ACUTE AND CHRONIC RADIATION INJURY TO THE LOWER GASTROINTESTINAL TRACT

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Radiation is an integral part of therapy for many pelvic cancers, including rectal, prostate, cervical, and uterine cancers, and has been shown to decrease local recurrence and increase patient survival. Radiation injury is a sequela of treatment that manifests different symptoms depending on the organ affected. The most common lower gastrointestinal symptoms are rectal bleeding, diarrhea, fecal urgency, and fecal incontinence, which can range in severity from mild and self-limiting to chronic, severe, or life threatening.1

Radiation side effects can occur acutely during therapy or much later and can even develop after several decades. Acute-onset radiation toxicity is defined as occurring within 3 months of therapy, whereas late-onset or chronic disease typically presents at least 6 months after treatment. The technique of the administered radiation therapy correlates with the timing of onset of symptoms. Newer intensity-modulated radiation techniques (IMRTs) allow for the delivery of higher doses of radiation directly to the tumor. With these techniques, surrounding normal tissues receive lower doses of radiation compared with conventional therapies such as three-dimensional conformal technique (3D-CRT). Patients whose therapy is administered using 3D-CRT are more prone to the development of late-onset disease when compared with patients undergoing IMRT.1

Disease Pathology

The therapeutic effect of radiation occurs due to the disruption of DNA synthesis in cells undergoing mitosis.2 Cellular changes occurring throughout a course of radiation therapy are ultimately what lead to radiation injury and its complications.3 The gut mucosa has a relatively high mitotic rate, and the high cell turnover makes it susceptible to radiation damage.2 Fractionated radiation causes repetitive injury to tissues, and the inflammatory response to each radiation fractionation may not resolve within 24 hours or prior to the next radiation dose, resulting in an accumulating response. At the end of a course of radiation therapy, the nondiseased tissue that is included in the field is dramatically different from what it was at the beginning. Acutely, the mucosal barrier of irradiated tissues becomes disrupted, inflamed, and increasingly permeable because of cell death in the crypt epithelium [see Figure 1]. This leads to increased bacterial exposure and stimulation of cytokines, including interleukins and tumor necrosis factor-α (TNF-α). Chronic changes include mucosal atrophy, intestinal wall fibrosis, and sclerosis of the vascular structures [see Figure 2]. Endothelial dysfunction leads to increased neutrophil recruitment on the endothelial cell surface, which increases inflammation and ultimately leads to the creation of a procoagulant surface by downregulating the activity of nitric oxide synthase, thrombomodulin, and plasminogen. This can ultimately lead to increased inflammation or even suppression of the inflammatory response depending on the dose and schedule of radiation. Important end results are the activation of the coagulation system by way of increased thrombin and the formation of new blood vessels, specifically telangiectasias, by way of radiation-induced angiogenesis. Both inflammation and angiogenesis in the treatment field can clinically manifest as rectal bleeding.1,3

Risk Factors

Factors that are either specific to the administered radiation therapy or specific to the patient have been shown to increase the risk of developing radiation injury [see Table 1]. It has been well demonstrated that higher doses of radiation, especially to the anterior rectal wall, increase the incidence and severity of late-onset rectal bleeding.4,5 Serious gastrointestinal toxicity is rare when the total radiation dose administered does not exceed 50 Gy.6 A correlation has also been observed between the volume of small bowel irradiated and the incidence of small bowel complications.7 For instance, 50% of patients who receive 60 Gy of radiation to a third of their small bowel volume would be expected to develop radiation enteritis in 5 years, whereas the expected dose that would elicit the same response if the whole volume of small bowel were irradiated is 55 Gy. For the colon, the dose to elicit toxicity in 50% of the population is 65 Gy for a third of the volume and 60 Gy for the whole volume.8 Certain radiation techniques, such as opposed and extended field radiation, are associated with high rates of radiation injury,
Evaluation and Treatment of Radiation-Induced Gastrointestinal Injury

Consider pharmacologic prevention, especially in high-risk patients

Beclomethasone dipropionate enemas, amifostine enemas or injections, oral probiotics

Radiation therapy

Acute symptoms

(< 3 months)

Chronic symptoms (> 6 months)

Persistent or severe symptoms

Mild symptoms, no anemia → observation, reassurance

Resolution of symptoms → observation

Initial workup

Colonscopy
Sigmoidoscopy with barium enema
Transrectal or endoanal ultrasonography
Anorectal physiology

Findings consistent with radiation injury

Pharmacologic therapy: oral metronidazole, sucralfate enemas, oral vitamin A, short-chain fatty acid (butyrate) enemas

Persistent symptoms, acute or severe

Endoscopic therapy:
• First line: thermal ablation with argon plasma coagulation, formalin application
• Alternative: thermal coagulation with laser or bipolar
• Newer techniques still being investigated: cryoablation, radiofrequency ablation

Changes not consistent with radiation proctitis → additional workup

Evaluate for secondary malignancy: computed tomography, magnetic resonance imaging, positron emission tomography
Evaluate remainder small bowel: upper endoscopy, small bowel contrast study, capsule study
Workup for malabsorption: breath tests, selenium-75 homocholic acid conjugated with taurine scanning

Persistent symptoms, chronic in nature

Hyperbaric oxygen therapy

Persistent, severe, or life-threatening symptoms

Surgical therapy:
• Diversion without resection
• Resection without anastomosis
• Resection with anastomosis, with or without diversion

Mild symptoms, no anemia → often self-limiting, observation, reassurance

Persistent or severe symptoms

Acute symptoms

(< 3 months)

Initial workup

Colonscopy
Sigmoidoscopy with barium enema
Transrectal or endoanal ultrasonography
Anorectal physiology

Findings consistent with radiation injury

Pharmacologic therapy: oral metronidazole, sucralfate enemas, oral vitamin A, short-chain fatty acid (butyrate) enemas

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Resolution of symptoms → observation
as are short-course radiotherapy regimens, which employ larger fraction sizes over a shorter time period. \(^9\) Preoperative, as opposed to postoperative, chemoradiotherapy in the multimodal treatment of rectal cancer leads to statistically lower toxicities, as does the concurrent administration of adjuvant chemotherapy and radiotherapy.\(^{10,11}\)

Certain patient-related risk factors also increase the likelihood of developing radiation injury, namely conditions with a common end point of increased inflammation and endothelial dysfunction.\(^{1}\) Patients with inflammatory bowel disease, such as Crohn disease or ulcerative colitis, are at a greater than 20% risk of developing severe acute gastrointestinal toxicity following radiation.\(^{12}\) Collagen vascular diseases such as systemic lupus erythematosus, scleroderma, polymyositis, and dermatomyositis have been associated with severe late radiation effects, although, interestingly, rheumatoid arthritis does not demonstrate a similar association.\(^{13}\) Diabetes has been shown to be an independent risk factor for late-stage gastrointestinal and genitourinary toxicity following radiation therapy, and when diabetic patients also have hypertension, the risk of late toxicities is even higher.\(^{14,15}\) Patients who are heavy smokers (defined as at least one pack per day) and who have abnormally low body mass indexes (BMIs; defined as less than 18.5) are at increased risk. An association with abnormally high BMIs is less clear.\(^{16,17}\) Genetic predispositions have also been demonstrated. For instance, heterozygotes carrying the ataxia-telangiectasia gene have been shown to experience increased severe late effects of toxicity.\(^{18}\) Lastly, previous abdominal and pelvic surgery has been associated with an increased risk of radiation enteropathy, perhaps owing to adhesions that fixate the small bowel in a nonanatomic position in the pelvic radiation field.\(^{19}\)

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**Table 1** Risk Factors Predisposing Patients to the Development of Radiation Injury

<table>
<thead>
<tr>
<th>Treatment-related risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher radiation doses</td>
</tr>
<tr>
<td>Higher volume of irradiated small bowel</td>
</tr>
<tr>
<td>Extended- or opposed-field radiation techniques</td>
</tr>
<tr>
<td>Short-course radiotherapy</td>
</tr>
<tr>
<td>Postoperative chemoradiotherapy</td>
</tr>
<tr>
<td>Concurrent administration of chemotherapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient-related risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Inflammatory bowel disease (Crohn disease, UC)</td>
</tr>
<tr>
<td>Connective tissue disorders (SLE, scleroderma, polymyositis, dermatomyositis, excluding RA)</td>
</tr>
<tr>
<td>Heavy smoking (at least one pack per day)</td>
</tr>
<tr>
<td>Abnormally low BMI (&lt; 18.5)</td>
</tr>
<tr>
<td>Previous abdominal or pelvic surgery</td>
</tr>
<tr>
<td>Genetic predisposition (AT heterozygotes)</td>
</tr>
</tbody>
</table>

AT = ataxia-telangiectasia; BMI = body mass index; RA = rheumatoid arthritis; SLE = systemic lupus erythematosus; UC = ulcerative colitis.
Disease Prevention

A number of strategies have been proposed to prevent or minimize the damage to normal tissues and subsequent radiation-induced injury [see Table 2]. These should be especially considered in high-risk patients. The topical administration of a glucocorticoid such as beclomethasone dipropionate has been shown to reduce the risk of rectal bleeding following pelvic radiation in randomized trials. Sucralfate enemas have also been studied but have not been shown to reduce the likelihood of radiation toxicity and rectal bleeding in the acute period or later. The oral administration of sucral fate has also been studied but was not shown to reduce proctitis symptoms and was actually associated with increased rectal bleeding. Mesalazine (5-aminosalicylic acid [5-ASA]) enemas were also previously studied as a possible preventive measure, but trials failed to demonstrate an improvement in symptoms, and some studies actually demonstrated worsened rectal toxicity and bleeding. Amifostine is an organic triphosphate and was the first cytoprotective drug to be used in clinical practice. It was initially shown to reduce radiation toxicities such as mucositis and dysphasia in patients receiving therapy for head and neck and lung cancers. When applied to the treatment of radiation-induced proctitis, both intrarectal enemas and subcutaneous injections of the drug were shown to reduce mucositis, and the subcutaneous form was also effective in preventing urinary toxicities such as nocturia and dysuria. Octreotide acetate has been widely used for the prevention of chemotherapy-induced diarrhea, but randomized trials in which it was administered intramuscularly prior to and during radiation therapy failed to demonstrate any reduction in the incidence or severity of diarrhea. Probiotics have been shown to be effective in the prevention and treatment of diarrhea induced from a variety of etiologies, including infectious and antibiotic associated, in both adults and children. Studies to date have suggested a possible beneficial effect of probiotics for the prevention of radiation-induced diarrhea, but further studies are needed to clearly demonstrate a statistically significant effect.

Clinical Presentation

ACUTE INJURY

Acute injury occurs within the first few months following radiation therapy. It is primarily an inflammatory response and tends to be self-limited. Symptoms such as bleeding, diarrhea, urgency, and incontinence are reported in up to three quarters of patients. The majority of acute injuries heal spontaneously, although it may take up to 6 months after the cessation of radiation therapy. On histologic examination, acute injury is usually confined to the mucosa with findings of decreased mitotic rate, thickened lamina propria, and patchy proliferation of fibroblasts, whereas the submucosa and blood vessels remain normal. Local skin toxicity in the radiated field can be significant. Dermatitis, from mild to severe, with desquamation and ulceration can occur. The relationship between toxicity symptoms in the acute phase following radiation therapy and the development of a more chronic condition remains controversial. Although the development of chronic injury has not been directly related to initial acute symptoms, there is some suggestion of an association that may be related to the dose of radiation administered as both the acute and chronic syndromes occur more frequently with higher doses.

Table 2 Investigated Prophylactic Therapies to Prevent Radiation Injury

<table>
<thead>
<tr>
<th>Medication</th>
<th>Strategy</th>
<th>Administration</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>Reduce inflammation</td>
<td>Enema</td>
<td>Reduction in rectal bleeding</td>
</tr>
<tr>
<td>Mesalazine (5-ASA)</td>
<td>Reduce inflammation</td>
<td>Enema</td>
<td>No benefit or worsened rectal bleeding</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Mechanical shielding</td>
<td>Enema Oral</td>
<td>No significant reduction in toxicity</td>
</tr>
<tr>
<td>Amifostine</td>
<td>Prevention of DNA damage</td>
<td>Enema Subcutaneous</td>
<td>Reduced morbidity</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Reduction of gastrointestinal secretion and motility</td>
<td>Intramuscular and subcutaneous</td>
<td>Failed to reduce the incidence or severity of diarrhea</td>
</tr>
<tr>
<td>Probiotics</td>
<td>Promote intestinal bacterial flora</td>
<td>Oral</td>
<td>Suggested benefit in reducing diarrhea, but further studies are needed</td>
</tr>
</tbody>
</table>

5-ASA = 5-aminosalicylic acid.
CHRONIC INJURY

Chronic proctitis arises in up to one fifth of patients and usually develops at least 6 months following radiation therapy. Symptons include rectal bleeding, diarrhea, fecal urgency, and fecal incontinence, and the reported incidence of these symptoms varies widely (see Table 3). Unlike the pathogenesis of acute injury, vascular changes include subintimal fibrosis, platelet thrombi, and endothelial degeneration and ultimately lead to relative ischemia. These vascular changes, in combination with severe lamina propria fibrosis and crypt distortion, distinguish chronic from acute injury. Rectal bleeding is the most common symptom of chronic radiation proctitis, occurring in up to 50% of patients but requiring transfusion in only one third of cases and further intervention in less than 6%. Bleeding occurs secondary to the formation of friable telangiectasias that develop as the mucosal capillaries attempt to compensate for the relative ischemia resulting from vascular changes. This ischemia can also make the bowel wall prone to perforation, ulceration, or abscess or fistula formation (see Figure 4). Whereas bleeding is often self-limited and resolves without intervention, symptoms such as strictures, abscesses, and fistulae are unlikely to resolve without intervention and often require surgery (see Figure 5). Fecal urgency and incontinence can manifest in 3 to 53% of patients as a result of connective tissue fibrosis that leads to decreased rectal compliance. Given the significant variation in both the type and severity of symptoms, a scoring system, such as the one developed by Talley and colleagues (see Table 4), can be useful to objectively measure proctitis.

It is important to note that chronic radiation injury is not limited to bleeding and changes in bowel habits. Chronic skin changes may occur in the radiated field with “woody” induration of the perianal and gluteal areas. Some studies have also shown an increased rate of small bowel obstructions in irradiated rectal cancer patients compared with those who underwent surgery only. Urinary dysfunction is also reported, albeit less commonly than gastrointestinal symptoms. Lastly, increased rates of deep vein thromboembolisms and fractures of the pelvis and femoral neck have also been reported in patients undergoing preoperative radiation therapy in addition to surgery for rectal cancer as opposed to those undergoing surgery alone.

Table 3: Reported Frequencies of Symptoms of Chronic Radiation Proctitis

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Reported Frequency (%)</th>
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</thead>
<tbody>
<tr>
<td>Rectal bleeding</td>
<td>Up to 50</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Up to 50</td>
</tr>
<tr>
<td>Fecal incontinence</td>
<td>3–53</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>9–13</td>
</tr>
<tr>
<td>Urinary dysfunction</td>
<td>3–4</td>
</tr>
</tbody>
</table>

Figure 3: Severe perianal dermatitis following pelvic radiation.

Figure 4: Radiation proctitis with ulceration.
Assessment and Diagnosis

IDENTIFICATION OF POSTRADIATED PATIENTS

Diagnostic workup for radiation injury should be focused on those patients who have clinically significant signs, such as a documented decreased hematocrit or a transfusion requirement, or symptoms that are persistent and have a deleterious effect on quality of life.1 A thorough history should address all symptomatology relevant to the gastrointestinal tract, as well as urinary, sexual, and neurologic symptoms that may also be manifestations of radiation injury.53 Questionnaires such as the LENT-SOMA (late effects in normal tissues – subjective, objective, management, analytical) and the Radiation Therapy Oncology Group questionnaires have been developed to assess the severity of symptoms experienced by postradiation patients, although their clinical utility is debatable.54 Initial laboratory tests should include hematologic and biochemical profiles, as well as tumor markers, and can help direct further testing.55 Patients’ overall nutritional status should be taken into account in addition to the status of their cancer and overall prognosis. Perineal examination should be performed to evaluate for internal or external skin and tissue changes such as dermatitis, ulceration, fistulae, or masses.

Endoscopic evaluation, by either sigmoidoscopy or colonoscopy, with biopsies to allow for tissue diagnosis, is often the most useful initial investigation. The classic appearance of radiation proctitis is erythema, friability, and ulceration of the mucosa of the bowel wall as well as prominent telangiectasias. The spectrum of findings on endoscopy ranges from mild to severe and may include necrosis of tissues [see Figure 6, Figure 7, and Figure 8].56 Colonoscopy may be more

Table 4  Scoring System for Symptoms and Endoscopic and Histologic Results56

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom</td>
<td></td>
</tr>
<tr>
<td>Urgency</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding per rectum (per week)</td>
<td>0</td>
</tr>
<tr>
<td>Quantity of blood per rectum (per week)</td>
<td>None</td>
</tr>
<tr>
<td>Diarrhea (days per week)</td>
<td>0</td>
</tr>
<tr>
<td>Number of stools</td>
<td>≤ 1</td>
</tr>
<tr>
<td>Rectal pain</td>
<td>None</td>
</tr>
<tr>
<td>Endoscopy (rectum)</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>None</td>
</tr>
<tr>
<td>Granularity or edema</td>
<td>None</td>
</tr>
<tr>
<td>Telangiectasia</td>
<td>None</td>
</tr>
<tr>
<td>Ulcer</td>
<td>None</td>
</tr>
<tr>
<td>Histology (rectum)</td>
<td></td>
</tr>
<tr>
<td>Overall grade</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Figure 5  Severe radiation proctitis with fistula (arrow).

SECONDARY CANCERS

In addition to symptomatology that can have a detrimental effect on quality of life, pelvic radiation also carries an increased risk of the development of a second cancer. DNA changes, including diploid and aneuploid DNA, have been demonstrated in rectal tissue in both acute and chronic proctitis following radiation. Studies have reported a threefold higher risk of rectal cancer after radiation for pelvic malignancies, including cervical and prostate cancers.34,49,50 The relationship to radiation dosage is not clear, and it has been shown that rectal cancer can arise without clinical proctitis at the time of radiation therapy.51 Radiation for rectal cancer has also shown an increased risk of secondary cancers in adjacent organs, mostly commonly the prostate, colon, and urinary bladder, although overall the combined risk of either a rectal cancer recurrence or a secondary malignancy remains lower in radiated compared with nonradiated patients.52

Colorectal cancer, although rare following radiation therapy, may develop within the pelvis or in the perineum. A third of such patients may present with symptoms that are not related to the pelvic tumor, including pain, weight loss, and anemia.

Endoscopic examination should be performed to evaluate for internal or external skin and tissue changes such as dermatitis, ulceration, fistulae, or masses. Endoscopic evaluation, by either sigmoidoscopy or colonoscopy, with biopsies to allow for tissue diagnosis, is often the most useful initial investigation. The classic appearance of radiation proctitis is erythema, friability, and ulceration of the mucosa of the bowel wall as well as prominent telangiectasias. The spectrum of findings on endoscopy ranges from mild to severe and may include necrosis of tissues [see Figure 6, Figure 7, and Figure 8]. Colonoscopy may be more
challenging in postradiation patients owing to the relative immobility of the sigmoid colon secondary to fibrosis, luminal narrowing, and possible stricture formation. However, it is important to exclude more proximal sources of rectal bleeding such as colonic adenocarcinomas, diverticulae, or arteriovenous fistulae. Computed tomographic (CT) colonography, barium enemas, and cross-sectional imaging can be useful adjuncts to endoscopic imaging. Barium enema and CT colonography may reveal masses in the more proximal colon; there are also characteristic radiologic features suggestive of late radiation injury, including ulceration, stenosis, fistulae, decreased bowel distensibility, and intestinal fixation. These studies can be useful in demonstrating the extent of disease. Transrectal and endoanal ultrasonography has been used in the workup of rectal complications following pelvic radiation. Characteristic findings of radiation injury include thickening of the perirectal connective tissue, obscuring of the submucosal layer of the rectal wall, and scarring of the musculature. Anorectal physiology may be undertaken when symptoms are primary functional, such as fecal urgency and incontinence, and most often demonstrates decreased compliance associated with decreased first sensation volumes, lower resting anal canal pressures, and lower maximal tolerated rectal volumes.

SECONDARY TESTING

If first-line workup is either unrevealing or not consistent with radiation proctitis, the range of possible etiologies to explain a patient’s symptoms must be expanded. It is important to rule out cancer recurrence or the development of a secondary malignancy as the etiology of a patient’s symptoms, particularly if the symptoms are more constitutional and include significant weight loss. Cross-sectional imaging, such as CT or magnetic resonance imaging (MRI), is frequently used. CT may demonstrate acute radiation injury findings such as bowel wall edema and enhancement of the mucosa with contrast [see Figure 9]. Chronic changes of radiation injury to the pelvic structures include thickening and increased density of the perirectal fat, fascia, and rectal wall and fibrosis between the sacrum and rectum. Edema and enhancement of the mucosa are no longer present in the chronic phase of injury [see Figure 10]. MRI may demonstrate increased signal uptake indicative of inflammatory changes as well as a characteristic pattern of varying edema [see Figure 11]. However, both CT and MRI can fail to differentiate between postradiation changes and recurrent malignancy. Positron emission tomography (PET) is not considered to be first-line testing for colorectal cancer, but it has been shown to be more accurate in differentiating postradiation change from recurrent malignancy than other cross-sectional imaging modalities.
Figure 9  Helical computed tomography (CT) in the transverse (a) and sagittal (b) planes after intravenous administration of iodinated contrast shows an inflamed rectum (arrows), which has increased mucosal enhancement (star) as well as heterogeneous enhancement in the wall with fluid attenuation in the wall consistent with edema, indistinctness of the outer rectal wall, and edema in the perirectal fat (arrowheads), all consistent with acute proctitis.

If symptomatology is more suggestive of an upper gastrointestinal etiology, investigation of the remainder of the gastrointestinal tract may be carried out with upper endoscopies, small bowel contrast studies, or capsule endoscopies. If a satisfactory diagnosis to explain a patient’s symptoms cannot be established, it may be worthwhile to pursue workup of small bowel bacterial overgrowth and malabsorption syndromes with investigations such as glucose, xylose, lactulose, and hydrogen breath tests to evaluate for carbohydrate malabsorption and selenium-75 homocholic acid conjugated with taurine (SeHCAT) scanning to work up possible bile acid malabsorption.

Medical Therapy

PHARMACOLOGIC THERAPIES

Medical therapy is the first line of treatment for radiation injury. The pathology of radiation-induced injury is not an inflammatory one; however, historically, treatments were aimed at...
significant reduction in rectal bleeding, an improvement in endoscopic scores, and an increase in hemoglobin values when compared with placebo in small, randomized trials.68,69 Other similar studies, however, failed to demonstrate this difference.45

nutritional strategies
Although nutritional support is certainly important when treating patients with radiation injury, previously studied specific diets such as elemental or exclusionary diets have failed to demonstrate clinical efficacy.9 The strategy of “bowel rest” by using parenteral nutrition has also been explored to treat radiation enteritis and has been shown to improve nitrogen balance and clinical parameters compared with patients receiving an elemental feeding.70 Bowel rest and parenteral nutrition have also been studied as an alternative to immediate surgery for patients with radiation enteritis–associated bowel obstruction. Some studies have demonstrated resolution of intestinal obstruction and equivocal or improved overall survival with this strategy, although others have shown higher rates of clinical recurrence with bowel rest and parenteral nutrition when compared with patients who had surgery.71–73

hyperbaric oxygen therapy
If medical therapies fail to control the symptoms of radiation therapy, hyperbaric oxygen therapy can be considered for the treatment of ongoing, chronic symptoms.1 Hyperbaric oxygen therapy acts by promoting neangiogenesis and revascularization. There is a significant ischemic component to the disease pathology leading to radiation toxicity,

Figure 11   Magnetic resonance imaging (MRI) of the pelvis with transverse T2-weighted images with fat suppression (STIR) (a) and transverse T1-weighted, fat–suppressed, contrast-enhanced images after administration of a gadolinium-based contrast agent (b). The inflamed rectum (arrows) has increased signal intensity on the T2-weighted images (in b) in the mucosa more than the wall consistent with edema as well as increased mucosal enhancement (in b). As on computed tomography, there is indistinctness of the outer rectal wall and edema in the perirectal fat (arrowheads), both consistent with acute proctitis. Extensive anterior subcutaneous and muscular edema are seen, which are changes from radiation toxicity.

Figure 11   Magnetic resonance imaging (MRI) of the pelvis with transverse T2-weighted images with fat suppression (STIR) (a) and transverse T1-weighted, fat–suppressed, contrast-enhanced images after administration of a gadolinium-based contrast agent (b). The inflamed rectum (arrows) has increased signal intensity on the T2-weighted images (in b) in the mucosa more than the wall consistent with edema as well as increased mucosal enhancement (in b). As on computed tomography, there is indistinctness of the outer rectal wall and edema in the perirectal fat (arrowheads), both consistent with acute proctitis. Extensive anterior subcutaneous and muscular edema are seen, which are changes from radiation toxicity.

reducing inflammation, perhaps because of the misleading term proctitis. With this concept in mind, therapies such as steroids and mesalazine have previously been proposed as first-line therapies.63 A systematic review of both randomized and nonrandomized prospective trials suggest that these therapies are of little benefit to patients.64 Other therapies that have been investigated include pentoxifylline, tocopherol, vitamin E, thalidomide, probiotics, and rebamipide. Studies to date have failed to convincingly demonstrate a clinical benefit of these therapies, although future studies may be warranted.59 Antimotility agents such as loperamide or codeine phosphate may be transiently useful for symptomatic relief of diarrhea but do not treat the underlying pathology and are unlikely to provide a sustained effect.7 If stools are difficult to pass or patients have chronic constipation, however, stool softeners may help minimize trauma to friable gastrointestinal mucosa.

Pharmacologic therapies that have demonstrated clinical benefit in randomized trials include metronidazole, sucralfate enemas, vitamin A, and short-chain fatty acid enemas [see Table 5]. Metronidazole is an antibiotic that kills primarily anaerobic bacteria. A randomized trial found that 4 weeks of therapy with oral metronidazole in combination with oral mesalazine and betamethasone enema decreased rectal bleeding, mucosal ulcers, diarrhea, and edema for up to 12 months after treatment when compared with treatment with mesalazine and betamethasone alone.65 Sucralfate is a sucrose sulfate–aluminum complex that has shown a better clinical response in a small randomized trial when administered as an enema twice daily over 4 weeks when compared with patients receiving oral sulfasalazine in combination with rectal prednisolone, although a difference in endoscopic improvement was not demonstrated.66 Vitamin A has been shown to be beneficial for wound healing, and in one small, randomized trial, oral therapy demonstrated a statistically significant reduction in symptoms of radiation proctopathy compared with placebo.67 Short-chain fatty acid therapies, primarily using butyrate, have shown a
injury, and the high oxygen pressure leads to the maturation of telangiectasias and has been shown to increase the vascular density of soft tissues several-fold. It also reduces damage secondary to free radicals, stimulates tissue regeneration, and decreases fibrosis to improve the compliance of the bowel. The successful use of this therapy for treatment of radiation injury, specifically the treatment of severe hemorrhage secondary to radiation colitis, was reported in 1993. For a time, all the evidence supporting the use of this therapy was derived from impressive results from case series, such as an early report from 1997 of 14 patients treated in 100% oxygen at two atmospheres. Eight patients experienced complete resolution of symptoms, and another reported substantial improvement. Larger case series followed and also showed promising results, such as the 2007 report of 65 patients with chronic radiation enteritis who were treated with hyperbaric oxygen. An overall response was demonstrated in 68% of patients, and 43% showed a complete response. In 2008, a randomized controlled trial treated 150 patients with radiation proctitis refractory to other therapies with either hyperbaric oxygen treatment at 2.0 atmospheres absolute or sham treatment with air at 1.1 atmospheres absolute for 30 to 40 sessions. Hyperbaric oxygen therapy led to a significant improvement in patients’ radiation proctitis as graded by the LENT-SOMA scoring system, an improvement in quality of life, and an overall 32% absolute risk reduction between the groups with a number needed to treat of 3. Hyperbaric oxygen is a safe, well-tolerated, noninvasive therapy that also offers the advantages of possibly reversing progressive changes and improving associated urinary problems. The disadvantages of hyperbaric oxygen therapy are the significant time commitment, as it can constitute up to 8 weeks of daily 90-minute treatment sessions; the limited availability, as it is only offered in specialized centers; and its significant expense. Additionally, the claustrophobic effect can be difficult for some patients, and potential side effects include otic barotrauma and transient myopia, although these tend to be mild and transient.

**Endoscopic Therapy**

If medical management fails, endoscopic therapy should be suggested to address acute or clinically significant bleeding or in the case of unavailability of hyperbaric oxygen therapy. Endoscopic therapy is especially useful in controlling hemorrhage secondary to telangiectasias as opposed to bleeding secondary to diffuse proctitis [see Figure 12]. There are several possible modalities, all of which are invasive and have the potential for serious procedure-related complications and side effects. These risks should be thoroughly discussed with the patient, and experienced practitioners should carry out endoscopic therapy with caution.

**THERMAL COAGULATION**

Thermal coagulation is one of the most common modalities used and encompasses the use of argon plasma, laser coagulation, and bipolar probes. The common therapeutic benefit is the destruction of bleeding vessels, but the effect can also extend into the mucosa and submucosa, which can damage these already ischemic tissues and led to subsequent

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**Table 5** Pharmacologic Therapies that Have Demonstrated Clinical Benefit in Randomized Trials

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Study</th>
<th>Administration</th>
<th>Duration of Treatment</th>
<th>Follow-Up</th>
<th>Study (n)</th>
<th>Treatment Groups</th>
<th>Statistically Significant Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole</td>
<td>Cavcic et al&lt;sup&gt;45&lt;/sup&gt;</td>
<td>Oral</td>
<td>4 weeks</td>
<td>12 months</td>
<td>60</td>
<td>Oral metronidazole plus oral 5-ASA and betamethasone enema versus identical 5-ASA and betamethasone treatment without metronidazole</td>
<td>Reduction in the incidence of rectal bleeding and mucosal ulcers; decreased diarrhea and edema</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Kochhar et al&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Enema</td>
<td>4 weeks</td>
<td>4 weeks</td>
<td>37</td>
<td>Oral sulfasalazine with prednisolone enemas versus sulfone enemas and oral placebo</td>
<td>Improved clinical response</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Ehrenpreis et al&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Oral</td>
<td>90 days</td>
<td>90 days</td>
<td>19</td>
<td>Oral retinol palmitate versus placebo</td>
<td>Reduction of rectal symptoms as measured by the Radiation Proctopathy System Assessments Scale</td>
</tr>
<tr>
<td>Short-chain fatty acids</td>
<td>Pinto et al&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Enema</td>
<td>5 weeks</td>
<td>6 months</td>
<td>19</td>
<td>Short-chain fatty acid enemas versus placebo</td>
<td>Decrease in number of days of rectal bleeding; improved endoscopic score; higher hemoglobin values; remission of clinical symptoms</td>
</tr>
<tr>
<td></td>
<td>Vernia et al&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Enema</td>
<td>3 weeks</td>
<td>3 weeks</td>
<td>20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>5-ASA = 5-aminosalicylic acid (mesalazine). </sup>
Ulceration in up to 50% of patients in one study.\textsuperscript{79} Ulcerations do have the potential to cause pain, to inhibit healing, and to lead to stricturing that can affect bowel function. Other potential side effects include worsened bleeding, bloating, cramping, tenesmus, fistulae formation, and perforation. The reported efficacy is high, however, at between 76 and 100%, and it is a widely used therapy.\textsuperscript{78}

Bipolar diathermy places two electrodes across a mucosal bleeding point and uses the tissue as a conductor. It has been successfully used, but its continuous use is impeded by char formation on the tips of the electrodes.\textsuperscript{80} Argon plasma coagulation (APC) avoids this issue by avoiding physical contact between the electrode and the patient. It is the most widely used thermal coagulation technique and is generally considered the safest and the cheapest.\textsuperscript{1} It coagulates to a depth of 0.5 to 3 mm and generally requires two or three treatments for maximum benefit [see Figure 13]. Adverse effects occur in up to 18% of patients and tend to be mild. In addition to improving rectal bleeding, patients can also experience improvement in other symptoms, including urgency and diarrhea.\textsuperscript{2} Laser therapy, generally with a neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, is another option for endoscopic coagulation but is infrequently used because of the greater cost and safety risk, especially in terms of ocular hazards, when compared with APC.\textsuperscript{2}

**FORMALIN APPLICATION**

The application of 4 to 10% formalin solution to the bowel mucosa causes cauterization of newly formed blood vessels to prevent further bleeding. Reported efficacy varies between 48 and 100%, and similar to thermal coagulation, it can cause pain, ulceration, stricturing, and perforation, as well as formalin-associated colitis and serum sickness.\textsuperscript{78,81} One small randomized trial comparing APC and topical formalin treatment demonstrated comparable efficacy in controlling rectal bleeding following radiation for prostate cancer.\textsuperscript{80} Although there are other options for the application of formalin, such as enemas, application via endoscopy or transanal examination under anesthesia is less likely to cause burns.\textsuperscript{2}

**CRYOABLATION**

Endoscopic cryoablation is a newer technique with an efficacy of 70 to 100% reported in pilot studies.\textsuperscript{76} Observed therapeutic effects include clinical improvement as measured by the Radiation Proctitis Severity Assessment Scale (RPSAS) and decreased density of rectal telangiectasias.\textsuperscript{83} Side effects include rectal ulceration as well as perforation. Cryoablation is not yet widely used and is still being investigated.

**RADIOFREQUENCY ABLATION**

Endoscopic radiofrequency ablation (RFA) for the treatment of radiation injury is being explored in the context of clinical trials. Previous studies have demonstrated its efficacy for mucosal ablation of the esophagus, and case reports and small case series have reported efficacy in the treatment of chronic radiation proctitis by way of reepithelialization of squamous mucosa over areas of hemorrhage without any adverse side effects observed.\textsuperscript{84-86} Although this technique is promising, more studies are needed before it can be widely recommended.

**Surgical Therapy**

Surgical management of this patient population is very high risk, and even when carried out at specialized tertiary or quaternary care centers, operative morbidity and mortality are significant. Surgery
should be considered only in patients who are reasonably fit and have a realistic life expectancy. The most common operative complications include anastomotic leakage, if an anastomosis is created, and fistula formation. Complications occur in up to 30% of patients, and between 40 and 60% will require multiple laparotomies for management. Subsequent intestinal failure can result, which leads to in-hospital death in up to one third of patients. Indications for surgery include the failure of all other therapies to control symptoms such as bleeding or incontinence; septic complications resulting from perforation, abscesses, or fistulae; and bowel obstruction caused by stricture that cannot be treated with conservative management.

Surgical Strategies

The simplest, and often the most desirable, surgical option is diversion without resection, which can avoid complications such as hemorrhage and fistulae formation that may occur if more extensive dissection is required in fibrotic, irradiated tissues. This may not effectively treat symptoms such as bleeding and discharge, however, as the source of these symptoms remains in place. When the stoma is formed, irradiated tissue should be avoided, which may require the use of the transverse colon or ileum rather than the sigmoid or left colon. Loop stomas or mucous fistulae may be used to avoid the risk of a stump blowout. If a stoma is being created as a temporizing measure until a future resection, it may be preferable to use the small bowel to avoid interruption of the colon’s blood supply. Attempts at resection should only be considered for the management of severe and life-threatening bleeding that is refractory to other therapies or for the treatment of perforation, fistulae, or severe strictures. Options for resection include the Parks procedure, which entails resection of the mucosa and anastomosis of the colon to the dentate line inside the rectum, as described by Allen-Mersh and colleagues, and the use of colonic J pouches or ileocolic reservoirs, as described by von Flue and colleagues.

Summary

Radiation therapy is indispensable for improving survival in a variety of pelvic cancers. Radiation injury is an unfortunate consequence that can have a detrimental effect on patients’ quality of life. Consideration should be given to prophylactic therapy prior to radiation, particularly in those who are high risk. Bleeding is the most common manifestation of this disease, and persistent or severe symptoms mandate appropriate workup. Treatment should start with first-line pharmacologic options and then progress to hyperbaric or endoscopic therapies as appropriate. Surgical intervention is high risk and should be avoided whenever possible.

References


