

POINT/COUNTERPOINT

Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Habib Zaidi, Geneva University Hospital, Geneva, Switzerland: habib.zaidi@hcuge.ch; Jing Cai, The Hong Kong Polytechnic University, Hong Kong: jing.cai@polyu.edu.hk; and/or Gerald White, Colorado Associates in Medical Physics: gerald.white@mindspring.com. 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.

Whole-body parametric PET imaging will replace conventional image-derived PET metrics in clinical oncology

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OVERVIEW

Current clinical whole-body PET imaging protocols reflect the trend followed in conventional nuclear medicine in that they are optimized to produce the best image quality for qualitative visual interpretation instead of quantitative assessment of biological parameters. Multibed acquisitions are commonly performed to produce a static PET image depicting the three-dimensional spatial distribution of the tracer uptake over the acquisition time frame. Conventional semi-quantitative image-derived PET metrics, such as the Standardized Uptake Value (SUV), are then used in the context of clinical oncology. Methodological developments reported in recent literature seem to indicate reasonable evidence that clinically adoptable dynamic whole-body imaging protocols enable quantitative parametric imaging (map representing clinically relevant set of physiological parameters at the voxel level), especially when combined with direct 4D reconstruction to achieve better noise properties. These advances stimulated the integration of these developments in the form of a commercial package (*FlowMotion MultiParametric PET*) supplied to end users by Siemens Healthineers. While some think that parametric whole-body imaging is the future and will be integrated in clinical protocols to support conventional SUV imaging in clinical oncology studies, others keep on watching arguing that the pilot results reported in the literature are still embryonic and that the clinical relevance of the technique still remains to be demonstrated. This is the topic addressed in this month's Point/Counterpoint debate.



Arguing for the proposition is Richard Leahy, Ph.D. Dr. Leahy is Dean's Professor and Chair of the Ming Hsieh Department of Electrical Engineering — Systems at the University of Southern California. He holds joint appointments in Biomedical Engineering and Radiology. His research interests lie in the application of signal and image processing to the formation and analysis of biomedical images, with applications in neuroimaging and molecular imaging using PET, MRI, and EEG/MEG. Dr. Leahy is a Fellow of the IEEE and the recipient of the 2010 Hoffman Medical Imaging Scientist Award from the IEEE Nuclear and Plasma Sciences Society. He was general conference chair for IEEE ISBI 2004 and Fully3D 2013 and has held editorial positions with IEEE Trans Med Imaging, Physics in Medicine & Biology and Neuroimage. He has published more than 200 papers in the field of biomedical signal and image processing.



Arguing against the Proposition is Ronald Boellaard, PhD. Dr. Boellaard is a full professor at the Amsterdam University Medical Centers, VUMC and at the University Medical Centre Groningen. His main research interests focus on quantification of oncological, cardiac, and brain PET/CT and PET/MR studies, including pharmacokinetic analysis and full quantification of new PET radiotracers. Moreover, he is the first author of the European guideline for quantitative multi-center FDG PET/CT imaging (EJNMMI 2010, 2015). He is actively participating as PI for several national and international research projects on the validation of quantitative PET imaging biomarkers. He is the member of the EARL scientific board, chairing the accreditation programs, and former member and chair of the EANM physics committee and currently member of the EANM Neuroimaging committee and involved in the QIBA FDG PET/CT and amyloid imaging profiles committees. He has (co-)authored more than 300 peer-reviewed publications.

FOR THE PROPOSITION: RICHARD LEAHY, PH.D.

Opening statement

The SUV is the most commonly used image-derived metric for semi-quantitative assessment of metabolic function with FDG PET in clinical oncology. SUV has been shown to correlate well with the local metabolic rate of FDG in different tumor types, especially when normalized for plasma glucose levels. However, in addition to mathematical factors (e.g., ROI, volume averaging) that can alter the accuracy of SUV, there are a number of biologic and human factors which can variably and unpredictably impact SUV that have been thoroughly reported by many investigators^{1,2} (e.g., injected dose, alterations in blood pool activity, time of imaging, and the user analyzing the study). Therefore, it is not surprising that the correlation between uptake measurements made in an identical manner at different clinical sites is relatively low ($r^2 = 0.705$) and significantly different than the standard reference measurement ($P < 0.05$).³ Most important, SUV measurements depend heavily on the postinjection scan time.¹ These factors account for documented intersubject as well as intrasubject variability of SUV measurements. Quantitative parametric imaging in clinical whole-body oncology would remove or reduce many of these factors.

Recent developments in both PET hardware and algorithms have made whole-body parametric imaging clinically viable. Sensitivity and time-of-flight improvements in detector technology make it possible to image a subject in a short time so that two (or more) pass whole-body scans are now practical. Scanners with large axial fields of view and continuous bed motion⁴ make the implementation of a whole-body dynamic protocol feasible in clinically acceptable time frames. Further, advancements in PET image reconstruction and analysis enable parametric imaging directly either from list-mode data in a two-pass protocol⁵ or through novel implementations of traditional parametric estimation in a whole-

body setting.⁶ Initial clinical applications of whole-body parametric imaging have demonstrated encouraging results.⁷

With all the above developments, whole-body parametric imaging protocols are far more straightforward than earlier dynamic studies. Arterial blood sampling is not required, and scan times are similar to the standard whole-body protocols of a few years ago. Consequently, they would not add significant burden to the technicians or clinical work-flows, another early hurdle to adopting quantitative imaging in the clinic. A reproducible quantitative imaging method will allow improved standardization and reliability which would benefit all oncological applications using PET. Truly quantitative PET will not only solve the known weakness of static FDG PET in oncology: the inability to accurately differentiate between malignancy and infection/inflammation,⁸ but will also improve staging as well as early treatment response evaluation in clinical oncology.⁹ The absence of a whole-body parametric imaging package from any of the major vendors has limited our ability to perform widespread evaluation. As these become available, given the fact that the protocols are practical and that we know that parametric parameters provide more reliable indicators of malignancy, we believe whole-body parametric PET imaging will eventually replace conventional image-derived PET metrics in clinical oncology.

AGAINST THE PROPOSITION: RONALD BOELLAARD, PH.D.

Opening Statement

Full kinetic analysis of (dynamic) PET studies is considered to be the (gold) standard. Quantitative kinetic analysis allows a more accurate and precise assessment of specific tracer uptake or, in case of, for example, FDG and glucose metabolism. The latter is important when patients show variations in input functions, which is the tracer concentration in plasma available for tissue uptake over time, that is, the bio-availability of the tracer (FDG). Quantification by means of SUV is based on normalizing the PET signal by the net injected activity over patient weight and by definition assumes that (the shape of) input functions are the same between subjects and/or longitudinally. The good correlation seen between SUV and the net influx rate constant, K_i , derived from Patlak analysis suggests that this assumption may be valid under certain circumstances.¹⁰ However, the relationship between SUV and K_i may change under treatment,^{11–14} meaning that a change in SUV may be caused by a change in the input function/bio-availability of the tracer rather than by a change in tumor characteristics alone. Under these circumstances, a more accurate quantitative approach is required.

Recently, whole-body parametric PET imaging has become a reality allowing to generate full quantitative parametric images for the whole body.¹⁵ There is, however, a price to pay. The slow kinetics of FDG requires to follow the tracer uptake for at least 45–60 min, in order to generate these Patlak whole-body parametric PET images.¹⁶ The required long scan duration will seriously reduce patient throughput and

comfort. This is especially frustrating because the improvements in PET technology¹⁷ that enabled whole-body parametric imaging also enabled the acquisition of whole-body static images in less scan time (because of improved sensitivity, time of flight, and improved reconstruction methodologies) and thus higher patient throughput. Likely, whole-body parametric imaging will not replace conventional (static) PET imaging in clinical oncology. However, only when it has been demonstrated if and for which specific questions it would provide clinical benefit over conventional imaging, it may find a (modest, but validated) place in clinical practice. The suggestion made by Prof. Richard Carson during his Henry N. Wagner, Jr., MD Lectureship at the annual SNMMI meeting 2018 to perform a whole-body dynamic scan during the (unused) 60 min uptake phase of the patient firstly scheduled for an FDG PET/CT examination is therefore warmly welcomed. In this way, we may collect evidence if and when we should perform whole-body parametric imaging. However, we likely should accept that there may not be sufficient benefit to justify its use for all patients and that static whole-body imaging may be sufficient for most types of clinical questions. Moreover, static imaging protocols may also be required to assure availability of diagnostic PET imaging based on visual assessment for as many patients as possible. Therefore, I believe that whole-body parametric PET imaging will not fully, but only partially replace conventional image-derived PET metrics in clinical oncology.

Rebuttal: Richard Leahy, Ph.D.

I believe my opponent, and I share the view that there are potential clinical advantages to quantitative whole-body PET. But as he also notes, PET has become a victim of its own success: 30-60 min scan times, which were common in the earlier days of PET, are now viewed as impractical. The question comes down to whether the added clinical impact justifies the additional complexity and scan time. This in turn raises two issues: (a) to what degree can improved quantitative accuracy impact cancer staging and assessment of treatment response and (b) will new developments in modern scanner technology further enable dynamic whole-body scans so that they are viable and cost-effective in a clinical setting? The verdict is still out on the first of these questions. As my opponent notes in supporting Dr. Carson's idea of using dynamic scanning during the uptake phase, more studies are required to determine when dynamic whole-body scans will prove beneficial. Commercial manufacturers are also starting to make multi-pass continuous bed motion acquisition protocols available¹⁸ so that dynamic whole-body PET will be increasingly feasible in the clinic. With this capability available, we can expect to see a rapid increase in the number of whole-body dynamic studies that will provide evidence for the potential impact of whole-body dynamic studies. With respect to the second issue, improved image registration and reconstruction methods coupled with parametric or population-based models for the input function will likely provide practical solutions to problems associated with patient motion, accurate attenuation

correction, and the impracticality of arterial blood sampling. A more fundamental limit is the time constants associated with tracer kinetics. With FDG PET, this requires scanning over a period of 30 minutes or more. If Patlak models are used, data need not be acquired for the full period since as few as two passes are sufficient for parameter estimation, which presents minimal additional stress to the patient. Further, if PET/MRI scanners become widely adopted, then multicontrast MR protocols that complement the PET scan could be interleaved or performed simultaneously with PET data acquisition with total scan times similar to those common in clinical MR scans today. While it may take some time, and may not be appropriate in all cases, dynamic whole-body PET/CT or PET/MRI will surely have an important place in the clinic in the future.

Rebuttal: Ronald Boellaard, Ph.D.

There seems to be consensus among the debaters that the SUV correlate well with metabolic rate of FDG in different tumor types and, yet, that there are a number of biologic and human factors which can result in unpredictable SUVs.^{1,2} The detrimental effects of some of the factors listed by Prof Leahy, such as uncertainty in injected dose, time of imaging, and the user analyzing the study, can be easily mitigated by proper standardization and harmonization of the imaging procedures.¹⁹ Alterations in blood pool activity is indeed one of the main sources of variability for which the application of whole-body dynamic scanning may be required, as also indicated in my earlier statement. Yet, also here more simplified approaches should be considered, such as the recently proposed standardized uptake ratio (SUR) which is the SUV normalized to blood pool activity.²⁰ Use of SUR would, at least, partially compensate for alterations in blood pool activity and seems to outperform SUV for specific studies.²⁰ The main advantage of the use of SUR is that it can be obtained with a (short) static imaging protocol. For some clinical applications SUR could be a good alternative for SUV while for others whole-body parametric Patlak imaging may be required. Likely SUV will suffice for the majority of cases provided it has been obtained in a standardized and harmonized manner.¹⁹ The main goal is to identify which approach best fits the clinical need, while avoiding use of too complicated or too simple approaches. Therefore, we should "simplify as much as possible but not more" (adapted from Albert Einstein).

CONFLICT OF INTERESTS

Dr. Boellaard and Dr. Leahy have no relevant conflict of interests.

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