

Regarding: “Olloni A, et al. Heart and Lung Dose as Predictors of Overall Survival in Patients With Locally Advanced Lung Cancer. A National Multicenter Study”



To the Editor:

We have read the article by Olloni et al.¹ with great interest. In a unique cohort, the authors investigate the impact of lung and heart irradiation on overall survival in patients receiving radiotherapy for locally advanced NSCLC. The authors report that a model containing radiation dose-volumes of (left) heart, lungs, and the four heart chambers, in addition to the clinical variables of age, body mass index, sex, performance status, dose to gross tumor volume, and log gross tumor volume, most accurately predicts survival.

The authors are to be commended for their use of principal component analysis (PCA) to resolve issues arising from collinearity between dose-volume variables. Rather than selecting a small number of dose-volume variables, this approach combines information from many of them, thus making good use of all dosimetry information in the data set. Nevertheless, we do have some questions related to the interpretation and conclusions of their analyses.

First, on the basis of a lack of association between PCA₅ (reflecting mostly lung dose) and survival, the authors infer that lung dose might be less important for survival than heart dose. Nevertheless, this lack of association might well be explained by limited variation of lung dose in the data set. Although selecting the number of components based on cumulative variance is a

common approach,² here, it produced several components with only limited variance, as seen in Figure 1. PCA₅ contains only approximately 2% of total variation in dose-volume histogram parameters. Including more lung-related variables (i.e., individual variables for lung lobes) and increasing the variation in lung doses (e.g., by adding patients with esophageal cancer) might have produced different conclusions.

Second, because PCA₁ (describing whole heart irradiation) had the strongest association with survival, the authors suggest that in the relationship between base of heart and survival reported by others, dose to the base of the heart might simply have been a surrogate for dose to the whole heart. Such interpretation would require finding a lack of association of a component reflecting heart base dose with survival. The lack of such a component suggests that the independent variation of dose in the heart base in the study population is too low to permit an interpretation in terms of the impact of dose to the heart base on survival. Furthermore, besides being reproduced in multiple cohorts,³ this specific sensitivity of the heart base has also been reported in preclinical research.⁴ Researchers from Manchester University and The Christie National Health Service Foundation Trust are currently performing a clinical trial to test the effect of cardiac base avoidance. Such a prospective test will provide data with sufficient variation in the variable of interest, without being hampered by confounding and indication bias, to critically test the hypothesis that the base of the heart is a critical substructure for survival.

To summarize, we advise a stricter selection of principal components with sufficient variance, and broadening the case mix to increase variance in dose.

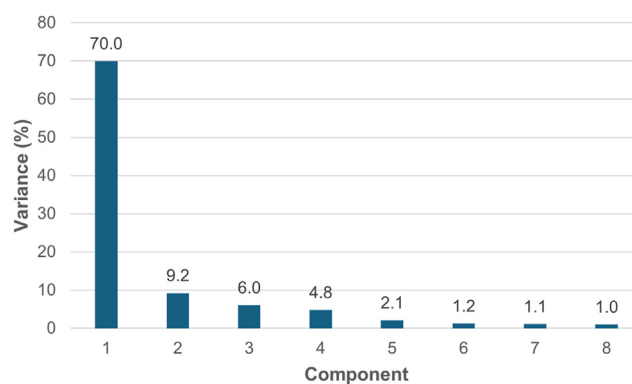


Figure 1. Variances of principal components for primary model, Olloni et al.¹

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Cite this article as: Hessels AC, Frederiks ML, Muijs CT, van Luijk P. Regarding: “Olloni A, et al. heart and lung dose as predictors of overall survival in patients with locally advanced lung cancer. a national multicenter study.” *JTO Clin Res Rep*. 2024;5:100718.

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ISSN: 2666-3643

<https://doi.org/10.1016/j.jtocrr.2024.100718>

Despite these points, we are very impressed by this well-performed study in a large cohort and are looking forward to future work from these colleagues.

CRediT Authorship Contribution Statement

Arno C. Hessels: Conceptualization, Writing – original draft, Writing – review and editing, Visualization.

Mark Frederiks: Writing – review and editing, Visualization.

Christina T. Muijs: Writing – review and editing, Supervision.

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