JACC: CARDIOONCOLOGY VOL. 6, NO. 6, 2024

EDITORIAL COMMENT

Elucidating the Signal from the Noise

Mapping Cardiac Conduction Events to Cardiac Substructure Radiation Exposure

Florence K. Keane, MD,[a] Tomas G. Neilan, MD, MPH,[b] Rachel B. Jimenez, MD[a]

The short- and long-term effects of radiotherapy (RT) on cardiovascular structure and function in patients with cancer are reasonably well established. While initial studies identified a linear relationship between whole heart dose and the subsequent risk of major coronary events in patients with breast[1] and lung[2,3] cancer, there is increasing recognition that the type of cardiac dysfunction that these patients develop after radiation therapy is as influenced by the extent of exposure to specific cardiac substructures.[4] This more nuanced understanding of radiation-associated cardiac injury is not only more physiologically intuitive, but also importantly, in the modern era of radiation oncology, increasingly clinically actionable. Advances in RT simulation, treatment planning, and delivery have facilitated the delineation and intentional avoidance of cardiac substructures. Therefore, radiation oncologists can begin to make informed calculations regarding both a patient's individual risk of cancer recurrence and their individualized risk of subsequent radiation-associated cardiac morbidity, tailoring the radiation plan to limit both concerns. However, to accomplish this, it will be critical to identify precise, reliable, empirically derived cardiac substructure thresholds to guide treatment planning.

In this issue of *JACC: CardioOncology*, Butler et al[5] report on 539 patients who received definitive-intent RT at their institution from 2004 to 2022 for thorax-based cancers (non-small cell lung cancer [NSCLC] 42.7%, breast cancer 32.3%, Hodgkin lymphoma 22.1%, and esophageal cancer 3.0%) and evaluated their subsequent risk of grade ≥3 atrial fibrillation (AF) based on cardiac radiation exposure. The authors contoured the pulmonary veins (PVs), left atrium (LA), left coronary arteries, and sinoatrial (SA) node for all patients according to standard guidelines.[6] A Mayo AF risk score was calculated for all patients. The authors chose to focus on the maximum radiation dose exposure (DMax) to the PVs and LA, rather than on the mean or volumetric metrics, hypothesizing that the single-dose maximum to these structures could induce sufficient injury to cause AF.

At a median follow-up of 58.8 months, the 5-year incidence of AF for the overall cohort was 5.2% (95% CI: 4.9%-5.4%), with a total of 35 events. The DMax to the PVs varied by cancer type (highest median DMax of 73.1 Gy in patients with lung cancer, lowest median DMax of 2.2 Gy in patients with breast cancer). Recapitulating the relationship between exposure and injury, the 5-year incidence of AF by cancer type was 11.1% for NSCLC, 8.3% for esophageal cancer, 1.3% for breast cancer, and 0.8% for Hodgkin lymphoma. Maximum doses to the SA node, higher left coronary artery V15 (the volume of the left coronary artery receiving at least 15 Gy), and higher coronary artery calcium scores were not associated with AF, but there was an increased risk of grade ≥3 AF with higher DMax to the combined PVs and to the individual PV substructures on univariable analysis. On multivariable analysis, higher DMax to the PVs, higher LA volume, higher Mayo AF risk score group, and greater smoking pack-years were associated with a higher risk of AF. A spline analysis identified that a PV DMax >39.7 Gy was associated with a significantly higher risk of AF even when stratifying by MARFS group.

These results represent an important addition to a growing body of literature highlighting the association between cardiac substructure dose exposure and

From the [a]Department of Radiation Oncology, Massachusetts General Hospital, Boston, Massachusetts, USA; and the [b]Department of Medicine, Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2024.10.007

subsequent cardiac injury, specifically the PVs with risk of AF. However, while this evidence is additive and practice informing, threshold dose metrics for the PVs cannot yet be considered established, as prior retrospective studies have identified alternative exposure-injury relationships. For example, Atkins et al[7] reported on rates of grade ≥3 arrhythmias in 748 patients with locally advanced NSCLC treated with definitive RT from 1998 to 2014. The 2-year incidence of AF was 8.0%. Their analysis found that the volume of the PV receiving ≥5 Gy was associated with risk of AF. In addition, the volume of the PV receiving ≥55 Gy was associated with non-AF and non-atrial flutter supraventricular tachycardia, rather than with AF. Walls et al[8] also analyzed the association between PV dose and the risk of AF in 420 patients with NSCLC treated with definitive intent RT from 2014 to 2020. Importantly, the majority of the patients included in this study were treated with intensity-modulated radiotherapy (IMRT), a radiation technique that permits for the meaningful reduction of high doses of radiation to sensitive anatomic structures, including the heart and cardiac substructures. In the Walls et al study,[8] at a median of 21.8 months after completion of RT, the rate of new grade ≥3 AF was 6.0%, and the authors found differing dose thresholds for the right vs left PVs.

Additionally, it is recognized that dose to the PVs may not be the sole or primary driver for the induction of AF. As noted previously, Butler et al found that higher LA volume was also associated with increased risk of grade ≥3 AF. Similarly, a series of 238 patients[9] with localized esophageal cancer treated with definitive RT from 2007 to 2019 reported that increasing dose to the LA was associated with AF risk, with the incidence of AF increasing by 30% with each 10-Gy increase in the mean LA dose. The association of dose to the SA node with risk of AF is less well defined, but in a retrospective series of 560 patients[10] with localized non-small cell and limited stage small cell lung cancer treated with definitive RT between 2008 and 2019, higher DMax to the SA node was associated with risk of AF. There are limitations associated with each of these retrospective analyses, and importantly, neither Butler et al nor Walls et al[8] found associations between SA node dosimetry and the development of AF.

Complicating management further is that radiation techniques have dramatically evolved over the past 15 years. The shift from 3-dimensional conformal radiotherapy (3DCRT) to IMRT has enabled increased sparing of normal tissues, including cardiac substructures. Whether PV constraints based on 3DCRT treatment plans still apply in the era of IMRT is an open question. The percentage of patients treated with IMRT in published series varies widely, from 21.9%[7] to 70%.[8] Butler et al do not report the breakdown of 3DCRT and IMRT in their cohort, but based on the time period of their analysis, many of the patients included were likely treated with 3DCRT, rather than with IMRT. With the improved normal tissue sparing of IMRT, does a DMax constraint of 39.7 Gy to the PVs still apply? Or will that need to be further refined in the era of IMRT?

There are a few steps that are needed to advance our current understanding of cardiac substructure dose and injury with the eventual goal of obtaining empiric, accurate cardiac substructure dose thresholds to utilize in treatment planning. First and foremost, accurate contouring is critical. As Butler et al note, precisely delineating the PV can be complex due to variations in patient anatomy, fluctuations in size and shape during the cardiac cycle, and variability due to patient sex and body mass index. A consensus atlas has been published and should be referenced when contouring the PVs.[6] Second, even with consensus definitions, the contouring process is labor-intensive and training may be required for radiation oncologists unfamiliar with cardiac substructure anatomy. Artificial intelligence and the development of autocontouring tools for the cardiac substructures will ease this burden but are not yet validated nor widely available. Finally, prospective studies designed with cardiac-focused endpoints are critical in answering this question. The RADCOMP (Radiotherapy Comparative Effectiveness) trial, a randomized trial comparing conventional radiation with proton therapy for patients with breast cancer, aims to evaluate the 10-year risk of major cardiac events comparing these 2 radiation treatment modalities, and it has collected centrally contoured cardiac substructure doses on over 1,200 patients to meaningfully elucidate dose-injury relationships. Results from this trial as well as from additional studies in lung and esophageal cancer patients are needed. Until then, continued multidisciplinary collaborations between radiation oncologists and cardio-oncologists should be supported to mutually assist in identifying patients most at risk of cardiac injury from radiation and optimize their cardiovascular management before, during, and following needed cancer therapy.

JACC: CARDIOONCOLOGY, VOL. 6, NO. 6, 2024
DECEMBER 2024:946–948

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Rachel B. Jimenez, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114, USA. E-mail: rbjimenez@mgb.org. X handle: @RachelJimenezMD.

REFERENCES

1. Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368(11):987–998. https://doi.org/10.1056/NEJMoa1209825

2. Dess RT, Sun Y, Matuszak MM, et al. Cardiac events after radiation therapy: combined analysis of prospective multicenter trials for locally advanced non-small-cell lung cancer. *J Clin Oncol*. 2017;35(13):1395–1402. https://doi.org/10.1200/JCO.2016.71.6142

3. Wang K, Eblan MJ, Deal AM, 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(13):1387–1394. https://doi.org/10.1200/JCO.2016.70.0229

4. Atkins KM, Bitterman DS, Chaunzwa TL, et al. Mean heart dose is an inadequate surrogate for left anterior descending coronary artery dose and the risk of major adverse cardiac events in lung cancer radiation therapy. *Int J Radiat Oncol Biol Phys*. 2021;110(5):1473–1479. https://doi.org/10.1016/j.ijrobp.2021.03.005

5. Butler S, No H, Guo F, et al. Predictors of atrial fibrillation after thoracic radiotherapy. *JACC CardioOncol*. 2024;6(6):935–945.

6. Walls GM, McCann C, Ball P, et al. A pulmonary vein atlas for radiotherapy planning. *Radiother Oncol*. 2023;184:109680. https://doi.org/10.1016/j.radonc.2023.109680

7. Atkins KM, Zhang SC, Kehayias C, et al. Cardiac substructure radiation dose and associations with tachyarrhythmia and bradyarrhythmia after lung cancer radiotherapy. *JACC CardioOncol*. 2024;6(4):544–556. https://doi.org/10.1016/j.jaccao.2024.07.005

8. Walls GM, McCann C, O'Connor J, et al. Pulmonary vein dose and risk of atrial fibrillation in patients with non-small cell lung cancer following definitive radiotherapy: an NI-HEART analysis. *Radiother Oncol*. 2024;192:110085. https://doi.org/10.1016/j.radonc.2024.110085

9. Miller ED, Wu T, McKinley G, et al. Incident atrial fibrillation and survival outcomes in esophageal cancer following radiotherapy. *Int J Radiat Oncol Biol Phys*. 2024;118(1):124–136. https://doi.org/10.1016/j.ijrobp.2023.08.011

10. Kim KH, Oh J, Yang G, et al. Association of sinoatrial node radiation dose with atrial fibrillation and mortality in patients with lung cancer. *JAMA Oncol*. 2022;8(11):1624–1634. https://doi.org/10.1001/jamaoncol.2022.4202

KEY WORDS radiation physics, lung cancer, esophageal cancer, thoracic oncology, breast cancer, lymphoma