In Reply to Yavas et al.

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To the Editor: We thank Yavas et al for their interest in our study, their letter, and the points they raise.[1] The authors refer to the RTOG 0617 trial[2] in patients with non-small cell lung cancer, in which dose escalation led to more treatment-related deaths and dose-volume parameters such as heart V5 and V30 were related to this excess mortality. It is known from the literature that heart dose is associated with grade ≥3 cardiac events, and patients who develop cardiac complications have significantly worse overall survival.[3]

In our study we focused on the mean dose to left ventricular (LV) myocardial segments in relation to the mean extracellular volume (ECV) in those segments. When aiming to map and quantify myocardial fibrosis as a direct consequence of radiation dose to the heart, we believe that this is a more accurate approach than the use of volumetric parameters of the whole heart, in which the spatial information is lost. Nevertheless, we evaluated the relation between mean LV ECV and dose volume-parameters such as V5, V30, and V40. These DVH parameters of the heart highly correlate with the mean heart dose. If both study groups are included, these parameters were all statistically significantly ($P < .001$) related to the mean LV ECV, but within the nCRT group no relation was found. This might be due to the small sample size, which is less of a problem when we take all LV segments into account.

Yavas et al also raised the question of whether concurrent chemotherapy might have contributed to the effect of the radiation therapy on ECV. A dose effect relationship was seen over the entire dose range. However, even in the low-dose segments, the ECV was significantly higher than in our older control patients, which might indicate an additional effect of chemotherapy.

As stated in the paper, we agree that further research in large prospective cohorts is needed to determine the clinical relevance of developing elevated mean LV ECV after thoracic irradiation. We would like to emphasize that our patient cohort contains long-term survivors of esophageal cancer. Because patients with cardiac toxicity have worse overall survival rates, our study design initiated a selection bias. This only strengthens our interest in a large prospective trial. How does myocardial fibrosis develop over time, and what role does this pathology play in treatment-related deaths?

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Disclosures: none.