Radiation Proctitis

Radzislaw Trzcinski, Michal Mik, Lukasz Dziki and
Adam Dziki

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Abstract

Pelvic radiotherapy (RT) has become a vital component of curative treatment for various pelvic malignancies. The fixed anatomical position of the rectum in the pelvis and the close proximity to the prostate, cervix, and uterus, makes the rectum especially vulnerable to secondary radiation injury resulting in chronic radiation proctitis (CRP). Clinical symptoms associated with CRP are commonly classified by the EORTC/RTOG late radiation morbidity scoring system. Rectal bleeding is the most frequent symptom of CRP occurring in 29–89.6% of patients. Endoscopy is essential to determine the extent and severity of CRP as well as to exclude other possible causes of inflammation or malignant disease. Typical endoscopic findings of rectal mucosal damage in the course of radiation-induced proctitis include friable mucosa, rectal mucosal hypervascularity, and telangiectases. There is no consensus available for the treatment of CRP, and different modalities present a recurrence rate varying from 10 to 30%. CRP can be managed conservatively, and also includes ablation (formalin enemas, radiofrequency ablation, YAG laser or argon plasma coagulation) as well as some patients require surgery. Although modifications of radiation techniques and doses are continually being studied to decrease the incidence of CRP, trials investigating preventive methods have been disappointing to date.

Keywords: pelvic malignancies, radiotherapy, radiation proctitis

1. Introduction

The discovery of X-rays in 1895 by Wilhelm Röntgen was followed 2 years later by the discovery by Walsh of the damaging effects of X-irradiation on the gastrointestinal tract. In 1912, Regaud et al. described delayed changes in the small intestine of a dog following irradiation. Krause and Ziegler believed that harmful effects of X-irradiation on the small intestine

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were caused by the proliferation of intestinal bacteria [1–4]. In 1917, the first clinical report of a patient who developed severe intestinal injury following the use of radiation therapy for treatment of malignant disease was published [4]. Then, in 1930, Buie gave the first description of factitial proctitis, which referred to chronic radiation-induced injury to the rectum in a group of patients who had undergone pelvic irradiation [3, 5].

Radiotherapy (RT) has now become a common treatment for many cancers involving the pelvis, with around 12,000 patients undergoing pelvic radiotherapy in the UK each year, over 100,000 American patients annually receiving therapeutic pelvic radiation and up to 300,000 patients per year worldwide [2, 6, 7]. Pelvic radiotherapy is a vital component of curative treatment typically used in urological, gynecological and gastrointestinal tract cancers (prostate, urinary bladder, cervical, uterine, rectal and anal malignancies). Pelvic radiation is administered either as neoadjuvant or adjuvant therapy. After pelvic irradiation, the rectum is the commonest site of injury within the gastrointestinal tract. The fixed anatomical position of the rectum in the pelvis and the close proximity to the prostate, cervix and uterus make the rectum especially vulnerable to secondary radiation injury resulting in proctitis [8–16].

The anterior rectal wall is in close proximity to and partly in continuity with the therapeutic target organs (prostate, uterus) [17, 18]. Although the development of late gastrointestinal toxicity following pelvic radiotherapy is not entirely dose related, there is a rapid rise in the number of rectal complications when the cumulative mean rectal dose and the cumulative maximum dose exceed 75 Gy, and there is also evidence that the incidence of severe complications rises sharply above a total dose of 80 Gy [19–21]. Treatment for prostate carcinoma typically receives 75 Gy over 7 to 8 weeks, and cervical carcinoma might receive 45 Gy of the typical external beam radiotherapy (EBRT) plus a variable dosing of brachytherapy [22]. There is an increasing risk of rectal toxicity ranging from 2% for patients receiving ≤50 Gy to 15–18% for patients receiving ≥80 Gy [20].

Acute radiation proctitis is encountered by up to 75% of patients receiving conventional pelvic radiotherapy and is defined as an inflammatory process involving only the superficial mucosa. It occurs within 1–6 weeks of radiation treatment and is generally self-limited with symptom resolution often within 3 months after the onset of therapy [2, 4, 6, 8, 12, 23–25]. There is some evidence to suggest that moderate or severe chronic radiation proctitis is at least twice more likely to occur in those initially experiencing severe acute proctitis [22, 26]. Chronic radiation proctitis occurs months to years after treatment with a large majority within 2 years post radiotherapy, and this entity is a troublesome complication in those undergoing pelvic irradiation for any cause. The incidence of late complications is about 2.5–30%; although with improving techniques and newer modalities of radiation therapy and minimizing the dose of radiation to the rectum, the incidence is decreasing [2, 4, 6, 8, 12, 15, 20, 22–24, 27–31].

The development of postradiation rectal toxicity is not entirely dose, volume and fractionation schedule related. It also depends on a complex interaction of physical, patient-related and genetic factors, but these have been poorly characterized to date [7]. Many patients suffer progressive disease that may be life-long. There are a number of predisposing factors that may play a role in the increased risk of developing chronic radiation proctitis: age > 60 years, low BMI, diabetes, cardiovascular disease, hypertension, peripheral vascular disease, use of

anticoagulants, inflammatory bowel disease, hormonal therapy, collagen vascular disease, atherosclerosis, preexisting inflammatory bowel disease, smoking, pelvic inflammatory conditions, previous abdominopelvic surgery and possibly secondary anatomical changes with intraabdominal adhesions leading to immobility of intestinal loops in the radiation field (e.g., hysterectomy), radiation dosages to the lower pelvis >54 Gy, the volume of rectum irradiated, RT technique and dose per fraction, previous concomitant or subsequent chemotherapy, ataxia-telangiectasia gene and HIV infection [2, 4, 6, 8, 12, 16, 20, 22, 24, 32, 33].

2. Pathology

Any part of the gastrointestinal tract may be affected by the radiation [4]. Radiotherapy induces long-term changes in bowel function as a result of progressive endothelial dysfunction, which includes ischemia and subsequent fibrosis. The same processes may cause dysfunction in other pelvic organs; therefore, Andreyev et al. defined this disorder as "pelvic radiation disease" (PRD). "Proctitis" suggests that there is an ongoing inflammation, whereas there is inflammation during and immediately after radiotherapy, but, by 3 months or more, inflammation has been replaced almost entirely by progressive ischemia and fibrosis. PRD currently affects as many each year as develop inflammatory bowel disease (IBD) has a spectrum of symptoms identical to IBD and shares some of its pathological features. Unlike IBD, however, we know that PRD starts with the initiation of radiotherapy. During therapeutic irradiation of a pelvic malignancy, parts of distal small bowel, caecum, transverse and sigmoid colon and rectum are often also irradiated. Additionally, the pancreas and proximal small bowel may also receive some irradiation if para-aortic nodes are treated. Moreover, in the chronic phase of the disease, there is minimal inflammation; "-itis" signifies inflammation, and so describing the situation as "-itis" is misleading. So, Andreyev et al. suggest the term "radiation proctopathy" to be better. This is not further discussed here because they go beyond the scope of this chapter which focuses mainly on chronic radiation proctitis [27, 34–36].

3. Clinical features

Radiation-induced bowel toxicity has been dominated by the application of scoring scales that are based on clinical symptoms [7, 27]. Intensity of chronic radiation proctitis is also scored with regard to clinical symptoms. Numerous grading systems are used in the literature to assess rectal toxicity following radiotherapy. Currently, clinical symptoms associated with CRP are most commonly classified by the EORTC/RTOG late radiation morbidity scoring system (the European Organization for Research and Treatment of Cancer/Radiation Therapy Oncology Group score for late rectal toxicity) (**Table 1**) [3, 7, 22, 26, 28, 34, 37–40].

Chronic radiation proctitis may be associated with diarrhea, tenesmus, mucus discharge, ulcers and abdominal/rectal pain, but bleeding is the most common symptom with potential iron deficiency anemia that may require hospitalization and even blood transfusions. Refractory bleeding is a real challenge to clinicians. The frequency of rectal bleeding after RT

Proctitis grades	Radiation-induced clinical symptoms
0	None
1	Mild diarrhea, mild cramping, bowel movements up to five times daily, slight rectal discharge or bleeding, mild anal pain and mild rectal tenesmus
2	Moderate diarrhea and colic, bowel movements more >5 times daily, excessive rectal mucus or intermittent rectal bleeding
3	Obstruction or persistent bleeding requiring surgery
4	Necrosis/perforation/fistula
5	Fatal toxicity (sepsis, multiple organ dysfunction syndrome)

Table 1. The EORTC/RTOG scoring system (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer score for late radiation proctitis).

is said to occur in 29–89.6% of patients, and it is the second most common reason for referral to a gastroenterologists after radiotherapy. Some degree of abdominal or rectal pain affects up to 30% of all patients after radiotherapy, and it influences daily living in about 10%. Patients may present symptoms of obstructed defecation because of strictures accompanied with constipation, rectal pain, urgency and sometimes fecal incontinence. Fistulas into adjacent organs (e.g., vagina) may also occur[4, 6–8, 10, 12, 16, 23, 25, 29, 31, 35, 40, 41].

Because of the nature of radiation injury, the incidence of severe complications (transfusion-dependent bleeding, fistula formation, rectal stricture and bowel obstruction, perforation, secondary malignancy) increases with time. Estimates of the significance of these severe consequences of radiotherapy have varied between 0.5 and 30%, but more reasonable estimates suggest that these occur between 15 and 20% over 20–30 years [4, 7, 12, 42]. Late injury to the rectum usually occurs in the first 2–3 years after treatment and the incidence then plateaus [25, 43].

4. Endoscopic findings

Each patient who has undergone radiotherapy for pelvic malignancies and reports symptoms suggestive of radiation-induced proctitis should be suspected of this entity, even if irradiation was performed many years ago. Endoscopy, in any case, is important to determine the extent and severity of chronic radiation proctopathy as well as to exclude other possible causes of inflammation or malignant disease [8]. Abnormal endoscopic findings after pelvic radiotherapy include congested mucosa, telangiectasia, erythema or pallor, ulceration, stricture, fistula and necrosis. Fragile rectal mucosa is prone to bleeding. Telangiectasia of the rectal mucosa which are very frequent and a major cause of bleeding may resolve spontaneously after 3 years. However, the prevalence of telangiectases in unselected patients is unknown [8, 18, 29, 31, 32, 43].

Endoscopic evaluation of acute radiation proctitis shows edematous, dusky red rectal mucosa, whereas endoscopy of chronic radiation proctitis shows mucosal atrophy, ectatic superficial capillaries, tortuous blood vessels, telangiectasias, variable stenosis, strictures and fistulas [6]. Characteristic endoscopic changes of rectal mucosal damage in the course of radiation proctitis are shown in **Figure 1**.
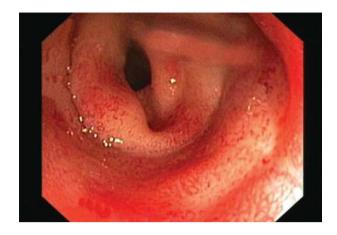
Figure 1. Typical endoscopic appearance of rectal mucosal damage in the course of radiation proctitis—congested and friable mucosa, extensive rectal mucosal hypervascularity, tortuous blood vessels and telangiectases.

It is also important to highlight that due to the possibility of initiating chronic, poorly healing wounds and the risk of possible complications of sepsis, fistula formation and also the increased risk of bleeding, biopsy of devitalized rectal tissues should be avoided as they do not contribute to the diagnosis of chronic radiation proctopathy. Rectal biopsy is only justified if any malignancy is suspected or in a case of important therapeutic consequences [8, 12, 44].

5. Differential diagnosis

Radiation-induced proctitis should be suspected in any patient after pelvic radiotherapy who presents the symptoms of this entity. Acute radiation proctitis may mimic allergic or eosinophilic colitis, but the history will allow accurate diagnosis. However, endoscopy is essential to exclude other causes of acute or chronic proctitis such as infectious colitis, inflammatory bowel disease, diversion colitis, ischemic colitis, angiodysplasia, diverticular colitis and concomitant other malignancies [6, 8].

6. Treatment: medical and surgical

Radiation-induced proctopathy is unlikely to find one treatment modality that works for all patients. Acute radiation-induced proctitis is managed conservatively and includes hydration, antidiarrheals and steroid or 5-aminosalicylate enemas [12].

There is no consensus available for the treatment of chronic radiation proctopathy, and the different modalities present a recurrence rate varying from 10 to 30%. Chronic radiation-induced proctitis can be managed conservatively (anti-inflammatory agents, sucralfate, short-chain fatty acids, hyperbaric oxygen therapy, antioxidants) and also includes ablation (formalin

enemas, radiofrequency ablation, YAG laser or argon plasma coagulation) and surgery [12]. There was also a case report of successful treatment of a patient with severe refractory hemorrhagic radiation proctitis with low dose of oral thalidomide [6, 45]. It is very important to realize, when considering invasive treatment that chronic radiation-induced proctitis can improve over time without any treatment [8].

6.1. 5-Aminosalicytic acid (5-ASA)

The mechanism of anti-inflammatory action of 5-ASA is the inhibition of prostaglandin synthesis. 5-ASA may also inhibit folate-dependent enzymes and free radical-scavenging activity [12].

6.2. Steroids

Steroids (prednisone, betamethasone, hydrocortisone) have multiple mechanisms of action that produce anti-inflammatory effects which extend from stabilization of lysosomes in neutrophils to prevent degranulation to upregulation of anti-inflammatory genes via binding to glucocorticoid receptors [12]. Steroids have been used to treat radiation proctitis both alone and in combination with other agents [28]. The addition of *metronidazole* to oral mesalazine and betamethasone enemas was associated with a reduction in rectal bleeding, diarrhea and ulcers [8].

6.3. Sucralfate and pentosan polysulfate (PPS)

Sucralfate (2–3 g of sucralfate in a 15–20 ml suspension, oral sucralfate, paste) adheres to mucosal cells and stimulates epithelial healing and the formation of protective epithelial barrier while PPS (a synthetic derivative of a glycosaminoglycan) is thought to reduce epithelial permeability and prevent adherence similar to sucralfate. Moreover, sucralfate has been found to induce a better clinical response than anti-inflammatories in patients with CRP. Based on a Cochrane review, sucralfate enemas were more effective than corticosteroid or mesalazine enemas [8, 12, 22, 28, 35, 39]. A novel method of rectal administration of sucralfate via a low-volume sucralfate paste (two sucralfate 1 g tablets mixed with 4.5 ml of water) was reported by McElvanna et al. Clinical improvement was reported in 73% of patients, and 32% had resolution of all symptoms [39].

PPS, a fibrinolytic, anti-inflammatory and mucoprotective agent, resolved symptoms in nine of thirteen patients with established chronic radiation proctitis [20].

6.4. Short-chain fatty acids (SCFAs)

Short-chain fatty acids are the main energy source for colonocytes and stimulate colonic mucosal proliferation. The most important product of SCFA is butyric acid. They also exert a vasodilatatory effect on the arteriole walls to improve blood flow. SCFAs were found to accelerate the healing process, with a significant early reduction in bleeding episodes and endoscopic scores. One of two small randomized, placebo-controlled trials noted more rapid improvement in symptoms and endoscopic findings in a group of patients using a butyrate-containing SCFAs solution over a 5-week period compared with placebo controls [12, 22, 28].

6.5. Formalin

Formalin application has been demonstrated to be generally effective and safe in hemorrhagic proctitis and, however, may cause complications such as chronic anorectal pain, fever, fecal incontinence, rectosigmoid necrosis with or without perforation, enteric fistula formation, anal and rectal strictures as well as pelvic sepsis. Topical formalin instillation (4% solution, formalin-soaked pads with up to 10% solution) may be repeated in case of recurrent bleeding and combined with other methods [9, 12, 20, 31, 35, 40, 41, 46, 47]. Formalin enemas probably reduce mucosal blood flow, sclerose and seal fragile telangiectasias through chemical cauterization to prevent further bleeding with reported success rate of 48–100%. Direct contact with formalin for 2–3 minutes (via formalin solution installation through endoscope or Foley catheter or soaked gauze) causes chemical cauterization of neovasculature [9, 12, 35, 40, 41, 47].

6.6. Antioxidants

As oxidative stress is thought to be an important factor in the development of chronic radiation proctitis, antioxidants have been used in an attempt to limit tissue damage. The use of vitamins E (400 IU three times daily), C (500 mg three times daily) and A (10,000 IU twice daily for 90 days) significantly reduced proctitis symptoms (diarrhea, bleeding, urgency) [8, 12, 48].

6.7. Endoscopic treatment

A variety of endoscopic coagulation devices (e.g., Nd:YAG laser, argon plasma coagulation, bipolar electrocoagulation, and heater probe) deliver thermal coagulation to the focal bleeding telangiectasia and should be reserved for patients suffering from significant hemorrhagic proctitis. There have been also reports on endoscopic balloon dilatation and stenting for radiation-induced rectal strictures [12, 28].

Argon plasma coagulation (APC)—monopolar diathermy is used to ionize the argon gas which coagulates the telangiectatic vessels in a noncontact fashion (0.8–3.0 mm from the target). Many gastroenterologists consider APC as the treatment of choice for CRP. A complete resolution of bleeding is obtained in 70–80% of patients, but an average of three treatment sessions is required. On the other hand, we have to realize severe complications that may happen after this procedure which is performed in chronically ischemic tissues (deep ulceration, fistulation, rectal stenosis, rebound bleeding, long-term pain, perforation, rectovaginal fistula and even bowel explosions in inadequately prepared bowels). The development of rectal ulcers after APC is thought to be a consequence of thermal injury. On the basis of anecdotal evidence, APC is commonly ineffective in patients with very heavy bleeding [8, 12, 15, 20, 25, 31, 35, 47, 49].

YAG laser coagulation has a similar benefit as APC with a limited depth of penetration and the possibility for precise application. The major risk for laser coagulation is transmural necrosis, with perforation or stricture formation. Nevertheless, the laser is expensive and not widely available [8, 12, 20, 31].

Trans-anal rectoscopic ball diathermy (TARD)—monopolar diathermy coagulation is used to coagulate radiation-induced hemorrhagic telangiectasia (RIHT). Treatment involves applications of

monopolar diathermy to the rectal mucosa over the affected areas, targeting the central "feeding vessel" of the telangiectatic spots. TARD is a safe and effective modality with 85% of patients reporting immediate symptomatic control with no significant morbidity [46].

Endoscopic cryoablation (cryospray ablation therapy) involves noncontact application of liquid nitrogen or carbon dioxide gas to the tissue and offers superficial ablation of mucosa in patients with CRP. Cryotherapy has been suggested as a safe and effective method for bleeding in CRP. Hou et al. reported a series of ten patients with hemorrhagic radiation proctitis treated with endoscopic cryoablation. Overall subjective clinical scores improved as determined by the Radiation Proctitis Severity Assessment Scale from 27.7 to 13.6 ($p = 0.003$), and symptom improvement correlated with endoscopic improvement. Cryotherapy is novel and up to date, and there is very limited data [15, 24, 47].

6.8. Hyperbaric oxygen therapy (HBOT)

HBOT involves patients breathing pure oxygen in a pressurized room or tube. Under these conditions, the lungs can gather more oxygen than at normal air pressure. Higher oxygenated blood may inhibit bacterial growth and stimulate the release of growth factors and stem cells; thus, it affects and promotes wound healing. Increased oxygen pressure to telangiectatic vessels reverses the ischemic component of chronic radiation proctopathy and promotes angiogenesis with healing of rectal mucosa. Two randomized controlled trials (RCTs) and one nonrandomized comparative study examined HBOT for treatment of radiation proctitis. First, RTC showed a significantly greater proportion of HBOT patients demonstrating at least moderate healing of proctitis in comparison with sham treatment group immediately after completion of treatment (87.5 vs. 62.5%, $p = 0.0009$). The second RTC reported that treatment with HBOT significantly decreased the prevalence of radiation proctitis compared to symptomatic treatment alone at 6-month follow-up (76.9 vs. 42.9%, $p = 0.026$). The nonrandomized comparative study found that HBOT patients required statistically more blood transfusions than APC (argon plasma coagulation) patients at 1-month ($p = 0.03$) and 2-month follow-up ($p = 0.04$). This difference was nonsignificant after 3 months. Side effects after HBOT may include barotrauma (ear pain), myopia and confinement anxiety [8, 24, 31, 47, 50].

As late radiation injury is characterized by abnormal angiogenesis, the future will show whether it will be possible to develop drugs to treat radiation proctitis with angiogenic factors as their target. Inhibitors of angiogenic factors such as angiogenin and fibroblast growth factor 1 (FGF1) might be also effective for treating CRP [51].

6.9. Surgery

Surgery is a feasible curative option for severe cases refractory to medical treatment; however, there is no universally agreed surgical first-line approach in the literature, indicating which patients should undergo surgery nor which surgical procedure is optimal. On the other hand, surgery in previously irradiated patients is often extremely difficult because of fibrosis within the abdomen and carries significantly higher risks of complications and mortality than surgery in nonirradiated patients. Thus, surgery is reserved solely as a last resort; nevertheless, the challenge for clinicians is to develop an evidence-based consensus to decide when

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Indications for surgery

- Failure of conservative treatment (intractable bleeding)

- Strictures and rectal obstruction

- Rectal or rectosigmoid perforation

- Fistulas (e.g., recto-vaginal, rectovesical, recto-urethral)

- Uncontrollable rectal pain

Table 2. Indications for surgery in patients with chronic radiation proctitis.

the benefits of surgery outweigh the risks in the group of patients refractory to conservative treatment [7, 8, 14, 23, 28, 41]. Reported data on the increasing risk over time of complications requiring operative intervention show that 4–10% of patients are affected over 5–10 years and up to 20% over 20 years [27]. Generally, approximately 2.6–10% and even up to one-third of the patients will undergo surgery due to complications of radiation proctitis. The preferred surgical approach is not universally agreed. Surgery for CRP mainly involves either diverting loop colostomy or resection without primary anastomosis. The issue with diversion alone for CRP is that it does not remove the damaged tissue, and leaving it in situ leaves the patient at risk of further bleeding, perforation, obstruction and abscess formation. Therefore, some authors advocate that if patients are fit enough, resection should be the first-line therapy, and defunctioning stoma reserved for patients who are poor surgical candidates for resection. Another option is resection with loop ileostomy. Diversion of stool or the urinary stream with an ostomy or a suprapubic catheter should be considered in almost all cases where repair is attempted. In cases of complicated fistulous disease, particularly when accompanied by significant pain and incontinence, a proctectomy or pelvic exenteration with or without reconstruction is recommended. In cases of severe and intractable bleeding, proctectomy may be the only option [8, 12, 20, 23, 41]. The most common indications for surgical management in patients with chronic radiation proctitis are shown in **Table 2** [12, 20, 23, 28].

When surgical treatment is needed, most studies demonstrate poor outcomes with complication rates of 15–80% (sepsis, wound dehiscence, bowel obstruction, de novo rectal fistula) and a mortality of 3–9% and even up to 25% [8, 12, 20]. In contrary to diversion alone, major resectional surgery carries higher morbidity and mortality risks. Mortality and morbidity vary from 0 to 44% and from 0 to 11% for diversion only vs. 0–100% and 0–14% in cases of resectional surgery [23].

7. Prevention

Although modifications of radiation techniques and doses are continually being studied to decrease the incidence of radiation-induced proctitis, trials investigating preventive methods have been disappointing to date. The role of pharmacological and nutritional therapy in reducing radiation-induced gut disease has been evaluated in a variety of experimental settings, including animal models (e.g., pravastatin, teduglutide). Agents that reverse fibrosis

might be useful but need to be taken for many months to produce benefit. Many treatments have potential antifibrotic activity (liposomal copper-zinc superoxide dismutase, pentoxifylline with or without high-dose vitamin E and hyperbaric oxygen). Balsalazide used 5 days before and up to 2 weeks after pelvic radiotherapy proved an improvement in toxicity grades, particularly pertaining to proctitis. Diets enriched with glutamine, arginine and vitamin E have been shown to have a protective effect on the intestinal mucosa of rats treated with radiotherapy. However, there are no trials assessing the role of dietary supplements in attenuating the development of chronic radiation enteritis in humans [2, 7, 12, 35, 48]. Preventative measures (e.g., the use of rectal misoprostol, oral or rectal sucralfate) have not made a significant contribution to decrease the incidence of radiation proctitis. However, data available in the literature are ambiguous. Khan et al. found that misoprostol rectal suppositories given prior to each radiotherapy session reduced acute and chronic proctitis syndrome [12, 22].

Optimizing the radiotherapy planning by using planning constraints reduces the irradiated rectal volume and, thus, decreases the risk of rectal toxicity. Appropriate packing to push the rectum and bladder away from the radioactive source helps in reducing the incidence of radiation proctitis. There is also evidence in favor of genetic variants in the development of radiation toxicity. Therefore, there is a role for further studies to identify high-risk patients based on genetic biomarkers [4, 8].

Author details

Radzislaw Trzcinski*, Michal Mik, Lukasz Dziki and Adam Dziki

*Address all correspondence to: trzcinskir@wp.pl

Department of General and Colorectal Surgery, Medical University of Lodz, Lodz, Poland

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