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Injury to the rectum from irradiation, seen on endoscopic examination.

Radiotherapy side effects: Understanding pelvic radiation disease

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As many as 50% of patients undergoing pelvic radiation therapy define their quality of life as degraded due to subsequent chronic changes to their bowel function, such as diarrhea or fecal incontinence.¹⁻³ These late effects are common—in some cases, even life-threatening—and clearly significant for patients. But frequently, they go clinically undetected or remain untreated.¹⁻³

This lack of posttreatment symptom management is due, in part, to a

widespread use of symptoms-driven diagnoses (eg, chronic proctitis, enteritis, cystitis) rather than making a cause-describing diagnosis.^{1,4} Persistent inflammation rarely underlies late radiation toxicities, leading some researchers to reject the use of terms denoting inflammatory conditions to describe late radiotherapy-associated toxicities.⁴

EVOLVING CLINICAL PERCEPTION

Radiotherapy-associated chronic toxicity is frequently seen as an assemblage of indistinct complaints or symptoms, rather than a definable disease. Its effects are “rarely accurately measured or fully appreciated,” reported an international team of researchers led by H. Jervoise N. Andreyev, PhD.⁴ Late toxicities can be difficult to differentiate from other disorders. For example, symptom-based (eg, rectal bleeding) toxicity checklists or scales do not measure the duration of symptoms, which is an important consideration when attributing symptoms to prior radiotherapy (eg, rectal bleeding is attributable to radiotherapy only if the anterior rectal wall was irradiated; in up to 33% of cases, postradiotherapy rectal bleeding is due to causes other than the radiotherapy).⁴

Treatment success is typically defined in terms of tumor control or eradication, rather than the long-term well-being of the patient.⁵ However, chronic toxicities can arise months or even years after radiotherapy is completed, so oncology treatment teams may never become aware of them, and other clinicians may not attribute them to a history of pelvic radiotherapy.¹

Experts have made a concerted effort to move away from describing chronic pelvic radiotherapy-associated toxicities as individual symptoms, recognizing them instead as manifestations of a single phenomenon referred to

as *pelvic radiation disease*.⁴ Andreyev’s team defined pelvic radiation disease as transient or longer-term problems, ranging from mild to very severe, that arise in noncancerous tissues as a result of radiation treatments to tumors of pelvic origin.⁴

DIVERSE SYMPTOMS

The development of new symptoms affecting the bowel, urinary tract, sex organs, bones, or skin during or after radiotherapy may be pelvic radiation disease, note Andreyev and colleagues.⁶ Postradiotherapy rectal bleeding should prompt assessment of other potential manifestations of pelvic radiation disease, such as urinary or fecal incontinence.

The molecular and physiologic mechanisms leading to pelvic radiation disease are complex, and symptoms related to gastrointestinal and urinary tract dysfunction can be diverse, frequently arising from separate lesions within different parts of the GI tract.^{1,4}

Diabetes nearly doubles the risk of disease 5 years after radiotherapy.

Radiotherapy can cause ulceration, acute inflammation, cell death, and edema in healthy nontarget tissues, which can be investigated with flexible rectosigmoidoscopy.⁶ These injuries can also lead to chronic ischemia and fibrosis, which are predominantly submucosal changes.⁶

Objective clinical findings do not always match patient-reported symptoms.^{1,4} Symptoms can include such

problems as anal ulceration and bleeding, bloating and constipation, fatigue and lethargy, flatulence, hemorrhoids, insomnia, mucus discharge or steatorrhea (elevated levels of fat in feces caused by diminished intestinal absorption), nausea, abdominal or anal pain, and even the loss of a sense of taste.¹ Late rectal bleeding appears to be a direct, dose-dependent side effect of radiation therapy, whereas other chronic toxicities of the urinary tract and intestinal mucosa, including incontinence, appear to be long-term exacerbations of acute toxicities (sometimes referred to as *consequential late effects*) and are independent of radiation dose.⁴ Bowel obstruction, fistulas, and secondary cancers triggered by radiation to nontarget tissues represent potentially life-threatening late toxicities stemming from pelvic radiotherapy.¹

The evidence base for pelvic radiation disease risks and treatments remains limited; few clinical trials or prospective studies of pelvic radiotherapy have been published.^{1,3} Irradiation of nontarget, healthy tissues ultimately underlies pelvic radiation disease; however, total and per-fraction radiation doses, the volume of irradiated tissues, and concomitant administration of chemotherapy or biologic agents all appear to modulate risk.⁶

RISK ASSESSMENT

Few data are yet available about how widespread use of radiotherapeutic modalities with improved targeting, such as intensity-modulated radiotherapy (IMRT), will affect the incidence of pelvic radiation disease.⁴ Early data suggest IMRT and 3D conformal radiotherapy are associated with late GI toxicity rates of 6% and 15%, respectively, among patients treated for prostate cancer; 3.6% and 3.0%, respectively, among patients treated for cervical cancer; 7% and 3%, respectively, among patients treated for anal tumors; and

9.5% and 20%, respectively, among rectal cancer patients also undergoing neoadjuvant chemotherapy.⁶ In general, chemoradiotherapy and radiation dose intensification can improve tumor control rates, but these also increase the risk of acute and chronic toxicities.⁴

Comorbidities and other patient factors also modulate risk. For example, diabetes nearly doubles the risk of pelvic radiation disease 5 years after radiotherapy.⁶ Tobacco use, inflammatory bowel disease, scleroderma, or a history of pelvic or abdominal surgery also appear to increase the risk of pelvic radiation disease.⁶

Patients should be educated that these effects may mimic other disorders.

Detecting late toxicities following pelvic radiotherapy traditionally depends primarily on patients completing symptoms-based questionnaires, but these tools are problematic for several reasons.¹ Questionnaire-based assessments cannot reliably distinguish symptoms that are radiotherapy-associated chronic toxicities from symptoms with other causes.¹ Patients' definitions of symptoms such as diarrhea can vary, as well; furthermore, patients sometimes deny stigmatizing conditions such as fecal incontinence. Patients should be educated before radiotherapy is undertaken and after its completion about the risks of late toxicity and that these effects may mimic other disorders.

"Patients may not be their own best advocates," cautions Andreyev.¹ They may deny symptoms they have taken drastic measures to prevent to avoid social embarrassment. For example,

patients experiencing debilitating urgency of defecation may prevent fecal incontinence by never leaving the house; thus staying, at most, only a few seconds away from the bathroom, or not eating for many hours before they go out.

MANAGEMENT

Symptom management is based on gastroenterologic assessments and nurse-led patient needs assessments. Some patients may need a referral to a urology or gastroenterology specialist, hyperbaric oxygen services, a pain management team, or psychological support.¹

In cases of extreme bowel obstruction, surgery may be necessary despite the fact that fibrotic scarring leaves patients with pelvic radiation disease at higher risk of complications from surgery.⁶ Endoscopic thermal coagulation therapy using argon plasma, laser, or heater probe can reduce pelvic radiation disease-associated bleeding; however, these treatments may cause pain, strictures, fistula, and perforation.⁶ Endoscopic formalin or cryoablation are also frequently used for bleeding, but these too have a risk of perforation, rectal ulcers, and pain.⁶

The term *radiation proctitis* implies that late pelvic radiotherapy toxicities are driven by inflammation, and this sometimes leads to inappropriate treatments with corticosteroids or other antiinflammatory agents, such as 5-aminosalicylic acids.⁶ These drugs do not offer any benefits to patients with pelvic radiation disease, according to a 2002 systematic review of clinical trial data.⁷

Opiate antagonists can reduce diarrhea in these patients and bleeding can be ameliorated with a 4-week course of oral metronidazole or sucralfate enema treatments.^{1,6} Fecal incontinence can be more challenging, although there is limited evidence that phenylephrine gel may help. One very small prospective, controlled study of 19 patients

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found that fecal incontinence declined among patients who received oral vitamin A (retinol palmitate, 10,000 IU/d for 90 days).^{1,6,8} ■

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