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COMMENTARY

PET/MRI—knocking on the doors of the rich and famous.

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ABSTRACT

Since 2010 the portfolio of positron emission tomography (PET)-based imaging has been expanded by industry with the introduction of combined whole-body PET/MRI systems with the intent of merging PET-based molecular imaging with the strengths of MRI. PET/MRI has created a lot of hype in the scientific community but comparatively little traction in the clinic. The first years of whole-body PET/MRI were used to address inherent technical challenges; however, it is now time to make use of the full potential of this integrated imaging modality. This opinion piece highlights the continuing challenges for the clinical adoption of PET/MRI and cautions against putting too much emphasis on comparisons with clinical PET/CT. In order for PET/MRI to enter clinical practice, cross-specialty co-operation must be pursued with rigour and use-case scenarios must be propagated, following long-awaited expansion of reimbursement strategies and protocol standardization.

Innovation is key to healthcare advancement. In recent years, innovations in imaging have led us to diagnose and treat disease earlier, to monitor patients more effectively and, lately, to computer-based systems that are capable of predicting disease progression and probabilities for survival.¹ With current X-ray and CT imaging, morphological and anatomical information can be obtained with high spatial resolution and reasonable tissue contrast in a matter of seconds with fully digital functionality at low ionizing radiation doses. Ultrasound and MRI have bridged the gap between purely anatomical imaging and the assessment of organ function (e.g. blood flow, signaling pathways). Furthermore, molecular imaging with PET and single photon emission computed tomography (SPECT) have enabled the evaluation of functional and molecular pathways involved in disease.

All of the above commercially available imaging techniques have been in clinical use since the 1980s. The introduction of combined PET/CT imaging systems in 2000 heralded a new era. Dual-modality PET/CT was conceived to address the need to imprint anatomical information on highly sensitive but lower spatial resolution PET images, and, as a secondary benefit, brought along CT-based attenuation correction. PET/CT was a “technical evolution” that led to a “medical revolution” [Johannes Czernin, Los Angeles,

personal communication]. When PET/CT was first introduced, some critics argued that the same benefits, intrinsic co-registration of function and anatomy, could be achieved with software fusion; however, this was simply not true for the applications outside the brain.² Following its introduction, the market for PET/CT grew exponentially. During the first 3 years of its market entry, more than 500 systems were sold worldwide. Within 7 years, all PET systems were only being offered in combination with CT. Today, there are over 5000 PET/CT systems operational worldwide and new PET/CT sales account for about 10% of the sales of CT-only systems. There is countless evidence of the clinical value of PET/CT,³ and in a way its introduction can be regarded as a “market pull”, meaning there was a clear clinical need from the market for this type of imaging modality as attested by its growth. But, has this been the case also for PET/MRI?

A combination of PET and MRI was first suggested by Bruce Hammer who holds the original patent to this combination (US patent US 4939464 A). He was followed by a few imaging pioneers who engaged in a combination of PET and MRI for use in mice.⁴ Their efforts were driven by the higher soft tissue contrast of MRI compared with CT and by the benefits of using MRI for longitudinal imaging of small animals. The first PET/MRI prototype for applications in humans was proposed by Siemens Healthcare in

2006. Because PET and MRI cannot be easily combined physically, or even be integrated without major alterations of the system design, developing a fully integrated PET/MRI concept was a costly endeavour. By 2008, only six prototype systems had become available to lead users, and much work had to be done to solve major methodological challenges, such as stable system functionality and MR-based attenuation correction.

Despite the lack of a true market pull, industry has continued with PET/MRI development, their support having exceeded that previously for PET/CT, both in terms of manpower and financing thus far. Since 2010–12 three major vendors have engaged in PET/MRI system design for applications in humans. Systems available today are based on an MR-compatible PET detector ring that is immersed into a 3 T MRI system, thus, representing a fully integrated system design compared with the co-planar design of a PET/CT system where the PET and CT components are mounted with an axial offset.⁵ These fully integrated PET/MR systems are frequently referred to as “simultaneous PET/MR systems”, which is, however, incorrect, since they allow for the acquisition of only a given MR sequence together with a temporally limited corresponding emission scan of the PET at the time.

It is interesting to look at the early adopters of PET/CT and PET/MRI. In both cases they were not short of funding. Early installations of PET/CT and PET/MRI were mainly in nuclear medicine departments with variable support from radiologists. Here, it was not so much a question of radiologists having no interest, but an issue of permitting them to get involved. When PET/CT started, the first publications were on the use of low-dose CT, also for the purpose of attenuation correction,⁶ an admittedly interesting subject from a physicist's perspective but of only fair clinical importance when considering the entire workflow and the accuracy of the imaging technique. This was followed by publications comparing PET and low-dose CT without contrast agents to stand-alone PET and/or fully fledged CT. Both strategies reflected the initial focus on PET/CT as a nuclear medicine rather than a truly integrative device. Nevertheless, PET/CT has led to grounds for a common communication between the specialties. Some PET/CT adopters have excelled in the clinical adoption of combined PET/CT imaging as a consequence.⁷ Complementary expertise was channelled into protocol design and employed for integrated reading.⁸ Frequently, at least on a local level, PET/CT replaced dedicated CT imaging when clinically indicated.

Sir George Bernard Shaw once said “If history repeats itself, and the unexpected always happens, how incapable must Man be of learning from experience”. How true for PET/MRI. When it first came to the market, with a price tag about twice that of early PET/CT systems, it was adopted by leading nuclear medicine departments—again. As before, the first publications that came out were on attenuation correction, albeit MRI based, and how one could localize PET findings much better on Dixon-type MR images, an equivalent to a low-dose CT.⁹

To date most PET/MRI studies have been in comparison to PET/CT with a single-injection, dual-imaging time point protocol;

as a consequence, results have been unconvincing in the sense that the clinical effect of PET/MRI was not superior to that achieved with PET/CT.¹⁰ This is to be expected for two reasons. First, in most cases it was the PET result that rendered the final diagnosis, and, second, the MR components in the PET/MRI were not utilized to their full diagnostic potential. The primary strength of PET/CT is its fast whole-body screening capability. This is not the strength of PET/MRI. Hicks and Lau pointed this out long before whole-body PET/MRI came to the market: “A PET/MRI design that is focused on providing multi-parametric sampling of individual lesions identified on PET/CT will provide a practical and cost-effective solution.”¹¹ This reflection was resonated at the 6th Tübingen PET/MR Workshop (<http://www.pet-mr-tuebingen.de>) when the majority of the attendees came to conclude that perhaps the unique selling point of integrated PET/MRI is the ability to “zoom into the tumour phenotype” for a lesion previously spotted on PET/CT.

PET/MRI has had a rough start and to succeed it needs to step away from PET/CT as a sparring partner. The ever-emerging argument of PET/MRI mimicking the capabilities of PET/CT (and many more) at a much reduced ionizing radiation exposure is weak in the light of recent advances in CT dose reduction techniques and reconstruction of CT and PET images with much reduced count statistics while maintaining prior noise levels¹² and the diversely considered risk of ionizing radiation exposure.^{13,14}

PET/MRI has arrived at the threshold of the clinics of the rich and famous. However, to move beyond this, PET/MRI must change its focus and the imaging community must address a number of challenges. First, it has to become cheaper. Operational costs in the USA are of the order of US\$10,000 per square meter of hospital space. Thus, a PET/MRI operation raises running costs of US\$300,000 a year, in addition to its steep price tag and any additional restructuring prior to installation. Second, it needs to be reimbursed appropriately. In Europe, PET is not reimbursed at large and neither is an intrinsic combination of PET and MRI. Reimbursement, however, comes—in theory—with clinical proof points. Therefore, to counter this, PET/MRI users must work together to pool their data and generate good quality clinical data both retrospectively and prospectively to keep pressuring healthcare authorities. Third, PET/MRI, and PET/CT alike, call for integrated reading. This may be established through new educational plans or training schemes that eventually lead to some kind of “hybrid imaging expert”. Early efforts in training recommendations (*e.g.* within the USA) for PET/MRI of the brain¹⁵ and body¹⁶ are encouraging in this direction. Fourth, PET/MRI acquisition needs to be guided by consensus recommendations similar to that for [¹⁸F]-fludeoxyglucose-PET/CT.¹⁷ Thus far, the main scientific associations have failed to produce such recommendations on an international scale, which presents another obstacle to a fast clinical adoption of PET/MRI.

Two further issues must be considered. Drivers for PET/MRI do not just come from the imaging community. Thus, the imaging community has to work collaboratively with referring specialists outside of the imaging community to better understand

their clinical requirements and how PET/MRI can meet these. To some extent, the continuous drive towards making PET/MRI work in a whole-body context may not have been worth the effort because it made a user mimic PET/CT pathways to date. Instead, and this is the final requirement, PET/MRI must be explored for its intrinsic capabilities of a multi-parametric assessment of disease. Not only does PET/MRI offer intrinsic motion compensation of the emission data and even an image-derived input function as a part of parametric PET imaging, but it also serves

a multitude of functional, anatomical and even molecular information through MR-based time-of-flight, contrast-weighted imaging and spectroscopy. All this unique information should be gathered following a conscious protocol planning procedure in a collaborative environment. Looking at the current societal landscape of the medical specialties and at the departmental structures in most hospitals, we are nowhere near to an efficient and fulfilling use of this new imaging modality that has so much to offer for the benefit of our patients.

REFERENCES

- James ML, Gambhir SS. A molecular imaging primer: modalities, imaging agents, and applications. *Physiol Rev* 2012; **92**: 897–965. doi: <https://doi.org/10.1152/physrev.00049.2010>
- Townsend DW. Multimodality imaging of structure and function. *Phys Med Biol* 2008; **53**: R1–39. doi: <https://doi.org/10.1088/0031-9155/53/4/R01>
- Petersen H, Holdgaard PC, Madsen PH, Knudsen LM, Gad D, Gravergaard AE, et al. FDG PET/CT in cancer: comparison of actual use with literature-based recommendations. *Eur J Nucl Med Mol Imaging* 2016; **4**: 695–706. doi: <https://doi.org/10.1007/s00259-015-3217-0>
- Wehrl HF, Judenhofer MS, Wiehr S, Pichler BJ. Pre-clinical PET/MR: technological advances and new perspectives in biomedical research. *Eur J Nucl Med Mol Imaging* 2009; **36**(Suppl. 1): S56–68. doi: <https://doi.org/10.1007/s00259-009-1078-0>
- Rausch I, Quick HH, Cal-Gonzalez J, Sattler B, Boellaard R, Beyer T. Technical and instrumental foundations of PET/MRI. *Eur J Radiol* 2017; Epub ahead of print. doi: <https://doi.org/10.1016/j.ejrad.2017.04.004>
- Hany TF, Steinert HC, Goerres GW, Buck A, von Schulthess GK. PET diagnostic accuracy: improvement with in-line PET-CT system: initial results. *Radiology* 2002; **225**: 575–81. doi: <https://doi.org/10.1148/radiol.2252011568>
- Antoch G, Vogt FM, Freudenberg LS, Nazaradeh F, Goehde SC, Barkhausen J, et al. Whole-body dual-modality PET/CT and whole-body MRI for tumor staging in oncology. *JAMA* 2003; **290**: 3199–206. doi: <https://doi.org/10.1001/jama.290.24.3199>
- Beyer T, Antoch G, Müller S, Egelhof T, Freudenberg LS, Debatin J, et al. Acquisition protocol considerations for combined PET/CT imaging. *J Nucl Med* 2004; **45**: (Suppl. 1): 25S–35.
- Eiber M, Martinez-Möller A, Souvatzoglou M, Holzapfel K, Pickhard A, Löffelbein D, et al. Value of a Dixon-based MR/PET attenuation correction sequence for the localization and evaluation of PET-positive lesions. *Eur J Nucl Med Mol Imaging* 2011; **38**: 1691–701. doi: <https://doi.org/10.1007/s00259-011-1842-9>
- Spick C, Herrmann K, Czernin J. 18F-FDG PET/CT and PET/MRI perform equally well in cancer: evidence from studies on more than 2,300 patients. *J Nucl Med* 2016; **57**: 420–30. doi: <https://doi.org/10.2967/jnumed.115.158808>
- Hicks RJ, Lau EW. PET/MRI: a different spin from under the rim. *Eur J Nucl Med Mol Imaging* 2009; **36**: (Suppl. 1): S10–14. doi: <https://doi.org/10.1007/s00259-008-0966-z>
- Lell MM, Wildberger JE, Alkadhi H, Damilakis J, Kachelriess M. Evolution in computed tomography: the battle for speed and dose. *Invest Radiol* 2015; **50**: 629–44. doi: <https://doi.org/10.1097/RLL.0000000000000172>
- Brenner DJ, Hall EJ. Cancer risks from CT scans: now we have data, what next? *Radiology* 2012; **265**: 330–1. doi: <https://doi.org/10.1148/radiol.12121248>
- Weber W, Zanzonico P. The controversial linear no-threshold model. *J Nucl Med* 2017; **58**: 7–8. doi: <https://doi.org/10.2967/jnumed.116.182667>
- Jadvar H, Subramaniam RM, Berman CG, Boada F, Colletti PM, Guimaraes AR, et al. American College of Radiology and Society of Nuclear Medicine and Molecular Imaging joint credentialing statement for PET/MR imaging: brain. *J Nucl Med* 2015; **56**: 642–5. doi: <https://doi.org/10.2967/jnumed.115.155218>
- Subramaniam RM, Jadvar H, Colletti PM, Guimaraes A, Gullapali R, Iagaru AH. American College of Radiology and Society of Nuclear medicine and Molecular imaging joint credentialing statement for PET/MR imaging: body. *J Nucl Med* 2017; Epub ahead of print.
- Boellaard R, Delgado-Bolton R, Oyen WJ, Giammarile F, Tatsch K, Eschner W, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. *Eur J Nucl Med Mol Imaging* 2015; **42**: 328–54. doi: <https://doi.org/10.1007/s00259-014-2961-x>