intestinal transit, altered gastric emptying, enzymatic digestion and malabsorption reflecting anatomical disruption and stasis, bacterial overgrowth, altered bile acid secretion and absorption and hepatic insufficiency. Hepatopancreatobiliary resections carry the inherent risk of subsequent biliary strictures (which may be due either to benign fibrosis at the anastomosis or disease recurrence) resulting in obstructive jaundice. In the past, many patients had limited survival after primary cancer surgery but symptom complexes which were common—for example, after upper GI surgery for peptic ulceration—are now being observed in long-term cancer survivors, although many clinicians will no longer be familiar with these.

### Non-resectional ablation techniques

Radiofrequency or microwave ablation and tumour embolisation with a variety of agents including radioactive beads are being used increasingly with both palliative and curative intent to treat liver tumours. Complications include bleeding, ulceration, ischaemia or perforation of adjacent bowel, abscess formation, hepatic artery aneurysm and tumour track seeding.

### GI SYMPTOMS: THE ACUTE SYNDROMES

The presentation of GI side effects can be acute, subacute or chronic (table 1).

Many acute and subacute problems related to cancer treatments will be managed by oncologists. However, increasingly, potentially life-threatening complications of modern treatments present via emergency departments.<sup>29</sup>

### Acute syndromes: key facts

- ▶ Urgent cross-sectional imaging may help assessment and management
- ▶ Perform early upper GI endoscopy and duodenal biopsies and duodenal aspirate and lower GI endoscopy with biopsies for diarrhoea
- ▶ Flexible sigmoidoscopy rather than colonoscopy is usually adequate initially
- ▶ Always consider taking biopsies and asking for histological evidence of viral infection, especially if multiple ulcers are seen, even if there has been bleeding
- ▶ Ensure platelet support is available before endoscopic intervention when the platelet count is below  $80 \times 10^9$
- ▶ Avoid biopsies from areas of obvious radiation-induced change unless absolutely necessary
- ▶ Colonoscopy is contraindicated in neutropenic enterocolitis
- ▶ Infections in the neutropenic patient can kill quickly; early empirical treatment may be required
- ▶ Seek early specialist help

### Infection

Neutropenic sepsis is a common complication of cancer chemotherapy precipitating GI symptoms, which usually respond quickly to antibiotics. In patients with worsening or severe diarrhoea, one single stool specimen is sufficient for the detection of bacteria or toxins, however three separate specimens are required to exclude parasitological causes with sufficient diagnostic sensitivity. Early endoscopic assessment is also mandatory as stool culture may not detect viral infection, toxin-negative *Clostridium difficile* or drug-induced colitis. Endoscopy in a neutropenic patient predisposes to sepsis, although the degree of the increased risk is unclear. Febrile neutropenic patients should already be on antibiotic therapy. Recent British Society of Gastroenterology guidelines (grade C

**Table 1** Presentation of gastrointestinal side effects: acute, subacute or chronic

| Aetiology                | Acute  | Subacute  | Chronic  |
|--------------------------|--|---|--|
| Infection                | Bacterial<br>Viral<br>Fungal<br>Opportunistic  | Small bowel bacterial overgrowth                          | Small bowel bacterial overgrowth   |
| Inflammation (acute)     | Neutropenic enterocolitis<br>Perforation<br>Haemorrhage<br>Graft versus host disease<br>Pancreatic insufficiency | Graft versus host disease                                 | Graft versus host disease  |
| Inflammation (chronic)   |  | Bowel obstruction/strictures,<br>Pancreatic insufficiency | Graft versus host disease  |
| Ischaemic/fibrotic       | Gastric outflow obstruction  | Graft versus host disease,<br>Pancreatic insufficiency    | Biliary strictures<br>Bowel obstruction<br>Enteropathy and loss of physiological functions<br>Graft versus host disease<br>Pancreatic insufficiency<br>Malabsorption |
| Metabolic                | Malabsorption<br>Hepatic insufficiency   | Malabsorption   |  |
| Vascular (ischaemia)     | Mesenteric vascular insufficiency<br>Mesenteric thrombosis<br>Veno-occlusive disease                             |   | Enteropathy and loss of physiological functions  |
| Vascular (proliferative) |  |   | Telangiectasia causing bleeding  |

evidence: expert opinion) suggest that afebrile patients with a neutrophil count  $<0.5 \times 10^9/l$  need to be offered antibiotic prophylaxis only for GI endoscopic procedures associated with high risk of bacteraemia such as variceal sclerotherapy, oesophageal dilation, laser therapy and endoscopic retrograde cholangiopancreatography with biliary obstruction. Gram-negative aerobic (and, less frequently, anaerobic) bacteria including *Escherichia coli* are the most likely pathogens in these conditions, and the choice of prophylactic antibiotics should reflect the local sensitivities of organisms.<sup>30</sup>

The two most important treatable pathogens which regularly cause severe morbidity or death in patients receiving treatment for cancer are cytomegalovirus (CMV) and *C difficile* (10% are toxin-negative). The type of endoscopic assessment which best identifies stool culture-negative pathogens is not clearly defined. However, upper GI endoscopy with duodenal biopsies and aspirate and flexible sigmoidoscopy with left colonic biopsies seem to produce results equivalent to full colonoscopy and ileal biopsy<sup>16 31 32</sup> while avoiding the need for full bowel preparation and reducing risk.

CMV infection may affect the whole GI tract but is most commonly found in the oesophagus and colon. Common symptoms include diarrhoea (up to 80%), bleeding (up to 64%), fever (up to 50%) and abdominal pain (19–50%). Endoscopy may demonstrate the presence of multiple ulcers. Serology, viral culture and PCR techniques are not reliably positive for 3 or 4 weeks after the onset of symptoms. Earlier diagnosis may be available using the newer shell vial assay and from examination of endoscopic biopsies. Biopsies should be taken both from the centre/base of ulcers (site of highest yield for CMV) and from the edge (which gives a higher yield in herpes simplex virus infection).<sup>33 34</sup> In a sick immunosuppressed patient with relevant symptoms, early empirical treatment with ganciclovir should be considered.

The typical endoscopic appearance of *C difficile* at flexible sigmoidoscopy is often diagnostic in toxin-negative patients. However, pseudomembrane formation requires neutrophil involvement, and the typical macroscopic and microscopic appearance may be altered or be completely absent in neutropenic patients.<sup>35</sup> Immunosuppressed patients with *C difficile* are at high risk of early progression to fulminant toxic megacolon, so delay in investigation and treatment is potentially dangerous.

Many other pathogens including amoebae, giardia, viruses such as herpes simplex virus, rotavirus or adenovirus, bacterial pathogens and fungi may be responsible for symptoms. Recurrent infections with different organisms in immunosuppressed patients may mandate repeated endoscopic reassessments at short intervals. More than one pathogen may be responsible.

Anorectal sepsis in neutropenic patients is a frequently forgotten cause of morbidity. Clinical assessment by an experienced colorectal surgeon supplemented by MRI scanning can often be helpful in detecting an occult site for recurrent infection.

### Typhlitis and neutropenic enterocolitis

Typhlitis and neutropenic enterocolitis carry a high mortality rate because of the risk of rapid progression to ischaemia, necrosis, haemorrhage, perforation and multisystem organ failure. Typhlitis follows chemotherapy-induced neutropenia and is characterised by inflammation localised to the caecal wall, possibly caused by bacterial invasion. If other parts of the GI tract are involved (eg, the terminal ileal wall or elsewhere), the term 'neutropenic enterocolitis' is more appropriate. Bowel wall

thickening with or without dilation is usually seen on cross-sectional imaging. Clinical features include fever, abdominal pain, nausea, vomiting and diarrhoea. Colonoscopy is contraindicated as it carries a very high risk of perforation.

Data on the optimal management are limited. Bowel rest, intravenous fluids, parenteral nutrition, broad spectrum antibiotics and normalisation of neutrophil counts are usually recommended.<sup>36</sup> When inflammation is limited to the caecum and terminal ileum, clinical experience suggests that most patients can be managed conservatively. The presence of a local mass needs repeated imaging to exclude abscess formation or perforation. Perforation, persistent GI bleeding and clinical deterioration may mandate surgical intervention. As in the management of any acute severe colitis, frequent clinical reassessment and early surgical consultation is advised.

### Haemorrhage

Causes of bleeding include chemotherapy-induced ischaemia (particularly induced by taxanes<sup>13 37</sup> and bevacizumab<sup>38</sup>), infections (particularly CMV and Candida), graft versus host disease (which can occur after stem cell transplantation when the newly transplanted material attacks the transplant recipient's body), autoimmune colitis after treatment with ipilimumab,<sup>11</sup> acute radiotherapy-induced ulceration, drug- or radiotherapy-induced inflammatory bowel disease, neutropenic enterocolitis and oxaliplatin-induced portal hypertension.<sup>39</sup> Patients should be managed like any other high-risk GI bleed. Experienced endoscopists must be involved from the onset. Although endoscopy may be more hazardous, early endoscopic therapy may also be life-saving.

Thrombocytopenia is common in patients with cancer undergoing chemotherapy. Endoscopists should be aware that, even with apparently adequate platelet counts, chemotherapy-induced platelet dysfunction may affect normal homeostatic mechanisms. There are no robust data as to the minimal safe platelet count for safe therapeutic endoscopy. Endoscopists should consider ensuring in advance that platelet support is available should it be required when performing therapeutic procedures in patients with a platelet count below 50–80 000/ $\mu$ l.

The endoscopic appearance may not be diagnostic without biopsy. However, even flexible endoscopic biopsy under direct vision can be hazardous in the presence of thrombocytopenia, incipient ischaemic necrosis or previous radiotherapy, especially brachytherapy. Endoscopic intervention may be sufficient for bleeding from discrete sites, but interventional radiology with embolisation or surgery may be required in extensive mucosal change. Hyperbaric oxygen therapy is probably the treatment of choice for radiotherapy-induced bleeding occurring at multiple sites throughout the small and/or large bowel.<sup>40–42</sup>

### Perforation

Perforation may result from spontaneous tumour necrosis, which may or may not be due to chemotherapy or progression of cytotoxic drug-induced ulceration, often on a background of adjunctive corticosteroid or non-steroidal anti-inflammatory drug treatment. The antivascular endothelial growth factor monoclonal antibody bevacizumab causes ulceration, fistulation or free perforation in 0.9% of patients within 1 year of treatment.<sup>43</sup> This may be at the primary tumour site but also within colonic diverticula or otherwise normal areas of stomach and duodenum. Bevacizumab may increase the risk of stent-related<sup>44</sup> and spontaneous perforation and is associated with bleeding, poor wound healing and thromboembolism. Two



tyrosine kinase inhibitors, erlotinib and gefitinib, are also associated with bowel perforation. Surgical treatment is essential as long as the patient is fit enough, and therapeutic resection may be the best approach if the primary tumour has perforated. If circumstances permit, referral to a specialist surgeon is indicated.

### Mesenteric ischaemia and infarction

Spontaneous mesenteric vascular insufficiency can be induced by the hypercoagulable state associated with some cytotoxic agents.<sup>45</sup> This can affect both diseased and unaffected small bowel. The mortality rate is high and a high degree of suspicion is needed to diagnose ischaemia. The aetiology may be venous or arterial and expert radiology may help in assessment and management. Optimal management of acute intestinal ischaemia requires early assessment by an experienced surgical team. The options—depending on the general state of the patient—include full anticoagulation if the bowel is viable, through to staged resection, often requiring repeat laparotomies and open abdomen techniques.

Chemotherapy-associated mesenteric ischaemia can present with acute abdominal pain, but also can produce small bowel strictures causing small bowel obstruction. It must be treated by a combination of nutritional support, repeated clinical assessment by experienced surgeons and appropriate anticoagulation.

### Hepatic veno-occlusive disease/portal vein thrombosis

This is a very frequent cause of early mortality among patients receiving high-dose chemoradiation or stem cell transplantation.<sup>46</sup> Activation of the coagulation cascade and inflammatory processes following endothelial injury results in a hypercoagulable state. The possibility must always be considered in patients presenting with jaundice, pain or ascites. Many patients will, however, have rather non-specific symptoms or biochemical changes and early CT scanning with contrast may be diagnostic. Early anticoagulation may be life-saving.

### Bowel obstruction

Obstruction usually affects the small bowel or, after pelvic radiotherapy, the sigmoid. Several factors may contribute in individual patients. It may develop as a result of benign causes such as changes in intestinal transit, medical causes (see below), adhesions or radiotherapy-induced fibrosis, or malignant causes such as recurrent cancer or peritoneal carcinomatosis.

### Acute small bowel obstruction

This should be managed conservatively initially with analgesia, intravenous fluids, nutritional support and nasogastric aspiration unless there is suspicion of strangulation requiring emergency surgery. Cross-sectional imaging, which sometimes is difficult to interpret accurately, may be helpful to estimate the level of obstruction and whether it is complete or incomplete. The possibility of multiple sites of partial obstruction needs to be carefully considered as this may limit surgical options.

### Subacute bowel obstruction

Experience suggests that important medical causes include abnormal electrolyte balance, opioid drugs, small bowel bacterial overgrowth, excessive faecal loading, severe fat malabsorption and excessive dietary fibre.

A trial of antibiotics and/or a low-fat diet (if steatorrhoea is present) and/or treatment with a bile acid sequestrant as appropriate may help. If the radiology suggests focal colonic

faecal loading or a colonic site of obstruction or there is iron deficiency anaemia, colonoscopy should be considered. Excess fibre in the diet may precipitate subacute obstruction if a stricture is present. Some patients are very sensitive to opiates and can have prolonged colonic inertia even following small doses.

If low-fibre diets are indicated they should be prescribed by a qualified dietitian, should initially be time limited and the clinical benefit from the diet reviewed. Additional laxatives may be required. Data may emerge for the role of hyperbaric oxygen in treating patients with subacute obstruction due to radiation-induced fibrosis from the national ongoing HOT 2 trial (EudraCT No 2008-002152-26).

Surgery with a view to releasing adhesions or resecting strictures after previous pelvic radiotherapy can be particularly challenging because of dense abdominal fibrosis, and carries significantly higher risks of complications (eg, anastomotic leakages, postoperative intra-abdominal sepsis and intestinal fistulation) than surgery in a non-irradiated patient. Such surgery should be performed only by experienced surgeons with a low threshold for proximal faecal diversion. If an enteric motility disorder is also present (not uncommon), surgery may not lead to resolution of the symptoms.

### Obstruction due to recurrent cancer

If cancer is present, the nature of the intervention should be influenced by the expected prognosis of the recurrence. Selected patients with no ascites, life expectancy >2 months and good performance status may benefit from palliative decompressive surgery, but placement of self-expanding metal stents (if possible) appears to offer a better outcome.<sup>47</sup> Expert medical management with opioids, antispasmodics (eg, hyoscine butyl bromide), antiemetics, antisecretory agents (eg, octreotide), corticosteroids and nasogastric tubes or venting gastrostomies can be effective in helping to control symptoms. Early input from surgeons and palliative care specialists should be sought.<sup>48</sup>

### GI SYMPTOMS: THE CHRONIC SYNDROMES

The GI tract can only respond to pathological processes in a limited number of ways, so different pathological processes may produce identical symptoms. Many patients treated for cancer have other pre-existing illnesses and lifestyles which predispose to cancer and also to chronic GI symptoms after cancer treatments.<sup>16 49</sup> New incidental GI conditions may develop or manifest themselves coincidentally around the time the cancer is treated or thereafter. Patients may be taking medications or have made dietary changes affecting GI function.

There are ample data to suggest that symptom clusters often labelled as 'typical syndromes'—for example, 'bleeding from

#### Chronic syndromes: key facts

- ▶ Symptoms are unreliable at identifying the underlying cause
- ▶ Many cancer treatments have systemic effects and are not limited by normal anatomical boundaries
- ▶ Patients may not report even severe symptoms reliably
- ▶ Patients and clinicians may differ as to what constitute significant symptoms.

proctitis' or 'subacute obstruction due to adhesions'—are unreliable at predicting the true underlying cause of symptoms.<sup>50–55</sup> Part of the reason for this is that many cancer treatments are systemic and do not respect conventional anatomical boundaries. One-third of symptoms confidently attributed to cancer therapy are found after investigation to be unrelated to the cancer treatment.<sup>51</sup> A more valuable approach is to pay attention to the full clinical picture and consider all options.<sup>50 51</sup>

**Incidence and prevalence figures**

GI side effects are underestimated in the literature and within clinical trials.<sup>56–58</sup> Case notes frequently do not record side effects except when patients require surgery as part of their management.<sup>59 60</sup> When prospective data are available,<sup>3</sup> they are invariably based on symptom questionnaires rather than objective markers. Many current questionnaires are inadequately sensitive, do not use reproducible methodology and ignore issues important for patients—for example, severe flatulence or urgency of defaecation.<sup>49 61–65</sup> Focusing on symptoms without confirmatory objective investigations is also potentially misleading. Common bowel disorders produce identical symptoms to those arising as side effects of cancer therapies.<sup>3 49 66</sup> There is an urgent need for better tools which

can be applied in routine clinical practice to measure side effects accurately.<sup>67</sup>

**Clinician, patient and treatment factors**

Some patients will not report symptoms because they are too embarrassed or feel nothing can be done.<sup>10</sup> Clinicians may not understand the significance of patients' symptoms or their relationship to previous cancer treatments or simply ignore them.<sup>61</sup> Health professionals seeing these patients need to develop strategies to identify proactively unexpected symptoms potentially amenable to treatment.

Different problems and rates of late effects occur depending on specific treatments and how they are combined. Table 2 shows the rate and nature of problems for a wide variety of cancers and table 3 shows how different treatments for the same cancer can have different toxicity profiles.

The non-specific nature of these post-treatment symptoms, which often occur in combination, requires a systematic approach to unravel the associated, sometimes complex, clinical causes. In patients attending a specialist clinic for late GI effects after cancer therapy, more than half were found to have more than one cause for their symptoms.<sup>50</sup> For each specific symptom there are a number of potential diagnoses. Using a systematic

**Table 2** Rate and nature of chronic gastrointestinal problems after cancer treatment in patients at different tumour sites

| Cancer site       | Numbers of diagnoses annually in UK | Numbers undergoing treatment with curative intent | Treatment modalities                    | Survival at 5 years after radical treatment | Percentage affected by chronic symptoms affecting quality of life  | Types of chronic GI symptoms  |
|-------------------|-------------------------------------|---|---|---|--|---|
| Oesophago-gastric | 13 000                              | 20%   | Chemotherapy<br>Radiotherapy<br>Surgery | 25–30%                                      | 50% (?)  | Anorexia<br>Diarrhoea<br>Nausea<br>Reflux<br>Weight loss  |
| Pancreas          | 6500                                | 10–15%  | Chemotherapy<br>Radiotherapy<br>Surgery | 14%–25%                                     | N/A  | Malabsorption<br>Weight loss  |
| Colorectal        | 38 600                              | 90%   | Chemotherapy<br>Radiotherapy<br>Surgery | 50%   | Colonic surgery: 15%<br>Rectal surgery: 33%<br>Short-course radiotherapy: 66%<br>Chemoradiation + surgery: 50% | Wind<br>Bleeding<br>Diarrhoea<br>Frequency<br>Incontinence<br>Tenesmus  |
| Anal              | 1000                                | 80%   | Chemoradiation (Surgery)                | 40%–70%                                     | N/A  | Urgency<br>Bleeding<br>Frequency<br>Incontinence  |
| Gynaecological    | 18 000                              | 90%   | Surgery<br>Radiotherapy ± Chemotherapy  | Variable<br>Depending on tumour type        | 40% after treatment which includes radiotherapy  | Urgency<br>Bleeding<br>Diarrhoea<br>Flatulence<br>Frequency<br>Incontinence<br>Malabsorption<br>Pain              |
| Head and neck     | 9000                                | 90%   | Chemoradiation<br>20–25%<br>Surgery     | >50%  | Up to 50%  | Urgency<br>Dysgeusia<br>Dysphagia<br>Dependency on tube feeding<br>Pain<br>Trismus<br>Weight loss                 |
| Urological        | 50 000                              | 80%   | Chemotherapy<br>Radiotherapy<br>Surgery | 75%   | 30% after radiotherapy   | Xerostomia<br>Bleeding<br>Constipation<br>Diarrhoea<br>Flatulence<br>Frequency<br>Incontinence<br>Pain<br>Urgency |

Data compiled from a number of references<sup>3 68–79</sup> see also <http://info.cancerresearchuk.org/cancerstats/types/>

**Table 3** Frequency of chronic toxicity from different treatments for rectal cancer

| Symptoms                 | Surgery alone | Preoperative radiotherapy | Postoperative radiotherapy |
|--------------------------|---------------|---------------------------|----------------------------|
| Any incontinence         | 5–38%         | 51–72%                    | 49–60%                     |
| Toilet dependency        | 6%            | 30%                       | 53%                        |
| Loose stool              | 2–5%          | N/A                       | 25–29%                     |
| Bowel obstruction        | 4–11%         | 5–13%                     | 11–15%                     |
| Excellent bowel function | 32%           | 14%                       | N/A                        |

Data compiled from a number of references.<sup>80–93</sup>

algorithmic approach, there are standard tests which may elucidate the diagnosis or diagnoses causing each specific symptom.<sup>3 50 51 94 95</sup> For each diagnosis made, a number of possible established and experimental therapies are available. Anecdotal evidence suggests that such a systematic approach can improve symptoms by an average of 70–90%. The efficacy of such an algorithmic approach in patients with GI symptoms after pelvic radiotherapy is currently being tested in a large, almost completed, randomised clinical trial (ORBIT study, ISRCTN 22890916).

### HISTORY, EXAMINATION, INVESTIGATIONS AND TREATMENT

To date, there has been no coordinated approach to improve the lot of this group of patients. Health professionals who regularly see these patients—medical and clinical oncologists, GI, urological and gynaecological surgeons, specialist nurses and general practitioners—may not have the expertise to manage these patients' symptoms optimally. However, when they identify patients who need and want help—and table 4 suggests that almost all the patients who would benefit from help can be identified with just three simple questions—they must have an established referral pathway for those patients. Most patients should be referred to gastroenterologists but appropriate referral pathways, either to regional centres or locally, are best developed after discussion within the local cancer multidisciplinary team.

### Managing symptoms

A systematic approach to managing symptoms will only function usefully if a clinician can clearly elicit an accurate history from the symptomatic patient who has often undergone complex multimodal treatments. Many patients do not understand precisely the details of previous cancer treatments, which sometimes have gone on for years and may still be continuing,

#### General management strategies: key facts

- ▶ Gastrointestinal symptoms identified as starting after cancer treatment are frequently not related to the cancer treatment
- ▶ Many patients have more than one cause for symptoms
- ▶ Many cancer treatments are systemic and may cause side effects throughout the gastrointestinal tract
- ▶ Symptoms are unreliable at predicting the underlying cause
- ▶ Inappropriate treatment has a significant potential for causing harm (box 5)
- ▶ Most patients need appropriate investigation before treatment
- ▶ Contacting the oncologists and surgeons for details of previous treatments frequently changes management.

**Table 4** Questions to identify patients in need of specialist assessment

| Critical minimal questions indicating need for GI referral                                  | Critical minimal indicators to consider endoscopic assessment                       |
|---|---|
| Are they woken from sleep to defaecate?   | Is the patient $\geq 5$ years after radiotherapy (screening for second malignancy)? |
| Do they have troublesome urgency of defaecation and/or faecal leakage/soiling/incontinence? | Is there any rectal bleeding?   |
| Do they have any GI symptoms preventing them from living a full life?                       |   |

Data compiled from references<sup>96 97</sup>

and are frequently frightened that any persistent symptom is a manifestation of recurrent cancer. Contacting the oncologists and surgeons at the cancer centre for precise details of previous treatments frequently changes management.

### History

In addition to a detailed history relevant to the GI tract, it is important to remember that, especially after previous pelvic radiotherapy, patients will also often have other urinary, sexual, psychological and occasionally neurological symptoms which influence or are influenced by their GI problems. Bone disease (eg, pelvic insufficiency fractures) and lymphoedema are also common and may also have not been previously detected or dealt with and may be the cause for some or all of their problems.<sup>90 92 98 99</sup>

Dietary habits—excess fibre (from 'healthy eating'), inadequate fibre, alcohol excess or unhelpful nutritional supplements (eg, excess selenium causing nausea, diarrhoea and halitosis)—may contribute to or be the sole cause of chronic GI symptoms surprisingly commonly. Consultations which include input from the patient's partner often improve the quality of the history obtained.

### Examination, investigations and treatment

An appropriate physical examination is required. Basic initial investigations should include haematological and biochemical profiles, inflammatory and tumour markers. In addition, clinical experience and limited published data suggest that a number of other tests are particularly worthwhile in patients who are symptomatic after cancer treatments (box 1).<sup>50</sup>

Specific investigations should be tailored for the principal symptoms and should reflect an understanding of the potential aetiologies. For example, there are at least 13 different causes for diarrhoea after pelvic radiotherapy, most of which require different treatments, and five different causes for new-onset steatorrhoea (table 5).

Faecal incontinence affects up to 50% of patients after rectal cancer and one in five patients after pelvic radiotherapy. Few

#### Box 1 Useful initial investigations

- ▶ Vitamin B12 levels
- ▶ Thyroid function tests
- ▶ Coeliac screen
- ▶ Selenium homocholic acid taurine (SeHCAT) scan
- ▶ Glucose hydrogen/methane breath test
- ▶ Upper GI endoscopy + duodenal aspirate
- ▶ Flexible sigmoidoscopy

**Table 5** Common physical causes for diarrhoea or steatorrhoea after cancer treatment

| Diarrhoea                                    | Steatorrhoea                     |
|--|----------------------------------|
| Bile acid malabsorption                      | Bile acid malabsorption          |
| Carbohydrate malabsorption                   | Free fatty acid malabsorption    |
| Constipation with overflow                   | Intestinal lymphangiectasia      |
| Dietary/alcohol problems                     | Pancreatic insufficiency         |
| Drug side effects                            | Small bowel bacterial overgrowth |
| Endocrine abnormalities                      |                                  |
| Infection                                    |                                  |
| New/recurrent neoplasia                      |                                  |
| New-onset primary inflammatory bowel disease |                                  |
| Rapid transit                                |                                  |
| Short bowel syndrome                         |                                  |
| Small bowel bacterial overgrowth             |                                  |
| Stricture formation                          |                                  |

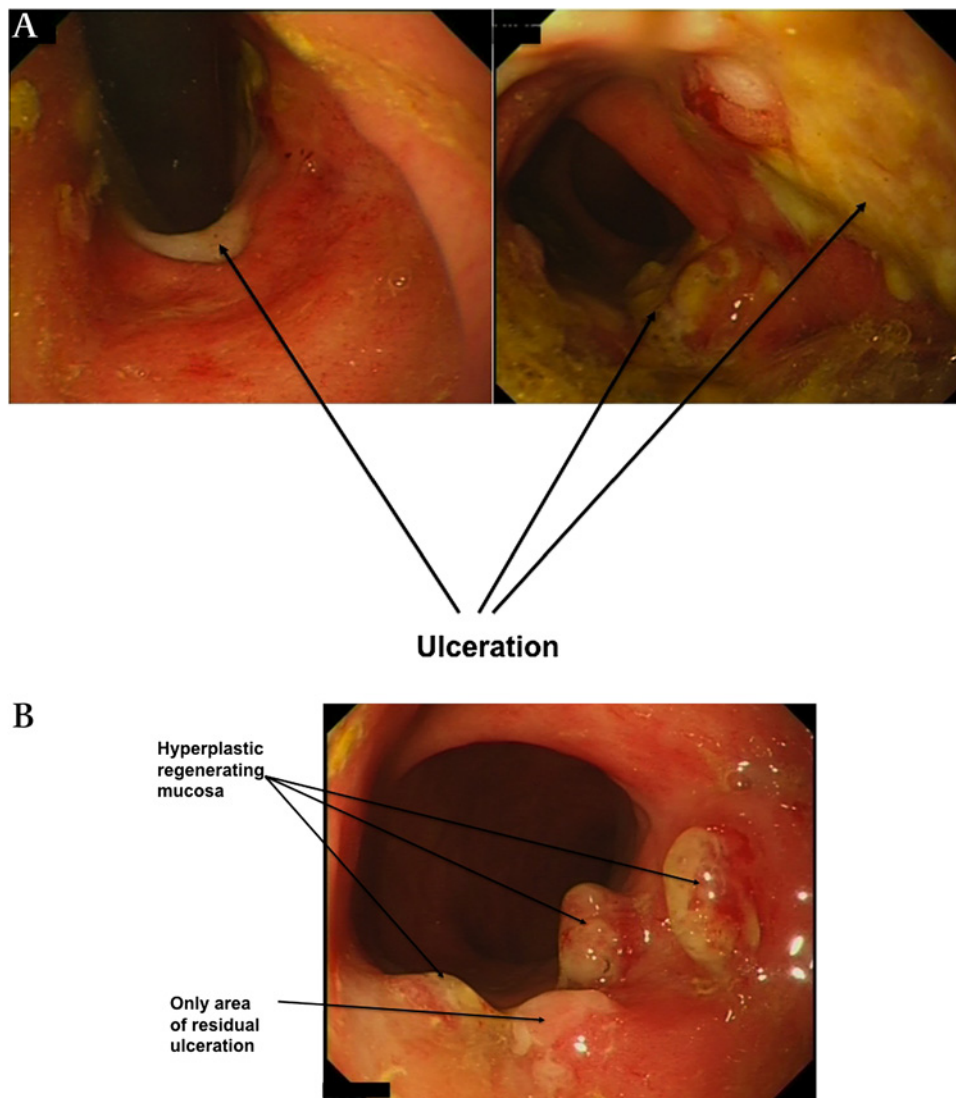
patients are referred for specialist evaluation, let alone support by incontinence services. Most commonly, evaluation is offered by coloproctologists. However, in those who have had pelvic radiotherapy or chemotherapy, faecal incontinence is often at

least partly due to small bowel causes leading to intestinal hurry (especially small bowel bacterial overgrowth and bile acid malabsorption). Appropriate investigations are required when loose stool or erratic bowel function is present, and standard therapeutic approaches to faecal incontinence aimed mainly at local anorectal causes have proved to be ineffective.<sup>61</sup>

### Rectal bleeding from radiation-induced telangiectasia after pelvic radiotherapy

The dose of radiotherapy delivered to the anterior rectal wall determines the risk of bleeding from telangiectasia.<sup>100</sup> Bleeding occurs in 50% of patients after pelvic radiotherapy but impairs quality of life requiring intervention in fewer than 6%. Telangiectases often heal spontaneously over 5–10 years. Patients with any rectal bleeding should be offered at least flexible sigmoidoscopy because of the high prevalence of unexpected pathology. All currently available interventions (endoscopic, surgical and hyperbaric oxygen therapy) for radiotherapy-induced bleeding are not risk-free. The only four treatments with any evidence of benefit in randomised trials (of very variable quality) are sucralfate enemas,<sup>101</sup> 4 weeks of treatment with metronidazole,<sup>102</sup> vitamin A<sup>103</sup> and hyperbaric oxygen therapy (figure 1A,B).<sup>42</sup>

**Figure 1** (A) Painful rectal ulceration following argon beam ablation for radiation-induced bleeding after treatment for prostate cancer. (B) Almost complete resolution of ulceration after 40 sessions of hyperbaric oxygen therapy.





Many gastroenterologists consider that argon plasma coagulation (APC) is the treatment of choice. However, it should be used with considerable caution in this patient group. It is not widely appreciated that the published literature can be interpreted as showing that the serious complication rate for APC when used for radiation proctopathy is potentially as high as 26%.<sup>9–51</sup> Some of these disastrous complications—such as explosions following use of APC in inadequately prepared bowel—are preventable. Others, such as the occurrence of deep ulceration,<sup>104–106</sup> fistulation,<sup>107</sup> stricture formation,<sup>104 108 109</sup> bleeding,<sup>105 106 110</sup> perforation<sup>105</sup> and severe sometimes chronic pain,<sup>110–112</sup> reflect the risk of any thermal therapy in chronically ischaemic tissues. It may be that restricting argon flow rates and wattage and very precise and brief application of the argon catheter would reduce complication rates,<sup>113</sup> but this has not been proved. Anecdotal evidence suggests that, where bleeding is heavy, APC frequently fails. In specialist centres, serious complications of previous APC treatment in this patient group continue to be seen regularly.

The other treatment commonly prescribed is regular application of corticosteroid enemas. The evidence from randomised trials suggests minimal or no benefit from their use.<sup>114</sup> This is unsurprising as the chronic pathophysiology of radiation-induced damage is largely ischaemic and not inflammatory.<sup>24</sup> If topical treatment is used, sucralfate enemas (box 2) are clearly more effective than corticosteroid enemas.<sup>114</sup>

All the options for treatment of radiation-induced telangiectasia are listed in table 6. Evidence for long-term outcomes from any of the treatments is very scanty.

In the absence of any comparative studies of the various major treatment modalities of radiation-induced rectal bleeding, one clinical approach for patients with radiation-induced rectal bleeding which reduces risk to a minimum is as follows:

Step 1: Investigate with flexible endoscopy to determine the cause of the bleeding.

Step 2: Optimise bowel function and stool consistency which may reduce the amount of bleeding.

Step 3: If bleeding is not affecting quality of life (eg, staining clothes, causing anaemia, interfering with daily activities), reassure and do nothing further.

Step 4: If bleeding affects quality of life, stop/reduce anti-coagulants if possible and, if very severe, start sucralfate enemas (box 2),

Step 5: Discuss definitive treatment to ablate the telangiectasia with the patient; current options include:

### Box 2 Making up and using sucralfate enemas

#### 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 twice a day into the rectum
- ▶ Retain the enema for as long as possible
- ▶ Initially roll through 360° to coat the entire rectal surface
- ▶ Lying prone then best covers anterior wall rectal telangiectasia, the likely area of greatest bleeding

**Table 6** Therapeutic options for radiation-induced rectal bleeding

| Treatment modality                  | Comments  |
|-------------------------------------|---|
| Medical therapies                   |   |
| Sucralfate enemas                   | 1 RCT, <sup>101</sup> several case series   |
| Metronidazole                       | 1 RCT <sup>102</sup> used for 4 weeks in combination with corticosteroids and mesalazine (these last two agents probably ineffective if used alone). Possibly contraindicated if patient has already developed chemotherapy-induced peripheral neuropathy |
| Vitamin A (retinol palmitate)       | 1 small RCT <sup>103</sup> and no endoscopic assessment performed   |
| Sulfasalazine                       | Case series   |
| Thalidomide                         | Case report   |
| Short chain fatty acids             | Inconclusive RCT <sup>115</sup>   |
| Rebampide enema therapy             | Case series (not available in the UK)   |
| Other therapies                     |   |
| Hyperbaric oxygen treatment         | 1 RCT, <sup>42</sup> several case series  |
| Endoscopic laser ablation           | Multiple case series, different lasers used.  |
| Endoscopic argon plasma coagulation | Multiple case series, serious complication rate 7–26%   |
| Endoscopic formalin application     | Multiple case series, outcomes poorly assessed  |
| Surgical application of formalin    | Multiple case series, outcomes poorly assessed  |

Other references.<sup>6 7 116</sup>

RCT, randomised controlled trial.

- a. hyperbaric oxygen therapy (advantages: supported by RCT evidence, may reverse progressive changes caused by radiotherapy, may improve other symptoms such as urinary problems; disadvantages: time-consuming (8 weeks of daily treatment), expensive and patients may need to travel long distances to their nearest unit);
- b. argon plasma coagulation (advantages: easily available and simple; disadvantages: significant risk and unproven efficacy in heavy bleeding);
- c. formalin therapy (advantages: simple to perform; disadvantages: long-term outcomes poorly known, small risks of serum sickness, severe proctitis or chemical burn to the skin if there is spillage).

### Dysphagia/retching/nausea after cancer therapies including upper GI surgery

This is a common cause for referral. A suggested approach is given in table 7. Clinical experience suggests that gastric bile reflux and small bowel bacterial overgrowth are commonly forgotten causes of nausea in patients during and after cancer therapy. Strictures are often found on endoscopy and an approach to stricture management in the upper GI tract is shown in table 8. If nausea and vomiting persist after metabolic causes have been excluded, endoscopy with or without radiology have revealed no cause and trials of routine therapy have not helped, a brain scan should be considered.

### Dumping syndrome

When gastric emptying is rapid it leads to 'dumping syndrome', characterised by GI and vasomotor symptoms that occur after meals. This can be soon after meals or delayed for up to several hours. The physiological causes are complex, but include the high osmolarity of small bowel contents and reactive hypoglycaemia. The diagnosis of early dumping is usually made on clinical grounds, although rarely gastric scintigraphy is helpful. Late dumping can be diagnosed by measuring blood glucose when patients are symptomatic. If the presentation is atypical, the rare possibility of an insulinoma should be considered. Initial management should be dietary advice to reduce the volume and

**Table 7** Investigation and management of dysphagia/retching

| Investigations of choice                | Differential diagnosis                                    | Therapeutic options  |
|---|---|--|
| CT+PET scan±endoscopy                   | Tumour progression/recurrence                             | Refer back to MDT  |
| Endoscopy                               | Benign stricture  | Dilation±self-expanding plastic/removable metal stent, long-term acid/bile suppression, dietetic advice/enteral feeding tube   |
|   | Inflammatory (acid/bile/pepsin-related)                   | Sucralfate/proton pump inhibitor/promotility agents  |
|   | Infection (fungal/viral small bowel bacterial overgrowth) | Specific antibiotic  |
| Radiological contrast swallow±endoscopy | Spasm/abnormal peristalsis                                | Calcium channel antagonists, low-dose antidepressants  |
|   | Dysmotility/reflux/slow transit through upper GI tract    | Sucralfate/proton pump inhibitor/promotility agents (domperidone, low-dose erythromycin (250 mg bd), paroxetine, subcutaneous naloxone), dietetic advice, enteral feeding tube |

MDT, multidisciplinary team; PET, positron emission tomography.

osmolarity of food presented to the small intestine and the avoidance of fluids taken with meals. Loperamide, guar gum or pectin to slow gastric emptying may be helpful. For late dumping, acarbose may sometimes help. Octreotide or lanreotide are helpful in the short term. Studies have shown mixed results when these drugs were evaluated longer term. Surgical revision of the roux-en-Y anastomosis is a complex procedure but can be effective in selected cases.

### ROLE OF HEALTH PROFESSIONALS IN THE LATE EFFECTS TEAM

Cancer clinical nurse specialists (CNS) are ideally placed to undertake the end of treatment assessment with the patient. The CNS is usually in contact with the patient throughout their cancer journey. They undertake a key role in the liaison with all members of the multidisciplinary team as well as care providers in the community or referring units. They will be available to offer support and information to patients and their carers and increasingly take on a 'key worker' role ensuring the smooth running of the patient pathway.

The CNS is an autonomous practitioner who may run their own nurse-led clinics during treatment or in follow-up and many continue to develop their role, taking on advanced assessment and prescribing as part of their practice. They should encourage patients to seek help for any new symptoms. It is essential that they are able to recognise those with ongoing effects of their therapy so they can identify them to the oncologist and to support referral for gastroenterological opinion.

Patients who are well informed about their disease and its treatment, the possible effects they may experience and services available to help and support them have a greater chance of achieving a better quality of life within the constraints of their

condition. Many sources of information are available to patients, but they may need direction to information that is of a high quality and is relevant to them; they may need help to interpret the information. They should be offered information in a language and format that is acceptable to them so that they can make decisions regarding their care and condition where possible. It may also be helpful to direct patients to local support groups where they exist.

Specialist dietetic help is often required (boxes 4 and 6). Weight loss and weight gain (the metabolic syndrome) can be problems after cancer treatment. However, new groups at risk are frequently being defined. As many as 40% of patients with metastatic colorectal cancer at presentation have lost significant amounts of weight and have not regained it at 1 year.<sup>118</sup> About 10% of patients develop very severe toxicity (mostly bowel toxicity) after chemoradiation for cervical cancer, which can lead to significant nutritional issues.<sup>119</sup>

Often these patients have complex causes for their symptoms which need multiple investigations by the gastroenterologist,<sup>51</sup> and then joint management by the gastroenterologist and dietitian (box 3) which may include dietary fibre manipulation, reduced fat diets and changes in carbohydrate intake, especially lactose and fructose. In these patients, dietary adequacy and mineral and vitamin status are often compromised and need formal assessment and, if necessary, treatment with dietary advice or specific micronutrient supplements.

### Box 3 An approach to other common problems after pelvic radiotherapy

#### Mucus discharge/leakage

- ▶ Ensure that fibre intake is not excessive
- ▶ Provide pelvic floor and toileting exercises
- ▶ Stool bulking agent and/or antidiarrhoeal agent

#### Excess rectal flatulence

Consider:

1. Dietary: excess/deficiency of fibre intake and inadequate fluid intake
2. Colonic faecal loading
3. Small intestinal bacterial overgrowth
4. Organic cause (eg, neoplasia, inflammatory bowel disease)

**Table 8** Endoscopic management of oesophageal strictures<sup>117</sup>

| Nature of stricture          | Advice  |
|------------------------------|---|
| Anastomotic/tumour/radiation | Should be performed only by experienced endoscopists<br>If tumour is present, endoscopic intervention should only occur after MDT discussion<br>Dilate to a maximum diameter of 15–20 mm<br>Dilate for 20–60 s if using a balloon<br>Dilation >12 mm not required for stent insertion<br>Do not exceed diameter of the stricture by >7–8 mm per session<br>Risks are increased after chemotherapy/radiotherapy/if tumour is present<br>Temporary/permanent stent placement may be required after dilation |

**Box 4 Research priorities****Important research themes**

- ▶ How are patients with chronic GI effects of cancer therapies best detected?
- ▶ What are the best objective tools to measure the severity of chronic gastrointestinal problems?
- ▶ What are the best objective biomarkers of damage to non-cancerous tissues?
- ▶ What are the frequency and nature of chronic GI symptoms after different cancer treatments which affect patients' day to day activities?
- ▶ How can quality of life scores be used to quantitate ongoing symptoms?
- ▶ Who should manage chronic symptoms?
- ▶ By what stage should patients be referred for specialist evaluation?
- ▶ What treatments work for late side effects?
- ▶ How are chronic side effects best prevented?

**Important achievable clinical trials which are urgently required**

- ▶ Randomised trials of optimal therapy for faecal incontinence/anterior resection syndrome after surgery
- ▶ Randomised trials of conservative treatment versus hyperbaric oxygen/argon plasma coagulation/intrarectal formalin for radiation-induced bleeding
- ▶ Randomised trials of nurse-led management versus doctor-delivered care for GI late effects
- ▶ Randomised trials of promotility agents for gastroparesis after upper GI surgery
- ▶ Randomised trials of antifibrotic agents soon after completion of radiotherapy to ameliorate chronic progressive fibrosis and hence symptoms
- ▶ Randomised trials of PEG feeding versus nasogastric tube feeding to prevent chronic feeding problems in patients undergoing treatment for head and neck malignancy

**High quality clinical series which will quickly impact clinical outcomes**

- ▶ What are the physiological abnormalities which accompany chemotherapy-induced diarrhoea (eg, lactose intolerance, bile acid malabsorption, small bowel bacterial overgrowth)?
- ▶ Small bowel bacterial overgrowth after cancer treatment, what organisms and when?

**Important unanswered questions**

- ▶ Outcomes of low-fibre diets for intermittent small bowel obstruction
- ▶ Role of low-fat diets in patients with steatorrhoea

**CONCLUSIONS**

Substantial progress has been made in treating cancer. However, there are convincing and consistent data that large numbers of people have chronic physical morbidity after cancer treatment which commonly affects the GI tract and impacts adversely on daily activities. There is a professional obligation to identify systematically patients with such unmet needs and to develop appropriate referral pathways where they do not currently exist.

This multidisciplinary guidance is designed to help those clinicians who wish to understand better the underlying pathology and current management options for physical symptoms. It is hoped that it may form the starting point for multidisciplinary team discussions to enhance care for these patients and for educational programmes for trainees who need to know how to manage these issues. Systematic education about the optimal management of severely symptomatic

**Box 5 Clinicians beware!****Clinicians beware!**

- ▶ Fixed, impassable and easily perforated sigmoid on endoscopy in patients with gynaecological cancer after combination chemotherapy + radiation ± surgery.
- ▶ Endoscopic biopsy of the anterior rectal wall in patients who have had brachytherapy is associated with a 2% rate of fistula formation
- ▶ Mesalazine exacerbates acute radiation-induced intestinal inflammation
- ▶ There is minimal chronic inflammation after radiotherapy so corticosteroids have no role in the management of chronic symptoms
- ▶ Patients with steatorrhoea are usually misdiagnosed as having diarrhoea
- ▶ Hepatic veno-occlusive disease is an emergency
- ▶ Small bowel bacterial overgrowth can cause any GI symptom including subacute obstruction
- ▶ Tissues which have been exposed to radiation may not heal normally after biopsy or polypectomy
- ▶ Endoscopic or surgical intervention in irradiated tissues is an intervention within a potentially ischaemic field
- ▶ There is a reported rate of serious complications of 7–26% for argon beam ablation of rectal radiation-induced telangiectasia
- ▶ Only two treatments have been shown with any degree of conviction in controlled trials to be effective for radiation-induced rectal bleeding from telangiectasia: sucralfate enemas and hyperbaric oxygen therapy
- ▶ Don't forget common medical causes of recurrent subacute obstruction
- ▶ Low levels of faecal elastase only diagnoses pancreatic insufficiency reliably after small bowel bacterial overgrowth has been excluded

### Box 6 Dietetic requirements for patients after cancer treatment

- ▶ Patients should be managed by registered dietitians
- ▶ Implement a time-limited trial of dietary changes
- ▶ Routinely assess patients with malabsorption for dietary adequacy
- ▶ Do not prescribe long-term dietary restriction(s) that provide no benefit
- ▶ Monitor nutritional status (weight, anthropometry, vitamin and trace element levels)

patients is sorely lacking, despite the fact that the number of affected patients in the UK currently equals the number of patients diagnosed annually with primary inflammatory bowel disease, and is increasing by 3% per year. This patient group can undoubtedly gain substantial benefit from a more coherent approach to care for their ongoing and often disabling and distressing symptoms.

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