Radiation proctitis: a decade's experience

Wong M T C, Lim J F, Ho K S, Ooi B S, Tang C L, Eu K W

ABSTRACT

Introduction: Pelvic radiotherapy is an essential component of potentially curative therapy for many pelvic malignancies; however, the rectum consequently often sustains collateral injury.

Methods: The researchers retrieved patient data that was prospectively gathered over a ten-year period between January 1995 and December 2004. The relevant details, including gender, age, pelvic pathology for which radiotherapy was administered, the presenting symptoms, the interval between radiotherapy and the onset of symptoms, the mode of diagnosis, treatments received, length of hospital stay and duration of follow-up, were analysed.

Results: During the period under review, 77 patients were admitted for the treatment of radiation proctitis, with a median follow-up period of 14 (range 1–61) months. There were 23 male and 54 female patients, with a median age of 63.9 (range 37–89) years. The most common underlying cancers were gynaecological (63.6 percent), prostate (18.2 percent) and colorectal (15.6 percent) cancer. The most common presenting symptom was bleeding per rectum (89.6 percent), with a change in bowel habits a distant second (10.4 percent). The median latent period between the completion of radiotherapy and the onset of symptoms was 24 (range 3–68) months. The majority of the patients (72.5 percent) received non-surgical treatment, most commonly using topical 4 percent formalin solution to arrest the bleeding, with more than half the patients requiring repeat treatments. 14 (18.2 percent) patients required colorectal resections for intractable bleeding, intestinal obstruction or intra-abdominal sepsis.

Conclusion: Radiation proctitis can be a therapeutic challenge, even in the most experienced hands. The majority of patients who present with per rectal bleeding can be treated using topical modalities, while surgery may offer the only chance of relief from life-threatening symptoms.

Keywords: formalin, per-rectal bleeding, proctitis, radiation

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Department of Colorectal Surgery, Singapore General Hospital, Outram Road, Singapore 169608

Wong MTC, MBBS, FRCS, FAMS
Associate Consultant

Lim JF, MBBS, FRCS, FAMS
Consultant

Ho KS, MBBS, FRCS
Senior Consultant

Ooi BS, MBBS, FRCS, FAMS
Associate Professor

Tang CL, MBBS, FRCS, FAMS
Associate Professor

Eu KW, MBBS, FRCS, FAMS
Professor and Head

Correspondence to:
Prof Eu Kong Weng
Tel: (65) 6321 4677
Fax: (65) 6226 2009
Email: eu.kong.weng@sgh.com.sg

INTRODUCTION

Pelvic radiotherapy is an essential component of treatment for many pelvic malignancies. During the course of pelvic radiotherapy, the rectum may be damaged, as it lies within the field of irradiation. Tissue changes can occur early in the course of radiation therapy; these include mucosal cell loss, acute inflammation in the lamina propria, eosinophilic crypt abscess formation and endothelial swelling in the arterioles.[1,2] Cessation of radiotherapy can lead to an initial improvement, but can also progress with or without a period of quiescence, with subsequent fibrosis of connective tissue and arteriolar endarteritis. These latter changes result in rectal tissue ischaemia, leading to eventual mucosal friability, where patients present with bleeding, ulcers, strictures and fistulation.[3,4] In this study, the researchers sought to review our experience in the management of radiation proctitis over a ten-year period.

METHODS

Patient data that had been prospectively gathered over a ten-year period between January 1995 and December 2004 was retrieved and the relevant details were analysed. These included gender, age, pelvic pathology for which radiotherapy was administered, the presenting symptoms, the interval between radiotherapy and the onset of symptoms, the mode of diagnosis, treatment received, the number of repeat treatments, the symptom-free interval between treatment sessions, the length of hospital stay and duration of follow-up. The database only comprised patients who were admitted for treatment, and outpatient encounters were thus not available for this study. In addition, the total dosage of radiation was not available for all patients and was thus not included for analysis.

RESULTS

During the period under review, 77 patients (23 male and 54 female) were admitted for the treatment of radiation

Table I. Underlying pathologies requiring radiotherapy.

Pathology	No. (%) of patients
Uterine/cervical cancer	49 (63.6)
Prostate cancer	14 (18.2)
Colorectal cancer	12 (15.6)
Urachal cancer	1 (1.3)
Bladder cancer	1 (1.3)
Ovarian cancer	1 (1.3)

Table II. Modes of presentation.

Mode of presentation	No. (%) of patients
Per rectal bleeding	69 (89.6)
Change in bowel habits (strictures/obstruction)	18 (13.0)
Sepsis (fistula/gangrene/peritonitis)	7 (6.49)

proctitis. The median age of presentation was 63.9 (range 37–89) years. 49 patients required radiotherapy for uterine/cervical cancer, 14 patients had prostate cancer, 12 had colorectal cancer and one patient had prostate cancer, followed by colorectal cancer several years later. Of the remaining three patients, one had urachal cancer, one had bladder cancer and another had ovarian cancer, all of whom required surgery followed by combined chemoradiation. The distribution of malignancies for which pelvic radiotherapy was performed is listed in Table I.

The most common presenting symptoms were bleeding per rectum and intestinal obstruction from strictures and sepsis (Table II). It is important to note that the total number of patients shown in Table II exceeds 77, as 18 patients (23.3%) had more than one symptom at presentation.

The median latent period between the completion of radiotherapy and the onset of symptoms was 24 (range 3–68) months. The median haemoglobin level was 9.5 (range 3.9–14.1) g/dL. The majority of the patients (61.0%) did not require blood transfusions; of those who did require it, a mean of one pint was transfused. The median duration of hospitalisation and follow-up was four (range 1–20) and 14 (range 1–61) months, respectively. The majority of the patients (88.3%) were first evaluated endoscopically (flexible sigmoidoscopy or colonoscopy), as rectal bleeding was the most common symptom; in contrast, those who presented with perianal or peritoneal sepsis underwent immediate surgery.

In the 69 patients with per rectal bleeding, the majority (up to 80%) received topical treatment, with either 4% formalin (72.5%), Argon plasma coagulation (APC) treatment or colifoam enemas. Seven patients required surgical resection upfront for concurrent symptomatic rectal strictures and seven others were managed conservatively with a spontaneous cessation of bleeding. Their clinical course varied subsequently. Among the 50 patients who received a topical formalin application, 30 (60%) did not require further treatment. Half of the patients with recurrent bleeding were successfully treated with a single repeat application of formalin, while the rest were treated with APC, colifoam enemas and surgery. Among the seven patients who underwent initial surgery, none of them required further treatment. Conversely, in the group of seven patients who were initially managed conservatively, all eventually required treatment at a mean of seven months after the initial presentation, either in the form of topical treatments or surgery. It is interesting to note that topical treatments other than 4% formalin (APC or colifoam enemas) appeared to be less effective, with all these patients requiring a repeat treatment in order to successfully arrest bleeding, with a majority requiring eventual surgery. Table III shows the treatment outcomes for per rectal bleeding.

A total of 18 patients presented with a change in bowel habits secondary to radiation-induced strictures; 14 patients had concurrent per rectal bleeding, with eight requiring surgery (proximal diversion) and the other six receiving topical treatment. Three patients presented with acute intestinal obstruction requiring surgery and one patient presented with milder symptoms of constipation and was managed conservatively with laxatives. All 11 patients who underwent surgery had definitive resolution of their symptoms. With regard to topical treatments, 4% formalin appeared to be more effective than colifoam enema at arresting the concurrent bleeding. Table IV shows the treatment outcomes for patients with a change in bowel habits.

All seven patients who presented with sepsis underwent early surgery and recovered uneventfully. Five patients had rectovaginal fistulae and required a defunctioning colostomy, one had a rectal perforation with peritonitis and required an anterior resection with proximal diversion, and one patient presented with Fournier's gangrene, for which surgical debridement and a defunctioning colostomy were performed.

On the whole, however, more than half the patients (53.2%) required repeat treatments for recurrent per rectal bleeding, with a mean symptom-free interval of 13.6 months between the first and second presentations. Formalin appeared to be the most effective in repeat treatments, with more than 75% of patients requiring only one additional application to arrest bleeding. In addition, 26.8% of patients who had rebleeding required

Table III. Treatment outcomes for per rectal bleeding (n = 69).

Initial treatment received (No. of patients)	Subsequent treatment required (No. of patients)
Formalin application (50)	No further treatment (30) Repeat formalin application (16) APC treatment (1) Colifoam enemas (1) Surgery (2)
Surgery (7)	No further treatment (7)
No treatment initially (7)	Formalin (4) APC (1) Surgery (2)
APC treatment (3)	Repeat APC (1) Surgery (2)
Colifoam enemas (2)	Formalin (1) Surgery (1)

APC: Argon plasma coagulation

a combination of treatment modalities to secure eventual haemostasis.

DISCUSSION

Radiation proctitis refers to radiation-induced rectal mucosal injury, with an incidence rate varying from 5%–20% in published studies.[5-7] Acute radiation proctitis occurs during or within three months of the administration of radiotherapy. Chronic radiation proctitis either continues from the acute phase or begins after a latent period of at least 90 days. The latter form of proctitis occurs more commonly in patients with severe acute proctitis and in those with predisposing conditions of diabetes mellitus, inflammatory bowel disease, hypertension, peripheral vascular disease, or even chemotherapy.[4,8] While it is believed that an advanced tumour stage and a total radiation dose exceeding 5,000 cGy also increase the risk of having late complications, there remain no definite predictors for disease progression to date.

The prognosis of radiation proctitis remains unclear. Though rarely life-threatening, radiation proctitis may eventually progress to become chronic with morbid sequelae including persistent bleeding, strictures and fistulae and rarely, carcinomatous change.[9] In this series, the most common presentation was per rectal bleeding (89.6%), although the majority of patients did not require any blood transfusions (61.0%). Although seemingly benign, up to one-third of patients (32.5%) actually required surgery, of which 18 were performed in an emergency setting. None of our patients developed carcinoma of the anorectum on follow-up. Adding to the therapeutic challenge is the fact that there remains no universally accepted standard for grading the severity of radiation proctitis, and this is partly due to the fact that there are neither specific nor consistent radiological or histological features,[10] and endoscopic findings are not easily reproducible between observers.[11]

In this series, per rectal bleeding was the predominant presenting symptom (89.6%), either alone (66.2%) or in combination with other symptoms (23.4%). Radiation-induced strictures leading to a change in bowel habits was a distant second, but more often required surgery for the relief of symptoms. Sepsis was the third most common symptom, and all the patients who presented with it required surgery. Rarer symptoms, such as mucoid per rectal discharge, tenesmus and altered frequency of stools, can also occur, but these often require only conservative measures and patient reassurance. The investigation of choice remains endoscopy, not only to exclude other causes of per rectal bleeding and changes in bowel habits, but also to determine the proximal extent of the radiation damage so as to treat the affected areas more precisely. Thus, apart from those requiring emergency surgery, all our patients first underwent endoscopic evaluation prior to commencing treatment.

Non-surgical interventions usually form the first line of treatment. These include the use of topical formalin applications, rectal enemas of steroids or thermal therapy, such as bipolar electrocautery and heater-probe therapy, as well as hyperbaric oxygen therapy. In our unit, the choice of treatment varies according to the primary surgeon and is thus not a true reflection of the efficacy of one modality over another. More than half of our patients (53.2%) required repeat treatments for persistent symptoms, with a mean symptom-free interval of just over one year (13.6 months). Hence, it is essential for patients to be closely monitored even after initial successful haemostasis,

Table IV. Treatment outcomes for change in bowel habits (n = 18).

Presenting symptom (No. of patients)	Initial treatment received (No. of patients)	Subsequent treatment required (No. of patients)
Concurrent per rectal bleeding (14)	Surgery (8)	No further treament (8)
	Topical formalin (5)	No further treatment (5)
	Colifoam enema (1)	Formalin (1)
Intestinal obstruction (3)	Surgery (3)	No further treatment (3)
Constipation (1)	No treatment (1)	Formalin (1)

so as to be able to deal with recurrences and refractory symptoms that may arise. The results of this study show that the topical application of 4% formalin solution appeared to be effective as the sole modality in just over half the patients with per rectal bleeding (51.9%). The rest of the patients required repeat treatments with either formalin or other topical agents, such as APC or colifoam enemas. Only two patients eventually required surgery for intractable bleeding.

In radiation proctitis, it is postulated that recurrent bleeding occurs due to vascular telangiectasia and non-healing mucosal ulceration from underlying endarteritis obliterans. Formalin helps to sclerose and seal these fragile neovasculature and has been widely used. Its success relies on the accurate localisation and application at all the affected areas. In contrast, thermal coagulation relies on the coagulation of focal bleeding sites rather than the entire friable mucosa, allowing for scarring and epithelisation to occur over time. Our department has adopted the topical formalin application since September 1991. This was first reported in 1993,[12] and the results of that study indicated that it was a safe and effective treatment for haemorrhagic radiation proctitis. These findings have since been validated in subsequent series.[13-15] In most cases, formalin therapy can be performed in the outpatient or day surgery setting, without anaesthesia. Lignocaine jelly is particularly useful in patients with concurrent piles or fissures. A rigid sigmoidoscope is introduced into the rectum with the patient in the left-lateral or lithotomy position. The most proximal extent of the lesion is visualised and a gauze soaked in 4% formalin is carried on a pair of biopsy forceps, introduced and laid in contact with the haemorrhagic surface until bleeding stops, for no more than 2–3 minutes, as studies have shown that systemic toxicity arises following more prolonged contact with formalin.[16] Adequacy can be guided by the visible blanching of the mucosal surface. The process is then repeated until the most distal extent of the diseased rectum has been treated, the latter being more easily dealt with using a proctoscope.

This series has shown that the initial treatment of per rectal bleeding with APC was not as effective, with all patients eventually requiring either repeat sessions or surgery. We believe this may be partly attributed to the adoption of APC usage only after the year 2000, which was later compared to formalin. However, APC treatment has the distinct advantage of being able to reach more proximally affected parts of the rectum as it is delivered using the colonoscope. Furthermore, APC only coagulates the superficial mucosal layer, causing minimal discomfort for the patient, and it can be safely performed in the endoscopy suite. As such, we feel that it has the potential to complement topical formalin application and can be used in combination to treat the proximal and distal rectum concurrently. This series has also revealed that all the patients failed initial conservative management for per rectal bleeding, and should thus be either offered empirical treatment at the time of diagnosis with formalin or APC, or at least be followed up closely following a course of stool softeners and antibiotics such as metronidazole. Our experience with topical steroid enemas has been disappointing, with all the patients eventually requiring further treatment, including surgery. A systematic review of these various non-surgical interventions has suggested that the use of sucralfate may be better than steroids, which in turn may have a greater effect if used with metronidazole.[17]

Fortunately, surgery is often a last resort to be used when severe complications occur, such as refractory bleeding, strictures leading to intestinal obstruction or sepsis. Surgery can range from a simple proximal diversion to a formal resection with or without an anastomosis. In this series, up to a third (32.5%) of the patients required surgical intervention at some point during follow-up, which is certainly a testament to the challenges of treating this seemingly innocuous condition. This could largely be due to the often irreversible underlying pathology of connective tissue fibrosis and obliterative endarteritis. The majority of the patients received a proximal diversion, especially when an anastomosis was created, a prudent precaution to

take whenever one attempts to anastomose a previously irradiated bowel. It is noteworthy that all the patients who underwent an anterior resection with proximal diversions ultimately had their stomas reversed and there were no leaks thereafter. Thus, when appropriately indicated, surgery can offer an effective solution.

In summary, our findings reveal that per rectal bleeding is the most common presentation (89.6%) of radiation proctitis, with symptoms manifesting at a median of 24 months after the completion of radiation therapy. The most frequently used modality of treatment was the topical application of 4% formalin, which effectively arrested bleeding in more than half (60%) the patients following a single session. The rest of the patients had recurrent bleeding after a median of 13.6 months, and topical formalin was once again usually effective after a single session. Surgery was indicated only in the setting of uncontrolled sepsis, non-resolving intestinal obstruction or intractable bleeding, with all patients achieving a lasting resolution of symptoms thereafter. Conversely, in the eight patients who were initially managed conservatively, all eventually required treatment to arrest recurrent bleeding.

It is important to highlight that the overwhelming feature of the data in the existing literature is that of either a single institution's or an individual's experience of only a specific intervention administered in the absence of controls. Even in comparative studies, few background details have been provided regarding the tumour stage or radiation dose used; interventions have often not been standardised so that there has been substantial variation in the dosages and duration. This lack of robust data does not allow for credible conclusions to be made with regard to the best treatment modalities to be employed. This general paucity of information might relate to the actual low incidence of late radiation proctitis and the difficulties that exist in compiling a series that is large enough to be randomised between therapies. Nonetheless, we felt that a review of our institutions' data and the existing literature would be helpful in our continued appreciation of this challenging disease entity.

In order for the treatment of radiation proctitis to become evidence-based, good quality placebo-controlled studies need to be conducted to support the treatment modalities recommended. There is also a need to establish a consensus regarding universally accepted diagnostic criteria and a grading system for radiation proctitis. This will not only be useful in guiding treatment practices and eventual follow-ups, but it will also allow for more meaningful comparison of data and the establishment of multicentre randomised studies.

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