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REVIEW

Gastrointestinal radiation injury: Prevention and treatment

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Abstract

With the recent advances in detection and treatment of cancer, there is an increasing emphasis on the efficacy and safety aspects of cancer therapy. Radiation therapy is a common treatment for a wide variety of cancers, either alone or in combination with other treatments. Ionising radiation injury to the gastrointestinal tract is a frequent side effect of radiation therapy and a considerable proportion of patients suffer acute or chronic gastrointestinal symptoms as a result. These side effects often cause morbidity and may in some cases lower the efficacy of radiotherapy treatment. Radiation injury to the gastrointestinal tract can be minimised by either of two strategies: technical strategies which aim to physically shift radiation dose away from the normal intestinal tissues, and biological strategies which aim to modulate the normal tissue response to ionising radiation or to increase its resistance to it. Although considerable improvement in the safety of radiotherapy treatment has been achieved through the use of modern optimised planning and delivery techniques, biological techniques may offer additional further promise. Different agents have been used to prevent or minimize the severity of gastrointestinal injury induced by ionising radiation exposure, including biological, chemical and pharmacological agents. In this review we aim to discuss various technical strategies to prevent gastrointestinal injury during cancer radiotherapy, examine the different therapeutic options for acute and chronic gastrointestinal radiation injury and outline some examples of research directions and considerations for prevention at a pre-clinical level.

Key words: Radiation enteritis; Radiation proctitis; Prevention; Treatment; Gastrointestinal radiation injury

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INTRODUCTION

External beam radiotherapy is a common treatment modality for wide varieties of cancers. Approximately 70% of all cancer patients receive radiotherapy during the course of their disease, while radiotherapy plays a central role in 25% of all cancer cures[1-2]. Radiotherapy is a cost effective treatment, accounting for only 5% of the total cancer care expenditure[3]. This estimate has increased over the last decade with the wide use of modern technological innovations in simulation, delineation, dose calculation and radiation treatment delivery[4].

Gastrointestinal radiation injury is an important problem for two main reasons. First, it causes morbidity associated with a significant economic burden[5] and a significant reduction in patient's quality of life[6,7]. Second, it limits the dose of radiation that can be used to control cancer, as radiotherapy-related side effects often limit the tolerability for patients. Clinical manifestations of gastrointestinal

radiation injury can present acutely during or soon following radiotherapy due to acute mucosal injury and inflammation or they can present insidiously within few months or years after radiotherapy due to a chronic process of transmural fibrosis and vascular sclerosis.

Radiation toxicity to the gastrointestinal tract can be reduced by either of two strategies: technical strategies, which aim to physically shift the radiation dose away from the normal tissues or through biological strategies which aim to modulate the cellular and tissue response to ionising radiation.

TECHNICAL STRATEGIES FOR PREVENTION

Attention to detail regarding both radiotherapy planning and radiation delivery methods can minimise the risk of intestinal toxicity during pelvic radiotherapy. Multiple field planning and delivery can reduce the radiation dose to normal intestine as well as minimise the volume of small intestine exposed to radiation in the pelvis[8].

Physical manoeuvres and tissue expander techniques

The impact of different physical measures such as patient position during pelvic radiotherapy have been evaluated in a randomized trial of supine and prone positioning in patients undergoing conformal radiotherapy for prostate cancer. There were significant improvements for small bowel, rectal wall and bladder wall doses in the supine position[9].

Another study utilised combined manoeuvres to displace the small intestine from the pelvis during radiotherapy by bladder distension, lower abdominal wall compression with the patient in prone position using two-field and four-field planning radiographs of contrast-enhanced small bowel[10]. The results demonstrated in 50% of patients the four-field volume of pelvic small bowel was significantly less in the prone position than in the supine position. Similarly, other techniques such as the use of a "belly board" while the patient is in the prone position where the opening in the table allows the abdomen to fall below the level of the table, displaces the small bowel by the effect of the gravity during radiotherapy. These technique were found to reduce the volume of the small intestine within the pelvis by a mean of 66%[11].

Pre-treatment small bowel contrast studies can assess the location and mobility of the small bowel and hence, determine the optimum treatment position that could minimise the volume of small intestine within the pelvis[12]. Tissue expander techniques have been used to minimise the volume of exposed small bowel within the irradiation field during abdominal and pelvic external beam radiotherapy. Studies have shown a reduction of 50% in the risk of chronic intestinal complications with the use of intra-pelvic tissue expander[13]. Other techniques used to minimise the radiation dose to the rectum include transperineal injection of human collagen to increase the distance between the prostate gland and anterior rectal wall. The mean reduction in dose to the anterior rectal wall was 50% with no rectal toxicity reported[14].

Prophylactic surgical techniques

Various prophylactic surgical therapies were also employed to reduce the small intestinal exposure during pelvic radiotherapy such as insertion of biodegradable mesh slings, intra-pelvic breast prostheses or omentoplasty during operative resection whenever postoperative radiotherapy may be indicated[15-20]. Mesh slings were found to reduce the volume of small intestine exposed by 50%[21,22] while other techniques such as pelvic reconstruction, omentoplasty and transposition of the large bowel were found to reduce the volume of bowel at risk by 60%[22,23]. Prostate gland immobilization and rectal wall sparing has been suggested by the use of endorectal balloons during prostate cancer radiotherapy. Endorectal balloons are reported to be well tolerated by patients and showed a significant rectal wall sparing effect during three-dimensional conformal radiotherapy and intensity-modulated radiotherapy for prostate cancer[24,25].

Optimised planning and delivery techniques

A significant improvement in the safety of radiotherapy treatment has been achieved through the use of optimised planning and delivery techniques which aim to reduce the field size, focus the radiation beam into the lesion and minimise the volume of exposed surrounding tissues in the radiation field[10]. Multiple field arrangements may also reduce normal tissue toxicity during pelvic radiotherapy.

The dose-volume histogram is a plot of a cumulative dose-volume frequency distribution, that graphically summarizes the simulated radiation distribution within a volume of interest of a patient which would result from a proposed radiation treatment plan[26]. It provides a graphic display of a simulated radiation treatment plan and generates valuable information on the dose distribution within the volume of interest[27]. The dose-volume histogram is used to predict the development of radiation toxicity and to identify low and high risk patient groups[28]. Careful review of the dose-volume histogram of both the intended targets as well as the structures of avoidance constitutes a standard part of the assessment of the radiation treatment plans in modern radiation therapy.

Three-dimensional conformal techniques which comprise computerised tomography scanning simulation techniques and intensity modulated radiation therapy are associated with a reduced risk of normal tissue toxicity and allow a higher radiation doses to be used compared to conventional two dimensional methods[29-32]. Computerised tomography scan simulation techniques were found to reduce the volume of the bowel unintentionally irradiated by 5% compared to conventional radiotherapy[33].

Intensity modulated radiation therapy allows clear definition of both target lesions and surrounding normal tissues and hence the ability to apply two different inten-

sities of radiation (high and low) within the same treatment field[34,35]. It represents the ultimate combination of treatment planning and delivery which provides the most flexible delivery of radiation to complex targets while minimising radiation doses to surrounding critical structures. It does so by utilizing sophisticated planning algorithms such as inverse planning and multiple small beams of varying intensity, to optimally deliver the treatment. Intensity modulated radiation therapy was associated with a significant reduction in toxicity following pelvic radiotherapy in prostate cancer patients[36]. It was also associated with a reduction of 15%-18% in intestinal volume unintentionally irradiated compared to conventional two dimensional radiotherapy, and a 10%-13% reduction in intestinal volume unintentionally irradiated compared to three-dimensional computerised tomography simulation techniques[33]. Furthermore, intensity modulated radiation therapy has been found to reduce acute and late toxicity and maintains good long term quality of life even when high radiation doses are administered to prostate cancer patients[37-39]. In 208 head and neck cancer patients treated with intensity modulated radiation therapy it was found that intensity modulated radiation therapy was associated with reduced late toxicities without jeopardising local cancer control and overall survival[40]. The long-term quality of life has been compared among survivors of head and neck cancer patients whom were treated with either intensity modulated radiation therapy or three-dimensional conformal radiotherapy. The study results have shown that the early improvement in quality of life associated with intensity modulated radiation therapy was maintained and become more magnified over time[41].

Brachytherapy is another advanced technique in which the source of radiation is implanted within the malignant tissues (interstitial brachytherapy) or within a cavity in its immediate vicinity (intra-cavitary brachytherapy). The sources can be permanently inserted and emits their radiation over a prolonged period of time (low dose rate) or temporary and emit over a short period (high dose rate). In this fashion, a high radiation dose is limited to the target lesion sparing the surrounding normal tissues. Brachytherapy alone or in combination with external beam radiotherapy can reduce normal tissue toxicity without compromising treatment efficacy in prostate cancer[42,43]. Brachytherapy can be an option for patients with history of inflammatory bowel disease and it is well tolerated in low risk prostate carcinoma[44].

Combining target definition on a daily basis and adjusting the treatments to account for target motion is referred to as image guided radiotherapy techniques[45]. Stereotactic radiation therapy can focus an extremely narrow ionizing radiation beam on a small target from different directions using an immobilisation system. The high accuracy of this technique has enabled targeting a small lesions such as brain metastatic lesions[46]. Stereotactic radiation therapy uses a small number of high doses of radiation to target small lesions. It has been used in the treatment of early-stage non-small-cell lung cancer, prostate cancer, renal-cell carcinoma, and liver cancer, and in the treatment of oligometastases in the lung, liver, and spine[47]. Stereotactic radiation therapy is associated with high local control rates of cancer[48] and it was evaluated in the treatment of prostate cancer using an accelerated form of hypofractitionation through fewer but larger treatment fractions. The early results of this new technique suggest that it may induce an initial prostate specific antigen response similar to that seen with conventional fractionation radiotherapy but with fewer acute side effects. Disease control and chronic toxicity have not yet been fully evaluated[49]. The use of higher (often > 10 Gy) daily radiation doses in stereotactic radiation therapy needs to be carefully considered in view of the potential for more severe side effects[50]. The impact of the image guided radiotherapy techniques has been shown in a large study with 331 patients treated with high-dose intensity modulated radiation therapy with fiducial marker-based position verification for prostate cancer which allowed daily correction of the prostate position using the fiducial markers. The results showed that high dose was well tolerated with lower rate of acute toxicity, which provide possibilities for further dose escalation[37].

High-energy proton beams stop abruptly in the tissue at the end of their range and deposit most of their energy there, in this fashion, they provide dose distributions that are superior to X-rays when used in comparable beam configurations[51] In addition, they are more densely ionising along their treatment path, and therefore a higher quantum of energy to kill the cancer cell and high linear energy transfer. With proton beam radiation therapy a smaller volume of normal tissues is irradiated at high dose levels for most anatomic sites than is feasible with any photon technique[52]. Clinical studies have shown that proton beam therapy in patients with hepatocellular carcinoma has been shown to be effective, safe and well tolerable[53]. Proton beam therapy allows large tumour volumes to be irradiated to high doses without significant dose exposure to surrounding normal tissue which make it a promising modality for the treatment of large-volume tumours[54]. However, they have yet to show significant advantages in comparison with the conventional radiation therapy.

MEDICAL THERAPY FOR GASTROINTESTINAL RADIATION INJURY

Although technical strategies have achieved a significant degree of normal tissue protection during radiotherapy delivery, biological strategies may offer additional future promise. A wide variety of pharmacological agents, nutritional supplements, biological response modifiers, and dietary measures have been investigated for potential benefit to prevent or minimize the severity of intestinal tissue injury induced by ionising radiation exposure.

SUPPORTIVE TREATMENT

Patient selection for radiotherapy

Patient risk profile for developing radiation toxicity merits a careful consideration while assessing individual patient for radiotherapy treatment. Co-morbid diseases such as vascular disease, hypertension, diabetes mellitus and atherosclerosis[55], inflammatory bowel disease[56-58], collagen vascular disease[59] and human immunodeficiency virus (HIV) infection[60,61] have been linked to an increased risk of toxicity following external beam radiotherapy.

Nutritional status and effect of diet during radiotherapy

Patient general health and nutritional status during radiotherapy may affect outcomes. Measures to improve patient nutrition such as dietary counselling, oral supplements and intensive nutrition intervention have been associated with an improved outcome in terms of body weight, morbidity, and quality of life during and after radiotherapy[62,63]. McGough *et al*[64] reviewed the efficacy of nutritional intervention on bowel symptoms during pelvic radiotherapy in data from 2646 patients. They found no evidence base for nutritional interventions identified to mitigate bowel symptoms following radiotherapy. However, the role of probiotic supplements, low fat diet and elemental diet was recommended for further evaluation. Subsequent studies on elemental diet identified the difficulty of patients tolerance to large volumes of elemental diet regimen during radiotherapy period[65,66]. The effect of high-potency probiotic preparation VSL3 has been investigated in double-blind, placebo-controlled trial of 490 pelvic radiotherapy patients. The results showed more diarrhoea and daily bowel movements in the placebo group compared with VSL3 recipients[67].

Biological, chemical and pharmacological therapy

Biological, chemical or pharmacological interventions to ameliorate the effect of radiation injury on gastrointestinal tract can be categorized according to the time of administration with respect to radiation exposure. Agents administered prior to radiotherapy for normal tissue prophylaxis are described as radioprotectors. Agents administered during the course of radiotherapy to minimize the injury are called mitigators, while agents administered to ameliorate an established injury are called treatment[68].

The complexity of the pathophysiology of intestinal radiation injury along with the increasing prevalence of the problem has attracted significant research interest in exploring the effectiveness of many agents. Treatment of delayed radiation injury is challenging as it is often refractory to different therapeutic modalities[69].

At the pre-clinical level, there has been a significant interest to test the efficacy of different agents to modulate the biological process implicated in radiation induced tissue injury and normal tissue damage (Table 1).

At the clinical level, there are no formal trials to reliably assess the effectiveness of most of the suggested therapies; hence most of the evidence is obtained from small studies which are often from a single centre. In addition, the results reported in many studies are often directly related to the radiation toxicity scale in use and its sensitivity, specificity as well as to methods of interpretation and grading of symptoms reported by patients.

Topical therapy

Topical therapy for radiation proctitis has been tried with different agents. Local instillation of formalin has been reported to be effective in the treatment of severe haemorrhagic radiation proctitis[70]. Sodium butyrate enemas were reported to improve the acute symptoms of radiation proctitis with no impact on the incidence and severity of late proctitis[71]. Steroid enemas and other topical steroid preparations, commonly prescribed for other anorectal inflammatory conditions have also been in use for symptom relief in radiation proctitis, but without conclusive evidence of efficacy.

Hyperbaric oxygen was suggested to exert its therapeutic role in chronic radiation proctitis through induction of neovascularization that reverses tissue hypoxia[72,73] with trophic effect on vasculogenic stem cells[74]. Treatment of chronic radiation proctitis with hyperbaric oxygen has shown promising results in a large randomized double-blind trial with 120 patients with long term follow up. Hyperbaric oxygen therapy significantly improved the healing responses in patients with refractory radiation proctitis with enhanced bowel-specific quality of life[75].

A recent systematic review demonstrated the therapeutic benefit of hyperbaric oxygen based on the evidence and expert consensus opinion. The review demonstrated its efficacy in patients with radiation damage to the anus and rectum and refractory chronic radiation injury[73].

Anti-inflammatory agents

Anti-inflammatory agents were suggested to reduce the severity of acute intestinal inflammation following irradiation. 5 aminosalicylic acid (5-ASA) has been studied, but most have reported no benefit or even worse symptoms with the use of 5-ASA compared to placebo[76-79]. Sulphasalazine showed clinical improvement in symptoms in a case series of four patients[80]. Balsalazide has been suggested to improve proctitis and toxicity grade in patients undergoing prostate cancer radiotherapy, in a study of 27 patients[81]. Taken together, the clinical evidence on therapeutic role of 5-ASA are not sufficient to recommend routine use in radiation injury.

Antioxidants

Antioxidants were suggested to have cytoprotective effects by reducing cellular oxidative stress following radiation injury to intestinal tissue. A sustained therapeutic benefit after 4 wk therapy with vitamin E and C has been reported in a study involving twenty patients with chronic radiation proctitis[82]. More studies will be required to assess the therapeutic role of different antioxidant agents.

Table 1 Examples of putative intestinal radioprotectants tested in pre-clinical studies

Biological agent	Suggested effect/mechanism	Suggested radioprotection
Glutamine, arginine enriched diet[103]	Enhanced mucosal healing	Protective effect on rat intestine compared to control
Vitamin- E[104]	Reduction of oxidative stress	Protective effect on rat intestine compared to control
Captopril[105]	Inhibition of pro-inflammatory enzyme angiotensin-1-converting enzyme	Protective effect on mouse intestine compared to control
Rofecoxib[106]	Selective Inhibition of cyclooxygenases -2 enzyme	Protective effect on rat intestine compared to control
Clopidogrel[107]	Inhibition of platelets aggregation with reduced vascular sclerosis	Protective effect on rat intestine
Thalidomide[108]	Protection to microvascular bed	Attenuated injury to rat endothelial cells of micro vascular bed compared to control
Simvastatin[109]	Attenuate endothelial cell injury	Attenuated delayed intestinal injury in rats
Glucagon-like peptide-2 (GLP-2)[110]	Increased mucosal mass	Intestinal trophic and protective effect to rat intestine
Octreotide[111,112]	Modulation the inflammatory effects mediated by over expression of NFκB	Ameliorated inflammation and injury in rat intestine
Prostaglandin E-2[113]	Pro-proliferative and anti-apoptotic effect on intestinal epithelium	Increased crypts survival
Anti-Transforming growth factors beta receptor[114]	Biological inhibition of extracellular remodeling	Reduced intestinal injury and fibrosis compared to IgG treated control mice
Toll like receptor 5 agonist derived from Salmonella flagellin[115]	Activation of intestinal immune response *via* NFκB signalling pathway	Protective effect to mice intestine
Intestinal sterilisation[116] Germ-free raised mice	Reduced number of translocated bacteria, sepsis and inflammation	Reduced intestinal cell apoptosis
Probiotic bacteria[117] (*Lactobacillus species*)	Restored intestinal microbiota imbalance	Reduces intestinal damage, sepsis and death in rodents

Amifostine

Amifostine is a scavenger of reactive oxygen species. Its protective effects have been related to its ability to minimise the injurious effects of free radicals on intestinal cells[83]. Amifostine has been investigated for both systemic and topical routes of administration during radiotherapy. Intravenous amifostine administered daily before radiotherapy has been shown to reduce the incidence of radiation proctitis during pelvic radiotherapy[84,85]. Similarly, rectal suspension of amifostine in two doses (1 g in 18 patients and 2 g in 12 patients) administrated daily before radiation therapy for prostate cancer has resulted in significant improvement in acute and late bowel quality of life toxicity parameters, more noticeable with higher doses[86]. Despite the results of these studies and that of many others, the updated clinical practice guidelines for the prevention and treatment of mucositis published in 2007[87] concluded that data on amifostine are mostly obtained from small, single-centre studies with conflicting results. The group concluded that intravenous amifostine daily administration prior to radiotherapy may prevent radiation proctitis in patients who are receiving standard-dose radiotherapy for rectal cancer (Level Ⅲ evidence, grade B recommendation)[87].

In previous studies, amifostine has been shown to reduce the incidence of xerostomia in patients during head and neck radiotherapy[88]. The American Society for Clinical Oncology recommended its use in 2002 published guidelines[89]. However, the recommendation has been subsequently withdrawn in the guidelines update in 2008 due to an insufficient data[90].

Sucralfate

Protection of mucosal cells has been suggested with sucralfate (aluminium sucrose octasulfate). A beneficial effect of sucralfate has been previously reported in two double-blind placebo-controlled studies in patients who received pelvic radiotherapy. It reported that the frequency of defecation and stool consistency were improved by sucralfate[91,92]. Sucralfate enemas have been evaluated in 26 patients with radiation-induced proctitis with persistent rectal bleeding and the results showed a reduction in the severity of rectal bleeding in all patients with sucralfate enemas after four weeks treatment[93]. However, in another study the therapeutic effect of sucralfate rectal enemas were evaluated compared to placebo, both administered during the course of prostate cancer radiotherapy. The results showed no difference in the rate of rectal bleeding between sucralfate and placebo treated group after a median follow-up of five years[94]. The therapeutic benefits of oral sucralfate have also been assessed in a prospective randomised placebo-controlled study on fifty one patients receiving pelvic radiotherapy. Results from 44 study subjects showed significantly increased diarrhoea in the sucralfate group which led to cessation of the trial. The study concluded that sucralfate cannot be recommended for prophylaxis of acute radiation to the rectum and may even worsen the symptoms[95]. Similarly, the lack of effect of micronized sucralfate mouthwash has been reported in a randomized, controlled trial in radiation-induced oral mucositis patients[96]. Despite extensive investigation, clinical data on sucralfate have shown variable results, which do not support its protective role

for routine clinical use.

ENDOSCOPIC MANAGEMENT, BIOPSY AND LASER CAUTERY

A variety of endoscopic therapies have been tried for the treatment of chronic radiation injury such as the heater probe, bipolar electrocoagulation and argon plasma coagulation with newer methods of endoscopic ablation such as radiofrequency ablation and cryotherapy[97]. Endoscopic treatment has been used primarily aimed to treat bleeding rectal telengectasia. Argon plasma coagulation therapy has been shown to be effective and safe treatment for treatment of rectal bleeding resulting from chronic radiation injury[98,99]. Caution should be applied however when considering the use of these invasive techniques following high dose treatment delivery. For instance the use of rectal wall biopsy and laser cautery has been associated with the development of recto-urinary fistulae[100-102] in men treated with brachytherapy for prostate cancer.

CONCLUSION

Prevention of gastrointestinal toxicity starts with a thorough assessment of patient risk profile before radiotherapy. There is no prophylactic or therapeutic agent available to radiotherapy patients proven to mitigate the acute and chronic symptoms of gastrointestinal radiation injury or to allow safe radiation dose escalation for better control of cancer. Many therapeutic agents are in use, but often with little evidence base. The recent advances in radiotherapy planning and delivery techniques provide a considerable degree of protection to the gastrointestinal during external beam radiotherapy. Newer techniques such as image guided radiotherapy techniques, stereotactic therapy and proton beam therapy may confer additional protection. On the other hand, a better understanding of the pathophysiology of intestinal radiation injury will allow the development of more effective biological strategies that could increase the end organ resistance to radiation toxicity. In this regard, modulation of various cellular and cytokine pathways that have been implicated in the development of the acute pathological process of radiation injury can give future promise. In addition to targeting different mechanisms mediating chronic inflammatory and fibrotic process that underlie the delayed pathological changes in the gastrointestinal tract, such approaches may provide new therapeutics insights to this problem.

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