Chronic radiation proctitis: issues surrounding delayed bowel dysfunction post-pelvic radiotherapy and an update on medical treatment

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Caroline Henson

***Abstract*:** Late onset bowel dysfunction post-pelvic radiotherapy is an increasingly common clinical scenario which is related to improved oncological treatments and cancer survival. 50% of patients develop bowel symptoms after pelvic radiotherapy which affects quality of life. Historically, bowel symptoms post-pelvic radiotherapy have been labelled 'chronic radiation proctitis', although it is increasingly recognised that these symptoms are due to dysfunction of the gastrointestinal (GI) tract at numerous points. The evidence-base is poor and comprises often small, heterogenous, single centre unblinded studies. This article critically reviews the evidence for the medical treatment options for 'chronic radiation proctitis', which include anti-inflammatory drugs, antibiotics, sucralfate, formalin and hyperbaric oxygen. The difficulties in extrapolation from the literature to clinical practise are also explored. From the available evidence, rectal sucralfate appears to have greater efficacy than anti-inflammatory agents, which are more effective if used with oral metronidazole. Furthermore, hyperbaric oxygen is emerging as promising treatment for radiation toxicity. However, bowel dysfunction post-pelvic radiotherapy is a complex clinical condition which reflects multi-site GI tract pathologies both related and unrelated to previous oncological treatments. From this review article a clear need for an adjustment to both diagnosis and treatment of these patients, as well as for further research, emerges.

***Keywords*:** radiation proctitis treatment, radiation injury, late radiation toxicity, gastrointestinal, bowel dysfunction, pelvic radiotherapy,

Introduction

In the UK radiotherapy is a well-established treatment for pelvic malignancies, with 11,000–12,000 patients per year receiving pelvic radiation therapy, often with curative intent [Andreyev *et al.* 2005]. Currently it is estimated that severe gastrointestinal (GI) toxicity, i.e. fistulation, transfusion-dependent bleeding, stricture formation and secondary cancers, occurs in 5% of patients at 10 years [Nostrant *et al.* 1995]. This is felt to be an underestimate and does not include patients who develop more common symptoms of loose stool, urgency, faecal incontinence and tenesmus, which account for significant morbidity and poor quality of life for many patients post-pelvic radiotherapy. It is estimated that 90% of patients develop a permanent change in their bowel habit after pelvic radiotherapy, 50% of which have an associated reduction in their quality of life [Andreyev, 2007]. The largest obstacles to the successful management of these patients are accurate diagnosis and access to effective treatments.

There must be a comprehensive diagnostic approach to exclude other causes of bowel dysfunction, including malignant disease. Andreyev and colleagues reported a series of 265 patients who developed delayed onset GI symptoms post-pelvic radiotherapy [Andreyev *et al.* 2005]. 12% of patients had a new neoplastic lesion, one third of patients had a diagnosis unrelated to previous radiotherapy and more than half of the patients had at least two separate diagnoses. Many of

Correspondence to:
Caroline Henson, MBBS, MRCP (UK)
Department of Gastroenterology, Wythenshawe Hospital, Southmoor Road, Manchester M23 9LT, UK
CarolineHenson06@aol.com

these diagnoses were easily treatable, e.g. thyroid dysfunction, pancreatic insufficiency and malabsorption of fatty acids and bile acids.

There is no unified approach to the assessment and treatment of delayed GI symptoms post-pelvic radiotherapy. This is likely to be a reflection of the paucity of evidence available. GI symptoms are often given the label chronic 'radiation proctitis' (CRP), although arguably this is an oversimplification of symptoms which are more likely to be due to dysfunction of the GI tract at various points [Andreyev, 2007]. External beam radiotherapy to the pelvis can cause injury to the small bowel, terminal ileum, caecum, transverse colon and rectosigmoid. The GI symptoms may therefore be a result of several different physiological abnormalities throughout the GI tract. This is, however, a relatively new consideration and many people refer to 'radiation proctitis' to describe all GI symptoms post-pelvic radiotherapy. Such an approach can be unhelpful and clinically unsuccessful unless it is clearly confirmed that symptoms are due to radiation injury.

Given the morbidity of delayed GI dysfunction post-pelvic radiotherapy and the negative impact on quality of life, there is an imperative to develop a better understanding of this complex clinical scenario. The aim of this article is to review the available data for the medical management of CRP and discuss the wider issues surrounding current practice in this field.

Pathophysiology of radiation injury to the GI tract

The initial step in radiation injury to the GI tract is cell death and cell depletion leading to the loss of epithelium and villi [Dörr, 2009]. This causes oedema and subsequently mucosal inflammation [Denton *et al.* 2002], which in turn can lead to ulceration and sepsis. In time, this extends to the submucosa and triggers a regenerative response leading to either repair or the development of severe ulceration, fibrosis and stricturing. An obliterative endarteritis, submucosal fibrosis and new vessel formation lead to the clinical symptoms of rectal bleeding, strictures, tenesmus and diarrhoea [Leiper and Morris, 2007].

Whilst the risk factors for the development of GI tract radiation injury post-pelvic radiotherapy are not fully understood, certain factors have been associated with an increased risk of bowel toxicity. Radiotherapy-specific factors include volume of tissue irradiated, radiotherapy dose and the type and delivery of radiotherapy [Fiorino *et al.* 2009a, 2009b; Andreyev, 2007]. Other factors include previous surgery, the concomitant use of chemotherapy, smoking, genetic susceptibility and the presence of other medical conditions, e.g. diabetes, hypertension, HIV and inflammatory bowel disease [Andreyev, 2007].

Treatment of chronic 'radiation proctitis'

Treatment options are numerous, encompassing oral or rectal 5-aminosalicylic acids (5ASAs), oral metronidazole, rectal steroids, sucralfate or formalin and hyperbaric oxygen. The current evidence base for the efficacy of these treatments is poor, with many of the studies being small, largely single-centre, uncontrolled, unblinded studies. There is no standardized approach for the evaluation of such patients to ensure accurate diagnosis on entry to the trials. This is a significant confounding factor in the current research, given that over half of patients who develop GI symptoms post-pelvic radiotherapy have at least two discrete diagnoses [Andreyev *et al.* 2005].

Anti-inflammatory agents

Kochhar and colleagues reported a randomized, double-blind, controlled trial of oral sulphasalazine (500 mg TDS) and rectal prednisolone (20 mg) *versus* rectal sucralfate (2 g BD) and oral placebo in the treatment of CRP [Kochhar *et al.* 1999]. This was a small trial of 37 patients, 36 women treated for cervical cancer and 1 man treated for prostate cancer. The mean duration since completion of radiotherapy was 8.3 months. Patients were excluded if they had taken steroid therapy in the preceding 2 weeks. Symptoms were assessed using an in-house scoring system for diarrhoea, bleeding, tenesmus and endoscopic appearance. The duration of treatment and the follow-up period was 4 weeks.

This study reported a significant clinical and endoscopic improvement in favour of rectal sucralfate over anti-inflammatory treatments. There was a clinical improvement of 94% *versus* 54% for sucralfate and anti-inflammatories, respectively, and an endoscopic improvement of 71% *versus* 47%. The endpoints were clinically relevant, i.e. symptomatic improvement and mucosal healing.

Unfortunately there was no assessment of histology or effect on quality of life. There was also no long-term data with a follow-up period of only

4 weeks. Another limitation of this study was that there was no explanation for the five patients who were lost to follow up.

Rougier and colleagues reported a comparison of the efficacy of rectal betamethasone (5 mg BD) *versus* rectal hydrocortisone (90 mg BD) [Rougier *et al.* 1992]. There were 32 participants, 29 women and 3 men, whose initial pathology was gynaecological cancer in 23 cases and colorectal/anal tumours in 9 cases. The course of pelvic radiotherapy had been completed at least 6 months prior to the onset of symptoms. The diagnostic criteria used was a flexible sigmoidoscopy and an assessment of the degree of bleeding. The total duration of treatment was 4 weeks and the follow-up period was also 4 weeks. The endpoints of the study were bowel activity, rectal bleeding, tenesmus and endoscopic grading. Patients were assessed in this way at 14 and 28 days. There were no complications of treatments but two people were lost to follow up.

This study found a nonsignificant improvement in terms of endoscopic appearance in favour of rectal hydrocortisone. There was a nonsignificant reduction in rectal bleeding (38% *versus* 21%) in favour of hydrocortisone. Rectal betamethasone was reported as poorly tolerated in 10 out of 14 *versus* 2 out of 16 in hydrocortisone group.

The major limitations of this study were the presence of more severe disease in betamethasone group, poor tolerance of the enema in betamethasone group, a short follow-up period and no assessment of the impact of treatment on quality of life. These factors may have skewed the results to favour rectal hydrocortisone.

Cavcic and colleagues reported a study comparing oral mesalazine (3 g/day) and rectal betamethasone +/− oral metronidazole (400 mg TDS) [Cavcic *et al.* 2000]. The patients were allocated into the groups rather than randomized. The total number of participants was 60 and they were treated for 1 year. The efficacy of treatment was assessed in terms of the effect on rectal bleeding, diarrhoea and rectosigmoidoscopy appearances. These assessments were performed at 4 weeks, 3 months and 12 months.

There was a significantly lower incidence of rectal bleeding and mucosal ulceration, and a significant decrease in diarrhoea and mucosal oedema in metronidazole group at all assessments. There was a 92% *versus* 42% reduction in rectal bleeding in favour of the metronidazole group. A total of 23 out of 24 *versus* 8 out of 12 patients experienced reduction in diarrhoea and rectal erythema in favour of the metronidazole group and 22 out of 24 *versus* 7 out of 12 had decreased rectal ulceration. There were no reported adverse events.

The limitations were the lack of randomization and assessment of effect of treatment on quality of life. This study does seem to suggest that metronidazole can improve symptoms and mucosal healing in combination with anti-inflammatory treatments.

There are several other small studies and case series assessing 5ASAs in the treatment of CRP, which show variable results.

Short chain fatty acids

Short chain fatty acids (SCFAs) are produced by colonic bacteria and are the main oxidative fuel for the colonic mucosa. They have a trophic effect on the rectal mucosa and stimulate mucosal blood flow [Denton *et al.* 2002]. It was therefore postulated that they might be effective in the treatment of CRP.

Talley and colleagues reported a prospective, randomised, double-blind, placebo-controlled crossover pilot trial of 15 patients: 2 women and 13 men. The underlying diagnosis was prostate cancer in 12 patients, 1 case of cervical cancer and 2 of rectal cancer [Talley *et al.* 1997]. All patients had been treated with pelvic radiotherapy a mean period of 12.2 months earlier. The participants were assessed using an in-house symptom score (rectal pain, bleeding episodes, quantity of blood, days of diarrhoea, number of stools and urgency). There was also endoscopic and histological assessment. The patients were randomized to normal saline placebo or enema of butyrate twice daily. Patients were given 2 weeks of the first treatment, followed by a 1-week washout period, then crossed over to 2 weeks of the other treatment. Three patients dropped out.

There was a nonsignificant improvement in symptom scores on SCFAs. There was no assessment of the effect on quality of life, very small numbers of participants and a short duration of treatment.

Pinto and colleagues reported a randomised, prospective, double-blind, placebo-controlled trial of SCFAs in the short-term treatment of CRP. The total number of participants was 19, 1 man and

18 women [Pinto *et al.* 1999]. The baseline characteristics of the treatment and placebo groups were comparable. The endpoints of the study were adverse events, haemoglobin level, number of episodes of rectal bleeding in the preceding week, endoscopic assessment by two assessors and biopsies for quantification of mucosal DNA and protein content. These assessments were performed at 5 weeks and 6 months. The duration of treatment was 5 weeks. There were 7 patients lost to long-term follow up.

At the 5-week assessment, there was found to be a significant reduction in days of rectal bleeding and endoscopy score, and a significant increase in haemoglobin in the treatment group. There was a significant decrease in mucosal DNA and protein content in the mucosal biopsies in both groups, with a nonsignificant trend in favour of SCFAs. At 6 months the endoscopic scores and number of days of rectal bleeding were similar in both groups, suggesting that there is no sustained benefit of treatment with a short course of SCFA enemas. There were no adverse events recorded.

Whilst this study did include longer-term follow up and used two endoscopic assessors to validate endoscopic scoring, the study was grossly underpowered and there was no information regarding the effect of treatment on quality of life. It was also not possible, given that individual patient data was not published, for the data from these two studies to be combined.

Benefit has been shown for SCFAs in several small case series and reports [Pinto *et al.* 1999; Talley *et al.* 1997; Al-Sabbagh *et al.* 1996; Mamel *et al.* 1995]. There is, however, no robust evidence base to support the use of rectal SCFAs in the treatment of CRP.

Sucralfate

Sucralfate is a highly sulphated polyanionic disaccharide. The mechanism of action is thought to be stimulation of epithelial healing and the formation of a protective barrier overlying damaged mucosal surfaces [Denton *et al.* 2002]. Pentosan polysulphate (PPS) is the synthetic derivative of glycosaminoglycan, which is present in the surface of the bladder, vasculature and gastrointestinal tract lining [Denton *et al.* 2002]. PPS reduces epithelial permeability and prevents adherence. Both of these have been studied in the treatment of CRP.

Kochhar and colleagues performed a prospective, randomised, double-blind, controlled trial involving sucralfate, which has been analysed previously [Kochhar *et al.* 1999]. This study reported a significant clinical and endoscopic improvement in favour of rectal sucralfate over anti-inflammatory treatments.

Other small studies have been reported [Kochhar *et al.* 1999; Grigsby *et al.* 1990]. They are both well-designed prospective trials into the efficacy of sucralfate and PPS, respectively. Kochhar and colleagues reported 26 cases of CRP treated with sucralfate which showed a benefit at 4 months. Grigsby and colleagues reported 13 cases of CRP treated with PPS which showed a benefit at 1 year.

Formalin

Formalin was initially used in the treatment for radiation cystitis. It acts as a chemical sclerosant of blood vessels [Denton *et al.* 2002]. Formalin has been studied as a treatment for rectal bleeding in CRP.

There have been numerous published reports of the use of formalin, the majority of which are retrospective series with no control group. There are no randomized controlled trials. The study designs, outcomes and treatments are heterogeneous. A variety of formalin application techniques, from irrigation to direct application, and formalin concentrations, from 3.6% to 10%, have been used. Objective scoring systems have not been used to assess response to treatment and the statistical analysis has not been published. Data has not been collected regarding the effect on quality of life.

Denton and colleagues collated and analysed the available data for the use of formalin in CRP [Denton *et al.* 2002]. A total of 208 patients had been enrolled in studies. There was a mean follow-up period of 6 months. Each report claimed benefit in reducing rectal bleeding, raising the question of reporting bias. There were 11 serious side effects, including 5 cases of anal ulceration, 2 rectal strictures, 2 cases of faecal incontinence and 2 cases of anal pain. It is difficult to determine whether some of these adverse events were actually a consequence of the original radiation injury. The duration of effect was reported to be 3 months.

Hyperbaric oxygen

Hyperbaric oxygen (HBO) is the only therapy found to increase the number of blood vessels in irradiated tissue [Bennett *et al.* 2005]. There is an 8–9-fold increase in vascular density of soft tissues over air breathing controls. HBO stimulates collagen formation at wound edges through the elevation of local tissue oxygen tensions which leads to new microvasculature and allows re-epithelization to occur. It has been postulated that HBO could be used in the treatment of CRP.

Unfortunately, the research into the use of HBO in CRP is heterogeneous and largely in the form of retrospective case series or reports with only one prospective observational case series [Williams *et al.* 1992]. Only two studies had a baseline assessment of severity of CRP with histological or symptom scores. There was marked variability in terms of duration of treatment, number of treatments and pressures of HBO used. There was no quality of life assessment.

HBO appears to be a safe treatment with only minor adverse events recorded related to transient aural barotrauma. HBO may well be of value for refractory CRP but the quality of current data is poor.

Warren and colleagues reported 14 cases of CRP treated with varying doses of HBO [Warren *et al.* 1997]. The authors report a response rate of 64%, with complete symptomatic resolution in 57%. There was a follow-up period of 14 months and no adverse events. Girnius and colleagues reported nine patients with refractory haemorrhagic proctitis who had failed previous therapy [Girnius *et al.* 2006]. All patients had some response to HBO and seven had complete resolution of their rectal bleeding. Similarly, Jones and colleagues found that 8 out of 10 patients with refractory CRP responded to HBO [Jones *et al.* 2006].

Dall'Era and colleagues studied the efficacy of HBO in 27 patients with treatment-resistant CRP [Dall'Era *et al.* 2006]. The treatment regime was 100% oxygen at 2.4 atmospheres of hyperbaric pressure for 90 minutes for 5–7 days weekly for an average of 36 sessions (range 29–60). A total of 48% had complete resolution of bleeding and 28% had significantly fewer bleeding episodes, 21% had complete resolution of rectal ulceration and 29% had improvement in rectal ulceration. There was an overall improvement in two thirds of these previously treatment-resistant patients.

Although the data appears promising, there is marked variability between these studies and they individually lack statistical power. There needs to be a prospective, randomised, placebo-controlled, double-blind trial to clearly define the role of HBO in the treatment of CRP. Other issues relating to HBO are cost and access to treatment, given the potential workload and the fact that HBO is not widely available.

Discussion

Using the available data, rectal sucralfate is more effective than anti-inflammatory agents. Anti-inflammatory agents are more effective if used with oral metronidazole. Rectal hydrocortisone is better than rectal betamethasone. HBO is a promising technique and the HOT II Trial (Dr Andreyev and Dr Yarnold) is currently recruiting patients to examine HBO in a more robust way.

The current studies regarding the treatment for CRP are generally small and heterogeneous, resulting in noncomparable data sets. The studies are rarely controlled. The data is difficult to interpret and extrapolate for use in day-to-day practice. Other causes for symptoms are not clearly excluded, which could account for the lack of clear evidence of efficacy. Also there is little in the way of standardized assessments of severity of CRP pre- and postintervention.

There also appear to be issues in terms of case identification. Oncological treatment in the UK tends to be provided at tertiary centres, but the patients who develop CRP are a widely scattered population. Given the poor understanding of delayed onset bowel dysfunction post-pelvic radiotherapy, and the impression that there is little that can be done to help, many patients may not be disclosing symptoms or being screened for this condition. This may be contributing to the lack of well-powered, multicentre, randomised, controlled trials.

In the current body of literature, little consideration is given to the initial tumour type, stage and grade or the dose or nature of the radiotherapy given. The method for determining diagnosis is not specified and indeed there is no agreed definition or diagnostic criteria. There is no standardized, validated site-specific scoring system

for severity of CRP for baseline measurements and assessment of treatment. The development of such a tool would significantly improve the interpretation and measurement of the effect of individual treatments. There are variable protocols for administration of the same treatments, therefore comparisons cannot be made easily between trials of the same interventions.

There is also striking absence of data regarding whether these interventions have a positive impact on the patient's life and ability to function, as determined by quality of life assessments. Such data could be useful adjunctive information, within the limitation of the phenomenon of the 'response shift'. This refers to the observation that people who experience prolonged periods of adversity, e.g. deterioration in health, can fail to show the expected reduction in quality of life [Carver and Scheier, 2000].

Conclusions

Late-onset bowel dysfunction post-pelvic radiotherapy encompasses numerous conditions both related and unrelated to previous oncological treatment. To date there has been a disjointed approach to these patients and management based on minimal evidence. This has lead to a patchy, poor-quality service for patients with this often-debilitating condition. On the basis of the current research it is difficult to suggest a management algorithm, but it is clear is that we need to increase our professional awareness. We must ensure that we approach patients with late onset bowel dysfunction post-pelvic radiotherapy with the same diagnostic intelligence as if they had not had radiotherapy. This will prevent the delayed diagnosis of other benign or malignant conditions of the GI tract which may be responsible for the clinical presentation.

We must develop strategies to better identify cases and perform well-designed treatment trials. It would seem appropriate to develop a network of interested doctors within the UK who wish to take on the challenges of managing the late complications of pelvic radiotherapy on the GI tract. The first step would be to audit the current practice and establish nationally accepted guidelines.

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Conflict of interest statement

None declared.

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