REVIEW ARTICLE

Radiotherapy Induced Tissue Injury: Mechanisms, Symptoms & Management

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Previous literature reviews in the field of cancer and radiation research have focused primarily on the molecular and pathological findings observed in cancer patients receiving radiotherapy. This article goes a step further to provide the primary care physician a systematic review of the signs and symptoms associated with the adverse effects of radiation therapy and their implications for treatment and long-term prognosis. A review of relevant literature was conducted for articles published within the past 10 years and of these, 21 were included in this review. From a primary care standpoint, this study focused strongly on clinically relevant side effects as a result of radiation therapy in the gastrointestinal, pulmonary, cardiac, and dermatologic systems. Thus, by providing clinical knowledge regarding the treatment and management of these patients, physicians may improve quality of life and overall survival.

INTRODUCTION

Cancer is the second leading cause of death in the United States. It is estimated that more than 1.6 million new cases of cancer will be diagnosed in 2014, and of these, almost two-thirds will be treated with radiation therapy.[1] While the benefits of using radiation therapy in the treatment of cancer have been well established, the development of acute and chronic adverse effects and their implications on long-term morbidity and mortality remain largely unknown. Conversely, recent advances in radiation oncology have led to significant improvements in patient outcomes by adjusting therapy to patient specific factors including tumor size, normal tissue radiosensitivity, and radiation dosage.[2] As such, the current goals of mainstream radiation therapy are to maximize tumor reduction and minimize radiation-induced adverse effects.[3] Clinical knowledge of the signs and symptoms most frequently associated with radiation-induced toxicity is vital in cancer survival due to the fact that radiation toxicity may limit the use of some treatment modalities. It has been well established that toxicity-related interruptions in radiation therapy are associated with decreased patient survival.[4] While acute radiation toxicity tends to be self-limiting, late-onset toxicity may have a severe impact on quality of life many years after radiation exposure. In addition to the use of therapeutic interventions to reduce side effects, careful management of disease progression is an important factor in improving quality of life and prognosis.[3] The aim of this article is to provide the primary care physician a systematic review of signs and symptoms associated with the side effects of radiation therapy and their implications for current treatment modalities and long-term prognosis. For a comprehensive review regarding the underlying pathology and diagnostic studies related to radiation-induced damage, the reader is encouraged to refer to additional outside articles.

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MATERIALS & METHODS

A systematic review of the literature was done from 2004 to 2014 by use of PubMed and Medline databases. The search terms included radiation therapy, acute and late toxicity, pathophysiology, management, gastrointestinal, radiation pneumonitis, cardiac toxicity, and radiation dermatitis. References were screened and selected for inclusion in this review based on relevance and of these, 21 were included in this review.

GASTROINTESTINAL TOXICITY

It is estimated that over 200,000 patients a year undergo radiation therapy for pelvic and gastrointestinal cancer.[4] Of the patients treated with pelvic radiation therapy, 60-80% will experience acute bowel toxicity, as well as significant long-term impacts on their quality of life.[4] Further, as many as 50% of patients receiving pelvic radiation therapy experience chronic GI dysfunction or changes in bowel habits.[4,9] Considering these findings, clinically significant adverse effects and radiation toxicity remain a health concern.[4] It has been shown in epidemiological studies that smoking and previous metabolic syndromes, such as hypertension, diabetes, and inflammatory bowel disease, increase the risk of acute and chronic radiation enteropathy.[9] Psychosocial factors

involved in cancer diagnosis and treatment have also been implicated in GI dysfunction.[9] In addition, the intestines are more susceptible to radiation exposure during pelvic radiation therapy due to their large surface area. Surprisingly, physicians investigate complaints of gastrointestinal issues made by patients receiving radiation therapy less frequently than those not receiving radiation therapy.[4] Thus, the identification and management of new onset symptoms are key in modifying therapeutic and long-term outcomes.

Acute bowel toxicity presents within the first couple of weeks of radiation therapy as diarrhea, nausea, and abdominal pain. These symptoms typically subside 3-4 weeks after the conclusion of therapy.[4] In general, the treatment of acute radiation enteropathy is primarily symptomatic. It is important to mention that severe complications, although only thought to occur in 4-8% of patients 5-10 years after treatment, are life threatening and include fistulation, sepsis, stenosis, gastrointestinal failure, and secondary malignancies.[10] These life threatening complications are treated as emergencies and surgical intervention is indicated.[10] The exact mechanisms resulting in acute radiation toxicity have not yet been fully elucidated; however, epithelial injury has been associated with degeneration of the mucosal layer and the release of inflammatory mediators.[4]

Symptoms of chronic bowel toxicity typically occur between six months and three years following radiotherapy and include diarrhea, rectal bleeding, abdominal cramping, constipation, and changing bowel habits.[9] Similarly, the exact mechanisms involved in chronic toxicity remain unclear. Management of symptoms is focused primarily on the treatment of the underlying functional deficits.[9] This implication highlights the importance of recognizing the underlying pathology as it determines the appropriate treatment modality. For example, radiotherapy-related diarrhea is frequently reported following pelvic radiation therapy and has been associated with physiological changes in bowel motility, small-bowel bacterial overgrowth, and malabsorption of bile salts and carbohydrates.[4] Awareness of the symptoms associated with radiation-induced bowel toxicity and the appropriate diagnostic studies are fundamental in the management of an increasing population receiving radiation therapy. In addition, a better understanding of the pathological process of gastrointestinal toxicity is necessary to identify possible therapeutic interventions in the goal of preventing interruptions in cancer therapy and improving patient quality of life.

PULMONARY TOXICITY

Lung and bronchus cancer are the leading causes of cancer related death in the United States. It is estimated that 224,000 new cases of lung and bronchus cancer will be diagnosed in 2014 and continues to be a global health burden.[1] Thoracic radiation therapy is an essential treatment modality in the treatment of lung cancer, as well as a variety of other thoracic tumors. Unfortunately, clinically significant tissue toxicity is a frequent dose-limiting adverse effect in patients receiving radiation therapy, consequently reducing the effectiveness of therapy.[11] Radiation pneumonitis (RP) and pulmonary fibrosis (PF) are the most common severe adverse effects in these patients and represent a significant barrier to patient outcomes and overall survival rates.[11] It has been reported that between 5-50% and 1-43% of patients undergoing thoracic irradiation experience radiation pneumonitis and pulmonary fibrosis, respectively.[12,13] Further, a number of patient-related factors have been linked to the development of RP, such as prior lung disease, reduced pulmonary function, genetic factors, and old age. In addition, the radiation dose rate, absorbed radiation dose, and the volume of lung irradiated are factors that determine the level of risk of developing radiation-induced lung injury (RILI).[11] However, a general consensus has not yet been established regarding lifestyle and comorbidity risk factors due to the frequent contradictions between studies.[12]

The exact mechanism of radiation-induced lung injury is complex and has not been described in detail; however, it is suggested that tissue repair and cellular signaling pathways associated with chronic inflammation are involved and include inflammatory mediators, immune cell recruitment, and macrophage activation among others.[11] For example, TGF-β, a cytokine produced by inflammatory cells after radiation-induced tissue damage, is involved in a wide range of cellular signaling pathways implicated in RILI, such as inducing the differentiation of fibroblasts into matrix-producing myofibroblast, inhibiting epithelial cell proliferation, and controlling the breakdown of connective tissue.[11] The pathological changes associated with RILI are described in a three-step process that involves a latent phase, exudative phase, and fibrotic phase.[3] The latent phase is described as occurring up to three months after radiation therapy, yet no significant histological findings are typically observed. During the exudative phase, acute inflammation is observed, as well as inflammatory cell infiltration and thickening of the interstitium. Consequently, alveolar gas exchange is reduced. Finally, the fibrotic stage is characterized by permanent fibrosis, which contributes to the reduction in the number of alveoli, thickening of alveolar septae, and thickening of the alveolar wall.[11, 12] The alveolar-capillary complex is the most radiosensitive component of the lung and is highly resistant to treatment.[11]

RP represents the acute phase of radiation-induced lung injury (RILI) and typically occurs 1-6 months after radiation therapy.[11] Clinical manifestations of RP typically appear 1-3

months following radiation therapy and include a dry cough, dyspnea, fever, respiratory insufficiency, and chest pain.[11, 12] While there is little evidence supporting the effectiveness of therapeutic intervention, symptoms are frequently managed with oral corticosteroids.[14] The onset of radiation-induced pulmonary fibrosis, a chronic phase of RILI, typically occurs months to years after treatment.[12] Progressive pulmonary fibrosis by this stage is usually permanent and may lead to late complications that include cor pulmonale and respiratory insufficiency.[13] In addition, both the acute and late toxic events reduce the capacity to recover from ongoing or future pulmonary challenges and in some cases, may be fatal.[12] The current approach in the treatment of RILI is focused on balancing the inflammatory component of lung injury. For example, amifostine, a free radical scavenger, is a therapeutic agent currently in clinical use to reduce the oxidative stress associated with radiation exposure.[11] In addition, the neutrophil elastase inhibitor, sivelestat, has been shown to significantly reduce collagen deposition and prevent fibrotic changes associated with RILI.[11] While a few pharmacological agents are in current clinical use, further research into the effectiveness of existing and future therapeutic agents is necessary. It is also important to recognize that clinical factors, such as concurrent chemotherapy, re-irradiation, and the recent withdrawal of steroids are associated with an increased risk of RP and may require more extensive monitoring.[13]

Currently, imaging studies are the mainstream tool for evaluating pulmonary toxicity. MRI imaging has largely replaced the use of commuted tomography (CT) and X-rays in order to avoid further radiation exposure in radiation-susceptible patients.[11] Radiographic findings of RILI show areas of infiltration and scar formation near or around the site of radiation exposure. In addition, pulmonary function testing, forced vital capacity, and carbon monoxide diffusion capacity are also utilized clinically as a measure of lung injury.[12] Despite a number of diagnostic modalities and scoring systems, RP is largely diagnosed based on the clinical symptoms following radiation therapy. Current research is focused on the association between specific serum biomarkers and RILI to provide better diagnostic measures for tissue damage. Due to the fact that cytokines are associated with the fibrotic and inflammatory changes associated with RP, these biomarkers offer a potential mechanism to monitor tissue toxicity during radiation therapy. Studies have shown that elevated plasma levels of both TGF-β and IL-6 are associated with an increased risk of RP.[3, 11]

Thoracic radiation therapy exposes other critical organs to radiation damage, such as the heart, trachea, bronchus, and esophagus. Although, the trachea and bronchus are at increased risk for radiation exposure, they appear to be relatively radioresistant.[3] Nevertheless, radiation esophagitis, a common adverse effect following thoracic radiotherapy, remains a dose-limiting complication in the treatment of lung cancer. Research estimates that as many as 30% of patients undergoing pulmonary chemoradiation experience radiation esophagitis, most commonly complaining of dysphagia.[3] Progression of this disease may lead to severe complications, such as esophageal stricture and ulceration, which may require immediate hospitalization and surgical intervention.[3, 15] Thus, complications of radiation esophagitis have implications on quality of life and ultimately, overall survival. Monitoring and managing of these symptoms is fundamental to enhance patient outcomes. In addition, the utilization of modern radiation techniques that involve risk planning, avoidance of at risk organs, and planned dose/volume irradiation are essential in reducing esophageal toxicity.[3,15] Therapeutic interventions for radiation esophagitis are primarily aimed at symptomatic relief using agents such as topical analgesics; however, current research on the effectiveness of radioprotective agents is ongoing and may provide additional strategies for the prevention of radiation damage.[3]

CARDIAC TOXICITY

Thoracic radiation therapy is indicated in the treatment of a number of thoracic malignancies, such as Hodgkin' lymphoma, lung cancer, breast cancer, and other mediastinal cancers.16 Although vast improvements in radiation techniques over the past few decades have increased cancer survival rates and reduced radiation-induced adverse effects, cardiovascular disease remains one of the most severe and life-threatening complications, carrying clinically significant morbidity and mortality.[8] Radiation-induced heart disease (RIHD) is considered a disease of long-term cancer survivors and is the leading cause of non-malignant mortality in these patients.[17] As such, little data is currently available regarding the long-term benefits of modern tissue-sparing radiation techniques on reducing RIHD. In fact, cancer survivors who underwent radiation therapy as a child are at increased risk for developing late cardiac complications. It is estimated that cardiovascular complications manifest within 3 to 29 years after completion of radiation treatment with an incidence between 10% and 30% by 5 to 10 years.[11,13] Lifestyle factors, such as prior cardiovascular disease, obesity, young age, diabetes, hypertension, and smoking further compound cardiac risk. Systemic chemotherapy has also been recognized as having a synergistic effect with concurrent radiotherapy in the development of cardiovascular disease.[16] In addition, several studies have shown a significant increase in cardiovascular-related mortalities in patients receiving left-sided radiotherapy as opposed to right-sided radiotherapy.[16] Management of these risk factors and the use of routine screening protocols are crucial in preventing morbidity and mortality. While there are no uniform guidelines for screening and monitoring post-

irradiation cardiac damage, a baseline evaluation of cardiac function is recommended to monitor disease progression.[17]

The features of RIHD are complex and are further compounded by the specific underlying malignancy. Acute and chronic cardiac adverse effects of thoracic radiation therapy include pericarditis, coronary artery disease, valvular dysfunction, conduction system disruption, and heart failure.[17] In general, acute RIHD must be considered in any patient presenting with cardiovascular complaints at the time of radiation treatment; however, these complications are not usually clinically significant.[16] For example, acute pericarditis, a now uncommon complication due to advancements in radiation techniques, may present similarly to traditional forms of acute pericarditis with symptoms of fever, pleuritic chest pain, dyspnea, and tachycardia.[16] Acute pericarditis is not considered a dose limiting complication and is frequently resolved with bed rest and NSAIDS.[18] Conversely, as many as 10% to 20% of patients experience chronic pericarditis within 5 to 10 years after radiation therapy.[16] Imaging techniques are frequently utilized in the evaluation of pericarditis to assess the extent of pericardial thickening, the presence and quantification of pericardial effusion, and for monitoring disease progression.[17] Imaging modalities, such as an echocardiogram, cardiac computerized tomography, and cardiac magnetic resonance are useful for establishing a diagnosis and to rule out more serious underlying pathology, for example cardiac tamponade.[16, 17]

Radiation exposure is widely correlated with coronary artery disease (CAD). While the exact mechanism is still under investigation, coronary vascular damage is thought to be a consequence of an increased production of free radicals, an increase in vascular permeability, and the release of inflammatory mediators.[18] Subsequently, intimal proliferation and fibrosis leads to vessel stenosis, as well as the development of clinically significant cardiac complications. The pathological changes associated with radiation-induced coronary artery disease (RICAD) share many histopathologic features with atherosclerosis.[18] In fact, risk factors for developing RICAD remain the same as those associated with non-irradiated CAD.16 Similarly, the diagnostic and management approach to RICAD parallels those with CAD in the general population. Patients with RICAD typically present with angina, dyspnea, and heart failure.[18] Surgical intervention has been shown to be just as effective for RICAD as in atherosclerotic disease.[13] In addition, both coronary artery bypass graft and percutaneous intervention have been widely employed in the treatment of appropriately selected patients.[16] Thus, clinical knowledge regarding this late complication has important implications in reducing the incidence of severe consequences, such as stroke or myocardial infarct since successful treatment modalities are available. From a primary care standpoint, long-term cardiovascular follow-up is essential in reducing negative outcomes in these patients.

DERMATOLOGIC TOXICITY

Radiation dermatitis is one of the most common adverse effects associated with radiation therapy for breast, perineal, and prostate cancers.[3] Despite modern radiation techniques, it is estimated that as many as 90% of patients that undergo radiation therapy develop a skin reaction.[19] Patients with radiation dermatitis usually develop erythema, itching, telangiectasias, alopecia, and ulcerations.[3] Severe skin reactions may be painful and lead to more serious complications, such as infection, necrosis, and permanent scarring.[20] Radiation dermatitis also carries a significant psychological burden.[19] In addition to the emotional impact of cancer diagnosis and treatment, patients suffering from radiation dermatitis experience a reduced quality of life.[19] It is thought that inflammatory mediators associated with damage to the epidermis contribute to the development of radiation dermatitis. Chen et al. showed that IL-1, an inflammatory cytokine, plays a significant role in modulating skin toxicity in a mouse model for radiation dermatitis.[21] Clinically, acute exposure typically produces symptoms within 10-14 days. It is widely accepted to use moisturizers to reduce skin irritation. In addition, topical steroids are commonly used prophylactically to prevent radiation dermatitis; however, evidence is limited regarding the effectiveness of this therapy.[3,19] Further investigation is necessary to determine the value of topical steroids and other pharmacological agents in the treatment of skin toxicity.

CONCLUSION

Vast improvements in radiation techniques and risk management over the past few decades have led to increased cancer survival rates and reduced radiation-induced adverse effects. While the benefits of using radiation therapy in the treatment of cancer have been well established, the development of acute and chronic adverse effects and their implications on long-term morbidity and mortality remain largely unknown. Literature surrounding late radiation toxicity is limited due to the fact that these adverse affects have only recently become prevalent in an aging population receiving curative treatment for cancer. While the primary care physician may not be directly treating the cancer patient undergoing radiation therapy, there is a strong likelihood that the physician will encounter patients treated in this manner. Developing a plan to identify acute and chronic side effects of radiation therapy is important in the management of the entire patient. Collaboration with the specialist will allow for an optimal care plan for the patient and could minimize patient anxiety and reduce unnecessary diagnostic testing.

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