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Title: Response to Oymak et al

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LETTER TO THE EDITOR

Dear editor,

We read with much interest the comments by Oymak et al [1] regarding our recent manuscript "Long term radiological features of radiation-induced lung damage"[2]. In our opinion radiation-induced lung damage (RILD) is an important but still poorly understood clinical problem. We thank the authors for their interesting comments and we are pleased to note their enthusiasm for our approach.

Regarding the limitations in patient selection of our study highlighted by Oymak et al, we did not collect data on pre-existing lung disease or smoking history. In IDEAL-CRT the majority of the subjects were treated with 3D-conformal radiotherapy (3D-CRT)[3]. In the patient subset described in our study, 89% had 3D-CRT and 11% had IMRT. No patient received any radiotherapy beyond that prescribed in the study during the twelve month follow-up period.

We acknowledge that there are many clinical confounding factors that add complexity to the study of RILD, including pre-existing lung conditions and choice of combination therapies[4]. These are likely to obscure correlations with dosimetry and lung function. CT findings of parenchymal change, volume reduction and pleural reactions occurred with sufficient frequency to be consistent with RILD. The six patients were excluded due to significant overlapping pathology that would obscure the described findings. All CT changes described were relative to a baseline scan acquired prior to radiotherapy. Most relevant chronic lung diseases progress slowly and would not be expected to change in twelve months. However, an interaction between radiotherapy and these diseases cannot be ruled out.

Finally, we agree that incorporating dosimetry information is crucial to understand RILD. The dose distribution achieved with different RT techniques will impact toxicity[5,6]. Dose distributions have been typically reduced to global measures (such as mean lung dose) when investigating toxicity. It becomes relevant to consider regional characteristics with the widespread of new RT technologies such as IMRT. Parenchymal change is regional and occurs inside the radiation field. Distortions of the anatomy and pleural reactions likely reflect dose at distant locations. This was discussed in our study. To properly investigate the regional dose relationships accurate image registration techniques are required between baseline and follow up CT scans[7]. This is challenging considering the degree of anatomical change at 12-month follow up, but is a focus of our future work.

To conclude, our methods were designed to describe RILD in greater detail than previously and so demonstrate that there is much scope to objectively grade changes. We hope our study motivates objective scoring of RILD, which will enable correlation with dosimetry and clinical outcomes as well as understanding the impact of clinical confounding factors. Further research on larger patient groups treated with different RT modalities is required to uncover the dose and clinical relationships referred to by the authors.

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