POINT/COUNTERPOINT

Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Jing Cai, The Hong Kong Polytechnic University, Hong Kong: jing.cai@polyu.edu.hk, and/or Habib Zaidi, Geneva University Hospital, Geneva, Switzerland: habib.zaidi@hcuge.ch. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.

Treatment planning based on lung functional avoidance is not ready for clinical deployment

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OVERVIEW

Current radiotherapy treatment planning for lung cancer does not account for regional differences in pulmonary function. Functional avoidance radiotherapy has been proposed to overcome this limitation by intentionally minimizing dose to higher functioning lung areas while favoring radiation deposition in lower functioning regions. Preliminary studies have demonstrated the potential dosimetric advantages of functional avoidance treatment planning over conventional treatment planning in its ability to maximally spare functional lung tissue. While some believe that lung functional avoidance radiotherapy in clinical trials is well justified and supported by currently available evidences, others have concerns regarding its fundamental assumptions and technique limitations and therefore consider it not to be ready for clinical deployment. This is the topic of this month's Point/Counterpoint debate.

Arguing for the Proposition is Amit Sawant, Ph.D. Dr. Sawant is currently an Associate Professor in the Department of Radiation Oncology at the University of Maryland, Baltimore. He obtained his Ph.D. from the University of Michigan, Ann Arbor. His current research is focused on developing novel forms of real-time multimodality image guidance (surface photogrammetry, MRI, CT), functional imaging in lung stereotactic-body

radiotherapy (SBRT), higher order treatment planning using graphics processing unit (GPU)-based high-performance

computing, thermal therapy, and small animal image-guided radiotherapy.

Arguing against the Proposition is Tokihiro Yamamoto, Ph.D. Dr. Yamamoto is currently an Assistant Professor in the Department of Radiation Oncology at the University of California Davis. He received his Ph.D. in Medical Physics and Engineering from Osaka University, Japan in 2007. After completing his Ph.D., he received postdoctoral training in the Department of Radiation Oncology at Stanford University,

California. He has published 38 peer-reviewed articles and one book chapter. He currently serves on the editorial board of *Advances in Radiation Oncology*. His main scientific interests are focused on developing and investigating novel imaging technologies and integrating these innovations into clinical radiotherapy to improve clinical outcomes.

FOR THE PROPOSITION: Amit Sawant, Ph.D.

Opening Statement

Lung functional avoidance (LFA) radiotherapy aims to create plans that spare higher functioning lung regions by redirecting dose through functionally compromised regions. While the concept is promising, I have serious concerns regarding our current understanding of image-based functional mapping, image validation techniques, and LFA planning assumptions. Consequently, I am compelled to argue that LFA planning is not ready for clinical deployment.

First, our understanding of image-based interpretation of lung function is incomplete/incorrect. Current imaging measures specific ventilation (V_s) = volume of fresh gas delivered/volume of resident gas. In fact, gas exchange is proportional to the ratio of *alveolar* ventilation (V_a) = the delivery of fresh gas, to perfusion (Q).¹ V_a is nonlinearly related to V_s , and can be computed using regional density.² However, these corrections are not applied in current LFA planning. CT-based LFA strategies, which use ventilation only or perfusion only, are even farther from accurately mapping lung function. Lung cancer patients frequently present with comorbidities (COPD, pulmonary hypertension), which can cause significant V/Q mismatches.^{1,3} Thus, regions showing high ventilation but poor perfusion (and vice versa) may be incorrectly classified as “highly functional”. Furthermore, regional ventilation and perfusion exhibit significant gravitational dependence and therefore vary with body position.⁴ Thus, a normally functioning region in the upright state may be incorrectly classified as “low-functioning” when imaged in the supine state.

Second, objective validation of image-based functional assessment is challenging due to lack of high-resolution ground-truth data. Strictly quantitative validations are based on comparing global measurements (e.g., spirometry or arterial and venous blood gases) with those obtained by summing image-based V/Q measurements. These metrics lack spatial information and are therefore insufficient for RT planning — the same global measurement may be obtained from vastly different functional maps (corresponding to vastly different plans). Validation is even more challenging in 4DCT-based ventilation maps, which are susceptible to several errors and uncertainties, e.g., 4DCT image artifacts, intertechnique variability, and variability between parameters and algorithms used for deformable image registration (DIR).⁵ For example, the best of 23 DIR combinations, evaluated in the highly valuable multi-institutional VAMPIRE challenge, generated functional maps that showed very modest correlation with the ground truth — median (range) $r_s = 0.5$ (0.24–0.73).⁶

Finally, following conventional radiotherapy planning, LFA plans also model the lung simplistically — as a uniform, parallel-functioning organ. While gas exchange itself occurs in parallel-functioning alveoli, the critical steps before and after gas exchange are performed by branching serial structures, i.e., airways and pulmonary vessels, which may appear in V/Q scans as relatively “low-functioning” regions. By focusing primarily on V/Q maps, current LFA strategies run the risk of redirecting dose, thereby causing potentially irreparable damage to the conduits upstream (lobar/peripheral airways) or downstream (pulmonary vessels) from the sites of gas exchange.

Undoubtedly, LFA-based planning has potential. However, before rushing to clinical deployment, much groundwork needs to be done to understand image-based assessment of lung physiology and pathophysiology; develop solid validation techniques, perhaps, using novel “functional” phantoms; and correctly account for the serial as well as the parallel nature of the lung.

AGAINST THE PROPOSITION: Tokihiro Yamamoto, Ph.D.

Opening Statement

Radiotherapy for lung cancer is limited by substantial pulmonary toxicities, including shortness of breath, radiation pneumonitis, pulmonary fibrosis, and lung function loss, which diminish quality of life.⁷ The current paradigm of radiotherapy is largely based on anatomical imaging with the assumption that all lung tissues are equally important. However, there have been many studies suggesting that this assumption is not valid and that dose–response is heterogeneous for the lung. Functional avoidance radiotherapy that preferentially avoids irradiating functional lung regions identified by functional imaging has potential to reduce pulmonary toxicity, which is supported by four key evidences:

- (1) *Dosimetric significance of functional avoidance.* There are a number of studies showing that functional avoidance treatment planning can significantly reduce the functional lung dose with intensity-modulated radiotherapy (IMRT) compared to standard treatment planning. For example, our previous study has shown significant reductions in the mean dose of the functional lung by about 2 Gy without significantly increasing the doses to other critical structures.⁸
- (2) *Reduced pneumonitis risk with functional avoidance.* Faught et al. have recently demonstrated the potential for functional avoidance treatment planning to reduce the risk of grade ≥ 2 pneumonitis by 5%–8% on average for the lung cancer population (up to 52% for individual patients) compared to standard treatment planning through translating the reduction in the functional lung dose to an estimated reduction in the normal tissue complication probability (NTCP).⁹
- (3) *Dose-dependent reductions in regional lung function.* Evidence indicates dose-dependent reductions in regional ventilation¹⁰ and perfusion.¹¹ Zhang et al. have demonstrated significant dose-dependent reductions in perfusion (that progress with time up to 1.5 yr after treatment) at almost all the studied time points (0.1–12 yr after treatment).¹¹
- (4) *Improved toxicity prediction with regional lung function information.* Regional ventilation and perfusion at baseline have the potential to increase the predictive power for pulmonary toxicity.^{12,13} Farr et al. have demonstrated that the dose–function metrics based on perfusion (e.g., functional mean lung dose) are all significantly associated with grade ≥ 2 pneumonitis, whereas most of the standard dose–volume metrics (e.g., mean lung dose) are not significantly associated with pneumonitis.¹³

In summary, functional avoidance radiotherapy is a compelling concept supported by the above evidences showing its potential to reduce pulmonary toxicity. Clinical trials are a

logical next step to provide evidence for the clinical significance of functional avoidance radiotherapy. Several early phase clinical trials are currently underway to investigate the feasibility or efficacy of lung functional avoidance radiotherapy with different imaging methods, including: (a) CT ventilation imaging being investigated at the University of California Davis (NCT02308709), University of Colorado (NCT02528942), and University of Wisconsin (NCT02843568), (b) hyperpolarized ^3He MRI ventilation imaging investigated at the London Health Sciences Center (NCT02002052), and (c) SPECT ventilation-perfusion imaging investigated at the University of Washington (NCT02773238).

Rebuttal: Amit Sawant, Ph.D.

Dr. Yamamoto and I both agree that preserving postradiotherapy lung function is important. Where we disagree is whether our image-based assessment techniques are (a) accurate and (b) sufficient to accomplish this goal. In my opinion, the evidence presented by Dr. Yamamoto falls short of meeting both (4DCT-based studies) or at least the latter (perfusion-based studies) of these criteria.

The cited 4DCT-based ventilation studies, showing increased dose-sparing of functional lung and reduced NTCP,^{8,9} should be interpreted with caution. My main concern is validation. 4DCT-derived maps are usually validated against much lower resolution nuclear imaging ventilation maps. This is much like taking a Rorschach test — one sees what one wants to see. Even setting aside the resolution mismatch, the correlation between 4DCT-derived and SPECT/PET ventilation maps is modest — correlation and Dice coefficients hover around 0.5.^{6,14,15} To me, this is a problem needing urgent solution, not evidence to launch clinical trials.

SPECT perfusion imaging, while accurate, does not by itself provide a complete enough picture to guide LFA planning. For example, the study by Theuvs et al. found >20% difference in the perfusion dose-response in the anterior vs the posterior regions of the lung, attributed to potential gravitational dependence,¹⁰ — typically not accounted for in SPECT-based LFA planning. Furthermore, while the Zhang study found dose-dependent reduction in regional perfusion,¹¹ an earlier investigation from the same institution found that a reduction in regional perfusion does not necessarily associate with reduction in global lung function because (a) postradiation tumor shrinkage may result in functional improvement of other lung regions, and/or (b) perfusion alone, without ventilation, may not represent regional gas exchange.¹⁶

In summary, while LFA planning has potential, it is our responsibility as imaging physicists to address the known technical and fundamental issues before we can safely deploy this strategy to change a patient's radiation treatment.

Rebuttal: Tokihiro Yamamoto, Ph.D.

Dr. Sawant made good points about the limitations to the current strategies of lung functional avoidance radiotherapy.

First, the difference in “ventilation” measurements between imaging methods is often not well acknowledged.¹⁷ Alveolar ventilation, specific ventilation, and gas distribution are related but not identical to each other. Additionally, little is known about the difference between ventilation, perfusion and gas exchange in the radiation oncology context. Second, validation of functional imaging methods is challenging. There have been extensive validation efforts on CT ventilation imaging through cross-modality comparisons, while little effort has been made on other imaging methods. Validation of functional imaging will ultimately require comparisons with ground truth (e.g., histopathology). Third, the exact etiology of functional abnormalities identified by imaging is often not clear, e.g., whether it is attributable to abnormalities in airways, blood vessels and/or parenchyma. Methods for assessing airways and vessels may provide additional benefit. However, it is not clear whether these issues are as critical as discouraging clinical trials.

There is a compelling rationale for early phase clinical trials of functional avoidance radiotherapy. Pulmonary toxicity remains a significant clinical problem. There is supporting data that demonstrate the potential for functional avoidance to reduce toxicity as described in my opening statement. Even though gas exchange is considered most physiologically relevant, evidence exists for both ventilation and perfusion, suggesting that ventilation alone or perfusion alone may provide clinical benefit. Validation of functional imaging methods is important, while it is unclear what level of evidence is required to provide sufficient validation, e.g., how strong should the image correlation be in cross-modality comparisons? Kida et al. have demonstrated only moderate correlations between CT ventilation and SPECT ventilation images (average voxel-based correlation: 0.40), but good agreements between two functional avoidance treatment plans based on those images (average difference: <1%, 95% limit of agreement: <2% for most metrics).¹⁸ In the light of complexity of functional avoidance strategies, I believe early phase clinical trials should rather be encouraged in parallel with further investigations into the issues mentioned earlier.

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CONFLICTS OF INTEREST

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