Radiation proctitis – a review

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Abstract

Acute radiation proctitis is usually transient and self-limiting while chronic radiation proctitis is frequently relentless and progressive if untreated. The actual incidence of acute and chronic radiation proctitis is difficult to determine due to the sparse number of prospective studies available. The management of chronic radiation proctitis has so far been unrewarding as treaunent options are limited, and of varying and inconsistent efficacy. Therapeutic strategies are not well defined and there is lack of consensus on the standard therapeutic strategy. Clinical response to different forms of treatment are also difficult to predict even though endoscopic interventional modalities utilising argon plasma coagulation and formalin application have shown promising results and are beginning to emerge as effective first line agents in the management of chronic radiation proctitis. Surgical intervention is associated with high risk of complications because of the impaired healing potential of surrounding irradiated tissue and is usually reserved for unrelenting symptoms or the development of fistulation to surrounding pelvic organs. This paper reviews the clinical features, pathology and management issues related primarily to chronic radiation proctitis.

Key words: acute, chronic, radiation proctitis, haemorrhagic

Introduction

Radiation proctitis has been reported to occur in 5-10% of patients who undergo pelvic irradiation (Roche *et al.*, 1996) and may be acute, chronic or recurrent. The severity of the condition varies and less than 5% of patients who have had previous pelvic irradiation are at risk of suffering from severe manifestations of radiation proctitis (Otchy & Nelson, 1993; Gililinsky *et al.*, 1983). Although the prevalence of radiation proctitis is decreasing with the more widespread use of sophisticated modes of radiation delivery, clinical manifestations, the most common of which is rectal bleeding, can be troublesome and relentless. The haemorrhagic form of chronic radiation proctitis may be associated with severe blood loss requiring massive blood transfusions which can on rare occasions be life threatening.

Radiation Damage and Clinical Features

The majority of patients who suffer radiation proctitis have previously undergone radiation for pelvic malignancy, the most common of which is cervical cancer in females and prostatic cancer in males. For these conditions, conventional external beam therapy has been the predominant mode of radiation delivery, often supplemented in the case of cervical cancer, by intracavitary radium or caesium implants. The untoward effects of radiation depend on the radiation dose delivered and the extent to which normal surrounding tissue is exposed (Niemerko & Goitien, 1993). External beam therapy delivering doses in excess of 5000cGy is associated with increased risk of radiation damage which may be as high as 30% when doses exceed 7000 cGy (Charneau *et al.*, 1991). Additional supplemental intracavitary irradiation also contributes to an increase in the risk of subsequent chronic radiation proctitis (Deitel & Vasic, 1979).

Radical radiotherapy for pelvic malignancy is currently being superseded by focussed and conformal irradiation techniques. Apart from the use of linear accelerators, these newer techniques utilise three dimensional tumour visualisation and planning systems enabling delivery of higher doses of radiation which, result in better tumour control and at the same time reducing the radiation damage to surrounding normal tissues (Ling & Fuks, 1995). Conformal radiotherapy has been found to result in reduced untoward effects of radiation including radiation proctitis when compared with conventional external beam therapy in a randomised controlled trial on patients undergoing irradiation for prostatic carcinoma (Dearnaley *et al.*, 1999).

The untoward effects of radiation can manifest within days or weeks (acute) or be delayed for a few months or years (chronic) following treatment. Acute radiation

injury manifests shortly following irradiation and results from direct injury to the intestinal mucosa (Novak *et al.*, 1979). It principally affects rapidly dividing cells, is usually selflimiting and more often affects the small compared to the large bowel. Clinical manifestations of acute radiation proctitis usually manifest within two to four weeks of radiation therapy (Zimmermann & Feldmann, 1998). Diarrhoea is the most common symptom affecting up to two thirds of patients followed by abdominal pain and rectal bleeding (Anseline *et al.*, 1981). The management of acute radiation proctitis is supportive with rehydration and anti-diarrhoeal therapy. Symptoms usually resolve within a few weeks of completing radiotherapy (Coia *et al.*, 1995).

Chronic radiation proctitis can manifest months to years following radiotherapy. Damage in this case is secondary to chronic fibrosis and vascular endothelial injury. Concomitant chemotherapy, diabetes and previous abdominal surgery can augment tissue damage (Anseline *et al.*, 1981). Clinical manifestations of chronic radiation proctitis include rectal irritation, rectal urgency (tenesmus), blood and mucus in the stool, loose bowel motions and rectal bleeding which have been classified as symptoms of proctitis by the Radiation Therapy Oncology Group (RTOG) (Pilepich *et al.*, 1987). Rectal discomfort or rectal pain may also occur. Radiation injury may result in severe chronic radiation proctitis, the clinical manifestations of which can include obstruction, ischaemia and perforation (Tomori *et al.*, 1999; Pricolo & Shellito, 1994). Fistulation from the rectum into neighbouring organs, most commonly involving the bladder and vagina, can also occur secondary to pelvic irradiation (Jao *et al.*, 1986).

Pathology

Acute radiation injury results in the accumulation of acute inflammatory cells in the lamina propria and the occasional formation of crypt abscesses. As the effects of radiation on epithelial cells are reversible, regeneration usually occurs when the insult ceases. On the other hand the chronic effects of radiation injury result primarily from microvascular injury.

Endothelial damage leads to thrombus formation within the microvasculature, subsequent progressive arteriolar narrowing and tissue ischaemia (Haboubi *et al.*, 1988). Consequent subintimal fibrosis then results in capillary fragility and venular telangiectasia (Babb, 1996). Impaired regeneration or the loss of the intestinal mucosal and submucosal layers results in atrophic changes seen as mucosal pallor on endoscopy (Kwitko *et al.*, 1982). In an analysis of 18 irradiated rectal specimens, Richter *et al.* (1998) demonstrated reduced levels of thrombomodulin, an endothelial cell surface protein which following radiation can lead to release of fibrosis producing inflammatory cytokines such as tumour growth factor B (TGF-B). Modulation of the microvasculature can reduce radiation-induced damage in normal tissue. However this modulation through an increase in thrombomodulin can also, on the other hand, promote tumour invasiveness through the reduction of tissue hypoxia and cell damage.

These phenomena may form the basis for further investigation of therapeutic strategies on tumour control and antitumour therapy with less untoward effects of radiation.

Endoscopic Findings

The endoscopic features reported in patients with radiation proctitis have been inconsistent because of the lack of standardised description and endoscopic scoring systems. Endoscopic appearances typical of inflammatory bowel disease are not commonly encountered. On endoscopy the rectum may be normal or may be seen to be friable, and exhibit mucosal pallor, telangiectasia, contact bleeding and ulceration (Swaroop & Gostout, 1998).

To facilitate comparison of data and to evaluate the untoward effects of the different radiation delivery techniques an objective endoscopic scoring system for the evaluation of radiation proctitis has been proposed (Wachter *et al.*, 2000). This scoring system based on a scale of six and standard terminology proposed by the European Society for Gastrointestinal Endoscopy (Crespi *et al.*, 1996) includes 5 endoscopic features including mucosal congestion, telangiectasia, ulceration, necrosis and stricture (Wachter *et al.*, 2000). Although useful for comparison, these endoscopic features have been reported not to correlate with the risk of rectal bleeding (Wachter *et al.*, 2000).

Treatment

Steroids and 5-aminosalicylic acid (5-ASA) compounds

Although anti-inflammatory agents like steroids and 5-aminosalicylic (5-ASA) compounds in the form of enemas and suppositories are used in the treatment of radiation proctitis, they are not as effective as in the treatment of ulcerative proctitis. Steroids, which are often hydrocortisone based, are usually administered rectally. Sulphasalazine can be given both orally or as an enema. Combination treatment of steroids and 5-ASA, the active component of sulfasalazine, for chronic radiation proctitis is not unusual but the majority of patients ultimately requires other intervention especially when symptoms are prolonged.

We have managed five patients with chronic haemorrhagic radiation proctitis, all of who were treated with hydrocortisone enemas prior to their referral and had

this treatment continued under our care (Gul *et al.*, 2001). One patient continued bleeding and was successfully treated with sucralfate enema. Over a mean follow up period of 6 months, one patient had recurrent rectal bleeding with an associated fall in the haemoglobin. Baum *et al.* (1989) reported a slight improvement in only one of four patients who were treated with 4g of nightly 5-ASA enemas. Moreover this effect was not sustained. Steroids and 5-ASA therefore, although well established in the treatment of inflammatory bowel disease are of limited value in the management of chronic radiation proctitis.

Metronidazole

Although metronidazole on its own has not been shown to be effective in radiation proctitis, the combination of oral metronidazole with steroid enemas and mesalazine has been reported to be more effective in controlling diarrhoea and rectal bleeding when compared to steroid enemas and mesalazine in a randomised trial incorporating 60 patients with chronic radiation proctitis (Cavcic *et al.*, 2000).

Sucralfate

Sucralfate, the aluminium salt of sucrose octasulphate, which is widely used in the treatment of peptic ulceration, acts as a local cytoprotective agent, through forming an adherent complex that binds to damaged mucosa. Sucralfate has been reported by O'Brien *et al.* (1997) to possess properties that promote angiogenesis and reduce epithelial microvascular injury. Kochhar *et al.* (1991) found that rectal sucralfate enemas were more effective than the combined therapy of rectal steroids and oral sulphasalazine in the treatment of chronic haemorrhagic radiation proctitis in a prospective double blind controlled trial over a short period. Kochhar *et al.* (1999) subsequently reported on the long-term efficacy of rectal sulcralfate enemas (20mls of 10% sucralfate) where 24 of 26 (92%) patients with haemorrhagic radiation proctitis responded to treatment, and 17 of 24 (71%) had no recurrent bleeding over a mean follow-up period of 45 months. All seven patients who experienced recurrent bleeding after remission responded to further treatment with rectal sucralfate enemas (Table 1).

Although there are no other reported substantial prospective studies on rectal sucralfate enemas in the treatment of radiation proctitis, we have been using rectal sucralfate enemas (2gm in 20mls of water) in the treatment of chronic radiation proctitis (Gul *et al.*, 2001). We have since increased our cohort of patients to 11 over a 28 months period. Rectal sucralfate suspension was effective in all 11 patients in procuring symptomatic improvement. Recurrent rectal bleeding has occurred in two patients over a mean follow up period of 10 months. Repeat therapy with sucralfate was employed successfully in one patient and the remaining patient had topical formalin application as the affected area of the rectum was within easy reach of the rigid sigmoidoscope. Even though the number of subjects in our study is small, sucralfate enema can be considered as a useful first line agent in managing patients with chronic haemorrhagic radiation proctitis.

Table 1. Treatment modalities and outcome in the management of chronic radiation proctitis*

Method	No. of Patients	Response Rate	Follow Up	Relapse Rate
Pharmacological Agent				
Topical Sucralfate				
Kochar *et al.* (1999)	26	24 (92.3%)	45.5 months (median)	7 (29.1%)
Topical Formalin				
Yegappan *et al.* (1998)	55	36 (67%)	35 months (mean)	19 (34.5%)
Mathai & Seow-Choen (1995)	29	17 (59%)	12 months (median)	Not reported
Endoscopic				
Laser				
Chapuis *et al.* (1996)	20	15 (75%)	36 months (median)	-
Viggiano *et al.* (1993)	47	41 (87%)	14 months (median)	-
Argon (APC)				
Silva *et al.* (1999)	28	26 (92%)	10 months (mean)	-
Tam *et al.* (2000)	15	15 (100%)	24 months (median)	-
Kaasis *et al.* (2000)	16	16 (100%)	10.7 months	1 (6.2%)

*Only studies with 15 or more patients have been included

In contrast to its role in chronic radiation proctitis, sucralfate enemas have been reported, in a double blind controlled trial comprising 86 patients, as having limited efficacy in cases of acute radiation proctitis (O'Brien *et al.*, 1997). In a more recent study, Kneebone *et al.* (2001) conducted a double-blind randomized trial incorporating 335 patients who received either oral sucralfate suspension or placebo during radiotherapy. No significant difference was found between the two groups with regards to stool frequency but more importantly, there was increased bleeding in the sucralfate group. The cause of the increased bleeding in the sucralfate group is difficult to explain but the study confirms the ineffectiveness of oral sucralfate in the management of acute radiation proctitis.

Hyperbaric Oxygen

Hyperbaric oxygen improves oxygen transport in ischaemic tissue (Zel, 1990), promotes angiogenesis and development of granulation tissue through enhanced leukocyte activity and fibroblast proliferation (Hader *et al.*, 1993). Charneau *et al.* (1991) initially reported it as useful in the treatment of chronic radiation proctitis. Symptomatic response to hyperbaric oxygen therapy has subsequently been reported in 9 of 14 (64 %) (Warren *et al.*, 1997), 10 of 18 (55.6%) (Woo *et al.*, 1997) and 4 of 4 (100%) (Kitta *et al.*, 2000) patients with chronic radiation proctitis. However, the follow-up period in these studies was limited. The lack of widespread availability of hyperbaric oxygen and its potential untoward effects such as middle ear and sinus barotrauma, toxicity to the respiratory and central nervous systems, claustrophobia, euphoria and visual disturbances (Brady *et al.*, 1989) may be factors limiting its widespread use.

Short Chain Fatty Acids

Short chain fatty acids (SCFA) play a vital role in maintenance of colonic integrity and metabolism and once absorbed are used preferentially as fuel for colonic epithelial cells (Cook & Selin, 1998). SCFA improve nutrient delivery to the colonic mucosa and have been found to be effective in the treatment of ulcerative colitis (Scheppach *et al.*, 1992). However their role in chronic radiation proctitis has not been adequately evaluated. Al-Sabbagh *et al.* (1996) managed 7 patients with SCFA evaluating improvement in clinical, endoscopic, and pathological parameters of radiation proctitis. Four weeks of treatment with SCFA enemas resulted in clinical improvement in all patients. No significant changes were detected in endoscopic and pathological parameters. Pinto *et al.* (1999) reported that SCFA were more effective than placebo in their study encompassing 16 patients. However a double blind randomised control trial comprising 12 patients failed to show any benefit of SCFA in the form of butyric acid enemas (Talley *et al.*, 1997).

Endoscopic Treatment

Laser Coagulation

Endoscopic electrocoagulation utilising the Neodymium: Yttrium-Aluminium-Garnate (Nd:YAG) laser has been used effectively in the treatment of chronic radiation proctitis (Fantin *et al.*, 1999). Barbatzas *et al.* (1996) managed 9 patients at a median of 4 months after the onset of rectal bleeding with the Nd:YAG laser repeating this monthly until bleeding stopped. An average of three treatment sessions were required and only a single patient required transfusion after completion of treatment over a follow-up period of 2 years. There were no treatment-related complications. Chapuis *et al.* (1996) managed 20 patients with the Nd:YAG laser and obtained a 75% response rate over a follow up period of 3 years. Viggiano *et al.* (1993) reported significant improvement in 87% (41 of 57) of patients in terms of control of rectal bleeding and blood transfusion requirement when patients with chronic radiation proctitis were treated with the Nd:YAG laser (Table 1). A paint-on technique delivering 4,000 – 5,000 joules over 3 therapeutic sessions has been recommended to ensure efficacy. Patients who relapse with recurrent bleeding can undergo repeated treatment safely (Lucarotti *et al.*, 1991).

The argon laser has also been reported to be effective in the treatment of chronic radiation proctitis by Taylor *et al.* (1999) who utilised the technique to treat 14 patients, of which 10 (70%) required further treatment for relapse over a 3-5 months follow-up period. Endoscopic methods however are limited by high running costs and the need for specialised equipment. In addition, rectal damage and resulting strictures and perforations may occur as complications of treatment by the Nd:YAG laser and less frequently, the Argon laser (Hunter *et al.*, 1984; Taylor *et al.*, 1993).

Argon Beam Plasma Coagulation

Argon beam plasma coagulation (APC) utilises sprayed argon gas, ignited by a spark generated by a bipolar electrosurgical unit to result in the coagulation of the superficial layer of the rectum to a depth of 2-3mm (Fantin *et al.*, 1999). It is less expensive and is safer than laser therapy. Complications are uncommon and thus far only 2 cases of subclinical rectal strictures have been reported, even though the authors (Tam *et al.*, 2000) who reported these complications had a 100% response rate with this modality (Table 1). Multiple treatment sessions are usually required which may be as frequent as two to four applications.

Silva *et al.* (1999) reported symptomatic improvement in 26 of 28 patients (93%) (mean follow-up 10 months) treated by argon beam coagulation (Table 1). Kaasis *et al.* (2000) in their retrospective analysis of 16 patients with chronic radiation proctitis managed with a mean of 3.7 APC treatment sessions found an improvement in all patients. Seven of the 16 patients had no recurrent rectal

bleeding while the rest had negligible symptoms (Table 1). Taieb *et al.* (2001) utilised argon plasma coagulation in 11 patients with chronic radiation proctitis who were resistant to medical treatment, which had included topical steroids, 5-aminosalicylic acid and occasionally sucralfate. Seven of the patients required blood transfusions depicting the severity of the proctitis. The bleeding stopped in 9 patients and was greatly reduced in 2 during a mean follow-up period of 19 months. Tjandra & Sengupta (2001) demonstrated similar efficacy in their management of 12 patients who did not respond to topical formalin therapy. At a median follow-up of 11 months, 10 patients (83 percent) had a significant reduction in the severity and frequency of bleeding, with complete cessation in 6 (50%). The median number of treatment sessions was two and the number of sessions correlated with the extent of the proctitis.

Formalin

Rubinstein *et al.* (1986) initially reported on the management of haemorrhagic proctitis by application of formalin to the rectal mucosa on a single patient. This arose as a result of reports on the effective management of haemorrhagic radiation cystitis through the instillation of 10% intravesical formaldehyde (Donahue & Frank, 1989), a form of therapy utilised as early as 1969 (Brown, 1969). Formalin (formaldehyde) is oxidized to formic acid following absorption. Formic acid, which has a half life of 90 minutes, is excreted through the urine as a sodium salt or may be further oxidised to carbon dioxide and water (Goodman & Tephly, 1975). Direct contact of formalin with the rectal mucosa is required resulting in chemical cauterisation of the inflamed and telangiectatic radiation affected mucosa which manifests as mucosal blanching on endoscopy (Seow-Choen *et al.*, 1993). Treatment can be achieved by direct gauze application or rectal instillation of formalin. Direct gauze application under vision appears to be the better technique as it minimises contact with normal rectal mucosa and the perianal skin thereby reducing the risk of formalin induced damage to these structures.

Mathai & Seow-Choen (1995) reported their experience with formalin application under direct vision in 29 patients with radiation proctitis (diagnosed by endoscopy and histology), of whom, 15 had showed no response to previous medical treatment including steroid enemas. They reported that after a mean follow-up period of one year, 22 of the 29 patients (76%) had no subsequent bleeding, 5 had minor bleeding, and 1 had continued bleeding requiring transfusion and 1 patient developed a rectal stricture (Table 1). Yegappan *et al.* (1998) utilised topical formalin application in 55 patients with radiation proctocolitis, 49 (89%) of who had successful control of bleeding (Table 1). Roche *et al.* (1996) similarly reported therapeutic efficacy of formalin application in a smaller cohort of 6 patients, all of whom were asymptomatic and complication free at one year follow-up with 4 patients benefiting immediately following a single treatment session.

Rectal instillation with 4% formalin allowing formalin – mucosal contact time of 15 minutes followed by normal saline rectal irrigation (to neutralise) has been reported to control bleeding in all eleven patients with haemorrhagic radiation proctitis over a two year follow-up period (Counter *et al.*, 1999). However, of the 11 patients, 4 suffered complications in the form of minor liquid stool incontinence (2), rectal ulceration (1) and anal stenosis (1).

Surgery

The indications for surgical intervention in chronic radiation proctitis include intractable symptoms, which fail to respond to medical treatment and radiation induced fistula formation. Rectal resection with primary anastomosis, rectal excision followed by end colostomy and oversew of the rectal stump (Hartmann's procedure) and abdomino-perineal resection have been performed for the treatment of radiation proctitis. However, surgery in a previously irradiated field is hazardous and is fraught with potential complications including bleeding, anastomotic leaks, sepsis and damage to neighbouring vital structures such as the ureter. Patients who have previously undergone incomplete rectal resection and who have a residual stump (Hartmann's procedure) have been reported to subsequently suffer from further symptoms including bleeding, mucus discharge and tenesmus (Gilinsky *et al.*, 1983).

Techniques to restore bowel continuity and restore rectal reservoir function such as colo-anal pouch construction have been performed for radiation proctitis but reported to be complicated by tenesmus, rectal urgency and rectal incontinence (Browning *et al.*, 1987; Gazet *et al.*, 1985).

Following abdomino-perineal resection of the rectum impaired wound healing may result in wound complications especially in the perineal wound. Cooke & De Moor (1981) reported successful construction of a colo-anal anastomosis in 37 patients who had previous radiation for carcinoma of the cervix. The success of this technique, in which only a single patient developed pelvic sepsis, was attributed to continuous pelvic irrigation carried out for 72 hours post-operatively. Rectal continence for flatus and liquid stool was reported to be present in 75% of their patients at one-year follow-up. von Flue *et al.* (1996) restored adequate rectal reservoir function in two patients after rectal resection for radiation proctitis through the construction of a neo-rectal reservoir utilising the ileum and caecum. However, one patient developed a low rectal cancer within the previously irradiated segment of bowel. A colonic J-pouch has also been utilised as a neo-rectal reservoir with a satisfactory functional outcome (Lucarotti *et al.*, 1991).

The surgical treatment of radiation induced fistula formation is complex and is frequently plagued by complications and resultant fistula recurrence. Advancement flaps although not a major or hazardous surgical undertaking has been used but results have been disappointing. Tissue interposition utilising a tongue of mobilised omentum or other well vascularised tissue has also been reported (Graham 1965; Bricker *et al*., 1986). Radical surgery with extensive excision of the fistula together with accompanying neighbouring radiation affected tissue and subsequent colo-anal anastomosis although painstaking may be the optimal therapeutic strategy. The surgical treatment of radiation proctitis and radiation induced fistula formation is complex and beset by potential complications and should ideally be performed by surgical units regularly undertaking similar procedures.

Summary

The overall management of radiation proctitis is gradually improving though clear guidelines on the ideal form of treatment options that are available continue to be ill defined. Interventional agents in the form of argon plasma coagulation and local formalin application, in managing chronic radiation proctitis, have shown promise even though their long term effectiveness has yet to be confirmed. Despite the possibility of requiring prolonged treatment, pharmacological agents such as sucralfate still appear to play a role especially in cases of mild radiation proctitis or in institutions where sophisticated equipment and the expertise for thermal energy application are not available.

Management of chronic haemorrhagic radiation proctitis should be tailored to suit the facilities available within an institution. The establishment of a treatment protocol is of valuable importance as the condition may be managed in the early stages by a number of different medical specialties, which includes surgeons, gynaecologists, gastroenterologists or even oncologists. This would help avoid treatment-related delays and unnecessary morbidity. Failure of medical treatment and formalin application should prompt the physician to refer the patient to a centre with available resources of dealing with complicated cases. Surgery should be reserved for patients with unrelenting and intractable symptoms and ideally only undertaken by those experienced in managing this condition.

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