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REVIEW ARTICLE

Combined PET/MRI: Multi-modality Multi-parametric Imaging Is Here

Summary Report of the 4th International Workshop on PET/MR Imaging; February 23–27, 2015, Tübingen, Germany

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Abstract

This paper summarises key themes and discussions from the 4th international workshop dedicated to the advancement of the technical, scientific and clinical applications of combined positron emission tomography (PET)/magnetic resonance imaging (MRI) systems that was held in Tübingen, Germany, from February 23 to 27, 2015. Specifically, we summarise the three days of invited presentations from active researchers in this and associated fields augmented by round table discussions and dialogue boards with specific topics. These include the use of PET/MRI in cardiovascular disease, paediatrics, oncology,

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neurology and multi-parametric imaging, the latter of which was suggested as a key promoting factor for the wider adoption of integrated PET/MRI. Discussions throughout the workshop and a poll taken on the final day demonstrated that attendees felt more strongly that PET/MRI has further advanced in both technical versatility and acceptance by clinical and research-driven users from the *status quo* of last year. Still, with only minimal evidence of progress made in exploiting the true complementary nature of the PET and MRI-based information, PET/MRI is still yet to achieve its potential. In that regard, the conclusion of last year's meeting "the real work has just started" still holds true.

Key words: PET/MRI, Hybrid imaging, Molecular imaging, PET/CT, PET, MRI, Quantification, Attenuation correction, Oncology, Neurology, Cardiology, Multi-parametric imaging

Introduction

Clinicians, basic scientists, researchers, representatives of industry, potential future buyers and generally interested onlookers assembled again in the university town of Tübingen, Germany, in February 2015 to discuss recent developments and explore possible future directions for hybrid imaging with combined positron emission tomography (PET)/magnetic resonance imaging (MRI). The number of attendees was 180, up 10 % from 2014 with most attendees coming from Europe (65 %), the USA (12 %) and Asia (9 %). Registrations for the workshop were again fully booked out in advance, attesting to the great interest in the potential of PET/MRI technology. Ever receptive to the dynamics of such a rapidly changing field, the organisers made changes to the programme of previous years to allow for more discussion on specific, emerging topics. Preceding the three days of the workshop, there were two days dedicated to tutorials and "hands-on" practical sessions specifically aimed at new users.

While previous workshops have grappled with many of the technical issues associated with a novel technology [1–3], this workshop produced evidence of a maturing body of methodologies using PET/MRI. Reflecting an increasing number of installations in clinical facilities, there were more presentations detailing the use of PET/MRI in clinical practice. Thus, the meeting heard presentations not just from basic scientists and researchers in nuclear medicine, who have been key in developing the technology, but also from pharmacologists, radiologists and radiation oncologists who have started to use the combined PET/MRI systems to probe a deeper understanding of pathophysiology and pharmacokinetics at the tissue level.

The main themes that emerged from this workshop were of an increasing emphasis on quantitative imaging with both PET and MRI and a clearer need to define the signals of greatest interest in understanding the tissue micro-environment with multi-parametric imaging techniques. The point was made that MRI had been multi-parametric from its inception. However, combined with PET, a major challenge is to select the most appropriate MR sequences and radiopharmaceutical targets to produce maximal complementary information (*e.g.* images, parametric maps and quantitative values) for specific organs, tissues or the whole body. The choice of appropriate MR sequences was discussed also in past PET/MRI workshops with little general agreement, thus, supporting the general view that to date insufficient evidence is available on optimum task-specific imaging protocols and little advancement has been made on standardised imaging protocols.

Another common view that emerged from the discussions was that PET/MRI should not try to compete with 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG)-PET and PET/X-ray computed tomography (CT) in clinical practice for the majority of existing applications as such comparisons were thought to be futile, given the extremely high sensitivity and specificity of FDG-PET/CT in many oncology applications [4]. PET/CT performs exquisite morphological and molecular imaging examinations, but has restrictions compared to MRI due to the limited tissue contrast of CT imaging in many situations. It was postulated during discussions that PET/MRI will potentially go further than PET/CT in that, in addition to producing morphology and molecular imaging signals, it may also provide images and multi-parametric maps reflecting the tissue micro-environment, thus, potentially identifying heterogeneity and evolving phenotypes in disease progression; that is, PET/MRI is capable of producing three types of data: morphological, functional and molecular. This was considered a potential "paradigm shift".

As in previous summary reports, we will attempt to provide succinct individual topic summaries and indicate major outcomes of the discussions. Likewise, we highlight the progress achieved and comment on areas with only limited advances. And finally, we will adhere again to the general conventions of previous reports to indicate progress (↑), steady state (↔) and regression (↓) in key aspects of PET/MRI. The key to the summary tables of changes in PET/MRI with respect to the status of the previous year is shown below.

Dialogue Board 1: PET/MRI in Cardiovascular Diseases

The Issues

Non-invasive imaging of cardiovascular disease (CVD) encompasses two distinct organ systems (heart and arterial vessels) both of which pose different challenges for clinical imaging and PET/MRI in particular. Several imaging technologies allow for assessing the morphology and function of the heart. While echocardiography is most widely used clinically for the assessment of the heart geometry, valve function and myocardial contractility, MRI is now increasingly recognised as the non-invasive standard for a number of cardiac investigations and measurements such as cardiac mass, volume and ejection fraction. MR-based perfusion measurements and tissue characterisation (*e.g.* through late gadolinium enhancement and other MR techniques) are entering clinical routine. However, similar and complementary parameters can be derived from PET and single photon emission tomography (SPECT) measurements with the advantage of a wider range of specific radiopharmaceuticals that can be used to probe various aspects of cardiac pathology such as post-ischemic inflammation and nerve function. While new concepts for molecular imaging are currently being pursued with MRI, clinical translation of these methods is, however, often lacking [5, 6].

PET and MRI provide many similar measurements in cardiac imaging, *e.g.* imaging of myocardial perfusion or viability. However, the biological interpretation may be different for each modality, as PET imaging is based on molecular and metabolic processes (*e.g.* FDG-PET for imaging myocyte viability after myocardial infarction), while MRI provides surrogate imaging biomarkers for various underlying pathologies (*e.g.* late gadolinium enhancement for scar assessment). Given this, it will be important to define which measurements are best performed with PET and which with MRI to provide complementary measurements, to maximise the potential information that can be provided in a single examination.

In addition to studying various pathologies of the heart such as myocardial infarction and non-ischemic cardiomyopathies, imaging of atherosclerosis remains a significant challenge for any new imaging technology. MRI is currently assumed to be the gold standard for whole-body characterisation of the arterial vessel wall with respect to the presence, size and characterisation of atherosclerotic plaques. Molecular imaging approaches with PET and MRI targeting inflammation as the key parameter for plaque vulnerability are becoming increasingly available both in pre-clinical and clinical imaging [7, 8]. A synergistic combination of PET and MRI could allow for a comprehensive, multi-parametric characterisation of individual plaques in man—most likely promoting a personalised assessment of individual risk, treatment option and efficacy.

Recent Advances or Achievements

Most of the evidence that was presented at the workshop was from pilot studies in post-ischemic myocardium and cardiomyopathies. Nensa *et al*. demonstrated the general feasibility of cardiac PET and MRI for a variety of cardiac pathologies, including myocardial ischemia, infarction and inflammation [9–11]. Aside from the general feasibility of being able to perform synchronous cardiac PET/MRI examinations, technical issues such as producing an accurate attenuation correction dataset—even in the presence of cardiac motion—have dominated developments to date.

New Evidence That Has Been Reported

Little has been reported to date for PET/MRI of vascular inflammation in man. Kjaer and colleagues reported on the usefulness of MR-based anatomical delineation of artery vessel walls in pilot PET/MRI studies of inflammation in vulnerable plaques [12–14]. The use of FDG and other PET tracers for the evaluation of inflammation and other features of the vulnerable plaque (*e.g.* activated macrophages) is increasingly being accepted [15]. For MR-only imaging, T1 mapping has been suggested as a potential surrogate marker of therapeutic response and outcome in diffuse myocardial processes, such as fibrosis or storage diseases [16]. This adds a new dimension to the assessment of myocardial diseases, and transfer of T1 mapping to combined PET/MRI studies appears straightforward (Table 1).

Future Challenges

The vision for the future of PET/MRI in cardiology is immense; put simply, the discussants felt that PET/MRI will replace PET/CT in the investigation of many cardiovascular diseases. One panelist even suggested that cardiovascular disease could emerge as *the* primary key application for PET/MRI; however, currently, only a few centres seem to focus on this area. In ischemic heart disease, PET/MRI is a powerful tool since it combines the gold standard for perfusion (PET) with the gold standard for function (gated cine MRI), enables the detection of chronic subclinical infarction (late enhancement on MRI) and adds additional molecular information such as post-ischemic inflammation from either PET or MRI. While late-enhancement MRI is considered an important step towards tissue characterisation, more specific techniques, such as longitudinal relaxation time (T1) of the myocardium as well as extracellular volume (ECV), are currently being investigated for their use as potential new imaging biomarkers [17, 18] for mapping. Possible applications of these MR-based biomarkers include the very early detection of cardiomyopathies (such as Fabry disease), myocarditis in patients receiving chemotherapy with cardiotoxic agents (*e.g.* Herceptin) or cardiac

Table 1. Progress indicators for PET/MRI in cardiovascular diseases (CVD)

	2012	2013	2014	2015
Resolution of methodological issues for CVD imaging (MR-AC, motion correction)	NA	↗	↗	↔
Develop analysis tools for standard CVD applications	NA	↔	↔	↔
Identification of key parameters/biomarkers from PET and MR to avoid redundancy in PET/MRI data	NA	↔	↗	↗
Standardised imaging protocols	NA	↔	↔	↔

NA not applicable

involvement in systemic diseases (*e.g.* systemic sclerosis) before functional abnormalities or clinical symptoms become apparent. However, the role of T1 mapping and ECV fraction mapping for the clinical management of patients remains to be defined.

One acute challenge for cardiac investigations is to determine which studies are best measured using the PET modality and which should use MRI—the measurement of myocardial perfusion being an example of a measurement that can be performed by both modalities with comparable diagnostic accuracy [19, 20]. Alternately, these combined measurements could be used for cross-validation and calibration of each imaging methodology.

In addition to the previously mentioned applications, PET/MRI using FDG as the radiotracer was perceived as mainly having a potential role in cardiovascular imaging of myocarditis, vasculitis and myocardial sarcoidosis but also with the potential use of new emerging PET radiotracers of inflammation [21]. Further, MR-based perfusion imaging in the context of combined PET/MRI was considered a promising diagnostic adjunct when assessing multi-vessel disease where a quantitative regional assessment of myocardial perfusion is warranted.

Two major hurdles remain for cardiovascular PET/MRI. Firstly, while cardiac PET and MRI as well as simultaneous PET/MRI are gathering momentum, the translation of preclinical insight into clinical practice is hindered by the lack of adequate mouse models, *e.g.* for vulnerable plaques. Secondly, quantitative cardiovascular PET/MRI requires reliable correction for motion and partial volume effects. Of note, algorithms for MRI-based motion compensation and resolution modelling have been suggested [22, 23] but have not translated into broader clinical adoption and validation.

Dialogue Board 2: PET/MRI in Paediatrics

The Issues

In paediatrics, FDG-PET (and PET/CT) imaging is an integral part of patient management for Hodgkin's lymphoma. PET imaging also has a role in staging and therapy control of patients with non-Hodgkin's lymphoma and solid tumours, including sarcoma, neuroblastoma and CNS tumours [24]. The use of PET is supported by guidelines regarding clinical aspects [25] and commonly accepted dose reference levels of injected radioactivity [26–28].

The use of PET/MRI in paediatric oncology imaging as a means for mitigating the radiation dose from the CT component of PET/CT examinations has been well recognised previously [29, 30]. Further dose reduction, if desired, could be achieved by trading off lower injected radiotracer activities at the expense of extended emission scan times, assuming constant image quality and no further advances in performance of the PET system in use [31]. Extended imaging times in these patients may require longer anaesthesia times that, in turn, may pose a higher risk than the perceived risk from exposure to ionising radiation.

Recent Advances or Achievements

Radiation dose reduction techniques in CT continue to be developed [32] and, thus, represent a potential challenge to one of the main arguments in favour of the use of PET/MRI in paediatrics, namely the minimisation of radiation dose.

New Evidence That Has Been Reported

The panelists agreed that clinical evidence for moving paediatric patients with sarcoma and CNS diseases from PET/CT to PET/MRI was growing. In these patients, both PET and MR imaging are currently performed and could be replaced by a dual-modality PET/MRI examination, with a separate CT of the lungs being performed upon clinical need. In PET/MRI, the available MR image information was shown to add to the information from the PET or PET/CT, particularly for the characterisation of FDG-negative soft tissue lesions [30]. Further, the panelists demonstrated that effective patient exposure as low as 2.5 mSv can be achieved in routine paediatric whole-body FDG-PET/MRI examinations with high image quality. Schäfer and colleagues from Tübingen promoted the idea to further reduce dose to 1 mSv through additional optimisation of the acquisition protocol. Active PET/MRI users discussed the optimum amount of radiotracer injected and consequences for imaging protocols. The administered radioactivity levels recommended by the European Association of Nuclear Medicine (EANM) [28] are considered to be the upper limit in paediatric imaging. It was suggested in the discussions that total radioactivity levels could be reduced further by 33 % without degrading image quality. Some users envisage using even lower

Table 2. Progress indicators for PET/MRI in paediatric oncology

	2012	2013	2014	2015
Clinical evidence on the usefulness of PET/MRI in paediatric oncology	↔	↗	↗	↗
Reduced radiation exposure as a key driver for PET/MRI of children	↗	↑	↑	↔
Initial results of a complementary role of advanced MR techniques for restaging of lymphoma patients	↔	↔	↗	↔

amounts of radioactivity without compromising image quality and recommend a reduction of these values for PET/MRI by lengthening PET acquisition times to match that of the MRI examination, with a corresponding decrease in the amount of radiotracer administered (Table 2).

Future Challenges

Standard MRI-derived attenuation correction algorithms for PET (MR-AC) may remain a critical challenge in paediatric PET/MRI given the relatively higher fraction of bone to soft tissue in children compared to adults. Unless significant improvements in MR-AC become available, a separate low-dose CT may need to be acquired to estimate accurate attenuation coefficients in these patients. That issue notwithstanding, paediatric imaging of positron emitting radiopharmaceuticals appears to be one of the current key applications for PET/MRI.

Finally, all discussants agreed that they would gladly shift all of their paediatric PET/CT studies to PET/MRI if they were able to.

Dialogue Board 3: PET/MRI in Oncology

The Issues

To date, the majority of PET examinations performed worldwide have been in the clinical setting of whole-body cancer imaging, exploiting the ability to screen the entire body for functional or metabolic anomalies with a single radiotracer injection. It is recognised that multi-slice CT is a robust and fast imaging method for anatomical-morphological imaging [32]. Thus, it now seems obvious in retrospect that the combination of PET and CT would be an ideal approach to target clinical indications for whole-body oncology imaging, and it has done so very successfully. Likewise, it was also perhaps inevitable that the first clinical applications using PET/MRI would be a comparison with conventional PET/CT investigation for cancer. However, it is now acknowledged that this straightforward start-up for PET/MRI may have hindered the development of new and unique applications for this new form of hybrid imaging (see, *e.g.* Fig. 1). MRI, for example, is a tool often employed to resolve selected diagnostic challenges, mainly in a loco-regional context. The added specificity of PET should improve the sensitivity of MRI in the context of combined PET/MR imaging.

Quantitative comparisons between PET/CT and PET/MRI based on, for example, standardised uptake value (SUV) have rarely demonstrated acceptable levels of agreement [33–35]. In single-injection, PET/CT–PET/MRI studies, this lack of agreement can partly be attributed to the known temporal changes in SUV values in solid tumours imaged at different times after injection.

Recent Advances or Achievements

In the discussions of this dialogue board, the emerging value of PET/MRI in oncology was felt to be in its ability to provide a comprehensive metabolic/molecular phenotype of the individual, allowing the clinician to perform tumour differentiation at different sites in the body and to assess the heterogeneity of individual lesions. Decisions such as, for example, where to biopsy or which part of a heterogeneous tumour to biopsy, would be ideally guided by such a whole-body parametric [*e.g.* FDG, diffusion-weighted imaging (DWI), T1] mapping approach (Fig. 2). One suggestion in this context was that, for whole-body imaging of FDG-avid tumours, adding DWI-MRI was generally of little additional value while increasing the total examination time substantially. However, whole-body DWI could be of value in combination with more specific tracers, such as [^{18}F]fluorothymidine (FLT), [^{18}F]fluoroethyltyrosine (FET), [^{18}F]dihydroxyphenylalanine (F-DOPA) or [^{68}Ga]HBED-CC (referred to as "[^{68}Ga]PSMA" (prostate-specific membrane antigen) which it targets).

For routine clinical questions, the scenario of "CT-guided PET/MRI" might be increasingly relevant in the future. Many patients in centres that have access to a PET/MRI system will have a staging CT prior to being discussed in, for example, a multi-disciplinary team meeting or tumour board (*e.g.* lung cancer). This could be followed by a PET/MRI study to focus on the specific region where diagnostic questions remain (*e.g.* CNS, adrenal glands, *etc.*). As part of the combined PET/MRI study, a whole-body PET scan can be performed for screening without elaborate MR sequences. In addition, patients with a primary indication for an MRI examination should be considered ideal candidates for a combined PET/MRI examination from now on at sites where a PET/MR system is available. Examples of this include cancer involving brain, breast, prostate, liver, pancreas and head/neck.

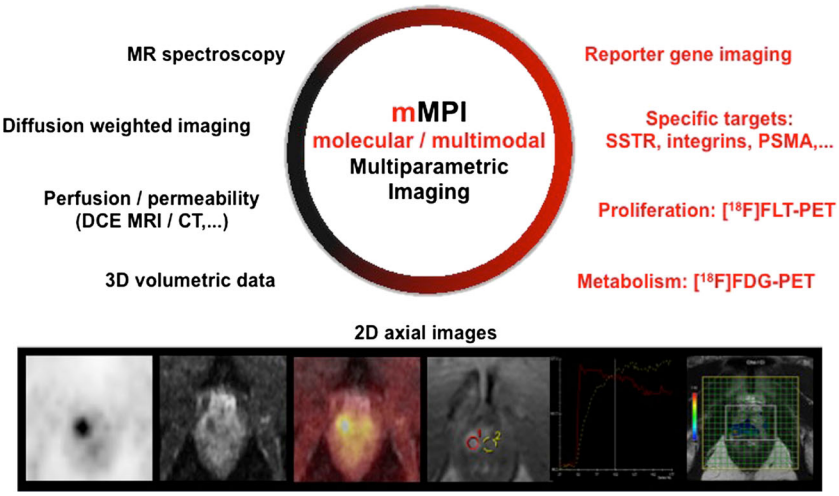

Fig. 1 Combined PET/MRI as a multi-modality multi-parametric imaging tool, which combines the multi-parametric imaging features of MRI and the molecular information from PET tracers in PET/MRI. The *lower panel* shows an example of this approach in a patient with primary prostate cancer on the right side (from *left* to *right*): the tumour shows intense ^{11}C-choline uptake, low ADC values in DWI, early intense contrast enhancement in DCE-MRI and elevated choline-to-citrate ratios in MR spectroscopy (materials courtesy of A.J. Beer and M. Eiber).

Finally, one suggestion during the discussions was that PET/MRI might be better applied to regional imaging after whole-body PET/CT staging has been performed, which is in line with a perspective voiced by Hicks and Lau early in the development of PET/MR imaging [36]. This will allow more time to be spent on imaging specific regions to better understand the tissue micro-environment as well as the metabolic status of the cancer, which may, however, be a time-consuming process that requires two PET scans, a scenario that is primarily limited to research-driven questions. Still, this would represent a fundamental shift in thinking away from whole-body PET/MRI examinations to limited, regional ones.

Irrespective of the imaging sequence, full integration of all of the acquired data will be crucial in these emergent applications, so that the PET and MRI studies are not considered/reported in

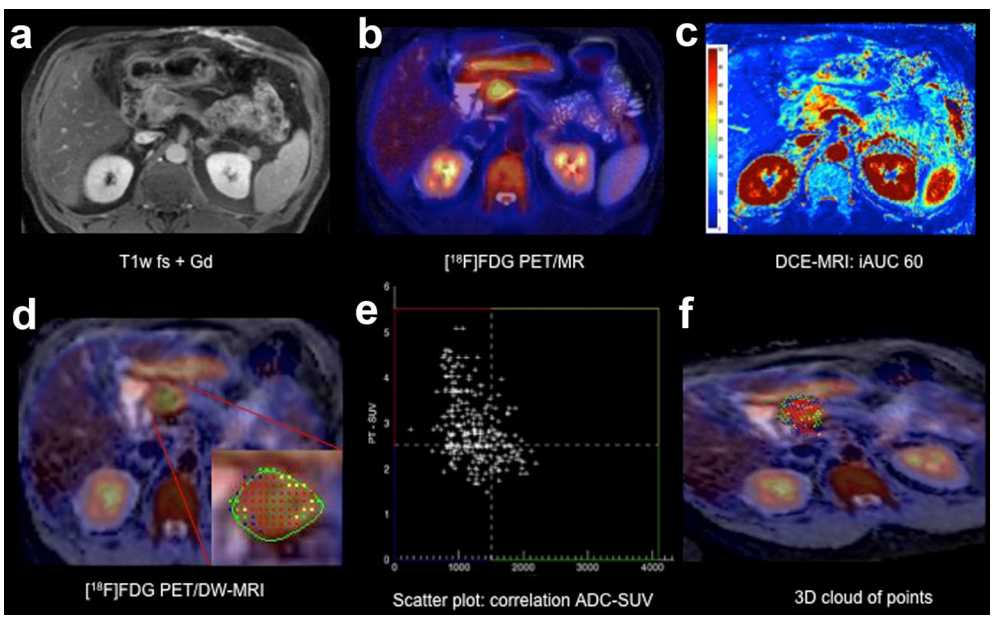

Fig. 2 Voxel-by-voxel analysis of different parametric images in FDG-PET/MRI in a patient with primary pancreatic adenocarcinoma (**a**–**c**), using the software Anima M^{3}P (MunichHeart Software, Nekolla and van Marwick, 2013). The combined analysis of the ADC map fused with PET (**d**) results in a scatter plot of the tumour showing the correlation of ADC values and FDG uptake on a voxel-by-voxel basis (**e**), which can then be superimposed on the anatomical images in 2D (**d**, *right lower corner*) and also in 3D (**f**). Coded in *red* are the tumour areas with highest metabolic activity and most restricted water movement, suggesting areas with the highest tumour cell density and activity, which could, *e.g.* be used for biopsy planning (materials courtesy of A.J. Beer).

isolation, but combined to give a more complete characterisation of the tissues being studied (Fig. 3).

New Evidence That Has Been Reported

Recently, several promising imaging probes have emerged for assessing the prostate and the brain, two organs that are well suited to imaging with combined PET/MRI. One of the most promising class of novel radiotracers are the PSMA-specific ligands used for prostate cancer imaging, like the commonly used compound [^{68}Ga]PSMA developed by the Heidelberg group [37]. Combined PET/MR imaging with this agent appears to be an ideal combination for patients with low-level serum prostate-specific antigen (PSA) increases, considering the diagnostic superiority of MRI of the pelvis compared to CT [38]. Some even suggest that prostate cancer diagnosis could be one of the key applications of PET/MRI in clinical routine. PET and MRI in combination with [^{18}F]fluorocholine (FCh) together with high-resolution T2w-MR imaging has been shown to increase the specificity of prostate cancer imaging significantly [39]. The combination of multi-parametric MR imaging with FCh and highly specific radiotracers, such as [^{68}Ga]PSMA in a dual-tracer approach, appears to enable very accurate tumour characterisation [39]. Hartenbach and colleagues from Vienna presented the protocol of a prospective, randomised clinical trial (RAPID) on the assessment of patients with clinically suspected prostate cancer after multi-parametric metabolic hybrid imaging. Table 3 summarizes the progress indicators for PET/MRI in oncology.

Future Challenges

The panel was in agreement on balancing the occasionally unsubstantiated preference for whole-body imaging protocols using PET/MRI with protocols that target selected regions of the body with or without a prior whole-body PET/CT exam. Further, the panel stressed the need to empower studies that target true synergistic effects of PET and MRI in the context of quasi-simultaneous (synchronous) acquisitions. In particular, panelists agreed on exploring potential combinations of PET and MRI information for the characterisation of features such as cellularity and proliferation, hypoxia and perfusion, metabolism and perfusion, as well as drug delivery and perfusion. Combinations such as these will help to establish PET/MRI as a multi-parametric imaging system for the profiling of tumour biology with the aim of achieving better prognostic stratification. Moreover, post-processing and advanced visualisation tools for the image data will be of paramount importance to define new combined parameters of tumour biology, which are clinically relevant and also easy to communicate and demonstrate to clinical partners (Figs. 2 and 3).

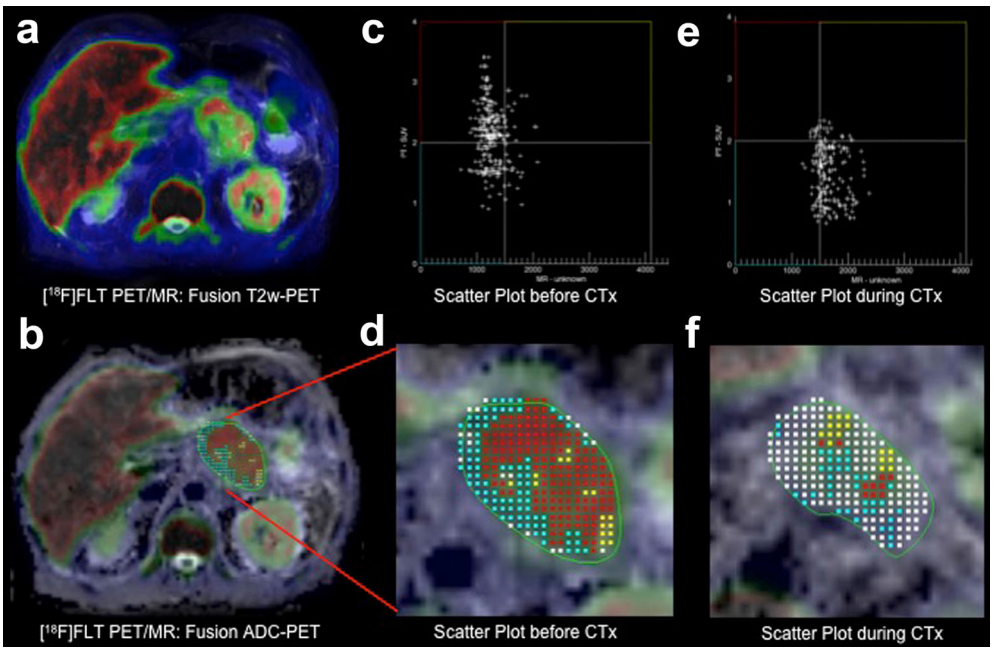

Fig. 3 **a** [^{18}F]FLT-PET/MRI of a patient with pancreatic adenocarcinoma undergoing FOLFIRINOX chemotherapy. **b** Fusion of the ADC map and FLT PET and voxel-by-voxel analysis of the tumour area using Anima M^{3}P (MunichHeart Software, Nekolla and van Marwick, 2013). The *scatter plot* shows the correlation of proliferative activity (*y*-axis) and restricted water movement (*x*-axis) before chemotherapy (CTx) (**c**, **d**) and early after start of CTx (**e**, **f**): tumour size has not shrunken substantially; note, however, a dramatic change in tumour biology in the scatter plot with lower SUVs and higher ADCs. Moreover, the shape of the cloud of points has changed during CTx and is more homogeneous compared to the situation before CTx. This suggests that the patient is a responder which was confirmed by CT restaging after completion of chemotherapy (materials courtesy of A.J. Beer).

Table 3. Progress indicators for PET/MRI in oncology

	2012	2013	2014	2015
Diagnostic quality of PET in PET/MRI equivalent to PET quality in PET/CT	↔	↔	↗	↗
Resolving quantitative bias from MR-AC	↘	↔	↔	↔
Clinical data available on diagnostic accuracy of PET(/MRI) in oncology	↔	↔	↘	↔
PET/MRI protocol standardisation	↓	↔	↘	↔
Definition of key clinical applications	↔	↔	↗	↗

More specific questions raised during this dialogue board discussion included whether PET/MRI is equivalent to separate PET/CT and MRI examinations and, further, what true advantages can be gained from simultaneous PET and MR imaging. Finally, considering that oncological studies are the mainstay of PET imaging today, how will the advantages of combined PET/MRI be assessed from a health-care evaluation perspective, and how does each modality influence relevant clinical endpoints?

Dialogue Board 4: PET/MRI in Neurology

The Issues

The combination of PET and MRI has already demonstrated itself to be potentially superior to the single-modality approach in the management of neurological diseases. PET/MRI was described by one of the panelists as "the 'perfect couple' for imaging neuro-degenerative disorders" (Fig. 4). In suspected Alzheimer's disease, for instance, a single PET/MRI examination using amyloid plaque-targeting radiotracers could be useful in eliminating other possible causes of cognitive impairment, such as brain tumour, encephalitis or vascular lesions as well as providing both pathology and neuronal injury biomarker information [40]. Such a single examination is expected to have sensitivity and specificity exceeding 80 % [41, 42].

One indication of the flexibility that PET/MRI can provide was in a novel protocol using an ^{15}O-producing dedicated "baby cyclotron" and fully-automated radio-synthesis device. Cerebral blood flow, cerebral metabolic rate of oxygen and oxygen extraction fraction can be assessed quantitatively within a short scanning period of 8 min during sequential slow-bolus inhalation of [^{15}O]oxygen and [^{15}O]carbon dioxide [43, 44]. The logistical complexity could be improved by means of inhalation of labelled gases instead of intravenous administration and non-invasive determination of the arterial input function without the need for arterial blood sampling [45]. The application of this rapid imaging technique could be used to validate MR-based stroke imaging concepts by means of assessing direct pathophysiological status, and to provide stroke imaging opportunities to improve diagnostic procedures and therapeutic strategies in a number of clinical situations.

Over the recent years, the number of publications in the field of brain PET/MRI has continued to increase steadily with the main foci being on basic research of brain function and brain diseases, the improvement of attenuation correction algorithms and the clinical evaluation of brain PET/MRI. As reported from the past Tübingen workshops, the use of PET/MRI in brain imaging is likely to be a key application [1–3].

Recent Advances or Achievements

Panelists agreed to disagree about whether the accuracy of current attenuation correction of the PET data in a combined PET/MRI examination was clinically acceptable. One panelist suggested that attenuation correction of brain PET images based on an MRI Dixon sequence [46] was inaccurate and not acceptable for clinical use and that "PET/MRI produces an inferior PET scan". The divergent perspectives were exemplified in statements like "accurate attenuation correction is still an issue, particularly when assessing lateral aspects of the brain and the cerebellum" *versus* "the attenuation correction problem is potentially solved for the brain", with the latter statement being supported by first results from predicting bone information from anatomic T1w-MR images [47] or from proton density-weighted zero time imaging [48]. Alternatively, it was suggested that a separate, low-dose CT scan of the head can be acquired and co-registered to the emission data for the purpose of robust CT-based attenuation correction [49].

Further, panelists shared their experience with imaging protocols from clinical routine and research protocols. Law and colleagues from Copenhagen reported a 17-min clinical protocol that included sequences such as UTE, volumetric interpolated brain examination (VIBE), T1 magnetization-prepared rapid gradient echo (T1 MPRAGE), T2 fluid attenuation inversion recovery (T2 FLAIR), DWI and T2w imaging. Another protocol suggested by Barthel and colleagues from Leipzig for dementia FDG-PET/MRI brain examinations included the acquisition of the following data: Dixon VIBE for generating MR-derived attenuation correction maps, T2 FLAIR, T2 turbo spin echo (T2 TSE), T1 fast low angle shot (T1 FLASH), susceptibility-weighted imaging (SWI), T1 MPRAGE, resting state echo planar imaging (EPI) and glucose metabolism (FDG-PET). The MRI

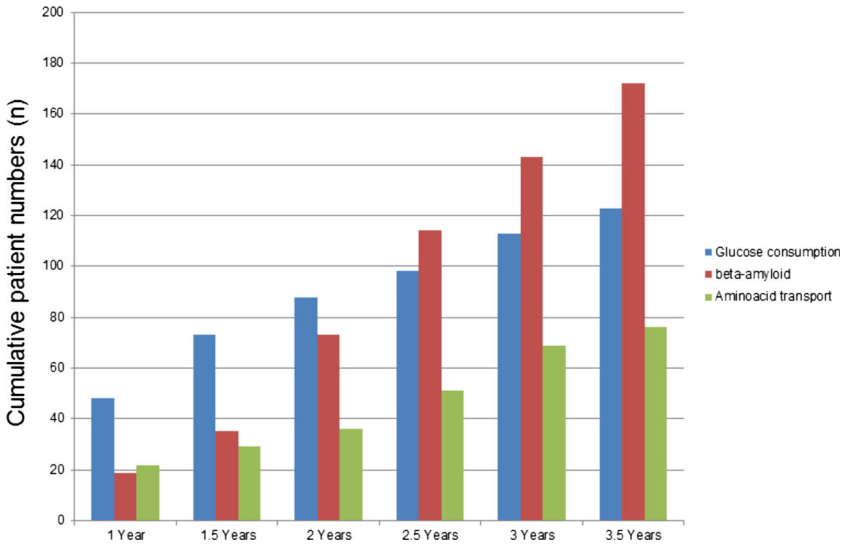

Fig. 4 Example of annual throughput of patients undergoing PET/MR imaging of the brain, demonstrating a continuously growing number of imaging examinations at this site of an early adopter of PET/MRI.

component of this protocol was the rate-limiting step and required 40 min of acquisition time.

New Evidence That Has Been Reported

Neurodegeneration

One panelist presented a single centre experience from 100 patients with mild cognitive impairment or Alzheimer dementia. All patients underwent an integrated amyloid imaging PET/MRI examination. The data support the notion that fully integrated amyloid PET/MR imaging is feasible in clinical routine and helps provide all biomarker information required to support clinical diagnosis. Drzezga *et al*. [40] provided proof regarding the efficacy of FDG-PET/MRI for the classification of dementia disorders through the provision of fully-integrated information on brain metabolism, functional connectivity and anatomical structure (Table 4).

Neuro-oncology

Law and colleagues presented their single centre experience with FET-PET/MRI in the management of brain tumours. It was pointed out that small PET-positive findings close to the skull may be overlooked since PET activity can be severely underestimated in areas close to bone due to the current limitations of MR-AC. Conservative imaging approaches may require the additional acquisition of a low-dose CT with every FET-PET/MRI until Dixon-based AC methods can be improved or replaced [49].

Neuroscience

Preliminary data were discussed regarding associations between changes of neuronal activity (*i.e*. glucose metabolism or perfusion) and functional connectivity (*i.e*. BOLD) in human subjects undergoing integrated FDG-PET/*f*MRI studies in a state of rest and during different conditions (eyes open *versus* eyes closed) [50]. Such studies have previously been performed with small animal PET/MR imaging [51].

Future Challenges

Future challenges for brain PET/MRI studies include optimising the required MR sequences with regard to reducing the total acquisition time and the data handling task of storage, display, processing and image interpretation of the large number of available multi-parametric datasets.

The group agreed that the potential use of PET/MRI for disease stratification in movement disorders, in imaging patients with neurological symptoms in the presence of arterial-venous malformations and in age-related studies of brain physiology *versus* processing of time-dependent

Table 4. Progress indicators for PET/MRI in neurology

	2012	2013	2014	2015
Improved understanding of brain physiology and function through the use of combined PET/MRI	↔	↗	↗	↗
Methodological progress for improved quantification of PET/MRI neurological examinations (AC, IDIF, SUV)	↔	↔	↗	↗
MR-based motion correction for routine clinical use	↓	↘	↔	↔

functions of the brain should be explored. Further, all post-surgical brain tumour patients would generally be candidates for follow-up MR imaging and may, thus, be suitable candidates for combined amino acid transport (*e.g.* FET) PET/MR imaging.

The main technical challenge currently limiting the routine clinical use of neurological PET/MRI is reproducible and fast attenuation correction. An acceptable solution for the uncomplicated adult patient may be expected first, but for paediatric patients or patients with metal implants, further development is needed. Today, a number of advanced MR-guided attenuation correction methods have been developed at different academic institutions and are reported to be reliable for brain applications [47, 52, 53]. Pending further clinical validation, these methods are candidates for rapid implementation into commercial PET/MRI devices by the vendors. In the meantime, low-dose CT transmission data of the head may be used [49]. Regarding clinical patient groups for combined PET/MRI scans, dementia is the obvious choice with FDG or an amyloid PET agent.

Dialogue Board 5: Advanced PET/MRI—Multi-parametric Imaging

The Issues

The appreciation of the role of quantitative imaging in tumour phenotyping, prognostication and response assessment to targeted therapies is increasing. It cannot be stressed too greatly that one of the potential drivers for PET/MRI is improved quantitative information provided by a multi-modality imaging approach. One example is the use of MRI navigator sequences to estimate a time-dependent motion vector that can then be incorporated into the PET reconstruction algorithm to further improve spatial resolution and reduce motion artefacts [54], or the use of the MRI data in attenuation correction of the PET emission data [55].

The next logical step beyond this is to combine the different signals into a series of individual parameters that have clinical relevance. This invites the use of the emergent fields of radiomics and large-scale data mining to be applied to the PET/MRI environment. It is clear that a number of groups are now starting to investigate these novel areas and are likely to be the subject of future developments.

Recent Advances or Achievements

The panelists reported on continuous refinement of strategies for MR-AC that included the integration of bone structure mapping and the acceptance of attenuation map templates for special MR coils, radiotherapy (RT) tables and ancillary devices, thus, making way for quantitative PET/MRI-guided radiation therapy planning [55–57]. Also, MR-based motion compensation has advanced beyond initial pilot data [54] towards more refined applications in neurology.

As numerous groups test different approaches to image manipulation, metrics need to be put in place by which to assess the degree of relative variation of these algorithms. Ladefoged from Copenhagen presented an automated toolbox for such standardised metrics for image-based comparisons. During the development of the toolkit, it became clear that intra- and inter-subject comparisons benefit from quantitative measures of regional differences more than a "mean error for the entire brain". Reporting only the result averaged over an entire patient cohort has proven insufficient for assessing the regional accuracy, and metrics to detect outlier performance should therefore be used.

New Evidence That Has Been Reported

Wehrl and colleagues from Tübingen reported their initial experiences with simultaneous triple-modality PET/MR-EEG measurements in epilepsy patients. These data allow not only the assessment of brain function with slow, medium and fast time scales, but also open the domain for mapping brain connectivity using simultaneous metabolic, functional and electrical measurements. This would also integrate into the field of *cometomics* [58], which combines functional connectivity measurements derived from *f*MRI techniques with metabolic information derived from PET (Table 5).

Future Challenges

Advanced PET/MRI permits new approaches towards the integration of the full range of multi-modality, multi-parametric data (both, in spatial and temporal domain) in order to address specific diagnostic or scientific questions. Future challenges for advanced PET/MRI include the harmonisation of imaging protocols as well as the adoption of effective data mining strategies to extract valuable information from the acquisition of 3D longitudinal imaging of multiple imaging biomarkers.

Multi-parametric PET/MRI acquisitions can provide large datasets which can be defined as "big data", which in most cases today is still analysed manually, *e.g.* by subjective image fusion, visual inspection and evaluation. However, manual workflows are cumbersome and not acceptable in large-scale clinical scenarios. Therefore, one challenge for PET/MRI analysis will be the development of an intuitive platform to effectively perform image-based large-scale data mining. Specific feature selection and extraction as well as the validation of these data mining procedures, the generation of an image-based disease-specific probability map and similar remain a challenge that not only affects PET/MRI but has implications for computer-aided medical diagnosis in general.

Of note, data mining techniques often rely on the acquisition of specific input data [59], which mandates the use of standardised or harmonised approaches towards data

Table 5. Progress indicators for PET/MRI in multi-parametric imaging

	2012	2013	2014	2015
Fully-integrated PET/MRI exclusively offers the largest variety of multi-parametric biomarkers	↔	↗	↑	↑
Validation of advanced multi-parametric biomarkers in clinical research (beyond "image fusion")	↘	↔	↗	↗
Contributions of small animal imaging to the understanding of multi-parametric biomarkers	↔	↗	↑	↑
Using standardised approaches for assessing the accuracy of PET/MRI and towards multi-parametric image analysis	NA	NA	NA	↗

NA not applicable

acquisition and quantification. However, such harmonisation approaches often compete with innovation in order to utilise the latest state-of-the-art imaging sequences or tracers for certain diagnostic and scientific assessments. As stated by a panelist during the 2013 workshop, "everybody wants standards, but once standards are available nobody wants them anymore" [2]. This observation still holds true and little has changed in the perception of the need of imaging standards, which poses a major bottleneck to in-depth, multi-parametric imaging today.

Roundtable Discussion—PET/MRI Key Applications

The Issues

Prior to this workshop, the organisers selected the panelists well in advance to allow them adequate time to prepare for this important roundtable discussion. They included individuals with diverse backgrounds in nuclear medicine, pharmacology, radiology, radiation oncology, neurology, cardiology and physics. Most panelists felt that PET/MRI today was still primarily a tool for research. In areas where PET/MRI was applied clinically, panelists urged the adoption of standardised protocols with patient-friendly, limited total examination times. Given the wide range of experiences with PET/MRI in clinical applications, the panelists (and audience) with experience in PET/MRI considered key applications of this technique to be in imaging with tracers other than FDG, while key applications for more recent adopters appeared to lay in indications that were primarily indications for MR-only imaging but which could be extended to a combined PET/MRI examination. At the time of writing, the number of clinical PET/MRI installations was approximately 70 systems, which led one panelist to suggest that "… key applications cannot be defined today since PET/MRI is not widely available to the people".

Recent Advances or Achievements

It was noted that cancer imaging studies of prostate and brain tumours were better performed with MRI than CT, and, thus, PET/MRI should be an ideal application in these two particular tumour types. For example, the potential information contained in PET/MRI scans of the prostate includes localisation and staging, perfusion and cellularity (MRI), phenotyping and metabolism (PET) and detection of recurrence (PET and MRI). With the advent of ^{68}Ga-labelled prostate imaging agents and the information from morphological imaging and DWI, discussants felt that recurrent disease would be detectable and characterisable at low levels of circulating serum PSA and hence at an earlier stage using PET/MRI [60]. For brain tumours, the potential biological signals of interest include vascularisation (MRI), perfusion (MRI) as an index of drug delivery and metabolic phenotyping (PET), ideally merged in a multi-parametric manner to derive a voxel map of "malignancy". Quantitative imaging of biomarkers and the imaging of expensive chemotherapies *in vivo* were proposed as an important application, possibly unique to combined PET/MRI in the near future (Fig. 3).

New Evidence That Has Been Reported

Neurological applications stand to benefit greatly from a combined, simultaneous PET/MRI investigation approach [40]. The ability of MRI to add perfusion, diffusion and other signals to morphological imaging should greatly assist in the interpretation of PET signals in applications such as dementia imaging with amyloid-targeted tracers. Dementia remains likely to be one of the key applications in neurological PET/MRI. Simultaneous PET/MRI acquisitions were thought to be essential in neuro-receptor pharmacokinetic studies. Of note, dynamic PET imaging has a long history of studying various neurotransmitters in the brain associated with the dopamine, serotonin and opioid systems, and combining it with MRI should give greater insight into dynamic processes *in vivo* [61] (Table 6).

In cardiology, it was suggested by the panelists that PET/MRI may replace PET/CT in many indications. In addition to studying myocardial perfusion and metabolism, new imaging targets are emerging, such as visualisation of vulnerable plaques, matrix metalloproteinases (MMPs) to demonstrate macrophage activity in post-ischemic tissues and plaques, cardiomyopathies, pre- and post-synaptic innervation and sympathetic and para-sympathetic innervation.

Paediatric imaging with PET/MRI benefits greatly due to both the reduction in radiation dose by avoiding CT imaging as well as the advantage of combining examinations in a single session, which is especially important if anaesthesia or sedation is used. However, technological developments

Table 6. Progress indicators for key applications for PET/MRI

	2012	2013	2014	2015
Paediatric oncology is a key application of PET/MRI	↗	↗	↑	↑
Dementia is a key application of PET/MRI	↗	↑	↑	↑
Neuro-oncology is a key application of PET/MRI	↗	↗	↗	↔
Cardiovascular imaging is a key application of PET/MRI	↔	↔	↔	↗
Multi-centre evaluation of clinical PET/MRI	↓	↘	↘	↘
Multi-parametric imaging is a key driver for PET/MRI	↔	↗	↗	↗

will likely see the radiation dose from CT to continue to decrease by perhaps three- to fourfold in the next few years, and, thus, radiation exposure may become less of a specific key driver for PET/MRI in comparison to other logistic issues. Additionally, the point again emphasised by the panelists was that PET/MRI is *not* just a replacement for PET/CT, but has unique, intrinsic advantages that are only just beginning to be explored.

Future Challenges

The convenience of simultaneous PET and MRI examinations was mentioned on a number of occasions; however, all agreed that this alone did not justify the high initial cost of the equipment. Instead, indications that require simultaneous acquisition of PET and MRI data should be defined (and validated) more formally in order to derive key applications for PET/MRI that should become a diagnostic device reserved for these specific acquisitions.

Cost was also mentioned as a barrier to introducing new key applications due to the limited number of clinical sites with access to the technology. One possible application not highlighted in previous workshops was that PET/MRI may assist the radiation oncologist to address critical bottlenecks currently experienced in the delivery of radiotherapy by better defining tumour location and metabolic phenotype. The magnitude of the financial investment for a PET/MRI installation may appear daunting at first, but panelists suggested that part of the investment could be recuperated through selected MRI-only scanning on the PET/MRI system, thus, necessitating that the MRI component of the system remains able to perform all or most procedures that a stand-alone MRI system will perform.

Summary

Combined PET/MRI has established itself as the emerging imaging modality for the second decade of the new millennium. Combined PET/MRI is both an “eye-catcher” and a “brain-teaser” alike. Many groups, having worked with PET or MRI, have focussed their interests and capacities on exploring the potential of integrated PET/MRI for clinical and research questions. This reiterates the opinion shared by many early adopters and observers that “as a tool for biological and pathophysiological investigation, combined PET/MRI has unsurpassed capabilities”.

When PET/CT imaging was introduced, it *solved* a lot of the existing problems at the time for PET systems with transmission measurements for attenuation correction based on radionuclide sources (*e.g.* greatly improved throughput due to shorter overall acquisition times, generation of AC maps, *etc.*), while, in contrast, PET/MRI has *introduced* a lot of problems. As can be seen when reviewing this series of workshops [1–3], many technical problems are now well understood and steady improvements in methodology have helped increase the acceptance level of PET/MRI. However, in terms of investment in human capital and greater integration of clinical reports, there has been a degree of opposition by some and limited willingness to establish an adequate platform for cross-specialty training, a problem that is not unique to PET/MRI but is shared with many combined imaging modalities that essentially create a “new” type of image. This current shortage of sufficiently trained hybrid imaging experts together with the limited number of agreed key applications of PET/MRI has led to the slower adoption of PET/MRI compared to PET/CT. Other factors, particularly the higher initial capital and operational costs, also contribute to this situation. One possible solution for offsetting the high costs of combined PET/MRI might be to include it in drug testing. This refers to its use as a tool for selecting appropriate patients to be included in a clinical trial and to monitor therapy response. The great potential of such a strategy is exemplified by a recent anti-amyloid drug testing trial in Alzheimer’s disease in which around one third of the patients included solely based on clinical testing were negative for amyloid in PET imaging, *i.e.* did not present the target for the drug [62].

Panelists agreed that paediatric imaging is a key application for PET/MRI, however mainly for the advantage of the convenience of a single examination (referred to during the meeting as “the triviality of comfort”). Further, attendees acknowledged the fact that several promising radiolabelled PET probes have emerged specifically for prostate and brain cancer imaging, both of which are considered two key areas of interest for PET/MRI. On that note, attendees assigned a low priority to the development of new, dual-labelled (*i.e.* PET and MRI) probes of the same physiological processes. In view of research applications of PET/MRI, this workshop conceded that while the

simultaneous acquisition of quantitative PET and MRI data should be explored for a range of tracers and indications, the limited accuracy and reproducibility of routine implementations of MR-AC remains a hindrance to the wider adoption of PET/MRI. Both in research and clinical applications, future PET/MRI protocols should be ready to integrate algorithms for MR-based motion compensation, which is seen as a potential major methodological advantage over PET/CT. In a poll taken on the final day of the meeting, attendees were asked whether they considered PET/MRI technology a maturing technology that had passed the initial peak of (inflated) expectations and the subsequent trough of disillusionment [63] and was entering a phase of slow gradual improvement; 75 % of the attendees agreed with the description compared to only 61 % at the previous workshop in 2014 [3].

In conclusion, workshop attendees reaffirmed that PET/MRI is an increasingly exciting hybrid imaging modality. If placed in the hands of well-trained and open-minded experts, this technique will help continue the evolution from "Unclear Medicine" (single modality imaging with PET and SPECT), through "New Clear Medicine" (dual modality structure/function imaging with PET/CT and SPECT/CT) to "Multi-modality Multi-parametric Imaging" (structure plus function plus micro-environment with PET/MRI). The age of multi-modality, multi-parametric imaging is, indeed, here.

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