Systematic review for non-surgical interventions for the management of late radiation proctitis

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Chronic radiation proctitis produces a range of clinical symptoms for which there is currently no recommended standard management. The aim of this review was to identify the various non-surgical treatment options for the management of late chronic radiation proctitis and evaluate the evidence for their efficacy. Synonyms for radiation therapy and for the spectrum of lower gastrointestinal radiation toxicity were combined in an extensive search strategy and applied to a range of databases. The included studies were those that involved interventions for the non-surgical management of late radiation proctitis. Sixty-three studies were identified that met the inclusion criteria, including six randomised controlled trials that described the effects of anti-inflammatory agents in combination, rectal steroids alone, rectal sucralfate, short chain fatty acid enemas and different types of thermal therapy. However, these studies could not be compared. If the management of late radiation proctitis is to become evidence based, then, in view of its episodic and variable nature, placebo controlled studies need to be conducted to clarify which therapeutic options should be recommended. From the current data, although certain interventions look promising and may be effective, one small or modest sized study, even if well-conducted, is insufficient to implement changes in practice. In order to increase recruitment to trials, a national register of cases with established late radiation toxicity would facilitate multi-centre trials with specific entry criteria, formal baseline and therapeutic assessments providing standardised outcome data.

Keywords: radiotherapy; complications; proctitis; systematic review

Pelvic radiotherapy is an essential component of curative therapy for many cancers of the urological, gynaecological and gastrointestinal tracts. In the treatment of pelvic malignancy there is a need to minimise the risk of chronic radiation injury to normal tissue without compromising the possibility of cure. The gastrointestinal tract and in particular the rectum, is the site most frequently affected. The prevalence of severe toxicity such as fistulation, stricture formation, transfusion-dependent bleeding or secondary cancers after pelvic radiotherapy is unknown but has been estimated to be 5% at 10 years (Nostrant, 1995) although this may be an underestimate (Komaki et al, 1995; Tan et al, 1997; Denton et al, 2000). Much more common may be lesser side effects such as diarrhoea, urgency, faecal incontinence and tenesmus which in recent studies have been suggested to impair quality of life considerably (Kollmorgen et al, 1994; Schultheiss et al, 1997).

Acute radiation proctitis refers to radiation-induced injury of the rectum, during or within 3 months of radiotherapy. Chronic radiation proctitis can continue from the acute phase or begin after a latent period of at least 90 days (median time 8–12 months) (Eifel et al, 1995) and may be more common in those who develop severe acute proctitis (Denham et al, 1999), and in those with diabetes, inflammatory bowel disease, hypertension or peripheral vascular disease. Most of these risk factors have been defined by studies dependent on suboptimal assessment of rectal toxicity. Other factors which may increase the risk of late complications include tumour stage, and the total dose and fractionation of radiation, although the severity of radiation damage may not be entirely dependent on the radiation dose (Schwarchuk et al, 2000).

Whether a patient as developed chronic proctitis may be assessed in various ways. Changes in symptoms such as irregularity of bowel dysfunction, rectal blood loss or pain may be graded according to criteria stated in systems such as LENT SOMA and the Franco-Italian Glossary (Chassagne et al, 1993). The criteria for the grade of severity varies with the scoring system used, emphasising the need for a single universally agreed measure, but there are no described specific radiological features which define radiation proctitis (Capps et al, 1997). Endoscopically, proctoscopy, rigid sigmoidoscopy or flexible sigmoidoscopy may be used but it is recognised that these different methods may not produce reproducible findings between observers (Baron et al, 1964). Tissue biopsy may be inconclusive. The few small longitudinal studies of ano-rectal physiological parameters following RT that have been published are contradictory (Iwamoto et al, 1997; Yeoh et al, 2000).

In other inflammatory conditions affecting the bowel, symptoms and measures of disease activity may correlate poorly (Yoshida, 1999) and there has been little research to determine how endoscopic or radiological appearances relate to bowel function. Severe fibrosis with strictureting may provide incontrovertible evidence of radiation-induced damage but radiation-induced bowel changes are also seen in patients without symptoms and sometimes
it can be hard to attribute the patients’ bowel habit directly to physical damage caused by radiation to the rectum.

New gastrointestinal symptoms may be triggered for many reasons. Firstly, therefore, in the patient who has undergone radiotherapy, it may be difficult to untangle the relative contribution of psychological and physical damage to bowel function. Secondly, when there is severe physical radiation-induced damage present in the rectum, it is possible that patients will also have other sites of bowel damage, perhaps leading to bile salt or fat malabsorption. Thirdly, published series may not represent a true cross section of irradiated patients. There is some data suggesting that the reported number of cases with chronic radiation proctitis and a proportion of patients who seek help for subsequent symptoms is a fraction of the true prevalence (Yeoh and Horowitz, 1987; Ooi et al, 1999). Experience from both oncological and gastroenterology practice has long shown that unless directed questions are asked and exact answers pursued that patients may not tell their physicians about their specific gastrointestinal symptoms, particularly if they feel the physician is not in a position to do anything about them. The medical treatment of radiation proctitis is not clearly defined and management is often difficult. This is in part, due to problems establishing the diagnosis and also because a proportion of the biological changes may not be reversible.

The aim of this study was to examine systematically the non-surgical treatments that have been proposed for this condition and the quality of the evidence that suggests those treatments may be efficacious.

MATERIALS AND METHODS

(1) Criteria for considering studies for this review:

Types of studies
Randomised studies were included preferentially for analysis. Conclusions from the non-randomised, non-controlled data were drawn if there was insufficient evidence from randomised controlled trials.

Types of participants
Patients must have been diagnosed with a pelvic malignancy and undergone pelvic radiotherapy as part of their treatment schedule, subsequently developing radiation proctitis of any grade, continuing from completion of radiotherapy for more than three months, or occurring more than three months after completion of radiotherapy.

Interventions
Studies were included which described the use of non-surgical interventions for the treatment of late radiation proctitis and the specific intervention was used either vs a placebo/nothing or against other therapies.

(2) Search strategy for identification of studies:

Concepts
(A) Synonyms for radiation therapy
(B) Synonyms for the spectrum of lower gastrointestinal radiation toxicity
(C) Concepts A and B combined with the Boolean operator 'AND'

A filter was not used because any type of study was considered. This basic strategy was expanded for text and MeSH terms before being applied to a sequence of databases. Relevant studies were identified and the inclusion criteria were then applied.

Databases
In order to be as comprehensive as possible search strategies were employed to identify all relevant studies irrespective of language. First, electronic databases were searched. The time frame used was from April 2001 back to 1966 (Table 1). Secondly, reference lists of identified studies and the relevant chapters of major oncology and gastroenterology text books were searched. Thirdly, groups and individuals likely to hold unpublished data were approached (Table 2).

(3) Methods of the review:

A final list of all potential relevant articles was created in one core database and were assessed independently by two reviewers to determine whether they complied with the preceding inclusion criteria for this the review. Where differences existed they were resolved by consensus and when necessary in consultation with a third reviewer. Included studies were graded according to the criteria used by the NHS executive (Table 3).

(4) Statistics:

Dichotomous data is expressed as the odds ratio. Uncertainty in each treatment is expressed using 95% confidence intervals (95% CI). Continuous data, i.e. symptom scores, were converted to the weighted mean differences and an overall weighted mean difference was calculated with standard errors. The Cochrane Review Manager software RevMan 4.1 was used for estimation of overall treatment effects/meta-analysis of results. Both fixed and random effects models were used to calculate a weighted average of the treatment effects across the studies under review. Sensitivity analyses as well as including study quality (quality of allocation concealment) also included year of publication, the type of outcome measures, and random and fixed effects models if appropriate.

Table 1 Databases searched for this review

| Databases searched for this review |
|-----------------------------------|
| **Electronic databases** |
| 1. MEDLINE – on OVID. Searched from 1966 to 2001. |
| 2. EMBASE – on OVID. Searched from 1980 to 2001. |
| 3. CANCERCD – on Silver Platter. Searched from 1980 to 2001. |
| 4. Science citation index (SCI) on BIDS ISI from 1991 to 2001. |
| 5. CINAHL – on OVID. Searched from 1980 to 2001. |
| 6. Database of Controlled trials Register (CENTRAL/CCTR Cochrane Library 2001). |
| **Grey Literature** |
| 1. Dissertation Abstracts – on Silver Platter. Searched from 1961 to 2001. |
| 2. The National Health Service National Research Register – via CD-ROM March 2001. |
| 3. Index to Scientific and Technical Proceedings (ISTP) – on BIDS ISI. 1982 – 4/2001. |
| 4. SIGLE – via BLAISE Line British Library Current Edition. |
| 5. Boston Spa Conferences – via BLAISE Line British Library Current edition. |
| 6. Inside Conferences – via BLAISE Line British Library Current edition. |

Table 2 Groups and individuals contacted for further unpublished data related to this topic

| Groups and individuals contacted for further unpublished data related to this topic |
|----------------------------------|
| 1. Individual authors of the relevant studies |
| 2. Every member of the UK Link-Gynaecology Oncology Group |
| 3. Every member of the EORTC Gynaecological Oncology Group |
| 4. Letters were published in ‘Clinical Oncology’ and ‘Palliative Medicine’ explaining the review and requesting unpublished data |
| 5. Gynaecological Oncology Cochrane Review group |
| 6. Gastroenterologists who have an interest in this field |

EORTC=European Oncology and Radiation Therapy Collaboration.
RESULTS

Using the search strategy described, studies were identified, of which 62 met the inclusion criteria, and included three randomised controlled trials (Table 4).

Studies using anti-inflammatory agents

First line treatment of this condition is conventionally with anti-inflammatory agents. Seven studies were identified which used such agents. The highest level of evidence was provided by three randomised controlled trials (grade IC).

Kochhar et al, 1991, Grade IC, India Radiation-induced proctosigmoiditis. Prospective, randomised, double-blind controlled trial of oral sulfasalazine plus rectal steroids vs rectal sucralfate (n=37). There were 36 females treated for cervical cancer and one male treated with prostate cancer. The mean duration from the completion of radiotherapy was 8.3 months. Exclusion criteria were the use of steroids in the last 2 weeks. Symptoms were assessed using an in-house scoring system for diarrhoea, bleeding, tenesmus and endoscopic appearance. According to the score the cases were then graded. Baseline characteristics in both groups were comparable. Patients were randomised to either, rectal prednisolone 20 mg b.d. and oral sulfasalazine 500 mg t.d.s. (n=18) or rectal sucralfate suspension 2 g b.d. with oral placebo t.d.s. for sulfasalazine (n=19). There were three drop-outs in the anti-inflammatory group and two in the sucralfate group. Treatment was continued for 4 weeks.

Eight out of 15 in the anti-inflammatory group showed clinical improvement compared to 16 out of 17 in the sucralfate group. Seven out of 15 in this group showed endoscopic improvement compared to 12 out of 17 in the sucralfate group, and the degree of improvement was greater in the sucralfate compared to the anti-inflammatory group. The odds ratio for clinical improvement was 14.0 (95% CI 1.46–134.26). No difference in endoscopic appearance was detected between the sucralfate and the anti-inflammatory groups, odds ratio 2.74 (95% CI 0.64–11.76). The response was only reported for the 4 week follow-up period. There was no quality of life assessment.

Rougier et al, 1992, Grade IC, France Rectites radiques: efficace comparee de deux types de corticoides adminstre localement (n=32) (Radiation proctitis: comparing the efficiency of local administration of two types of corticosteroids). There were 29 females and three males, treated with radiotherapy for 23 gynaecological malignancies and nine colorectal or anal tumours. All had completed radiotherapy a minimum of 6 months ago. The diagnosis of radiation proctitis was graded on flexible sigmoidoscopy and on the degree of bleeding. Two rectal steroid preparations were compared, 5 mg betamethasone enema b.d. (n=16) or 90 mg hydrocortisone acetate mousse b.d. (n=16). The outcomes used were bowel activity, rectal bleeding, tenesmus with endoscopic grading. They were assessed clinically and endoscopically at 14 and 28 days. Two patients were lost to follow-up from the betamethasone group, and no treatment related complications were reported.

Over the 4 weeks of treatment the endoscopic appearance improved in a greater proportion of the hydrocortisone group (12 out of 16) than the betamethasone group (5 out of 14), odds ratio 5.40 (95% CI 1.12–26.05). There was no difference in the reduction of bleeding between the hydrocortisone group (6 out of 16) and the betamethasone group (3 out of 14), odds ratio 2.20 (95% CI 0.43–11.22). The response was only reported for the 4 week follow-up period. Potential bias in this study includes more severe inital disease in the betamethasone group and also that...
the betamethasone enema was poorly tolerated in 10 out of 14 compared with 2 out of 16 in the hydrocortisone group. There was no quality of life assessment.

**Cavic et al, 2000, Grade IC, Croatia** Metronidazole in the treatment of chronic radiation proctitis: clinical trial (n=60) Sixty patients with rectal bleeding and diarrhoea were allocated to treatment with metronidazole (3 x 400 mg orally per day), mesalazine (3 x 1.5 g orally per day), and betamethasone enema (daily) or mesalazine and betamethasone enema, but without metronidazole, for 1 year. The efficacy of metronidazole was assessed on the basis of rectal bleeding, diarrhoea, and rectosigmoidoscopy in all patients. The incidence of rectal bleeding and mucosal ulcers was significantly lower in the metronidazole group at 4 weeks (P=0.009), 3 months (P=0.031), and 12 months (P=0.029). There was also a significant decrease in diarrhea and oedema in the metronidazole group, after 4 weeks of treatment (P=0.044), 3 months (P=0.045), and 12 months (P=0.034). One year after treatment, 22 out of 24 of the metronidazole group demonstrated a reduction in the grade of their rectal bleeding compared to 5 out of 12 in the group treated with mesalazine and betamethasone, odds ratio 15.40 (95% CI 2.43 – 97.68). Similarly 23 out of 24 in the metronidazole group compared to 8 out of 12 had experienced reduction in their diarrhoea and rectal erythema, odds ratio 11.50 (95% CI 1.11 – 118.71). The rectal ulceration at 1 year had decreased in 22 out of 24 of the metronidazole group compared with 7 out of 12 of the group treated with anti-inflammatories alone, odds ratio 7.86 (95% CI 1.24 – 49.84). No side effects were reported.

**Studies using SCFA enemas**

Short chain fatty acids (SCFA) are the main oxidative fuel of colonic mucosa and their use may be impaired in chronic radiation proctitis. SCFA are predominantly produced in the colon by anaerobic bacterial fermentation of non-absorbed carbohydrates, in dietary fibre. Butyric acid is the most important. SCFA also exert a trophic effect on the colonic mucosa by stimulating the physiological pattern of proliferation and promoting cellular differentiation. In the setting of radiation induced ischaemia, the associated mucosal atrophy may interfere with mitochondrial fatty acid oxidation so supplementation of SCFA in the form of enemas could overcome this deficiency and improve the energy supply to colonocytes. Moreover, the dilator effect of SCFA on arteriolar walls may improve mucosal blood flow. Five reports of four studies were identified in this section. Two were randomised studies.

**Talley et al, 1997, grade IC (Australia)** Short-chain fatty acids in the treatment of radiation proctitis: a prospective randomised, double-blind, placebo-controlled, cross-over pilot trial (n=15) Two females and 13 males; 12 prostate, one cervix and two rectum, treated with pelvic radiotherapy a mean period of 12.2 months earlier were assessed using an in-house symptom score (six items: rectal pain, rectal bleeding episodes, quantity of blood, days of diarrhoea, number of stools and urgency). Endoscopic and histological scores were also calculated. The patients were randomised to receive either a normal saline placebo enema or a 60 ml enema containing 40 mm of butyrate administered twice a day. Each treatment was prescribed for 2 weeks with a 1 week washout period between treatments. Three patients failed to complete the course. The total symptom score at baseline treated from 2–11 (median 5.5). There was a non-significant improvement in symptom scores on the active treatment, mean score 3.5 (range 3–5) compared with 4.5 mean score (range 3–6) for those receiving placebo. The results are published in the form of the median value (plus interquartile range) for the average placebo period and active period and the raw data is required from the authors before the results can be dichotomised. There was no quality of life assessment.

**Pinto et al, 1999, grade IC, (Portugal)** Short chain fatty acids are effective in short term treatment of chronic radiation proctitis. Randomised, prospective double blind, controlled trial (n=19) Nineteen patients (one male and 18 females) with grade III chronic radiation proctitis were randomised to SCFA enema, 60 ml b.d. for 5 weeks (n=10) or a placebo (n=9). Baseline characteristics of each group were comparable. The specific outcome variables monitored for a period of 6 months were: adverse effects, number of days of rectal bleeding in the previous week and haemoglobin. The endoscopic appearance was scored for: hyperaemia and neovascularisation, friability, oedema and erosions by two independent assessors who were blinded to the treatment. Biopsies for mucosal DNA and protein content were also measured.

One patient from the SCFA arm and two from the placebo arm did not complete the trial. At 5 weeks the patients treated with SCFA had a significant reduction (4.4 to 1.4) in the number of days per week of rectal bleeding (P=0.001) whereas in the placebo group it fell from 5.1 to 3.4 (P=0.12). Haemoglobin levels at the end of the treatment period were higher in the SCFA group, 13.1 + 0.9 vs 10.7 ± 2.1 g dl⁻¹ (P=0.02) and the endoscopic scores had decreased significantly in both groups but were significantly lower in the SCFA group (P=0.02). Changes in DNA and protein concentration decreased in both groups but significantly more so in the placebo treated group (P=0.05). In long term follow-up two patients failed to complete the course from the placebo group because of severe bleeding leaving nine in the SCFA arm and five in the placebo group. At the end of the 6 months the endoscopic score was similar in the two groups. No adverse events related to either of the groups were noted and there was no quality of life assessment. As a consequence of the way the data has been reported we have presented this data as a weighted mean difference (WMD) which for endoscopic scores was 1 (−2.33 to 4.33), a statistically non-significant difference between SCFA and placebo. For the rectal bleeding episodes per week the WMD was −2 (−4.4 to −0.4), again a statistically non-significant difference, but perhaps showing a trend to less days of rectal bleeding with the SCFA enema.

**Other studies**

In addition, two non-randomised series were identified. Mamel et al (1995) (IIIC), in an open study of six cases using SCFA reported a significant improvement in clinical and mucosal response although this is not statistically assessed. Al-Sabbagh et al (1996) (IIC) in their prospective pilot study of seven cases demonstrated a significant improvement for rectal bleeding but not endoscopic appearances. The duration of the response is not stated other than for the treatment period of 4 months in Al-Sabbagh et al (1996). Quality of life data was not presented.

Although there were two trials in this category using the same intervention against a placebo, they are not directly comparable due to differences in the outcome measurements and method of data presentation. Talley et al (1997) was a cross-over study and used a cumulative score encompassing the number of episodes of rectal bleeding per week. Pinto et al (1999) recorded the number of days on which rectal bleeding occurred. Although both sets of cases were scored endoscopically, this is not on the same scale so

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that the numbers are not comparable. Additionally, regardless of the different scales, because of the absence of individual patient data we were unable to dichotomise and combine the data. Talley et al (1997) reported no benefit from the use of SCFA (but the treatment period of 2 weeks was short), and Pinto et al (1999) also reported no significant improvement either endoscopically or on rectal bleeding. It is not surprising that neither of these trials yielded any significant results. These numbers are small for any type of study but especially for prospective, randomised ones and therefore statistically underpowered.

Studies using sucralfate and pentosan polysulphate

Sucralfate is a highly sulphated polyaniionic disaccharide. In this setting, its postulated mechanisms of action include stimulation of epithelial healing and the formation of a protective barrier. Pentosan polysulphate (PPS) is a synthetic derivative of a glycosaminoglycan which is present in the surface of the bladder, vessels and the gastrointestinal tract lining. The ability of PPS to reduce epithelial permeability and prevent adherence has been extrapolated to the large bowel. Eight relevant references were identified addressing the effect of these agents in chronic radiation proctitis. One is a RCT, two prospective open studies, and four studies describe the effect of rectal sucralfate in case reports or small series with one report of the effect of oral sucralfate.

Kochhar et al, 1991, Grade IC, India Radiation-induced proctosigmoiditis. Prospective, randomised, double-blind controlled trial of oral sulphasalazine plus rectal steroids vs rectal sucralfate (n=37). The strongest evidence for the use of sucralfate comes from the evidence presented in this trial, which compares the use of anti-inflammatories with rectal sucralfate. Criticisms of this study are that the allocation concealment is not clear and there is no explanation for those cases lost to follow-up. The endpoints used to evaluate response, i.e. scores for clinical and mucosal effect, are useful and show that the odds ratio for the beneficial effect of sucralfate on clinical outcomes is 14.0 (95% CI 1.46–134.26) and 2.74 (95% CI 0.6–11.75) for mucosal response. The duration of follow-up was only 4 weeks.

Other studies
In addition seven non-randomised studies were identified. In two prospective studies Kochhar et al (1999), followed 26 cases treated with rectal sucralfate, and Grigoby et al (1990) described 13 cases treated with oral PPS, IIC. Both are well conducted with definitive outcomes of response and show a benefit for the use of rectal sucralfate for a period of 4 months and oral pentosan for 1 year, respectively. Of the retrospective reports (four describe the use of rectal sucralfate as a case report (Kochhar et al, 1988), and series of three, eight and three patients respectively (Ladas and Raptis, 1989; Kochhar et al, 1990; Stockdale and Biswas, 1997). All showed a benefit in both clinical and mucosal outcome, although the majority of these were not graded or scored to demonstrate significant differences. One report outlines the beneficial effect of oral sucralfate in established chronic radiation proctitis in three isolated cases for a minimum of 3 years (Sasai et al, 1998). Morbidity related to sucralfate was not reported and there was one case of a rash with oral pentosan. The treatment intervals were generally short and none provide any quality of life data.

Formalin therapy

In radiation proctitis, vascular telangiectasia and non-healing mucosal ulceration, perhaps due to an underlying obliterator arteritis, may lead to severe recurrent haemorrhage. Formalin may sclerosis and seal fragile neovascularisation in radiation damaged tissues preventing further bleeding. Application directly to the mucosa produces local chemical cauterisation. It can stop bleeding by sealing the neovascularised telangiectatic spots and ulcers. The success of bleeding control is related to the accurate localisation and application of formalin to all the affected points.

We identified 15 references relating to the use of rectal formalin. Three were prospective case series (level IIC evidence) and 12 were retrospective reports (level III). These reports are quite heterogeneous (Table 5). None used a control group or quoted any quality of life data. The severity of radiation proctitis is graded in only one report. The technique and the concentration of formalin used vary. The two main approaches use irrigation of formalin (five reports), either 3.6% formalin solution (n=2) or 4% formalin solution (n=3). The other method (described in 10 reports) is the direct application of gauze soaked in formalin, and although most reports used 4% formalin (n=9) there was one report that used 10% solution. None of the reports used an objective scoring system to assess the response to treatment, but two reports described the effect in terms of changes of haemoglobin level. The remainder described the response in terms of the transfusion requirements or the effect

| Reference | Level of evidence | % Formalin technique | n | Resp rate | Duration of response | Morbidity | QOL | Mortality |
|-----------|-------------------|----------------------|---|-----------|---------------------|-----------|-----|---------|
| Rubinstein et al, 1986 | IIC | 3.6% – irrigation | 1 | 100 | 14 months | 0 | 0 | 0 |
| Reimer et al, 1987 | IIC | 3.6% – irrigation | 2 | 100 | 14 months | 0 | 0 | 0 |
| Seow-Choen et al, 1993 | IIC | 4.0% – direct | 8 | 100 | 6 months | 1 (stricture) | 0 | 0 |
| Isenberg et al, 1994 | IIC | 4.0% – direct | 2 | 100 | 3 months | 0 | 0 | 0 |
| Correa et al, 1994 | IIC | 4.0% – irrigation | 14 | 64% CR | 6 months | 0 | 0 | 0 |
| Mathai and Seow-Choen, 1995 | IIC | 4.0% – direct | 29 | 75 | 12 months | 1 (stricture) | 0 | 3-cancer |
| Biswal et al, 1995 | IIC | 4.0% – direct | 16 | 81 | 11 months | 0 | 0 | 0 |
| Chapuis et al, 1996 | IIC | 4.0% – direct | 14 | 71 | 3 months | Not clear | 0 | 0 |
| Sacclandres et al, 1996 | IIC | 4.0% – irrigation | 16 | 81 | not stated | 4 anal ulcers | 0 | 0 |
| Rochte et al, 1996 | IIC | 4.0% – direct | 6 | 100 | 12 months | 0 | 0 | 0 |
| Faragher and Bailey, 1997 | IIC | 10.0% – direct | 7 | 100 | not stated | 1 (anal pain) | 0 | 0 |
| Goldinger, 1998 | IIC | 4.0% – direct | 1 | 100 | not stated | 0 | 0 | 0 |
| Yegappan et al, 1998 | IIC | 4.0% – direct | 55 | 89 | not stated | 0 | 0 | 0 |
| Counter et al, 1999 | IIC | 4.0% – irrigation | 11 | 67 | 20 months | 2 incon, 1 anal | 0 | 0 |
| Coyoli et al, 1999 | IIC | 4.0% – direct | 7 | 86 | 17 months | 1 bleeding sten | 0 | 0 |

CR=complete response (a complete response is the confirmed resolution of the initial features determined at a specific interval); incont=incontinence; n=number of cases; PR=partial response (a partial response is a 50% reduction in the initial features determined at a specific interval); QOL=quality of life; resp rate=responsive rate; sten=stenosis.
on bleeding. Statistical analysis was not presented in any of these reports.

In summary, 208 patients were described with a mean follow-up of 6 months. In each of the reports there appeared to be benefit from the use of formalin in chronic haemorrhagic proctitis, but this may be subject to reporting bias. Serious side effects were reported in 11 patients with five cases of anal ulceration, two rectal strictures, two patients with faecal incontinence and two with anal pain. Minor side effects were not frequently reported. Duration of effect cannot be assessed reliably from the data available but appears to be a minimum of 3 months. The absence of quality of life data means the impact of this treatment from the patient’s perspective cannot be addressed.

Thermal coagulation therapy

Endoscopic coagulation with a variety of devices has been reported to be effective for the control of radiation-induced bleeding. The technique generally used is coagulation of focal bleeding telangiectasia rather than the entire friable mucosa. Several treatment sessions are often required. Scarring and re-epithelisation with more normal tissue tend to occur over time.

Sixteen relevant studies were identified. Apart from one RCT and one prospective series the remaining 14 are retrospective series or reports. Although these case series all refer to the use of ablative therapy in late radiation proctitis, different types of coagulation probes or lasers are described. Eight look at the use of the YAG laser, four at Argon lasers, three at bipolar cautery and two at heater probes. The results of these studies are described in Table 6.

Jensen et al, 1997, (USA) grade IC. A randomised prospective study of endoscopic bipolar electrocauagulation and heater probe treatment of chronic rectal bleeding from rectal telangiectasia (n=21) Selection criteria included pelvic RT at least 2 years earlier, rectal bleeds at least three times per week, anaemia, having failed 1 year of medical therapy and consideration for surgery, and a life expectancy of 2 years. Chronic radiation proctitis was confirmed endoscopically but not graded in 21 cases (18 with carcinoma of the prostate and three with cervical cancer). Patients were randomised to treatment with a heater probe (n=9) or a bipolar electrocauagulation probe (n=12). Treatment sessions were repeated with the same probe till the bleeding resolved and a mean of four sessions per case were administered for both probes. The physicians who subsequently assessed the patients were blinded. All other treatments were discontinued. Assessment was repeated every 4–6 weeks until bleeding stopped and then every 4–6 months for 1 year. If new telangiectasia were noted they were retreated by the same probe.

In both the bipolar probe and the heater probe the mean fall in severe bleeds per case was statistically significant at P<0.05. In the 12 months of endoscopic treatment vs 12 months medical therapy the severe bleeding episodes (defined as a bleed provoking and unscheduled hospital assessment) diminished significantly for the bipolar probe (75 vs 33%) and heater probe (67 vs 11%). The weighted mean difference did not show a significant difference

Table 6 Results of reports for the effects of thermal therapy in late radiation proctitis

| Author              | Power | Response rate | Duration (months) | Side effects (SE)                  |
|---------------------|-------|---------------|-------------------|------------------------------------|
| YAG laser           |       |               |                   |                                    |
| Chapuis et al., 1996 | 40 W  | 30/34         | 6–64              | 4 mucous discharge, 1 acute prostatitis, 1 rectal structure |
| Leuchter et al., 1982 | 60 W  | 1/1 CR        | 24                | None                              |
| Alquiust et al., 1986 | 30–40 W | 2/4 CR    | 12                | 1 tenesmus                        |
| Alexander and Dwyer, 1988 | 80–90 W | 6/8      | 21                | 3 ieus, 1 abdominal pain           |
| Jacobs, 1989        | NA    | 2/2           | 12                | NA                                |
| Lucarotti et al., 1991 | 80 W  | 5/5           | 18                | NA                                |
| Carbatzas et al., 1996 | 20–30 W | 6/9 PR     | 24                | NA                                |
| Taylor et al., 2000 | 4–10 W | 15/23         | 6                 | 2 rectal ulcers                    |

| Argon Laser         | Flow rate | Power | RR | Duration (months) | SE   |
|---------------------|------------|-------|----|-------------------|------|
| Buchi and Dixon, 1987 | 1.5–2.5 ml s⁻¹ | 3.5 W and 7–8 W | 3/3 | 6                 | 1 had cramps |
| O’Connor, 1989      | 0.5 pulses | 1.5 W | 5/5 | 5                 | None          |
| Taylor et al., 1993 | 1.5–2.5 ml s⁻¹ | 3.5 W and 7–8 W | 14/14 | 22                | None          |
| Silva et al., 1999  | 1.5 l min⁻¹ | 50 W  | 26/28 | 10                | None          |
| Fantin et al., 1999 | 3 l min⁻¹ | 60 W  | 7/7  | 18                | None          |
| Kaassis et al., 2000 | 0.6 l min⁻¹ | 40 W  | 16/16 PR | 10                | None          |
| Tam et al., 2000    | 2.0 l min⁻¹ | 60 W  | 15/15 PR | 24                | 2 rectal strictures |

| Bipolar and heater probe | Modality | Power | RR  | Duration (months) | SE   |
|--------------------------|----------|-------|-----|-------------------|------|
| Fuentes et al., 1993     | Heat probe | 20 J pulse⁻¹ | 8/8 | NA                | None          |
| Mannoury et al., 1991    | Bipolar  | setting 5, 2 s pulses | 4/4 | 9/12              | None          |
| Haulk, 1996              | Bipolar  | 2–5 W or 11–25 W | 8/8 | 4/12              | None          |
| Jensen et al., 1997      | Heat probe | 10–15 W, 1 s pulses | 12/12 | 24/12            | None          |
|                          | Bipolar  | 10–15 J   | 9/9  | 24/12             | None          |

CR=complete response; J=Joules; L=Litres; min=minutes; NA=not available; PR=partial response; RR=response rate; s=seconds; W=Watts.

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between the two treatments 0.30 (95% CI −0.35 to 0.90). The reduction in the units of blood transfused per case pre- and post-treatment was only statistically significant in the group treated with the heater probe and the weighted mean difference reflected this (−3.2; 95% CI −4.58 to −1.82). The increase in the haematocrit compared with the baseline was statistically significant for both groups and comparing the effects of the two groups the weighted mean difference favoured the heater probe (−2.90; 95% CI −5.22 to −0.58). During follow-up endoscopy there was resolution of the telangiectasia, scarring or epithelial replacement in all cases in both groups. Patient interviews before, and 6 months after treatment revealed that rectal bleeds, tenesmus and their general health had improved. There were no recorded side effects.

Other studies None of the references in this section state the grade of the proctitis and one study (Silva et al, 1999) uses a formal score to quantify rectal bleeding pre- and post-treatment allowing an objective comparison to be conducted. Generally, outcome assessments used are presence or absence of bleeding, control of bleeding, haemoglobin pre- and post-treatment and transfusion requirements. The point at which transfusion occurs is rarely described making transfusion requirements and haemoglobin values relative measures. The impression is that thermal coagulation therapy has a useful role in haemorrhagic radiation proctitis that is refractory to other medical treatments. This cannot be statistically supported because of the quality of the reports and the size of the trials.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO) has an angiogenic effect and has been shown to cause an eight- or nine-fold increase in the vascular density of soft tissues over air-breathing controls. The subacute and chronic phases of radiation wounds are particularly suited to this form of therapy, HBO acts to stimulate collagen formation at the wound edges through elevation of local tissue oxygen tensions. New microvasculature dependent on collagen matrix, is greatly enhanced in this setting and allows re-epithelialisation to occur.

Nine relevant references were identified, reporting treatment in 86 cases that were followed up for a mean period of 15 months (Table 7). Eight were retrospective series or reports and there was only one prospective observational case series (Williams et al, 1992: level IIC). All of these reports were case series with heterogeneous characteristics. In only two of these reports (Feldmeier et al, 1996; Gouello et al, 1999) were there full baseline assessments of the degree of chronic radiation proctitis with a score or a grade of the histological or symptomatic features. Also the pressures of HBO and duration of the treatment sessions varied. The number of treatments depended on degree of the lesion. Assessment of response was usually with a vague description of the resolution of symptoms but not parameters that could be scored and used for statistical analysis. The duration of response was inconsistently recorded. Quality of life data was not recorded in any report. Side effects were reported in eight cases but were largely transient, minor and related to aural barotrauma. Therefore, although the impression is that HBO may be of value for large bowel chronic radiation changes that are refractory to other treatments, the degree of benefit and the cumulative effect or duration of response cannot be quantified because of the methodology and quality of the data.

Miscellaneous interventions

Oxidative stress is thought to be a major mechanism in the development of chronic radiation proctitis and agents with anti-oxidant properties have been used in an attempt to limit tissue damage in radiation injury. We identified one series investigating the effect of vitamins C and E in the treatment of 10 cases with established chronic radiation proctitis who presented with one or more symptoms including rectal bleeding pain urgency or tenesmus. The severity and frequency of symptoms and a score of the lifestyle impact were used to assess response before and after treatment for 1 year and all reported a sustained improvement in their initial symptoms without side effects (Kennedy et al, 2001).

Strictures of the rectosigmoid junction and rectum are a recognised consequence of late radiation damage. The narrowing results in acute or episodic periods of large bowel obstruction, often decades after the original radiation therapy. Non-surgical dilatation has been attempted. Three relevant studies were identified and included two case reports of the use of a dilator (Triadafilopoulos and Sarkisian, 1990) or stent (Yates and Baron, 1999) and one series of four cases which were endoscopically dilated (Johansson, 1996). Although the strictures are described they are not scored and the absence of a formal baseline assessment and objective response means that the effect which appears to be beneficial in each report cannot be quantified, nor can the duration of response be determined from the data available. Side effects include one case of brief post dilatation bowel pain and another case of perforation. Quality of life issues are referred to in one report where the patients’ general health was felt to improve as a result of the treatment (Yates and Baron, 1999).

Table 7 Hyperbaric oxygen results

| Author          | n      | HBO details       | Follow-up | Response rate | Side effects                  |
|-----------------|--------|-------------------|-----------|--------------|------------------------------|
| Charneau et al, 1991 | 1      | 2.5 ata, 82 bx, 90 min b.d. | 11 months | 1 PR         | None                         |
| Williams et al, 1992 | 3      | 2 ata, mean 44 bx, 90–120 min | 36 months | 2 PR         | 1 perforated ear drum        |
| Nakada et al, 1993 | 1      | 20 ata, mean 30 bx, 90 min | 7 months  | 1 PR         | None                         |
| Feldmeier et al, 1996 | 7      | 2.4 ata, mean 30 bx, 90 min | NA        | 4 PR         | None                         |
| Warren et al, 1997  | 14     | 2 ata, mean 40 bx, 90 min | 14 months | 8 CR         | None                         |
| Woo, 1997         | 18     | 2 ata, mean 24 bx, 105 min | 1 PR      |              | 5 visual trauma               |
| Gouello et al, 1999 | 36     | 2.5 ata, 45 bx, 90 min | 12 months | 9 CR         | 1 aural trauma, 1 angina     |
| Kitta et al, 2000  | 4      | 2 ata, mean 45 bx, 60 min | 3 months  | 1 CR         | None                         |
| Bem et al, 2000   | 2      | NA                | 10 months | 2 CR         | None                         |

ata=atmospheres of pressure; b.d.=twice a day; CR=complete response; HBO=Hyperbaric oxygen; n=number of cases; NA=not available; PR=partial response; bx=treatment sessions.
DISCUSSION

This review of the literature for non-surgical interventions for the management of late radiation proctitis has identified a number of treatment approaches supported by varying levels of evidence. Six controlled studies are reported, three relate to the comparison of different rectal steroid preparations and the comparison between anti-inflammatory agents and rectal sucralfate, two use short chain fatty acid enemas and one contrasts the effect of bipolar electrocoagulation vs the heater probe. These show that the use of sucralfate may be better than anti-inflammatory agents, which in turn may have greater effect if used with metronidazole. Rectal hydrocortisone may be better than betamethasone.

The reports describe slightly different interventions and outcome parameters so that they cannot be compared and a summary statistic cannot be derived. Ironically the wealth of case series although of interest, can only give an impression of effect and cannot be collectively summarised to produce a cumulative response rate or duration of effect. The overwhelming feature of the data presented here is that the majority of references describe one individual’s or one centre’s experience of a specific intervention administered without comparison to a control or another agent. In many cases, it is not clear how extensively patients have been investigated and whether other causes for their symptoms have been excluded. The reasons for the paucity of controlled studies may relate to the relative rarity of late radiation proctitis and the logistic difficulties that exist in compiling a series large enough to be randomised between therapies.

There were a number of specific problems with the details available in many of the identified reports. First, few background details were available with particular respect to the tumour stage and radiation details. Secondly, the method of determining the diagnosis was only occasionally documented. Late radiation proctitis may be less easy to grade accurately on rigid sigmoidoscopy compared to flexible sigmoidoscopy and there is also anecdotal evidence that some of the bowel preparations commonly used for flexible endoscopic examinations may exacerbate the changes seen. None of the endoscopic scoring systems take these factors into consideration but clearly the mode of assessment needs to be recorded for subsequent comparisons. Thirdly, there was rarely a formal baseline assessment of the symptoms and where this was stated the scoring systems were often different so that the grade could not be used as a comparison with other cases. Fourthly, the outcome measures, where used, were variable as was the scoring of the response when performed. The duration of the responses and the side effects of treatments were not always stated. Quality of life scores either before or after the intervention were hardly ever recorded. Deterioration in presenting symptoms may not always relate to failure of the intervention but may be a consequence of tumour or disease progression although this is often difficult to determine as the two scenarios are often indistinguishable. Therefore specific details regarding the method of ascertaining a failed response need to be stated. Finally, interventions were not standardised so that there were substantial variations in dose and administration. These combined factors serve to produce a very heterogeneous cohort of reports that cannot be scored or graded to produce subclasses and objective response rates unless more information is available. A proposed scheme to address all these issues might include:

(1) A detailed account of the determination of the diagnosis including background details such as precise radiation prescription and absence of infection.
(2) Scored symptoms as in Ulcerative Colitis (UC) with the Colitis Activity Index (Rachmilewitz, 1989) or the Ulcerative Colitis Scoring System (Schroeder et al, 1987), before and after the specific intervention.
(3) Scored endoscopic appearance (as for UC e.g. Baron score (Baron et al, 1964) and the Colitis Endoscopic index (Rachmilewitz, 1989)), before and after the specific intervention.
(4) Scored histological assessment (as for UC) which should be standardised.

The outstanding issue is the degree to which radiation induced damage to the rectum contributes to symptoms in this group of patients and how much comes from residual tumour, psychological factors, co-incident small intestinal damage or other changes within the abdomen and pelvis outside the bowel. Some of the areas that need to be addressed include:

(1) How should late radiation proctitis be staged and how should endoscopic, radiological, physiological and quality of life assessments be combined to assess the patient’s needs best?
(2) Who needs intervention?
(3) What treatments are effective?
(4) Is there an optimal step up treatment approach?
(5) How should patients be followed up after treatments, how long for and what parameters should be measured subsequently?

Implications for practice and research

If the management of late radiation practice is to become evidence based then good quality placebo-controlled studies need to be conducted to support the treatment options recommended. This review suggests that late radiation proctitis is not reported very often by patients to the clinicians who deliver the pelvic radiotherapy and as a result a number of fundamental issues remain to be clarified. First, the true incidence of the disease is not clear. Therefore, physicians caring for patients who have undergone pelvic radiotherapy need to be more aware that this group may develop problematic symptoms which may need detailed questioning to elicit and which may require specialist gastroenterological assessment to characterize in detail. Secondly, there is an urgent need to define clearly the diagnostic criteria and a unified grading system by which late radiation proctitis can be categorised. Without such a system, it is unlikely that meaningful randomised studies, particularly in a multi-centre setting, can be designed.

We propose that cases should be enrolled into regional or centralised registers of radiation toxicity or that all such patients should be referred to regional centres with an interest in radiation-induced gut toxicity. In this way terminology, baseline assessments including comorbidity and the documentation of therapeutic effect could be standardised. Interventions could be randomised and outcome data could be pooled to assess the response to treatment objectively. This approach would provide an evidence base of results of different treatments to develop an integrated care pathway for this difficult condition.

REFERENCES

Alexander TJ, Dwyer RM (1988) Endoscopic NdYAG laser treatment of severe radiation injury of the lower gastrointestinal tract: long-term follow-up. Gastrointest Endosc 34(5): 407–411
Alphrist DA, Gostout CJ, Viggiano TR, Pemberton JH (1986) Laser therapy for severe radiation induced rectal bleeding. Mayo Clin Proc 61: 927–931

Al-Sabbagh R, Sinicrope FA, Sellin JH, Shen Y, Roubein L (1996) Evaluation of short-chain fatty acid enemas: treatment of radiation proctitis. Am J Gastroenterol 91(9): 1814–1816
Baron JH, Connell AM, Lennard-Jones JE (1964) Variation between observers in describing mucosal appearances in proctocolitis. BMJ 1964: 89–92
Iwamoto T, Nakahara S, Mibu R, Hotokozaka M, Nakano H, Tanaka M (1997) Effect of Radiotherapy on anorectal function in patients with cervical cancer. Dis Colon Rectum 40(6): 693 – 697
Jacobs M (1989) YAG laser treatment for radiation proctitis. Gastrointest Endosc 35(4): 335 – 356
Jensen DM, Machicado GA, Cheng S, Jensen ME, Jutabha R (1997) A randomised prospective study of endoscopic bipolar electrocoagulation and heater probe treatment of chronic rectal bleeding form rectal telangiectasia. Gastrointest Endosc 45: 20 – 25
Johansson C (1996) Endoscopic dilation of rectal strictures. A prospective study of 18 cases. Dis Colon Rectum 39: 423 – 428
Kaissis M, Oberti E, Burtin P, Boyer J (2000) Argon plasma coagulation for the treatment of hemorrhagic radiation proctitis. Endoscopy 32(9): 673 – 676
Kennedy M, Bruninga K, Mutlu EA, Losurdo J, Choudhary S, Kesavaraman A (2001) Successful and sustained treatment of chronic irradation proctitis with antioxidant vitamins E and C. Am J Gastroenterol 96: 1080 – 1084
Kitta T, Shinohara N, Shirato H, Otsuka H, Koyanagi T (2000) The treatment of chronic radiation proctitis with hyperbaric oxygen therapy in patients with prostate cancer. BJU Int 85: 372 – 374
Kochhar R, Mehta SK, Aggarwal R, Dhar A, Patel F (1990) Sucralfate enema in ulcerative rectosigmoid lesions. Dis Colon Rectum 33: 49 – 51
Kochhar R, Sharma SC, Gupta DB, Mehta SK (1988) Rectal sucralfate in radiation proctitis. Lancet 1988: 400
Kochhar R, Patel F, Dhar A, Sharma SC, Ayyaragi S, Aggarwal R, Goenka MK (1991) Radiation-induced proctosigmoiditis. Prospective, randomized, double-blind controlled trial of oral sulphasalazine plus rectal steroids versus rectal sucralfate. Dig Dis Sci 36(1): 103 – 107
Kochhar R, Srinam PV, Sharma SC, Gole RC, Patel F (1999) Natural history of late radiation proctosigmoiditis treated with topical sucralfate suspension. Dig Dis Sci 44(5): 973 – 978
Kollmorgen G, Meagher A, Wolff B, Pemberton J, Martenson J, Istrup D (1994) The long-term effect of adjuvant post-operative chemoradiotherapy for rectal carcinoma on bowel function. Ann Surg 220(5): 676 – 682
Komaki R, Brickner TJ, Hanlon AL (1995) Long term results of the treatment of cervical carcinoma in the United States in 1973, 1978 and 1983. Patterns of Care Study (PCS). Int J Radiat Oncol Biol Phys 31: 973 – 982
Ladas SD, Raptis SA (1989) Sucralfate enemas in the treatment of chronic prostatipation proctitis. Am J Gastroenterol 84: 1587 – 1589
Leuchter RS, Destrill E, Dwyer RM, Hacker NF, Castoldi TW, LaGasse LD (1982) NdyAG laser therapy of rectal stenosis due to radiation therapy. Obstet Gynecol 59: 655 – 657
Lucarotti ME, Mountford RA, Bartolo DC (1991) Surgical management of intestinal radiation injury. Dis Colon Rectum 34(10): 865 – 869
Mamel JJ, Chen P. Combs W, Tanabe I (1995) Short-chain fatty acid enemas are useful for the treatment of the chronic radiation proctitis. Gastroenterology 108: A305
Manoury V, Brunetiaux J, Mebazaa S (1991) Bipolar electrocoagulation treatment for hemorrhagic radiation injury of the lower digestive tract. Dis Colon Rectum 34(7): 492 – 493
Mathai V, Seow-Choen F (1995) Endoluminal formalin therapy for haemorrhagic radiation proctitis. Br J Surg 82(2): 190
Nakada T, Kubota Y, Sagawa T (1993) Therapeutic experiences of hyperbaric oxygen therapy in radiation colitis. Dis Colon Rectum 36: 962 – 965
Nostrant TT (1995) Radiation injury. In: Textbook of Gastroenterology, Yamada T, Alpers DH, Owyan C, Powell DW, Silverstein FE (eds). New York: Lippincott
Ooi BS, Tjandra JJ, Green MD (1999) Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: an overview. Dis Colon Rectum 42(3): 403 – 418
O’Connor JJ (1989) Argon laser treatment of radiation proctitis. Arch Surg 124(6): 749
Pinto A, Fidalgo P, Cravo M, Midoes J, Chaves P, Rosa J, Brito M, Leitao CN (1999) Short chain fatty acids are effective in short term treatment of Chronic radiation proctitis. Randomised, double blind, controlled trial. Dis Colon Rectum 42(3): 788 – 796
Rachmilowitz D (1989) Coated mesalazine (5-aminosalicylic acid) vs sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. Br Med J 298: 82 – 86
Reimer E, Rasmussen RB, Rubenstein EB, Ilsen T, Sorensen L (1987) Formalin treatment of severe radiation induced haemorrhagic proctitis. Ugeskr Laeger 149: 1194 – 1196
Roche B, Chautems R, Marti MC (1996) Application of formaldehyde for treatment of hemorrhagic radiation-induced proctitis. World J Surg 20(8): 1092 – 1094
Rougier P, Zimmerman P, Pignon JP, Kac J, Crespon B, Zrihen E, Charbit ME (1992) Recrites radiques: efficace comparee de deux types de corticoides administre localement. Med Chir Dig 21: 91 – 93
Rubenstein E, Ibsen T, Rasmussen RB, Reimer RB, Sorensen BL (1986) Formalin treatment of radiation induced haemorrhagic proctitis. Am J Gastroenterol 81: 44 – 45
Sacclarides TJ, King DG, Franklin JL (1996) Formalin installation of refractory radiation induced haemorrhagic proctitis. Dis Colon Rectum 39: 196 – 199
Sasai T, Hiraishi H, Suzuki Y, Masuyama H, Ishida M, Terano A (1998) Treatment of chronic post-radiation proctitis with oral administration of sucralfate. Am J Gastroenterol 93: 1593 – 1595
Schultheiss T, Lee R, Hunt M, Hanlon A, Peter R, Hanks T (1997) Late GI & GU complications in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 37(1): 3 – 11
Schroeder KW, Tremaine WJ, Ilstrup DM (1987) Coated oral 5 aminosalicyclic acid therapy for mildly to moderately active ulcerative colitis: A randomized study. N Engl J Med 317: 1625 – 1629
Seow-Choen F, Goh HS, Eu KW, Ho YH, Tay SK (1993) A simple and effective treatment for hemorrhagic radiation proctitis using formalin. Dis Colon Rectum 36(2): 135 – 138
Schwarchuk M, Jackson A, Zelefsky M, Venkatraman E, Cowen D, Levegrun S (2000) Late rectal toxicity after conformal radiotherapy of prostate cancer (i): multivariate analysis and dose response. Int J Radiat Oncol Biol Phys 47(1): 103 – 113
Silva RA, Correia AJ, Dias LM, Viana HL, Viana RL (1999) Argon plasma coagulation therapy for haemorrhagic radiation proctosigmoiditis. Gastrointest Endosc 50: 221 – 224
Stockdale AD, Biswas A (1997) Long-term control of radiation proctitis following treatment with sucralfate enemas. Br J Surg 84: 379
Taylor NA, Chen F, King D, Jones M, Talley NJ (1997) Short-chain fatty acids in the treatment of radiation proctitis: a randomized double-blind, placebo-controlled, cross-over pilot trial. Dis Colon Rectum 40: 1046 – 1050
Tam W, Moore J, Schoeman M (2000) Treatment of radiation proctitis with argon plasma coagulation. Endoscopy 32(9): 667 – 672
Tan LT, Jones B, Gee A, Kingston RE (1997) An audit of the treatment of carcinoma of the uterine cervix using external beam radiotherapy and a single line source of brachytherapy technique. Br J Radiol 70: 1259 – 1269
Taylor JG, Disario JA, Bush KN (1993) Argon laser therapy for hemorrhagic radiation proctitis: long-term results. Gastrointest Endosc 39(5): 641 – 644
Taylor JG, Disario JA, Bjorkman DJ (2000) KTP laser therapy for bleeding from chronic radiation proctopathy. Gastrointest Endosc 52(4): 353 – 357
Triantafillidis JK, Dadioti P, Nicolakis D, Mericas E (1990) High doses of 5-aminoalicyclic acid enemas in chronic radiation proctitis: comparison with betamethasone enemas. Am J Gastroenterol 85: 1537 – 1538
Warren DC, Fehan P, Slade JB, Cianci PE (1997) Chronic radiation proctitis treated with hyperbaric oxygen. Undersea Hyperb Med 24(3): 181 – 184
Williams JA, Clarke D, Denis EJ, Smith S (1992) The treatment of pelvic soft tissue radiation necrosis with hyperbaric oxygen. Am J Obstet Gynecol 167(2): 412 – 416
Woo TC, Joseph D, Oser H (1997) Hyperbaric oxygen treatment for radiation proctitis. Int J Rad Oncol Biol Phys 38: 619 – 622
Wurzer H, Schafhalter-Zoppoth I, Brandstatter G, Strand H (1998) Hormonal therapy in chronic radiation colitis. Am J Gastroenterol 93(12): 2536 – 2538
Yates MR, Baron TH (1999) Treatment of a radiation-induced sigmoid stricture with an expandable metal stent. Gastrointest Endosc 50(3): 422 – 426
Yegappan M, Ho YH, Nyma D, Leong A, Eu KW, Seow-Choen F (1998) The surgical management of colorectal complications from irradiation for carcinoma of the cervix. Ann Med 27: 627 – 630
Yeoh E, Horowitz M (1987) Radiation enteritis. Surg Gynecol Obstet 165(4): 373 – 379
Yeoh E, Botten R, Russo A, McGowan R, Fraser R, Roos D, Penniment M, Borg M, Sun W (2000) Chronic effects of therapeutic irradiation for localized prostatic carcinoma on anorectal function. Int J Radiat Oncol Biol Phys 47(4): 915 – 924
Yoshida EM (1999) The Crohn’s Disease Activity Index, its derivatives and the Inflammatory Bowel Disease Questionnaire: a review of instruments to assess Crohn’s disease. Can J Gastroenterol 13(1): 65 – 73