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EDITORIAL COMMENT

Association of Cardiac Substructure Radiation Dose With Arrhythmia

Time to Move Away From Mean Dose

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Radiation therapy (RT), combined with chemotherapy and adjuvant immunotherapy, remains the standard treatment for unresectable non-small cell lung cancer (NSCLC).[1] Cardiotoxicity occurs earlier in patients with lung cancer compared with lymphoma and breast cancer, more significantly affecting survival because of increased age, greater comorbidities, and lower fitness levels. Thus, minimizing cardiotoxicity has emerged as a priority in thoracic radiation oncology.

Although historical cardiotoxicity studies were focused on mean heart dose and pericarditis endpoints, recent studies have included assessment of cardiac substructure doses and recognition of additional cardiac toxicities. Although the contemporary literature has focused on ischemic events and heart failure because of their associations with mortality,[2] conduction abnormalities have been less well explored. Arrhythmia is an important cardiotoxicity for both patients and health care systems because of the need for monitoring, medications, and/or hospitalization for complications.

In a study reported in this issue of *JACC: CardioOncology*, Atkins et al[3] addressed gaps in the literature regarding RT-related arrhythmia. These data were obtained through an endpoint-specific analysis of cardiac substructures within a large institutional data set, with adjustment for relevant oncologic and cardiologic factors and competing risk for death. They examined various arrhythmia subtypes, including atrial fibrillation (AF), atrial flutter, other supraventricular tachyarrhythmias (SVTs), bradyarrhythmia, and ventricular tachyarrhythmia (VT). The median time to onset for arrhythmia was 1.6 years, highlighting that this "late toxicity" might not be so late in patients with NSCLC. Significant associations were found between arrhythmias and dose to relevant cardiac substructures, even after adjustment for confounders, supporting the hypothesis that cardiac irradiation dose distribution influences arrhythmia risk. Top candidate cardiac substructure dose metrics were selected for multivariable analysis on the basis of area under the curve. Pulmonary vein volume receiving 5 Gy or higher (V5) was associated with AF, left circumflex coronary artery V35 with atrial flutter, pulmonary vein V55 with other SVTs, right coronary artery V25 with bradyarrhythmia, and the left main coronary artery V50 with VT. On the basis of what is known about the pathophysiology of arrythmias, these relationships are plausible.

For each substructure, a threshold was derived to illustrate the ability of the newly identified dose metrics to discriminate between high- and low-risk cases. Dose thresholds for the coronary arteries were lower than for the chambers, perhaps reflecting the differences in tolerance for potential damage; for example, lower relative levels of inflammation and fibrosis would cause severe dysfunction in the small lumens of the coronary arteries. With validation, these thresholds could serve as dose limits for RT planning.

Moreover, it is current convention that most dose constraints are applied to all patients, without considering individual patient factors. However, the investigators found that some arrhythmia subtypes had an association with pre-existing factors whereas

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others did not, with AF, VT, and bradyarrhythmia more often in patients with previous coronary heart disease. This observation supports the concept of variable dose limits on the basis of baseline cardiac status, although validation is needed.

There is a strong rationale for different toxicity thresholds for different cardiac regions, because of their differing constituent cell populations. This demands that the volume receiving a range of doses be interrogated, rather than the mean or maximum dose alone. The consequence of this multidimensionality is that a large number of dose metrics, which exhibit great collinearity, must be considered. Specifically for cardiac dose analyses, there is also collinearity of radiation dose among groups of substructures, because of their spatial intimacy, and the members of these groups can also vary according to the spatial relationship of the tumor with the heart. When a toxicity is truly attributable to a substructure, as opposed to when it is actually a surrogate for an adjacent substructure, can be difficult to discern. The use of "area under the curve" values to select candidate dose metrics from a range of almost 300 per toxicity in this study maximizes the opportunity to find the critical metric, but at the theoretical cost of more false-positive findings. That multiple testing corrections were not applied by the investigators was substantiated by hypothesis testing being limited to the final multivariable model, which might be of potential methodologic concern.

Similarly, there is no consensus on the optimal method of selecting other factors for multivariable analysis. Choosing these on the basis of univariable regression results that meet arbitrary criteria is a commonly used method but risks excluding known clinically relevant factors. Using established clinically pertinent factors chosen a priori is potentially more clinically sound, and the investigators used a combination of both methods. Similarly, although it is widely acknowledged that the inclusion of continuous data is superior in clinical models such as those reported, dichotomization can be useful in RT toxicity studies, as the output might serve directly as a clinically implementable dose constraint for treatment planning. There is a lack of agreement on which of these options is most applicable, but the answer might vary according to the aim of the study, with the former being more useful for discovery projects (as used in this study) and the latter for validation studies.

Atkins et al[3] are to be applauded for this study, with its multiple findings providing a major contribution to the field. The investigators have validated that the pulmonary veins are key dosimetric mediators in relation to the development of AF, which was described recently.[4] Furthermore, the investigators link these structures to other SVTs. Also aligning with the original pulmonary vein study, the role of the sinoatrial node was shown to be weaker than first reported.[5] Ventricular arrhythmias have not been subject to a specific dosimetric analysis to date, so resolving this to the left main stem coronary artery dose represents both a novel approach and result. These cardiac regions constitute the anatomical heart base, for which an abundance of clinical evidence has accumulated in recent years.[6,7] Unsupervised analysis of RT plans consistently identifies the heart base as the region where radiation dose was most influential for survival. This has been validated in several cohorts,[8,9] and a retrospective data set,[10] with the latter study also demonstrating an association between the heart base and cardiac events. Whether a specific substructure or substructures within the composite volume of the heart base underpin the mortality detriment observed, or whether a group of radiosensitive tissues that reside in this region collaboratively drive excess mortality, is unknown. The data presented strongly suggest a role for arrhythmia as a mediator of death in patients with NSCLC with high radiation doses to the heart base.

Considering the external validity of the study findings, the RT treatment modality used for most patients has been upgraded, but the greater range of doses available for analysis as a result allow a more comprehensive evaluation of the dose-endpoint relationship. The study also predates the era of adjuvant immunotherapy, but it is highly unlikely that durvalumab lowers the risk for cardiotoxicity. Furthermore, that a sophisticated myocardial wall subgroup analysis did not yield different results compared with conventional "whole chamber" delineation will be reassuring for those who have invested in substructure autocontouring tools that adhere to the atlas.[11]

In conclusion, this study serves as an exemplar for the design of future RT cardio-oncology studies. The investigators report fully integrated oncology-cardiology clinical data and high-quality substructure segmentation. Finally, these spatially and physiologically elaborate data serve as a reminder of the magnitude of the complexity surrounding the physics and biology of the heart with respect to RT: we are past "the point of no return" for mean heart dose.

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