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**Abstract:**

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Title: In Regard to Kabarriti et al.


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In a recent analysis, Kabarriti et al\textsuperscript{1} reported an association between increasing prior mean radiotherapy (RT) lung dose and worse mortality in 107 cancer patients with coronavirus disease 2019 (COVID-19). The study was accepted as a pre-print and then promoted on social media (since deleted). While pulmonary toxicity associated with RT is an important issue, we have several concerns about the methodologies and conclusions of this study.

Notably, clinical factors linked with worse outcomes in COVID patients, including smoking history and comorbidities\textsuperscript{2-4} such as diabetes or COPD, were not included. Several oncologic factors that have a substantial impact on mortality also were unaccounted: cancer stage and recurrence status, treatment intent (i.e. definitive or not), or other recent cancer treatment, which is associated with a higher risk of a severe event with infection than without recent treatment\textsuperscript{5}. Furthermore, a recent comprehensive COVID-19 study\textsuperscript{6} of 105 and 536 age-matched patients with and without cancer, respectively, found a higher risk of severe events in patients treated with recent surgery or immunotherapy, but not RT.

Another major issue is the uncontrolled confounding variable of cancer diagnosis. The authors note that both lung cancer diagnosis and mean lung dose (MLD) >4 Gy were significantly associated with mortality; however, they decline to perform multivariate analysis due to a high correlation between the two variables. Of the listed histologies however, only locally advanced lung cancer would be expected to generate a MLD >4 Gy. The lack of reporting of these known confounding factors and the failure to complete multivariate modelling makes it impossible to interpret the relationship between mean lung dose and mortality. Such a severe limitation on interpreting the study results should at least be mentioned in the discussion.

From a patient perspective, the study may have unintended, negative consequences. Some lung cancer patients, not alerted to the significant limitations and conflicting findings with earlier studies, contemplated cancelling their scheduled RT because of the perceived tremendous risk of death if they contracted COVID-19. Others, having already completed RT, were frightened to leave their house, even if medically necessary.

In summary, we applaud the authors for their effort in raising awareness to a potential negative prognostic factor for COVID patients; however, we feel that the significant omissions noted above limit the applicability of this analysis. We urge caution in overstating the results in the manuscript as well as online to avoid potential distress to vulnerable patient populations.
References


