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, and/or Jing Cai, The Hong Kong Polytechnic University, Hong Kong: jing.cai@polyu.edu.hk. 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.

Current commercial techniques for MRI-guided attenuation correction are insufficient and will limit the wider acceptance of PET/MRI technology in the clinic

Ciprian Catana, MD, Ph.D.
Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA, USA,
(Tel: 617-643-4885; E-mail: ccatana@nmr.mgh.harvard.edu)

Harald H. Quick, Ph.D.
Erwin L. Hahn Institute for Magnetic Resonance Imaging, University of Duisburg-Essen, Essen, Germany
High Field and Hybrid MR Imaging, University of Duisburg-Essen, Essen, Germany,
(Tel: +49-201-183-6071; E-mail: harald.quick@uni-due.de)

Habib Zaidi, Ph.D., Moderator

(Received 16 April 2018; accepted for publication 3 May 2018; published xx xxxx xxxx)

[https://doi.org/10.1002/mp.12963]

OVERVIEW

Whole-body hybrid PET/MR imaging has been used since its introduction in 2010 in clinical and research settings for diagnosis, staging and restaging, assessment of response to treatment, and radiation therapy planning. However, the quantitative potential of PET/MRI is challenged by the lack of reliable and accurate MRI-guided attenuation correction (MRAC) owing to the lack of direct relationship between MRI signal, reflecting proton density and relaxation time properties, and electron density, which is linked to photon attenuation properties of biological tissues. Despite the progress made during the last decade, MRAC is still in its infancy and remains problematic particularly in whole-body imaging. While some think that current techniques implemented on commercial systems for MRAC do not constitute a viable solution and are hampering the wider acceptance of PET/MRI technology in the clinic, others think that, despite their limitations, these techniques provide adequate correction fulfilling the requirements of the different clinical applications of this technology. This is the topic of this month's Point/Counterpoint debate.

Arguing for the Proposition is Ciprian Catana, MD, PhD. Dr. Catana received his MD degree from the University of Medicine and Pharmacy Targu-Mures, Romania in 2001. Subsequently, he conducted his Ph.D. research in Biomedical Engineering at the University of California Davis, where he designed and built an MR-compatible PET insert for a small animal 7-Tesla MRI system. For his postdoctoral training, he moved to the Athinoula A. Martinos Center for Biomedical Imaging, Department of Radiology, Massachusetts General Hospital in 2007 and started to focus on translating integrated

PET/MRI from the preclinical to the clinical arena. Dr. Catana is now the Director of Integrated MR-PET imaging at the Martinos Center and an Associate Professor in Radiology at Harvard Medical School. Over the last decade, he has concentrated on further developing and validating this novel technology, identifying and implementing methods to best exploit the combined data, and developing quantitative PET/MRI for human use. Working closely with dozens of basic science researchers and physician–scientists, Dr. Catana is currently applying these advanced tools to the study of normal brain and neuropsychiatric diseases as well as exploring the clinical potential of this technology for whole-body oncological applications. Dr. Catana has authored more than 75 peer-reviewed manuscripts and book chapters and holds or has filed provisional patent applications for several technological and methodological innovations in the field of PET/MRI.

Arguing against the proposition is Harald H. Quick, PhD. Dr. Quick earned his master in Biomedical Engineering from the University of Applied Sciences Aachen, Germany. He then worked as MRI researcher in the Department of Radiology, University Hospital Zurich, Switzerland, followed by a faculty appointment and research position in the Department for Radiology and Radiological Sciences, Johns Hopkins University, Baltimore, USA. Dr. Quick earned his PhD in MR

Physics and Radiological Sciences at the University of Duisburg-Essen. In 2009, he was appointed full Professor for MR imaging at the Institute of Medical Physics (IMP), the University of Erlangen-Nurnberg where he founded and headed the Section for PET/MR Hybrid Imaging and acted as the Deputy Director of the IMP. In this function, Dr. Quick was responsible PI for the world's first installation of an integrated PET/MR system. In 2014, Dr. Quick was appointed Professor for High-Field and Hybrid MR Imaging at the University Hospital Essen. He is also the Director of the Erwin L. Hahn Institute for MRI, a 7-Tesla high-field MRI facility of the University Duisburg-Essen. Dr. Quick has authored more than 200 scientific publications, including more than 20 book chapters. He holds 15 patents in the fields of PET/MR and MRI. His main research foci are hardware and methods development and clinical application of PET/MR and 7-Tesla MRI.

FOR THE PROPOSITION: Ciprian Catana, MD, Ph.D.

Opening Statement

MRAC has always been very challenging because bone and lung tissue cannot easily be imaged using MRI; motion introduces attenuation–emission data mismatches; truncations are present due to differences between the MRI and PET fields of view; and metallic implants lead to susceptibility artifacts.[1] Even using the latest techniques, significant quantification bias and artifacts can be introduced.[2] Nevertheless, many studies have shown that this bias does not have a substantial impact on the data interpretation in numerous clinical scenarios. Similarly, the clinical impact of artifacts can be minimized by carefully analyzing the nonattenuation-corrected PET images or correlated morphological MR images. However, to increase its clinical acceptance, PET/MRI has to be used for advanced applications for which accurate MRAC is a requirement that still has to be met, such as quantitative longitudinal therapy monitoring studies. For many of these applications, the MRAC-related quantification bias and variability are comparable to or exceed the expected effect sizes.

Head MRAC appears to be the most advanced and therefore closest to routine clinical use. Perhaps, motivated by several early reports that demonstrated spatial biases,[3] improved methods to generate head attenuation maps are now commercially available. However, are these sufficient and widely accepted in the clinic? Scanner qualification for multicenter trials would demonstrate the data obtained are of sufficient quality and comparable to PET/CT devices. Unfortunately, no PET/MRI scanner is used for the Alzheimer's Disease Neuroimaging Initiative (ADNI) or other similar multicenter clinical trials, in spite of the obvious advantages in terms of patient convenience and opportunity to properly address other factors that bias the PET data quantification.[4,5] There are several additional explanations for this situation: PET/MRI control databases are not available and those derived from PET/CT have not been validated for analyzing PET/MRI data; MRAC methods developed for human tissue fail when used to generate attenuation maps for the image quality phantom and dedicated acquisition and processing protocols are needed[6]; widely accepted methods and metrics for assessing the accuracy of different MRAC methods are lacking. Encouragingly, head MRAC methods proposed by several academic groups are very accurate[7] and could potentially be used to address many of these issues but need to be adopted and disseminated by vendors before they can be used in the clinic.

Arguably the bar is set unreasonably high (e.g., using PET/CT-specific criteria for qualifying an integrated PET/MRI scanner) and even CT-based attenuation correction (AC) is only the silver standard approach. However, just like numerous studies (including those aimed specifically at validating CT against transmission-based AC) were needed for optimizing and establishing this approach and educating and convincing the clinicians of its utility,[8] similar efforts are still required in the PET/MRI field. Until this happens, MRAC will considerably slow down the clinical acceptance of this promising technology, especially for whole-body applications.

AGAINST THE PROPOSITION: Harald H. Quick, Ph.D.

Opening Statement

In the year 2010, the first two whole-body PET/MR hybrid systems reached product status and became commercially available. In 2014, a third PET/MR model was introduced to the market. Since then, the number of worldwide installations of integrated PET/MR systems has steadily increased to 145 installations worldwide today (March 2018). While clinical application today is at full swing, on the methodological side, PET/MR demanded for new techniques and innovative solutions.[9] From the beginning, particularly attenuation correction (AC) has been a hot topic of debate and it continues to be.

The initial method for MRAC used fast MR imaging sequences, such as Dixon-VIBE to obtain images of patient tissue distribution and for subsequent tissue class segmentation.[10] This general method of tissue segmentation from MR images today is established in all currently available PET/MR systems.[11] Although MRAC techniques generally provide robust and reproducible results in most clinical applications, initial clinical studies have indicated a small but systematic underestimation of PET quantification in PET/MR studies when compared to PET/CT.[12] These differences mostly can be attributed to three methodological challenges of MRAC.[9,13] First, MRAC lacks information about the attenuating properties of bone. Second, MRAC often shows signal truncations along the patient arms that are then not

considered in MRAC. Third, the use of ancillary hardware components, such as radiofrequency coils in the field of view of the PET detector, causes additional attenuation of photons.

Numerous innovative solutions for attenuation, truncation, and motion correction have been suggested and scientifically evaluated during the past years. Of these, some of the most accurate and practical developments have found their way from research into commercial product applications of all PET/MR systems. Recent studies have demonstrated the technical feasibility, accuracy, and robustness of the following new MRAC features: (a) inclusion of bone by implementation of a bone model[14]; (b) implementation of MR-based truncation correction[15]; (c) improved MRAC featuring higher spatial resolution, a bone model and truncation correction.[16] Not only general improvements but also only relatively minor quantitative effects on PET quantification have been reported in these studies when applying each of these new MRAC strategies.[14,1516] This indicates that the initial MRAC methods using Dixon-VIBE already performed well in a clinical setting and, furthermore, this reflects that the initial limitations of MRAC have now been overcome.

To come back to the opening statement — current commercial available attenuation correction techniques across all PET/MR systems have matured today to provide fast, accurate, and robust PET quantification in PET/MR. Thus, I do not see MRAC or other technical factors as a limiting factor for wider acceptance of PET/MR in the clinic. In my opinion, the wider acceptance of PET/MR is potentially limited by the fact that PET/MR examinations are inherently more complex than PET/CT examinations, which have implications on imaging workflow and long examination times. Furthermore, PET/MR often requires reading by an experienced nuclear medicine and a radiology-trained specialists. Not least, PET/MR systems compared to PET/CT are more expensive — and reimbursement in some countries is still challenging.

Rebuttal: Ciprian Catana, MD, Ph.D.

I agree with Dr. Quick that substantial progress has been made to address many of the initial MRAC methodological challenges. While certainly sufficient for numerous clinical applications, current approaches unfortunately still fail in some scenarios. To give just one example beyond the brain studies already mentioned, let us consider a lung or liver cancer patient who undergoes serial PET/MRI examinations before and after significantly losing weight due to surgery and/or chemoradiotherapy. Can we confidently state truncation artifacts did not bias the initial PET estimates? Or that respiratory motion-induced attenuation–emission mismatches did not introduce artifacts in the follow-up data as the patient lost the ability to perform breathholds? Have signal voids around surgical clips biased the regional estimates? Were the same MR image and bone mask pairs selected from the database at the two visits to eliminate bone misclassification bias when using the model-based method[14]? Without larger studies to thoroughly test these recently proposed approaches we cannot answer in the affirmative, which suggests the current commercial MRAC methods do not yet provide the level of accuracy required for longitudinal whole-body PET studies.

Dr. Quick mentioned several additional factors that could limit the wider acceptance of PET/MR in the clinic. In my opinion, the relative impact of these factors is hard to assess. While PET/MRI are indeed more complex than PET/CT examinations (albeit not more so than two separate PET/CT and MR examinations), they also provide a much richer dataset that could considerably help clinicians and improve patient management.[17] Joint readings are often performed at many institutions even for PET/CT examinations and are required when additional MR examinations are needed. PET/MRI is indeed expensive. However, to justify the higher costs compared to PET/CT and convince the larger community (beyond the early adopters) to embrace this promising technology and fully exploit its unique capabilities (e.g., to obtain in a single imaging session temporally and spatially matched quantitative multiparametric measurements of metabolism, morphology, function, etc.),[18] the data obtained from these devices have to be at least as reliable, which underscores the need to further improve MRAC methods.

Rebuttal: Harald H. Quick, Ph.D.

I agree with Dr. Catana that the bar for MRAC in integrated PET/MR is set unreasonably high, especially when considering that CT-based AC in PET/CT compared to PET transmission scans is only a silver standard. Regarding the ongoing discussions within the PET/MR community, the expectations on the role of MRAC seem to exceed the expectations on CT-based AC in PET/CT. At this point, lets remind us what is really clinically needed; AC shall deliver fast, accurate, robust, and repeatable correction of PET data for a broad range of clinical applications.

Admittedly, the variety of currently available algorithms for MRAC challenges the clinical users. Unlike in PET/CT, where a single, fast "push-button" whole-body CT scan provides all the necessary information required for AC, similar corrections in PET/MR resemble a "LEGO construction kit": multiple "building blocks" are needed to form a whole-body dataset for MRAC in PET/MR. As listed in my opening statement, this includes Dixon and UTE sequences, bone models, MR- and PET-guided truncation correction, and CT-based templates to correct for RF coils and other hardware. This rather complex approach leads to a certain inhomogeneity when using different MRAC methods, as not only one single version of AC exists, as is the case for PET/CT. Thus, at single PET/MR sites, the latest version of current MRAC methods is available, while others use different methods, different vendors, and different AC applications.

Despite the outlined complexity of the topic, I like to conclude with a statement from the 6th Tübingen International Workshop on PET/MR[19]: *"There was general agreement between the participants and many clinical users that MRAC has been solved to the degree required for clinical use based on accepted image metrics."* This statement is supportive of my view: we have the tools and methods for accurate and

robust clinical use of PET/MR already at hand. Given the mentioned broad variety of MRAC methods, there is, however, further need toward quality control and standardization efforts in PET/MR AC.[6] This is an ongoing process also in PET/CT — even 18 yr after its clinical introduction.[20,21]

CONFLICTS OF INTEREST

Dr. Catana and Dr. Quick have no relevant conflicts of interest.

REFERENCES

1. Attenberger U, Catana C, Chandarana H, et al. Whole-body FDG PET-MR oncologic imaging: pitfalls in clinical interpretation related to inaccurate MR-based attenuation correction. *Abdom Imaging*. 2015;40:1374–1386.
2. Izquierdo-Garcia D, Catana C. MR imaging-guided attenuation correction of PET data in PET/MR imaging. *PET Clin*. 2016;11:129–149.
3. Andersen FL, Ladefoged CN, Beyer T, et al. Combined PET/MR imaging in neurology: MR-based attenuation correction implies a strong spatial bias when ignoring bone. *Neuroimage*. 2014;84:206–216.
4. Catana C, Drzezga A, Heiss WD, Rosen BR. PET/MRI for neurologic applications. *J Nucl Med*. 2012;53:1916–1925.
5. Hutchcroft W, Wang G, Chen KT, Catana C, Qi J. Anatomically-aided PET reconstruction using the kernel method. *Phys Med Biol*. 2016;61:6668–6683.
6. Boellaard R, Rausch I, Beyer T, et al. Quality control for quantitative multicenter whole-body PET/MR studies: a NEMA image quality phantom study with three current PET/MR systems. *Med Phys*. 2015;42:5961–5969.
7. Ladefoged CN, Law I, Anazodo U, et al. A multi-centre evaluation of eleven clinically feasible brain PET/MRI attenuation correction techniques using a large cohort of patients. *Neuroimage*. 2016;147:346–359.
8. Kinahan PE, Hasegawa BH, Beyer T. X-ray-based attenuation correction for positron emission tomography/computed tomography scanners. *Semin Nucl Med*. 2003;33:166–179.
9. Quick HH. Integrated PET/MR. *J Magn Res Imaging*. 2014;39:243–258.
10. Martinez-Moller A, Souvatzoglou M, Delso G, et al. Tissue classification as a potential approach for attenuation correction in whole-body PET/MRI: evaluation with PET/CT data. *J Nucl Med*. 2009;50:520–526.
11. Beyer T, Lassen ML, Boellaard R, et al. Investigating the state-of-the-art in whole-body MR-based attenuation correction: an intra-individual, inter-system, inventory study on three clinical PET/MR systems. *MAGMA*. 2016;29:75–87.
12. Drzezga A, Souvatzoglou M, Eiber M, et al. First clinical experience of integrated whole-body MR/PET. Comparison to PET/CT in patients with oncological diagnoses. *J Nucl Med*. 2012;53:845–855.
13. Quick HH. Systems, physics, and instrumentation of PET/MRI for cardiovascular studies. *Curr Cardiovasc Imaging Rep*. 2017;10:17.
14. Paulus DH, Quick HH, Geppert C, et al. Whole-body PET/MR imaging: quantitative evaluation of a novel model-based MR attenuation correction method including bone. *J Nucl Med*. 2015;56:1061–1066.
15. Lindemann ME, Oehmigen M, Blumhagen JO, Gratz M, Quick HH. MR-based truncation and attenuation correction in integrated PET/MR hybrid imaging using HUGE with continuous table motion. *Med Phys*. 2017;44:4559–4572.
16. Oehmigen M, Lindemann ME, Gratz M, et al. Impact of improved attenuation correction featuring a bone atlas and truncation correction on PET quantification in whole-body PET/MR. *Eur J Nucl Med Mol Imaging*. 2018;45:642–653.
17. Miles KA, Voo SA, Groves AM. Additional clinical value for PET/MRI in oncology: moving beyond simple diagnosis. *J Nucl Med*. 2018;. https://doi.org/10.2967/jnumed.117.203612.
18. Catana C, Guimaraes AR, Rosen BR. PET and MR imaging: the odd couple or a match made in heaven? *J Nucl Med*. 2013;54:815–824.
19. Bailey DL, Pichler BJ, Guckel B, et al. Combined PET/MRI: Global warming-summary report of the 6th international workshop on PET/MRI, March 27-29, 2017, Tubingen, Germany. *Mol Imaging Biol*. 2018;20:4–20.
20. Boellaard R. The engagement of FDG PET/CT image quality and harmonized quantification: from competitive to complementary. *Eur J Nucl Med Mol Imaging*. 2016;43:1–4.
21. Hristova I, Boellaard R, Galette P, et al. Guidelines for quality control of PET/CT scans in a multicenter clinical study. *EJNMMI Phys*. 2017;4:23.