Radiation-induced small bowel disease: latest developments and clinical guidance

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Abstract: Ionizing radiation is commonly used to treat a number of malignancies. Although highly effective and now more targeted, many patients suffer side effects. The number of cancer survivors has increased and so there are more patients presenting with symptoms that have arisen as a result of radiotherapy. Radiation damage to small bowel tissue can cause acute or chronic radiation enteritis producing symptoms such as pain, bloating, nausea, faecal urgency, diarrhoea and rectal bleeding which can have a significant impact on patient's quality of life. This review outlines the pathogenesis of radiation injury to the small bowel along with the prevention of radiation damage via radiotherapy techniques plus medications such as angiotensin-converting enzyme inhibitors, statins and probiotics. It also covers the treatment of both acute and chronic radiation enteritis via a variety of medical (including hyperbaric oxygen), dietetic, endoscopic and surgical therapies.

Keywords: chronic radiation enteritis, pelvic radiation disease, radiation enteritis treatment, radiation enteropathy

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Introduction

Radiotherapy is a mainstay of oncological treatment for a variety of malignant diseases and is commonly administered to the abdomen and pelvis of patients with gastrointestinal (GI), urological and gynaecological cancers. It is recognised that patients may subsequently develop a range of GI side effects. It is important that these symptoms are both recognized and then acted upon by the various healthcare professionals who may encounter these patients in primary care and hospital practice.

This review outlines the pathophysiology of radiation enteritis, discusses how its incidence may be reduced and details the current management for both acute and chronic presentations.

What is radiation-induced small bowel disease?

'Radiation enteritis' is a term traditionally used to define injury to the small intestine resulting from radiotherapy. This excludes injury to the colon and rectum which are described as 'radiation colitis', 'radiation proctitis' or 'radiation proctopathy', respectively. These presentations are not covered in this review, but it is important for the clinician to remember the overlap between various radiation-induced GI injuries given the proximity of the colon and rectum to the small bowel. It is also important to recognize that patients may also have co-existing urological, sexual and psychological problems [Andreyev, 2007a]. The common term 'radiation enteritis' is a misnomer, and the terms 'radiation enteropathy' or 'radiation mucositis' have been used as a more accurate description of the disease process. There has been a recent consensus that 'pelvic radiation disease' most accurately describes the phenomena of GI injury secondary to radiotherapy, however 'radiation-induced small bowel disease' is probably the most accurate description of the disease process and will be used within this paper. Radiation injury to the small bowel can be subdivided into acute and chronic forms. Acute radiation-induced small bowel disease usually presents with colicky abdominal pain, bloating, loss of appetite, nausea, diarrhoea and faecal urgency during or shortly after a course of radiotherapy. Almost all patients receiving pelvic or abdominal radiotherapy experience some form of GI symptoms [Andreyev, 2007b]. Patients usually notice these symptoms during the second week of treatment (when tissue

damage and inflammation is probably at a maximum), and they characteristically peak by the fourth to fifth week (when histological changes are stable or improving) [Khalid *et al.* 2006].

Severity varies, with approximately 15–20% of patients requiring an altered therapeutic course. It is usually self-limiting, often resolves within 3 months and frequently only requires supportive measures [Do *et al.* 2011].

Chronic small bowel radiation disease typically develops between 18 months and 6 years after a completed course of radiotherapy, but has been reported to present up to 30 years later [Kountouras and Zavos, 2008]. It is a more common entity than many doctors think: 90% of patients who receive pelvic radiotherapy develop a permanent change in their bowel habit [Olopade *et al.* 2005]. It is also problematic, 50% of patients with pelvic irradiation describe their quality of life has been adversely affected by a variety of GI symptoms [Widmark *et al.* 1994; Crook *et al.* 1996; Gami *et al.* 2003] with 20–40% (depending on tumour type) rating the effect on quality of life as moderate or severe [Andreyev, 2007b].

Chronic enteropathy presents in many different ways including post-prandial pain, acute or intermittent small bowel obstruction, nausea, anorexia, weight loss, bloating, diarrhoea, steatorrhoea and malabsorption of selected or multiple nutrients [Theis *et al.* 2010]. These can arise from damage to the small bowel itself or associated phenomena such as bile salt malabsorption, bacterial overgrowth or lactose intolerance.

Pathogenesis

Radiotherapeutic injury is complex and healing varies from normal wound healing as a result of repetitive injuries [Denham and Hauer-Jensen, 2002]. Ionizing radiation causes several typical changes in tissues in the bowel. These are characterized by inflammation or cell death including mucosal cell loss, acute inflammation in the lamina propria, eosinophilic crypt abscess formation and swelling of the endothelial lining of arterioles [Theis *et al.* 2010]. These may resolve but can develop into a more chronic change with persistent cytokine activation in the submucosa and fibrosis of connective tissue with arteriolar endarteritis [Wong *et al.* 2010]. These changes result in tissue ischaemia, leading to mucosal friability and neovascularization as well as progressive fibrosis [Theis *et al.* 2010]. This can lead to multiple areas of small bowel dysfunction plus stricturing disease. Clinical presentation will depend on the degree and extent of tissue damage together with the site of injury [Lange *et al.* 2009; Kennedy and Heise, 2005]. This article concentrates on the therapeutic aspects of radiation-induced small bowel disease, however it is important to recognize the complexities of the underlying pathogenesis beyond that of which we have described above.

Symptom severity is related to the amount of radiation encountered. Symptoms may occur after just 5–12 Gy in a fractionated course, but usually occur at higher doses [Theis *et al.* 2010]. By way of illustration, the Royal College of Radiologists recommend that an acceptable treatment regimen for prostate cancer is 74–78 Gy to the prostate in 37–39 fractions over 7.5–8 weeks [Board of the Faculty of Clinical Oncology of the Royal College of Radiologists, 2006]. Intestinal damage is also related to the radiation regime, the size and site of the treatment field, the area of normal bowel that is exposed, the use of concurrent chemotherapy and the presence of radiation implants [Kennedy and Heise, 2005]. Other patient factors affecting the severity of symptoms include previous surgery to the abdomen or pelvis, diverticular or pelvic inflammatory disease, hypertension, smoking, diabetes and poor nutrition. These may all decrease blood flow to the bowel wall, increasing the risk of radiation injury [Kennedy and Heise, 2005].

Clinical assessment

Although GI symptoms, including those from radiation-induced small bowel disease are the most common of all of the chronic physical side effects of cancer treatment and have the greatest impact on quality of life [Andreyev, 2007b], fewer than 20% of affected patients are referred to a gastroenterologist [Andreyev *et al.* 2003]. Problems are under-reported by patients who may be embarrassed, feel they are not related to their prior oncological treatment or may accept them as inevitable consequences of successful cancer therapy. Patients receiving radiotherapy should be thoroughly educated to look for potential GI side effects, including radiation-induced small bowel disease and self-presentation should be encouraged. GI symptoms are also under-recognized by doctors who may not specifically ask about patient's 'bowels' [Andreyev *et al.* 2012].

Groups such as Macmillan Cancer Support have aimed to increase the knowledge of both the medical profession and the general public of the long term morbidity that can occur after treatment through 'Cancer Survivorship' initiatives and joint guidance was published in 2012 by the British Society of Gastroenterology, Association of Coloproctology of Great Britain and Ireland, the Royal College of Radiologists and Macmillan [Andreyev *et al.* 2012].

Acute problems can be recognized and managed by oncologists who need to exclude other causes such as infection. If systematic enquiry reveals that a patient has chronic abdominal symptoms that are adversely affecting their quality of life or have 'alarm' features such as rectal bleeding or weight loss then they should be referred to a gastroenterologist for prompt assessment. Practitioners should consider using the Royal Marsden algorithm [Andreyev, 2007b] which directs investigations on the basis of symptoms. It is vital to realize that each symptom may have several underlying causes and many patients have numerous symptoms. It is also important to consider the possibility of recurrent cancer or a malignancy at a different site. Surgeons should also be aware that prior radiation therapy is a risk factor for stricturing disease and adhesions which can present as subacute or intermittent small bowel obstruction.

As well as symptoms resulting from GI damage, there are secondary phenomena that are directly related to the radiotherapy. For example, diarrhoea can arise solely from dysfunction of the large and/or small bowel with decreased transit time from prior irradiation [Theis *et al.* 2010]. In addition, it could arise from any of the following: small bowel bacterial overgrowth, bile salt malabsorption from terminal ileal damage, malabsorption of lactose or other fermentable sugars, pancreatic exocrine insufficiency, or colitis. It could also be due to colorectal cancer and a range of other causes not directly linked to the prior oncological treatment including coeliac disease, inflammatory bowel disease, thyrotoxicosis, psychological issues, side effects of medication and alcohol excess [Andreyev, 2007b; Theis *et al.* 2010].

Prevention of radiation-induced small bowel disease

Oncologists have developed techniques to reduce radiation-induced small bowel disease including modifications to radiotherapy regimes and medications that may reduce tissue damage. Clinical guidance is outlined in Box 1.

Box 1. Prevention of radiation-induced small bowel disease: clinical guidance.

- Use of modern imaging and radiotherapy techniques to minimize radiation exposure to normal tissues
- Consideration of circadian rhythm effects and use of evening radiotherapy sessions
- Continue angiotensin-converting enzyme inhibitors and statins and consider their introduction if appropriate
- Consider use of probiotics
- Consideration of surgical techniques to minimise radiation exposure to the small bowel if appropriate and surgical team are experienced and competent at the procedure involved.

Radiotherapy techniques

A reduction in field size, multiple field arrangements, conformal radiotherapy techniques and intensity-modulated radiotherapy (IMRT) can reduce toxicity related to radiotherapy [Portelance *et al.* 2001; Randall and Ibbott, 2006]. IMRT maximizes the sparing of normal tissues by creating various treatment shapes and steep dose gradients [Mundt *et al.* 2002; Roeske *et al.* 2000]. It uses multiple beams with a highly nonuniform dose across the field whereas conventional radiotherapy typically uses a small number of beams with uniform intensity. Studies have shown a decrease in radiation dose to the bowel of up to 40% by using IMRT rather than three-dimensional conformal or conventional whole pelvic radiotherapy [Portelance *et al.* 2001; Nutting *et al.* 2000].

Image guidance techniques may also further improve radiotherapy administration. For example, megavoltage and kilovoltage cone beam computerized tomography provides a three-dimensional patient image immediately prior to radiotherapy, both improving cancer targeting and reducing the dose received by normal tissue. It has been shown that the lower doses of radiation to the bowel with these therapies also correlate with lower levels of toxicity and symptoms [Guerrero Urbano *et al.* 2006].

Access to these techniques are increasing (it is estimated that 81% of UK centres now have

access to IMRT) [Ahmad *et al.* 2012]. Although these methods are extremely promising, chronic symptoms can present up to three decades after radiotherapy, therefore long-term data will take many years to be realized.

Patient positioning and positioning devices

A variety of patient positions and positioning devices (such as a belly board, a positioning device designed to reduce the irradiated small bowel volume of patients undergoing treatment in the pelvic region by small bowel displacement whilst lying prone) have been trialled attempting to minimize inadvertent exposure of normal bowel to ionizing radiation.

A review analysing 46 papers concerning the influence of the patient position during the treatment of pelvic malignancies showed that a prone position generally results in a lower irradiated small bowel volume than the supine position [Wiesendanger-Wittmer *et al.* 2012]. However, a more significant reduction of the irradiated small bowel volume can be achieved by the additional use of a belly board in prone position, for both 3D-CRT (Conformal Radiotherapy) and IMRT treatment plans. It was also noted that a full bladder can also reduce the irradiated small bowel volume. However, there are little long-term data available at present assessing the long-term effect of these treatments on the GI tract.

Circadian rhythm

Animal studies have shown that when mice were irradiated at different times of the day, a clear circadian rhythm was observed in the number of apoptotic cells in the intestinal crypt [Ijiri and Potten, 1988]. This is thought to be due to the effect of circadian rhythm on cell proliferation cycles, and tissue appears to be more radiosensitive if its cells have greater proliferative capacity and divide more rapidly. Studies of cellular proliferation in the human rectal mucosa have shown the highest proliferative activity occurring in the morning between 03:00 and 11:30 and the least activity occurring 12 hours later [Ijiri and Potten, 1990; Buchi *et al.* 1991].

A prospective trial randomized 229 patients who received radiotherapy for cervical carcinoma to treatment in the morning (08:00–10:00) or evening (18:00–20:00) [Shukla *et al.* 2010]. The incidence of acute radiation-induced small bowel disease in the two arms was assessed and reported in terms of various grades of diarrhoea. Total number of patients with diarrhoea as well as those with more severe diarrhoea were found to be significantly greater in patients treated in the morning when compared with those receiving the identical radiation regime in the evening. The oncological therapeutic response in the two arms was similar.

Although timing of treatment may reduce morbidity from radiotherapy, a logistical problem exists in centres with limited capacity for evening treatments.

Medications

Statins and angiotensin-converting enzyme inhibitors. It has been noted that GI toxicity from radiotherapy is lower in patients taking antihypertensive and cholesterol-lowering agents (specifically angiotensin-converting enzyme [ACE] inhibitors and statins). ACE inhibitors block enzymatic conversion of angiotensin I to angiotensin II which plays a critical role in blood pressure homeostasis. *In vitro* studies have confirmed the anti-inflammatory, antifibrotic and antithrombotic potential of statins in irradiated human cells [Gaugler *et al.* 2005; Haydont *et al.* 2005, 2007] and low-dose lovastatin has been shown to be radioprotective in human endothelial cells [Ostrau *et al.* 2009].

A retrospective, nonrandomized cohort study of 308 pelvic radiotherapy patients assessed the impact of statins and ACE inhibitors on the development of GI symptoms [Wedlake *et al.* 2012]. GI symptomatology was recorded prospectively before radiotherapy, weekly during treatment and 1 year later using the Inflammatory Bowel Disease Questionnaire. Use of statin or statin + ACE inhibitor during radical pelvic radiotherapy significantly reduced acute GI symptoms.

Probiotics. A probiotic is a preparation containing viable and defined microorganisms in large numbers sufficient to alter the host's microflora [Kligler and Cohrssen, 2008].

Radiation therapy may disturb the indigenous gut flora which are important in maintaining a normal mucosal function [Berthrong, 1986] and there is emerging evidence that probiotics may have a radio-protective effect.

There have been a total of five randomized controlled trials of varying quality and size regarding probiotics in radiation-induced small bowel disease [Salminen *et al*. 1988; Delia *et al*. 2007; Urbancsek *et al*. 2001; Giralt *et al*. 2008; Chitapanarux *et al*. 2010]. Agents investigated include the probiotic preparation VSL#3 (a probiotic containing eight strains of live lactic acid bacteria and bifidobacteria) and live lactobacillus acidophilus plus bifidobacterium bifidum. Although some trials have shown a significant improvement in diarrhoeal symptoms and decreased antidiarrhoeal medication use, study design and patient numbers do not enable us to fully advocate probiotics at this time. Full safety testing of individual compounds followed by larger, well-designed double-blinded randomized controlled trials are required.

Amifostine. Amifostine is a cytoprotective adjuvant used in cancer chemotherapy. It reduces rates of xerostomia when administered before head and neck cancer radiotherapy [Jha *et al.* 2012]. Preliminary studies suggest amifostine may also protect against radiation-induced bowel toxicity [Athanassiou *et al.* 2003; Ben-Josef *et al.* 2002; Leonard *et al*. 2005] but further research is required to define its true value.

Antioxidants. Cytotoxic effects of ionizing radiation on GI epithelium have been hypothesized to be related to oxidative stress. Animal studies have shown that vitamin E and/or selenium treatment prior to radiotherapy help to minimize oxidative stress [Felemovicius *et al.* 1995; Mutlu-Türkoğlu *et al.* 2000] indicating that antioxidant pretreatments may have some beneficial effects against radiation induced intestinal injury [Empey *et al.* 1992]. Further studies of these agents are required.

Teduglutide. Teduglutide is a glucagon-like peptide-2 analogue. Animal studies have shown increased intestinal crypt stem cell survival when given prior to whole-body irradiation in mice [Booth *et al.* 2004]. This suggests in theory that it may provide a useful protective role in preventing radiation-induced intestinal injury but further work is required in humans.

Dietary supplementation. Glutamine and arginine have been shown to have a protective effect on the intestinal mucosa of rats treated with radiotherapy [Yavas *et al.* 2012]. Clinical studies, however, have shown that glutamine did not protect against acute radiation-induced small bowel disease in humans [Kozelsky *et al.* 2003; Vidal-Casariego *et al.* 2013].

There is no evidence that a lactose-restricted diet will prevent radiation-induced small bowel disease despite its utility in the treatment of some patients diarrhoea arising from radiotherapy [Stryker and Bartholomew, 1986]. A recent review of 22 studies regarding the efficacy of nutritional interventions to counteract acute gastrointestinal toxicity during therapeutic pelvic radiotherapy [Wedlake *et al.* 2013] looked at the evidence for elemental formula, low- or modified-fat diets, low- or high-fibre diets, low-lactose diets, probiotics and symbiotics. The authors found that there is insufficient high-grade evidence to recommend nutritional interventions at present, and that further high-quality trials are required.

Sucralfate. Sucralfate is a highly sulphated polyanionic disaccharide used to treat dyspepsia. It is thought to stimulate epithelial healing and form a protective barrier over damaged mucosal surfaces [Denton *et al.* 2002]. There is randomized controlled evidence that sucralfate can help in the treatment of bleeding in radiation proctitis, but there is no evidence that it is of use in the prevention of radiation-induced small bowel disease. A randomized double-blind study showed no significant difference between sucralfate and placebo in this setting [Martenson *et al.* 2000].

Surgical techniques

Surgical placement of absorbable mesh slings and silicone prostheses have been described to prevent radiation-induced small bowel disease [Devereux *et al.* 1984; Kavanah *et al.* 1985; Sener *et al.* 1989; Rodier *et al.* 1991; Beitler *et al.* 1997; Sugarbaker, 1983]. These interventions are aimed at reducing toxicity by excluding the small bowel from irradiated areas. However, the results have not been consistently reproduced in clinical practice and are not routinely used in many centres.

Complete exclusion of the small bowel by mesh sling in the early postoperative period should prevent the small bowel from becoming adhered into the pelvis. After mesh absorption, it is thought that the small bowel retains enough

mobility that it may be temporarily excluded from the pelvis by simple positioning methods [Waddell *et al.* 1999]. One case series of 60 patients had polyglycolic acid mesh slings inserted after resection of rectal or gynaecological malignancies. All patients received postoperative radiotherapy in standard fractions. At a mean follow up of 28 months, no cases of radiation-induced small bowel disease were seen [Devereux *et al.* 1988]. A study of 45 patients with resectable carcinoma of the rectum showed similar results [Dasmahapatra and Swaminathan, 1991].

Space-occupying silicone prostheses have been used to exclude the small bowel from the pelvis [McGinley *et al.* 1980], however they may develop a mass effect on surrounding structures resulting in moderate hydronephrosis [Nguyen and Hamper, 1997].

Repeat surgery may be necessary to remove the prosthesis after completion of the radiation therapy, although inflatable saline implants have been developed to reduce this problem [Sezeur *et al.* 1990].

Treatment of acute radiation-induced small bowel disease

Patients with acute enteritis may experience a wide variety of symptoms.

Treatment can be divided into supportive and dietary interventions as well as specific medical and surgical therapies. In severe cases, the subsequent oncological regimen may have to be revised.

Supportive treatments

Numerous medications can be prescribed that have no role in correcting the underlying pathophysiology of the condition but are aimed at minimizing symptoms.

The first-line treatment for acute radiation induced diarrhoea is antidiarrhoeal medication such as loperamide or cophenotrope [Wadler *et al.* 1998]. Bismuth subsalicylate has also been recommended for diarrhoea and nausea [National Cancer Institute, 2012], but as with many of these supportive treatments, the evidence base comes from clinical experience and consensus opinions only. Patients may also benefit from an anticholinergic antispasmodic agent to alleviate bowel cramping, analgesics for pain or anti-emetics for nausea [National Cancer Institute, 2012]. It is important to note that symptoms often stop upon completion of the radiotherapy regimen. Clinicians should provide reassurance along with education about the potential for chronic problems [Andreyev *et al.* 2012]. There is also emerging evidence that bile acid malabsorption can occur in the acute setting and this should be considered by clinicians [Harris *et al.* 2012].

Dietary treatments

Intestinal villi can be damaged by radiation therapy resulting in a reduction or loss of digestive enzymes leading to malabsorption of nutrients [Czito and Willett, 2010]. It is important to ensure sufficient calorific and fluid intake which may be difficult in this setting; a dietician can provide targeted advice. A number of dietary modifications have been suggested for the treatment of symptoms of radiation-induced small bowel disease but there is only limited evidence to say that they are beneficial.

A diet that is lactose free, low fat and low residue may have a benefit on patients' symptoms. However, results from other trials evaluating the effect of lactose-restricted diets on radiation-induced diarrhoea have provided contradictory results [Stryker and Bartholomew, 1986; Bye *et al.* 1992]. It is important to consider that if taking this approach then lactose-free nutritional supplements should be used.

In clinical practice, a pragmatic approach is suggested which may be assisted by keeping a food diary correlating to symptoms.

Octreotide

The somatostatin analogue octreotide is used in the treatment of chemotherapy-induced diarrhoea and radiation-induced small bowel disease [Yavuz *et al.* 2002]. It is an octapeptide that mimics natural somatostatin and decreases gut motility. A randomized controlled trial comparing octreotide acetate (100 μg three times daily) with diphenoxylate hydrochloride plus atropine sulphate (2.5 mg four times daily) in acute radiation-induced small bowel disease showed that diarrhoea resolved more quickly and a decrease in the number of patients needing to discontinue

pelvic radiotherapy in the octreotide arm [Yavuz *et al.* 2002].

5-Aminosalicylic acids

There is no evidence of the benefit of 5-aminosalicylic acids (5-ASAs) in acute or chronic radiation-induced small bowel disease and it has been shown that they may increase symptoms in the acute setting [Gibson *et al.* 2013].

Surgery

Surgery is very rarely required in acute enteritis. Where possible, it should be avoided because of poor wound healing and concerns about leakage from surgical anastomoses [Galland and Spencer, 1986]. It may of course be necessary to operate in some patients who have had recent radiotherapy but surgeons should be wary and cautious in doing so.

Treatment of chronic radiation-induced small bowel disease

Patients with abdominal symptoms that occur after prior radiotherapy need thorough assessment and investigation by a gastroenterologist and a treatment plan which may involve other healthcare specialists. Treatments can be divided into those that target specific secondary entities that commonly occur after radiotherapy and supportive, nutritional, mediations and other interventions that aim to counteract the effect of the enteropathy.

Supportive treatments

As per the acute setting, patients may need symptom-based medications either intermittently or on a regular basis. Again, this includes antimotility agents, analgesics and anti-emetics. One small trial has assessed the efficacy of loperamide in patients with chronic radiation-induced small bowel disease, showing improvement in intestinal transit times, bile salt absorption and diarrhoea [Yeoh *et al.* 1993].

Secondary effects of chronic radiation-induced small bowel disease

Antibiotics for small bowel bacterial overgrowth

Damage to the small bowel creates areas of dysmotility and stasis leading to bacterial overgrowth [Husebye *et al.* 1995]. Unlike the colon, which is rich in bacteria, the small bowel usually has fewer than 104 organisms per millilitre [Quigley and Quera, 2006]. When bacterial overgrowth occurs, the most common isolates from the jejunum are *Escherichia coli, Streptococcus, Lactobacillus, Bacteroides* and *Enterococcus* species [Bouhnik *et al.* 1999].

Broad-spectrum antibiotics are also utilized: these include tetracycline, co-amoxiclav, ciprofloxacin and rifaximin. Local antibiotic guidance should be followed. Patients often need to have repeated courses and many require long-term maintenance therapy at a lower dose. Some clinicians advocate the use of a rotation of different antibiotics to reduce the risk of resistance [Quigley and Abu-Shanab, 2010].

Although probiotic therapy has been used in the prevention and treatment of acute radiation-induced small bowel disease, there is currently no evidence of their effectiveness in the chronic setting.

Cholestyramine and colesevelam for bile salt malabsorption

A total of 95% of bile acids are absorbed in the terminal ileum and radiation damage to this area can cause bile acid malabsorption (BAM) [Andersson *et al.* 1978]. This can be tested for by a Se-HCAT study, however this investigation is not widely used and many clinicians advocate empirical treatment. BAM is thought to be responsible for symptoms in 35–72% of patients with chronic radiation-induced small bowel disease suffering from diarrhoea [Theis *et al.* 2010; Andreyev *et al.* 2005; Danielsson *et al.* 1991; Ludgate and Merrick, 1985; Arlow *et al.* 1987]. It responds well to cholestyramine, however this is not very palatable and 68% of patients discontinue it after 1 year [Kamal-Bahl *et al.* 2007]. Alternatives are colestipol and colesevelam which also bind bile salts. Colesevelam is better tolerated and there is evidence for its benefit in this setting; however, it is not currently licensed for this indication and is relatively expensive compared with other agents [Puleston *et al.* 2005; Wedlake *et al.* 2009].

Nutrition and related therapies

There has been research into the exclusion of certain foods and the use of nutritional

supplements in chronic radiation-induced small bowel disease, but again evidence for their benefit is variable.

When considering exclusion diets, it is important to get dietetic input. Patients can be assessed for lactose as well as other carbohydrate intolerances using techniques such as breath testing. The reduced sensitivity of these noninvasive tests mean that an empirical but guided trial of exclusion may be necessary. Lactose-free diets in patients with lactose intolerance have been shown to be effective [Beer *et al.* 1985]. We have also used a FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and pylols) exclusion diet in some of these patients who have subsequently reported an improvement in their symptoms, however there is currently no published trial assessing this approach.

Anecdotally, some patients do seem to relate exacerbations of their symptoms with the ingestion of specific foods. One study of 26 women with chronic radiation-induced small bowel disease compared with 21 normal controls showed that 50% of the patients noticed an increase in symptoms upon consumption of bran muffins, berries, cabbage, brussel sprouts, broccoli, tossed salad, Caesar salad, baked beans, lentils and nuts in comparison with 14% in controls. A total of 85% of these patients could only tolerate smaller portions of these foods. The study suggests that smaller, more frequent portions may improve tolerance of certain foods and reinforces careful history taking and an individualized approach for all patients [Sekhon, 2000].

It is important that patients receive sufficient calorific intake and where possible support is given via the enteral route. Some patients will require the long term use of highly calorific nutritional supplements: so-called 'sip' feeds. Regular measurement and supplementation of vitamins and minerals including iron, folic acid, vitamin B12, vitamin D, magnesium, calcium, trace elements and fat-soluble vitamins are important.

In some patients, parenteral support with fluid and electrolytes is necessary. Intestinal failure due to extensive enteropathy from prior radiotherapy is a recognized and relatively common indication for home parenteral nutrition (PN). The management of these patients should be coordinated at specialist centres. The latest British artificial nutrition survey showed that 3.8% of patients in the UK on home PN had radiation enteropathy [Smith *et al.* 2011].

It has been shown that intestinal rest with PN can improve clinical and radiological findings in patients with small bowel radiation injury [Loiudice and Lang, 1983] and that nutritional autonomy and survival may be improved if patients are treated initially with intestinal rest and home PN [Gavazzi *et al.* 2006]. However, it has also been reported [Silvain, 1992] that patients with chronic radiation-induced small bowel disease may be more likely to suffer clinical recurrence if treated conservatively with PN support compared with those undergoing surgical intervention [Scolapio *et al.* 1999, 2002].

Hyperbaric oxygen

Hyperbaric oxygen (HBO) decreases tissue hypoxia in bowel affected by ischaemic damage from ionising radiation by encouraging angiogenesis. An antibacterial effect has also been hypothesized [Bennett *et al.* 2012]. HBO is the only therapy found to increase the number of blood vessels in irradiated tissue [Bennett *et al.* 2012] and may allow the treatment of multiple sites of small bowel. The treatment is administered over several weeks in hyperbaric chambers.

A systematic literature review showed that 67 of 74 publications reported positive results when HBO was delivered as treatment for, or prevention of, delayed radiation injury [Feldmeier and Hampson, 2002].

A large multicentre study in the UK, the Hyperbaric Oxygen Therapy II (HOT-II) study, has finished recruiting and its results are eagerly awaited. Although HBO therapy is largely safe to use, it is limited by the availability of chambers.

Pentoxifylline and tocopherol

Pentoxifylline is a xanthine derivative and tocopherols are a class of chemical compounds with vitamin E activity [Hamama *et al.* 2012]. It has been suggested that the combination of these medications may decrease radiation-induced

fibrosis through antioxidant effects [Gothard *et al.* 2005]. A study of 30 patients with chronic radiation enteritis or proctitis showed symptomatic improvement in 71% of patients treated with this combination therapy, compared with 33% of patients who received supportive treatment alone [Hille *et al.* 2005]. Further research is required to fully evaluate these therapies.

Anti-inflammatory agents

Studies regarding the use of aminosalicylates in chronic radiation-induced small bowel disease are limited. Sulphasalazine has been examined in a case series of four patients with chronic radiation-induced small bowel disease, all patients showed clinical and radiological improvement over the course of 1 year of therapy [Goldstein *et al.* 1976]. Another study has shown that methylprednisolone may enhance the effect of parenteral nutrition-facilitated 'intestinal rest', but there is no significant evidence to suggest that corticosteroids are of use in these patients [Loiudice and Lang, 1983].

Endoscopic therapies

Occasionally patients may present with melaena or iron-deficient anaemia. Telangiectasia may form at any site in the intestine which has been irradiated and can be difficult to locate. Capsule endoscopy may be helpful but should be avoided in those with strictures. Argon plasma coagulation is well described in the management of radiation proctopathy [Leiper and Morris, 2007], but has also been successfully used for radiation-induced lesions in the distal duodenum [Toyoda *et al.* 2004] and ileum [Pasha *et al.* 2007] and can be administered into the jejunum as well via double balloon enteroscopy. It should be used judiciously given the risk of perforation particularly in abnormal tissue. Enteroscopy may also prove to be an alternative to surgery to treat small bowel strictures [Haruta *et al.* 2005; Kita *et al.* 2007].

Surgery

Surgery is challenging in patients with prior abdominal radiotherapy. There are often adhesions and the intestine may be very fibrotic and difficult to handle [Jao *et al.* 1986; Luna-Pérez *et al.* 2001]. Wound healing can also be difficult [Luna-Pérez *et al.* 2001]. There are certain patients, particularly those with strictures and obstructive symptoms, who need surgery as they cannot get symptomatic control or are persistently nutritionally compromised by their small bowel disease. Patients with extensive small bowel involvement are at risk of short bowel syndrome or a high-output proximal stoma both of which are significant management challenges. It is important to note that one operation can lead to another further increasing the risks of a short bowel. It is imperative that those considered for surgery have a thorough evaluation by radiological and other techniques and are managed by a multidisciplinary team that involves nutritional support and a surgeon who has experience in managing these patients [Andreyev *et al.* 2012].

A study of surgical treatment for radiation-induced small bowel disease assessed 48 patients who underwent extended intestinal resection with anastomosis showed a significant postoperative morbidity of 21.7%. Overall survival after radiation-related complication in patients without neoplastic disease recurrence was 89%, 79% and 69%, at 1, 3 and 5 years after surgery, respectively [Onodera *et al.* 2005].

Conclusion

A clearer picture of the management of radiation-induced small bowel disease is beginning to emerge. However, the optimal ways of preventing radiation induced damage to the small bowel as well as effective management for all patients is still unclear. New radiotherapy techniques continue to decrease inadvertent exposure to adjacent normal tissue and preventative agents including ACE inhibitors and statins are exciting areas of future research. The treatment of radiation-induced small bowel disease is largely supportive in the acute phase. For those with GI problems that have arisen in the years following radiotherapy, the key is recognition and referral for specialist advice from a gastroenterologist who has an interest in this field. Suggested clinical guidelines are outlined in Table 1. Patients need a targeted work-up for each of the symptoms they have, as many of these have several potential causes. Specific treatments can be offered as well as considering the valuable input from other healthcare professionals, e.g. dieticians. Emerging treatments such as HBO offer promise. The small

Table 1. Clinical guidance for treatment of radiation-induced small bowel disease.

All patients	Acute radiation-induced small bowel disease	Chronic radiation-induced small bowel disease
Thorough clinical assessment including referral to a gastroenterologist Consideration of differential diagnoses for each symptom and secondary causes of GI symptoms such as SBO and BAM Supportive treatments such and antidiarrhoeals, anti-emetics etc (consensus opinion from National Cancer Institute guidelines) Nutritional assessment and support if required (consensus opinion from National Cancer Institute guidelines)	Liaison with radiotherapy provider in case modification of treatment regimen is required Supportive treatments and reassurance of patient that symptoms often resolve after course of radiotherapy is completed (consensus opinion from National Cancer Institute guidelines) Consider octreotide for the treatment of persistent diarrhoeal symptoms (RCT data) Avoid 5-ASA compounds (RCT data)	Referral to a gastroenterologist Investigate and treat secondary effects of radiation-induced small bowel disease Monitor for nutritional deficiencies and provide dietetic input. Consider TPN if evidence of intestinal failure Hyperbaric oxygen for refractory symptoms (RCT data) Consider pentoxifylline and tocopherol (non RCT data) Consider endoscopic therapies if available and symptoms such as recurrent anaemia and/or bleeding (RCT data) Surgery can be considered in specialist centres for refractory cases but caution is advised due to high morbidity

5-ASA, 5-aminosalicylic acid; BAM, bile acid malabsorption; GI, gastrointestinal; RCT, randomized controlled trial; SBO, small intestinal bacterial overgrowth; TPN, total parenteral nutrition.

subset of patients who require an operation to alleviate their problems should be directed towards surgeons who have an experience in dealing with this challenging situation.

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