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The Evaluation and Management of Visceral Complications in Radiation Fibrosis Syndrome Part 1

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Abstract

External beam ionizing radiation is a fundamental component of cancer treatment and is incorporated into approximately 50% of cancer treatments. Radiation therapy causes cell death directly by apoptosis and indirectly by disruption of mitosis.

Purpose of Review This study aims to inform rehabilitation clinicians of the visceral toxicities of radiation fibrosis syndrome and how to detect and diagnose these complications.

Recent Findings Latest research indicates that radiation toxicity is primarily related to radiation dose, patient co-morbidity, and concomitant use of chemotherapies and immunotherapies for the treatment of cancer. While cancer cells are the primary target, surrounding normal cells and tissues are also affected. Radiation toxicity is dose dependent, and tissue injury develops from inflammation that may progress to fibrosis. Thus, radiation dosing in cancer therapy is often limited by tissue toxicity. Although newer radiotherapeutic modalities aim to limit delivery of radiation to non-cancerous tissues, many patients continue to experience toxicity.

Summary To ensure early recognition of radiation toxicity and fibrosis, it is imperative that all clinicians are aware of the predictors, signs, and symptoms of radiation fibrosis syndrome. Here, we present part 1 of the visceral complications of radiation fibrosis syndrome, addressing radiation-related toxicity in the heart, lungs, and thyroid gland.

Keywords Radiation fibrosis · Cardiac toxicity · Pulmonary Toxicity · Thyroid toxicity · Cancer survivorship

Introduction

External beam ionizing radiation is a fundamental component of curative and palliative treatment regimens of many cancers alongside surgical treatment, chemotherapy, immunotherapy, and hormone therapy [1]. As many as 50% of patients currently receive radiotherapy as part of their treatment regimen [2], and this number is expected to grow in the future [3]. While clinical outcomes have improved in cancer treatment, each mode of therapy confers risk of acute and chronic toxicity to affected organs [4]. Radiotherapy injures both tumor cells and the non-cancerous surrounding cells. Radiation injury is caused by an inflammatory cascade that often becomes dysregulated by cellular/endothelial damage that overwhelms repair pathways and may result in the replacement of normal tissue with fibrotic tissue. Fibrosis adversely affects multi-organ function, and thereby impacts long-term health and quality of life among cancer survivors [5]. Since early recognition and management of radiation toxicity are essential to minimizing injury and optimizing health outcomes, multi-disciplinary understanding and collaboration are needed.

Radiation fibrosis and the effects on viscera are dependent on the radiation field, the absorbed radiation dose, and the sensitivity of the involved organs. The next two papers will focus on the visceral effects of radiation therapy and include risk factors for development, available predictors, a timeline of clinical manifestation, symptoms at presentation,

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and initial diagnostic and treatment considerations. Of note, most treatment recommendations in this area are based on observational data and expert consensus opinion as there is a paucity of randomized clinical trials available for treatment approaches at this time.

Special Considerations for CCS

Over 80% of childhood cancer patients will go on to become long-term survivors [6]. Yet, the lifelong, cumulative burden of chronic health conditions consequent to therapy in this group far exceeds that of the general population [7]. Radiation therapy is a significant contributor to this excess morbidity [6]. Literature shows that as pediatric treatment regimens have moved to reduce exposure to radiotherapy, late mortality among childhood cancer survivors (CCS) has progressively declined [8]. Nonetheless, radiotherapy remains integral in the cure of many childhood cancers, and although childhood cancer is rare, adult CCS are a growing, medically complex population [6]. Survivorship programs dedicated to caring for CCS provide individualized, guideline-based care plans to ensure that CCS receive critical surveillance as they age from childhood into adolescence and adulthood [9•].

The Measurement, Mechanism, and Evolution of Radiation Therapy

It is important to understand the basic terminology of radiation dose measurement. The radiation dose absorbed by a specific organ or tissue per unit of mass is referred to as the *absorbed dose*. It is expressed in the units of gray (Gy) and is often a calculated entity [10].

Ionizing radiation results in cell damage by acting as a physical agent that forms ions and deposits energy in the cells and tissues it passes through. This deposited energy kills cancer cells either directly by apoptosis or indirectly by causing deoxyribonucleic acid (DNA) injury resulting in mitotic disruption that is ultimately fatal [11]. Normal cells are better able to repair and resume usual function compared to cancer cells, typically protecting them from radiation-induced injury. However, the repair processes of normal cells can be overwhelmed at higher doses of ionizing radiation or in the presence of sensitizing agents. Many early and late toxicities of radiation therapy are dose dependent. That is, as radiotherapeutic dosing increases, injuries are more rapid, toxicities are more severe, and late effects may present within a shorter timeframe [12•]. To minimize toxicity, the improvements in radiation therapy over the last century have focused on directing the radiation beam to cancer cells with more precision to better protect non-cancer cells.

Radiation fibrosis syndrome refers to tissue injury from radiation which presents in the form of fibrosis. Susceptibility to radiotoxicity is dependent upon tissue maturation and capacity for repair at the time of exposure [13••]. Understanding of radiation fibrosis syndrome has primarily been observed in adult survivors of childhood cancers, treated with higher doses of radiation therapy to the thorax and abdomen (e.g., Hodgkin lymphoma).

Modern external beam radiation therapy includes various modes of radiation therapy to reduce the dose delivered to normal tissue. Recent advancements include three-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic radiosurgery (SRS), and stereotactic body radiation therapy (SBRT). While photon beams (x-rays and gamma rays) are used in conventional radiation, there is now evidence for the use of other particles [11]. Proton beam therapy reduces the radiation dose to normal tissues by allowing for more precise dose delivery [11]. (see Table 1).

Cardiovascular Complications of Radiation Fibrosis Syndrome

Cardiovascular disease is the leading cause of non-malignancy related death in cancer survivors [14, 15]. Ionizing radiation affects all structures of the heart, and its impact may manifest acutely or long after completion of therapy (see Fig. 1). Late onset of adverse outcomes is more commonly seen among adult survivors of childhood, adolescent, and young adult cancers [15]. In fact, childhood cancer survivors (CCS) have a more than fivefold increased risk of serious cardiovascular disease and death at a much younger age compared to the general population [16••, 17]. Patients treated with left chest, mediastinal, thoracic spine, and head and neck radiation therapy are at increased risk for adverse cardiovascular and cerebrovascular events [18]. Risk factors for cardiac complications from radiation therapy include the total dose of radiation received, the volume of the heart radiated, concomitant use of anthracyclines, younger age at the time of radiation, and pre-existing cardiovascular disease [19•]. Cardiotoxicity occurs as a direct effect of ionizing radiation on cardiac substructures and vasculature, as well as the indirect impact on development of comorbid conditions, such as diabetes, hypertension, and dyslipidemia [12•]. Among CCS, exposure to doses as low as 5 Gy have been linked with long-term cardiac dysfunction [12•, 13••]. Early detection of these complications is paramount to improving patient outcomes, so clinicians should be aware of the presenting symptoms and consider the use of diagnostic studies and subspecialty referrals for further evaluation.

Table 1 Evolution of external beam ionizing radiation techniques

Type of external radiation	Three-dimensional conformal radiation therapy (3D-CRT)	Intensity-modulated radiation therapy (IMRT)	Image-guided radiation therapy (IGRT)	Stereotactic radiosurgery (SRS)	Stereotactic body radiation therapy (SBRT)	Proton beam therapy
	Uses computer software to deliver radiation to precisely shaped targets	Uses multiple radiation beam-shaping devices to deliver radiation in many fractions	With each radiation therapy session, uses imaging studies, i.e., CT/MRI/PET to increase target accuracy	Uses accurate image-guided tumor targeting and patient positioning to deliver high doses of radiation in fewer fractions	Like SRS therapy with a corporeal target	Uses proton beam therapy instead of photon beam therapy
Advancement compared to conventional radiation therapy	More precise targeting of radiation beam	Radiation beam is sculpted and modified in intensity and contour to allow cancer cells to receive different doses from surrounding normal tissues	Image-guided therapy improves precision and limits the radiation exposure to normal tissue	Used primarily to treat tumors in the brain and spine. Reduces both the number of treatments and the radiation field which limits the exposure to normal tissue	Used primarily to treat tumors in the lung. Again, reduces both the number of treatments and the radiation field	Reduces the dose administered to normal tissues because of rapid dose fall off

Coronary Artery Disease

Coronary artery disease (CAD) is the most common radiation-induced cardiovascular disease, with an incidence rate of 85% [20]. Both adolescents and adults have an increased risk of fatal myocardial infarction when treated with mediastinal or thoracic radiation in doses > 35 Gy [21, 22]. The cascade of inflammation and repair that follows the radiation insult leads to platelet aggregation and thrombosis within damaged blood vessels [23, 24], which ultimately accelerates atherosclerosis and causes CAD in younger patients.

CAD often presents with chest pain, dyspnea, or fatigue. However, symptoms may be atypical in patients with radiation-induced CAD due to damaged nerve endings [19•]. The affected coronaries seen on presentation are typically influenced by the distribution of the radiation dose. Coronary lesions from radiation therapy are typically longer, more concentric, and tubular [20] which may impact both surgical and percutaneous treatment options. As it stands now, there are conflicting reports on the use of coronary artery bypass grafting versus percutaneous coronary intervention for the treatment of radiation-induced CAD. Therefore, focus should be on modifying other risk factors that contribute to CAD.

Valvular Disease

Valvular disease in patients treated with radiation tends to manifest decades after completion of therapy, with a mean interval of 23 years, as seen in patients with Hodgkin lymphoma [25]. Furthermore, there is a linear increase in risk of valvular heart disease with a total dose of radiation to the affected valve above 30 Gy/m^2 [25]. Among those treated with mediastinal radiation, valvular disease seems to most significantly impact the left side of the heart, specifically the aortic and mitral valves. This suggests higher left-sided pressures may accelerate the development of radiation-induced pathology [26, 27]. In addition, the aortic valve is most frequently impacted due to its proximity to the radiation field and most commonly manifests as aortic insufficiency and aortic stenosis [27]. Management is either surgical valve replacement or transcatheter valve replacement. Notably, a history of mediastinal or chest radiation seems to increase both mortality and complication rates of either treatment option [19•].

Cardiomyopathy

There are several forms of non-ischemic cardiomyopathy secondary to radiation exposure: hypertrophic cardiomyopathy from valvular disease, restrictive cardiomyopathy

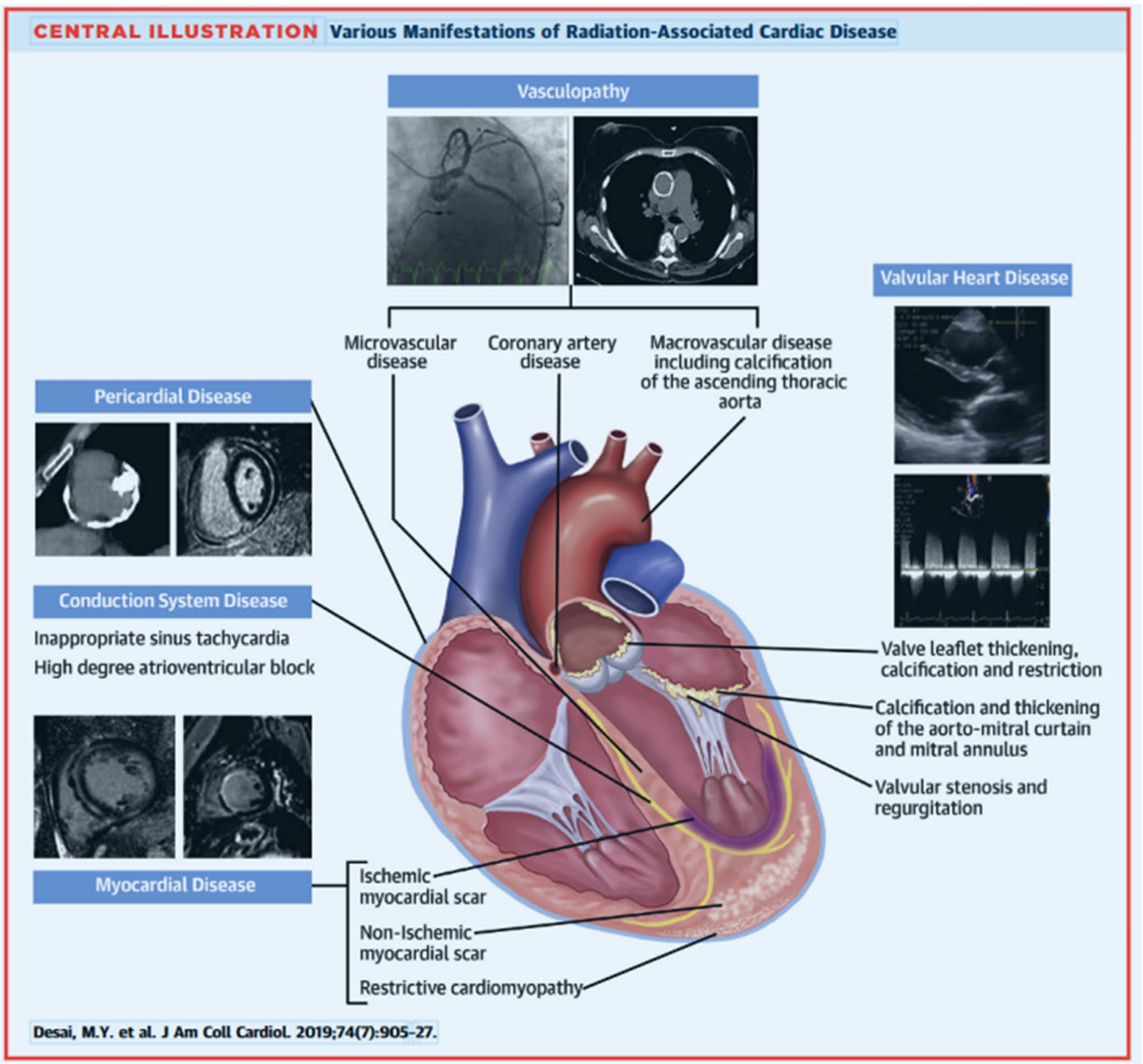

Fig. 1 Manifestations of radiation-associated cardiovascular disease. Reprinted from the Journal of American College of Cardiology, Vol. 74, M.Y. Desai et. al., "Prevention, diagnosis, and management of radiation-associated cardiac disease: JACC Scientific Expert Panel." Pages 905–908, Copyright (2019), with permission from Elsevier

from constrictive pericarditis, and myocardial fibrosis [19•]. Diastolic dysfunction in radiation-induced cardiomyopathy is more prevalent than systolic dysfunction [20], and the right ventricle is more affected than the left ventricle [20] which is best explained by the fact that the right ventricle sits more anteriorly in the chest and in the direct pathway of the radiation beam. Cardiomyopathy results from fibrosis in all three layers of the heart — epicardium, pericardium, and myocardium — which may explain why it is more likely to present as heart failure with preserved ejection fraction. The overall prevalence of cardiomyopathy is ~ 10% in patients who received chest or mediastinal radiation [20]. Among breast cancer patients treated with radiotherapy, 35% developed heart failure, and of those, 64% had manifested with preserved ejection fraction, while 31% had reduced ejection fraction. Concomitant administration of anthracyclines — a commonly used class of chemotherapy agents known to independently cause cardiotoxicity — augments the adverse impact of radiotherapy [19•]. Management is akin to that used for non-radiation induced cardiomyopathy, using pharmacologic agents such as beta-blockers, angiotensin receptor blockers, ACE-inhibitors, diuretics, and aldosterone

inhibitors. Management should also include optimizing other risk factors for diastolic dysfunction such as obesity.

Pericardial Disease

Pericarditis develops due to inflammation and impaired drainage to the pericardial surface in addition to fibrotic changes of the parietal pericardium [20]. Pericardial disease from radiation therapy may be asymptomatic, presenting as pericardial calcification and incidental findings of pericardial thickening or effusion. If symptomatic, it presents as heart failure due to constrictive pericarditis, acute pericarditis, and cardiac tamponade [19•]. Acute pericarditis, an often self-limiting condition, was much more common prior to the introduction of contemporary radiotherapy, occurring in up to 80% of patients following radiation exposure [28•]. While the incidence rate has decreased since the reduction in radiotherapy dosing was adopted in 1995, it is estimated that 6–30% of patients will still develop pericarditis [20].

Management of pericardial disease includes anti-inflammatory therapy for acute pericarditis, pericardiocentesis for large effusions or cardiac tamponade, pericardial window for recurrent pericardial effusions, and pericardial stripping for constrictive pericarditis [20]. History of chest or mediastinal radiation is the greatest predictor of adverse surgical outcomes for pericardial stripping [19•]. The decision to treat radiation-induced constrictive pericarditis with pericardial stripping should be determined alongside the patient after a thorough discussion of risks, benefits, and therapeutic goals.

Conduction Abnormalities

The conduction system can be affected both directly by radiation resulting in fibrosis from inflammation and indirectly by fibrosis from ischemia in the myocardium [29]. This is not a common manifestation of radiation-induced cardiac disease, occurring in ~ 5% of all patients treated with chest or mediastinal radiation [20]. Radiation-induced conduction abnormalities can manifest as prolonged QT interval, ventricular tachycardia, sinus node dysfunction, atrioventricular blocks, fascicular blocks, and bundle branch blocks, with right bundle branch block occurring more often than left bundle branch block [30]. Additionally, patients may present with reduced exercise tolerance from autonomic dysfunction indicated by an elevated resting heart rate and abnormal heart rate recovery presumed to be related to reduced vagal tone from radiation injury [31]. Radiation-induced arrhythmias are managed much like arrhythmias unrelated to radiation with telemetry, Holter monitor, anti-arrhythmic medications, pacemakers, and defibrillators when indicated. Since radiation often causes fibrotic change in all layers of the cardiac structure, subpectoral approaches to implantable devices may be considered [20].

Screening and Management Recommendations

Current screening and management of radiation-therapy associated cardiovascular complications includes primarily identifying, modifying, and treating cardiovascular risk factors such as diabetes, hypertension, dyslipidemia, tobacco use, and obesity [20]. The recommendation for screening procedures include an annual electrocardiogram (ECG) for patients who have received thoracic, mediastinal, or neck radiation. Echocardiography is currently recommended at the 5- and 10-year mark [20] following thoracic, mediastinal, or neck radiation, but should be done sooner if the patient reports any changes in symptoms or reports new symptoms concerning for cardiac disease such as fatigue, dyspnea, decreased exercise tolerance, chest pain, palpitations, syncope, or presents with new arrhythmia such as tachycardia. A screening stress test or coronary CT should be completed at 10 years after radiation therapy to the chest or neck [20]. For patients who are high risk because they received > 35 Gy radiation to the chest or mediastinum, echocardiography, cardiac MRI, or coronary CT should be done in asymptomatic patients beginning 5 years after completion of radiation therapy, or sooner for patients who have symptoms [19•, 32].

Special Considerations for Cardiotoxicity in Childhood Cancer Survivors

CCS experience the onset and impact of modifiable cardiovascular risk factors (hypertension, diabetes, obesity, tobacco use) at a much younger age than peers, which augments the risk of cardiovascular toxicity in this population [16••]. Among those exposed to chest-directed radiation, hypertension significantly increases the risk of coronary artery disease, heart failure, valvular disease, and arrhythmia; in combination with other risk factors, this risk is further amplified [33]. Despite these staggering risks, recent findings show that many CCS are not only underdiagnosed but also undertreated for these comorbid conditions [16••].

Like adults, cardiotoxicity in CCS can present with shortness of breath, dyspnea on exertion, orthopnea, chest pain, and/or palpitations. However, younger patients may present with atypical symptoms, including nausea and vomiting [17, 34]. Moreover, some CCS may have subclinical disease for many years, without any overt limitations in physical activity [17]. Since adult CCS are often too young for typical screening protocols, their disease may be easily overlooked [17].

To identify chronic toxicity, adult CCS should receive surveillance and healthcare directed at their cancer history [16••]. In the USA, the principal clinical practice guidelines

for long-term follow-up of CCS are produced and maintained by the Children's Oncology Group [34]. Those who received ≥ 15 Gy of radiation are presently recommended to have a baseline electrocardiogram and routine echocardiography — with the interval depending on cumulative exposure risk — to assess for cardiac toxicity throughout their lifetime [16••, 34].

Pulmonary Complications of Radiation Fibrosis Syndrome

Early recognition of radiation-induced lung injury (RILI) is important and requires an astute clinician. Though potentially fatal, RILI manifests with non-specific symptoms in both early (i.e., radiation pneumonitis) and late (i.e., radiation fibrosis) presentations [35, 36•]. A recent clinical trial underscores the clinical importance of RILI. In the Lung-ART trial, post-operative radiotherapy (PORT) after resected non-small cell lung cancer (NSCLC) reduced risk of cancer relapse; however, deaths after radiation were higher, in part due to cardiopulmonary complications (especially pneumonitis) [37••].

The lungs are one of the most sensitive organs to radiation therapy, and doses of thoracic radiation are often limited by strategies to avoid RILI. Indeed, RILI can result even when the lungs are not the primary target of radiation (e.g., thyroid, esophageal, or breast cancers).

Pathophysiology and Pathology

In general, radiation injury begins with epithelial cell injury, endothelial cell injury, and inflammation which progresses to fibrosis in some patients. Table 2 outlines the 5 phases of RILI [35, 36•]. Biopsy is often unnecessary for diagnosis. If obtained, pathology may mimic acute respiratory distress syndrome or organizing pneumonitis [35, 36•].

Risk Factors

RILI most commonly affects patients with lung cancer, breast cancer, and those who receive whole body irradiation for bone marrow transplant. Historically, patients treated for Hodgkin lymphoma often presented years later with pulmonary fibrosis. Patient-related and treatment-related factors can predispose to RILI. The data on chronic obstructive pulmonary disease (COPD) and smoking predisposing to RILI has been conflicting. One thought is that already injured lung from cigarette smoke [38] and COPD [39] can perhaps tolerate radiation injury better than healthier lung tissue. That said, one known predictor of RILI is pre-existing interstitial lung disease which has been associated with a significantly increased risk for the development of high-grade radiation pneumonitis [40, 41].

Treatment-related factors include radiation dose, lung dose, type of radiation fractionation used, and concurrent therapies (especially chemotherapy and immunotherapy). Regarding radiation therapy, the recommendation is to limit lung dosing. Common parameters estimating lung radiation dosing include mean lung dose and the volume of lung receiving 20 Gy or more (V20). Achieving a mean lung dose of ≤ 20–23 Gy and V20 ≤ 30–35% of the normal lung is recommended [42]. Several treatment techniques are associated with less frequent and less severe RILI. Stereotactic body radiation therapy (SBRT) is associated with less frequent and lower grade RILI [43–45]. In breast and lung cancer treatment regimens, proton beam therapy may reduce risk of pneumonitis [46] and be a safe alternative in patients with co-morbid pulmonary fibrosis [47].

Several systemic cancer therapies increase the risk of RILI. The synergistic effects of cytotoxic chemotherapies such as taxanes, cyclophosphamide, vincristine, doxorubicin, bevacizumab, and mitomycin make them radiotherapy sensitizers. Combinations of these cytotoxic agents have a higher incidence of lung toxicity compared to single agents. In one study, the odds ratio for radiation pneumonitis was 1.6 in patients receiving concurrent chemotherapy compared to sequential chemotherapy [48].

In recent years, immunotherapy has significantly improved outcomes for patients with all stages of NSCLC. However, immunotherapy also impacts the risk of developing RILI. For perspective, rates of immune checkpoint inhibitor pneumonitis range from 2.7% to as high as 13% in patients with NSCLC and is associated with decreased

Table 2 Pathogenesis of RILI

	Timeline	Pathologic sequelae
Immediate phase	Hours to days	Leukocyte infiltration and inflammatory response
Latent phase	Days to weeks	Accumulation of thick secretions
Acute exudative phase	Weeks to months	Hyaline membrane formation
Intermediate phase	Months	Resolution of hyaline membranes, tissue repair, capillary regeneration
Fibrotic phase	Months to years	Collagen deposition and progressive fibrosis

Adapted from [35, 36•]

survival [49]. Recently, increasing numbers of studies are showing a trend towards increased toxicity with combined immunotherapy and radiation therapy in NSCLC. The KEYNOTE-001 trial showed an increase in pulmonary toxicity by 17% in patients who received pembrolizumab and prior radiation therapy [50]. In some studies, it was shown that pneumonitis occurs in areas of low and medium dose suggesting increased sensitivity to radiation of lung tissue resulting in toxicity even at lower doses [51•].

Presentation and Grading

There is no single diagnostic test to confirm RILI. Rather, RILI is a clinical diagnosis relying on a suggestive presentation, timeframe from completion of radiation, imaging findings, and exclusion of other potential etiologies. The most common symptoms and signs from RILI are dry cough, dyspnea, fatigue, and fever. Symptoms generally begin within 3–12 weeks of completion of radiation therapy, though may develop within 1 year after treatment. Physical exam may reveal inspiratory crackles and hypoxemia. Since current or prior tobacco use is common in thoracic malignancies, clinicians should recognize that patients with on-going tobacco use or co-morbid lung disease (e.g., chronic obstructive pulmonary disease) may have cough, dyspnea, and fatigue that are chronic in nature. Therefore, clinicians should clarify if symptoms are chronic, stable, new, or worsening. Finally, symptoms suggesting an alternative condition should be queried, including purulent sputum, orthopnea, hemoptysis, or chest pain.

Evaluation and treatment of RILI are based on severity. There are several grading systems available. Table 3 below compares the Radiation Therapy Oncology Group (RTOG), Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v 5.0), and the Southwest Oncology Group Criteria (SWOG) grading systems [52].

Differential Diagnosis and Evaluation

New or worsening symptoms or signs should prompt an evaluation for RILI. Evaluation is guided by a broad differential diagnosis, including infection, exacerbation of underlying disease, cardiogenic pulmonary edema, tumor-related symptoms (e.g., progression), treatment effect (e.g., chemotherapy or immunotherapy-related pneumonitis), and/or pulmonary embolus (PE). Thus, evaluation should consider complete blood count (CBC), inflammatory markers (ESR and/or CRP), respiratory viral panel, sputum culture, lung imaging (favoring CT imaging and consideration of CT angiogram based on the clinical picture; Fig. 2), and echocardiogram. Referral to specialty care should also be considered at this time.

Recall Pneumonitis

Radiation recall pneumonitis (RRP) is defined as an acute inflammatory reaction which occurs in the field of radiation after receiving triggering agents such as certain chemotherapeutic, immunotherapeutic agents, anti-tuberculosis drugs, antibiotics, simvastatin, and more recently, after COVID-19 vaccines [53•]. Frequency of RRP after individual medication is uncertain, though some studies report a high incidence (18.8%) in patients receiving immunotherapy [54•]. It is independent of radiation dose and radiologic findings in RRP mirror those in radiation pneumonitis. Though treatment is like patients with other forms of RILI, compared to pneumonitis due to radiation alone, RRP resolves faster with steroids (typical duration is 2–4 weeks) and rarely leads to pulmonary fibrosis [53•]. In a small series of 12 patients

Table 3 Radiation-induced lung injury grading

	RTOG [78]	CTCAE v 5.0 [79]	SWOG [80]
Grade 0	No changes		Normal
Grade 1	Asymptomatic or mild symptoms	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Radiographic changes, symptoms do not require steroids
Grade 2	Moderate symptoms of pneumonitis (severe cough) and radiographic changes (radiographic patches)	Symptomatic; medical intervention indicated; limiting instrumental activities of daily living	Steroids required or tap of effusion
Grade 3	Severe symptoms of pneumonitis and dense radiographic changes	Severe symptoms; limiting self-care and activities of daily living; oxygen required	Oxygen required
Grade 4	Symptoms of severe respiratory failure requiring assisted ventilation or continuous O_2	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Requires assisted ventilation
Grade 5	Death-related late effects of radiotherapy	Death	

Adapted with minor changes from Arroyo-Hernández M, Maldonado F, Lozano-Ruiz F, Muñoz-Montaño W, Nuñez-Baez M, Arrieta O (2021) Radiation-induced lung injury: current evidence. BMC Pulm Med. Link to Creative Commons License: https://creativecommons.org/licenses/by/4.0/

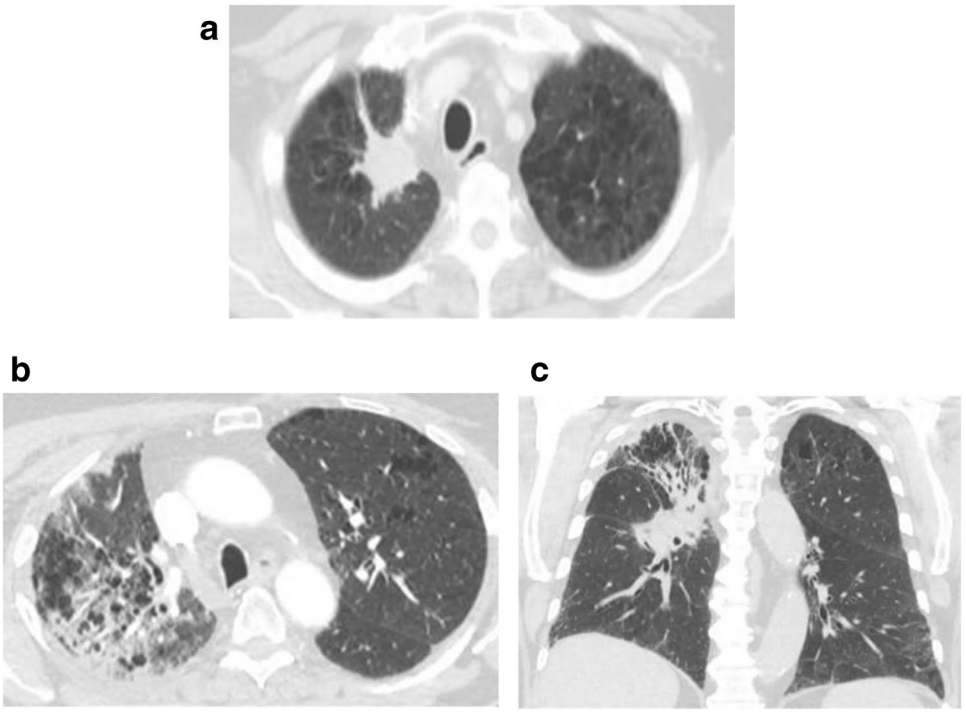

Fig. 2 Imaging findings of radiation pneumonitis. 1a. Right upper lobe tumor prior to radiation treatment. 1b. Right upper lobe status post radiation, with consolidation and ground glass adjacent to the tumor itself. 1c. Right upper lobe tumor status post radiation, with consolidation involving multiple lobes (non-anatomic distribution) and bronchiectasis consistent with developing radiation fibrosis

with RRP, 7 patients were rechallenged with chemotherapeutic agents while on concomitant steroid therapy and no evidence of recurrence of RRP was found [55].

Treatment

Since all pulmonary radiation is expected to cause radiographic change, treatment of RILI is only indicated in patients with symptoms, including grades II–IV in the CTCAE grading system. Though clinical trials are limited, treatment for acute RILI (radiation pneumonitis) prioritizes high dose steroids (commonly 1 mg/kg daily tapered over 8–12 weeks) and supportive measures, including supplemental oxygen and antibiotics as necessary. For high-grade disease (i.e., III–IV), clinicians should strongly consider hospitalization and use of intravenous steroids. In patients with steroid-refractory disease, other immunosuppressants can be considered (i.e., Azathioprine, Cyclosporine).

Special Considerations for Pulmonary Toxicity in Childhood Cancer Survivors

Literature shows that > 50% of CCS at risk for therapy-related pulmonary toxicity have abnormal pulmonary function, with the greatest prevalence occurring in those treated with lung-directed radiotherapy [59]. Toxicities range from subclinical irregularities on pulmonary function testing to severe, debilitating, or life-threatening conditions. The latency period to symptomatic disease may be decades after completion of therapy [60]. Known risk factors for pulmonary late effects include younger age at exposure, atopic history, and concurrent treatment with chemotherapeutic agents conferring lung toxicity, namely, bleomycin, tobacco use (even modest exposure), and substance use [34, 61].

Chronic pulmonary complications in CCS include restrictive or obstructive disease, pulmonary fibrosis, and spontaneous pneumothorax. Though patients may be asymptomatic after therapy, dyspnea and nonproductive cough may ultimately develop [60]. Late radiation fibrosis is refractory to treatment and mitigating modifiable risk factors is essential [60].

Childhood radiation exposure (particularly > 20 Gy) to the chest, abdomen, or spine (thoracic, lumbar, or whole) can impair normal bone growth and lead to scoliosis [34]. Among CCS, scoliosis has been associated with worse restrictive pulmonary function, self-reported functional impairment, and cancer-related pain [62]. As such, patients may require extensive pain management and/or physical or pulmonary rehabilitation.

CCS with pulmonary late effects have decreased physical function [63]. At-risk patients are recommended to have annual clinical evaluation for respiratory compromise, as well as baseline pulmonary function testing in the survivorship period. Counseling on the importance of healthy lifestyle habits and adherence to preventive care recommendations is imperative in this group [34].

Thyroid Complications of Radiation Fibrosis Syndrome

The thyroid is one of the most radiosensitive tissues in the body, and may be affected by radiation to the head, neck, or chest [10]. The most common radiation-associated complications of the thyroid gland include thyroid nodules, cancer, and radiation thyroiditis in the form of hypothyroidism. Higher radiation doses and younger age at exposure are associated with increased risk of subsequent thyroid pathology [61, 62], likely due to radiation-induced apoptosis and necrosis of normal thyroid follicles.

Thyroid Nodular Disease and Thyroid Cancer

The prevalence of thyroid nodular disease and malignancy by age are inversely proportional. While the prevalence of thyroid nodular disease increases with advancing age, the risk of malignancy in a new thyroid nodule declines with advancing age [63]. Despite a lower likelihood of thyroid malignancy with advancing age, thyroid nodules that are cancerous in older patients demonstrate higher risk histological pathology [63]. Patients with a history of head and neck radiation and a family history of thyroid cancer are also at a higher risk for a thyroid nodule that is malignant in nature.

Papillary thyroid neoplasms are the most common thyroid cancer resulting from radiation therapy [64, 65], and the risk persists many decades after exposure [64, 66–69]. The association between thyroid radiation and thyroid cancer may be enhanced in individuals who receive chemotherapy in addition to radiation therapy [70].

Hypothyroidism

While the process is not fully understood, radiation therapy can result in hypothyroidism both indirectly and directly: indirectly, by triggering an autoimmune response resulting in autoimmune thyroiditis, and directly, by radiation-induced apoptosis and necrosis resulting in eventual thyroid atrophy [71, 72•].

In adult cancer survivors, there are two recent studies looking at the correlation of hypothyroidism in patients treated with radiation for breast cancer and head and neck cancer. In breast cancer patients who received supraclavicular radiation, one small trial showed that there was a non-statistically significant increase in TSH levels at 3 and 6 months post-radiation [73•]. A larger single-center trial was completed in head and neck cancer patients treated with neck radiotherapy where the median time between completion of radiotherapy and thyroid function tests was 21 months. This study showed that 40.6% of patients developed hypothyroidism. The same study demonstrated that when the volume of the thyroid spared from radiation therapy was more than 5 cm^3, the risk of hypothyroidism decreased [74•].

Diagnosing Thyroid Complications

Diagnosis of both thyroid cancer and thyroid nodules is done by ultrasound imaging. Physical exam by thyroid gland palpation can also be used to detect thyroid nodules but is less sensitive when detecting smaller nodules; however, thyroid nodules < 1 cm in size are less likely to be cancerous [65]. Diagnosis of hypothyroidism and determination of whether a thyroid nodule warrants a fine needle aspiration is dependent on the results of serum TSH [75]. Both the American Thyroid Association and the National Comprehensive Cancer Network have algorithms to follow when presented with a thyroid nodule on either physical exam or an incidental radiographic finding. It is reasonable to begin annual screening with serum laboratory TSH and palpation of the thyroid gland within 1 year after radiation exposure. While screening thyroid ultrasounds are not routinely recommended at this time given that morbidity related to surgical intervention of the thyroid gland is greater than the risk of mortality of most thyroid cancers [65], if a nodule is palpated on physical exam, it is reasonable to consider a thyroid ultrasound and to have a patient-centered discussion regarding risks and benefits of the diagnostic work-up [65, 75].

Special Considerations for Thyroid Toxicity in Childhood Cancer Survivors

Thyroid dysfunction typically presents years to decades after childhood cancer treatment [62, 76]. Primary hypothyroidism is the most common pathology consequent to radiotherapy among CCS, particularly with exposure doses ≥ 20 Gy [61, 62]. Primary hyperthyroidism is far less common, but can occur, especially following doses ≥ 15 Gy [77]. In a small subset of CCS, primary hyperparathyroidism coexists with thyroid pathology [61].

Thyroid hormones are essential for normal growth and development; thus, timely diagnosis and management of thyroid dysfunction are critical in the pediatric age group [77]. Periodic assessment of parathyroid function and serum calcium levels may also be needed [61]. At-risk CSS require lifelong surveillance, including annual clinical/laboratory evaluation, and thyroid ultrasound as needed [34, 61, 77].

Conclusion

Radiation fibrosis syndrome is common in cancer survivors, and early recognition is crucial to long-term health. Thus, timely diagnosis and management of radiation toxicity is

Table 4 Visceral manifestation of radiation fibrosis syndrome, presenting symptoms, and initial management

Organ system	Radiation effect	Risk factors	Presenting symptoms	Initial management	Screening recommendation
Cardiovascular	Pericarditis	Chest or mediastinal radiation therapy	Dyspnea, pleuritic chest pain, fatigue	Echocardiogram Consider cardiology consult Consider cardiac MRI	Screen for symptoms, annual ECG, Echocardiogram every 5 years
	Myocarditis	Same as above	Chest pain, dyspnea, fatigue	Electrocardiogram Echocardiogram	Same as above, consider cardiac MRI
	Coronary artery disease from accelerated atherosclerosis	Diabetes mellitus; hypertension; inactivity; obesity; tobacco use	Chest pain, dyspnea on exertion, jaw claudication, abdominal discomfort, fatigue, decreased exercise tolerance	Electrocardiogram Echocardiogram Consider statin therapy Consider antiplatelet therapy	Same as above, add coronary angiography or stress test every 10 years
	Heart failure; diastolic dysfunction more common than systolic dysfunction	Concomitant anthracycline therapy	Chest pain, dyspnea on exertion, lower extremity swelling, weight gain, decreased exercise tolerance, fatigue	Electrocardiogram Echocardiogram Cardiology referral	Screen for symptoms, annual ECG, echocardiogram every 5 years
	Valvular disease; aortic stenosis and insufficiency most common	Chest, mediastinal, or head and neck radiation therapy	Chest pain, dyspnea on exertion, lower extremity swelling, weight gain, syncope, dizziness, palpitations	Electrocardiogram Echocardiogram Cardiology referral Consider CT surgery referral	Same as above
Pulmonary	Radiation pneumonitis	Radiation dose > 20 Gy involving > 35% of normal lung tissue; pre-existing interstitial pulmonary disease Concomitant cytotoxic chemotherapy agents	Pleuritic chest pain, dyspnea, cough	Baseline pulmonary function testing at the end of radiation therapy Chest X-ray Chest CT Pulmonary referral Consider systemic corticosteroid therapy	Screen for symptoms periodically during radiation therapy, and at least bi-annually afterwards; determine if symptoms are new, worsening, or chronic
	Radiation fibrosis	Same as above	Pleuritic chest pain, dyspnea, cough, fever, weight loss	Repeat pulmonary function testing Chest X-ray Chest CT Pulmonary referral Consider systemic corticosteroid therapy	Screen for symptoms periodically during radiation therapy, and at least bi-annually afterwards; determine if symptoms are new, worsening, or chronic
Thyroid	Thyroid nodules		Asymptomatic, weight change, hair/nail changes, constipation or diarrhea, anxiety or depression, dysphagia, fatigue	Refer to PCP Thyroid ultrasound Thyroid function tests Consider endocrine referral	Beginning 1 year after radiation therapy, complete annual thyroid palpation and serum TSH Consider thyroid ultrasound if abnormal exam or serum TSH
	Thyroid cancer		Often asymptomatic, may present with a thyroid nodule, hoarseness, weight loss, dysphagia	Refer to PCP Thyroid ultrasound Thyroid function tests Consider endocrine referral Consider ENT surgery referral	Same as above

Table 4 (continued)

Organ system	Radiation effect	Risk factors	Presenting symptoms	Initial management	Screening recommendation
	Hypothyroidism		Depression, hair and nail changes, constipation, fatigue, weight gain	Refer to PCP Thyroid function tests Consider endocrine referral	Same as above

essential for the well-being of patients, through and beyond oncology treatment. Since organ involvement and clinical presentation of radiation fibrosis syndrome is heterogenous, coordinating care among multiple clinicians (i.e., oncology, primary care, survivorship medicine, rehabilitation medicine, cardiology, pulmonary medicine, endocrinology) requires a multi-disciplinary approach. The information presented here, and summarized in Table 4, will help clinicians recognize and address radiation-related toxicity in the heart, lungs, and thyroid and function as an effective multi-disciplinary care team.

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Declarations

Conflict of Interest The authors declare no competing interests.

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