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Sinoatrial Node Radiation Dose and Atrial Fibrillation in Patients With Lung Cancer

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To the Editor

We read with interest the cohort study by Kim et al.[1] In a retrospective cohort of 560 patients with lung cancer treated with definitive chemoradiotherapy, they conclude that maximum radiotherapy (RT) dose to the sinoatrial node was most strongly associated with the development of post-RT atrial fibrillation. Their results support prior work that found that dose to the base of the heart most strongly associated with worse survival.[2] When considering the validity of their conclusions, a few points should be considered.

First, 26 of 560 patients (4.6%) developed atrial fibrillation, and 11 of 560 developed (2.0%) other cardiac events (cardiac death, acute coronary syndrome, coronary revascularization, heart failure),[1] both of which are notably lower than in prior RT cardiotoxicity studies (10%−14% for each).[3,4] The smaller numbers may reflect a patient population that has a lower burden of baseline cardiovascular disease and therefore a lower risk of post-RT events. An alternative explanation is that the true cardiac event rate was under estimated, given the challenges of retrospective assessment. Considering the low event rate, even a few additional events could significantly alter the analyses.

Second, newly diagnosed atrial fibrillation may have an acute precipitant, such as pneumonia, surgery, or pulmonary embolism. Such precipitants represent potential confounders for the development of post-RT atrial fibrillation beyond baseline cardiovascular disease. Can the authors provide additional details about the atrial fibrillation events in the cohort, including any potential precipitants and required interventions? Two

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prior, albeit small, studies found that of all cardiac events, arrhythmic events (mainly atrial fibrillation) showed the weakest associations with cardiac substructure dose.[4,5]

Third, in the competing risk regression analysis for atrial fibrillation within the small cell subgroup (Table 2 of the original article),[1] the subdistribution hazard ratio (sHR) point estimate for sinoatrial node maximum dose increased from 8.9 to 14.9 between univariable and multivariable analysis. An sHR of 14.9 is quite remarkable. We are concerned about model overfitting, as there were only 9 atrial fibrillation events in the small cell subgroup and 5 variables included in the multivariable model. Overfitting can artificially inflate the sHR.

During RT planning for lung cancer, should we be most protective of the sinoatrial node,[1] the left anterior descending artery,[3] other cardiac substructures, or a combination? As the authors point out,[1] validation studies will be essential. Additionally, future RT cardiotoxicity studies could analyze multiple different end points to understand how the “best” dosimetric predictor differs based on selection of end point (eg, atrial fibrillation vs major adverse cardiac events vs survival).

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