REVIEW ARTICLE

The clinician's guide to radiotherapy complications

Wojciech Fendler[1,2], Bartłomiej Tomasik[3], Katelyn Atkins[4], Konrad Stawiski[1], Justyna Chałubińska-Fendler[5], David Kozono[2]

1 Department of Biostatistics and Translational Medicine, Medical University of Lodz, Łódź, Poland
2 Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, United States
3 Department of Oncology and Radiotherapy, Faculty of Medicine, Medical University of Gdansk, Gdańsk, Poland
4 Department of Radiation Oncology, Cedars-Sinai Medical Center, Los Angeles, California, United States
5 Department of Radiotherapy, Military Medical Institute, Warsaw, Poland

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ABSTRACT

Radiotherapy is one of the oldest cancer treatment modalities, used for over 100 years. As its efficacy has been steadily increasing due to the introduction of novel treatment methods, adverse events (AEs) still pose a major obstacle limiting the therapeutic benefits in some patients and negatively impacting treatment outcomes. In light of the technological progress, the focus has been shifted from improving the efficacy to safeguarding patients from the most severe AEs through improvements of safety and accuracy of radiation delivery. Currently, with radiation therapy being an effective treatment associated with frequent therapeutic success and leading to increased and prolonged survival, the problem of treatment-related AEs is growing as there are numerous survivors whose health and quality of life may be adversely affected. Due to the limited access to radiation oncologists, patients presenting with AEs are often referred to other professionals for advice, and as survivorship prolongs, the AEs may aggravate current patient comorbidities or reveal undiagnosed diseases. Thus, it is important that doctors other than oncologists be familiar with the fundamentals of radiation therapy–related AEs and their management. In this review, we present the most common and severe AEs of radiotherapy associated with damage to the nervous, respiratory, cardiovascular, gastrointestinal, and urogenital systems. We also describe the pathogenesis of these AEs, and provide guidelines for prevention, risk assessment, diagnosis, and treatment. Novel findings and future perspectives in this field are also elucidated, including examples of ongoing clinical trials aimed not only at improving treatment outcomes but also at reducing the risk of radiotherapy complications in cancer treatment survivors.

Correspondence to:
Justyna Chałubińska-Fendler, MD, PhD, Department of Radiotherapy, Military Medical Institute, ul. Szaserów 128, 04-141 Warszawa, Poland, phone: +48 26 181 82 17, email: jchalubinska-fendler@wim.mil.pl
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Introduction Radiation therapy (RT) is an essential modality of cancer treatment and is used with curative or palliative intent in more than half of cancer patients.[1] External beam radiotherapy (EBRT) is the most common type of RT, typically using a linear accelerator to deliver treatment. Brachytherapy (BT), the other major form of RT, is performed by direct insertion of the radioactive source into the body to deliver the dose in close proximity to a malignant lesion. The latter method spares a greater amount of normal tissues from dose exposure, but requires an invasive procedure.[2]

The mechanism of cell killing from radiation is similar, regardless of the modality used, and is not limited to tumor cells. However, as the effects of radiotherapy are local or locoregional, the histologic properties of irradiated tissues influence the clinical presentation of toxicity. Organs in the human body consist of functional units and, based on their arrangement, they can be classified either as parallel (eg, the lungs) or serial (eg, the esophagus).[3] For parallel organs, the percentage of irradiated volume and mean dose are the dose-limiting factors. Conversely, serial organs cannot tolerate excessive doses even to very small areas because the damage of just one segment can affect the function of the whole organ.

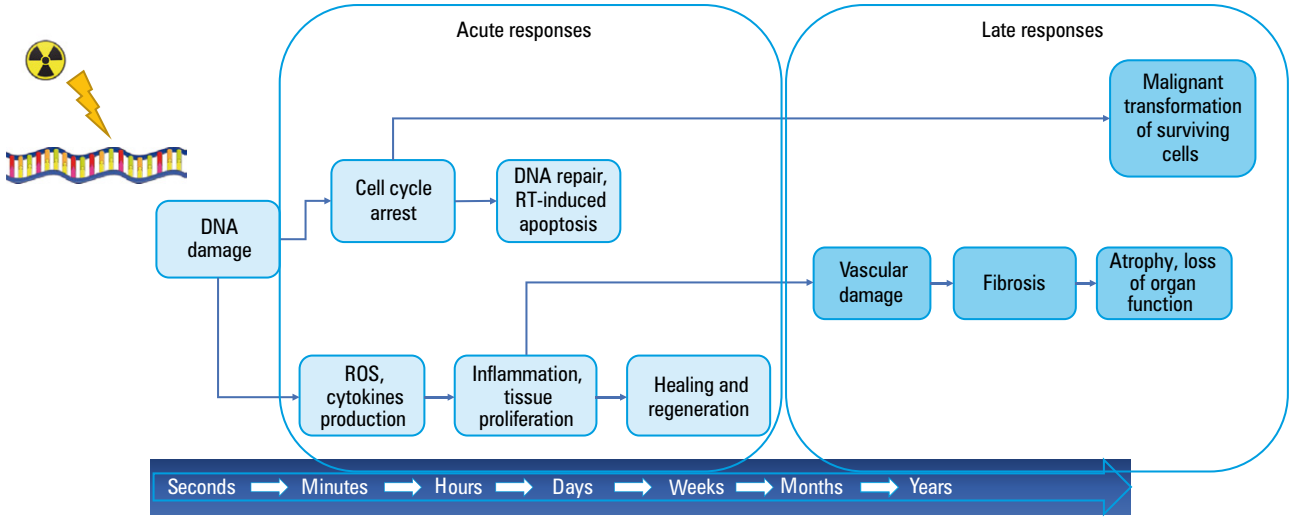

FIGURE 1 Outline of the timeline of radiation therapy–related complications and adverse events that may manifest early, late, or very late after treatment

Abbreviations: ROS, reactive oxygen species; RT, radiation therapy

Side effects of radiation can be also categorized as acute (observed typically within 3 months after treatment) or late (FIGURE 1).[4] The former usually begin during the course of RT and are mostly related to inflammation due to damage of rapidly dividing normal cells. These effects accumulate with time, reaching peak intensity after treatment completion or soon after. However, as normal tissue stem cells repopulate the damaged site, the acute symptoms usually resolve and full recovery is possible. Late effects are more problematic because they often involve tissues with slower cell turnover that cannot be completely repaired. Vascular damage, fibrosis, and damage to parenchymal cells are considered the most important factors leading to these toxicities. Radiation-induced secondary malignancies are also of some concern, especially in patients with a long life expectancy, for example, those with Hodgkin lymphoma, early breast cancer, or nonmalignant disorders.[5]

Despite tremendous technical advances that allow for a very precise dose administration, including intensity-modulated RT (IMRT), stereotactic body RT (SBRT), and image-guided RT (IGRT), the therapeutic window is often very narrow, leading to treatment-related adverse events (AEs).[6] To put this into perspective, in Poland, approximately 170 000 new malignancies are diagnosed each year. As of 2020, only 55 radiation therapy centers operated in Poland, treating more than 90 000 patients. In addition, today more than 1 million Polish citizens are cancer survivors who are free of cancer but may still experience therapy-related AEs, and this number is expected to rise rapidly. Reports from the United States show that approximately 5% of the population belong to this group.[7] Hence, with increasing numbers of cancer survivors and a relative lack of oncologists, family physicians and other specialists play an important role in cancer follow-up care and AE management.[8] In this review, we aim to describe the most common radiation-related toxicities in order to increase the understanding of radiation-related acute and late effects in different organ systems (FIGURE 2). We also provide a brief overview of the predictive capabilities of the existing biomarkers and risk scores together with future perspectives and ongoing clinical trials.

Cardiac complications Cardiac radiation exposure can result in serious acute and long-term cardiovascular toxicities which contribute to increased morbidity and mortality in survivors of these cancers.[9-11] Notably, radiation exposure to arterial vessels can modify the natural history of coronary artery disease (CAD) by triggering inflammation that accelerates disease progression.[12] This can manifest into the development of major adverse cardiac events, such as myocardial infarction, heart failure, unstable angina, the need for coronary revascularization, and even cardiac death. However, the spectrum of radiotherapy-associated cardiac toxicity (RACT) is broad and includes not just accelerated or increased risk of vascular disease (eg, CAD, subclavian or carotid stenosis), but also arrhythmias (eg, atrial fibrillation or flutter, supraventricular tachycardia, bradycardia, sick sinus syndrome, heart block), heart failure, restrictive cardiomyopathy, myocarditis, constrictive pericarditis and/or pericardial effusion, valvular dysfunction, and autonomic dysfunction.[10,11,13] The mechanisms of RACT, while complex and not completely understood, involve a combination of oxidative stress, DNA damage, and triggering of inflammatory and profibrotic cytokines that result in the development of fibrosis throughout important substructures of the heart—including blood vessels, myocardium, valves, and pericardium.[14]

Studies of RACT among survivors of breast cancer and lymphoma have typically observed a latency period of several years to more than

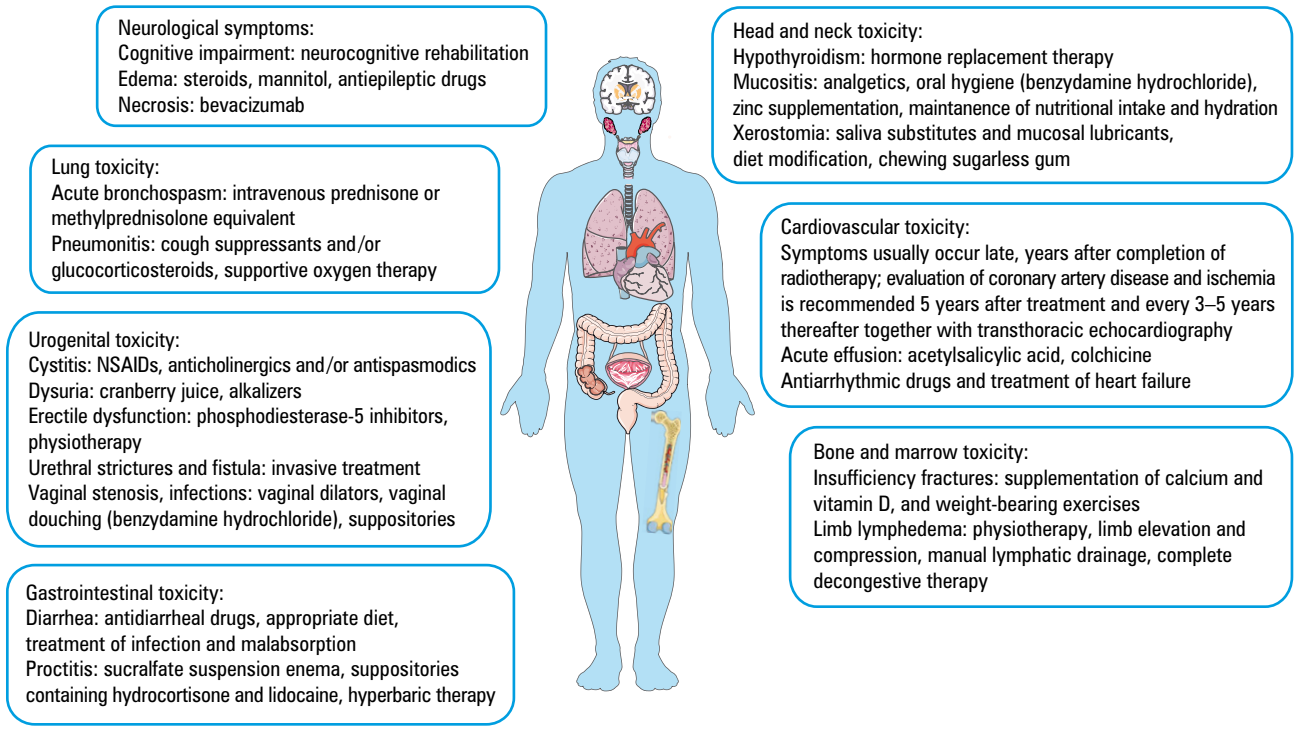

FIGURE 2 Overview of the symptomatic treatment of radiation-related toxicity arising in different regions of the body. Created using free medical images from https://smart.servier.com/.
Abbreviations: NSAIDs, nonsteroidal anti-inflammatory drugs

a decade.[9,11,15] Conversely, more recent data in patients with lung or esophageal cancer (who receive much higher cardiac radiation exposure due to tumor location and / or prescribed radiation doses) have shown that serious cardiac events, even cardiac death, can occur within 2 years following radiotherapy.[16] Therefore, it is paramount that we understand the importance of assessing baseline cardiovascular risk, the anticipated excess treatment-associated cardiac risk, and appropriate surveillance strategies.

Baseline cardiac risk stratification Epidemiologic studies have observed that the prevalence of cardiovascular disease (CVD) is both high and suboptimally managed in patients with cancer, including CVD rates of 17%, 33%, and 43%, in patients with breast, hematologic, and lung cancers, respectively.[17] Furthermore, it is estimated that less than half of these patients receive guideline--based medical therapy.[17,18]

Cardiovascular risk factors such as hypertension, hyperlipidemia, diabetes mellitus, smoking, and coronary artery calcifications (CACs) on computed tomography (CT) imaging are associated with increased risk of cardiac events following radiotherapy across multiple malignancy types. Specifically, the presence of pre-existing cardiovascular risk factors in patients with breast cancer who are treated with radiotherapy doubles the risk of a future major coronary event, while pre-existing ischemic heart disease confers more than a 6-fold increase the risk of a future cardiovascular event.[9] Importantly, however, even patients without pre-existing coronary heart disease are at a significant risk for cardiac events following thoracic radiotherapy. Recent data in patients with locally advanced non–small cell lung cancer (NSCLC) and without pre-existing coronary heart disease observe a nearly 25-fold increase in the hazard ratio of major adverse cardiac events with high radiation dose exposure to the left anterior descending coronary artery.[19] Additionally, patients with thoracic malignancies often undergo diagnostic CT or positron emission tomography–computed tomography (PET-CT) imaging studies as part of the oncologic standard of care, as well as radiotherapy-planning CT prior to treatment, which can provide an opportunity to repurpose these studies to assess the coronary atherosclerotic burden.[20] Indeed, CAC is one of the most robust predictors of atherosclerotic coronary vascular disease and future cardiac events and is a component of the current American College of Cardiology / American Heart Association primary prevention guidelines.[21,22] The presence of CAC on non–contrast-enhanced CT imaging should prompt formal cardiovascular risk assessment in patients without known coronary heart disease.[22]

Cardiovascular screening and surveillance following thoracic radiotherapy While there are no standardized cardiovascular surveillance recommendations for cancer survivors treated with thoracic radiotherapy, recently published expert consensus guidelines can provide guidance to physicians in terms of recommended screening to

aid detection of cardiac disease before the onset of symptoms.[23,24] These guidelines identified patients at high risk of cardiac toxicity as those characterized by any of the following: treatment with prescribed radiotherapy doses greater than 30 Gy with the heart in the treatment field, any thoracic radiotherapy dose with anthracycline exposure, younger age (<50 years old) with longer interval since radiotherapy, presence of pre-existing cardiovascular disease or cardiovascular risk factors, or higher radiotherapy fraction size (>2 Gy/day).[24-27]

The most recent expert consensus guidelines from the American Society of Clinical Oncology and International Cardio-Oncology Society (ICOS) generally recommend transthoracic echocardiography (TTE) as soon as 6 to 12 months after completion of therapy in patients at increased risk (using the above criteria), while the ICOS further recommends that in all patients, TTE by 5 years post treatment and serial TTE every 5 years thereafter may be useful.[24] Evaluation of CAD and ischemia is generally recommended 5 years after treatment completion and every 3 to 5 years thereafter.[25-26] The ICOS further emphasizes the importance of preventative therapy and early detection of CAD or nonobstructive CAD by screening patients without known coronary heart disease with stress testing, CAC detection (eg, reviewing the available CT imaging for the presence of CAC), and CT angiography, with a recommendation for continued screening every 5 years.[24] Lastly, it should be mentioned that patients who eventually require cardiac surgery after thoracic radiotherapy may have radiation fibrosis or scarring in the mediastinum that could impact surgical outcomes.[28]

Cerebral complications Radiation-induced brain injury manifests mostly as vascular injury leading to vasogenic edema.[29] Rapid aggravation of the pre-existing neurological deficits, headache, nausea, vomiting, blurred vision, and imbalance during walking are the most common symptoms. If prior extensive edema on imaging is present, it is recommended to start corticosteroid treatment 24 hours prior to RT. Severe edema is treated symptomatically using mannitol and intravenous dexamethasone. In refractory cases, the use of bevacizumab may be considered. Vascular edema occurring later, for example, 4 to 8 weeks after RT completion, represents a potential source of diagnostic misinterpretation (ie, pseudoprogression). Radiation-induced necrosis is an uncommon AE.

Late reactions include radiation-induced cognitive impairment. It is reported in up to 90% of adult brain tumor patients who survive more than 6 months after RT, in particular those who underwent whole brain radiotherapy and in patients with supratentorial tumors.[30] Major symptoms include dementia, decreased verbal and spatial memory, reduced attention, and novel problem-solving ability that impacts activities of daily living, substantially reducing patients' quality of life. The mini-mental status examination and Montreal Cognitive Assessment are the most commonly used tools to evaluate the patient's abilities before treatment and during surveillance. Other tests aimed to assess specific domains are used mostly only in clinical trials. Management of neurocognitive impairment is patient-specific, including neurocognitive rehabilitation and adaptive strategies.[31]

Hearing loss, vision loss, and vertigo are also possible late effects of brain radiation therapy.

Complications involving the head and neck region Due to its anatomical complexity, irradiation of the head and neck area may result in several significant toxicities. These occur in nearly all patients treated with curative doses, and in 50% of patients are grade 3 or higher according to the Common Terminology Criteria for Adverse Events (CTCAE).[32]

Acute mucositis appears typically during the second week of radical radiotherapy course and may lead to low caloric intake and improper hydration, even to life-threatening levels, requiring hospital admission and intensive nutritional support.

Adequate nutrition before and at the start of RT reduces mucositis severity. Patients maintaining good oral hygiene and using anti-inflammatory medications such as benzydamine hydrochloride develop acute mucositis later and of lower grade.[33]

Xerostomia is the most common long-term AE of the head and neck RT. It tends to improve with time but in many cases symptoms are persistent.[34] Replacement of dry, tough food with moist and softer equivalents can vastly improve nutritional status and quality of life. Some reports suggest that using a room humidifier can also be beneficial.[35] In addition, commercially available saliva substitutes and mucosal lubricants may provide temporary relief. In more severe cases, the existing salivary flow can be stimulated. Drugs used for that purpose are parasympathomimetic agents: pilocarpine and cevimeline; however, pilocarpine is currently not recommended for this indication.[36] Additionally, acidic or bitter substances are often used to stimulate salivary flow. Some reports also support the introduction of sweet substances, such as sugar-free hard candy.[37] Finally, chewing sugarless gum can provide both gustatory and tactile stimuli to increase salivary flow.[38] Oral pain may be treated locally with 0.2% morphine sulfate mouthwash and/or 1% to 2% lidocaine wash, the latter especially if morphine is not readily available.

RT-induced hypothyroidism develops relatively late, at a median of 1.5 to 2 years after treatment.[39] Studies with long-term follow-up have shown that more than 50% of patients in whom the head and neck area has been irradiated may be eventually affected. Central hypothyroidism, which is caused by damage to the hypothalamus

TABLE 1 Grading system of radiation pneumonitis and radiation-induced lung fibrosis based on the scale proposed by Kong et al[44]

Grade	Radiation pneumonitis	Lung fibrosis
1	Minimal or mild symptoms of dry cough or dyspnea on exertion, without evidence of tumor progression or other etiology, with radiographic evidence of acute pneumonitis	Radiographic evidence of radiation fibrosis without or with minimal dyspnea
2	Persistent, dry cough requiring cough suppressants or steroids, or exertional dyspnea with no tumor progression or other etiology presenting signs of acute RP on chest X-ray, requiring steroids	Radiographic evidence of radiation fibrosis causing dyspnea with minimal effort but not at rest; does not interfere with activities of daily living
3	Severe cough, unresponsive to narcotic antitussive agents, or dyspnea at rest, with radiographic evidence of acute pneumonitis, requiring oxygen (intermittent or continuous) treatment	Radiographic evidence of radiation fibrosis that causes dyspnea at rest, interferes with activities of daily living; home oxygen therapy indicated
4	RP causing respiratory insufficiency, requiring assisted ventilation	Radiation fibrosis causing respiratory insufficiency; requiring assisted ventilation
5	RP directly contributing to the cause of death	Radiation fibrosis directly contributing to the cause of death

Abbreviations: RP, radiation pneumonitis

or pituitary region, is significantly less common but should be considered in patients who were treated for nasopharyngeal cancer and brain tumors. Although relatively uncommon, hypothyroidism should also be considered in breast cancer patients in whom the supraclavicular region was irradiated.[40] According to current recommendations, serum levels of thyroid-stimulating hormone should be checked within 12 months of RT completion and repeatedly evaluated every 6 to 12 months.[41]

Additional AEs after RT of the head and neck region that may significantly reduce patients' quality of life include supraglottic edema and loss of taste. The edema may be treated via physiotherapy and typically reduces to an acceptable level within a year. However, loss of taste (or a reduction in basic tastes including sweet, sour, and bitter) may be permanent.

Pulmonary complications Radiation-induced lung toxicity (RILT) was first observed in humans in the mid-1920s and, despite colossal improvements in radiation techniques and beam energies, still occurs routinely in clinical practice. It affects between 5% and 25% of patients irradiated to treat lung cancer and other thoracic malignancies (mediastinal lymphoma, up to 10%; breast cancer, up to 5%).[42] The clinical course of RT is well characterized and manifests in 3 main phases. After a latent or sublatent period, during which symptoms may include a slight cough, the first evident signs of radiation pneumonitis (RP) may be seen after 6 to 8 weeks. Subsequently, 6 to 24 months after RT, progressive radiation-induced fibrosis may be observed in imaging studies and/or manifest clinically, similarly to lung fibrosis (LF) of other etiologies.[2]

RILT is a consequence of radiation-induced damage of pulmonary epithelium cells leading to their apoptosis, mitotic cell death, or senescence. These mechanisms result in typically asymptomatic sterile inflammation (2–6 weeks after RT) and the release of mediators (including interleukin 6) observed in the serum at elevated levels up to 6 to 8 weeks after RT. Pathology reports present this as depletion of type I pneumocytes and proliferation of type II pneumocytes. After normalization of interleukin 6 levels, the main cytokines that play a role include cell-death factors (tumor necrosis factor-α). This constitutes a second wave of RILT, which may clinically manifest as overt RP.[2]

Clinical manifestations of RP include: intense nonproductive cough, dyspnea, fever, impaired physical performance, and chest pain. Hemoptysis is very seldom present, and wheezes, crackles, or rhonchi may be absent in auscultation.

Computed tomography is the recommended diagnostic tool for RP. The history of prior RT and RP-associated lesions in imaging studies located within the irradiated areas are sufficient to make a diagnosis. CT imaging reveals "ground-glass" opacity and/or airspace consolidation as well as a halo or reversed halo sign. Other manifestations (eg, nodular) are seldom present.[43] Computed tomography also facilitates differential diagnosis as it may show disease progression, exclude infectious pneumonitis (as steroid therapy may be needed in the treatment of RP), or identify other pathologies. This is especially true for patients with lung cancer who often present with smoking-related comorbidities. PET-CT may also reveal out-of-field radiotracer uptake in patients who had undergone chemotherapy and RT; however, the costs and availability discourage from using this technique as the standard diagnostic tool.[42] The lesions may be observed on plain chest radiographs but the findings are usually nonspecific. RP is graded by numerous scales including the Radiation Therapy Oncology Group (RTOG) or Southwest Oncology Group criteria, and CTCAE. The 5-grade Kong scale, however, seems to be the most useful for general practitioners, as it also specifies the grade in terms of severity by required patient support (TABLE 1).[44]

Clinical management of radiation pneumonitis Depending on severity, an escalation approach to treatment is recommended, as outlined below.

- Grade 1 (mild symptoms or spotted by imaging): no intervention is needed, but the patient requires surveillance.
- Grade 2: more intense cough and / or dyspnea require cough suppressants and / or glucocorticosteroids. The recommended starting dose of prednisone is 0.5 to 0.75 mg/kg/day. After achieving symptom control, the total dose should be reduced by 10 mg per week as tolerated.[45] In cases of acute bronchospasm, intravenous prednisone or methylprednisolone equivalent may be required. Concurrent prophylaxis of *Pneumocystis jirovecii* (previously *carinii*) infections with cotrimoxazole can be implemented and glucose monitoring is necessary in case of secondary diabetes.
- Grade 3: typically necessitates supportive oxygen therapy, noninvasive at first, and oxygen saturation monitoring.
- Grade 4: respiratory insufficiency necessitates oxygen support including mechanical ventilation in an intensive care unit should oxygen saturation levels fall below 60%.

Preventative measures that reduce the risk of lung fibrosis after radiation pneumonitis The end stage of RILT is chronic LF. It may occur without a preceding diagnosis of RP; however, the disruption of immune homeostasis and development of chronic inflammation always take place at a cellular level. Persistent induction of proinflammatory cytokines (mainly tumror necrosis factor-β)[46] is promoted by bone marrow–derived macrophages that replace the primarily resident ones.[47] Foam cells are also often described in pathology reports because of phospholipid accumulation—similar to those found in lipid pneumonitis. Excessive collagen production and elastin deposition in the extracellular matrix is attributable to the activation of surviving epithelial cells. Clinically, further deterioration of lung function is observed with aggravating dyspnea on exertion being the main symptom. On radiological imaging studies, a "honeycomb" sign and its evolution on further chest CT scans may be observed.

This process is considered irreversible. Currently, pirfenidone and nintedanib are approved by the United States Food and Drug Administration (FDA) for the treatment of LF.[48] However, the registration was based on data from patients with idiopathic pulmonary fibrosis and early-stage LF. Consequently, patients with LF are referred for supportive treatment including home oxygen support and pulmonary physiotherapy. Therefore, the best way to manage RP is to avoid it altogether.

Primary prevention of radiation pneumonitis During RT planning, considering primary prevention of LF and RP, radiation oncologists take into consideration patient-related factors and dose volume (spirometry, diffusing capacity of the lungs for carbon monoxide, tumor volume). Higher tumor volumes result in higher dose-volume parameters; thus, some patients are not candidates for concurrent radiotherapy with full-dose chemotherapy, but rather sequential treatment or low-dose cisplatin chemoradiotherapy. Poorer spirometry results may necessitate more restrictions in plan requirements. Dose volume limits that prevent excessive risk of pneumonitis and LF in most patients include mean dose below 20 Gy, V20 below 35%, and V5 below 70%.[49]

Chemoprevention for radiation toxicity may be attempted using amifostine, but it is used very rarely due to intolerable side effects.[50] Protective effect of angiotensin-converting enzyme inhibitors in the prevention of LF caused by radiation was postulated; however, data confirming such effect are scarce and the level of evidence is low.[51]

Urogenital complications RT remains one of the most important modalities in the treatment of gastrointestinal and urogenital tumors, both by means of EBRT and BT.[52] A substantial decrease in radiation-related toxicities involving the pelvis and abdomen has been observed due to widespread use of 3-dimensional RT and IMRT. However, AEs in this region are still an issue and are associated with decreased quality of life.[53,54] An overview of the development of these symptoms is provided in FIGURE 3.

Complications involving the rectum and anal canal The rectum and anal canal are the 2 most important organs at risk in pelvic irradiation. High radiation doses received by specific organ volumes (eg, rectal wall V65 <10%, V50 <25%, V40 <45%, and V30 <75%)[55] can lead to symptoms such as rectal bleeding, diarrhea, tenesmus, and fecal incontinence, known as pelvic radiation disease.[56] Primary prevention includes reduction in dose volume parameters in treatment planning and intake of probiotics during RT. The use of systemically administered sulfasalazine (500 mg twice daily) may prevent radiation enteropathy.[57]

The treatment of diarrhea in the majority of patients is performed on an outpatient basis and does not differ from treatment of secretory diarrhea (proper hydration and diet, antidiarrheal agents including opioids, and local or systemic steroids to treat inflammation). It very seldom requires hospital admission, which is needed in cases of severe dehydration or to treat infections requiring antibiotics (especially rifaximin, ciprofloxacin, and doxycycline or antifungal agents).[58,59]

Local treatment of radiation proctitis, especially with rectal bleeding, includes sucralfate suspension enema, suppositories containing hydrocortisone and lidocaine, and, in the late phase of proctitis, hyperbaric therapy.

Both oral sucralfate and acetylsalicylic acid and its derivatives, for example, oral mesalazine, were once used for the treatment of late toxicities. These regimens are not currently recommended.

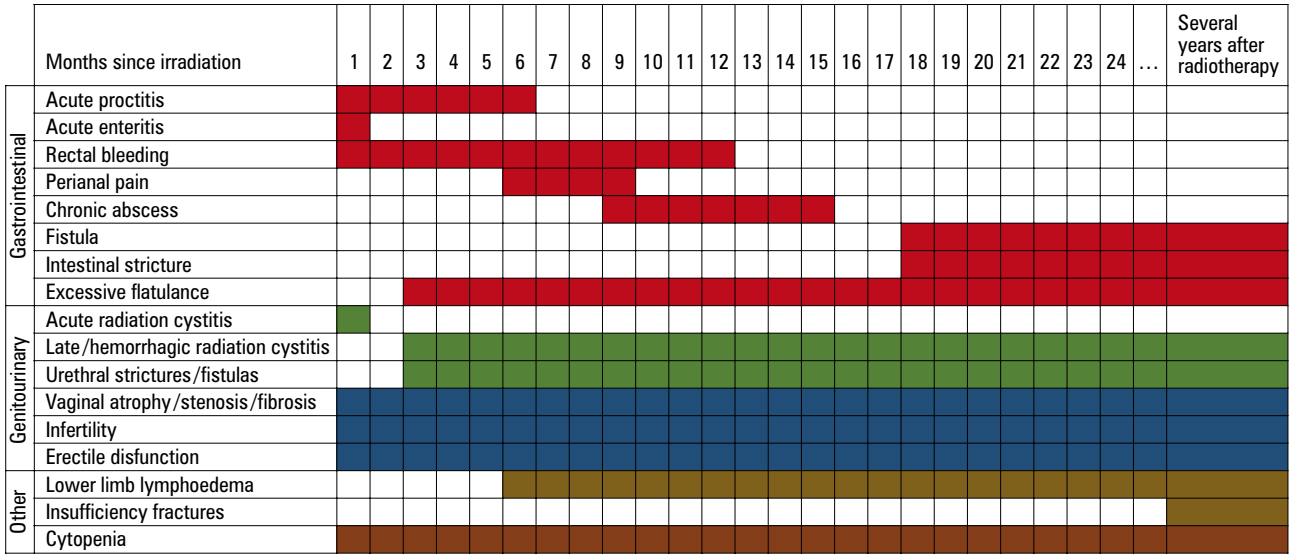

FIGURE 3 Timeline of expected side effects after radiation therapy of genitourinary cancers

Late radiation proctitis should not be treated with misoprostol suppositories. Severe late complications, such as bleeding fistulas, may eventually require surgical intervention.

Urinary complications Consequences of irradiation of normal tissues located in the bladder and urethra are edema, hyperemia, increased risk of infection, and inflammation of bladder and urethral mucosa.

These AEs constitute acute radiation cystitis. This condition presents as urinary urgency or incontinence, dysuria, cystalgia with bladder spasms, and sometimes hematuria.[60] Testing for urinary tract infections should be performed since these can result in similar symptoms.

Radiation cystitis usually resolves spontaneously within 4 to 6 weeks,[61] but may require therapy break, which may further lead to lower tumor control. Drugs may be given for symptomatic management (eg, oxybutynin or phenazopyridine).

Late radiation cystitis usually appears within the first 3 years following radiation. Late effects result in reduced bladder volume due to tissue fibrosis and telangiectasias.

Sexual and reproductive dysfunctions In women, these toxicities manifest as vaginal mucosal atrophy, fibrosis, and adhesions, which, in turn, result in vaginal stenosis, mucosal dryness, vaginal infections, and dyspareunia.[62] Those complications can be prevented with vaginal douching (benzydamine hydrochloride) and hyaluronic acid suppositories containing vitamin A, vitamin E, alpha-tocopherol acetate, and dienestrol.[63]

The role of vaginal dilators is not only to prevent from vaginal stenosis, but also to improve mucosal flexibility and its proper nutrition. Benefits include improvement in physiological vaginal fluid and reduction in discomfort during sexual intercourse and gynecological examination.

Transient and permanent fertility disorders are common AEs after pelvic RT. Total doses of 4 Gy or higher to both ovaries and uterus are associated with infertility and early menopause.[64] A testicular dose of less than 2 Gy can cause transient azoospermia, and greater doses lead to irreversible infertility.[65] In men, erectile function slowly declines over time after RT and is usually treated with phosphodiesterase-5 inhibitors and supported by pelvic floor physiotherapy.[66,67]

Bone and marrow complications As around 25% of bone marrow is located in the bones of the pelvis, it should also be taken into account as an organ at risk during RT planning.[68] Current RT techniques allow sparing of active bone marrow and can reduce the risk of cytopenias, also in patients undergoing chemoradiotherapy or immunotherapy.[69,70]

Insufficiency fractures are a late effect of pelvic irradiation. In patients receiving pelvic RT, the 5-year risk of insufficiency fractures is 6.8%, and among gynecologic patients, the lifetime risk is between 8% and 20%.[71] Calcium and vitamin D supplementation as well as weight-bearing exercises can be helpful in the prevention of these side effects.[72]

Pelvic RT can be associated with lower limb lymphedema occurring in 1 in 3 patients within 5 years after treatment.[73] It may be associated with more invasive lymph nodal staging or the use of conventional RT fields. This condition is hard to treat and may be relieved by physiotherapy, limb elevation, and compression.[74]

Predictable or inevitable: biomarkers applied in estimating the risk of radiotherapy complications Prediction of individual susceptibility to radiation toxicities is a factor that could, in theory, facilitate the optimization of RT, making it truly personalized. Different approaches can help achieve this ambitious aim. Estimation of radiation sensitivity

and the resulting efficacy of treatment in a given patient using genomic markers relies on polymorphisms in multiple genes as factored into the genomic-adjusted radiation dose score.[75] Recent validation of the model showed its promise, highlighting the importance of the biological impact of the dose rather than just its physical magnitude.[76] A different, more dynamic approach could rely on circulating biomarkers of radiation sensitivity of healthy tissues. Different biomarkers quantified in various biofluids have been proposed: microRNAs, metabolites, or proteins.[77-81] This strategy assumes that the individual's susceptibility might change over time and repeated testing may identify current, rather than genetically predetermined, susceptibility before starting treatment or during the course of RT. The principle of these tests relies on the manifestation of a cellular damage signal in the biofluids due to irradiation, and correlating the intensity of the signal with the incurred damage or a specific outcome after treatment.[81] Recent studies show that such tests based on a set of microRNAs[82,83] or protein biomarkers[84] reflect the radiation-associated damage to healthy tissue of the lungs, salivary glands, heart, and potentially other organs. However, calibration of such biomarkers remains a challenge due to issues related with prohibitive costs of recurrent testing, technical issues inherent to proteomic and genomic testing[85] or the lack of suitable references for nucleic acid-reliant biomarkers.[86] However, given the ease of access to quantitative polymerase chain reaction (qPCR) technology, it seems that the microRNAs hold the largest promise for actual clinical deployment due to the surge in qPCR diagnostics availability caused by the COVID-19 pandemic[87] and preserved evolutionary mechanisms regulating their expression[83] and stability in biofluids.[88] Nevertheless, given the novelty of these works, further validation and testing in different clinical scenarios are still needed before widespread use of such tools. Finally, there are currently no reliable tools for the prediction of long-term complications in cancer survivors. Given that this group of patients has substantially grown in number along with improvements in oncological care, strategies aimed at making RT safe as well as efficient are highly needed to avoid cardiac,[9] pulmonary, or neurological complications.

Clinical trials and future perspectives Clinical trials involving RT generally include specifications on dose limits to organs at risk. These are preferentially based on published data that report on the safety of RT regimens that have been tested in clinical trials or given as part of standard-of--care treatment. At times, when investigators wish to test a truly innovative and thus previously untested treatment, as was once the case for SBRT,[89] well-educated guesses based on preclinical data, extrapolation, and modeling may be needed to establish dose limits. Due to the risks, and the necessity to characterize them carefully, these treatments should only be attempted as part of well-regulated clinical trials. After the publication of these trials, additional data should be obtained on an ongoing basis via retrospective reviews and prospective data collection. Only then will there be sufficiently robust data to form evidence-based guidelines for RT planning dose limits, including QUANTEC[90] for standard fractionated treatment and more recently HyTEC[91] for hypofractionated treatment / SBRT.

The best means of avoiding radiation-associated AEs may be to decrease the prescribed dose of RT or omit RT altogether. For example, NRG-HN002 (NCT02254278)[92] was a phase II randomized trial that tested 2 regimens, administering a modestly lower RT dose of 60 Gy in 30 daily fractions (compared with the standard RT dose of 70 Gy in 35 daily fractions) to patients with HPV-associated oropharyngeal carcinoma. The arm testing IMRT with concurrent weekly cisplatin achieved a 2-year progression-free survival of 90.5%, meeting the prespecified end point for advancement to a phase III study. At the time of writing of this review, NRG-HN005 (NCT03952585) is enrolling patients to a phase II/III study, randomizing participants to receive standard chemoradiotherapy to 70 Gy versus reduced-dose RT to 60 Gy with cisplatin versus reduced-dose RT to 60 Gy with nivolumab. Because cytotoxic chemotherapeutics generally increase the sensitivity of normal tissues to RT to varying degrees, the use of other systemic agents (such as an immunotherapy drug, nivolumab) represents another approach toward reducing RT-associated AEs. The PRIME II trial[93] randomized women aged 65 years and older who underwent breast-conserving surgery for early breast cancer to receive whole-breast RT versus no RT. Although this study showed that whole-breast RT resulted in a significant but modest reduction in local recurrence, the 4.1% rate of ipsilateral breast tumor recurrence after 5 years in women randomized to no RT suggested that in some patients omission of RT may be considered.

Other trials have tested strategies to reduce radiation-associated AEs via addition of novel interventions. Amifostine, as previously mentioned, was approved by the FDA for the reduction of radiation-associated xerostomia, based on the results of WR-38,[94] a randomized study that showed statistically significant reductions in grade 2 or higher acute xerostomia from 78% to 51% and chronic xerostomia from 57% to 34%. As another example, studies have tested the efficacy of Mepitel film in preventing severe radiation dermatitis in patients treated with RT for breast[95] or head and neck[96] cancer. Among these, a study by Herst et al[95] in breast cancer patients showed that this film prevented moist desquamation and reduced skin reaction severity by 92%. Alliance A221803 (NCT04989504), a phase III study in patients undergoing postmastectomy RT, is pending activation as of this writing.

The impact of radiation-associated AEs on the overall outcomes of patients treated with RT

should not be understated. RTOG 0617,[97] a phase III trial that compared standard-dose (60 Gy) to high-dose (74 Gy) RT for the treatment of unresectable stage III NSCLC, famously failed to show a survival advantage with high-dose RT, and in fact, showed statistically worse median overall survival and worse treatment-related grade 3 or higher dysphagia and esophagitis. Lung ART,[98] a phase III trial that randomized patients with completely resected NSCLC with pathologic N2 involvement to receive postoperative RT versus no RT, showed no improvement in disease-free survival with postoperative radiation therapy, likely due to 2-fold increase in the number of severe cardiopulmonary toxicities.

In addition to the above, future directions toward maximizing patient outcomes and minimizing treatment-related AEs will depend on the ongoing pursuit of new technologies and innovations. These will include refinements in the precision of RT delivery, as have been seen with IMRT, IGRT, and related technologies. Other technologies are now starting to be adopted in selected RT clinics, such as magnetic resonance guidance and adaptive RT.[99] Still others, such as ultra-high-dose rate (FLASH) RT,[100] are under development, but may one day have a transformative effect on the therapeutic index of RT by further separating its effects on tumor versus normal tissues. Clinical trials will be key in distinguishing those advancements that truly improve outcomes from those that are merely novel.

Conclusions Clinical management of cancer survivors who have undergone RT requires knowledge of the multifaceted presentations of RT-induced complications. If managed properly, the impact of these sequelae on patients' quality of life and further survival can usually be successfully mitigated.

ARTICLE INFORMATION

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