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. 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 and in silico studies. 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. 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. Instead of decreasing the dose to prevent patients from developing unwanted side effects, more tailored solutions are feasible. van Baardwijk et al. 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, 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.

Esther G.C. Troost, MD, PhD
Aswin L. Hoffmann, MSc
Department of Radiation Oncology (MAASTRO)
GROW School for Oncology and Developmental Biology
Maastricht University Medical Centre
Maastricht, The Netherlands

Johan Bussink, MD, PhD
Department of Radiation Oncology
Radboud University Nijmegen Medical Centre
Nijmegen, The Netherlands

REFERENCES


In Response:

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

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Esther G.C. Troost, MD PhD, Department of Radiation Oncology (MAASTRO), Dr. Tanslaan 12, 6229 ET Maastricht, The Netherlands. E-mail: esther.troost@maastro.nl

Copyright © 2013 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/13/0805-00e47
bring up several salient points that warrant further discussion. The first issue raised is that with developing technology and in certain instances acute grade III esophagitis may be the dose-limiting factor for thoracic tumors. We agree that every clinical case is unique and the dose-limiting organ can be dependent on tumor location, tumor size, and treatment technique and design. However, the risk of radiation pneumonitis is still considered by many to be one of the most critical limiting factors in increasing doses to lung tumors.\(^2\) The aim of our work was to illustrate the concept of personalizing prescription doses, based on available single nucleotide polymorphism and radiation pneumonitis data. We believe the idea of personalized toxicity estimates can and should be expanded to other thoracic organs at risk as data become available and model accuracy improves.

For some of our simulations we noted that our model indicated lower tumor doses (implying dose de-escalation) than what was clinically delivered for a cohort of patients to keep the clinical severe pneumonitis at an acceptable level. We should underline that we are not suggesting the idea of dose de-escalation but rather this result is a product of our study design. For a percentage of our patient cohort, the simulation suggested dose de-escalation because at the time of treatment the physician made a clinical judgment to exceed constraints that we set for the nonlung organs (esophagus, spinal cord, and heart). When those patients were excluded from the study, the changes in prescription dose were approximately zero, indicating that the positive and negative changes in dose cancelled out; which can be expected when the same data set is used for generating the model and performing the simulation. With the above in mind, our results still show some patients for whom the model suggested a dose de-escalation to control the incidence of pneumonitis. For those patients, we completely agree with Troost et al. in that tumor control is of primary importance and “more tailored solutions are feasible.” Instead of dose de-escalation we cite some examples of redesigning the beam arrangement or replanning the patient with different treatment modalities (protons versus photons for example).\(^1\) The work done by Van Baardwijk et al.\(^3\) is also an excellent example of how the dose can be escalated while keeping toxicity rates at an acceptable level. There are many ways to adapt a treatment plan based on a patient’s personalized toxicity risk, and we feel it is important to characterize each step individually before a complete paradigm of treatment personalization is clinically implemented. The aim of our work was to characterize one step of the process rather than propose a complete solution.

The virtual trial presented in our work is a proof of principle study and should be placed in proper perspective. The personalized toxicity work is one step in a multistep complicated process. The model will not replace tumor control consideration, the clinical judgment of the physician, or vary patient and clinical scenarios. More work will be needed to determine how the results from personalized toxicity estimates can be properly incorporated into the treatment process.

Yevgeniy Vinogradskiy, PhD
Department of Radiation Oncology
University of Colorado
School of Medicine
Aurora, Colorado
Susan L. Tucker, PhD
Department of Bioinformatics and Computational Biology
University of Texas
MD Anderson Cancer Center
Houston, Texas
Zhongxing Liao, MD
Department of Radiation Oncology
University of Texas
MD Anderson Cancer Center
Houston, Texas
Mary K. Martel, PhD
Department of Radiation Physics
University of Texas
MD Anderson Cancer Center
Houston, Texas

REFERENCES


MARS: A Sense of Perspective and an Inconvenient Truth

To the Editor:

It is important to correct the record concerning the Mesothelioma and Radical Surgery (MARS) trial\(^1\) referred to in the November issue of the Journal of Thoracic Oncology by Hedi Kindler\(^2\) and Valerie Rusch et al.\(^3\) The points they raise here have been rehearsed at conferences around the world in the course of discussion of the place of extrapleural pneumonectomy (EPP) for malignant pleural mesothelioma. They merit examination and, in some instances, robust rebuttal.

MARS reported just 50 randomized patients, a small number.\(^1,4\) The Clinical Trials Awards and Advisory Committee (CTAAC) of Cancer Research, United Kingdom funded a 50-patient study to test feasibility, aware of the potential difficulty of recruiting and randomizing patients. At that time the sample size estimated to ensure that a randomized study would be 80% sure to detect a survival advantage attributable to EPP was 670 patients. This power calculation was based on the certificated time to death of 426 unoperated patients surgically diagnosed with malignant pleural mesothelioma compared with reported survival of patients who had EPP as part of completed multimodality therapy. Had MARS proceeded to the larger study, the 50 patients would

Disclosure: The authors declare no conflict of interest.

Address for correspondence: St Thomas’s Street, London SE15 5NY, United Kingdom. E-mail: tom.treasure@gmail.com

Copyright © 2013 by the International Association for the Study of Lung Cancer

ISSN: 1556-0864/13/0805-0048

e48