Balancing Radiation Pneumonitis Versus Locoregional Tumor Control in Non–Small-Cell Lung Cancer

To the Editor:

With great interest, we read the recent publication by Vinogradskiy et al.[1] The authors apply their radiation pneumonitis prediction model combining dose-volume and genetic components (single-nucleotide polymorphisms [SNPs]) for isotoxic mean lung dose determination. The five SNPs were found to predict for radiation pneumonitis and interestingly, they do not directly relate to lung injury, but rather to cellular repair and the tumor microenvironment.

The authors state that radiation pneumonitis is the dominant dose-limiting constraint in thoracic radiotherapy. This may have been the case for the cohort studied for 19% of the patients, mostly treated with three-dimensional conformal radiotherapy developed radiation pneumonitis of grade 3 or higher. With the introduction of highly conformal radiotherapy delivery techniques and by abandoning elective nodal irradiation, acute grade 3 esophagitis is increasingly the dose-limiting toxicity based both on clinical experience[2] and in silico studies.[3] As opposed to radiation pneumonitis, this burdensome side effect is not fatal but gradually develops during the course of (chemo)radiotherapy, lasting for several weeks thereafter necessitating analgesic medication and dietary alterations in the majority of patients. Moreover, late esophageal sequelae may develop, adversely influencing the patients' quality of life.

Vinogradskiy et al.[1] found that on the basis of the isotoxic physico-genetic model a reduction in prescribed dose would be necessary in 26 of the 141 patients studied. All but one of these patients belonged to the cohort that developed radiation pneumonitis. The mean clinically prescribed dose to this pneumonitis population was 64.7 Gy as opposed to 51.8 Gy predicted to be safe by the model. For a subset of the remaining patients, the dose could be slightly increased or decreased. This finding is intriguing keeping in mind that dose escalation in lung radiotherapy is thought to substantially increase local tumor control and ultimately survival.[4] Instead of decreasing the dose to prevent patients from developing unwanted side effects, more tailored solutions are feasible. van Baardwijk et al.[5] successfully pioneered an individualized approach escalating dose to maximal tolerance while keeping within the normal-tissue constraints, both theoretically and clinically. Both acute and late toxicity were acceptable. Additionally, MAASTRO clinic is currently conducting a randomized phase II trial including 18F-fluorodeoxyglucose-positron emission tomography information for tumor (subvolume) boosting (NCT01024829). On the basis of a recent in silico study,[3] Radboud University Nijmegen Medical Centre is carrying out the Individualized Dose Escalation in Advanced stage non-small cell Lung cancer using Volumetric Modulated Arc Therapy (IDEAL-VMAT) study (NCT01577212), whereby the irradiation dose is increased on an individual basis, taking into account multiple normal-tissue constraints.

For patients with both an unfavorable genetic profile and dose distribution, the radiation dose that can be safely administered on the basis of the proposed model is probably not curative. Therefore, the treating radiation oncologist may opt for a palliative protocol thereby decelerating tumor progression and alleviating tumor-associated complaints while preventing patients from unnecessary treatment-related side effects.

In summary, this article on model-based prescription provides new, yet prospectively unvalidated, tools for individualized dose-prescription in non–small-cell lung cancer patients. Radiation oncologists are encouraged to enhance radiation dose in patients with a favorable profile while seeking alternative therapeutic options in the remaining patients.

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In Response:

We would like to thank Troost et al. for their interest in our work regarding personalizing prescription doses using genetic data.[1] The authors

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