



Radiation Effects in the Mediastinum and Surroundings: Imaging Findings and Complications

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Radiotherapy is one of the cornerstones for treatment of patients with cancer. Although advances in radiotherapy technology have considerably improved radiation delivery, potential adverse effects are still common. Postradiation changes to the mediastinum can include different structures such as the heart, great vessels, and esophagus. The purpose of the article was to illustrate the expected variety of changes to the mediastinum and adjacent lung resulting from external beam radiotherapy and radiotherapy-induced complications to the mediastinum and to discuss different radiotherapy delivery techniques.

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Introduction

External beam radiation has been used in the treatment of a number of thoracic malignancies including lymphoma, carcinomas of the lung, esophagus, and breast as well as thymic epithelial neoplasms. Whether used as a primary therapeutic modality or in combination with chemotherapy or surgery, radiotherapy plays a central role in management of thoracic neoplasms, and it is estimated that more than 50% of all patients with cancer are treated with radiation.¹ Although the therapeutic goal of radiotherapy is to target adequate dose to the tumor itself, also known as the gross tumor volume, involvement of surrounding normal tissues is inevitable as into the volume irradiated, one also includes a margin of subclinical disease spread that is not appreciated by imaging, the clinical

target volume, as well as a planning target volume, which allows for uncertainties in planning or in treatment delivery. Thus, to achieve a potential cure or local control, normal surrounding tissues are routinely incorporated into the irradiated field. As the mediastinum houses many important structures, any radiation within it or next to it may cause adverse effects to adjacent critical structures including the heart, great vessels, thymus, esophagus, and lung. This has a particular effect in the younger patient population and long-term survivors as in these patient populations, the long-term effects of this treatment may manifest and even increase their mortality.² Sophisticated radiotherapy technologies such as 3-dimensional conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and proton therapy (PT) have been developed to minimize normal tissue radiation while permitting adequate delivery dose to the tumor.

Radiation Techniques

Owing to recent developments of new methods of radiotherapy delivery leading to highly conformal radiation to the target, knowledge of radiation treatment plans is essential for a better understanding of postradiation effects in the mediastinum. The main goal for radiotherapy planning and delivery is to achieve a better tumor delineation allowing target dose escalation while reducing toxicity to normal surrounding

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structures. Conventional 2D radiation portals have shown high local treatment failure rates, mostly reported in patients with non-small-cell lung cancer.^{3,4} Development of modern technologies for radiotherapy delivery allows treatment focused to the tumor, reducing dramatically the volume of normal tissue irradiated to high doses. 3D-CRT uses multiple beams with a variety of orientations to determine the target volumes to be treated, which enables delivery of maximal radiation exposure to the tumor while minimizing dose to normal structures. IMRT allows highly accurate conformal treatment shaped to the target with a steep fall in the dose to the neighboring normal tissues sparing radiation to a large volume of normal tissue while allowing highly accurate target coverage. Additionally, PT delivers its therapeutic dose to a certain depth (as defined by the Bragg peak) without a significant exit dose. As a consequence, PT has the ability to deliver high-dose radiation to the tumor while avoiding uninvolved mediastinal structures. PT offers an advantage over photon radiation delivery techniques for select situations such as for those tumors that have been irradiated and reirradiation is needed. Additionally, PT offers lower toxicity of normal tissues adjacent to the target. A retrospective study comparing PT with 3D-CRT and IMRT demonstrated that PT significantly reduced dose delivered to normal lung tissue (<10 Gy), heart, spinal cord, and in certain cases, esophagus.⁵ More sophisticated radiotherapy technologies, such as 4D imaging, permit delivery of highly accurate conformal treatment and reduced uncertainty related to the movement of the target due to patient respiratory motion.

Heart

The risk of cardiac toxicity associated with mediastinal radiotherapy is well known.⁶ It is mostly documented in patients with a greater likelihood for long-term survival such as patients with lymphoma or breast cancer although other irradiated intrathoracic malignancies may develop postradiotherapy cardiac complications as well. Cardiovascular disease was the third most common cause of death in patients followed long-term after radiotherapy for Hodgkin's disease, accounting for 12%-16% of mortality.^{7,8} Risk factors for radiation-associated cardiac toxicity include doses higher than 30 Gy, large volume of irradiated heart, younger age at exposure, longer time after the exposure, concomitant chemotherapy, and patient-specific factors such as diabetes, hypertension, and preexisting cardiac disease.⁹ All structures of the heart including the pericardium, myocardium, coronary arteries, valves, and conduction system have the potential to be damaged by irradiation leading to early and late cardiac adverse effects.

Pericardium

Approximately 20%-40% of patients who have received mediastinal radiotherapy develop pericarditis. Histopathologically early pericardial reaction after irradiation is characterized by increased vascular permeability, fluid extravasation, and inflammatory cell infiltration, which is observed weeks or

months after radiotherapy, leading to development of pericardial fibrin exudates and effusions.^{10,11} Late radiation changes in the pericardium are fibrous thickening characterized microscopically by collagen and fibrin deposition. Clinical symptoms of acute pericarditis can be seen occasionally, usually within weeks after cardiac irradiation.¹² Patients present with pleuritic chest pain, fever, tachycardia, and electrocardiographic abnormalities. Symptoms are usually mild and treated with nonsteroidal anti-inflammatory drugs. In few patients, a late adverse effect may occur up to 10 years after radiotherapy with development of chronic pericarditis. Symptoms from chronic pericarditis are variable ranging from asymptomatic patients incidentally diagnosed during follow-up computed tomography (CT) scans to a large pericardial effusion with pericardial tamponade requiring urgent pericardiocentesis. Electrocardiographic abnormalities detected are sinus tachycardia with PR and ST segments abnormalities in acute pericarditis and low QRS voltage and T-wave abnormalities in a chronic stage.¹³ Echocardiography is the method of choice for assessing pericardial fluid and estimating the volume of effusion and its hemodynamic effect. The chest radiograph is nonspecific and often underestimates the size and presence of pericardial effusions. A larger pericardial effusion is visualized radiographically as globular enlargement of the cardiac silhouette giving a typical water bottle configuration (Fig. 1). Using CT and magnetic resonance imaging (MRI), the normal pericardium thickness was found to be less than 2 mm.¹⁴ CT can easily detect fluid density surrounding the heart characteristic of a pericardial effusion (Fig. 1). When an intravenous contrast agent is used with either CT or MRI, enhancement of the thickened pericardium generally indicates inflammation. In the chronic setting, constrictive pericarditis can develop. Although differentiation between constrictive pericarditis and restrictive cardiomyopathy (CMP) is clinically difficult, imaging findings may be helpful in differentiating both entities. CT is better to assess calcified pericardium (Fig. 2), but cardiac MRI has the advantage of its improved contrast resolution as well as demonstrating the cardiac motion. Thus, it assesses better the pericardial involvement with increased thickness (>4 mm) and the septal flattening. It also shows the early diastolic bouncing characteristic of constrictive pericarditis, best seen on the 4-chamber view, which helps differentiate this entity from restrictive CMP.¹⁵

Myocardium

Patients treated with radiotherapy to the chest are more likely to develop CMP. Mulrooney et al¹⁶ found that young patients who survived radiotherapy were 6 times more likely than their siblings to develop congestive heart failure. Radiation can cause microcirculatory damage to the myocardium with consequent ischemia and late development of myocardial fibrosis. Microvascular damage may manifest initially with impaired myocardial contractile reserve, followed by left ventricular (LV) ejection fraction (EF) (LVEF) reduction and myocardial fibrosis.¹⁷ Restrictive CMP with LV diastolic dysfunction presents more frequently than dilated CMP with LV systolic dysfunction.¹⁸ Dose and volume irradiated are risk factors for

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