CHRONIC RADIATION PROCTITIS- A COMMON BUT DIFFICULT PROBLEM
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ABSTRACT

BACKGROUND
Pelvic radiation is increasingly being used for management of genitourinary and lower gastrointestinal malignancies. Radiation induced damage to rectum, colon can present as acute radiation proctitis or chronic radiation proctitis (CRP), which presents months later. In South East Asia including India, cancer cervix is very commonly treated by radiotherapy. Rectal complications are quite common in these cases. Pain, irregular bowel and most important bleeding which leads to anaemia- these make quality of life very poor for these patients. Diagnosis is confirmed by endoscopy. Management of CRP is also not standardized. Endoscopic, non-endoscopic, surgical- all have roles in management of this condition.

METHODS
Since 2010 to 2014 we have treated 40 patients of chronic haemorrhagic radiation proctitis in Medical College Kolkata. All had radiotherapy for carcinoma cervix. Patients were assessed clinically as well as endoscopically. Mild to moderate disease were treated with Sucralfate enema. Severe or refractory haemorrhagic proctocolitis was treated with low volume formalin instillation via sigmoidoscope. End point of treatment was cessation of bleeding, stable haemoglobin 10 gm% without blood transfusion.

RESULTS
Mean age found to be 66 years and 60% patients presented within one year of finishing radiotherapy. 33 patients (82%) presented with rectal involvement only and 29 patients (72%) had endoscopic grading 2 - 3. 26 patients (65%) improved after one installation of 4% formalin and only 10 patients needed more than two instillations.

CONCLUSIONS
Chronic haemorrhagic radiation proctitis is a common side effect of pelvic radiation. Prevention is desirable. Control of bleeding is a difficult problem. Drugs, topical application including formalin instillation, Argon plasma coagulation, RFA, laser all are effective treatment options keeping surgery reserved for complications like stricture or fistula. Our experience of low volume 4% formalin instillation is very effective.

KEYWORDS
Radiotherapy, Complications, Chronic Radiation Proctitis

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BACKGROUND
Radiotherapy for treatment of genitourinary and lower gastrointestinal malignancies can cause damage to rectum including left colon. It commonly leads to acute radiation proctitis. If symptoms persist more than 3 months after finishing radiotherapy or develop later, it is chronic radiation proctitis. Cancers of the cervix, prostate, rectum, bladder, testicles and uterus are commonly treated with pelvic irradiation. Among these, though prostate malignance is the most frequent in western countries,¹ in India cancer cervix is commonest disease treated with radiotherapy. Incidence of chronic radiation proctitis can be as high as 20 to 30%.¹²

The method of radiation delivery is an important predictor of the risk for radiation proctitis.¹ The rate of colorectal complications with brachytherapy is lower compared to external beam radiation. The use of newer conformal radiation therapy techniques maximizes the dosage directed to the tumour while minimizing the dosage of radiation to the rectum.¹² CRP may be more frequent in patients with inflammatory bowel disease, diabetes, hypertension or peripheral vascular disease and in those who develop severe acute proctitis.¹ There are several options of management primarily aimed to control bleeding and pain. Both medical and endoscopic treatments can be done keeping surgery last option. None of the treatment is absolutely successful and we need more studies to conclude. We present our experience in this paper.

METHODS
Between July, 2010 to June, 2014 over four years we have treated 40 patients with formalin instillation in Department of Surgical Gastroenterology, Medical College Kolkata which is a premiere medical institution in India. Patients were assessed clinically as per Modified Radiation Therapy Oncology Group rectal toxicity scale and endoscopic grading

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done as mentioned above. All patients with endoscopic grade 1-2 proctitis was initially managed with topical Sucralfate suspension applied through large syringe (1gm BD dose). Patients not responding to this treatment or endoscopic higher grade had 4% formalin instillation to control bleeding. We prefer direct instillation of low volume 4% formalin by catheter passed through flexible sigmoidoscope in contact with the lesions. The patients were consented for formalin treatment. A solution of 4% formalin was made by diluting 10% formalin with normal saline. This solution was drawn up into a 20 ml syringe. With the patient lying on their left lateral side, the solution was sprayed over the bleeding lesions through a catheter. The sigmoidoscope was then removed and the patient asked to continue to lie still in the left lateral position for 30 seconds. Once this time had elapsed the patient was asked to roll over onto their back for 30 seconds and then into the right lateral position and then prone, with each position being held for 30 s. Finally, the patient was asked to sit upright, leaning slightly forward for a further 30 s to ensure that the formalin had made contact with the entire rectal mucosa. The patient then returned to the left lateral position, the sigmoidoscope was reinserted and the remains of the formalin sucked out. The total mucosal contact time for the formalin was around 3 to 5 minutes. All patients were discharged on the same day as the procedure, usually within an hour, and followed up in the out-patient clinic 4 weeks later to assess their response to treatment and to check for any evidence of complications.

RESULTS
All patients were female aged 35 yrs. - 75 yrs. - mean age being 66 years. All patients had radiotherapy for CA cervix (either as curative treatment or postoperative adjuvant therapy) except three patients with endometrial CA. Average dose of radiotherapy/EBRT 48 GY (range 45-54 GY). 24 patients (60%) presented within 12 months of finishing radiotherapy and 20 patients (50%) needed blood transfusion. 33 patients (82%) presented with rectal involvement only and 29 patients (72%) had endoscopic grading 2-3. Three patients had associated radiation cystitis and one patient presented with rectovaginal fistula. Out of 40 patients 26 patients (65%) improved after one installation of 4% formalin and only 10 patients needed more than two instillations. Patients are on follow up every 6 months for three years then annual and end point of treatment set to have Hb 10 gm% without any iron or blood transfusion. There was no major complication. Only one patient developed severe colitis which could be managed conservatively. Patient with rectovaginal fistula had primary surgery.

DISCUSSION
CRP should be suspected in patients who develop symptoms such as diarrhoea, urgency, tenesmus or bleeding, usually 6 months or more after pelvic radiation exposure. Bleeding occurs due to oozing from a friable, ischemic mucosa, and the rupture of radiation induced telangiectasias and can lead to anaemia and the need for repeated blood transfusions. Diagnosis can be confirmed by colonoscopy or sigmoidoscopy. Endoscopic findings of CRP are mucosal pallor, telangiectasias, spontaneous haemorrhage, oedema and friability. Less frequent findings are ulcers, strictures and fistulas. Routine rectal biopsy is not necessary except to rule out other pathology like colitis, IBD or malignancy.

The diagnosis of radiation proctitis can be separated into two distinct categories, acute or chronic, based on the timing to the development of symptoms and they have different presenting symptoms, incidence, histopathological findings, and treatment approaches which are summarized in Table 1. Symptoms that develop within 3 months from the initiation of radiotherapy are classified as acute while those developing after are chronic. Brisk acute injury can persist into a consequential late effect, or late proctitis can develop in the absence of acute proctitis after a latent period of months to years after initial exposure. The median time for the development of chronic symptoms after radiation treatment is between 8 to 13 mo in the majority of series. Although, a few series do report a considerably longer latent period, with initial symptoms developing more than 30 years after completing radiation. A key distinction between acute and late proctitis is the relative lack of inflammatory infiltrate in the latter. Therefore, the term "proctitis" is misleading and better known as chronic radiation proctopathy. For diagnosis, assessment of severity, prognosis and response to treatment different scoring systems are followed. They are based on symptoms, endoscopic findings or both. Two commonly used clinical grading systems are LENT-SOMA Scale Rectum and Modified Radiation Therapy Oncology Group rectal toxicity scale (Table 2). LENT SOMA=Late Effects in Normal Tissues Subjective, Objective, Management and Analytic scales.* The possible range of summed results for the five questions is 0–20, where 0 indicates that no symptoms are present and 20 represents the worst possible symptomatology. Out of few endoscopic grading systems the one suggested by kocher et al is very useful.

Grade I - Erythema ± telangiectasia, mucosal oedema, thinning, pallor.
Grade II- Above findings plus mucosal friability.
Grade III - Mucosal ulceration ± necrosis.

Management of chronic haemorrhagic radiation proctitis is mostly conservative with surgical intervention needed for intractable bleeding, rectovaginal fistula, stricture or perforation. Available management options are listed in Table-3. Of different modalities of treatment most commonly used and effective are topical Sucralfate, steroid (with or without oral anti-inflammatory drugs, metronidazole), topical formalin and Argon plasma coagulation (APC).
Sucralfate

Sucralfate is a highly sulfated polyanionic disaccharide. This medication is thought to affect radiation proctitis via two mechanisms. First, Sucralfate mechanically protects the gastrointestinal mucosa by forming a protective coating on inner surface of the bowel. Second, it is thought to stimulate healing by increasing angiogenesis. Numerous studies have been performed using Sucralfate in oral and rectal preparation. One of the few randomized controlled double-blind trials in the treatment of radiation proctitis was reported by Kochhar et al. Patients were treated with a 4-wk course of oral sulfasalazine (3.0 g/d) and were randomly assigned to receive prednisolone enemas (20 mg twice daily) or Sucralfate enemas (2.0 g twice daily). Patients who were randomized to Sucralfate enemas tolerated treatment better and had a superior response compared to prednisolone enemas. The same authors reported this trial with long-term follow up, with a median of 45.5 mo after cessation of bleeding. No treatment complications were observed.

Despite mixed results for the oral preparation, the rectal preparation of Sucralfate can be considered an effective medical therapy for radiation proctitis with minimal side effects. Patients should be counselled on twice daily self-administration of Sucralfate enema, prepared using two 1 g tablets mixed with 4.5 ml of water to produce a paste like consistency or Sucralfate suspensions applied per rectal with large syringe.4,5

Formalin Therapy

Formalin therapy for CRP is based on its use in patients with haemorrhagic cystitis. Since Rubinstein’s work, in 1986, reported the first successful CRP treatment using a rectal wash with formalin, many authors have published on the treatment of haemorrhagic CRP using this therapy. Formalin functions as a local sclerosant and causes chemical cationization of telangiectasias. Success rates vary from 27% up to 100%. This difference can be explained by the wide variability in application technique and concentration.
Commonly it is used 4% solution instilled in the rectum, avoiding contact with anoderm or skin. Formalin can be administered as an enema, irrigation in small aliquots, or soaked pledgets of cotton wool applied under rigid sigmoidoscopic, proctoscopic or flexible endoscope guidance. Anaesthesia or sedation may be needed for pain. Formalin therapy can be repeated for two or three more applications until symptomatic improvement, especially with the cessation of rectal bleeding. Ulcers due to formalin application preclude repeating the procedure.

Patel et al. in a retrospective study, evaluated the combination of oral vitamin A with formalin application. The addition of vitamin A led to a significant decrease in the number of formalin sessions and a significantly shorter time for resolution. Supplementation with vitamin A also has a better success rate in controlling rectal bleeding than formalin alone (94% vs. 64%). There are also two small studies comparing formalin with APC. Yeoh et al. suggested that formalin and APC had similar success in managing haemorrhagic CRP. Nevertheless, Alfadhli et al. concluded that APC was significantly more effective (78.5% vs. 27.2%, p= 0.017) and safer (p= 0.001) than formalin. The advantages of formalin application include low cost, wide availability and good efficacy in general. Despite this, complications have been reported, including chemical colitis, anorectal pain, anal and rectal strictures, rectal perforation, fissures, incontinence and diarrhoea. Further studies are needed to determine the optimal method of delivery.

Argon Plasma Coagulation
Argon plasma coagulation (APC) is a non-contact thermal method of coagulation and haemostasis. It was designed to be an alternative to direct contact coagulation, with the advantage of increased safety due to a controllable depth of treatment penetration (maximum 2-3 mm). APC uses high-frequency energy transmitted to tissue by ionized gas. Unlike traditional bipolar devices, the current jumps from the probe to the target lesion, with the arc being broken once the tissue is desiccated. The theoretic advantage is a uniform, more predictable, and limited depth of coagulation (0.5–3 mm), which minimizes the risks of perforation, stenosis, and fistulization. APC has been used to treat a wide spectrum of bleeding lesions in the gastrointestinal tract and has been shown to be effective in controlling bleeding caused by radiation proctitis, although it may require multiple sessions (usually at 4-week intervals). Some patients may experience post procedure rectal pain and cramps, but major complications are rare. Special care is required to avoid spraying too close to the dentate line. In addition, APC may control bleeding even after other treatment methods have failed. APC remains one of the techniques most commonly reported on for the treatment of radiation proctitis, with a recent review showing around 80% of all current endoscopic specific literature conducted on APC. 

Surgical Therapy
Surgical approaches represent the most invasive treatment for radiation proctitis. Thus, these interventions should be reserved for those patients with either symptoms refractory to medical and endoscopic therapy or for patients with symptoms such as brisk haemorrhage, perforation, fistula or obstructing stricture. The need for such intervention is quite rare, and utilization is estimated to be less than 10% of all patient's with radiation proctitis. 

CONCLUSIONS
Chronic haemorrhagic radiation proctitis is a difficult problem. Prevention can be ideal. Newer conformal radiation therapy techniques like intensity-modulated radiation therapy and intensity-guided radiation therapy minimize the dose of radiation to the rectum while maximizing dose to the tumour. Amifostine is a prodrug that is metabolized to a thiol metabolite that is thought to scavenge reactive oxygen species. When administered intravenously, it has shown some benefit in preventing symptoms of acute proctitis as well as decreasing the severity of chronic proctitis symptoms. Sucralfate is extensively used for prophylaxis against acute radiation injury. However, placebo-controlled phase III trials have detected no benefit from either topical or oral sucralafate. Of all treatment modalities, most commonly used treatment options in our country are topical sucralfate with or without steroid enema, oral metronidazole, 5-ASA compounds. Topical formalin applications, usually 4%, as dab, instillation or endoscopic application is cheap, effective and well tolerated. Argon plasma coagulation (APC) is also effective but costly, need expertise and serious complications have been reported. Few head-to-head comparative trials have been performed on any treatments for radiation proctitis, though two have been reported in the literature between APC and formalin. First, a study by Alfadhli et al. retrospectively compared outcomes for 22 patients who were treated with APC alone (n = 11), formalin instillation alone (n = 8) or both (n = 3). Patients treated with APC had a significantly improved chance for control of rectal bleeding while those treated with formalin had an increased likelihood of adverse events including nausea, vomiting, cramps and rectal pain. The second study by Yeoh et al. reported on 30 men with intractable chronic proctitis after receiving radiation for prostate cancer. All men were randomized to APC or topical formalin. The treatment endpoint, reduction in rectal bleeding to at most once monthly, was achieved in 94% of the APC group and 100% of the formalin group after a median of 2 sessions in either arm. There were no differences between side effects of the two treatments, including anorectal symptoms or function. We do not have APC but over the years have managed successfully patients with chronic haemorrhagic radiation proctitis with sucralfate enema and topical formalin. Low volume formalin instillation is better and safer. 

REFERENCES


