Short communication

Interventional Cardiology

# Dose the simultaneous treatment of radiation therapy and immunotherapy accelerate the cardiac toxicity?

## Abstract

Multiple studies have reported that both radiation therapy and immunotherapy can cause cardiac toxicity. In a combined analysis of four consecutive, prospective multicenter RT trials for locally advanced NSCLC, the 24-month cumulative incidence of grade ≥ 3 cardiac events were observed to be as high as to 11%. Another post hoc analysis of six prospective trials in locally advanced NSCLC revealed that 23% of patients experienced one or more symptomatic cardiac events.

**Keywords:** Radiation therapy • Cardiac toxicity • Immunotherapy • Cardiomyopathy • coronary artery disease

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## Introduction

The short communication highlighted that certain immunotherapy drugs, such as checkpoint inhibitors, can trigger immune-related adverse events affecting the heart, including myocarditis and cardiomyopathy [1-3]. Radiation-Induced Heart Damage (RIHD) is one of the most common long-term adverse reactions in patients with thoracic malignant tumors who undergo RT. It often leads to acute and chronic injuries in various areas, including the pericardium, myocardium, coronary arteries, and cardiac valves [4]. The occurrence of Immunotherapy-Related Heart Damage (IRHD) may partially offset the survival benefits of ICIs treatment, and the utilization of combination immunotherapy may further increase the risk of treatment-related cardiac toxicity. Dose the simultaneous treatment of radiation therapy and immunotherapy accelerate cardiac toxicity?

One retrospective short communication [5], does not show an increase in cardiac events with thoracic radiation given concurrently with ICI. In our limited study, as compared to those who received non-concurrent RT, patients with concurrent RT and ICI had a significantly lower rate of cardiac events in our cohort. This may suggest a potential cardioprotective effect of thoracic RT given during ICI, although this needs to be validated in a larger prospective study with a strong statistical design, and the underlying molecular mechanisms of this effect need to be explored using basic models. If this possible cardioprotective effect is rigorously validated, then this might influence the findings of future clinical trials.

Since the combination of immunotherapy and radiation therapy can raise concerns about cardiac toxicity, what are the high-risk factors? Previous studies have identified radiation-specific factors [4], such as radiation dose, exposure volume and site, and RT technique, as well as dual ICIs [6], and immune status as influencing the incidence and severity of RIHD or IRHD [1]. Unfortunately, the current understanding of the high-risk factors for cardiac toxicity related to this combination is insufficient.

Radiation-Induced Coronary Artery Disease (RICAD) is emerging as a predominant

clinical manifestation, with an incidence rate as high as 85% in RIHD cases reported in the literature [7]. Cardiovascular adverse events associated with ICIs are rare and less than 1% and mostly involve myocarditis; however, when ICIs are combined with radiotherapy, the incidence increases [8].

Our report focuses on the nexus of radiotherapy and ICI therapy, highlighting the early onset of RICAD as a potential hazard even in patients without traditional cardiovascular risk factors. Incidences of RICAD are closely related to radiation dose, location, time, and other factors [9]. As radiotherapy technology advances, events in which the heart receives substantial doses of radiation (>30 Gy) are becoming less common, and traditionally, the heart has been considered a radioresistant organ that is unaffected by doses below about 30 Gy [10]. Patients who received radiotherapy for breast cancer experienced an increase in major coronary events by 7.4% per Gy of mean dose to the heart, regardless of the cardiac risk factors at the time of radiotherapy [11]. A similar absolute risk of major coronary events in relation to mean heart radiation dose was observed in NSCLC patients.

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A similar absolute risk of major coronary events in relation to mean heart radiation dose was observed in NSCLC patients [12]. Selecting the optimal radiation dose is crucial in minimizing cardiac adverse events and extending survival duration.

Radiotherapy has been demonstrated to play an important role in immunomodulation, including enhancing tumor antigen release, promoting immune cell activation and infiltration, and facilitating recognition of tumor cells [13]. Several studies have also confirmed the benefit of the combination of radiotherapy and immunotherapy in patients [14,15]. However, cardiotoxicity is rarely discussed, and clinical trials may underestimate its incidence as a result of late-onset and asymptomatic events. According to a preclinical study, PD-1 modulates radiation-induced cardiotoxicity through cytotoxic T-lymphocytes, and the use of PD-1 inhibitors aggravates the toxic effects [16].

The combination of radiotherapy and immunotherapy may indeed accelerate cardiac toxicity in the treatment of certain diseases, which is an issue that requires close attention. RICAD (radiation-induced cardiac injury) is a potential risk event that refers to the potential damage to the heart during the radiation therapy process.

The main effect of radiotherapy on the heart is the formation of pericarditis. If the dose is too high during radiotherapy, it can have an impact on cells, leading to acute inflammatory reactions and exudation, thereby forming pericarditis. The radioactive substances used during radiotherapy may also cause damage to the myocardium, leading to myocardial fibrosis and potentially leading to radiation-induced pancarditis. In addition, radiation therapy may also lead to symptoms such as asymptomatic heart failure, angina, and myocardial infarction.

## Conclusion

Therefore, in the treatment process of radiotherapy combined with immunotherapy, accelerated cardiac toxicity is an issue that requires close attention. In addition to radiation dose, exposure level and location, and RT technology, RICAD (radiation-induced coronary artery injury) should be given more attention. Because even in patients without traditional cardiovascular risk factors, the early onset of RICAD is a potential risk. It is very important to closely monitor and evaluate cardiac function. If any cardiac discomfort or abnormal symptoms occur, seek medical attention promptly and undergo corresponding examinations and treatments. At the same time, doctors also need to arrange the dosage and course of radiotherapy reasonably based on the specific situation of patients, to minimize the occurrence of cardiac toxicity.

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