Gastrointestinal symptoms after pelvic radiotherapy: a new understanding to improve management of symptomatic patients

Jervoise Andreyev

Gastrointestinal symptoms after pelvic radiotherapy, which affect quality of life, are substantially more common than generally recognised and are frequently poorly managed. These symptoms develop because radiation can induce change in one or more specific physiological functions in widely separated parts of the gastrointestinal tract that lie in the path of the radiotherapy beam. Radiation-induced changes are not confined by normal anatomical boundaries. Furthermore, pre-existing subclinical disease might be destabilised because of minor gastrointestinal changes induced by radiotherapy. New diseases might manifest after radiotherapy and be confused with symptoms induced by radiotherapy. Different functional deficits might cause the same symptoms. Many patients have more than one cause for their symptoms, which sometimes need very different treatments. Simple diagnostic tests that are used in other contexts, if applied appropriately to patients with new gastrointestinal symptoms after radiotherapy, can identify the underlying causes of new-onset symptoms. Starting treatment without knowing the cause of the symptom is commonly ineffective because prediction of the combination of treatments needed is difficult. Evidence suggests that many patients have unusual but highly treatable malfunctions of gastrointestinal physiology, which if correctly diagnosed may enable a patient with difficult symptoms to be helped.

Introduction

Researchers have investigated the effects of radiotherapy on some of the complex neurological, hormonal, muscular, immune, and enzyme functions of the human gastrointestinal tract, although definitive studies are few. Almost all information about the cellular and molecular response of the gastrointestinal tract to radiotherapy is derived from animal experiments. However, the relevance of animal studies is unclear because different animals respond to identical irradiation differently and because the doses delivered might not be comparable to those given to humans.

The available data suggest a sequelae of events where oedema progresses to an inflammatory, mainly mucosal, reaction that later extends to the submucosa. These events stimulate regenerative processes, which either induce mucosal repair or develop into severe inflammation with ulceration, finally producing fibrosis. These changes are mediated by a cytokine cascade, which might persist for decades.

Most patients starting pelvic radiotherapy will have normal gastrointestinal function apart from local tumour effects. During radiotherapy, normal tissues that surround the tumour will be exposed to some radiation (figure 1). The rectum and sigmoid are in close physical proximity to the tumour being treated and are at particular risk. The caecum is fairly fixed and may receive a sizeable dose. The transverse colon and small bowel frequently loop down into the pelvis and are at risk, so too is the proximal small bowel and pancreas when para-aortic nodes are irradiated.

Injury to the gastrointestinal tract depends on the type of radiotherapy given, the dose delivered to tissues, the way it is delivered, and how radiation energy dissipates through tissues. Specific doses that lead to an unacceptable risk of macroscopic pathological change in different parts of the gastrointestinal tract are well established. However, neither the doses of radiotherapy that will lead to permanent changes in gastrointestinal physiology, nor which patients are excessively sensitive to radiotherapy because of abnormal DNA-repair genes, are known. Furthermore, smoking; previous abdominal surgery; concomitant chemotherapy; and disorders such as diabetes, hypertension, pelvic inflammatory disease, HIV, connective-tissue disorders, and inflammatory bowel disease may increase the risk of acute and chronic problems after pelvic radiotherapy. There are no adequate data for the degree of risk posed by any of these factors.

Figure 1: Typical endoscopic appearance of radiation-induced telangiectasia in a patient with intermittent rectal bleeding after prostate irradiation

Changes are more marked on anterior rectal wall, which directly overlies the prostate.
The hypothesis underlying this review is that symptoms arise after pelvic radiotherapy because of changes to normal gastrointestinal physiology that are induced by radiotherapy. Although at present pathological changes caused by radiotherapy cannot be reversed, there is no reason why symptoms cannot be treated through identification and correction of physiological deficits that are induced by pathological changes. Here, I will discuss the changes induced in gastrointestinal physiology after pelvic radiotherapy, what symptoms these cause, and possible treatments for these acquired disorders of physiology. I aim to challenge clinicians to adopt a more-positive approach to the management of gastrointestinal symptoms that start after pelvic radiotherapy.

**Acute and chronic symptoms**

Acute changes in gastrointestinal physiology can occur in any part of the gastrointestinal tract that is exposed to radiotherapy. Some changes may lead to clinical symptoms; others remain subclinical. Symptoms tend to start during the second week of treatment (when histological change is probably at a maximum) and peak by the fourth to fifth week (when histological changes are stable or improving). Chronic radiation-induced toxic effects are substantially more common than generally recognised. 90% of patients given pelvic radiotherapy may develop a permanent change in their bowel habit after treatment; 50% may have their quality of life affected by gastrointestinal symptoms, and 20–40% (depending on tumour type) rate the effect on quality of life as moderate or severe. These data derive from patient-centred retrospective studies because there are almost no prospective studies that have assessed accurately the severity of long-term gastrointestinal toxic effects.

Figure 2 shows how radiotherapy can induce gastrointestinal symptoms. However, gastrointestinal symptoms might start for reasons other than direct radiotherapy-induced damage. For instance, the psychological effect of cancer and its treatment, or new minor gastrointestinal changes induced by radiotherapy might chronically destabilise pre-existing clinical or subclinical gastrointestinal problems. Moreover, new gastrointestinal disease might develop that is unconnected to radiotherapy.

Different pathological processes can produce identical symptoms. For example, diarrhoea after radiotherapy is triggered by 13 different mechanisms, reflecting changes in widely separate parts of the gastrointestinal tract. Patterns of symptoms might not define accurately the underlying cause probably because radiation does not adhere to anatomical boundaries. Starting treatment without knowing the cause of the symptom will frequently be ineffective because treatment for different causes of the same symptom vary widely and because the symptoms might not easily predict the cause.

Table 1 shows self-reported gastrointestinal symptoms that patients develop after pelvic radiotherapy. The way symptoms are elicited and recorded may determine the results obtained. People who do not have cancer will also have these symptoms, but few studies control for this factor. Most of these data are from retrospective studies and thus reflect the inherent biases of data obtained in this way. However, the frequency with which some symptoms affect patients’ quality of life is striking (table 1). If these symptoms developed in patients who have not had radiotherapy, they would be investigated and managed logically. Yet, most patients who have had pelvic radiotherapy are not referred for investigation on the development of gastrointestinal symptoms.

**Causes and management of symptoms**

### Loose stool or diarrhoea

Although psychological factors may contribute to episodes of loose stool after pelvic radiotherapy, specific physiological problems can commonly be defined, including small-bowel bacterial overgrowth, bile-salt malabsorption, carbohydrate malabsorption, changes in transit, development of strictures, neoplasia, or new-onset primary inflammatory bowel disease.

**Bacterial overgrowth**

Small-bowel bacterial overgrowth occurs in 25% of patients (Andreyev HJN, unpublished data) during the acute phase of radiotherapy. In the chronic setting, motility changes caused by radiotherapy are the main cause of such overgrowth—particularly that of gram-negative bacilli, which in 4–45% patients may cause various gastrointestinal symptoms. Three studies suggest that in 8–15% of patients with diarrhoea, the diarrhoea is caused by bacterial overgrowth and improves after antibiotic treatment.
Reliable diagnosis of bacterial overgrowth is difficult. Diagnostic techniques include breath tests, direct culture of small-bowel contents, or determination of bile-salt products in the blood. Some patients have low vitamin B12 levels, which normalise once bacteria are eradicated.

Optimum strategies for the management of bacterial overgrowth are not defined. Antibiotics with gram-negative activity, used for up to 2 weeks, may abolish symptoms within a few days of starting treatment. However, symptoms can recur any time after antibiotics are stopped—from a few days to many years later—because the underlying cause of bacterial overgrowth has not gone away. If symptoms return, retreatment with antibiotics might help. In patients with recurrent symptoms, use of antibiotics for a few days every month, or continually at the lowest effective dose, might be effective.

Sometimes advocated but unproven and off-label treatment for bacterial overgrowth includes the use of probiotics, prebiotics, promotility agents (eg, paroxetine or acupuncture), or dietary manipulation to change the small-bowel environment and reduce the potential for bacteria to thrive.

| Bile-salt malabsorption | Up to half of patients who develop diarrhoea acutely during radiotherapy will have bile-salt malabsorption because of a direct effect on the mechanisms of bile reabsorption; accelerated transit that reduces bile absorption; or colon damage that exacerbates symptoms. After radiotherapy, a chronic reduction in bile-salt malabsorption is common, but does not cause symptoms in most patients. Whether bile-salt malabsorption is a common cause of chronic diarrhoea is unknown. Four small retrospective studies (with a total of 69 patients) reported bile-salt malabsorption in 50–83%. However, a study from our unit that assessed 78 patients with chronic diarrhoea found only 1% incidence of bile-salt malabsorption. Possible reasons for this discrepancy are patient selection, definitions of diarrhoea, methods for identification of bile-salt malabsorption, or differences in planning of radiotherapy fields by oncologists such that patients treated in different centres present with a different range of symptoms. The gold standard for measurement of bile-salt malabsorption is the SeHCAT (selenium 75 homo-cholic acid conjugated with taurine) scan. Other methods of | See Online for webappendix |

### Table 1: Frequency and range of gastrointestinal symptoms reported after radical pelvic radiotherapy

<table>
<thead>
<tr>
<th>Gyneacological cancer</th>
<th>Rectal or anal cancer</th>
<th>Urological cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rectal bleeding</strong></td>
<td>23–26%</td>
<td>23–25%</td>
</tr>
<tr>
<td><strong>Bloating</strong></td>
<td>12–45%</td>
<td>13–32%</td>
</tr>
<tr>
<td><strong>Change in bowel habit</strong></td>
<td>75–89%</td>
<td>38–93%</td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td>21%</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Abdominal cramps</strong></td>
<td>12%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Diarrhoea (loose or soft stool)</strong></td>
<td>52%</td>
<td>5–60%</td>
</tr>
<tr>
<td><strong>Faecal incontinence</strong></td>
<td>25–47%</td>
<td>7–60%</td>
</tr>
<tr>
<td><strong>Excessive flatulence</strong></td>
<td>23–50%</td>
<td>14–59%</td>
</tr>
<tr>
<td><strong>Increased frequency of defaecation</strong></td>
<td>56%</td>
<td>5–39%</td>
</tr>
<tr>
<td><strong>Inability to differentiate solid from liquid stool or gas</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Lactose intolerance</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Mucus discharge</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Nausea</strong></td>
<td>10%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nocturnal defaecation</strong></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Pain (abdominal, rectal, anal, or perineal)</strong></td>
<td>14–52%</td>
<td>13–27%</td>
</tr>
<tr>
<td><strong>Sexual activity curtailed by bowels</strong></td>
<td>11%</td>
<td>5%</td>
</tr>
<tr>
<td><strong>Tenesmus</strong></td>
<td>14–21%</td>
<td>13–46%</td>
</tr>
<tr>
<td><strong>Defaecation urgency</strong></td>
<td>48–53%</td>
<td>14–57%</td>
</tr>
<tr>
<td><strong>Vomiting</strong></td>
<td>14%</td>
<td>0</td>
</tr>
<tr>
<td><strong>Weight loss</strong></td>
<td>0–83%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data are reported by patients (refs 76–84 are listed in webappendix) more than 3 months after radiotherapy for various gynaecological cancers, rectal cancers, anal cancers, or urological cancers. Data exclude symptoms such as depression, sexual dysfunction, or sleep disturbance, which may be associated partly with problems of the gastrointestinal tract and can have profound effects on quality of life. NA=not available. Appetite loss, fat intolerance, inability to differentiate the need to defaecate from micturition, steatorrhoea, unpredictability, and weight gain are also symptoms that have been reported by patients, but frequencies of these reportings are not available.
Review

measurement include breath tests, measurement of bile-acid concentrations, their precursors, or their breakdown products in serum or stool. Low vitamin B12 concentrations are a highly predictive, but not very sensitive, indicator of bile-salt malabsorption.

Bile-salt malabsorption responds to a diet that is very low in fat (ie, 10–15 g per day)29 or one that is rich in medium-chain triglycerides.26 However, these diets are difficult to maintain. Regular use of antidiarhoeal drugs such as loperamide or codeine phosphate, especially if taken 30–60 min before eating, may improve symptoms. Many patients do not find that dietary manipulation or antidiarhoeal drugs abolish unpredictable bouts of diarrhoea. Several series11,12,14,23,25,27 suggest that patients benefit from regular use of bile-acid sequestrants. Most of these data are for use of colestyramine; 4 g twice a day is usually enough. Several days are commonly needed before the benefit becomes apparent. One in four people cannot tolerate bile-binding resins. An effective and well tolerated alternative is colesevelam,29 which is not licensed as a bile binder but effectively treats hyperlipidaemia through a mechanism that includes the binding of bile in the gastrointestinal tract. Another possibility, if available, is cellulose acetate enteric coated colestyramine.30

All bile-acid sequestrants might cause deficiency in fat-soluble vitamins (ie, A, D, E, and K) and might elevate serum triglyceride concentrations. Therefore, long-term users of these agents should be monitored. Patients with bile-salt malabsorption who have a small-bowel length of less than 1 m might have depletion of their total bile-salt pool, in which case bile-acid sequestrants might exacerbate diarrhoea or precipitate steatorrhoea; chole-sarcosine is an alternative option.30

**Carbohydrate malabsorption**

De-novo lactose malabsorption occurs in 50% of patients by the fourth week of pelvic radiotherapy.31 The severity of malabsorption correlates with the length of small bowel irradiated.31 New-onset lactose malabsorption persists in about 5% of patients and frequently causes diarrhoea.13,29 Other brush-border enzymes with a role in final carbohydrate hydrolysis to monosaccharide units could be affected. In adults who have not had radiotherapy, malabsorption of disaccharide carbohydrates causes severe bloating and diarrhoea. Damage to monosaccharide-transport proteins on the luminal side of gut enterocytes could also affect absorption.

Investigation of carbohydrate malabsorption can include stool chromatography, oral-tolerance tests that measure blood or breath responses, use of isotope-labelled carbohydrate, and direct biopsy proof of enzyme deficiency. Dietary advice to avoid the unabsorbed sugars, which could include one or more of lactose, fructose, sucrose, and starches is needed and should be given by a qualified dietician because diets can be complex and lactose avoidance changes calcium intake, which might affect bone health.

**Changes in gastrointestinal transit**

Increased intestinal transit frequently occurs during pelvic radiotherapy. Whether small-bowel transit remains abnormally rapid after the end of radiotherapy or returns to pretreatment speeds is controversial. Two further studies38,39 have described the development of pseudo-obstruction in patients with severe late enteropathy (probably because of degeneration of the myenteric plexus). An interesting study,40 possibly compromised by its small size and validity of the diarrhoeal scoring tool used, found no association between diarrhoeal score and large-bowel injury, suggesting that other factors such as changes in transit might be important. However, another study41 suggested that small-intestinal transit is unimportant (unless the small bowel is substantially shortened) because faecal weight after ileal resection does not correlate with length of ileum resected, but with the amount of colon removed.

The investigation of transit or motility in the small bowel are of little clinical value in the management of most patients. Opioids taken 30–60 min before meals slow transit. Rotation of antibiotics might reduce the frequency of obstructive episodes in patients with pseudo-obstruction.

**Other possible causes of radiotherapy-related diarrhoea**

Other causes of diarrhoea include: large-bowel strictures (3–15% of patients with diarrhoea after pelvic radiotherapy); small-bowel strictures (9%); disease relapse (4–10%); new neoplasia in the gastrointestinal tract (8%); new-onset inflammatory bowel disease (ie, Crohn’s disease, or ulcerative, lymphocytic, or collagenous colitis—4%); or radiation proctopathy (33%).11,115

Strictures sometimes benefit from dilatation or stenting (although the risks of both procedures can be substantial), surgery, or hyperbaric oxygen therapy to try to modify the fibrotic process. Gastrointestinal polyps should be considered for endoscopic removal. Endoscopic surveillance should probably be discussed with all patients 5 years after radiotherapy. Large studies have concluded that after radiotherapy there is a significant risk of secondary colon cancer and rectal cancer;97 rectal (but not colon) cancer;116–118 or either rectal cancer or colon cancer but only in parts of the gastrointestinal tract that were included in the radiation field. To my knowledge, only one study119 has not identified any increased risk of colon cancer or rectal cancer, or both, after radiotherapy. New-onset inflammatory colitis needs standard treatment.

If, after investigations, no abnormality is noted (except chronic radiation proctopathy) no treatment strategies seem to be beneficial.42 Topical corticosteroids, although frequently prescribed, rarely help because inflammation is not a major feature. A small double-blind randomised trial43 assessed patients who reported symptoms related to proctopathy. Patients were randomly allocated without
further investigation to retinol palmitate or placebo, and a significant improvement in symptoms was seen in the treatment group. Hyperbaric oxygen might benefit patients with proctopathy. Toileting exercises, with or without regular use of a poorly fermented bulking agent (sterculia in preference to ispaghula) or loperamide, or both, might help. Off-label tricyclic antidepressants in low dose might reduce urgency. As a last option, stoma formation may be considered when rectal volume is severely reduced and medical management has failed.

**Causes of diarrhoea unrelated to radiotherapy**

Side-effects of drugs, poor diet, alcohol excess, constipation with overflow, thyroid dysfunction, and coeliac disease are frequent causes of diarrhoea, especially in elderly people. This situation is likely to be the same in those with cancer. Many people who have had cancer treatment decide to eat healthily and consume very large amounts of fibre, which precipitates their symptoms. It is essential not to be constrained by diagnostic labels previously attached to patients (commonly on the basis of inadequate investigation) and to consider all options.

In some patients, drugs with constipating side-effects (eg, verapamil or granisetron) help. Clays (eg, smectites), activated charcoal, or proabsorptive agents such as clonidine might help. In some countries, tincture of opium is used when other antidiarhoeal agents are ineffective. If a patient has functional short-bowel syndrome (and therefore diarrhoea), specific dietary changes may be worthwhile.

**Steatorrhoea**

Steatorrhoea is loose stool caused by the presence of excessive undigested fat (ie, >0.3 g per kg a day), which gives stool a grey, pale, greasy, putty-like appearance and sometimes leaves an oily pattern in the water of the lavatory pan; it is not well differentiated from diarrhoea by patients sometimes leaves an oily pattern in the water of the lavatory and is not well differentiated from diarrhoea by patients. Steatorrhoea causes un-. Faecal incontinence, urgency, tenesmus, mucus discharge, and frequency of defaecation. In some patients, drugs with constipating side-effects (eg, verapamil or granisetron) help. Clays (eg, smectites), activated charcoal, or proabsorptive agents such as clonidine might help. In some countries, tincture of opium is used when other antidiarhoeal agents are ineffective. If a patient has functional short-bowel syndrome (and therefore diarrhoea), specific dietary changes may be worthwhile.

**Radiation-induced pancreatic insufficiency**

The pancreas is thought to be fairly radioresistant. However, chronic pancreatic insufficiency can develop after pancreatic irradiation. Invasive tests of pancreatic function are rarely justified. The preferred non-invasive test is measurement of faecal elastase in a stool sample. The pancreas might seem completely normal on magnetic resonance cholangiopancreatography, even in the presence of severe radiotherapy-induced pancreatic insufficiency. Treatment is with pancreatic supplements and long-term, full-dose acid suppression.

**Free-fatty-acid malabsorption**

Malabsorption of free fatty acids occasionally occurs after small-bowel irradiation and might be related to the development of lymphangectasia (which is rarely the only cause of steatorrhoea). A low-fat diet (ie, 20–30 g a day), or occasionally a diet rich in medium-chain triglycerides, is needed in addition to optimum treatment of other causes of steatorrhoea.

**Other causes**

The sampling of blood to exclude other infrequent causes of steatorrhoea (eg, thyroid dysfunction, Addison’s disease, and coeliac disease) is inexpensive. 1% of patients referred for radiation-induced symptoms in our series had no evidence of radiation-induced toxic effects on investigation, but had undiagnosed hyperthyroidism.

**Faecal incontinence, urgency, tenesmus, mucus discharge, and frequency of defaecation**

A systematic review addresses the frequency, causes, and management of faecal incontinence after pelvic radiotherapy. Of all gastrointestinal symptoms that can occur after radiotherapy, faecal incontinence causes the greatest distress; however, it is the most difficult symptom for patients to discuss.

Little attention is paid to the issue of urgency of defaecation. However, the fear that defaecation cannot be deferred can be extremely socially incapacitating; patients can become housebound. Tenesmus commonly occurs when patients have urgency, and frequently these patients mention prominent mucus discharge.

Frequency of defaecation might be subjective and needs careful inquiry to understand what the patient means. Some patients might be disturbed by trivial changes in their life-long bowel habit (eg, twice a day rather than once a day) if they are not informed of this probable change after treatment. Others might label loose stool as frequency of defaecation, or vice versa. Some patients describe tenesmus as defaecation frequency. Clarification of the volume of stool passed on so-called frequent occasions may be instructive. Changes in stool consistency, reduced rectal volume, psychological issues, inflammation, or neoplasia in the lower gastrointestinal tract might increase the frequency of defaecation.
Table 2: Findings from flexible endoscopy of patients who had rectal bleeding after previous pelvic radiotherapy

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Findings on endoscopy</th>
<th>Ref*</th>
</tr>
</thead>
<tbody>
<tr>
<td>171</td>
<td>Symptoms are unreliable guide to underlying pathology; 33% unrelated to radiotherapy</td>
<td>64</td>
</tr>
<tr>
<td>90</td>
<td>25% of symptoms unrelated to radiotherapy</td>
<td>85</td>
</tr>
<tr>
<td>44</td>
<td>About 25% of symptoms unrelated to radiotherapy</td>
<td>86</td>
</tr>
<tr>
<td>26</td>
<td>65% of symptoms unrelated to radiotherapy</td>
<td>87</td>
</tr>
<tr>
<td>13</td>
<td>Colonoscopy changes management</td>
<td>88</td>
</tr>
</tbody>
</table>

*Refs 85–88 are listed in webappendix.

In all patients with these symptoms, rectal examination with assessment of anal tone and flexible sigmoidoscopy is the minimum investigation needed. In patients with frequency of defaecation or changes in stool consistency, a full blood screen is appropriate. Local rectal or sigmoid pathology, such as a mucus-secreting tubulovillous adenoma or carcinoma, might cause faecal incontinence, and flexible sigmoidoscopy will exclude inflammatory colitis or proctitis unrelated to pelvic radiotherapy (which occurs in about 2% of patients).15 Endoanal ultrasonography might define sphincter defects (eg, after childbirth or those caused by radiotherapy); anorectal physiology might direct management.

Only one retrospective study19 (from our unit) has been published about interventions for the management of patients with faecal incontinence after pelvic radiotherapy. In this study, the use of phenylephrine gel benefitted three quarters of all patients with incontinence who had not responded to other treatments, with a substantial benefit in 25% of patients who were treated. Because all these symptoms are commonly characterised by muscle spasm, several treatments exist that might help, including use of toileting exercises, biofeedback, correct use of antidiarrhoeal drugs, stool-bulking agents (eg, sterculia), and low doses of off-label antidepressants. Surgery to divert the faecal flow and stoma formation might have a role in the few patients who have substantial loss of rectal volume and who have not responded to other interventions.

Non-specific help should also be offered. If incontinence leads to major soiling, patients might be entitled to free laundry services or pads. Some countries have a network of lavatories that patients could access—eg, lavatories for disabled people that are not available to the general public. Patients might benefit from prescription of efficient skin-barrier protectants. Charities frequently offer useful support and advice.

**Rectal bleeding**

29–51% of patients have rectal bleeding after pelvic radiotherapy,14,60 and it impairs quality of life in 6% of patients.1 Incidence of transfusion-dependent bleeding is 1–5% of patients.6,62 Bleeding commonly improves spontaneously over time.6,63

All patients with any rectal bleeding should be offered assessment with at least flexible sigmoidoscopy; proctoscopy and rigid sigmoidoscopy are inadequate. Colonoscopy probably can be reserved for those with symptoms or signs that suggest pathological changes to the proximal colon.14 Several series have suggested that the nature of bleeding does not discriminate between different causes of bleeding, and that radiotherapy is not the cause of rectal bleeding in 25–60% of patients (table 2).

Unless blood loss causes anaemia or affects quality of life, most patients do not need treatment. Most patients might be reassured if they are informed that they will get intermittent bleeding (particularly when they strain or have bowels open frequently), that bleeding will reduce over years, and that adequate endoscopy has excluded other serious causes. All endoscopic and surgical interventions for radiotherapy-induced bleeding are not risk free, and the benefits of intervention should be weighed carefully against the risk of taking no action.

A Cochrane review44 has summarised the evidence for treatment of rectal bleeding from radiotherapy. Sucralfate enemas (2 g sucralfate suspension made-up with 30–50 mL water in a bladder syringe injected twice a day via a lubricated foley catheter passed through the anus into the rectum) are more effective than corticosteroid or mesalazine enemas. Oral metronidazole for 4 weeks is beneficial, but probably contraindicated in patients with pre-existing cytotoxic-induced neuropathy. Unproven and off-label treatment includes sulfasalazine, female sex hormones, short-chain fatty acids, vitamins C and E, and thalidomide.45,65

Three endoscopic treatment options exist: use of argon plasma coagulation, laser therapy, or formalin applied to affected mucosa. No data from randomised studies exist for these interventions. It is not clear from published studies how many patients received endoscopic treatment for serious, transfusion-dependent bleeding and whether their response differs from patients with less-severe bleeding. Furthermore, if radiation-induced rectal bleeding reduces with time, so-called effective treatment in these studies need to be viewed with caution in the absence of untreated control patients.

Table 3 shows the results of argon plasma coagulation, which must be done only after full bowel preparation because of the risk of explosion. The total number of serious complications recorded in these studies was five strictures, three ulcers, three explosions, two perforations, two rebound bleeds, one fistula, and six patients left with long-term pain (total=25; 7%) in 338 patients treated in the studies. However, if most complications occurred in patients who had transfusion-dependent bleeding (n=97), the frequency of serious complications would be 26%. However, whether or not this situation is the case, is unknown, but patients with transfusion-dependent bleeding have the highest frequency of rectal ischaemia and possibly the lowest potential for tissue repair after treatment. Anecdotal evidence suggests that argon
plasma coagulation is commonly ineffective in patients with very heavy bleeding. Endoscopists need to be very cautious with use of argon plasma coagulation until more-rigorous studies are done.

Table 4 shows results of laser treatment. These data include small numbers of patients, but they suggest that problems are commonly more substantial with argon plasma coagulation than with laser treatment. Because laser treatment is usually only done by expert endoscopists, it might bring greater benefit and a lower rate of complications.

Studies have described the application of formalin for radiation-induced bleeding from telangiectasia. Formalin probably reduces mucosal blood flow,\(^6\) which suggests that if telangiectasia develops because of ischaemia (although a study challenges this view\(^6\)) a treatment that worsens ischaemia might worsen the long-term outlook of these patients.

Formalin is used in two ways. It can be inserted into the rectum as a 4% solution in volumes between 20 mL and 80 mL, with a contact time of up to 15 min under general anaesthetic. A review\(^6\) has suggested that published studies of formalin vary substantially in quality, leading to difficulty in interpretation of the reported results. However, between 55% and 100% of patients responded to treatment, and the frequency of serious complications in 202 patients from 16 studies was 7%.\(^8\)

Alternatively, formalin-soaked pads with up to 10% solution can be applied topically to mucosa under direct vision through a rigid sigmoidoscope or proctoscope, or through use of a flexible endoscope. A large series\(^6\) of 100 patients has reported an effective treatment in 93% of patients and a frequency of serious complications of 1%. Patients with severe bleeding needed more treatment sessions than those with minor bleeding. The number of patients who did not respond to treatment or the number of transfusion-dependent patients (if there were any) who responded in this study is not stated. In one study,\(^7\) 20 mL of 5% formalin inserted via a flexible endoscope into the rectum directed to the appropriate area for 3 min produced good results and no toxic effects.

Hyperbaric oxygen therapy provides the best evidence that radiotherapy morbidity can be modified. This therapy seems to stimulate angiogenesis, fibroplasia, and tissue restructuring through an increase in oxygen gradients in ischaemic tissues. A systematic review\(^8\) has summarised the efficacy of hyperbaric oxygen in the management of radiation-induced bleeding and other symptoms. These data (none of which are randomised and much of which are retrospective) are encouraging, but they lack consistency in scoring of symptoms and response.

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number who needed blood transfusion</th>
<th>Flow rate of argon gas (L/min)</th>
<th>Power (W)</th>
<th>Number of patients with response</th>
<th>Number of patients with complete response</th>
<th>Number of patients with recurrence</th>
<th>Number of treatments per patient</th>
<th>Follow-up (months)</th>
<th>Side-effects of argon-beam ablation</th>
<th>Ref*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case report</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1·2</td>
<td>45</td>
<td>1</td>
<td>0</td>
<td>4</td>
<td>12</td>
<td>None</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Retrospective studies</td>
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<tr>
<td>28</td>
<td>15</td>
<td>1·5</td>
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<td>27</td>
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<td>2</td>
<td>1·8</td>
<td>1·15 (mean 10)</td>
<td>None</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>3·0</td>
<td>60</td>
<td>7</td>
<td>7</td>
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<td>18·24 (median 24)</td>
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<td>3·7 (mean)</td>
<td>8·28 (mean 10)</td>
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<td>26</td>
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<td>4</td>
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<td>3·25 (mean 20)</td>
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<td>7</td>
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<td>5·31 (median 10·5)</td>
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<td>Mean 31</td>
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<td>NA</td>
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<td>9</td>
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<td>1·5</td>
<td>7·30</td>
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<td>40</td>
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<td>NA</td>
<td>2</td>
<td>1·6</td>
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<td>25</td>
<td>25</td>
<td>1</td>
<td>1·7</td>
<td>7·34 (mean 17)</td>
<td>3 explosions, 1 perforation</td>
<td>104</td>
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<td>25</td>
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<td>21</td>
<td>0</td>
<td>1·4</td>
<td>6·26 (median 14)</td>
<td>1 pain</td>
<td>105</td>
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*Refs 89–105 are listed in webappendix. †Unclear whether this was a prospective or retrospective study. NA=not available.

Table 3: Studies that reported outcome of treatment of radiation-induced bleeding by use of argon-beam ablation of telangiectasia
criteria. Furthermore, hyperbaric oxygen is expensive and has a low risk of side-effects, including potential promotion of the growth of occult metastases.

A final treatment option is surgery to defunction or resect the bleeding area. However, these procedures have high morbidity. In view of the potential of all interventions to cause substantial harm to patients who may already have major problems, there is an urgent need for carefully designed multicentre randomised trials to assess the management of post-radiotherapy bleeding.

Subacute bowel obstruction

Intermittent obstructive symptoms might be due to a number of causes. CT scanning might identify physical obstruction from adhesions, radiotherapy-induced fibrotic stricture, tumour relapse, or a combination of these factors. A radiological water-soluble contrast follow-up study rarely provides definitive information. Barium studies are unwise in a patient with subacute or acute bowel obstruction. Commonly, cross-sectional imaging shows multiple matted loops of small bowel, some slightly dilated with no clear transition point from dilated bowel to that of normal bowel.

Bacterial overgrowth in the small bowel can mimic subacute bowel obstruction; so too can faecal loading in the right colon, which occasionally seems to precipitate subacute obstructive symptoms—possibly by increasing small-bowel dysmotility. Malabsorption of fat or bile salts can cause obstructive-like pain and vomiting. Pseudo-obstruction may develop occasionally.

To my knowledge, no data for optimum investigation of subacute obstructive symptoms have been published; investigations should be guided by local expertise. Colonoscopy should be considered if a colonic source of obstruction is suspected, or if the patient has iron-deficiency anaemia, to rule out presence of a new primary colon tumour.

Acute episodes are managed conventionally with analgesia and intravenous fluids, with or without a nasogastric tube. A trial of antibiotics, with or without a low-fat diet and treatment with a bile-acid binder, should be considered. If radiological films suggest colonic loading, a high-fibre diet might help maintain colon motility; however, this intervention will make the patient worse if a stricture is present, whereas a long-term low-fibre diet can resolve symptoms.

Surgery to release adhesions or resect strictures should not be undertaken lightly: patients should always be considered for an initial trial of medical management. Commonly, surgery can be very difficult, and is associated with substantially higher risks of complications in patients who have had radiotherapy than in those who have not had radiotherapy. Moreover, surgery might not resolve symptoms if other factors that contribute to symptoms are not addressed (eg, enteric motility disorder or recurrent bacterial overgrowth).

Flatulence

This symptom is common for people of any age, irrespective of whether they have had radiotherapy. However, distressing flatulence after pelvic radiotherapy is surprisingly frequent. The most common probable cause is a diet that is too healthy. Many patients who have been diagnosed with cancer start to consume a diet that is rich in fermentable fibre. Rarely, bacterial overgrowth
of the small bowel might cause wind, so too might uncomplicated diverticular disease or the taking of lactulose or ispaghula.

A reduction in foods that contain complex carbohydrates might help reduce flatulence (eg, pulses, peas, beans, lentils, Brussels sprouts, cabbage, artichokes, onions, spicy food, fizzy drinks, and bran); occasionally, a trial of antibiotics might help. In some patients, an increase in colon transit by use of a bulking agent (eg, sterculia) is useful, decreasing the time available for bacterial fermentation of complex carbohydrates in the colon.

**Conclusion**

In the past few decades, oncology research has focused on improving patient response and survival, and therefore adequate attention has not been paid to the long-term effects of treatment. To expect oncologists to have the expertise to manage all side-effects of cancer treatment is unreasonable, but they can enhance patient quality of life by identifying long-term problems that arise as a result of treatment—especially now that cancer treatment is increasingly effective and that many patients have long-term survival. On identification of problems, referral pathways should be in place so that every patient can see a specialist. Patients expect their symptoms to be given legitimacy, even if they cannot be cured; many will also need some long-term support. There are few chronic disorders where the effect on patients is so little recognised and for which there is such an absence of support.

Discussion of radiation-induced damage to the gastrointestinal tract in terms of radiation syndromes—ie, radiation proctopathy, colopathy, or enteropathy—is potentially misleading. This Review shows that patients develop symptoms that do not correlate with standard anatomical boundaries. Patients might be helped better if symptoms were viewed in terms of potential loss of specific gastrointestinal functions. Figure 3 shows a potential systematic approach to investigation of such symptoms.

Patients with radiation-induced gastrointestinal symptoms commonly have other pelvic problems that are related to the bladder or to sexual function, or both, which can have important emotional, physical, psychological, economic, and social implications. Patients might worsen other problems: if systematic investigation of symptoms produces evidence of clear functional abnormalities in the gastrointestinal tract, then effective treatment may have a wider effect than on gastrointestinal symptoms alone.

Patients who develop new symptoms should be investigated the same way as someone who has not had radiotherapy. The lack of randomised trials to prove that treatment works does not mean that treatment is ineffective: rather, it reflects the medical community’s lack of interest in this area. It is not only time to do some of those trials properly, but also to look at better medical interventions to prevent small-bowel damage in the first instance and at how a service is best delivered to those who need it.

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**Figure 3: Suggested algorithm for investigation of gastrointestinal symptoms in patients who have had radical pelvic radiotherapy**

Red boxes are symptoms; blue boxes are tests or interventions. SehCAT = selenium 75 homo-cholic acid conjugated with tauxine.

**Conflict of interest**

Search strategy and selection criteria

A search of the original published work from 1996 to 2007 was done by use of MEDLINE and EMBASE databases. Search terms included: “lactose intolerance”, “disaccharide malabsorption”, “diarrhoea”, “steatorrhoea”, “bile salt malabsorption”, “bacterial overgrowth”, “faecal incontinence”, “pancreatic insufficiency”, “gastrointestinal bleeding”, “argon”, “formalin”, “radiation proctitis OR proctopathy”, “radiation colitis OR colopathy”, “radiation enteritis OR enteropathy”, “prostate”, “gynaecological”, “bladder”, “rectal AND anal cancer”, “radiotherapy”, “late toxicity”, “gastrointestinal symptoms”, “gastrointestinal motility”, “ischaemia”, “fibrosis”, “second malignancy”, and “quality of life”. Lists of references were obtained and potentially relevant papers retrieved. Reference lists in every paper were scrutinised to identify other possible relevant studies. The primary outcomes recorded were the reported incidence of gastrointestinal symptoms, the mechanisms for the development of those symptoms, management solutions which were proposed, and the outcomes from treatment.
The author declared no conflicts of interest.

References


