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REVIEW

# Radiotherapy-induced Cardiotoxicity After the Treatment of Pulmonary and Mediastinal Solid Tumors

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**SUMMARY**

Thoracic tumors are extremely common and radiotherapy plays an important role in the treatment of these malignancies. Cardiac radiation exposure which is inevitable during thoracic radiotherapy may damage the heart muscle, valves, or coronary arteries. If a malignant thoracic disease can be successfully treated with the contribution of radiotherapy, long-term cardiac toxicity will become a critical factor in determining survival. Therefore, radiation oncologists have recently focused on efforts to provide local disease control without causing toxicity. Over time, advances in radiotherapy techniques have made it possible to significantly limit the dose of cardiac structures while effectively treating the thoracic tumor. Intensity-modulated radiotherapy techniques are beneficial in reducing the cardiac dose and therefore cardiac toxicity. Advanced particle radiotherapy applications such as proton therapy have the potential to improve tumor cell killing efficiency and reduce the risk of cardiac complications. Close and long-term cooperation between radiation oncologists and cardiologists is important in the follow-up of patients undergoing thoracic radiotherapy.

**Keywords:** Cardiotoxicity; lung cancer; thoracic radiotherapy; thoracic sarcomas; thymic tumors.



## Introduction

Cardiac disorders are not very common after thoracic radiotherapy, but they can manifest as a late side effect and can determine the long-term survival of patients with thoracic malignant disease. These may occur if the treated area includes the heart or mediastinum.

Lung cancer is one of the most common cancers and the leading cause of cancer death. Thymic tumors, which are generally located in the anterior part of mediastinum, are the most common primary mediastinal neoplasm in adults following lymphoma. Neurogenic tumors are the most often tumors arising from the posterior mediastinal compartment. Radiotherapy generally has been a part of the treatment of all these diseases for quite a while now.[1]

Recent series have shown that heart damage is one of the most important problems of chest radiotherapy. In the modern radiotherapy era, three-dimensional conformal radiotherapy and intensity-modulated radiation therapy (IMRT), recently stereotactic body radiation therapy (SBRT), and proton therapy appear to improve possibly survival with reduced toxicity of thoracic radiotherapy.[2]

## Radiation-induced Cardiovascular Complications

Radiation exposure may damage the heart muscle, valves, or coronary arteries. Actually, cardiac myocytes which are considered a kind of post-mitotic cells are much more resistant to radiation comparing with the

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cells which reveal rapid cellular turnover. The effects of radiation on the vascular endothelial cells are particularly important for radiotherapy because many late effects occur secondary to damage on blood vessels.[2,3]

Radiotherapy-induced cardiotoxicities are usually classified as early (acute) or late (chronic) effects according to the time of appearance of the symptoms. The acute effects include pericarditis and arrhythmias. The most common type of radiation-induced cardiac toxicity is pericarditis with a variable degree of pericardial effusion. About 50% of the cases occur within the first 6 months, reminder can be within 2 years. It is generally asymptomatic and disappears spontaneously in the majority of patients. Sometimes pericardial effusion ushers or foretells the tumor progression and then the clinical picture may be confusing for clinicians.[2]

The consequential late radiation effect, which is considered as another type of toxic effect of radiotherapy, is the result of acute damage that has not healed properly and persists to become a chronic lesion. Some cases (7-20%) of acute pericarditis can be persisting and transform into chronic pericarditis in the end. Developing chronic pericarditis in the majority of patients, the disorder occurs directly as a late reaction.[2,3]

The late effects of radiotherapy on the heart may be considered more serious than the acute effects. Since the radiation-induced late cardiac effects usually occur after 5 years of radiotherapy (mean 7-10 years), the occurrence of these effects is particularly important in patients who have a long life expectancy.[2,3]

Radiation-induced valvular disease is another common side effect of radiotherapy. The valves located on the left side of the heart have a higher incidence of damage due to the greater hemodynamic force imposed by the high pressure at the left. Moreover, since in the past thoracic radiotherapy was less homogeneous in delivering radiation dose to the patients, likely the left-sided valves have historically received greater radiation doses than those on the right.[2] Actually, the radiation-induced valvular disease generally comes out as damage in multiple valves. Although valve thickening occurs as high as 40-43%, valve dysfunction occurs in 2-8% of patients. The mean latent time to development of the dysfunction is generally more than 10 years. In about 10 years, the valvular disorder occurs in the form of valvular insufficiency, and in about 20 years, the disorder turns into stenosis.[2,3]

Radiotherapy may cause restrictive cardiomyopathy, often coexisting with some degree of constrictive pericardial disease. The restrictive feature is due to reduced ventricular compliance induced by microvascular damage, hypoxia and oxidative stress, and subsequent ischemia with reparative fibrosis. On the other hand, the cardiac irradiation associated with anthracycline chemotherapy results in a dilated cardiomyopathy.[2,3]

## Lung Cancers

Curative intent radiotherapy is offered to patients diagnosed with stage I-III or oligometastatic stage IV non-small cell lung cancer or limited-stage small cell lung cancer or chemotherapy-responsive extensive-stage small cell lung cancer. The information on radiation-induced cardiac toxicity is largely based on studies of lymphoma and breast cancer. Whereas, the total doses prescribed to the tumor for the patients with lung cancer (60-74 Gy for curative intent and 45-66 Gy pre or post-operative intent) are much greater than those for the patients with lymphoma (20-45 Gy). Radiotherapy doses used for thoracic tumors are summarized in Table 1. Besides, the integral dose of the heart is usually quite low in radiotherapy for breast cancer. On the other hand, generally speaking, lung cancers have a worse prognosis than other thoracic cancers. In diseases with such poor prognosis, it may sometimes be necessary to prioritize tumor control instead of minimizing toxicity.[2] During radiotherapy, a small portion (estimated at about 5%) of the cardiac volume was in the treatment field, and the remaining heart volume was mainly exposed to diffuse radiation.

Lung cancer and coronary heart disease have some similar risk factors. For instance, smoking is a well-known risk factor for both lung cancers and coronary artery diseases. This implies that in patients with lung cancer, there may already be coronary artery disease in several degrees and these patients tend to develop radiation-induced cardiac complications.[2,3] The most interesting information on coronary artery disease came from information obtained from the long-

**Table 1** Total radiotherapy doses used in various types of thoracic tumors

| Disease | Dose (GY*) |
|---|---|
| Lymphoma | 20-45 |
| Gastric cancer | 45-50 |
| Breast cancer | 45-66 |
| Esophageal cancer | 45-54** |
| Thymic tumors | 45-66 |
| Lung cancer | 45-74 |

*Gray; **Some groups use relatively higher total doses (60–66 Gy)

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term follow-up of patients who received radiation therapy for peptic ulcer between 1940 and 1960.[4] During RT, a small portion (estimated at about 5%) of the heart volume was in the treatment field and the remaining heart volume was mostly exposed to scattered radiation.

The cardiotoxic effects of commonly used drugs in combination with RT (platinum, taxane, etc.) are well known when used on their own (without RT). These may be associated with coronary artery thrombosis, arteritis, or spasm, or cardiomyopathy and thus, theoretically potentiates adverse effects of radiotherapy on the heart. However, the clinical data on the cardiac effects of these drugs in combination with radiotherapy as concomitantly or sequentially are insufficient. New systemic treatments of lung cancer, such as immune checkpoint inhibitors (nivolumab and pembrolizumab, etc.) or tyrosine kinase inhibitors (erlotinib and gefitinib, etc.), may also exert these cardiac toxic effects. There is not enough clinical data yet on the interaction of these drugs with radiotherapy in terms of cardiac toxicity.[2,3]

In particular, lung cancer cells show the expression of a ligand that suppresses the activities of killer T cells that would normally kill cancer cells, a process known as programmed death. Therapies have been developed that block this action of the cancer cell by binding with the ligand or receptor and thus effectively reactivate the body's own immunity against cancer. The realization that immune treatments can cause myositis has raised concern and great interest among clinicians. PD-1 and PD-L1 can be expressed in human cardiomyocytes. [5] Early animal studies showed that autoimmune myocarditis can occur after CTLA-4 inhibition and PD-1 deletion. Fortunately, this problem occurs at a relatively low rate and recedes with the administration of steroids. However, if steroid-resistant myositis occurs, it causes death in ~50% of patients.[6,7] Most serious cardiovascular events due to immune therapies begin early in the treatment course (median time 30 days).[6,7]

The immune response created by radiation therapy against tumor cells in the body shows that ionizing radiation can have a systemic effect on tumor cells. The use of immune treatments in combination with radiotherapy is a new and promising situation, but it is open to all kinds of surprises in terms of toxicity. In a preclinical model of irradiated mice with a highly sensitive image-guided small animal RT device, acute mortality was significantly increased when cardiac irradiation was combined with an anti-PD-1 inhibitor. The authors reported an increase in mortality due to CD8 T lymphocyte-mediated cardiac dysfunction after both single and multi-fractionated irradiation.[8] In phase III randomized PACIFIC study, durvalumab treatment for 1 year after curative chemoradiotherapy (54-66 Gy/27-33 fx with platinum based chemotherapy) and phase II ETOP NICOLAS Study, administration of nivolumab concurrent with curative chemoradiotherapy (66 Gy/33 fx with platinum-based chemotherapy) was found to be feasible in terms of toxicity.[9,10] However, the maturation of clinical data is necessary to establish conclusions on safety. Special care should be taken to limit doses of cardiac structures when radiotherapy is combined with immune therapies.

Postoperative radiotherapy (PORT) is indicated for most thoracic malignant neoplasms if the surgical margin is positive. Besides, in the past, PORT was a standard part of the treatment for N1 or N2 non-small cell lung cancer unquestionably. However, a meta-analysis of 9 randomized trials published in 1998 showed that PORT had a negative effect on overall survival in N0 and N1 disease when applied with older two-dimensional techniques and large treatment areas. This unexpected result gained unjust notoriety to radiotherapy in a postoperative setting and became a milestone for radiotherapy planning. Indeed, when the studies which are examined one by one seems PORT undoubtedly reduces the risk of local/regional failure and cancer-specific mortality. However, unfortunately, cardiac and pulmonary toxicities are very important factors affecting overall survival negatively. It is clear that postoperative target volumes need to be optimized because the therapeutic gain here exhibits a kind of narrow window. Miles et al.[11] have developed a mathematical model for predicting mortality risk based on the size of the irradiation field and confirmed that the higher irradiated volume means the greater risk of treatment-induced mortality. The interest is, therefore, to limit irradiation to the most at-risk lymph node regions to reduce cardiopulmonary toxicity. Chemotherapy treats the microscopic disease at sites under risk outside of the radiotherapy field and potentiates the local effectiveness of radiotherapy in the field. Thus, PORT can provide a significant overall survival benefit when applied with modern treatment techniques and selective elective compact treatment areas. Robinson et al.,[12] in a population-based study, have estimated about 4% benefit on the overall survival of PORT in the modern radiotherapy era. The preliminary results of the Lung-Art study in which postoperative selective elective small field irradiation was tested for N2 disease again emphasized the importance of toxicity.[13] The PORT volume should

be designed to be the most appropriate size based on the evidence to prevent relapse but not cause toxicity. Furthermore, in this application, IMRT is useful for keeping the heart dose at a relatively low level.

## Anterior Compartment of Mediastinum

### Thymic Tumors

Thymic tumors which are the most common primary tumors of the anterior mediastinum are spread out in a wide range of pathological spectrum between thymoma with relatively benign behavior and thymic carcinoma with relatively aggressive behavior nearly similar to lung cancers. Generally speaking, the treatment of thymic tumors may be required high doses of radiation similar to those used in lung cancer. In the setting of preoperative or PORT, 45-54 Gy doses make sense. To provide a curative treatment, it is necessary to administer 60-66 Gy doses of radiotherapy. However, any elective lymph node irradiation is not necessary at all. That's why that can be said the irradiated volume is generally a kind of small for thymic tumors. However, sometimes the tumor may exhibit close proximity to the heart. Besides, some tumors which have extracapsular extension may invade the cardiac wall(s) directly. Since the life expectancy can be relatively long, reducing the heart dose and irradiated heart volume is particularly important in the treatment of patients with this diagnosis (especially in thymoma). Since, especially for patients with thymomas, if complete surgical resection can be performed before or after radiotherapy, then the late cardiac effects of radiotherapy become a very important factor that determines long-term survival.[2,3]

## Posterior Compartment of Mediastinum

### Sarcomas

Mediastinal sarcomas are generally originated from neurogenic structures and usually found in the posterior mediastinum. Surgical resection is the main treatment option for most cases of mediastinal sarcoma. Complete resection of the more malignant forms of these tumors may not be possible, and additional treatment modalities may be necessary. Even if they are benign, some may not be resected completely because of their location and increased vascularity. Standard therapy consists of en bloc resection, with accompanying radiotherapy and/or chemotherapy pre or postoperatively if complete resection is not possible.[2,3,14]

Anthracyclines (doxorubicin, epirubicin, daunorubicin, etc.) are among the most preferred systemic treatment agents in the treatment of mediastinal sarcomas. Unfortunately, their efficacy in treating cancer is limited by cumulative dose-dependent cardiotoxicity, which can cause irreversible (Type I) heart failure. The cumulative dose limit is not the same for all anthracycline types. Thus, for doxorubicin, diastolic dysfunction has been reported to occur with cumulative doses of 200 mg/m$^2$ doxorubicin, followed by systolic dysfunction beyond 400-600 mg/m$^2$, although there are individual differences (Fig. 1). For epirubicin, which is also a commonly used anthracycline, a slightly higher cumulative threshold dose has been defined.[15,16] Cardiac exposure to radiation significantly increases the sensitivity of the myocardium to anthracyclines. Moreover, it is known that anthracycline-based chemotherapy regimens, when administered concurrently or sequentially with mediastinal radiotherapy, have a negative synergistic effect on the heart besides its effects on skin and soft tissues.[5,17]

## Radiotherapy Technique and Dose/Volume Parameters

The risk of cardiotoxicity depends on the total dose, fraction size, and irradiated volume. Historically, toxic dose values such as TD5/5 and TD50/5 have been suggested 40 Gy and 50 Gy for the whole heart, respectively. Recently, dose-volume parameters are accepted more delicate measurements to precede toxicity probabilities.[3,18,19]

Heart damage induced by older radiotherapy methods was more common and more extensive. In recent years, changes in radiotherapy field sizes and techniques have led to a remarkable reduction in cardiac dose. Conventional treatment planning for lung can-

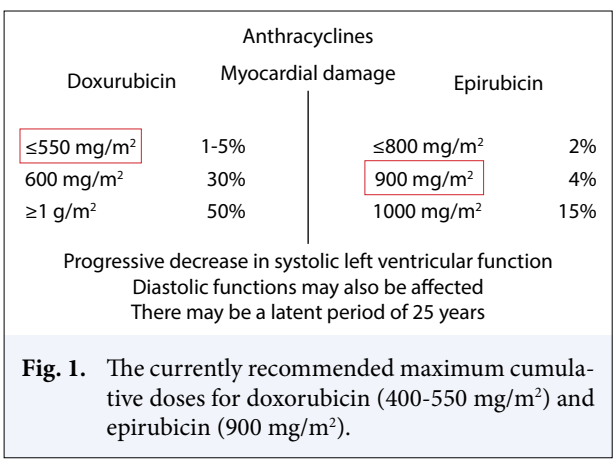


**Fig. 1.** The currently recommended maximum cumulative doses for doxorubicin (400-550 mg/m$^2$) and epirubicin (900 mg/m$^2$).

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cers includes initial anteroposterior and posteroanterior oriented fields treated to the dose accepted for spinal cord tolerance, followed by oblique boost fields designed to avoid the spinal cord. Modern three-dimensional radiation treatment planning facilitates the design of treatment fields that more conformally treat the site(s) at risk, and this appears to help focus the high dose on the target and spare critical normal tissues. Sometimes, non-axial beam orientations may help improve the therapeutic ratio. Especially for unresectable non-small cell lung cancer of the lower lobes, rotation of the boost field out of the axial plane will decrease the cardiac dose (Fig. 2). Treatment planning based on four-dimensional CT images and on-board image-guided adaptive treatment delivery helps the radiation oncologist track tumor motion and target the tumor precisely. Theoretically, it can produce lower heart doses. The non-randomized quality of life analysis derived from Radiation Therapy Oncology Group (RTOG) 0617 provides indirect evidence in support of routine use of IMRT in this setting.[20]

Sometimes, tumor progression may be more intimidating than cardiac adverse effects. Although a volume receiving 25 Gy and more (V25), <10% has been recommended to ensure risk of cardiovascular mortality of <1%, but unfortunately, this may be insufficient criteria. Cardiac toxicity risk is also related to the doses received by different the substructures of heart which are not taken into account by this constraint.[21] The heart is an example of organs with both serial and parallel array substructures (Fig. 3). The radiation dose in the coronary arteries, which is a serially sequenced structure, seems to have the most important effect on cardiac toxicity, especially in terms of the risk of myocardial infarction. However, the difficulty in the accurate and reproducible delineation of coronary arteries in routine

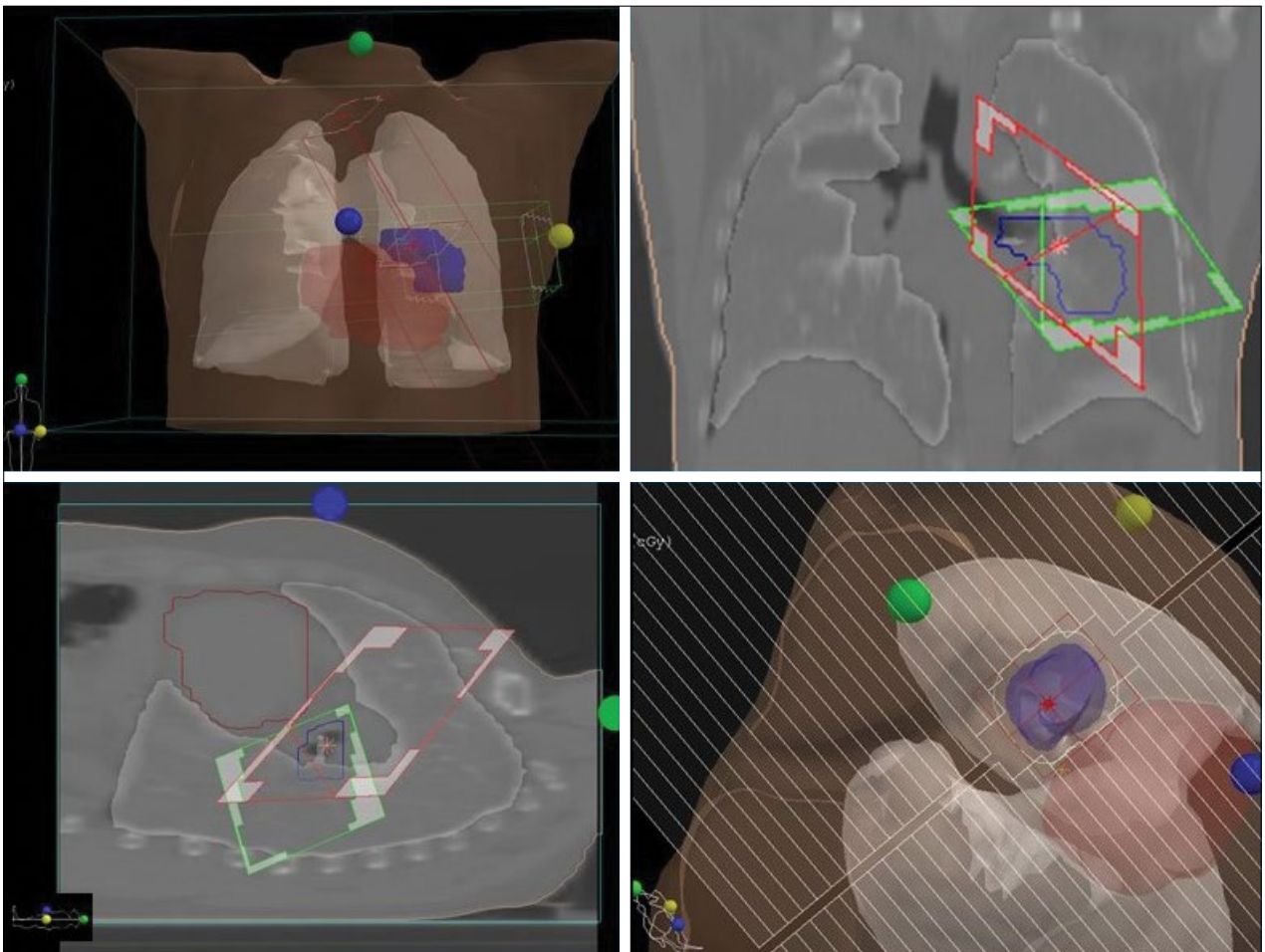

**Fig. 2.** A sample case for axial and non-axial beam orientations created to exclude heart from the radiotherapy field.

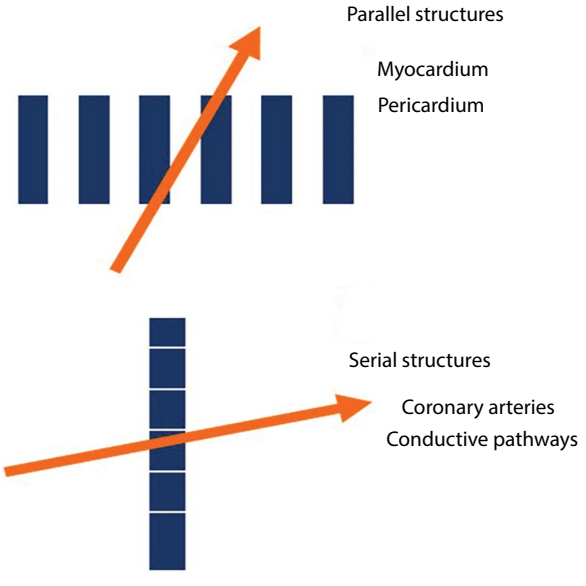


**Fig. 3.** The serial and parallel substructures of the heart.

practice and the great inter-individual variability, even with the help of international recommendations, makes it impossible at present to establish dose constraints to coronary arteries to be used in common practice.

Depending on the location of the tumor, the doses of the heart and its substructures show great variability. Therefore, the integral dose received by heart may be higher in patients with tumors of the left lung compared with the right, and central disease compared with the peripheral disease after radiotherapy. In Figure 4, axial and coronal PET/CT images of two patients with giant tumors of the left lung showing close proximity to the heart are seen. Indeed, each 1 Gy increase in mean heart dose causes ≈4% increase in cardiac complications. Nevertheless, in certain disease localization, it may be inevitable that the heart is exposed to considerable doses. Besides, dose limitations may need to be exceeded to treat highly aggressive cancers (such as locally advanced lung cancers). The primary Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) was published in 2010; endpoints for radiotherapy-induced cardiac complications were pericarditis (acute) and cardiac mortality (late). According to the QUANTEC, for acute pericarditis, V30Gy (in 1.8-2 Gy/day) should be <46% and the mean heart dose should be <26 Gy to keep toxicity rates under 15%.[3]

In the RTOG 0617 study, when patients were retrospectively grouped as <25% or ≥25% of heart V50, 1-year OS rates were 70.2% versus 46.8%, and 2-year

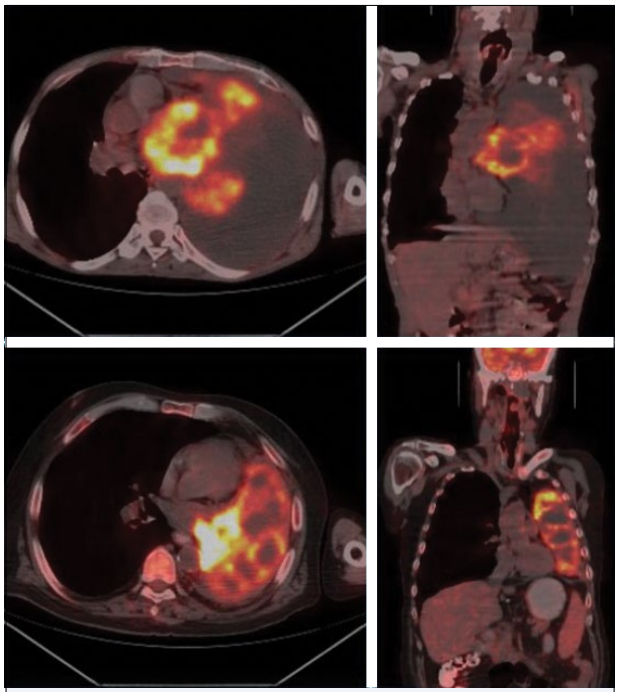

**Fig. 4.** The axial and coronal PET/CT images of two different patients with giant tumor located in close proximity to the heart.

OS rates were 45.9% versus 26.7%.[22] Therefore, V50 value below 25% emerged as a factor affecting survival. Some clinics recommend proton therapy in locally advanced diseases if the V50 value cannot be reduced below 25% with linear accelerator facilities. In the curative treatment of locally advanced NSCLC, there was no significant difference in overall survival in the randomized comparison of IMRT with passive scattering 3D proton therapy. Unfortunately, proton therapy did not have an advantage in terms of toxicity. It can be said that the rate of radiation pneumonitis (10.5% grade ≥3 radiation pneumonitis) in the proton therapy arm was disappointing. However, it has been observed that the heart dose can be reduced with proton therapy.[23] It is also a fact that proton therapy centers are still few or even not in some countries.

Irradiation under stereotactic conditions in the treatment of primary or secondary thoracic malignities has become a common treatment. There are limited data on cardiac toxicity associated with stereotactic radiotherapy. An important feature of SBRT is the use of ablative doses dividing the total dose in up to 5-8 fractions (instead of 25-35 fx).[24] The question then arises of potential late effects related to this hypofractionation. Since cardiac structures have a relatively low

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alpha/beta ratio, treatment with high doses per fraction may result in an increase in cardiac toxicity such as pericarditis and myocardial infarction.[25] Fortunately, the lesions targeted in SBRT are quite small and using advanced technology devices, a sharp reduction of the dose around the target can be achieved.

## Follow-up

Cardio-oncology is a new area in cardiology that concentrates on the detection, monitoring, and treatment of cardiovascular disorders that appear as a side effect of cancer treatment. Before thoracic radiotherapy, cardiovascular risk factors such as hypertension, ischemia, arrhythmia, dyslipidemia, diabetes mellitus, obesity, and electrolyte abnormalities should be controlled, monitored thereafter closely, and treated if necessary.

Late cardiovascular effects can be considered unpredictable and there is no confirmed blood test to predict radiation-induced cardiotoxicity.[26] An electrocardiogram is recommended before and immediately after completion of radiotherapy. Baseline assessment of left ventricular ejection fraction by echocardiography is recommended before initiation of any cancer treatment, especially the ones potentially cardiotoxic, to confirm baseline risk. On echo, radiotherapy-induced restrictive cardiomyopathy appears as an increased wall thickness and decreased left ventricular volume. For follow-up, ECG is repeated once a year and echo every 2-3 years.[27]

In clinic practice, after 5-10 years, many patients remain out of the follow-up of oncologists. In fact, the toxic effects of radiation on the heart increase after 5-10 years. That's why, after the thoracic radiotherapy, a strengthened and long-dated cooperation is necessary between the radiation oncologists and the cardiologists to detect and treat long-term cardiac complications.[27]

## Conclusion

It is difficult to treat or cope with the radiation-induced late heart toxicity once it has emerged. Treatment requires perseverance or even may not be possible due to the biological characteristics of the heart muscle. If the thoracic malignancy can be successfully treated, in the long term, radiotherapy-induced cardiac toxicity may become important as a determinant of survival. Therefore, it is extremely important to take the necessary precautions to prevent heart toxicity.

In the last period, the use of modern radiotherapy methods and devices has provided a remarkable reduction in the frequency of cardiac toxicity. If it is not necessary, the heart should not be irradiated redundantly. For all, if there is a constitutional necessity, a radiotherapy plan should be made in accordance with the recommended dose-volume values for cardiac structures. Since the risk of radiation-induced late cardiac toxicity begins often many years after radiotherapy, long-term follow-up is helpful.

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