

Chronic Radiation Proctosigmoiditis in Patients with Cervical Cancer

Juliyanti*, Dadang Makmun**

* Department of Internal Medicine, Faculty of Medicine

University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

** Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine,
University of Indonesia/Dr. Cipto Mangunkusumo General National Hospital, Jakarta

ABSTRACT

Complications in rectum and sigmoid due to radiation are usually called radiation proctosigmoiditis. It can be acute or chronic based on the onset of symptoms during radiation treatment. There are some treatment modalities aimed for reducing rectosigmoid bleeding and improving symptoms of chronic radiation proctosigmoiditis, which include medication, endoscopy and surgery. Most data about the effectiveness of those various modalities are provided by short-term studies with small sample size.

A female patient, 59 years old, came with a chief complaint of passing persistent fresh bright red bloody stool since 1 year before admission. The patient was then diagnosed with stage IIIB cervical cancer and she received 25 times of external radiation, 3 times of internal radiation and 3 times of chemotherapy. She was diagnosed with chronic radiation proctosigmoiditis and treatment to stop the bleeding was carried out by performing argon plasma coagulation through colonoscopy. The problems in the patient were formulated as chronic radiation proctosigmoiditis with malnutrition and iron deficiency anemia due to chronic bleeding. Non-pharmacological and pharmacological medications were administered.

Keywords: radiation proctosigmoiditis, argon plasma coagulation, medication

ABSTRAK

Komplikasi pada rektum dan sigmoid akibat radiasi sering disebut sebagai proktosigmoiditis radiatif. Proktosigmoiditis radiatif dapat bersifat akut maupun kronik berdasarkan jangka waktu munculnya gejala dengan saat radiasi diberikan. Modalitas terapi yang ditujukan untuk mengurangi perdarahan rektosigmoid dan memperbaiki gejala-gejala proktosigmoiditis radiatif kronik meliputi terapi medikamentosa, endoskopi, dan pembedahan. Kebanyakan data tentang efektivitas berbagai modalitas tersebut masih berasal dari skala kecil dan jangka pendek.

Pasien wanita, 59 tahun, datang dengan keluhan utama buang air besar (BAB) berdarah merah segar yang tidak sembuh-sembuh sejak 1 tahun sebelum masuk rumah sakit (RS). Pasien kemudian didiagnosis kanker serviks stadium IIIB dan diberikan radiasi eksternal 25 kali, radiasi interna 3 kali, dan kemoterapi 3 kali. Pasien didiagnosis proktosigmoiditis radiatif kronik dan dilakukan terapi untuk menghentikan perdarahan dengan tindakan koagulasi plasma argon melalui kolonoskopi. Dirumuskan masalah pada pasien adalah proktosigmoiditis radiatif kronik dengan malnutrisi dan anemia defisiensi besi akibat perdarahan kronik. Tata laksana non-medikamentosa maupun medikamentosa diberikan kepada pasien.

Kata kunci: radiasi, proktosigmoiditis, koagulasi plasma argon, medikamentosa

INTRODUCTION

Radiation causes cellular apoptosis resulting from deoxyribonuclease (DNA), protein and lipid damage that occurs in cells that are rapidly proliferative such as cancer cells.¹ Currently, radiotherapy is an essential treatment modality for malignancy in pelvic area (such as carcinoma of prostate, rectum, urinary bladder, cervix, uterine and testis), either as neoadjuvant or adjuvant treatment. The administered high-dose radiation causes damage to cancer cells as well as organs adjacent to the radiation field. The organs that most commonly affected are rectum and sigmoid. The prevalence of complication in colorectal cancer receiving brachytherapy usually is lower compared to those with external radiation. A study conducted by Lesperance shows prevalence rate for acute (6% vs. 43%) and chronic complications (2% vs. 21%) with brachytherapy when compared to external radiation.² Complications in rectum and sigmoid due to radiation are usually called radiation proctosigmoiditis. It can have acute or chronic nature based on the onset of symptoms during radiation treatment.

Treatment modalities aimed for reducing rectosigmoid bleeding and improving symptoms of chronic radiation proctosigmoiditis include medication, endoscopy and surgery. Most data about the effectiveness of those various modalities are provided by short-term studies with small sample size. Randomized controlled clinical trials comparing those various treatments are still very limited and there is still no strategy on optimal treatment. This manuscript is reporting a case of chronic radiation proctosigmoiditis, which had been treated with pharmacological treatment (medication) and the state-of-art endoscopy according to the best available and feasible clinical evidences in keeping with the availability of our facility at Cipto Mangunkusumo Hospital, Jakarta.

CASE ILLUSTRATION

A female patient, 59 years old, came with a chief complaint of passing persistent fresh bright red bloody stool since 1 year before admission. Since 2 years before admission, the patient often had bloody vaginal discharge along with lower abdominal pain and a 12 kg weight loss. The patient was then diagnosed with stage IIIB cervical cancer and she received 25 times of external radiation, 3 times of internal radiation and 3 times of chemotherapy. The patient had a regular visit to doctor office and had no complaint.

A year before hospital admission, she started to

have complaints of passing fresh blood clot from anal bleeding 3-4 times a day accompanied with pain around the anus and sometimes diarrhea. There was no complaint of fever or mass around the anus. The patient was very weak and hospitalized. She received red blood cell transfusions several times. Afterward, a complete fecal test and colonoscopy were performed. Fecal analysis gave an impression of Gram-negative bacterial infection. The patient was treated with antibiotics, but had no improvement. Results of colonoscopy showed that on the rectum and sigmoid, there was moderate hyperemia of the mucosa, telangiectasia lesions, large amounts of erosion with oozing of blood and several small-sized ulcers; while in descending, transversal and ascending colon up to caecum, the mucosa was smooth and normal. (figure 1)

The patient was diagnosed with chronic radiation proctosigmoiditis and treatment to stop the bleeding was carried out by performing argon plasma coagulation (APC) through colonoscopy. After 3 sessions of APC (the last APC was performed in 2 weeks before admission), the bleeding was reduced, but it had not been totally stopped; sometimes, there were blood spots on towel paper and during the third APC procedure, telangiectasia lesion was still found on the rectum. One month before admission, the patient had another complaint of passing blot clot from the anus and her body was weaker. The patient subsequently received red blood cell transfusion at the outpatient clinic of Hematology Department as much as 1000 mL about 10 days before admission and re-coagulation procedure using APC was planned. There was no complaint of fever, chest pain, palpitation, short of breath or urinary incontinence. There was no other comorbidity or allergy. No significant family history was found.

On physical examination when the patient was admitted to hospital, she was moderately ill with poor nutritional status (body mass index 14.2 kg/m²) and the vital signs were within normal limits. Another significant physical finding was only pale conjunctiva. The laboratory examination revealed iron deficiency anemia (hemoglobin 10 g/dL with microcytic hypochromic anemia on the peripheral blood smear and reduced iron level (41 pg/dL), reduced transferrin (15%) and ferritin (16.7 ng/mL) saturation, as well as hypoalbuminemia (3.1 g/dL). The laboratory parameters of liver function, renal function and hemostasis were normal.

The problems in the patient were formulated as chronic radiation proctosigmoiditis with malnutrition and iron deficiency anemia due to chronic bleeding. Non-

pharmacological and pharmacological medications were administered. The patient received low-fiber and low-fat diet of 1500 kcal, 1.5 g protein per kg body weight (60 grams) and 1000 mL intravenous crystalloid fluid per 24 hours, 500 mg transamin (tranexamic acid) 3 times daily, ferrous sulfate and sucralfate enema 2 grams twice a day through folley catheter inserted 10 cm into the anus.

Afterward, a colonoscopy with a repeat APC to stop bleeding was performed. During colonoscopy, telangiectasia lesions and 20 easy bleeding erosions were observed in the rectum and sigmoid. The lesions turned to white blackish in color after coagulation with APC was performed (figure 1). After the procedure, the patient received oral metronidazole and ciprofloxacin. Steroid enema was also planned; however, it was not feasible since currently, the treatment has not been available in Indonesia.

steroid enema namun tidak mampu laksana karena saat ini tidak tersedia di Indonesia.

DISCUSSION

The symptoms experienced by the patient were hematoschezia, diarrhea and tenesmus, which occurred in a year after the radiation treatment for her cervical cancer had been completed. A suspicion on the presence of radiation colitis should be considered; moreover, when antibiotic treatment had brought no improvement.

Colonoscopic findings in this patient was also consistent with the features of chronic radiation injury, i.e. in the rectum and sigmoid, there was moderate hyperemia mucosa, telangiectasia lesions and many erosions with oozing blood and several small-sized ulcers; while in descending, transversal and ascending colon up to caecum, the mucosa was smooth and normal. Therefore, it is concluded that the pathological lesions found in the rectum and sigmoid are chronic radiation proctosigmoiditis. Chronic bleeding through gastrointestinal tract and diarrhea may also cause iron deficiency anemia and malnutrition in this patient.

Since changes in vascularization, particularly in small blood vessels are important parts of chronic radiation proctosigmoiditis, any condition affecting microvascular circulation such as diabetes mellitus, hypertension or other vascular diseases increases the risk of developing this disease.³ The incidence of radiation proctosigmoiditis has been also reported to be more likely to occur in patients with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). In those patients, no other significant comorbidities have been found. Another mechanism that has been assumed to have contribution on the development of this disease is excessive oxidative stress; therefore antioxidant substances have been used recently as protectors against radiation-induced injury.⁴

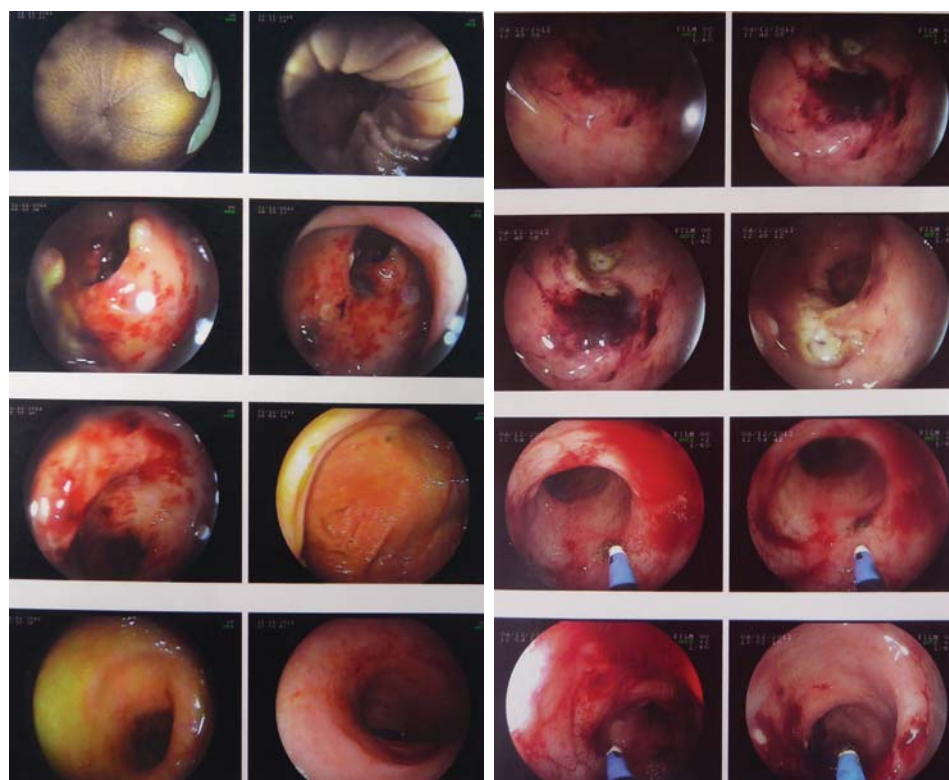


Figure 1. The first colonoscopy (left) and colonoscopy with the 4th APC (right)

The Radiation Therapy Oncology Group (RTOG) dan the European Organization for Research and Treatment of Cancer (EORTC) developed a classify the degree of radiation proctitis, starting from the asymptomatic to the fatal one.⁵ There was a persistent anal bleeding that disturb the patient's daily activity, but no fistula, obstruction or perforation was found.

No large-scale randomized blinded clinical trial has been conducted to evaluate treatment for proctitis or radiation proctosigmoiditis. Most of data were obtained from case reports and small-scale clinical trials. The evidences are not adequate to develop a firm treatment although some treatment modalities may seem promising. Despite the very various strategies available for treating this chronic radiation proctosigmoiditis, generally the treatment should be based on the pattern and severity of the disease.

The management of radiation proctosigmoiditis may include non-invasive or invasive treatment. The non-invasive treatment can be started by administering substances by oral, rectal or inhalation. The substances can be an anti-inflammatory, sucralfate, short chain fatty acid, hyperbaric oxygen or antioxidant. Invasive treatment includes ablation or coagulation (using endoscopy) as well as surgery. Patients with proctitis grade 3 may be treated with anti-inflammatory, antioxidant, sucralfate, hyperbaric oxygen and endoscopic modalities.

Anti-inflammatory substances such as sulfasalazine or its active metabolite of aminosalicylic acid (mesalamine) have low efficacy even when they are combined with steroids and antibiotics. The mechanism of action is through inhibition of prostaglandin synthesis and neutralization of free radicals. Other anti-inflammatory agents are usually combined with sulfasalazine or 5-aminosalicylic acid including prednisone, betametason, hydrocortisone and metronidazole. A study comparing the administration of betametason enema (5 mg twice daily) with hydrocortisone (90 mg twice daily) shows that hydrocortisone is more superior.⁶

The incidences of rectal bleeding and mucosa ulcers are found lower in the metronidazole group during the 4th week, 3rd month and 12th month. Diarrhea and edema are also improved in metronidazole group.¹² Steroid enema has not been available in Indonesia; therefore, it could not be administered for our patient. A new immunomodulator agent, WF 10 (immunokine®) with intravenous administration has also been reported to be useful for treating this disease.⁷

A novel study using colon irrigation with 1 liter water for 8 weeks accompanied with the administration of oral ciprofloxacin and metronidazole for 1 week in patients with chronic radiation proctitis has shown advantages and safety for this condition.⁸ The study also becomes the rationale for administering oral ciprofloxacin and metronidazole in patients following APC procedure in order to reduce bacterial load and promote healing.⁸ The treatment modality is even better than applying 4% formalin using endoscopy shown by a study in Thailand.⁹

Sucralfate is a sucrose sulfate-aluminium complex that can stimulate epithelial healing and produce a layer protector.¹⁸ Some studies show that administering topical sucralfate may improve proctosigmoiditis symptoms.^{10,11} Kocchar studied oral sulfasalazine (500 mg, 3 times daily), which is combined with steroid enema (20 mg prednisolone, twice daily) and compared the treatment with sucralfate enema (2 gram, twice daily). The study results showed that 53% subjects (8 out of 15) who had been treated with a combination of sulfasalazine-steroid and 94% subjects (16 out of 17) who received sucralfate enema had demonstrated clinical improvement, and 47% subjects in the combined sulfasalazine-steroid group showed improved endoscopic parameter versus 71% in the sucralfate enema group.¹² For our patient, 2 gram sucralfate enema was administered twice daily with a suggestion of performing a proper route of administration using foley catheter. It is a modified treatment using syrup preparation since the enema preparation has not been available.

Short-chain fatty acid is a major fuel for colonic mucosa and it can stimulates epithelial proliferation of colonic mucosa.¹³ An essential short-chain fatty acid is butyric acid, which is assumed that it is a product of carbohydrate metabolism by anaerobic bacteria in the colon.¹³ The fatty acid has vasodilatation effect on arterioles and therefore, it can improve circulation.¹⁴ Ischemia and loss of microvilli in colonic mucosa caused the radiation can disrupt the absorption of these fatty acids and it may contribute to mucosa changes as found in chronic radiation proctitis. Short-chain fatty acid supplementation can accelerate healing as it improves nutritional deficiency in colonocytes. A randomized controlled clinical trial on butyric acid enema (40mM) concludes that there is no significant improvement of signs and symptoms of the disease, which is contrary to the results of some case reports.¹³ However, available studies are still not valid and further studies on the benefits of this substance are

necessary. Therefore, such kind of treatment modality still can not be provided for our patient.

The rationale of giving hyperbaric oxygen therapy as an option of treatment was based on the developing pathological process, i.e. ischemia due to vascularization disorder on rectum and sigmoid wall. Theoretically, hyperbaric oxygen treatment can reduce tissue hypoxia through angiogenic and antibacterial effect.¹⁵ Data about the use of hyperbaric oxygen for chronic radiation proctitis is still very limited. A review of several case series shows increased probability of improved clinical condition using hyperbaric oxygen treatment (RR 1.75, number needed to treat = 5).¹⁶ However, hyperbaric oxygen is an expensive treatment modality and hardly available in every place (including at the Cipto Mangunkusumo Hospital) as it needs special equipments.

Invasive treatment has been performed using various endoscopic treatment modalities in management of radiative colitis. Although most of them are aimed to stop bleeding, but may be some have effects on alleviating symptoms. The technique should be used when the patient is refractory to all kinds of the abovementioned pharmacological treatment. Endoscopic therapy includes applying formalin, endoscopic coagulation and APC. Complications of those techniques may include bleeding, perforation, fistula and stenosis.

In chronic radiation proctitis, vascular teleangiectasia and persistent mucosa ulcer are caused by obliterative arthritis that leads to recurrent bleeding. Formalin causes hardening and clogging effect to the fragile neovascular so that it can prevent further bleeding through chemical cauterization. There are two usual methods, i.e. rectal instillation using formalin or direct method using formalin-soaked gauze.¹⁷

Direct topical application on mucosa produces better chemical cauterization, but the level of success extremely depends on accurate localization. Contact with formalin for 2-3 minutes causes whiten lesions. It has been reported that the level of success may reach 70-80%, but for some patients they may need repetitive treatment.¹⁷ A recent study concludes that endoscopic formalin treatment is more effective than sucralfate-steroid enema.¹⁸ Some studies reported equal results with lesser complications using low-dose formalin (4%).^{18,19} Perianal skin should be protected during the procedure to prevent stricture and skin damage. Applying formalin is generally safe; however, complications of bleeding, stricture and fistula have been reported. Direct injection exactly on the mucosa reduces the possibility of stricture, but it is hardly performed in large area and may cause fistula. It is

estimated that the effect of treatment can be maintained at least for 3 months.

Various modalities of endoscopic coagulation is effective to control radiation-induced bleeding using coagulation of focal bleeding on teleangiectasia.²⁰ Most studies are retrospective and show improved symptoms and reduced recurrent case after coagulation treatment using contact probe (heater probe or bipolar probe), laser neodymium: yttrium-aluminium-garnet (Nd:YAG) or argon plasma coagulation.⁶ Both methods, either contact or non-contact utilize heat flow for the coagulation process. Some procedural sessions are required to control the bleeding optimally.¹¹

APC uses high-frequency energy (monopolar diathermy), which is transmitted to the tissues through non-contact ionized gas. The capacity to control bleeding along the gastrointestinal tract has been shown and it has a very small penetration capacity, therefore, it is suitable as treatment for superficial bleeding. The available studies are retrospective and it covers a smaller size of sample.²⁰ However, all studies show a higher hemoglobin level and fewer symptoms in patients who had failure in pharmacological treatment previously and continue their treatment with APC.

Laser Nd:YAG had equal advantages as APC. This instrument also has a limited capacity to penetrate tissue; therefore, it is suitable for ceasing superficial bleeding. However, the supporting evidences are similar to APC, but with limited number of patients. High cost and availability of YAG laser and APC are the usual challenges.

In our patient, APC was performed to control bleeding. The patient had received 4 sessions of APC, which was expected that it may stop the ongoing chronic bleeding. If the APC treatment failed, we can try formalin application or using radiofrequency ablation. Radiofrequency ablation (RFA) can stimulate reepithelization with lesser incidence of stricture and ulceration. RFA may covers more extensive area in one go than heater or bipolar probes or APC, which moves only from one point to another point.¹⁸ The instrument is as portable as APC. Nikfarjam et al reported that refractory cases of APC actually can be controlled using RFA.²¹

Surgery is the last option for treatment of this condition. Less than 10% of patients require surgery.²² Usually, surgical procedures are aimed for specific symptoms and severe complication such as bleeding that unstopable with other modalities, perforation, stricture and fistula. When selecting surgical treatment, the risks must be considered thoroughly. Microvascular damage due to radiation not only causes proctitis

symptoms but also inhibits healing of the surgical wound. The most common indication to refer the proctitis patient to the surgical department is that colostomy or ileostomy should be performed.

The procedure of creating stoma is aimed to relocate fecal output so that it may reduce symptoms of pain, tenesmus infection and it serves as drainage of fecal discharge although it can not relieve the symptoms completely. Unfortunately, the procedure can only alleviating symptoms, but it can not reduce bleeding. When the bleeding is hardly controlled, proctectomy may be the only option. Most studies on surgical procedures for chronic radiation proctosigmoiditis show poor output with high rate of complications (15-80%) and the mortality rate may reach 3-9%.²² The data are based on symptoms and degree of severity; moreover, the data are obtained from various experiences at health care centers.

Special treatment is not necessary for those with mild symptoms and the symptoms may cease spontaneously in 6 months. Since pharmacological treatment is safe and effective, 2 x 2 gram daily sucralfate enema can be administered. For those without any response, endoscopic treatment can be performed. APC is more preferable since it has more practical use and the result can be predicted. Applying formalin and RFA are alternative treatment that can be done. However, the probability of complication that may need colon resection or colostomy must be considered when one wishes to choose the alternative treatment.

REFERENCES

1. Xiao M, Whitnall ND. Pharmacological counter-measures for the acute radiation syndrome. *Cur Mol Pharmacol* 2009;1:122-33.
2. Lesperance RN, Kjorstadt RJ, Halligan JB, Steele SR. Colorectal complications of external beam radiation versus brachytherapy for prostate cancer. *Am J of Surg* 2008;5:616-20.
3. Coia LR. Late effects of radiation therapy on the gastrointestinal tract. *Int J Radiat Oncol Biol Phys* 1995;5:1213-36.
4. Kennedy M, Bruninga K, Mutlu EA, Losurdo J, Choudhary S. Successful and sustained treatment of chronic radiation proctitis with antioxidant vitamins E and C. *Am J Gastroenterol* 2001;4:1080-4.
5. Kennedy GD, Heise CP. Radiation colitis and proctitis. *Clin Colon Rectal Surg* 2007;20:64-72.
6. Denton AS, Forbes A, Andreyev HJN, Maher EJ. Non surgical interventions for late radiation proctitis in patients who have received radical radiotherapy to the pelvis. *Cochrane Database of Sys Rev* 2002;1:1-34
7. Veerasarn, Boonnuch W, Kakanaporn C. A phase II study to evaluate WF10 in patients with late hemorrhagic radiation cystitis and proctitis. *Gynecol Oncol* 2006;1:179-84.

8. Sahakitrungruang C, Thum-Ummuaysuk U, Pati Wongpaisarn A, Atittharnsakul A, Rojanasakul A. A novel treatment for haemorrhagic radiation proctitis using colonic irrigation and oral antibiotic administration. *Colorectal Dis* 2011;13:79-82.
9. Sahakitrungruang C, Pati Wongpaisarn A, Kanjanasilp P, Malakorn S, Atittharnsakul P. A Randomized Controlled Trial Comparing Colonic Irrigation and Oral Antibiotics Administration Versus 4% Formalin Application for Treatment of Hemorrhagic Radiation Proctitis. *Dis Colon Rectum* 2012;55:1053-8.
10. Kochhar R, Sriram PV, Sharma SC. Natural history of late radiation proctosigmoiditis treated with topical sucralfate suspension. *Dig Dis Sci.* 1999;44:973-8.
11. Chun M, Kang S, Kil HJ. Rectal bleeding and its management after irradiation for uterine cervical cancer. *Int J Radiat Oncol Biol Phys.* 2004;58:98.
12. Kochhar R, Patel F, Scharma SC. Radiation-induced proctosigmoiditis: prospective, randomized, double-blind controlled trial of oral sulfasalazine plus rectal steroids versus rectal sucralfate. *Dig Dis Sci* 1991;1:103-7.
13. Pinto A, Fidalgo P, Cravo M. Short chain fatty acids are effective in short-term treatment of chronic radiation proctitis: randomized, double-blind, controlled trial. *Dis Colon and Rectum* 1999;6:788-96.
14. Aalkjaer C. Short chained fatty acids and the colon: how do they cause vasodilatation?. *J Physiol* 2002;3:674
15. Feldmeier JJ, Hampson NB. A systematic review of the literature reporting the application of hyperbaric oxygen prevention and treatment of delayed radiation injuries: an evidence based approach. *Undersea Hyperb Med* 2002;1:4-30.
16. Bennett MH, Feldmeier J, Hampson N, Smee R, Milross C. Hyperbaric oxygen therapy for late radiation tissue injury. *Cochrane Database of Sys Rev* 2005;3:1-32
17. Haas EM, Bailey HR, Farragher I. Application of 10 percent formalin for the treatment of radiation-induced hemorrhagic proctitis. *Dis Colon Rectum* 2007;2:213-7.
18. Ramakrishnaiah VPN, Javali TD, Dharanipragada K, Reddy KS, Krishnamachari S. Formalin dab, the effective way of treating haemorrhagic radiation proctitis: a randomized trial from a tertiary care hospital in South India. *Colorectal Dis* 2012;14:876-82.
19. Cullen SN, Frenz M, Mee A. Treatment of haemorrhagic radiation-induced proctopathy using small volume topical formalin instillation. *Aliment Pharmacol Ther* 2006;23:1575-9.
20. Rustagi T, Mashimo H. Endoscopic management of chronic radiation proctitis. *World J Gastroenterol* 2011;17:4554-62.
21. Nikfarjam M, Faulx A, Laughinghouse M, Marks JM. Feasibility of radiofrequency ablation for the treatment of chronic radiation proctitis. *Surg Innov* 2010; 17: 92-9.
22. Do NL, Nagle D, Poylin VY. Radiation proctitis: current strategies in management. *Gastroenterol Res Pract* 2011;1:1-9.

Correspondence
 Dadang Makmun
 Division of Gastroenterology
 Department of Internal Medicine
 Dr. Cipto Mangunkusumo General National Hospital
 Jl. Diponegoro No.71 Jakarta Indonesia
 Phone: +62-21-3153957 Facsimile: +62-21-3142454
 E-mail: hdmakmun@yahoo.com
