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Radiotherapy side effects: integrating a survivorship clinical lens to better serve patients

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ABSTRACT

The Canadian Cancer Society estimated that 220,400 new cases of cancer would be diagnosed in 2019. Of the affected patients, more than 60% will survive for 5 years or longer after their cancer diagnosis. Furthermore, nearly 40% will receive at least 1 course of radiotherapy (RT). Radiotherapy is used with both curative and palliative intent: to treat early-stage or locally advanced tumours (curative) and for symptom management in advanced disease (palliative). It can be delivered systemically (external-beam RT) or internally (brachytherapy).

Although technique improvements have drastically reduced the occurrence of RT-related toxicity, most patients still experience burdensome RT side effects (sEFFs). Radiotherapy sEFFs are local or locoregional, and manifest in tissues or organs that were irradiated. Side effects manifesting within weeks after RT completion are termed "early sEFFs," and those occurring months or years after treatment are termed "late sEFFs."

In addition to radiation oncologists, general practitioners in oncology and primary care providers are involved in survivorship care and management of RT sEFFs. Here, we present an overview of common sEFFs and their respective management: anxiety, depression, fatigue, and effects related to the head-and-neck, thoracic, and pelvic treatment sites.

Key Words Survivorship, radiotherapy, side effects, general practitioners in oncology, primary care providers

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INTRODUCTION

The Canadian Cancer Society estimated that 220,400 new cases of cancer would be diagnosed in 2019. Of the affected patients, more than 60% will survive for 5 years or longer after their cancer diagnosis[1]. Furthermore, nearly 40% of cancer patients receive at least 1 course of radiotherapy (RT)[2]. Radiotherapy is used with both curative and palliative intent: to treat early-stage or locally advanced tumours (curative) and for symptom management in advanced disease (palliative).

Although technique improvements have drastically reduced RT-related toxicity[3], most patients still experience burdensome RT side effects (sEFFs)[4]. Radiotherapy sEFFs are local or locoregional, and manifest in tissues or organs that were irradiated. Side effects manifesting during or within weeks after RT completion are termed "early sEFFs," and those occurring months or years after treatment are termed "late sEFFs"[4].

In addition to radiation oncologists, general practitioners in oncology and primary care providers are involved in survivorship care[5], including the management of RT-induced sEFFs. Here, we present an overview of common sEFFs and their respective management: anxiety, depression, fatigue, and effects related to the head-and-neck (HN), thoracic, and pelvic treatment sites.

SIDE EFFECTS AND THEIR MANAGEMENT

Distress, Anxiety, and Depression

Studies have shown an increase in distress, anxiety, and depression in patients undergoing radiation[6,7]. Although such problems tend to decrease upon RT completion, a significant number of patients still manifest psychological

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effects after treatment[7]. Patients with pancreatic cancer and lung cancer appear particularly vulnerable, higher rates of depression being associated with those diagnoses[8]. Radiotherapy-induced hypothyroidism, especially in patients with HN cancer, and secondary vitamin B_{12} malabsorption can contribute to psychological findings and should be ruled out[8].

Regardless of stage of diagnosis or treatment intent, depression and anxiety affect approximately 20% and 10% of patients respectively[9], but underrepresentation is a concern, given the lack of standardized distress screening programs across Canada[10]. Current guidelines therefore recommend that all patients be screened for distress at their initial post-treatment visit and at regular intervals thereafter, using validated tools such as the revised Edmonton Symptom Assessment System, the Distress Thermometer, or the Patient Health Questionnaire-2[10]. Screening should include an assessment of psychosocial needs and fear of recurrence, with referrals to appropriate resources being promptly made as required[10]. In patients diagnosed with depression, a multidisciplinary approach including both nonpharmacologic and pharmacologic interventions is encouraged[11].

Fatigue

Cancer-related fatigue is defined as "a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning"[12].

Patients often describe fatigue as one of the most distressing adverse effects of treatment[12]. Regardless of treatment site, RT has been reported to cause acute fatigue in up to 80% of patients, and chronic fatigue can persist in up to 30% for months to years after treatment[13]. The cause for persistent fatigue is likely multifactorial, but it has been suggested potentially to be secondary to persistent immune system activation or to late effects on major organ systems[14]. Guidelines recommend screening for cancer-related fatigue in all patients and taking prompt action for potential contributing factors such as anemia, pain, and cardiac or endocrine dysfunction[12]. Nonpharmacologic and pharmacologic treatments might aid in the management of cancer-related fatigue (Table I).

TABLE I Management strategies for cancer-related fatigue

Strategy	Application
Nonpharmacologic	• Physical exercise[12,15] • Yoga[16,17] • Cognitive behavioural therapy, mindfulness-based stress reduction techniques, educational therapies, supportive expressive therapies[12,18] • Acupuncture[19]
Pharmacologic	• Methylphenidate for fatigue that is refractory to nonpharmacologic interventions[12] • Modafinil not recommended[12]

Effects of HN RT

Approximately 80% of patients with HN cancer will receive at least 1 course of RT as part of their treatment[20]. A frequent early sEFF of HN RT is oral mucositis: acute inflammation or ulceration, or both, of the oral or oropharyngeal mucosal membranes. Oral mucositis can cause pain and negatively affect capacity to swallow, eat, and speak, which can be very distressing to patients[21]. Oral mucositis is graded on a scale of 1–4 based on severity; Table II summarizes its management[22].

Other common sEFFs of HN RT include alterations of taste, dysphagia, xerostomia, and hypothyroidism. The latter condition should be recognized because thyroid hormone can readily be replaced. Screening for thyroid dysfunction based on thyroid stimulating hormone levels should be performed every 6–12 months after RT[23].

Alterations of taste occur in more than 70% of patients[24]. Taste dysfunction can be partial or complete, and typically occurs 4–5 weeks after RT start[25]. Taste recovery can occur as early as 1 month after RT, and most survivors experience a complete return of taste 6–12 months after RT[26].

The risk of dysphagia in patients with HN cancer who receive RT is high, and its occurrence can negatively affect quality of life[27]. Radiotherapy-induced fibrosis can impair the swallowing musculature[28] and could lead to nutritional intake through enteral feeding. Radiotherapy-induced fibrosis is dose- and site-dependent[28], and concomitant chemotherapy can further affect swallowing[29]. The mainstay of management is behavioural swallowing interventions with exercise aids provided by speech–language pathologists[30]. Thus, early referral to a speech–language pathologist is warranted; interventions can be performed to prevent dysphagia onset (before or during treatment) or to minimize existing dysphagia (after treatment)[31]. For persistent and debilitating dysphagia, referral to an experienced gastroenterologist for endoscopic dilatation might be beneficial[31].

Lastly, xerostomia results from salivary gland dysfunction causing hyposalivation and is associated with swallowing, speech, and oral health problems[20]. Despite technique advancements such as intensity-modulated RT, approximately 40% of patients still experience burdensome xerostomia[20]. Increasing existing salivary flow (or replacing lost salivary secretions) and maintaining oral health (including treating dental caries and possible infections) are the mainstays of management[32]. After RT, dental visits are recommended at least once every 6 months[23]. Treatment options depend on the presence or absence of residual gland function. If gland function remains, mechanical gland stimulation with sugar-containing gums or xylitol- or sorbitol-containing candy can be attempted[32,33]. Salivary flow can also be stimulated by cholinergic medications such as pilocarpine at a recommended dose of 5 mg 3 times daily[32,33]. In the absence of gland function or upon saliva stimulation failure, mouthwashes and saliva substitutes can be used[33].

Notably, HN RT is also associated with other late sEFFs, including lymphedema and carotid artery stenosis (CAS). Lymphedema presents as local swelling because of damage to the lymphatic system, which can affect swallowing, speaking, and body image. Lymphedema management

TABLE II Clinical practice guidelines for oral mucositis[a]

Recommendations[b]	Suggestions[c]
• The panel recommends that benzydamine mouthwash be used to prevent oral mucositis in patients with head-and-neck cancer receiving moderate-dose radiation therapy (up to 50 Gy), without concomitant chemotherapy (I).	• The panel suggests that oral care protocols be used to prevent oral mucositis in all age groups and across all cancer treatment modalities (III).
• The panel recommends that sucralfate mouthwash not be used to prevent oral mucositis in patients receiving chemotherapy for cancer (I) or in patients receiving radiation therapy (I) or concomitant chemoradiation (II) for head-and-neck cancer.	• The panel suggests that 2% morphine mouthwash might be effective to treat pain from oral mucositis in patients receiving chemoradiation for head-and-neck cancer (III).
• The panel recommends that sucralfate mouthwash not be used to treat oral mucositis in patients receiving chemotherapy for cancer (I) or in patients receiving radiation therapy (II) for head-and-neck cancer.	• The panel suggests that 0.5% doxepin mouthwash might be effective to treat pain from oral mucositis (IV).
	• The panel suggests that systemic zinc supplements administered orally might be of benefit to prevent oral mucositis in patients with oral cancer receiving radiation therapy or chemoradiation (III).
	• The panel suggests that chlorhexidine mouthwash not be used to prevent oral mucositis in patients receiving radiation therapy for head-and-neck cancer (III).
	• The panel suggests that misoprostol mouthwash not be used to prevent oral mucositis in patients receiving radiation therapy for head-and-neck cancer (III).

I = high-power studies; II = low-power studies; III = nonrandomized or case–control studies; IV = descriptive and case studies; V = case-report evidence or clinical examples.

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[b] Based on level I or II evidence.
[c] Based on level III, IV, or V evidence, with panel consensus about the interpretation of such evidence.

includes lymph drainage and use of compression garments: referral to a certified lymphedema therapist is recommended[22]. If CAS occurs after HN RT, the risk for cerebrovascular disease increases. The risk appears greater in patients with other CAS risk factors, including smoking, dyslipidemia, diabetes, and coronary and peripheral artery disease[34]. In addition to carotid artery surveillance, screening and optimal management of CAS comorbid conditions are therefore recommended[34].

Effects of Thoracic RT

Common effects of thoracic RT include radiation-induced lung injury (RILI) and radiation-induced heart disease. Radiation-induced lung injury is a known complication in patients with lung, breast, esophageal, thymic, and hematologic malignancies who have undergone thoracic RT[35]. It affects 5%–20% of patients and can lead to dyspnea and chronic lung fibrosis, which can negatively affect quality of life[36].

Radiation-induced lung injury consists of an acute inflammatory phase, defined as radiation pneumonitis (1–3 months after RT), and a chronic fibrotic phase, also known as radiation fibrosis (6–24 months after RT)[37]. Although most patients receiving thoracic RT are at risk of developing RILI, certain factors such as smoking history, chronic obstructive pulmonary disease, and interstitial lung disease might increase the risk[35,36]. Older age and selected chemotherapies, immunotherapies, and targeted therapies also predispose patients to a higher risk of radiation recall pneumonitis. "Radiation recall" is a phenomenon in which patients develop pneumonitis after active RT treatments have been completed[35]. Radiation pneumonitis often presents with dyspnea, dry cough, and sometimes fever. A physical exam could be normal, but rare signs include pleural friction rub and rales[37]. Given those nonspecific findings, RILI must always be included in the differential diagnosis for these patients. Although investigations can guide its identification, radiation pneumonitis is a clinical diagnosis: treatment includes steroids in symptomatic patients[37]. Figure 1 summarizes RILI assessment and management.

Radiation-induced heart disease can present years after RT completion and can manifest as valvular disease, pericardial disease, coronary artery disease, cardiomyopathy, or conduction abnormalities[38]. Although RT dose is the most significant risk factor, other traditional cardiovascular disease risk factors such as diabetes, hypertension, obesity, and smoking increase the risk[39]. Survivors should have an annual physician visit and scheduled screening for radiation-induced heart disease, together with targeted symptom investigation. Promotion of healthy lifestyle habits—including diet, regular exercise, weight control, and abstinence from smoking—are of utmost importance[40]. Moreover, a baseline echocardiogram 6–12 months after RT should be considered for high-risk survivors[40]. Lastly, adult survivors of childhood cancers should also receive periodic evaluation for cardiac toxicity and cardiology referral, typically 5–10 years after RT, especially for survivors exposed to a 35 Gy dose to the chest (or at least 15 Gy if they also received an anthracycline)[41].

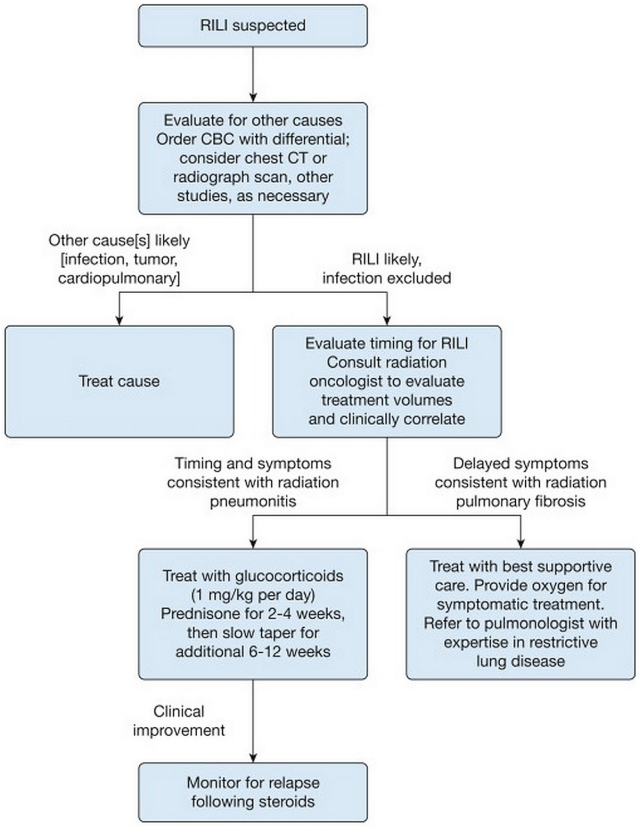

FIGURE 1 Clinical algorithm for the assessment and management of radiation-induced lung injury (RILI). Suspicion of RILI should be raised when a patient's physical examination findings correlate temporally (typically within 3 months) with completion of thoracic radiation. CBC = complete blood count; CT = computed tomography. Reprinted with permission (Elsevier) from Hanania *et al.*[35].

Effects of Pelvic RT

Compared with other cancer sites, pelvic cancers more frequently involve treatment with RT. Pelvic RT can lead to gastrointestinal toxicity, sexual dysfunction, and fertility concerns.

Pelvic radiation disease (PRD) is defined as mild-to-severe transient or long-term gastrointestinal symptoms secondary to RT of a pelvic tumour. Patients have reported PRD to have the greatest adverse effect on their quality of life[42]. Patients can present with up to 22 gastrointestinal symptoms, and given that each symptom can have more than one cause, symptoms should be investigated systematically[43]. Frequent SEFFs of pelvic RT are diarrhea, rectal bleeding, urgency, and fecal incontinence, all reported in up to 50% of patients[42,44]. In addition to pelvic RT, patient-related risk factors for PRD include diabetes, inflammatory bowel disease, collagen vascular disease, low body mass index, and smoking[45]. Table III summarizes the proposed work-up and management for gastrointestinal symptoms linked to PRD. Other pharmacologic (aminosalicylates, sucralfate, amifostine, corticosteroid enemas, bile acid sequestrants, famotidine, and selenium) and nonpharmacologic interventions (dietary modifications, green tea tablets, glutamine) currently have lower-certainty evidence of potential benefit[46].

Sexual dysfunction after pelvic RT is typically multifactorial and negatively affects patients[47]. In men, erectile dysfunction is a common late SEFF, being reported in up to 50% of patients at 5 years after RT[48]. Bladder and bowel dysfunction can also occur and lead to decreased intimacy and self-esteem[49]. Phosphodiesterase type 5 inhibitors, such as sildenafil and tadalafil, have been described as effective to treat RT-associated erectile dysfunction and should be considered for first-line treatment[47,49,50]. In women, SEFFs related to pelvic RT include vaginal dryness

TABLE III Common gastrointestinal symptoms and management[a]

Symptom	Investigations	Potential results	Management	Alternative diagnoses
Rectal bleeding	Complete blood count, coagulation profile, referral for flexible sigmoidoscopy	Radiation proctopathy with bleeding from telangiectasia	■ Optimize bowel function and stool consistency ■ Consider referral to a specialist for telangiectasia ablation if affecting quality of life	Hemorrhoids, primary inflammatory bowel disease, diverticular bleeding, new neoplasm
Bloating or abdominal cramps	Dietary history with or without test for carbohydrate malabsorption with or without biliary tree ultrasonography	Carbohydrate intolerance, irritable bowel disease, gallstones	■ Treat underlying ■ Referral to a gastroenterologist as clinically appropriate	Tumour recurrence
Diarrhea	Dietary and lifestyle assessment, medication review, referral for flexible sigmoidoscopy	Radiation proctopathy or colopathy and pelvic floor dysfunction	■ Antidiarrheals, stool bulking agents, pelvic floor and toileting exercises	Infectious causes, celiac disease, dietary causes, drug-induced causes
Fecal incontinence	Rectal exam, referral for flexible sigmoidoscopy	Pelvic floor dysfunction with radiation proctopathy and fecal incontinence or leakage	■ Pelvic floor strengthening exercises, stool bulking agents, consider referral to specialist for sphincter repair	Constipation with overflow diarrhea, previous sphincter surgery, childbirth
Tenesmus	Referral for flexible sigmoidoscopy	Radiation proctopathy	■ Pelvic floor strengthening exercises, stool bulking agents	New neoplasm, irritable bowel disease, anterior resection syndrome

[a] Adapted with permission from: Andreyev *et al.*[43] (https://creativecommons.org/licenses/by-nc/3.0/legalcode).

and stenosis, decreased sexual interest, and dyspareunia[49]. Vaginal dilators can help to improve vaginal elasticity and reduce fibrosis: their use has been associated with lesser rates of self-reported vaginal stenosis[51]. Experts recommend starting dilation 4 weeks after RT, at a frequency of 2–3 times weekly (1–3 minutes) for 9–12 months[52]. Referral to a trained physiotherapist for pelvic physiotherapy and education might facilitate dilator use and progress monitoring. Vaginal morbidity should be assessed before treatment, once every 3 months for the first 2 years after treatment, and then every 6 months thereafter[53]. Water-based non-hormonal lubricants might help vaginal dryness during intercourse[54]. Sexual counselling before treatment start might be beneficial, and referral to a psychologist or sexual health specialist could be warranted if sexual concerns arise[49,55].

Fertility should be explored before treatment in patients who are considering pregnancy after treatment completion. A multidisciplinary approach involving reproductive endocrinologists, gynecologists, and maternal–fetal medicine specialists is recommended[56]. Women who have had pelvic RT can be at increased risk for spontaneous miscarriages, preterm labor, low birth weight, and placental abnormalities[56]. These survivors should be closely followed by a multidisciplinary team throughout pregnancy[56].

SUMMARY

Radiotherapy treatments are associated with significant side effects that can negatively affect quality of life for cancer survivors. Although newer techniques in the field of radiation oncology have helped to reduce some of the adverse effects, further extensive research is needed to minimize RT-induced deleterious outcomes. All providers caring for cancer survivors, including general practitioners in oncology, should carefully assess and provide management for RT-related effects.

Key Points

- Radiation-induced side effects adversely affect quality of life for cancer survivors.
- Screening and management of RT-induced early and late effects are crucial parts of the survivorship care agenda.
- Family physicians and general practitioners in oncology are key providers in the management of comorbid conditions, promotion of healthy lifestyles, and treatment of RT-induced side effects.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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