

Review Article

A concise review of irradiation sequelae on the cardiovascular system in pulmonary malignancies

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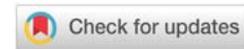
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Abstract

Pulmonary malignancies including Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC) are frequent cancers and remain to be a leading cause of cancer related mortality worldwide. Radiation Therapy (RT) has an integral role in management of both SCLC and NSCLC. It may be used as the single definitive modality, as part of curative combined modality management, and also for salvage treatment or recurrent disease settings in selected patients. Nevertheless, radiation induced toxicity constitutes an important concern in radiotherapeutic management of pulmonary malignancies. Among the adverse effects of pulmonary irradiation, radiation induced cardiotoxicity deserves utmost consideration. Several studies consistently underscore the importance of minimizing heart exposure as much as possible to avoid untowards cardiac morbidity and mortality.

There have been substantial advances which contributed to improved radiotherapeutic management of SCLC and NSCLC including improved staging and target definition by incorporation of molecular imaging, automatic segmentation procedures, Image Guided Radiation Therapy (IGRT), Breathing Adapted Radiation Therapy (BART), Adaptive Radiation Therapy (ART), Intensity Modulated Radiation Therapy (IMRT). Nevertheless, there is room for further achievements. Proton therapy for management of lung cancer has been suggested as a relatively newer treatment modality with promising results. Unique characteristics of proton therapy may allow for improved cardiac sparing along with reduced integral dose. Future trials are warranted to shed light on contemporary management of pulmonary malignancies with optimal cardiac sparing and reduced irradiation sequelae. Herein, we provide a concise review of irradiation sequelae on the cardiovascular system in pulmonary malignancies.

Introduction

Pulmonary malignancies including Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC) are frequent cancers and remain to be a leading cause of cancer related mortality worldwide [1-3]. Many lives are lost due to these cancers despite advances in diagnosis, staging, and management. Nevertheless, main modalities for management of pulmonary malignancies include surgery, Radiation Therapy (RT), and systemic therapies. There have been improvements in all treatment modalities and therapeutic strategies. Combined modality management has been adopted for achieving improved therapeutic outcomes, however, excessive toxicity has been a

concern in particularly intensified therapeutic regimens with potential to cause treatment interruptions, morbidity, and even mortality in some patients.

RT has an integral role in management of both SCLC and NSCLC. It may be used as the single definitive modality, as part of curative combined modality management, and also for salvage treatment or recurrent disease settings in selected patients. There have been substantial advances which contributed to improved radiotherapeutic management of SCLC and NSCLC including refined target definition by incorporation of molecular imaging, automatic segmentation procedures, Image Guided Radiation Therapy (IGRT), Breathing Adapted



Radiation Therapy (BART), Adaptive Radiation Therapy (ART), Intensity Modulated Radiation Therapy (IMRT), and radiosurgical applications such as Stereotactic Radiosurgery (SRS) and Stereotactic Ablative Body Radiotherapy (SABR) [4-50]. These advances are aimed at improving treatment outcomes for patients suffering from pulmonary malignancies. While enhancing the efficacy of management is a desired endpoint, improving the toxicity profile of radiation delivery thereby improving morbidity outcomes and quality of life are also important. Radiation induced toxicity constitutes an important concern in radiotherapeutic management of pulmonary malignancies. Herein, we provide a concise review of irradiation sequelae on the cardiovascular system in pulmonary malignancies.

Irradiation sequelae on the cardiovascular system in pulmonary malignancies

Given the considerable benefit of RT either as a single treatment modality or as part of combined modality management of both SCLC and NSCLC, irradiation has been traditionally incorporated in therapy of most patients with lung cancers. However, RT may cause a plethora of complications and adverse effects in treated patients including fatigue, sore throat and difficulties in swallowing with dysphagia, odynophagia, and esophagitis particularly in the setting of synchronous chemoradiotherapy administration, skin toxicity in the forms of dry, red, itching and peeling skin, pulmonary changes in the form of radiation induced lung injury which may manifest as radiation pneumonitis with dyspnea, fibrosis, radiation myelitis, and cardiovascular effects [51-54]. Cardiovascular effects of irradiation may include pericarditis, restrictive heart diseases, valvulopathies and coronary artery disease. Vigilant follow up is an indispensable part of management for RT of pulmonary malignancies given the risk of acute and late adverse effects including cardiotoxicity. Meticulous follow up is important taking into account the late manifestation of some cardiovascular side effects manifesting after long periods after RT. Among the adverse effects of pulmonary irradiation, radiation induced cardiotoxicity deserves utmost concern as addressed by several authors [54-66]. These studies consistently underscored the importance of minimizing cardiac exposure as much as possible to avoid untowards morbidity and mortality. Severity and incidence of radiation induced cardiovascular adverse effects may be affected by coexisting cardiovascular risk factors of the irradiated patients along with the RT dose and exposed cardiac volume [54]. A comprehensive review by Mrotzek et al. addressed cardiovascular damage associated with chest irradiation [54]. Even low dose cardiac exposure may adversely affect on cardiovascular structures, and dose to even small volumes of the left ventricle may be of particular concern. Combined modality management with RT and chemotherapy such as anthracyclines may add to the risk and severity of cardiotoxicity. Patients with smoking history may have a higher risk of cardiovascular complications. Advanced irradiation techniques with improved cardiac sparing capability may decrease cardiac exposure and relevant adverse effects. Breathing maneuvers, particle therapy, IGRT, IMRT, and focused irradiation techniques may offer an improved toxicity profile. The study by Wang et al. assessing cardiac

toxicity after RT for stage III NSCLC reported that cardiac events were relatively frequent following high dose thoracic irradiation and adverse effects were independently related with cardiac dose and baseline cardiovascular risk profile [55]. A review on cardiac toxicity of lung cancer RT underscores the importance of limiting heart exposure since heart dose may be a predictor of worse survival as shown in dose escalation trials [56]. A practical recommendation may be keeping the whole heart volume receiving 25 Gy or more below 10% and cardiac exposure should be minimized as much as possible in view of the relatively limited data in the literature [56]. The study by Wong et al. reported that higher maximum doses to bilateral ventricles were associated with poorer survival for patients undergoing SABR, which suggests that adverse effects of irradiation on the cardiovascular system should be considered even when the contemporary and sophisticated technologies are utilized for radiation delivery [66]. Clearly, dose volume parameters should be individually assessed thoroughly for consideration of irradiation sequelae on a patient by patient basis. Other factors such as the use of concomitant systemic agents and preexisting cardiac diseases and comorbidities should also be taken into account. Utilization of contemporary techniques should be strongly considered to improve the toxicity profile of radiation delivery for radiotherapeutic management of pulmonary malignancies.

Conclusion and Future Perspectives

Pulmonary malignancies including SCLC and NSCLC remain to be a leading cause of cancer related deaths around the globe. While RT composes an integral treatment modality for both SCLC and NSCLC, toxicity of irradiation is an important concern. Recent years have witnessed significant improvements in the discipline of radiation oncology with adoption of state of the art techniques in clinical practice. IGRT, BART, ART, and IMRT allow for improved patient management with reduced risks of radiation induced morbidity and mortality. Nevertheless, there is room for further achievements. More recently, proton therapy for management of lung cancer has been suggested as a relatively newer treatment modality with promising results [67-70]. Unique characteristics of proton therapy may allow for improved cardiac sparing along with reduced integral dose [67-70]. Combinations of contemporary techniques with proton therapy may further improve the toxicity profile of radiation delivery despite the need for stepwise clinical adaptation in light of high level evidence. Future trials are warranted to shed light on contemporary management of pulmonary malignancies with optimal cardiac sparing and reduced irradiation sequelae.

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