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REVIEW

# Gastrointestinal radiation injury: Symptoms, risk factors and mechanisms

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## Abstract

Ionising radiation therapy is a common treatment modality for different types of cancer and its use is expected to increase with advances in screening and early detection of cancer. Radiation injury to the gastrointestinal tract is important factor working against better utility of this important therapeutic modality. Cancer survivors can suffer a wide variety of acute and chronic symptoms following radiotherapy, which significantly reduces their quality of life as well as adding an extra burden to the cost of health care. The accurate diagnosis and treatment of intestinal radiation injury often represents a clinical challenge to practicing physicians in both gastroenterology and oncology. Despite the growing recognition of the problem and some advances in understanding the cellular and molecular mechanisms of radiation injury, relatively little is known about the pathophysiology of gastrointestinal radiation injury or any possible susceptibility factors that could aggravate its severity. The aims of this review are to examine the various clinical manifestations of post-radiation gastrointestinal symptoms, to discuss possible patient and treatment factors implicated in normal gastrointestinal tissue radiosensitivity and to outline different mechanisms of intestinal tissue injury.



**Key words:** Radiation enteritis; Radiation proctitis; Symptoms; Pathophysiology; Risk factors

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## INTRODUCTION

### *Radiation delivery methods*

Radiation therapy can be delivered by three main methods. External beam radiotherapy is a method in which radiation beam is delivered from outside the body to the target tumour through two or three-dimensional beam arrays using linear accelerators. Advances in planning and delivery techniques such as 3-dimensional simulation and intensity modulated radiation therapy are associated with a reduced risk of normal tissue toxicity and allow a higher radiation dose to be used compared to conventional two dimensional methods[1-4]. Enhanced target definition of both tumours and surrounding normal tissues and combining beams of varying intensity in intensity modulated radiation therapy allow for better dose delivery and improved tumour control with less toxicity[5,6]. Quantitative dose tracking to both normal tissues and tumors in the form of dose-volume histograms[7] provide a graphic display of a simulated radiation treatment plan and generate valuable information on the dose distribution within the volume of interest[8]. These are now common planning

tools in modern external beam radiation delivery. Brachytherapy is an internal form of radiation therapy where the radiation sources are implanted within or in close proximity to the target tumour to deliver a high dose of localized radiation. This procedure is a highly effective dose delivery method for certain tumours such as prostate and gynaecological cancers. The third method of the radiation therapy is the systemic administration of radioactive particles which is termed radioisotope therapy. In this method radioactive particles (radionuclides) are injected into the blood stream to be adsorbed specifically by the targeted tissue such as thyroid gland[9]. Gastrointestinal radiation injury most commonly occurs following external beam therapy.

A highly precise radiation delivery can be achieved through newer techniques such as image guided radiotherapy techniques which allow verification of the target position on a daily basis to account for internal target motion[10]. Stereotactic radiation therapy[11] can focus a narrow radiation beams on a small target such as early cancer or metastatic lesions[12].

## TREATMENT RELATED RISK FACTORS FOR GASTROINTESTINAL INJURY

### *Radiation dose, fractionation and field size*

Radiation dose is a major determinant of the severity of acute and late normal tissue toxicity[13-20], the desired optimal radiation dose is defined as the dose that maximizes the difference between "tumor" and "normal tissue" damage within the sigmoid shape dose-effect relationship curve[11]. With respect to the gastrointestinal tract, the severity of toxicity is reported as Grades of severity to different symptoms or clinical manifestations ranging from minor symptomatic changes to severe life threatening complications. Multiple toxicity grading systems have been developed to assess adverse events of cancer treatment[21]. Generally, Grade 1 and 2 radiation injury are frequent and they are often requiring no treatment although they can cause a considerable effect on patient quality of life. Examples of commonly used toxicity grading system to assess radiation injury severity are the Radiation Therapy Oncology Group[22] and the Common Terminology Criteria for Adverse Events grading system (Table 1)[21]. Radiation dose per fraction and altered fractionation schedules are important factors linked to increased risk of intestinal radiation toxicity[23]. The radiosensitivity of the cell depends on two factors, the intrinsic radiosensitivity which is linearly related to the radiation dose and it is represents the initial slope of the cell survival curve (alpha). The second factor is (beta) which represents the curvature of the cell survival curve and it is a factor of dose-per fraction and dose-rate variations in radiobiology[24].

The alpha/beta ratio represents the dose at which the linear and quadratic components of the Linear-Quadratic model contribute equally to cell killing and has been shown to have a connection to early and late radiation response[25]. In radiotherapy of tumors with long turnover time such as prostate cancer, the alpha/beta ratio is smaller than that of early reacting normal tissues. In this case, hypo-fractionation will be a better strategy for radiotherapy than the many small fractions used for other tumors[24,26,27].

A data analysis of 918 head and neck cancer patients reported a variable prevalence of mucositis between patients treated with continuous hyperfractionated accelerated radiotherapy (CHART) and patients received conventional fractionation radiotherapy. The incidence of Grade 3 confluent mucositis reported after CHART was 75% compared to 44% following conventional fractionation radiotherapy[28].

Modification of the radiation delivery regimes through

**Table 1 Example of some gastrointestinal symptoms grades following radiation injury**

| Grade | Gastrointestinal symptoms |
|---|---|
| | Nausea |
| 1 | Loss of appetite without alteration in eating habits |
| 2 | Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 h |
| 3 | Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ⩾ 24 h |
| 4 | Life-threatening consequences |
| 5 | Death |
| | Anorexia |
| 1 | Loss of appetite without alteration in eating habits |
| 2 | Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated |
| 3 | Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); IV fluids, tube feedings or TPN indicated |
| 4 | Life-threatening consequences |
| 5 | Death |
| | Haemorrhage-GI |
| 1 | Mild, intervention (other than iron supplements) not indicated |
| 2 | Symptomatic and medical intervention or minor cauterization indicated |
| 3 | Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e., hemostasis of bleeding site) |
| 4 | Life-threatening consequences; major urgent intervention indicated |
| 5 | Death |
| | Ulceration-GI |
| 1 | Asymptomatic, radiographic or endoscopic findings only |
| 2 | Symptomatic; altered GI function (e.g., altered dietary habits, oral supplements); IV fluids indicated < 24 h |
| 3 | Symptomatic and severely altered GI function (e.g., inadequate oral caloric or fluid intake); IV fluids, tube feedings, or TPN indicated ⩾ 24 h |
| 4 | Life-threatening consequences |
| 5 | Death |
| | Incontinence anal |
| 1 | Occasional use of pads required |
| 2 | Daily use of pads required |
| 3 | Interfering with ADL; operative intervention indicated |
| 4 | Permanent bowel diversion indicated |
| 5 | Death |

According to the Common Terminology Criteria for Adverse Events system v 3.0. IV: Intravenous; GI: Gastrointestinal; ADL: Activities of daily living; TPN: Total parenteral nutrition.

**Table 2 Summary of risk factors for gastrointestinal radiation injury**

| Risk factors | |
|---|---|
| Radiation techniques | Treatment volume, total dose, fractionation dose and schedules |
| Combined modality therapies | Surgery<br>Chemotherapy: Particularly concurrent |
| Medical co-morbidities | Vascular disease, connective tissue disease, inflammatory bowel disease, HIV |
| Genetic susceptibility | Single nucleotide polymorphism, ataxia telangiectasia |

HIV: Human immunodeficiency virus.

hypofractionation was also suggested to be safer than conventionally fractionated conformal radiotherapy in a randomized study of prostate cancer radiotherapy[29].

Treatment field size and intestinal volume irradiated are important factor and a key determinant of radiation toxicity. Bowel toxicity was found to be directly related to the volume of small intestine irradiated[13]. Moreover, irradiation to a larger volume of small intestine was reported to increase the operative mortality in rectal cancer patients treated with anterior and posterior field irradiation technique[30,31]. Furthermore, the impact of the field volume has been demonstrated in a randomized study of prostate cancer radiotherapy. Patients who were treated with conformal shielding with 48% less volume irradiation had less rectal toxicity at 5 years than patients treated with conventional radiotherapy, despite identical radiation dose[32,33] (Table 2).

### *Combined modality approaches*

Combined modality therapy increases the risk of radiation toxicity. Surgery or concurrent chemotherapy is linked to an increased incidence of radiation toxicity. Previous abdominal surgery increases the risk of radiation toxicity[34]. Anatomical changes that increases intestinal exposure to radiation such as postoperative small intestine prolapse into the pelvic cavity[13,35] or surgical adhesions that fix intestinal segments within the radiation field can all predispose part of the intestine to receive higher doses of radiation[36]. Combining prostatectomy with radiotherapy can increase rectal toxicity during prostate cancer treatment[37]. An analysis of acute toxicity was performed in 405 prostate patients in The European Organization for Research and Treatment of Cancer randomized trial 22863. In those patients it was reported that among other factors, previous genitourinary surgery was found to be predictive of lower gastrointestinal radiation toxicity[38].

Combining chemotherapy with radiation has been reported to increase the rate of acute intestinal toxicity, while the long term effect of this combination is not clear[20,39]. Oral mucositis was reported in more than 90% of patients treated with a combined chemo-radiotherapy regime for head and neck cancer[40,41] in comparison to another study which reported an incidence of oral mucositis in 62% of patients treated with radiotherapy alone[42]. Concurrent chemotherapy with radiation has also been reported to increase the risk of oesophageal radiation injury by 12-fold[43].

In a study of cervical cancer patients treated with chemoradiotherapy, the incidence of Grade 3 late intestinal toxicity increased from 10% to 26% in patients treated with both mitomycin and fluorouracil compared to a fluorouracil alone group, suggesting a possible role for the type of chemotherapeutic agent used as determinant of severity of gastrointestinal toxicity[44].

Different mechanisms have been suggested to explain the sensitizing effect of adding chemotherapy in increasing the risk of intestinal radiation injury. Examples of possible mechanisms are alterations in cell cycle kinetics, or synchronization of replicating cell populations. Halopyrimidines such as fluorouracil, fluorodeoxyuridine and iododeoxyuridine may sensitize tumors both by inhibiting effective DNA repair and by increasing the amount of radiation induced DNA damage[45-47].

## SYMPTOMS RESULTING FROM RADIATION INJURY TO THE GASTROINTESTINAL TRACT

### *Acute and chronic gastrointestinal radiation injury*

During external beam radiotherapy, ionising radiation enters and exits the body and therefore affects normal tissues surrounding the target tumour. The gastrointestinal tract which extends over a large surface area and any part of the gastrointestinal tract that falls within the radiation field can be affected, resulting in acute and chronic symptoms of gastrointestinal radiation injury (Table 3).

Clinical manifestations of gastrointestinal radiation injury can present during or soon following radiotherapy. These symptoms are related to acute mucosal injury and inflammation. Delayed symptoms occur a few months or years after radiotherapy and are attributed to a chronic process of transmural fibrosis and vascular sclerosis. Typically symptoms are considered "acute" if they occur within the course of treatment or up to 90 d following treatment. These are generally reversible. Chronic side effects are much less common and occur more than 90 d post radiation; they are less likely to reverse. The onset of delayed symptoms has been reported as much as after 30 years following radiotherapy[48].

### *Mouth, pharynx, and oesophagus*

During radiotherapy for head and neck or thoracic cancer, the upper gastrointestinal tract falls within the radiation field. Irradiation to this area results in acute mucosal injury causing mucositis and ulceration which manifests within the first two weeks in 30%-60% of patients, causing dysphagia and odynophagia[49]. In a study of 254 non-small-cell lung cancer patients, acute toxicity of Grade 2 or worse has been reported in 78% of patients[50]. Mucositis is debilitating, can be a dose limiting side effect and

**Table 3 Acute and chronic manifestations of gastrointestinal radiation injury**

| Clinical manifestations | Radiation tolerance dose TD5/5, TD50/5 (Gy) | Gastrointestinal organ |
|---|---|---|
| Oral mucositis occurs in > 90% of patients with concurrent chemotherapy[40] | Parotid gland: TD5/5 (32) TD50/5 (46)[60,179,180] | Mouth, salivary glands, hypopharynx, parotid |
| Xerostomia and altered saliva composition | | |
| Acute Grade 3-4 oesophageal injuries occur in 46%with concurrent chemotherapy[181] | TD5/5 (55-60) | |
| Dose > 58 Gy predicts Grade 3-5 acute oesophagitis[54] | TD50/5 (68-72)[60,179] | Oesophagus |
| 60 Gy resulted in Grade 3 toxicity in 42%[182] | | |
| Radiation can lead to late stricture and/or perforation of the oesophagus[53,60] | | |
| 40 Gy: Severe late toxicity in 7% including ulceration, gastritis and small-bowel obstruction/perforation[183] | TD5/5; (50-60) TD50/5 (65-70)[60,179] | Stomach |
| Elevated liver enzymes in 5%[184] | TD5/5; (30-50) | Liver Small intestine |
| (31.3-37 Gy resulted in RILD in 9.4%[66,185] | TD50/5; (40-55)[60,179] | |
| 45 Gy cause 5% Grade 3-4 toxicity and 14% with concurrent chemotherapy[71] | TD5/5; (40-50) | |
| Diarrhoea, abdominal pain in 20-70%[72] | TD50/5; (55-60)[60,179,180] | |
| Transmural fibrosis leading to obstruction in 5%-10%[68,77-78] | | |
| Intestinal fistulation occurs at a rate of 0.6% to 4.8%[68,79] | | Colon and rectum |
| 50 Gy 5 year estimate of small bowel obstruction is 11%[186] | | |
| Colitis in 25%-50% of patients[186] | Colon | |
| Grade 2-3 acute proctitis 40%[91] | TD5/5; (45-55) | |
| Chronic rectal symptoms in 6.7%-31%[91] | TD50/5 (55-65)[60,179,180] | |
| Acute symptoms of anus and rectal injury occur in up to 75% of patients during radiotherapy[187] | Rectum TD5/5; (60-61.38) TD50/5 (80-81.38)[60,179,180] | |

TD5/5: Radiation dose associated with 5% of patients' risk of delayed toxicity in 5 years; TD50/5: The radiation dose associated with 50% of patients' risk of delayed toxicity in 5 years. RILD: Radiation-induced liver disease.

is difficult to treat. Severe symptoms may require therapy interruption, or the provision of an alternative nutritional route to avoid dehydration and malnutrition. Therefore, elective percutaneous endoscopic gastrostomy tube insertion before radiotherapy is a recognized practice and it is associated with improved quality of life and a lower rate of hospital admissions[51,52]. In severe cases, acute radiation oesophagitis can lead to more serious complications such as significant bleeding or oesophageal perforation[53].

Clinical predictors for acute oesophageal toxicity include maximum radiation dose. A maximum dose of > 58 Gy was reported to predict the risk of Grade 3-5 oesophageal toxicity in 207 non-small-cell lung cancer patients treated with 3-dimensional conformal radiotherapy[54] while a dose of 50 Gy was significantly associated with Grade 2 or worse oesophagitis in another cohort 36 non-small-cell lung cancer patients[55]. In both studies patients received concurrent chemotherapy which is also a risk factor for oesophageal toxicity. The volume of the irradiated oesophagus has also been suggested to predict acute oesophageal toxicity[55]. In another series of 208 non-small-cell lung cancer patients treated with three dimensional conformal radiotherapy, concurrent chemotherapy and maximal point dose to the oesophagus > 60 Gy were found to be significantly associated with the risk of Grade 3-5 oesophageal injury[56]. The Quantitative Analyses of Normal Tissue Effects in the Clinic paper by Werner-Wasik *et al*[57] published in 2010 reviewed the published data on the dose-volume effect and concluded that it was not possible to identify the best threshold volumetric parameter for oesophageal irradiation given the variety of the volumetric metrics in the published data.

Delayed symptoms of oesophageal injury can manifest after several months following radiotherapy and include chronic ulceration, fistulisation or chronic dysphagia. Dysphagia can be secondary to tissue fibrosis and stricture formation or due to motility disorder induced by muscular or nerve injuries. Delayed oesophageal toxicity has been reported in 17% of non-small-cell lung cancer patients[50] and the median and maximal time to the onset of late toxicity was 5 and 40 mo respectively after radiotherapy.

### Stomach and duodenum

Gastric injury during radiotherapy occurs when the stomach falls within the radiation field of an adjacent tumour. Nausea, vomiting, dyspepsia and abdominal pain has been reported to occur early after radiotherapy to the upper abdomen in 50% of patients[58]. These symptoms result from acute mucosal injury causing erosions and ulceration of gastric and duodenal mucosa.

Later symptoms include chronic dyspepsia and abdominal pain due to chronic ulceration secondary to mucosal injury[59]. Rarely, gastric wall fibrosis can lead to gastric outlet obstruction. The radiation dose associated with 5% and 50% of patients risk of delayed gastric toxicity in 5 years (TD5/5 and TD50/5) have been estimated at 50 Gy and 65 Gy respectively for gastric ulceration or perforation. An accurate data on dose-volume constrain for partial gastric irradiation is not available. However, the threshold dose of 45 Gy to the whole stomach has been associated with ulceration in 5%-7% of patients[60,61].

### Liver injury

Following irradiation to the liver, radiation induced liver disease can occur in patients with normal pre-radiotherapy liver function, causing anicteric hepatomegaly and mild alkaline phosphatase serum level elevation. A more

severe derangement of liver function occurs in patients with pre-existing liver disease[62]. Radiation induced liver disease can progress to fibrosis, cirrhosis, and liver failure[63]. Abdominal imaging with computed tomography scan or magnetic resonance imaging can be helpful to show low-attenuation injury areas or areas of atrophy in the irradiated liver segment[64].

Risk factors for radiation induced liver disease include baseline liver dysfunction, Hepatitis B virus carrier status[65], mean dose > 30 Gy for partial liver radiotherapy, concurrent chemotherapy and volume of liver irradiated[66,67].

### Small intestine

The small intestine receives irradiation during radiotherapy of pelvic or abdominal malignancies. The degree of injury depends on the radiation dose and the volume of intestinal segment that falls within the radiation field[68,69]. Significant correlation has been suggested between the volume of irradiated small bowel and the likelihood of acute toxicity, regardless of the radiation dose delivered[70]. Other predictors of acute small intestine toxicity include the use of concurrent chemotherapy. This effect has been reported in 186 cervical cancer patients who received 45 Gy preoperative pelvic radiotherapy alone where 5% of patients experienced Grade 3-4 toxicity in comparison to 14% of 183 patients who received radiotherapy and weekly cisplatin[71]. The relatively fixed portions of the small intestine such as the duodenum and the terminal ileum are at increased risk of radiation toxicity as they are more susceptible to receive higher doses of radiation than the mobile parts of small intestine.

The radiation dose associated with delayed small bowel toxicity have been estimated by Emami *et al*[60]. The TD5/5 and TD50/5 doses for one third of small bowel irradiation were estimated at 50 Gy and 60 Gy respectively. The TD5/5 and TD50/5 for the whole-organ irradiation were 40 Gy and 55 Gy respectively. These doses estimates remained as a guide for two decades and more recent data were consistent with these ranges[60,61].

Clinically, nausea, vomiting and abdominal pain are early symptoms that can occur during the first two weeks following abdominal radiotherapy, and may be mediated by the release of inflammatory cytokines following radiotherapy. Diarrhoea and abdominal pain occur during the first two weeks of radiotherapy to abdominal or pelvic malignancies in 20% to 70% of patients[72]. This may be a result of direct radiation injury to the small intestinal mucosa causing epithelial atrophy, and reduced mucosal blood flow[73].

The acute symptoms usually settle within three weeks after completion of radiotherapy and the intestinal epithelium regenerates from stem cells at the base of the crypts.

Delayed symptoms of radiation small intestinal injury manifest months to years after radiotherapy with symptoms of diarrhoea, recurrent abdominal pains and malabsorption.

Chronic diarrhoea following radiotherapy can result from different pathophysiological processes such as bile salt malabsorption, bacterial overgrowth, fat malabsorption, rapid intestinal transit or lactose intolerance[74]. More chronic symptoms occur as a result of pathological abnormalities to the intestinal vascular compartment resulting in intestinal ischemia as well as progressive intestinal fibrosis leading to structural abnormalities such as strictures and fistulation. Bacterial overgrowth contributes to malabsorption and diarrhoea, particularly in patients with intestinal strictures[73,75].

Intestinal obstruction can complicate 5% to 10% of severe small intestinal radiation injury[76]. The rate of severe small intestinal complications following radiotherapy for rectal cancer can vary considerably depending on the tumor and treatment characteristics, Reports indicate rates of 0.8% to 13% for small intestinal obstruction[68,77,78] and 0.6% to 4.8% for intestinal fistulation[68,79]. Patients with severe small intestinal injury have a poor prognosis since surgery to manage strictures is complex and has been associated with poor outcomes[73,80].

### Colon and rectum

During abdominal and pelvic radiotherapy, the colon and rectum are commonly affected as their anatomical locations fall within the radiation field of a variety of cancers. The fixed portions of the colon, the caecum and the rectum are at greater risk of receiving higher doses of radiation than the remainder of the colon.

Acute radiation injury to the rectum and anal canal can result in a diversity of symptoms such as abdominal pain, diarrhoea, tenesmus, rectal pain, urgency, rectal discharge, incontinence, and fresh rectal bleeding. These symptoms occur primarily as a consequence of direct mucosal damage[81-83]. Acute radiation injury to the colon can be severe and in 5%-15% can lead to therapy interruption or treatment plan alteration[84].

A recent study showed that 47% of women who received radiotherapy for cervical or endometrial cancer reported symptoms of radiation intestinal injury affecting quality of life within 3 mo following therapy completion[85]. These results are consistent with a previous structured questionnaire study[86] which showed that 53% of patients had reported bowel symptoms significantly affecting their quality of life, whilst 81% of patients in the study described new-onset gastrointestinal problems after receiving radiotherapy.

The recent data on dose-volume effect in radiation induced rectal injury was reviewed by Michalski *et al*[87]. The incidence of Grade > 2 injury from different studies was variable according to dose, treatment parameters and scale used in each study. Among the recent studies reported, an incidence of 13.5% and 16% of Grade > 2 rectal injury. Identified predictors for Grade > 2 rectal injury or rectal bleeding include the volume of the rectum irradiated and a total radiation dose > 60 Gy during 3-dimensional conformal radiotherapy. The effect of concurrent chemotherapy has been observed in the

European Organization for Research and Treatment of Cancer study where patients received 45 Gy preoperative radiotherapy or radiotherapy and 5-flurouracil (5-FU). Grade > 2 diarrhoea occurred in 17% of radiotherapy alone group compared to 38% of radiotherapy and 5-FU group[88].

Delayed symptoms of radiation colonic injury are insidious and usually follow a progressive course. They can manifest after a latent period of few months or years. One study has reported a 15% incidence of bowel toxicity 20 years after receiving radiotherapy in a cervical cancer cohort[89]. Severe life threatening complications occur after radiotherapy such as fistulation, sepsis, perforation or bleeding at a rate between 4%-8% within 5-10 year time after radiotherapy[90]. Patients suffer from a variety of symptoms, such as abdominal pain, changing bowel habits with intermittent diarrhoea. Constipation can result from altered colonic motility due to fibrosis and stricture formation. An abnormal bowel transit can manifest as recurrent pain and increased risk of obstruction or pseudo-obstruction secondary to fecal loading. Excessive fibrosis can cause loss of ano-rectal compliance and manifests as urgency and frequency[73]. Faecal incontinence has been reported in up to 20% of patients and significantly reduces patients' quality of life[86,91].

Unlike radiation injury to the small bowel, radiation injury to the colon does not compromise nutrient absorption and malabsorption is uncommon[73].

Adverse effects of radiation to the pelvis primarily affect the colon and the rectum. However, other organs can be irradiated causing increased morbidity for example injury to the urinary tract or the genital system resulting in symptoms affecting quality of life were reported in 30% of patients[92-95]. A rare but serious complication of prostate brachytherapy is recto-vesical fistula which occurs with a low frequency of 1 in 250 to 1 in 1000 patients implanted[96-98].

Radiation exposure increases the risk of a secondary malignancy. Patients who received radiotherapy were shown to have significantly higher risk of developing second cancers both overall and in the areas that were exposed to the radiation field[99]. In an analysis of testicular cancer survivors which included 28 843 men, the risk of a second cancer was estimated. The patterns of second cancer suggested that many factors may be involved, including previous treatment received, but the precise roles of different factors is still to be clarified. It has been reported that secondary leukaemia was associated with both radiotherapy and chemotherapy, whereas excess cancers of the stomach, bladder, and possibly pancreas were associated mainly with radiotherapy[100]. This risk also includes colorectal cancer, which can occur more than 10 to 20 years after radiation exposure[99,101].

## PATIENT RELATED RISK FACTORS

### *Patient factors and individual variations*

Individual patient phenotypic factors have been suggested to influence the susceptibility to intestinal radiation injury. It was reported that older patient age is associated with an increased risk of developing reduced organ function after radiotherapy[102-104]. Body habitus has been reported as another susceptibility factor, where thin patients with narrow antero-posterior diameter can suffer an increased risk of intestinal radiation toxicity compared to normal individuals[36]. Smoking status has been associated with risk of chronic intestinal toxicity[20,105] as well as previous history of surgery[13,35,36].

### *Medical co-morbidities*

**Vascular disease**: Co-morbid vascular disease such as hypertension, diabetes mellitus and atherosclerosis were suggested to predispose patients to an increased vascular injury following radiation and subsequent intestinal wall ischemia and impaired tissue repair[74]. The microocclusive vascular disease in addition to increased blood viscosity in diabetes mellitus were suggested to predispose to intestinal tissue ischemia[106,107]. One study investigated the possible effect of diabetes mellitus during prostate cancer radiotherapy. The study reported higher rates of late genitourinary/gastrointestinal toxicities in diabetic patients than in non-diabetics (34% and 23% respectively). It was also noticed that diabetics developed complications earlier than the non-diabetics (10 mo and 24 mo respectively)[108].

**Inflammatory bowel disease:** Co-morbid inflammatory bowel disease (IBD) is considered in some institutions as a relative contraindication to radiotherapy for concerns of greater risk of acute and late side effects[109-111]. Intolerance to radiotherapy in IBD patients has been demonstrated in case reports[112,113] and in a larger retrospective analysis where the incidence of severe acute and late events was 21% and 29% respectively[114,115]. However, in a large retrospective analysis in patients with colorectal cancer, the data on treatment modality received for 170 colorectal cancer patients with history of IBD found no significant difference in cancer treatment modalities between patients with or without history of IBD. This observation points out that a history of IBD was not a barrier to receive radiotherapy treatment in this patient group[116].

It has been postulated that co-morbid IBD and intestinal inflammation may alter the acute tissue response to radiotherapy through inflammatory mediators, growth factors and cytokine cascades produced at the site of intestinal injury. Some mediators and cytokines were suggested to decrease the sensitivity to radiation injury e.g., fibroblast growth factor 2, prostaglandin-E2, tumor necrosis factor-α and interleukin (IL)-1 and IL-11. However, others were suggested to have mixed effects e.g., IL-12 protecting bone marrow-derived cells but sensitizing intestinal epithelial cells to radiation injury[117-123].

**Collagen vascular diseases:** Collagen vascular diseases (CVD) increases the risk of both acute and chronic radia-

tion toxicity, as has been reported by Chon *et al*[105] in 4 different studies in patients with and without CVD. On the other hand, radiation may cause an acute exacerbation of systemic symptoms in patients with CVD[124], possibility through release of fibroblast-triggering mediators by the inflammatory cells[105].

**Human immunodeficiency virus infection:** It has been reported that human immunodeficiency virus (HIV) infection induces a state of radiosensitivity because severe mucositis was observed in HIV patients who received radiotherapy for the treatment of Kaposi sarcoma[125,126]. Support for this hypothesis was found by an increased radiosensitivity of skin fibroblasts of HIV patients with Kaposi sarcoma compared to healthy control[127]. It was also noted in a study involving 59 HIV positive patients that T-lymphocytes of HIV infected individuals were considerably more sensitive to X-rays compared to that of HIV negative donors[128]. Housri *et al*[129] reviewed the recent evidence and suggested recommendations for radiotherapy in HIV patients, based on the strength of the best available evidence, and classified according to Strength of Recommendation Taxonomy. There was no conclusive evidence to support the need for special precautions for HIV patients during radiotherapy[130].

### *Genotypic variations*

It has been suggested that patient's genotype may impact their individual susceptibility to radiation toxicity. This can occur through inherited germ-line mutations in genes involved in DNA damage detection, DNA repair or cell cycle regulation[131-133]. Recently the term Radiogenomics has been introduced to refer to the science that aims to predict clinical radiosensitivity and to optimize radiotherapy treatment from individual genetic profiles[134].

Genetic variations are thought to be a key determinant of normal tissue radiosensitivity and may account for up to 80% of the inter-individual variations in normal tissue reaction to radiotherapy[135,136]. Support for this hypothesis was provided in a study of breast cancer radiotherapy, which reported the incidence and time to development of radiation-induced telangiectasia[137]. The results of the study revealed a wide range of variation suggesting that patient-related factors can explain 81%-90% of the patient-to-patient variation in telangiectasia level seen after radiotherapy despite similar radiation treatment given. The results further supported reports of other studies[138,139].

The state of extreme tissue radiosensitivity which has been identified in patients with germ-line mutations in genes involved in DNA damage detection or DNA repair e.g., Nijmegen breakage syndrome, Fanconi's anemia and Ataxia telangiectasia has supported the potential role of genetic variations as an important determinant of individual's radiation response. Nevertheless, this risk is probably confined to patients and carriers of those mutant genes and is not known to be relevant to other patients receiving radiotherapy[31,45,140,141].

Candidate gene studies, [single nucleotide polymorphism (SNP) association studies] have investigated the role of many genes which have been linked to different elements of the mechanisms related to the pathogenesis of radiation toxicity. Genes investigated include those involved in DNA repair such as *ATM*, *BRCA1*, *BRCA2*[142,143], apoptosis such as *TP53, BCL2*[144,145], antioxidant enzymes such as *SOD1*[146], and growth factors *FGF2*[147,148] and *VEGF*[147,148]. In this regard, an association has been suggested between candidate SNPs in the genes *TGFB1*, *SOD2*, *XRCC3*, *XRCC1* and late radiation toxicity in breast cancer patients[133,149]. Similarly, SNP association studies in pelvic tissue have suggested correlations between some risk genes such as *XRCC1*, *XRCC3*, *TGFB1*, *OGG1* and an increased risk of developing late gastrointestinal and genitourinary radiation toxicity following radiotherapy[150-152].

## MECHANISMS OF RADIATION INJURY

Ionising radiation induces double strand breaks in DNA. This triggers activation of a signalling pathway that leads to activation of tumour suppressor p53. Depending on the extent of the DNA damage, which depends on the radiation dose, and on other factors in the cellular milieu, p53 activation leads to cell cycle arrest and DNA double strand break repair, or apoptosis. In cancer radiotherapy, apoptosis of tumour cells is the desired outcome. However, intestinal crypt epithelial cells are quite sensitive to radiation and the killing of these cells leads to mucosal injury[153,154]. Specifically, when the dose of radiation is sufficient to kill all of the epithelial stem cells in a crypt, then as the epithelial cells migrate up the crypt and are eventually shed into the intestinal lumen; the crypt cannot be repopulated with epithelial cells, and consequently involutes. When this happens to a large proportion of crypts in a region of intestine, normal barrier function is lost which leads to the exposure of the normally sterile lamina propria to luminal microbes. This triggers an acute inflammatory response associated with immune cellular infiltrates; T lymphocytes, macrophages and neutrophils causing loss of epithelial cells as well as degradation of the extracellular matrix in the lamina propria due to enzymes and mediators released by the immune cells[155]. A further damage to the mucosal and submucosal tissues are caused by reactive oxygen metabolites which are produced in large amounts by activated leukocytes in the inflamed mucosa and this can induce significant damage to various cellular components, including structural and regulatory proteins, carbohydrates, lipids, DNA, and RNA[31].

During radiotherapy, ionising radiation kills crypt epithelial stem cells. As a result, crypts involute and epithelial barrier integrity is lost. This provides access of luminal microbes and their products to innate immune cells in the lamina propria, with activation of immune cells. An impaired recognition of bacterial translocation can further exacerbate the inflammatory process and promote

stricture formation by two possible mechanisms. The bacterial wall antigens could causes a secondary excessive up regulation of pro-inflammatory transcription factors, such as nuclear factor kappaB[156]. This might be followed by prolonged macrophage activation and induction of NADPH oxidase expression[157] leading to a further increased in oxygen radical secretion to eradicate bacteria leading to further tissue destruction[155]. Meanwhile translocated bacteria could directly stimulate neighboring mesenchymal cells via pattern recognition receptors leading to increased activation of immune cells[156,158].

The acute inflammatory process continues but eventually, after the cessation of radiation, through poorly understood mechanisms, crypts start to regenerate and this restores normal epithelial barrier function, which is followed by resolution of inflammation[159]. In some patients this inflammatory process becomes exaggerated for unknown reasons with severe ulceration and inflammatory process runs a chronic course characterised by extensive fibrosis and intestinal ischemia[160,161]. Recent observations in animal models of radiation injury indicate that repair after radiation may depend on the recruitment of mesenchymal stem cells from the bone marrow to the site of radiation injury. Mesenchymal stem cell mobilization and engraftment is thought to be induced by cytokines and potentially specific homing induced by chemokines, all of these are released by inflammation[162,163].

The final pathological outcome of the radiation injury in the intestinal tissue will depend on a complex crosstalk between various cellular components of the tissue within the extracellular matrix which eventually determine the process of tissue recovery or long term complications[73,164].

Radiation injury to the vascular compartment is thought to be a key feature in the pathological processes of intestinal radiation injury as well as an important determinant of both acute and chronic effects after radiotherapy[165,166]. It has been regarded as a major component in the initiation, progression and maintenance of delayed intestinal tissue damage and enhanced fibrosis which lead to loss of mucosal function and stricture formation[167,168].

Endothelial cell apoptosis has been implicated as the primary lesion leading to epithelial stem cell dysfunction and subsequent intestinal tissue damage following radiotherapy. Support for this hypothesis was found by identifying a state of radioresisitance following inhibition of endothelial apoptosis in experimental mice. Radiation-induced crypt damage, organ failure, and death from radiation injury were all prevented when the endothelial apoptosis was inhibited pharmacologically, by the administration of fibroblast growth factor or genetically by deletion of the acid sphingomyelinase gene[169]. However, subsequent studies challenged this concept by demonstrating an epithelial cell apoptosis at lower radiation doses which is insufficient to cause endothelial cell death. This result has been enforced further by experiments using high dose Boron therapy radiation, specifically targeted to the endothelium. The results showed no effect on epithelial stem cell survival[168,170].

Formation of new blood vessels (angiogenesis) is a crucial requirement for tumour growth and survival[171]. The tumour vasculature is prone to hypoxia which results in further production of proangiogenic factors by tumour cells. Angiogenesis inhibitors target tumour endothelial cells and cause inhibition of new vessel formation and a transient tumour hypoxia[172,173]. Although tumour hypoxia has been linked to increasing tumour radio-resistance, studies have shown that the administration of angiogenesis inhibitors improves tumour oxygenation and response to radiotherapy[174-177]. Different mechanism has been suggested for the radio-sensitising effect of combining angiogenesis inhibitors with radiotherapy[173]. Mazeron *et al*[178] has recently reviewed the clinical trials on angiogenesis inhibitors, but despite the promising value of these new agents, the biological basis for their synergistic effect and the safety and efficacy of these agents are still to be determined.

## CONCLUSION

Intestinal radiation injury is a significant clinical issue which is expected to increase in prevalence due to improved survival of cancer patients as well as to increased availability of radiotherapy as an affordable treatment option. Radiotherapy treatment can cause a wide variety of gastrointestinal side effects. Following radiation injury to the gastrointestinal tract, symptoms can present acutely or after a long period of time. Although severe intestinal injury is less common with the development of advanced radiotherapy planning and delivery techniques, a less severe degree of injury is common and continues to affect a considerable proportion of patients, significantly reduces their quality of life, ands an extra burden to the cost of health care. The accurate diagnosis and management of intestinal radiation injury represents a clinical challenge to practicing physicians in both gastroenterology and oncology. Despite the growing recognition of the problem and some advances in understanding the cellular and molecular mechanisms of radiation injury, relatively little is known about the pathophysiology of intestinal radiation injury or the exact factors that aggravate it. Patient and treatment related risk factors have been suggested although the exact influence posed by these factors is still to be better characterized. Combined modality therapies for cancer are commonly used and they increase the risk of radiation toxicity and further add to the problem. Medical co-morbid diseases such as vascular disease, inflammatory bowel disease and collagen vascular disease can pose a significant risk that can affect patient suitability to receive radiotherapy treatment. Genotypic variations can influence the risk of gastrointestinal radiation injury but future research findings on this area are needed to assess their clinical importance. A better understanding of the pathophysiology of radiation injury may provide the opportunity to develop more effective preventive and therapeutic strategies.

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