Radiation in Gastroenterology

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Abstract

The benefit of radiation is immense in the field of gastroenterology. Radiation is used daily in different gastrointestinal imaging and diagnostic and therapeutic interventional procedures. Radiotherapy is one of the primary modalities of treatment of gastrointestinal malignancies. There are various modalities of radiotherapy. Radiotherapy can injure malignant cells by directly damaging DNA, RNA, proteins, and lipids and indirectly by forming free radicals. External beam radiation, internal beam radiation and radio-isotope therapy are the major ways of delivering radiation to the malignant tissue. Radiation can also cause inflammation, fibrosis, organ dysfunction, and malignancy. Patients with repeated exposure to radiation for diagnostic imaging and therapeutic procedures are at slightly increased risk of malignancy. Gastrointestinal endoscopists performing fluoroscopy-guided procedures are also at increased risk of malignancy and cataract formation. The radiological protection society recommends certain preventive and protective measures to avoid side effects of radiation. Gastrointestinal complications related to radiation therapy for oncologic processes, and exposure risks for patients and health care providers involved in diagnostic or therapeutic imaging will be discussed in this review.

Keywords: Units of radiation; Use of radiation in gastroenterology; Radiation esophagitis; Radiation gastritis; Radiation enteritis; Radiation colitis; Radiation proctitis

Introduction

Radiation can be described as the emission of energy as electromagnetic waves or as moving subatomic particles. It originates from a source and travels through space as fast as light. Radiation is broadly classified into ionizing radiation and non-ionizing radiation. Ionizing radiation can ionize atoms by displacing an electron from an atom and can break molecules and

chemical bonds of living tissues, air, and water. In living organisms, ionizing radiation causes the ionization of water to produce H_2O^+ ions. X-rays, gamma rays, alpha particles, beta particles and positrons are forms of ionizing radiation. Non-ionizing radiation cannot ionize atoms or break molecules and chemical bonds, but they cause vibrations due to heat. Visible light, ultraviolet light, infrared light, radio waves, and microwaves are examples of non-ionizing radiation. We are surrounded by background radiation due to the presence of radioactive materials present in the space (cosmic radiation) and in the earth (terrestrial radiation). Cosmic radiation occurs due to charged particles, X-rays and gamma rays that come from the sun and stars. The radioactive materials present in the soil include uranium, thorium, radium, carbon, and potassium. Uranium can break down and get converted into radon gas which can be found in building materials, rocks, soil and well water. On an average, the annual natural radiation exposure to a person living in the United States (USA) includes 2.28 mSv (73%) due to inhalation of radioactive materials, 0.29 mSv (9%) due to ingestion of radioactive materials, 0.33 mSv (11%) from cosmic radiation, and 0.21 mSv (7%) from terrestrial radiation [1].

Ionizing radiation is widely used in different fields of medicine, including gastroenterology and hepatology, for diagnostic and therapeutic purposes. Gastrointestinal (GI) endoscopists get radiation exposure when they use X-rays/fluoroscopy to perform endoscopic retrograde cholangiopancreatography (ERCP), esophageal, gastroduodenal, and colonic stenting, endoscopic dilation, device-assisted endoscopies, and different interventional procedures where there is combined use of fluoroscopy and endoscopy.

Radiation therapy is administered to treat different malignancies. There are radiation hazards to the gastrointestinal tract (GIT) from diagnostic imaging and radiation therapy for various GI, urological, gynecological, intra-abdominal, and pelvic malignancies. Gastroenterologists also manage the various GI side effects of radiation therapy. This article will discuss the basic understanding of different units of radiation, various diagnostic and therapeutic uses of radiation in gastroenterology, the pathogenesis of radiation injury to the GIT, clinical effects of radiation therapy on the GI system, radiation hazards to the patients due to diagnostic and therapeutic GI imaging and procedures, occupational hazards of radiation to the GI endoscopists and the different preventive measures.

Radiation Units

Roentgen (symbol R) is a unit of exposure to ionizing radiation. It is used to quantify the number of ion pairs produced

in 1 kg/2.2 pounds (lbs) of air by ionizing radiation (X-ray or gamma radiation). 1 R is equal to 2.58×10^{-4} coulombs/kg of air. In other words, 1 R is the amount of X-rays or gamma rays needed to produce 2.58×10^{-4} coulombs of charge per kg of air at standard temperature and pressure. The radiation effect on the tissue is measured by the radiation absorbed dose (rad), i.e., the amount of energy from ionizing radiation per unit mass. In the International System of Units (SI), 1 gray unit (1 Gy) is termed when 1 Joule of energy is deposited per kilogram of tissue. In a conventional unit, 1 Gy is equal to 100 rads, and 1 rad is equal to 10 mGy. In practice, the dose equivalent to the absorbed dose is measured, as the different types of radiation do not cause the same biological effect. Sievert (Sv) is the unit of dose equivalent and calculated by multiplying the absorbed dose and a radiation weighting factor. X-rays and gamma rays have a radiation weighting factor of 1. As a result, the dose equivalent of 1 Gy is 1 Sv (1,000 millisieverts) in imaging studies [2]. Millisieverts (mSv) are generally used as the unit of radiation dose in imaging studies. Roentgen equivalent man (rem) is the older non-SI unit of radiation that causes the same amount of tissue injury as 1 rad of X-rays or gamma rays to humans. 1 rem is equivalent to 0.01 sievert, i.e., 10 rem = 100 mSv. In the USA, conventional and SI units are used to measure radiation doses [3].

Diagnostic Uses of Radiation in Gastroenterology

Radiation is used in different imaging studies to diagnose and evaluate various GI disorders. These include plain X-rays (chest X-ray, abdominal X-ray, acute abdominal series), contrast studies (barium esophagogram, upper GI series, small bowel follow-through, barium enema, defecography and X-ray fistulography), computed tomography (CT) scans of chest, abdomen and pelvis, CT angiography, CT venography, CT enterography, conventional mesenteric angiography, and virtual colonoscopy. Radiation is also increasingly utilized in fluoroscopically guided interventional procedures such as CT-guided biopsy of intra-abdominal organs or lesions and placement of vascular or non-vascular stents.

Therapeutic Uses of Radiation in Gastroenterology

Radiation plays a vital role as an integral component of multimodality treatment of various GI malignancies. In one study, a high percentage of patients with GI malignancies received radiotherapy: 80% of patients with esophageal cancer, 68% of patients with gastric cancer, 61% of patients with rectal cancer, 57% of patients with pancreatic cancer, 14% of patients with colon cancer and 13% of patients with gallbladder cancer [4]. The two main ways of delivering radiation to these malignant tumors include external beam radiation therapy (EBRT) or teletherapy and internal-beam radiation therapy (IBRT) or brachytherapy [5]. Another way of administering radiation is radioisotope therapy, in which radioactive particles are delivered in liquid form orally or intravenously into the systemic circulation. EBRT uses a radiation source outside the body (usually a linear accelerator), targeting the tumor tissue from a distance. It is the most common radiation therapy modality for treating various GI malignancies. Different types of EBRT include: 1) Three-dimensional conformal radiation therapy (3D CRT); 2) Intensity-modulated radiation therapy (IMRT); 3) Image-guided radiation therapy (IGRT); 4) Stereotactic body radiation therapy (SBRT); and 5) Tomotherapy [6].

In 3D CRT, the images from CT, magnetic resonance imaging (MRI), and positron emission tomography (PET) scans are analyzed by a computer program to conform to the tumor's shape so that radiation beams can be delivered to that area. In IMRT, many smaller beams are used, but higher intensity beams can be given in some tumor regions. In IGRT, the computer processes repeated images of CT, MRI, or PET scans during treatment to adjust radiation doses. This method allows accurate radiation treatment without damaging the normal tissue [7]. SBRT is a specialized form of EBRT in which focused radiation beams are targeted from different angles around the body to a well-defined tumor with extreme precision from a piece of special equipment using detailed imaging and three-dimensional computerized treatment planning. Another advantage of SBRT is that a high dose of radiation can be administered to the tumor over a short period. SBRT is generally considered for lymph node oligometastases from esophageal, gastric, and colon cancer [8]. Tomotherapy is a form of EBRT in which CT images are taken right before the radiation treatment. Then radiation is given in a spiral fashion for better precision and avoidance of normal tissue. Helical tomotherapy can deliver IMRT in a spiral pattern with high precision to treat complex malignant neoplasms [9]. The EBRT generally uses photon particles, but proton particles are also increasingly used. Although photon beams can reach the malignant neoplasms deep into the organs, they tend to scatter radiation along their path. They can go beyond the malignant neoplasms into the normal tissue. On the other hand, proton beams do not spread radiation on their way and are less likely to damage surrounding healthy tissue.

As a result, proton beam therapy can cause fewer side effects, but proton beam therapy is expensive and is not available in many centers in the USA. Many centers have recently adopted proton beam therapy to treat GI malignancies [10]. Before administering external beam radiation, the patient's general condition and comorbidities are considered. The objective of treatment is determined whether it is a curative treatment (i.e., intent to cure with a higher radiation dose) or palliative treatment (mainly to relieve symptoms). Sometimes EBRT is given alone or as part of neoadjuvant or adjuvant therapy. The radiation is planned after the radiation oncologist sees the patient and reads reports on what the biopsy or X-ray/CT/PET showed. The target volume, i.e., the volume of tissue to be irradiated, and risk organs, i.e., healthy tissue to be avoided, are defined by multiple CT scanning images. The boundaries of the target volume and risk organs are mapped directly in a dose-planning computer [11]. The radiation oncologist then calculates and prescribes the total radiation dose, number of fractions, each fraction dose, and the total duration of treatment. Then the medical dosimetrist designs an individualized

plan of treatment for the cancer patient. Most patients receive radiation treatment once a day, Monday through Friday, for 2 to 10 weeks, depending on the type of malignancy. EBRT is used to treat esophageal cancer, gastric cancer, pancreatic cancer, hepatobiliary cancer, colorectal cancer, anal cancer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma, and GI neuroendocrine tumors [12-14].

Regarding IBRT, radioactive materials are placed inside the tumor tissue (interstitial) or as close as possible to the tumor tissue inside the lumen or body cavity (endoluminal or intracavity) or administered intravenously (radioembolization) [15]. This therapy allows a higher dose of radiation to the tumor tissue without much damage to the surrounding radiosensitive tissue [16]. IBRT can be temporary or permanent. In temporary IBRT, a catheter is used to deliver radioactive materials for a specific period, which is later removed. In permanent IBRT, radioactive implants (seeds, wires, pellets, capsules, or rods) are permanently placed and lose their activity after a few months. IBRT is used for the definitive or palliative treatment of various GI malignancies, which include esophageal, rectal, anal, hepatic, and biliary malignancies [17]. Endoscopic ultrasound (EUS)-guided interstitial brachytherapy can be given in patients with advanced pancreatic cancer [18]. Radioisotope therapy can be given to bile duct cancer, liver cancer, neuroblastoma, non-Hodgkin's lymphoma, and painful osteoblastic bone metastasis [19, 20]. The radioisotopes can kill cancer without much damage to the surrounding normal tissue.

Pathogenesis of Radiation Injury to the GIT

The pathogenesis of radiation injury to the GIT is very complex. Intestinal cells are very radiosensitive as they are rapidly dividing cells. Ionizing radiation can cause both direct and indirect injuries to the GIT. Directly, it can damage DNA, RNA, proteins, and lipid. Indirectly, it can produce reactive oxygen species (ROS) and free radicals that can break down protein and DNA. Usually, most of the DNA damage is quickly repaired by the cell. If repair does not occur, radiation damage can either result in cell death (deterministic effects) or initiate a cascade of events that lead to genomic instability, alteration in transcription, and permanent DNA alteration (stochastic effects). As a result of DNA damage, multiple transduction pathways activate transcription factors like p53 and nuclear factor κB (NF-κB) [21]. Activated transcription factors can up-regulate proinflammatory cytokines (tumor necrosis factor-α, interleukin-1β (IL-1β), and IL-6), chemokines (IL-8 and monocyte chemoattractant protein-1), cell adhesion molecules (selectins and integrins), cell surface receptors and stress response genes [22]. Lipid peroxidation can set off the signaling of activator proteins (C-Jun and c-Jun N-terminal kinases) involved in cellular apoptosis, proliferation, and neoplastic process) [23]. The irradiated tissue can transfer signals to the surrounding non-irradiated tissue and cause abnormal physiologic functions and genomic instability [24].

Radiation treatment is planned per the dose-volume histogram as it may predict the severity of radiation injury [25]. The radiation dose to a particular organ is calculated as the percentage of that organ that will receive a specified amount and is reported as Ddose = volume (%). For instance, D25 = 40 means that 40% of that organ receives 25 Gy of radiation. The extent of radiation injury depends on the radiation dose, and the volume of tissue irradiated [26].

Radiation-induced GI injury is classified as an acute and chronic injury due to ionizing radiation in the digestive organs. Acute radiation-induced injury occurs when a hefty dose is given over a short period, disproportionately affecting mitotically active crypt cells. Histology may show mucosal edema, acute inflammatory infiltrate, eosinophilic infiltrate, apoptosis, cell lysis, erosions, and ulcerations. On the other hand, administering small doses of radiation repeatedly over long periods results in a chronic injury. Mitotically less active cells like endothelial cells and mesenchymal cells are affected in this type of injury. Radiation exposure leads to the activation of genes responsible for translating transforming growth factor-beta (TGF beta) that stimulates collagen deposition and fibrogenesis. Histology may reveal atypical epithelial cells, endothelial cells and fibroblasts, fibrosis, vascular ectasia, intimal thickening, luminal narrowing, and obliteration of small arteries, i.e., obliterative endarteritis [27]. Radiation-induced injury depends not only on the radiotherapy regimen but also on host factors, organ mobility, genetic susceptibility, and chemotherapy. Patients with diabetes mellitus, hypertension, atherosclerosis, collagen vascular diseases, inflammatory bowel disease (IBD), and human immunodeficiency virus (HIV) infection are at increased risk of radiation-induced toxicity [28-31]. The immobile parts of the GIT, such as the duodenum, terminal ileum, cecum, and rectum, are more vulnerable to receiving higher doses of radiation than the rest of the GIT [32].

Genetic susceptibility plays a significant role in selecting radiosensitivity, and certain germ line mutation diseases like ataxia-telangiectasia, Fanconi's anemia, and Nijmegen breakage syndrome are highly susceptible to radiation [33]. Concurrent chemotherapy also increases radiosensitivity and radiation injury to GIT [34].

Clinical Effects of Radiation Therapy on the GI System and Management

Most GI injury occurs from external beam irradiation (EBT) used for various malignancies.

Esophagus

Radiation esophagitis occurs when radiation therapy is given for lymphoma, head and neck, breast, lung, and mediastinal malignancies. Typically, acute radiation esophagitis occurs within 3 months after radiation therapy, whereas chronic radiation esophagitis occurs more than 3 months after radiation therapy [35]. Most patients present with dysphagia and odynophagia due to esophageal mucositis and ulceration within the first 2 weeks of initial radiation therapy [36]. Symptoms generally improve 2 to 4 weeks after completion of radiotherapy. Sometimes, acute radiation-induced esophagitis can be severe and

Table 1. Grading of Radiation Esophagitis (CTCAE Version 5.0)

	CTCAE version 5.0
Grade 1	Asymptomatic
Grade 2	Symptomatic; altered swallowing/eating; oral supplements indicated
Grade 3	Severely altered swallowing/eating; tube feeding, total parenteral nutrition, or hospitalization indicated
Grade 4	Life-threatening consequences; urgent operative intervention indicated
Grade 5	Death

CTCAE: Common Terminology Criteria for Adverse Events.

lead to significant bleeding and perforation [37]. Patients with chronic radiation-induced esophagitis may present with dysphagia secondary to esophageal stricture, non-healing chronic esophageal ulcer, or dysmotility due to neuromuscular injury. Rarely patients may present with intractable cough and recurrent aspiration pneumonia due to the formation of tracheoesophageal fistula [38]. Radiation esophagitis is graded as per the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) and the Radiation Therapy Oncology Group (RTOG) scale, as shown in Tables 1 and 2 [39, 40].

Radiation-induced esophageal stricture (RIES) is the most common complication of chronic radiation esophagitis. Patients present with dysphagia 3 to 8 (average 6) months after completion of radiotherapy. Cervical stricture and stricture length ≥ 2 cm are predictors of recurrent stricture [41].

Currently, there is no standard treatment for radiation esophagitis. Supportive care is the mainstay of treatment. Patients should get adequate hydration and nutrition. Dietary consult should be taken to modify diet and assess calorie intake. Sucralfate has been shown to improve dysphagia and esophagitis healing [42]. Patients can take a soft, pureed, bland diet. Hot and spicy food should be avoided. Proton pump inhibitors (PPI), oral lidocaine, and non-steroidal anti-inflammatory drugs can be given to lessen dysphagia. Patients should also take Nystatin swish and swallow prophylactically to prevent oral candidiasis. Different radioprotectants like amifostine and glutamine have been used prophylactically to avoid radiation esophagitis [43]. Endoscopic balloon dilation is the treatment of choice for RIES.

Stomach

Radiation-induced gastritis (RIG) occurs due to direct radiation injury followed by vasculopathy when the stomach receives radiation from radiation therapy to the nearby malignancy. This complication occurs about 2 to 9 months after initial radiation therapy [44]. Low-dose radiation (up to 15 Gy) can cause reversible gastric mucosal damage, including degeneration of epithelial cells and infiltration of chronic inflammatory cells in the lamina propria. Irreversible gastric mucosal damage can occur due to high-dose radiation, including hemorrhagic gastritis (hyperemic gastric mucosa, erosion, and capillary bleeding), ischemic gastric ulceration, and telangiectasia due to submucosal endarteritis, and gastric atrophy due to submucosal fibrosis [44, 45]. Patients with RIG generally present with nausea, vomiting, and dyspepsia. Patients rarely can present with upper GI bleeding due to hemorrhagic gastritis or symptoms of gastric outlet obstruction due to gastric wall fibrosis. Upper endoscopy is the diagnostic and therapeutic modality of choice. Currently, there is no standard guideline for treating RIG. The different modalities of treatment include conservative treatment (PPI, sucralfate, anti-emetics) for non-hemorrhagic RIG, endoscopic treatment (argon plasma coagulation, endoscopic band ligation, radiofrequency ablation, cryotherapy), oral prednisone, epsilon aminocaproic acid, and surgical resection for hemorrhagic RIG, and hyperbaric oxygen therapy for non-healing gastric ulcers [46-48].

Small intestine

Radiation enteritis occurs when the small bowel falls in the field of radiation therapy for various intra-abdominal and pelvic malignancies. Patients develop radiation enteritis more commonly when they receive radiation therapy for GI and gynecological malignancies than urological malignancies [49]. Radiation enteritis is classified into acute and chronic forms. Acute radiation enteritis starts during the first 2 weeks of ini-

Table 2. Grading of Radiation Esophagitis (RTOG Scale)

	RTOG scale
Grade 1	Mild dysphagia or odynophagia, requires soft diet, topical anesthetic or non-narcotic agents
Grade 2	Moderate dysphagia or odynophagia, requiring liquid diet or narcotic agents
Grade 3	Severe dysphagia or odynophagia with dehydration or weight loss (> 15% or pretreatment baseline), requiring nasogastric feeding
Grade 4	Complete stricture, ulceration, perforation or fistula
Grade 5	Death

RTOG: Radiation Therapy Oncology Group.

tiation of radiation therapy and usually peaks by the fourth or fifth week [50]. Patients generally present with anorexia, nausea, vomiting, colicky abdominal pain, bloating, and diarrhea. These symptoms are due to direct small intestinal mucosal damage by radiation, causing mucosal inflammation and the release of inflammatory cytokines. Treatment is mainly supportive. Patients should be given adequate hydration, fluid and electrolyte balance should be maintained, and anti-diarrheal agents like loperamide should be given to control diarrhea. Hydrocodone can be used for abdominal pain. Patients should be on a lactose-free and low-fat diet. Symptoms generally resolve within 3 weeks of completion of radiotherapy.

Chronic radiation enteritis develops 3 months to 30 years after radiation therapy [51]. The primary pathophysiology is segmental inflammation in the area of the radiation field and obliterative endarteritis that can lead to a state of chronic mesenteric ischemia leading to ischemic mucosal ulcers, neovascularization, fibrosis, stricture, and fistula formation. Patients may present with chronic diarrhea, steatorrhea, weight loss, nutritional deficiencies (particularly calcium, iron, and vitamin B12), abdominal pain, intermittent small bowel obstruction due to strictures and adhesions, small intestinal bleed due to angioectasia or mucosal ulcer, small intestinal fistula with skin or internal organs, and small intestinal perforation requiring surgery [52]. Patients rarely may present with nausea, vomiting, abdominal pain and distention, constipation, malnutrition, and failure to thrive due to intestinal pseudo-obstruction. Diarrhea in chronic radiation enteritis can be due to mucosal damage, small intestinal bacterial overgrowth (SIBO), bile acid malabsorption, lactose intolerance, or short bowel syndrome [53]. Diagnosis is established by imaging studies (CT or MR enterography), deep enteroscopy with biopsy, video capsule endoscopy (unless there is no stricture), and sometimes postoperatively [54, 55]. Imaging studies may show segmental wall thickening with luminal narrowing and evidence of fistulas between the small bowel, colon, urinary bladder, and vagina. Endoscopy may show mucosal edema, villous atrophy, stricture, angioectasia, and bleeding. Histology may show villous atrophy, submucosal edema, fibrosis, and chronic inflammatory cells infiltrating the lamina propria. Appropriate tests should be ordered for its different complications like lactulose or glucose breath tests for SIBO, lactose breath tests for lactose intolerance, and tests for bile acid malabsorption (serum fibroblast growth factor 19 (FGF19), fasting serum 7-α-hydroxy-4-cholesten-3-one (7αC4) level, fecal bile acid test, 75 selenium homocholic acid taurine (75SeHCAT) 7-day retention test). Suspected small intestinal pseudo-obstruction should be investigated by antroduodenal manometry, which may show a postprandial delay of migratory motor complex and attenuated postprandial motor response after a liquid-solid meal [56]. Treatment of chronic radiation enteritis is multidisciplinary and is directed towards the patient's clinical presentation. Patients with diarrhea should avoid a high-fiber diet [57]. Anti-diarrheal agents like loperamide, diphenoxylate-atropine combination, or bismuth subsalicylate can be taken as a necessary basis. Antibiotics are administered to patients with SIBO. Dairy products should be avoided in patients with lactose intolerance. Bile acid sequestrants (cholestyramine, colesevelam, colestipol) should be given to patients with bile

acid diarrhea. Patients with steatorrhea should take less fat and fiber in their diet but must take vitamin A, D, E, and K supplements. Small intestinal angioectasia should be treated by endoscopic thermal therapy or sometimes surgery if not amenable to endoscopic treatment [58]. Surgical intervention is also indicated for radiation-induced small bowel stricture, fistula, and perforation [59]. But surgery carries the risk of increased postoperative morbidity (30%) and mortality (5%).

Surgery in radiation enteritis is technically challenging because of diffuse fibrosis, adhesions between bowel loops, and difficulty recognizing healthy and irradiated bowel. The types of surgery include segmental resection with anastomosis, intestinal bypass, and strictureplasty. In patients with limited intestinal reserve and strictures located within long segments of irradiated bowel, strictureplasty is a safe and preferred technique to preserve the small bowel [60]. The risk of postoperative anastomotic leak is high, and extensive bowel resection may cause short bowel syndrome.

Colon

Radiation colitis can occur during abdominopelvic radiation therapy for prostate, rectal, cervical, uterine, ovarian, and urinary bladder cancer. Because of their fixed position, the cecum and rectum are more vulnerable to radiation injury than the rest of the colon. Other risk factors include a higher total dose of radiation (> 54 Gy) or the abdominal dose of > 1.5 Gy, age > 60 years, and radical hysterectomy [61]. Acute radiation colitis is due to radiation-induced mucositis and develops within 60 days of radiation exposure. Patients generally present with abdominal pain, diarrhea, and rarely colonic perforation or obstruction [62]. Imaging studies (CT or MRI) may show submucosal thickening with nodularity and irregularity of the mucosal lining. Acute radiation colitis is usually self-limiting in most cases, with a resolution of symptoms a few weeks after discontinuation of radiation therapy. In the acute phase, management is symptomatic and supportive care with hydration, correction of electrolytes, administration of anti-diarrheal agents, and rarely subcutaneous octreotide (150 µg, three times a day) if refractory to anti-diarrheal agents [63]. Chronic radiation colitis is a slowly progressive disease that results from obliterative arteritis and can develop 2 months (usually 6 months to 5 years) after the completion of radiation therapy [64]. Patients generally present with abdominal pain and chronic diarrhea. But other complications can occur, and these include constipation (due to altered colon motility and fibrosis), colon obstruction (due to stricture), colonic bleeding (due to ulcers or angioectasia), colon perforation, fistula formation, and late diagnosis of advanced colon cancer. Patients should be evaluated by colonoscopy and imaging studies like CT, MRI, or barium enema. Colonoscopy may show mild erythema, friability, angioectasia, erosions, and ulcers with or without stricture. A biopsy may confirm the diagnosis of chronic radiation colitis. CT or MRI may show colon wall thickening, mucosal abnormalities, stricture, sinus, or fistula. Barium enema may show similar findings and "omega sign" (in 60% of cases) due to retraction at the base of sigmoid colon

stricture [65].

Symptomatic treatment with anti-diarrheal agents is given to patients with diarrhea. Bleeding due to angioectasia can be treated with argon plasma coagulation (APC). Surgery (resection with diversion colostomy) is indicated for refractory symptoms, colon obstruction, colon perforation, fistulae, recalcitrant colonic bleeding, sepsis, and colon cancer. But surgery for chronic radiation colitis carries significant morbidity and mortality due to severe intra-abdominal adhesions [66].

Rectum

It is the most commonly injured part of the GIT after pelvic radiotherapy. Acute radiation proctitis is caused by direct radiation-induced superficial mucosal injury and generally occurs immediately after or within 3 months of initiation of radiotherapy [67]. The incidence varies with the modality of radiation (brachytherapy vs. external beam radiation), dose intensity (rectal volume irradiated with ≥ 60 Gy), and presence of other risk factors like the presence of IBD, HIV infection, or genetic predisposition. Patients present with crampy lower abdominal pain, diarrhea, mucus discharge, tenesmus, fecal incontinence, and rarely rectal bleeding. Proctoscopy may show mucosal erythema, edema, friability, and ulcerations. A careful rectal biopsy may show stromal edema, cryptitis, crypt distortion, crypt abscesses, surface epithelial atrophy, epithelial meganucleosis, absence of mitotic activities, and fibroblastic proliferation [68]. Acute radiation proctitis is usually self-limiting, and management is supportive care with enough hydration and control of bowel movements with anti-diarrheal agents. Some studies showed clinical, endoscopic, and histologic improvement after administration of sodium butyrate enema for 3 weeks [69, 70]. Chronic radiation proctitis is a slowly progressive disease that results from obliterative endarteritis, thrombosis, ischemia, necrosis, neovascularization, vascular ectasia, lamina propria, and submucosal fibrosis. Patients commonly present with rectal bleeding due to radiation-induced vascular ectasia, proctalgia, and rarely constipation with narrow caliber stool due to stricture formation, peri-rectal fistula, rectourethral fistula in men, rectovaginal fistula in women, and overflow incontinence 3 months (commonly 9 to 14 months up to 30 years) after completion of radiotherapy [71]. Proctoscopy with biopsy confirms the diagnosis of chronic radiation proctitis. Proctoscopic findings include telangiectasia, congested mucosa, friability, ulceration, and stricture [72]. A biopsy may show dilated and tortuous mucosal capillaries with microthrombi, distorted crypts, epithelial injury, Paneth cell metaplasia, lamina propria fibrosis, and absence of inflammatory cell infiltrate [73]. Because of lack of inflammation, some authorities named this entity chronic radiation proctopathy.

The treatment of chronic radiation proctitis depends on the clinical presentation. Patients with rectal bleeding are generally treated with endoscopic ablation of radiation-induced vascular ectasia (RVE) by argon plasma coagulation (APC) and/or sucralfate enema (10% suspension) 20 mL twice daily for 4 weeks. APC is a safe and effective endoscopic treatment, and an average of three to four sessions are required to stop rectal bleeding [74]. Kochhar et al showed in a small study that sucralfate enema, when given to patients with moderate to severe radiation proctitis, decreased rectal bleeding in 77% of patients at 4 weeks and 92% at 16 weeks [75]. Other treatment modalities to stop rectal bleeding due to RVE include topical application of formalin solution (3.6 to 10 %) on rectal mucosa by a sponge or gauze, neodymium/yttrium aluminum garnet (Nd:YAG) laser therapy, or hyperbaric oxygen therapy. In one study, two (range, 1 - 5) applications of 4% formalin solutions to the rectal mucosa showed complete cessation of bleeding [76]. Another study showed Nd: YAG application to RVE caused a significant reduction of rectal bleeding in 78% of patients with chronic radiation proctitis [77]. A randomized control of hyperbaric oxygen therapy showed substantial improvement in the healing of chronic refractory radiation proctitis [78].

Radiation Hazards to Patients Due to Diagnostic GI Imaging and

Interventional Procedures

Patients get exposed to radiation when they undergo diagnostic GI imaging and interventional procedures. The radiation exposure to a patient for some of these procedures is given as follows [79-81].

Diagnostic and therapeutic GI imaging

Diagnostic and therapeutic GI imaging includes: 1) CT scan of abdomen and pelvis without contrast: 7.7 mSv; 2) CT scan of abdomen and pelvis with and without contrast: 15.4 mSv; 3) Multiphase CT scan of abdomen and pelvis: 31 mSv; 4) CT angiogram abdomen: 7.4 mSv; 5) CT angiogram pelvis: 8.9 mSv; 6) PET/CT scan: 25 mSv; 7) CT colonography: 6 mSv; 8) Barium swallow: 1.5 mSv; 9) Upper GI study with barium: 6 mSv; 10) Barium enema: 6 mSv; 11) Chest X-ray: 0.1 mSv; 12) Abdominal X-ray: 1.2 mSv; 13) CT-guided biopsy of intra-abdominal organs: 9.3 mSv; 14) Therapeutic ERCP: 2 to 6 mSv.

X-rays are used during fluoroscopy to obtain dynamic video and cinematic functional imaging. Fluoroscopy time and dose-area product (DAP) are used in assessing radiation risk from diagnostic GI imaging and interventional procedures as they correlate well with long-term biologic risk. DAP is the product of the surface area irradiated multiplied by the radiation dose absorbed at the surface. It is calculated automatically by the fluoroscopy machine and expressed as $Gy.cm^2$ [82].

One study showed patients' radiation exposure during ERCP grade IV was lower with technician-controlled fluoroscopy than with endoscopist-controlled fluoroscopy [83]. Radiology technicians, radiologists, and gastroenterologists are trained to use radiation doses as low as reasonably achievable (ALARA) for obtaining good quality images. But even at low doses of radiation exposure from these various diagnostic GI imaging and interventional procedures, there can be a slight increase in the chance of developing malignancy in future years (stochastic effects) [84]. The radiation risk may increase with the amount of radiation exposure, repeated radiation ex-

Table 3. Radiation Injuries to Certain Organs

Organ	Radiation dose threshold (Gy)	Period of time to develop effect
Gastrointestinal mucosal lining loss	6	6 to 9 days
Reduced production of bone marrow hematopoietic cells	0.5	1 to 2 months
Ovaries - permanent sterility	2.5 to 6	< 1 week
Testes - temporary sterility	0.15	3 to 9 weeks
Permanent sterility	3.5 to 6	3 weeks
Skin - erythema	3 to 6	1 to 4 weeks
Temporary hair loss (depilation)	4	2 to 3 weeks
Death and scarring (necrosis)	5 to 10	1 to 4 weeks

posure, patient's heredity, young age, sex, and anticipated life expectancy [85, 86]. Children and females are at increased risk of developing cancer after radiation exposure. According to International Commission on Radiological Protection, 1% of patients may develop deterministic effects if exposed to > 0.1 Gy radiation. GI mucosa, bone marrow, ovaries, testes, and skin can get injured after a particular radiation dose, as shown in Table 3 [87].

Occupational Radiation Exposure to the GI Endoscopists

The GI endoscopists get exposed to three sources of ionizing radiation when endoscopic procedures are done under fluoroscopic guidance [88]. These include primary beam radiation, scattered radiation, and leakage radiation. The GI endoscopists get exposed to primary beam radiation when manipulating devices within the radiation field. The radiation dose varies from 5 to 20 mGy/h at the site of exit of the radiation beam. Scattered radiation is secondary radiation that travels in different directions when the primary beam radiation interacts with the patient's tissues. The radiation dose is 1 to 10 mGy/h at the operator's position. Leakage radiation is the third type of ionizing radiation emanating from the protective shielding of the X-ray tube other than the primary beam port. At the operator's position, the leakage dose rate is generally in the range of 0.001 to 0.01 mGy/h. The primary source of radiation exposure to the GI endoscopists and their staff in the fluoroscopy room is scattered radiation. The radiation exposure may vary from procedure to procedure. The fluoroscopy-guided procedures by GI endoscopists include therapeutic ERCP, esophageal, gastroduodenal, and colonic luminal stenting, device-assisted enteroscopy, push enteroscopy (rarely), direct percutaneous endoscopic jejunostomy (DPEJ), and various other interventional procedures where combined fluoroscopy, endoscopy, and EUS are required. These include endoscopic ultrasound-directed transgastric ERCP (EDGE), EUS-guided cholecystostomy (EUSC), and EUS-guided gastrojejunostomy [89-91]. The radiation exposure to the GI endoscopists while performing these procedures depends on multiple factors, particularly the duration of fluoroscopy time, patient's body weight, the type of fluoroscopic equipment (overhead tube vs. undercouch tube), use of a protective lead shield, high volume vs. non-high volume endoscopists, and magnification and high-resolution images. The predictors for a longer fluoroscopy time include the expertise of the endoscopist, the ERCP grade, pancreatic duct leakage, bile duct dilation, and brushing [92]. One prospective study found the mean fluoroscopy time for a therapeutic ERCP was 307 s [93]. Another study found the mean radiation exposure to the endoscopist during an ERCP was 42.6 µSv [94]. A small study of 57 ERCP cases showed average radiation exposure to different parts of the endoscopist body: thyroid - 5.4 µSv, forehead - 3.81 µSv, chest - 6.2 µSv, and hands - 27 µSv [95]. The annual total-body radiation exposure to the ERCP endoscopist varies from 3.35 to 5.87 mSv [96]. Radiation exposure to the GI endoscopists in other image-guided endoscopic procedures varies depending on multiple factors, which include the patient's body weight (higher BMI), the complexity of the procedure, fluoroscopy time, and the endoscopist's skill. GI endoscopists performing these interventional endoscopic procedures risk developing malignancy and cataract formation because of the cumulative risk of radiation [97]. Exposure to protracted low-dose radiation (< 100 mSv) can cause brain and neck tumors in physicians performing interventional procedures [98], early atherosclerosis with accelerated vascular aging in cardiac catheterization laboratory staff [99], and leukemia in radiation-monitored workers [100]. Occupational radiation exposure causing basal cell cancer of the skin has also been reported [101]. Prolonged exposure to low-dose radiation can increase the chance of breast cancer, as observed in female radiologic technologists [102].

As children have growing body tissues and organs, they are more sensitive to radiation as compared to adults. They receive various diagnostic X-rays as well as therapeutic radiation for different childhood malignancies like bone cancers, brain and spinal cord tumors, neuroblastoma, retinoblastoma, lymphoma, Wilms tumor and rhabdomyosarcoma. Children have a long lifespan, and as a result, after getting repeated diagnostic radiation exposure, they are more likely to develop radiation-induced malignancies in their lifetime. The US Food and Drug Administration suggests the parents to keep a record of children's imaging tests, discuss with the pediatrician about the risks and benefits of the tests, absolute necessity of the tests, radiation dose adjustment as per child's body weight and height, and also scope of using non-radiation imaging tests like ultrasound and magnetic resonance imaging.

Preventive and Protective Measures

Preventive and protective measures should be taken to reduce the harmful effects of ionizing radiation. The GI endoscopist and medical staff in the procedure room receive the most significant amount of radiation emitted during fluoroscopy. The shorter the fluoroscopy time, the lesser the chance of radiation injury to patients, GI endoscopists, and medical staff in the fluoroscopy room. So, fluoroscopy should be used when it is essential. Fluoroscopy time can be reduced by using less magnification and pulsed fluoroscopy (five images per second) instead of live or continuous fluoroscopy (35 images per second). Undercouch tube fluoroscopic equipment produces less scattered radiation, so it should be used instead of overhead-tube equipment. Radiation protective curtains mounted to the X-ray tube can reduce radiation exposure to the endoscopists and their team during ERCP [94]. Leaded drapes or leaded acrylic shields can also be suspended from the fluoroscopy table to reduce scattered radiation. The distance from the radiation source is also critical in reducing exposure from scattered radiation emissions as it follows an inverse square law. Increasing the distance from the radiation source two times can decrease the radiation exposure level four times. Only 0.5% to 5 % of radiation can be transmitted through leaded aprons. The GI endoscopist and the medical staff in the fluoroscopy room should wear front-covered leaded aprons (0.25 mm, 0.35 mm, or 0.5 mm thickness) with a tight thyroid collar shield to reduce radiation exposure. A 0.5-mm thick lead apron can attenuate 90% or more of scattered radiation. They should also use leaded eyeglasses with side shields (0.5- or 0.75-mm thickness) that can reduce radiation exposure to the eye lenses by 90% [103, 104]. According to the International Commission on Radiological Protection (ICRP), the annual limit of total body exposure to radiation should not exceed 50 mSv and a lifetime limit of 10 mSv multiplied by the individual's age in years [105]. To reduce the radiation-induced cataract formation in the medical staff, the ICRP recommended that the annual eye lens dose limit be 20 mSv, averaged over 5 years, with no year exceeding 50 mSv [106]. Cumulative radiation exposure to the thyroid gland (mean dose of > 50 - 100 mGy) can increase the risk of developing thyroid cancer, although the risk decreases at age 40 years and over [107]. The United States Nuclear Regulatory Commission requires the medical staff in the fluoroscopy room to wear a personal radiation monitoring badge (dosimeter) that can measure and record the total accumulated individual dose of ionizing radiation [108]. So, the GI endoscopists should follow the three fundamental principles to get radiation exposure to themselves as low as reasonably achievable: 1) Reducing the time of radiation exposure; 2) Keeping a safe distance from the radiation source; 3) Utilizing physical shielding of the body, neck, and eyes.

Conclusions

Radiation energy is universally used in the field of gastroenterology. There are conventional and international radiation units, both of which are used in the USA. Radiation is used in many diagnostic imaging, diagnostic and therapeutic interventional procedures, and radiotherapy. There are three modalities of radiation therapy: EBRT, IBRT, and radioisotope therapy, and they play a significant role in the treatment of various GI malignancies. The pathogenesis of radiation injury is complex, damaging the tumor tissue directly and indirectly through forming free radicals. Radiation injury may also cause inflammation, fibrogenesis, and neoplastic transformation in the normal surrounding tissue. Radiation therapy for various malignancies can cause acute and chronic esophagitis, gastritis, enteritis, colitis, and proctitis. Treatment is mainly supportive in these conditions. Different diagnostic imaging and interventional radiologic and GI procedures expose the patient to varying doses of radiation. But exposure to even low doses of radiation can increase the chance of developing malignancy. The GI endoscopists also get radiation exposure during fluoroscopy-guided procedures, which can slightly increase the likelihood of developing malignancy and cataracts in future years. The GI endoscopists and medical staff should take different preventive measures to reduce radiation exposure. Although there are tremendous benefits of using radiation in medicine and gastroenterology, the risk of radiation exposure to the patients, GI endoscopists, and medical staff is real. We should be constantly vigilant about these risks, and future research should be done to minimize these risks. We should follow the guidelines recommended by the ICRP, National Council on Radiation Protection and Measurements (NCRP), and Radiation Safety Committees.

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Conflict of Interest

The author declares no conflict of interest.

Author Contributions

Monjur Ahmed, MD solely made contribution to the work reported. Razin Ahmed overviewed the work.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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