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EDITORIAL COMMENT

Cardiac Risk Stratification Before Lung Cancer Radiation

Opportunities to Improve Care Through Personalized Radiographic Assessments*

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CARDIO-ONCOLOGY AND LUNG CANCER

Cardio-oncology ties together the 2 leading causes of death in the United States and is founded on the study of cancer treatment-related cardiotoxicity. As its own discipline, cardio-oncology challenges clinicians to tie together concepts from disparate specialties to holistically optimize patient outcomes. In this issue of *JACC: CardioOncology*, No et al[1] performed detailed analyses to improve risk stratification of factors associated with cardiac events after chemoradiation for locally advanced non-small cell lung cancer (NSCLC). In 233 patients, grade ≥3 cardiac events were closely associated with 1 oncologic risk factor (radiation dose to the coronary arteries) and 1 baseline cardiac risk factor (degree of coronary arterial calcification).[1] The work by No et al is important, with immediate implications for thoracic radiotherapy planning while improving cardiac assessments by thoughtful use of readily available radiographic information.

Given higher age and high prevalence of smoking (81% in this study), patients with lung cancer present with unique cardio-oncologic challenges distinguishing it from lymphoma and breast cancer, diagnoses that established prior understanding of radiation-associated cardiotoxicity. Patients with lung cancer often present with comorbid heart disease and elevated baseline risk; earlier and heterogeneous cardiac events occur after treatment. Yet, lung cancer remains difficult to cure, and cardiotoxic oncologic treatments are required to extend survival. Balancing these competing cardiac and cancer-related risks requires accurate baseline risk stratification (consistent with American Society of Clinical Oncology guidelines)[2] and a detailed understanding of treatment-related parameters such as heart dose. Within the last 5 to 10 years, understanding of cardiac effects for stage III NSCLC has rapidly increased, with initial recognition linking heart dose to toxicity followed by characterization of specific cardiac substructures (eg, coronary arteries) and cardiac event phenotypes.

RADIATION DOSES AND CARDIAC TOXICITY

Radiation doses are best understood as a visuospatial topographic map of differing radiotherapy intensities within carefully drawn targets and organs. Doses may be described as mean dose, maximum dose, or proportional volume of target/organ receiving certain threshold doses (eg, V15Gy [volume receiving 15 Gy or higher]). Modern radiation planning techniques allow for highly selective deposition of doses that conform to the shape of complex targets while simultaneously avoiding organs. These techniques allow clinicians to balance doses received by different organs and even organ substructures depending on the clinical context.

The heart is generally delineated in its entirety and assessed as 1 dosimetry organ at risk, but this belies its complex functional and structural architecture.

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Different types of cardiac events do not necessarily share the same pathophysiologic mechanism. Accordingly, recent studies have assessed doses received by atria, ventricles, pericardium, and coronary arteries. The left anterior descending (LAD) coronary artery is of particular interest. Atkins et al[3] analyzed over 700 patients receiving chemoradiation for NSCLC, finding that LAD dose (≥V15Gy) was the best predictor of major cardiac events. LAD dose was also confirmed to be predictive of cardiac events after breast cancer irradiation. The LAD is positioned in the anterior interventricular groove and may be directly in the path of 3-dimensional whole breast tangent fields that were historically standard before the modern usage of breath-hold, protons, and partial breast fields.[4]

No et al[1] affirm the importance of coronary arteries as an avoidance structure for radiation planning. With rigorous contouring of all individual coronary artery segments, the authors analyzed all left-sided coronaries (TotalLeft) not just the LAD. Compared with other metrics, TotalLeft V15Gy had the strongest association with cardiac events, both validating the results of Atkins et al[3] and increasing our understanding of radiation effects on vasculature. Classical radiation therapy–associated myocardial ischemia is thought to occur through a yearlong process of fibrosis and microvasculature damage that accelerates atherosclerosis. As the authors show, baseline coronary pathology (calcifications) was common and associated with cardiac events. It is plausible that doses to specific regions of baseline plaque accelerate obstructive disease and plaque vulnerability for rupture, increasing the occurrence of myocardial ischemia, infarction, and ventricular arrhythmias. It is also reasonable to conclude that coronary dose is the most important factor in lung cancer patients with a high prevalence of baseline coronary artery disease (CAD). However, one must acknowledge that events may not solely be the result of radiation exposure to specific coronary arteries given that left ventricle dose (and dose to myocardial microvasculature) was also strongly correlated with events. Moreover, cardiac sparing in general must be balanced against the need to minimize lung and esophageal doses, which also contribute to toxicity and outcomes.

RISK STRATIFICATION USING CORONARY CALCIFICATIONS AND OPPORTUNISTIC MEDICINE

Beyond detailed dosimetry analyses, No et al[1] also describe the use of calcifications (an incidental finding on radiation planning computed tomography [CT]) as a predictive baseline cardiac risk factor. With radiation planning software, the authors delineated and quantified individual calcifications within the previously contoured coronary arterial segments. Calcification burden was scored (per the Chiles et al[5] method) ordinally from none, mild, moderate, and heavy for each coronary segment and then summed to create a linear TotalLeft calcification score. Seventy-eight percent of patients had at least some calcifications (51% moderate or severe). As with coronary dose, baseline calcification burden was also significantly associated with cardiac events. Those in the highest quintile of calcification burden had a 5-year event rate of 28% (vs 11% in the remainder).

The sensitivity of coronary calcium CT to detect atherosclerotic CAD has led to increasing incorporation into screening guidelines in the general population for primary cardiac prevention.[6] In oncology, the assessment of coronary calcifications for cardiac risk stratification is a more recent consideration. The calcification data presented by No et al[1] validate our prior work in patients with NSCLC treated on prospective dose-escalation trials in which both calcification burden on planning CT and heart doses were associated with cardiac events.[7] In addition, a large Dutch study found that calcifications on planning CT in over 15,000 women receiving radiation for breast cancer were strongly predictive of cardiac events.[8]

Cardiac risk stratification across oncology is inconsistent given the heterogeneity of diagnoses, prevalence (or absence) of baseline cardiac risk, and competing priority of cancer treatment. Modification of treatment factors such as heart dose is commonly practiced before radiation planning, but baseline cardiac risk is not necessarily considered. In patients at particularly high cardiac risk (whether baseline or from treatment), “cross-purposing” of oncologic CT scans already obtained for diagnostic/planning purposes for coronary calcification assessment may better stratify patients in an opportunistic and cost-effective fashion. In contrast to complicated risk calculators incorporating history (that may be incomplete) and laboratory markers (that represent a snapshot in time), coronary calcium CT scans present objective radiographic findings that have accumulated over a lifetime. Practically, radiation oncologists may be more likely to notice calcifications while contouring on planning scans.

IMPLEMENTATION AND FUTURE DIRECTIONS

The work by No et al[1] illustrates the power of radiographic assessments to personalize care for patients

with thoracic malignancies and has implications for oncologists and cardio-oncologists alike. For the radiation oncologist, the data provide additional support for the specific delineation and minimization of left-sided coronary doses. Furthermore, treatment planning CTs can be used for coronary calcium quantification akin to echocardiography and nuclear stress testing for prechemotherapy cardiac risk stratification. Calcification assessment need not be overly complex; Chiles et al[5] found that simple visual calcification scoring of "mild, moderate, severe" on lung cancer screening CTs was essentially equivalent to complex Agatston scores. The finding of incidental coronary calcifications while contouring may influence radiation oncologists to prioritize lowering heart (and coronary) dose. However, it is also prudent to consider that the lungs and esophagus may be equally important to cardiac protection in certain patients and "the dose has to go somewhere." Future research is required to refine optimal dosimetry balances that consider all patient-specific cardiopulmonary, nutritional, and oncologic factors, a daunting endeavor where artificial intelligence may shine.

Radiation oncology inherently relies on CT, and a recent expert radiation oncology consensus statement summarized recommendations put forth by the Society of Cardiovascular Computed Tomography regarding the use of imaging for cardiac risk stratification in oncology.[9,10] Radiation planning CT scans are obtained for target/organ delineation, are of variable quality, and are not interpreted by diagnostic radiologists; cardiac substructures and coronaries are not easily discernable on these images. Data are quickly evolving but are heterogeneous, with endpoints consistently associating cardiac doses with toxicity but not necessarily overall survival. Thus, there is yet no standard regarding the use of cardiac substructures. Nonetheless, clinicians may reasonably choose to delineate and prioritize coronaries based on clinical judgment as well as consideration of risk factors determined during work-up, including incidental detection and assessment of calcifications.[9]

Pertinent to all oncologists, coronary calcifications are readily visible on diagnostic CT scans obtained for most thoracic malignancies. Calcification assessment is advocated for risk stratification in patients with breast cancer, where their presence even on mammography is associated with cardiac risk.[11] More consistent reporting and quantification of these incidental calcifications by diagnostic radiologists could aid in risk stratification before surgery and chemotherapy, a practice recommended by the Society of Cardiovascular Computed Tomography.[10] These principles apply to the treatment of all cancers with baseline or treatment-associated risks and are used in cardio-oncology clinics.

For the cardiologist, cardio-oncologist, and primary care provider, optimal care involves the consideration of cancer treatment as a unique cardiac risk factor. In patients beginning their cancer journey, the use of calcification data detected during radiographic cancer work-up may prompt changes in cardiac risk comanagement alongside cancer treatment. For public health, the detection of calcifications could even represent the initial diagnosis of CAD and function as concomitant cardiac screening for primary prevention and application of therapies known to reduce risks of future cardiac events. This is particularly pertinent in the lung cancer population; smoking leads to high prevalence of CAD and occurs at a higher rate in rural areas with less reliable health care access.[12,13]

For some patients, the diagnosis of cancer may be their first encounter with the health care system, underscoring accurate ascertainment of pre-existing, undiagnosed heart disease. For others, cancer screening leads to more early-stage, favorable cancer diagnoses (eg, ground-glass stage I presumed NSCLC and ductal carcinoma in situ), underscoring accurate prioritization of oncologic vs nononcologic prognoses, morbidity, and mortality. Ultimately, optimal care involves holistic integration of these concepts and specialties to comprehensively promote patient-centered medicine.

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REFERENCES

1. No HJ, Guo FB, Park NJI, et al. Predicting adverse cardiac events after radiotherapy for locally advanced non-small cell lung cancer. *J Am Coll Cardiol CardioOnc*. 2023;5(6):775–787. https://doi.org/10.1016/j.jaccao.2023.08.007.

2. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2017;35(8):893–911. https://doi.org/10.1200/JCO.2016.70.5400

3. Atkins KM, Chaunzwa TL, Lamba N, et al. Association of left anterior descending coronary artery radiation dose with major adverse cardiac events and mortality in patients with non-small cell lung cancer. *JAMA Oncol*. 2021;7(2):206–219. https://doi.org/10.1001/jamaoncol.2020.6332

4. Zureick AH, Grzywacz VP, Almahariq MF, et al. Dose to the left anterior descending artery correlates with cardiac events after irradiation for breast cancer. *Int J Radiat Oncol Biol Phys*. 2022;114(1):130–139. https://doi.org/10.1016/j.ijrobp.2022.04.019

5. Chiles C, Duan F, Gladish GW, et al. Association of coronary artery calcification and mortality in the National Lung Screening Trial: a comparison of three scoring methods. *Radiology*. 2015;276(1):82–90. https://doi.org/10.1148/radiol.15142062

6. Greenland P, Blaha MJ, Budoff MJ, Erbel R, Watson KE. Coronary calcium score and cardiovascular risk. *J Am Coll Cardiol*. 2018;72(4):434–447. https://doi.org/10.1016/j.jacc.2018.05.027

7. Wang K, Malkin HE, Patchett ND, et al. Coronary artery calcifications and cardiac risk after radiation therapy for stage III lung cancer. *Int J Radiat Oncol Biol Phys*. 2022;112(1):188–196. https://doi.org/10.1016/j.ijrobp.2021.08.017

8. Gal R, van Velzen SGM, Hooning MJ, et al. Identification of risk of cardiovascular disease by automatic quantification of coronary artery calcifications on radiotherapy planning CT scans in patients with breast cancer. *JAMA Oncol*. 2021;7(7):1024. https://doi.org/10.1001/jamaoncol.2021.1144

9. Wright JL, Amini A, Bergom C, Milgrom SA. Summary of cardiac computed tomographic imaging in cardio-oncology: an expert consensus document of the Society of Cardiovascular Computed Tomography. *Pract Radiat Oncol*. 2023;13(6):488–495. https://doi.org/10.1016/j.prro.2023.08.008

10. Lopez-Mattei J, Yang EH, Baldassarre LA, et al. Cardiac computed tomographic imaging in cardio-oncology: an expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT). Endorsed by the International Cardio-Oncology Society (ICOS). *J Cardiovasc Comput Tomogr*. 2023;17(1):66–83. https://doi.org/10.1016/j.jcct.2022.09.002

11. Bui QM, Daniels LB. A review of the role of breast arterial calcification for cardiovascular risk stratification in women. *Circulation*. 2019;139(8):1094–1101. https://doi.org/10.1161/CIRCULATIONAHA.118.038092

12. Skinner L, Staiger DO, Auerbach DI, Buerhaus PI. Implications of an aging rural physician workforce. *N Engl J Med*. 2019;381(4):299–301. https://doi.org/10.1056/NEJMp1900808

13. Parker MA, Weinberger AH, Eggers EM, Parker ES, Villanti AC. Trends in rural and urban cigarette smoking quit ratios in the US From 2010 to 2020. *JAMA Netw Open*. 2022;5(8):e2225326. https://doi.org/10.1001/jamanetworkopen.2022.25326

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