Cardiac dysfunction in cancer survivors after thoracic irradiation: A necessary evil?

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It is well established that a wide range of cardiovascular complications could occur from radiation therapy for thoracic malignancies, such as breast cancer, Hodgkin's lymphoma and non-small cell lung cancer. It is estimated that up to 60% of Hodgkin's lymphoma survivors develop radiation therapy (RT)-induced coronary artery disease (CAD), whereas breast cancer survivors receiving RT experience higher odds of vascular death and a high likelihood of developing CAD particularly when subjected to left sided chest radiation (Table 1).^{1–3} While the risk of developing RT-related CAD is not disputed in patients with thoracic malignancies, there is a considerable temporal delay between radiation exposure and development of symptomatic disease making the detection of this phenomenon quite challenging.

The risk of developing CAD is higher in patients subjected to RT at a younger age and also in patients with pre-existing traditional risk factors for atherosclerosis. Additionally, there appears to be a linear increase in risk with higher doses of RT as demonstrated in breast cancer patients, whereas one study found that for every 1 Gy (Gray) increase in mean heart dose a resultant 7.4% increase in major coronary events occurred.⁴ Similarly, a pooled analysis from dose-escalation studies in non-

small cell lung cancer showed higher cardiovascular event rates in patients receiving higher radiation doses to the chest.⁵ Despite the development of image-guided radiotherapy and three-dimensional dosimetry which reduce the cardiac radiation doses delivered during therapy, the risk of RT-related CAD remains a concern for cancer survivors.⁶

The pathophysiology of radiation-related CAD is complex and has been hypothesized in several prior studies. At the ultrastructural level, the irradiated vasculature observes increased pro-inflammatory cytokines including interleukin-6, C-reactive protein, interferon gamma, and tumor necrosis factor-alpha, leading to a pro-thrombotic state and sustained inflammation.^{7,8} The alteration in vascular hemostasis with the loss of endothelium-derived vasodilators along with increased pro-thrombotic factors results in increased microvascular fibrosis, reduced vascular reserve, and myocardial ischemia.⁹ At the macrovascular level, radiotherapy results in direct myocardial and endothelial injury resulting in collagen deposition in the capillary lumen, stenosis of the vessels, and fibrotic remodeling of the myocardium (Fig. 1).⁸ Therefore, whether alone or in combination with traditional cardiovascular risk factors, radiotherapy can both initiate and accelerate the development of atherosclerosis.

The diagnosis of RT-related CAD poses unique challenges due to the heterogeneous nature of the symptoms, the multiple possible etiologies, and the temporal delay from exposure to development of disease. Stress perfusion imaging studies have been carried out in breast cancer survivors showing perfusion abnormalities in 42% of women, but due to the small sample size and lack of long term follow-up the implications of these findings are limited.¹⁰ Myocardial flow reserve (MFR, mL·min⁻¹·g⁻¹), calculated as the ratio of stress to rest myocardial blood flow, is a measure of coronary vessel function and incorporates the effects of

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Figure 1. Cardiovascular complications of radiation therapy of chest malignancies.

focal epicardial and diffuse atherosclerotic disease as well as microvascular dysfunction. Positron emission tomography (PET) is considered the gold standard for myocardial blood flow quantification and the accuracy of these measures has been extensively studied and validated.^{11,12} MFR has emerged as a non-invasive quantitative diagnostic and prognostic marker of cardiovascular risk. Impaired flow reserve has been previously shown to predict adverse cardiac events in patients with and without established coronary artery disease.¹³ Cardiac event rates appear to increase exponentially for MFR values < 2 . In addition, there is an associated 3.4-fold increased risk of cardiovascular death with abnormal MFR, with multiple studies demonstrating this physiological marker's ability to distinguish between low and high-cardiac risk patients.^{13,14} Given the global and wide effect of RT on vascular structures, myocardial flow studies using PET offer an interesting avenue of research.

In this issue of the Journal, *Groarke et al*¹⁵ aimed to test the hypothesis that radiation therapy delivered to patients with thoracic malignancies is associated with an impairment of myocardial flow reserve (MFR) in a dose dependent manner. They employed a retrospective single-center analysis of 35 patients who had PET/Computed tomography (PET/CT) imaging for various cardiovascular indications. The median interval between the radiation episodes and the perfusion stress tests was

4.3 years [IQR 2.1, 9.7]. In order to correct for potential selection bias, the investigators included a control group of patients with a similar demographic and clinical profile who presented to their center's PET/CT laboratory. The control group was matched in terms of age, gender, ischemic heart disease history, and their Morise clinical risk score. The authors noted a significant inverse correlation between thoracic radiation therapy dose and coronary vasomotor function, as reflected by reduced MFR values both globally and in the left anterior descending (LAD) artery territory when compared to the control group. This relationship remained significant even after excluding those patients with known ischemic heart disease ($n = 6$). On the other hand, the MFR corresponding to the left circumflex and right coronary artery arteries did trend towards a difference but did not reach statistical significance ($P = .11$ and $.08$, respectively). Additionally, the investigators noted a dose dependent relationship between the amount of radiation and MFR reduction. More specifically, for every 1 Gy increase in mean cardiac radiation dose there was a significant decrease in MFR by 0.02 ± 0.01 points both globally and in the LAD coronary territory. Importantly, this relationship remained significant after correcting for the clinical risk profile, the ischemic burden on the index stress perfusion study, and the interval time from radiation to PET imaging.

Table 1. Cardiovascular complications of radiation therapy

Cardiac structure	Incidence	Time to onset after acute radiation therapy	Effects of radiation	Clinical sequelae
Myocardium	5–10%	Uncertain	Myocardial edema, inflammation and fibrosis	Systolic/diastolic dysfunction Or Overt Heart failure
Pericardium	8–30% 70% (<i>autopsy studies</i>)	5 years	Pericardial thickening and calcifications	Acute/chronic pericarditis Pericardial effusion Constrictive pericarditis
Conduction system	Up to 75%	1–23 years	Fibrosis of conduction pathways	RBBB Complete AV block Arrhythmias Sick-sinus syndrome
Vasculopathy	Up to 85%	9 years	Enhanced platelet deposition Plaque rupture Endothelial damage Microvascular injury	Ischemic heart disease Accelerated atherosclerosis with <i>Predilection for ostial/proximal vessels</i> Myocardial infarction Microvascular disease
Valves	Up to 81% (<i>Symptoms in < 30% of those affected</i>)	10 years (<i>asymptomatic</i>) 16.5 years (<i>symptomatic</i>)	Thickening of aorto-mitral curtain, annulus, valvular/sub-valvular apparatus	Valve stenosis Valve regurgitation

The findings of this study shed new light on the diagnosis of thoracic radiation associated adverse cardiovascular outcomes. This is a valuable study that will have important implications once replicated. That said, few limitations need to be pointed out. First, as the authors already recognize, the number of patients is relatively small ($n = 35$ in each group) which should lead to caution in terms of generalization and clinical extrapolation of the results before future large prospective studies are performed. Second, more than 50% of the patients had a presenting cardiovascular symptom for their PET/CT exam. Combining this with the fact that cardiovascular risk factors were highly prevalent in the study group (almost two thirds had hypertension, three-quarters had dyslipidemia, and more than 8 in 10 were overweight) can potentially confound the results even though the control group was statistically well matched. In addition, the differences in the MFR between the two groups were minor and falls within the reported variability of MFR measurement in clinical practice. Prior studies showed significant variability in repeat MFR measurements done on patients with abnormal PET studies (median difference of 22 days between the paired studies), with a correlation

coefficient $r = .34$ and reproducibility coefficient of 51%.¹⁶ This observation makes the inherent variability in measuring MFR an additional potential factor contributing to the observed differences in the study.

The major contribution of this study lies in the addition of a new powerful imaging tool for assessing manifest and subclinical radiation-induced ischemic heart disease. Despite the fact that consensus statements recommend for CAD screening in patients with prior exposure to thoracic radiation, these do not advise for a particular testing method.¹⁷ Groarke *et al's* data suggest that the MFR could even be employed as an earlier CAD screener, since MFR reduction is expected to occur prior to the occurrence of epicardial stenosis or clinical symptoms. Importantly, a PET/CT study on a hybrid PET/CT system also allows for the quantification of coronary and extra coronary calcifications during the index scan, which makes it an appealing and powerful tool for the detection of subclinical CAD and other cardiac (valvular, pericardial) calcifications in these patients. Furthermore, the low-dose CT attenuation correction images acquired routinely as part of PET studies can offer an additional layer of risk assessment since they can show calcifications in the patients'

visualized arterial trees such as the thoraco-abdominal aorta and its branches, which could be the consequence of prior radiation injury. Indeed, these were highly prevalent in the patients group exposed to thoracic radiation.¹⁵

Since this and other studies have demonstrated that even low doses of radiation have the potential to induce tangible effects both clinically and subclinically on imaging studies,^{4,15,18} it is therefore of paramount importance to employ strategies to mitigate potential adverse cardiovascular outcomes. As mentioned earlier, cardiovascular surveillance using cardiac imaging such as PET/CT will play an important role in the early detection of radiation effects on the vasculature and heart, leading to more aggressive and early interventions. For instance, some studies have suggested that statins, angiotensin converting enzyme inhibitors, and antioxidant drugs such as colchicine have the potential to lessen the effects of radiation on the heart.¹⁹ Lastly, improvement in radiotherapy delivery regimens to reduce the exposure of healthy nearby tissues to radiation remains the primary recommended approach for preventing RT-related CAD.²⁰ Multiple successful strategies have been implemented over the years to achieve this goal (e.g., deep inspiratory breath hold, three-dimensional conformal radiotherapy, intensity modulated radiotherapy, and volumetric arc therapy). However, despite successfully reducing cardiac doses, collateral radiation to the heart might remain an unavoidable side effect of thoracic radiotherapy, making early detection of coronary vascular damage using multifaceted modalities such as PET/CT, and employment of appropriate interventions and therapeutics, the best available opportunity for these vulnerable patients.

References

1. Van Nimwegen FA, Ntents G, Darby SC, Schaapveld M, Hauptmann M, Lugtenburg PJ, et al. Risk of heart failure in survivors of hodgkin lymphoma: Effects of cardiac exposure to radiation and anthracyclines. *Blood* 2017;129:2257–65.
2. Cheng Y, Nie X, Ji C, Lin X, Liu L, Chen X, et al. Long-term cardiovascular risk after radiotherapy in women with breast cancer. *J Am Heart Assoc* 2017;6:e005633.
3. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomised trials. *Lancet* 2000;355:1757–70.
4. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–98.
5. Wang K, Eblan MJ, Deal AM, Lipner M, Zagar TM, Wang Y, et al. Cardiac toxicity after radiotherapy for stage III non-small-cell lung cancer: Pooled analysis of dose-escalation trials delivering 70 to 90 Gy. *J Clin Oncol* 2017;35:1387–94.
6. Taylor CW, Povall JM, McGale P, Nisbet A, Dodwell D, Smith JT, et al. Cardiac dose from tangential breast cancer radiotherapy in the year 2006. *Int J Radiat Oncol Biol Phys* 2008;72:501–7.
7. Halle M, Gabrielsen A, Paulsson-Berne G, Gahm C, Agardh HE, Farnebo F, et al. Sustained inflammation due to nuclear factor-kappa B activation in irradiated human arteries. *J Am Coll Cardiol* 2010;55:1227–36.
8. Liu LK, Ouyang W, Zhao X, Su S, Yang Y, Ding WJ, et al. Pathogenesis and prevention of radiation-induced myocardial fibrosis. *Asian Pac J Cancer Prev* 2017;18:583–7.
9. Jaworski C, Mariani JA, Wheeler G, Kaye DM. Cardiac complications of thoracic irradiation. *J Am Coll Cardiol* 2013;61:2319–28.
10. Marks LB, Yu X, Prosnitz RG, Zhou S, Hardenbergh PH, Blazing M, et al. The incidence and functional consequences of RT-associated cardiac perfusion defects. *Int J Radiat Oncol Biol Phys* 2005;63:214–23.
11. El-Tallawi KC, Aljizeeri A, Nabi F, Al-Mallah MH. Myocardial perfusion imaging using positron emission tomography. *Methodist Debaque Cardiovasc J* 2020;16(2):114–21. <https://doi.org/10.14797/mdcj-16-2-114>.
12. El Fakhri G, Sitek A, Guerin B, Kijewski MF, Di Carli MF, Moore SC. Quantitative dynamic cardiac 82Rb PET using generalized factor and compartment analyses. *J Nucl Med* 2005;46:1264–71.
13. Murthy VL, Naya M, Foster CR, Hainer J, Gaber M, Di Carli G, et al. Improved cardiac risk assessment with noninvasive measures of coronary flow reserve. *Circulation* 2011;124:2215–24.
14. Al-Mallah MH, Sitek A, Moore SC, Di Carli M, Dorbala S. Assessment of myocardial perfusion and function with PET and PET/CT. *J Nucl Cardiol* 2010;17(3):498–513.
15. Groarke JD, Divakaran S, Nohria A, Killoran JH, Dorbala S, Dunne RM, et al. Coronary vasomotor dysfunction in cancer survivors treated with thoracic irradiation. *J Nucl Cardiol* 2020;2020:1–12.
16. Sdringola S, Johnson NP, Kirkeeide RL, Cid E, Gould KL. Impact of unexpected factors on quantitative myocardial perfusion and coronary flow reserve in young, asymptomatic volunteers. *JACC Cardiovasc Imaging* 2011;4:402–12.
17. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines: The task force for cancer treatments and cardiovascular toxicity of the European society of cardiology (ESC). *Eur Heart J* 2016;37:2768–801.
18. Carr ZA, Land CE, Kleinerman RA, Weinstock RW, Stovall M, Griem ML, et al. Coronary heart disease after radiotherapy for peptic ulcer disease. *Int J Radiat Oncol Biol Phys* 2005;61:842–50.
19. van der Veen SJ, Ghobadi G, de Boer RA, Faber H, Cannon MV, Nagle PW, et al. ACE inhibition attenuates radiation-induced cardiopulmonary damage. *Radiother Oncol* 2015;114:96–103.
20. Curigliano G, Cardinale D, Suter T, Plataniotis G, De Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO clinical practice guidelines. *Ann Oncol* 2012;23:155–66.

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