Clinical Applications of Hybrid PET/MRI in Neuroimaging

Valentina Garibotto, MD, Susanne Heinzer, PhD,*† Serge Vulliemoz, MD,‡ Renaud Guignard, MD,*§ Michael Wissmeyer, MD,* Margitta Seeck, MD,‡ Karl-Olof Lovblad, MD,* Habib Zaidi, PhD,* Osman Ratib,MD, PhD,* and Maria-Isabel Vargas, MD**

Purpose: We tested the performance and clinical applicability of combined protocols for brain imaging studies acquired on a new whole-body hybrid PET/MR scanner.

Patients and Methods: Fifteen patients [6 male and 9 female patients; mean (SD) age, 51 (30) y; range, 6–89 y] were scanned on a Philips Ingenuity TF PET/MR. Standard imaging protocols of both modalities were combined, using a "head coil" and contrast-enhanced fully diagnostic MR protocols. Attenuation correction of the PET images was performed using tissue segmentation of the MR image and incorporation of attenuation templates measured for coils and table.

The clinical indications evaluated are as follows: patients with cognitive disturbance of suspected neurodegenerative origin, presurgical evaluation of drug-refractory epilepsy, and brain tumor staging. For the first 2 indications, FDG PET imaging was performed, whereas for the last, fluoroethyltyrosine, an amino acid tracer, was used.

Results: In all cases (4 patients with neurodegenerative disease, 6 patients with epilepsy, and 5 patients with high-grade tumor), we obtained full diagnostic quality of both modalities and the total duration of the examination remained within a tolerable range (<2 hours). Twelve subjects had pathological findings: 11 of which were confirmed by clinical follow-up as true positive and 1 was confirmed as a false-positive result. For the 3 normal studies, the clinical follow-up confirmed the imaging findings as true-negative.

Conclusions: Acquiring both PET and MR in a single session on a hybrid system minimized patient discomfort while maximizing clinical information and optimizing registration of both modalities. In addition, in comparison to PET/CT, the effective dose (related to CT) was reduced, and this is particularly beneficial in the pediatric population.

Key Words: PET/MRI, hybrid imaging, neuroimaging, clinical applications

(*Clin Nucl Med* 2013;38: e13–e18)

Hybrid PET/MR is a recently developed technique that is gaining a growing interest from the medical community owing to its potential clinical applications.[1–5]

PET and MR are the methods of choice for neuroimaging, allowing to combine the metabolic information (glucose metabolism for various functional investigations, amino acid metabolism for tumor detection) provided by PET imaging, with the various morphological and functional parameters measured by MR.

In this respect, MR has clear advantages compared to CT and mainly to the non–contrast-enhanced CT, which is usually coupled to PET when a routine PET/CT investigation is realized.

There are already preliminary reports describing the potential clinical applications of hybrid PET/MR in brain imaging based on studies realized on a brain-dedicated prototype of hybrid PET/MR.[6,7] However, dedicated brain systems usually have limited availability, mainly confined to research centers. New whole-body PET/MR hybrid scanners that are currently available will presumably have a wider diffusion over the next few years, being able to perform both brain and whole-body imaging.

The aim of this study was to test the implementation of a new whole-body hybrid PET/MR sequential scanner when realizing brain studies in clinical routine. The specifications and performance characteristics of the Philips Ingenuity time-of-flight PET/MR have been described in detail elsewhere.[8] Some recent publications reported on the use of this tomograph for whole-body applications,[9–11] in 1 case of stroke and crossed cerebellar diaschisis,[12] and for investigating peripheral nerve involvement.[13]

In this work, we focused on 3 main referral indications, for which both PET and MR are routinely performed: cognitive impairment of probable neurodegenerative origin, presurgical evaluation of drug-refractory epilepsy, and brain tumor staging.

PATIENTS AND METHODS

Patient Population

Fifteen patients [6 male and 9 female patients; mean (SD) age, 51 (30) y; range, 6–89 y] were scanned on a Philips Ingenuity TF PET/MR (Geneva University Hospitals, Geneva, Switzerland). This device consists of the 2 separate scanners (the Ingenuity Time-of-Flight PET scanner and an Achieva 3T X-series MRI) linked through a single patient table, allowing for sequential imaging. Standard imaging protocols for both modalities were applied.

This study was approved by the ethical committee of the Geneva University Hospital.

Imaging Protocols

PET/MR studies consisted of diagnostic sequences using standard MR protocols corresponding to different clinical indications, a dedicated MR sequence acquired for PET attenuation correction (T1-weighted image fast-field echo termed atMR), and a 3-dimensional (3D) PET data acquisition.

The default atMR acquisition protocol consisted of an MR sequence suitable for deriving an attenuation map. The atMR images were converted to an attenuation map using the 3-segment algorithm, as described previously.[8] This map was used to correct PET images for attenuation using average tissue attenuation properties in contrast to CT-based attenuation correction implemented on commercial PET/CT scanners. Templates for the bed and the RF coils were added to the patient's attenuation map.

Depending on the clinical indication, the clinical MR part of the examination included T1-weighted and T2-weighted turbo-spin-echo sequences (T1w SE and T2w TSE), T2-weighted gradient echo sequences (T2w GE), 3D fluid-attenuated inversion recovery (FLAIR), gradient

Received for publication March 5, 2012; revision accepted April 23, 2012.

From the *Department of Medical Imaging and Information Sciences, Geneva University Hospital, Geneva; †Philips Healthcare AG, Zurich; ‡EEG and Epilepsy Unit, Neurology, Department of Neurological Sciences, Geneva University Hospital, Geneva, Switzerland; and §Department of Nuclear Medicine, Centre Antoine Lacassagne, Nice, France.

Conflicts of interest and sources of funding: This work was supported by the Swiss National Science Foundation under grants SNSF 31003A-125246 and 33CM30-124114 (K.O.L. and H.Z.) and by the Aetas Swiss foundation for Ageing Research (V.G.).

Reprints: Valentina Garibotto, MD, Division of Nuclear Medicine, Department of Medical Imaging and Information Sciences, Geneva University Hospital, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva, Switzerland. E-mail: valentina.garibotto@hcuge.ch.

ISSN: 0363-9762/13/3801–0e13

TABLE 1. PET and MRI Protocols According to the Clinical Indication

Clinical Indication	PET Tracer/Acquisition Protocol/Duration	MR Protocol	No. Subjects Included
Functional assessment for vascular* and/or neurodegenerative cognitive disturbances	^{18}F-FDG/static/15 min	T1w 3D, T2w TSE, 3D FLAIR, *3D TOF Willis, ASL, DTI	4
Epileptic focus localization	^{18}F-FDG/dynamic/45 min	T1w 3D, T2w TSE, 3D FLAIR, ASL, DTI	6
Brain tumor (recurrence or staging)	^{18}F-FET/static/10 min	T2w TSE, 3D FLAIR, perfusion, T1w SE, DTI, T1w 3D + gadolinium	5

* The sequence marked with the asterisk as well (3D TOF Willis) which is used for this specific indication only.

echo T2 or susceptibility-weighted imaging (SWI), perfusion and diffusion tensor imaging (DTI), and arterial spin labeling (ASL; Table 1).

A 15-minute ^{18}F-FDG PET acquisition was performed 30 minutes after IV injection of 250 MBq of the tracer.

For the investigation of neurodegenerative disorders, the uptake phase was done in a dimly lit room, with the patient lying quiet, to avoid any interference with the distribution of the tracer.

For epileptic focus localization, a list mode acquisition for 45 minutes starting with the tracer injection was preferred to estimate absolute quantitative glucose metabolism using the Patlak noninvasive analysis (data not shown): the clinical interpretation, however, was based on the last 15 minutes of the acquisition, reconstructed as a static image. The results presented in this work are based on these data.

The ^{18}F-fluoroethyltyrosine (FET) PET imaging was acquired 30 minutes after injection of 200 MBq of the tracer: the uptake phase was done on the PET/MR tomograph and was used for acquiring MR sequences to shorten the total scanning duration.

The injected activity was adapted according to the body weight for the pediatric cases, following the European Association of Nuclear Medicine guidelines.[14]

Each case was interpreted by a multidisciplinary team of nuclear physicians, radiologists, and neurologists.

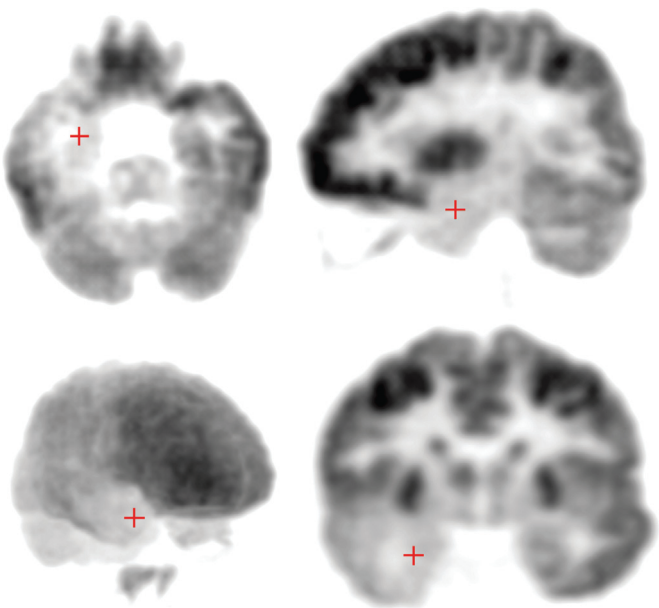

FIGURE 1. High-resolution PET image (time-of-flight reconstruction; slice thickness, 2 mm) showing clearly the medial temporal lobe hypometabolism observed in patient 7.

RESULTS

Scan Time

The duration of the T1w fast-field echo sequence for attenuation correction was 1 min 20 s. The mean (SD) duration of total diagnostic MR examination was 36 (22) minutes (range, 10–72 minutes). The PET duration was 10–15–45 minutes depending on the clinical indication (Table 1).

We used standard clinical MR and PET protocols; therefore, the duration of the examination was identical to the sum of 2 separate examination. However, the positioning, which usually takes between 3 and 10 minutes in our experience, depending on patient's compliance, was done only once, in comparison to examinations performed on 2 separate scanners.

PET and MR Image Quality

All acquired MR data sets provided diagnostic image quality (examples are provided in the figures). Magnetic susceptibility artifacts appeared in 2 cases due to an implant (ventriculoperitoneal drain for patients 14 and 15), very limited and with no impact on image interpretation. Motion artifacts were visible in 2 cases (patients 10 and 15).

Uncorrected PET data sets showed optimal image quality.

Corrected PET images, using the TOF technology, allowed reconstructing high-resolution images (slice thickness, 2 mm), ideal for depicting medial temporal lobe alterations (an example is provided in Fig. 1).

It should be noted that attenuation correction could introduce some bias associated with motion artifacts; however, these could be corrected by coregistration of the atMR with the PET image followed by subsequent offline reconstruction (Fig. 2).

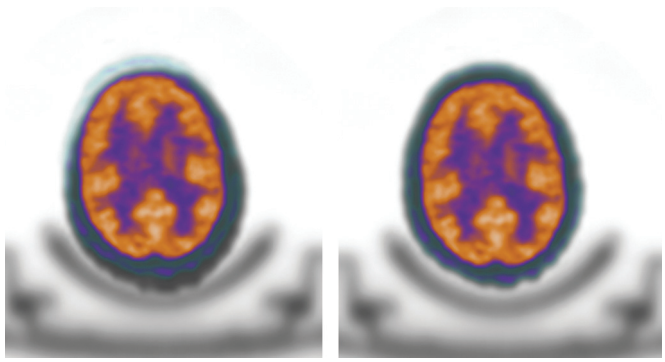

FIGURE 2. MR-guided attenuation correction after PET/MR realignment in patient 10. The images show the attenuation correction map before (left image) and after realignment (right image), fused with the attenuation-corrected PET images.

TABLE 2. Summary of Patients' Characteristics

Patient No.	Age, y	Sex	Indication	Examination Result	Follow-up Results
1	79	M	Cognitive disturbances, determination of the extent of functional impairment	Hypometabolism matching with focal vascular lesions, associated with bilateral temporoparietal metabolic reduction corresponding to the typical pattern of Alzheimer disease	Clinical confirmation of probable mixed dementia (Alzheimer disease and vascular dementia)
2	89	F	Clinically suspected degenerative dementia: differential diagnosis	Moderate cortical and subcortical atrophy, predominant in frontal and parietal regions, bilaterally, nonspecific; metabolic pattern typical for a Lewy body dementia, with a severe decrease in occipital associative cortices, and preservation of the metabolism in the precuneus	Clinical and imaging (DaTSCAN) confirmation of probable Lewy body dementia
3	63	F	Clinically suspected degenerative dementia: differential diagnosis	Moderate atrophy predominant in temporal and parietal regions, no significant hippocampal atrophy; metabolic pattern typical for a frontotemporal dementia	Clinical diagnosis of a probable frontotemporal dementia, supported by cerebrospinal fluid biomarkers (amyloid and tau protein)
4	71	F	Clinically suspected degenerative dementia: differential diagnosis	Frontotemporal atrophy, predominant on the left side, involving also the hippocampus; metabolic pattern typical for a frontotemporal dementia	Clinical diagnosis of a probable frontotemporal dementia
5	43	F	Presurgical evaluation of epilepsy	Hypometabolism matching with a right hippocampal sclerosis	Confirmation by clinical and EEG evaluations, resective surgery realized 5 mo after examination. Seizure-free at 3 mo
6	52	F	Presurgical evaluation of epilepsy	Hypometabolism matching with a right posterior cingulate cavernoma	Confirmation by clinical and EEG evaluations; the patient refused surgery
7	10	M	Presurgical evaluation of epilepsy	Hypometabolism matching with a right amygdalohippocampal dysplasia	Confirmation by clinical and EEG evaluations; surgical resection planned
8	41	M	Presurgical evaluation of epilepsy	No focal morphological or metabolic alterations	Ongoing, medical treatment
9	52	M	Presurgical evaluation of epilepsy	No focal morphological or metabolic alterations	Ongoing, medical treatment
10	37	F	Presurgical evaluation of epilepsy	Hypometabolism matching with	Confirmation by clinical and EEG evaluations, resective surgery performed 7 mo after examination. Seizure-free at 3 mo
11	53	M	Glioblastoma WHO grade 4, lesion assessment	High uptake matching with the MR lesion	Clinical progression, death
12	35	F	Oligodendroglioma WHO grade 2, lesion assessment	High uptake matching with the MR lesion	Chemotherapeutic treatment ongoing
13	69	M	Glioblastoma WHO grade 4, lesion assessment	High uptake matching with the MR lesion	Clinical progression, death
14	10	F	Medulloblastoma WHO grade 4, follow-up after surgery, radiotherapy, and chemotherapy	No significant uptake, o MR lesion, surgical sequelae	Ongoing; favorable clinical evolution and no signs of disease recurrence
15	6	F	Choroid plexus carcinoma after surgery and chemotherapy, lesion assessment	High uptake matching with newly appeared MR lesions showing a significant contrast enhancement, suspicious for tumor recurrence	Ongoing: morphological evolution compatible with a radionecrosis

Diagnostic Performance

The results obtained in individual cases are summarized in Table 2.

Imaging examples for the 3 clinical indications are shown in Figures 3 to 5.

Pathological PET and MR Findings

Twelve subjects had pathological findings, shown in detail in Table 2.

In 11 of the 12 cases, the PET/MR positive findings were confirmed as true-positive by clinical follow-up. For the remaining case, patient 15, PET and MR findings were suspicious for a tumor recurrence; however, the lesions had a favorable morphological evolution over time, with almost complete regression over a year. This evolution revealed that the lesion was in fact a radiation necrosis.

Normal PET and MR Studies

Three subjects had no pathological findings: for all 3, the clinical follow-up so far confirmed the initial imaging results.

In particular, for 2 cases (patients 8 and 9), a diagnosis of possible generalized epilepsy was retained. For patient 14, the clinical and imaging follow-up did not show any sign of tumor progression: for this reason, given that the images showed the surgical sequelae, but no new pathological finding, we classified this study among the "normal" studies.

DISCUSSION

This report demonstrates the feasibility of PET/MRI of the brain using a new whole-body PET/MR hybrid tomograph in a clinical setting.

Hybrid PET/MR is a recently developed technique, available on the market since approximately a year. The design of currently available systems reflects different solutions to solve the major challenges that rise when bringing these 2 technologies together.[15] First, for PET detectors to be compatible with MR magnetic field, photomultiplier technology must be replaced with magnetic field–insensitive avalanche photodiodes or silicon photomultipliers.[16,17] Alternatively, sequential imaging and proper shielding have been used.[4,5]

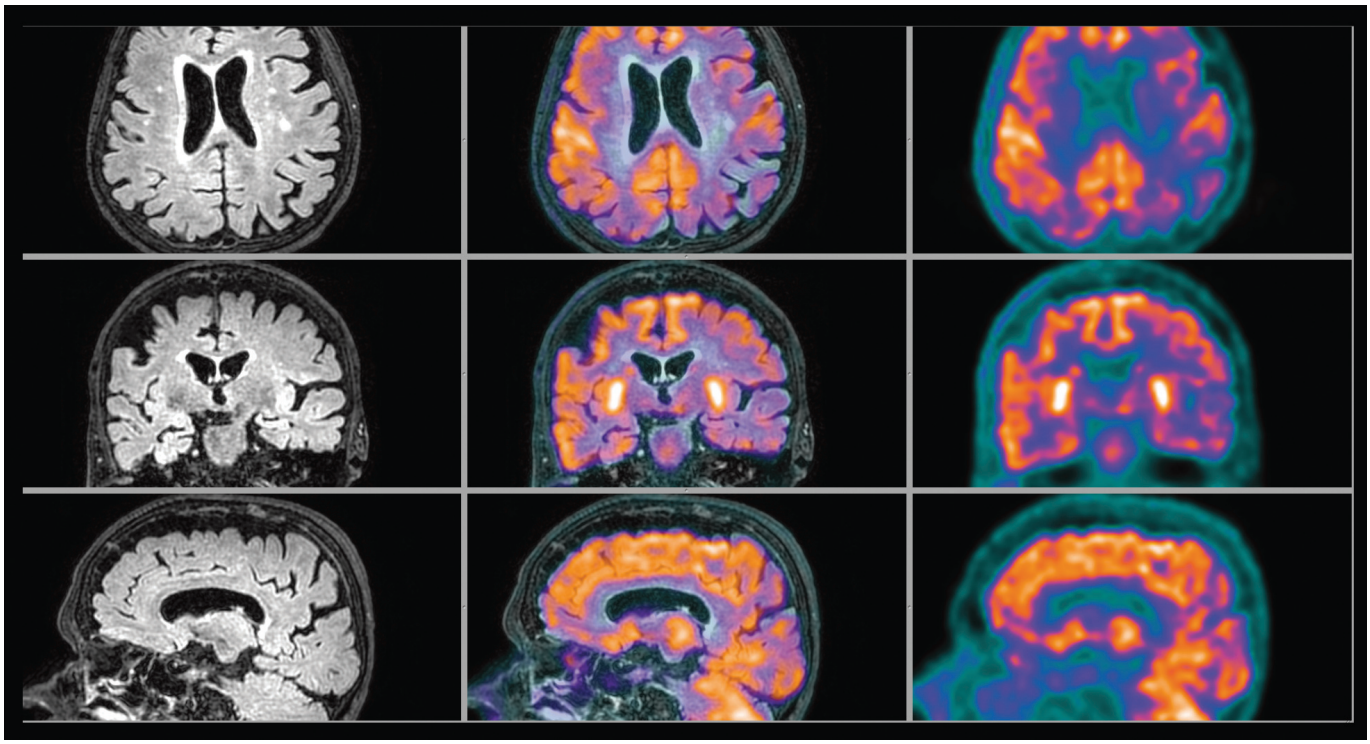

FIGURE 3. Patient 2: 89-year-old patient with probable Lewy body dementia. MR images show diffuse atrophy, without regional specificity, whereas FDG PET shows a significant posterior cortical hypometabolism, with preservation of posterior cingulate and precuneus metabolism, typically associated with Lewy body dementia.

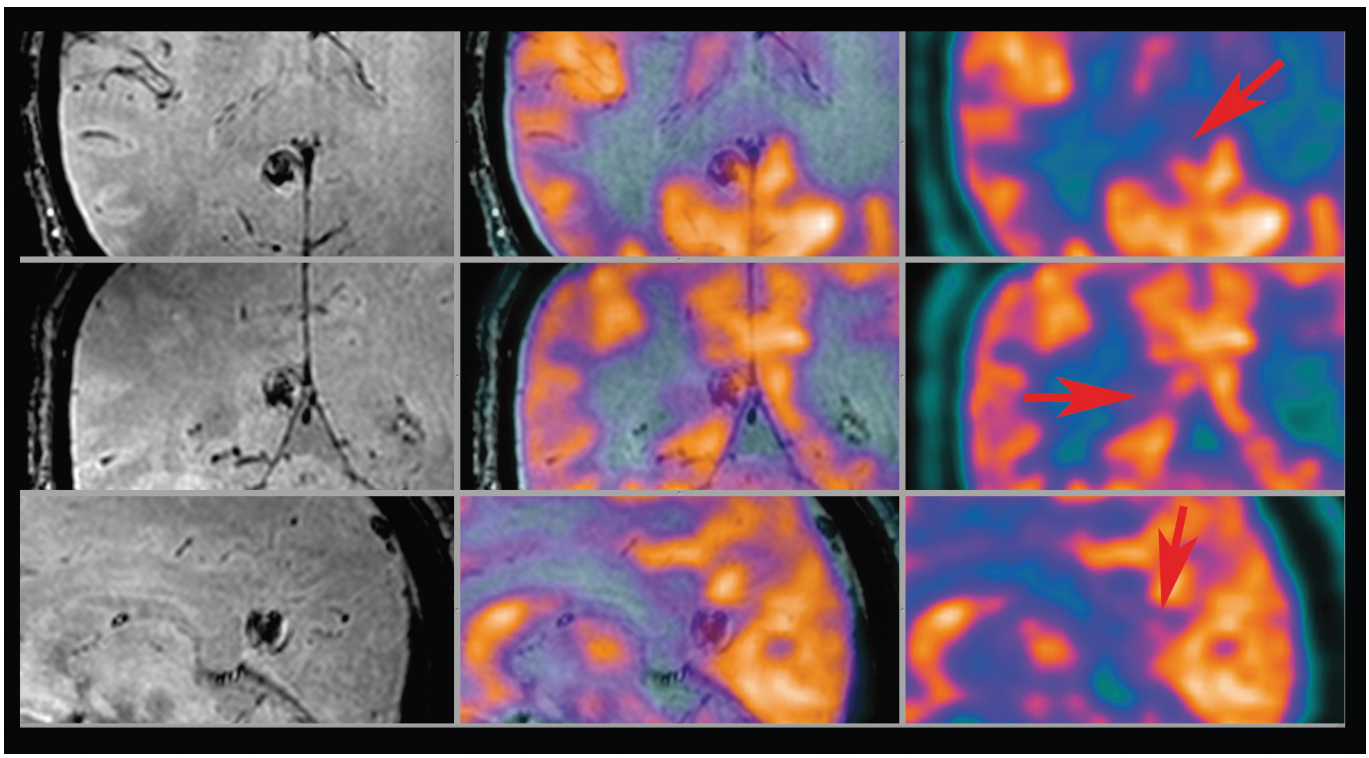

FIGURE 4. Patient 6: 52-year-old woman with epilepsy due to a cavernoma. The lesion is well characterized on the SWI image and corresponds to a small hypometabolic focus (indicated by the arrows), which could be easily missed reading the PET image alone.

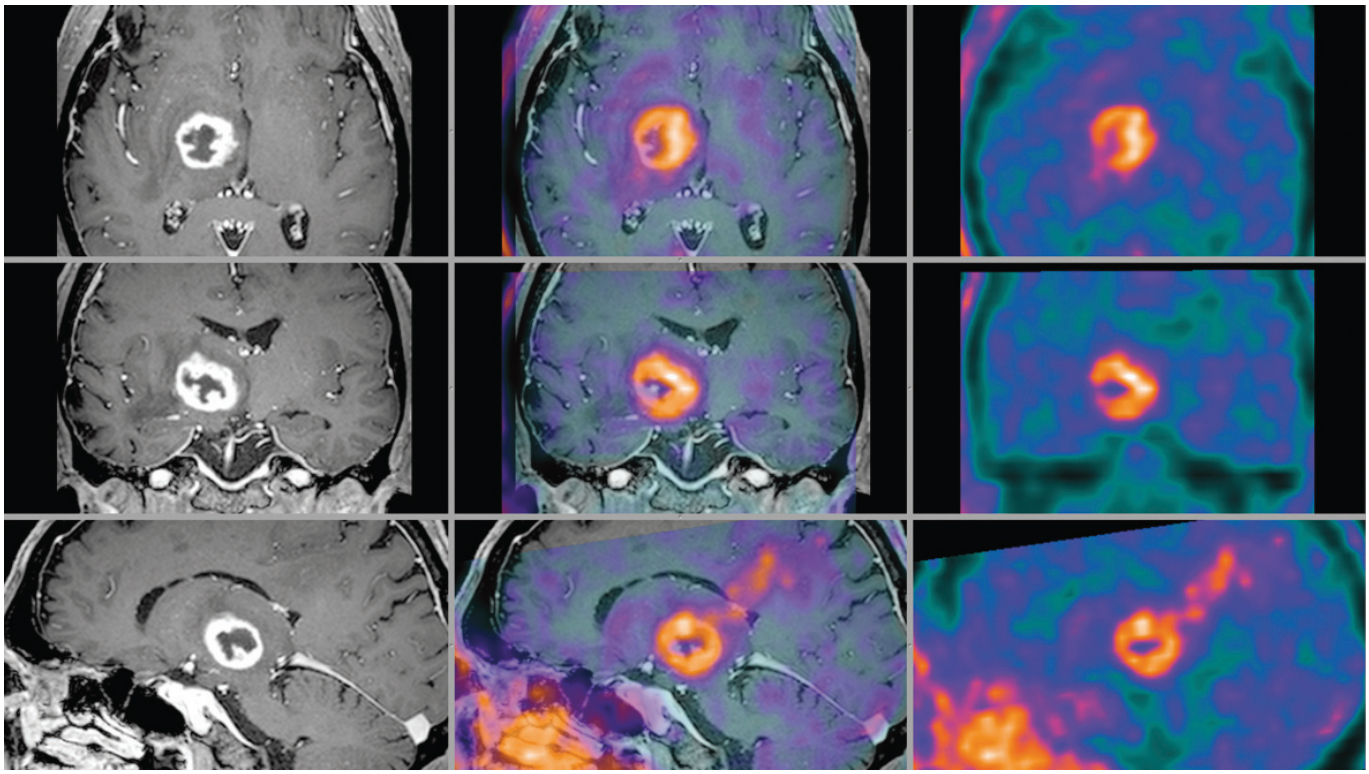

FIGURE 5. Patient 13: 69-year-old patient with a glioblastoma. The lesion shows a significant ring contrast enhancement on the T1w image after gadolinium administration and an intense FET uptake (estimated SUVmax, 3.4).

The system used in this work uses sequential imaging, allowing performing a fully diagnostic MR protocol with dedicated coils, equivalent to the standalone Achieva MR system.

For brain imaging, PET and MR are the methods of choice for clinical investigations and are currently performed systematically for all patients in 2 imaging sessions.

In our experience, with respect to the 3 main referral indications, that is, clinical suspicion of neurodegenerative dementia, epilepsy, and brain tumors, we had overall satisfactory results, obtaining all information that would normally be obtained with 2 separate examinations.

The main advantage associated with the hybrid technology is the fact that all relevant imaging information can be collected in 1 single session.

In addition, while a PET/MR study is longer than a standard diagnostic PET/CT study, it is still shorter than the total time that a PET/CT and an MR study would take today when performed on 2 separate scanners at different times.

This could be achieved by optimizing the MR protocol and by having to position the patient only once. This second issue is particularly important for patients with limited compliance, having some degree of executive and motor impairment, as might be often the case for patients investigated for neurodegenerative disorders or brain lesions.

In addition, the single imaging session, as compared with 2 separate sessions, is more comfortable for the patients and the caregivers, and it is especially important when additional procedures, such as anesthesia or sedation, are required.

This clearly benefits the patients that need both PET-CT and MR studies in their clinical workup, such as patients with neurological disorders.

Furthermore, this assures also that the patient's conditions are the same for the 2 studies, in particular with respect to disease progression, or with the effect of medications. This is not necessarily the case for a PET and an MR realized separately, which are often some days if not weeks apart.

Another factor that favors MR over CT for hybrid imaging devices is the reduction in radiation exposure, eliminating additional radiation dose to the patient owing to the use of ionizing radiation in CT (ranging between 220 and 450 μSv for a high-quality scan[18]).

The effective dose associated with the FDG and FET activity we administer is 4.75 and 3.3 mSv, respectively, in adults[18,19]; therefore, a high-quality brain CT scan might represent up to 12% of the total dose.

The reduced radiation exposure of PET/MR compared with PET/CT is of special interest in the pediatric population.[20,21]

We might also expect that PET and MR information are not only combined, but that there is an additional value owing to the cointerpretation of the 2 signals: encouraging multidisciplinary interpretation of the results is, in our experience, an added value to fully diagnostic hybrid imaging. In addition, the integration of MR parameters, such as regional perfusion, into the analysis of PET parameters, such as SUV and distribution volumes, may provide additional information.

In particular, concerning degenerative syndromes, we could observe a superior specificity of MR for vascular lesions (as for patient 1) and a superior specificity of PET metabolic patterns for Lewy body dementia and frontotemporal dementia (as found in patients 2, 3, and 4). This is consistent with literature data.[22,23]

For epilepsy, the fusion of morphological and functional information allowed identifying subtle metabolic alterations, which could easily be missed when interpreting the FDG images alone, as depicted in Figure 3: this observation is in line with previous reports

showing the added value of software fusion for PET and MR data for the presurgical investigation of cortical dysplasias.[24,25]

This study also shows some limitations of the hybrid PET/MR modality for brain studies.

First, the long examination duration might involve patient movement and motion artifacts. This aspect might further stimulate the research of fully hybrid solutions with simultaneous imaging. In our study, we observed significant motion in 2 of 15 subjects, which we managed to correct manually to obtain a satisfactory image fusion and attenuation correction. We limited the total examination duration by acquiring diagnostic MR images during the FET uptake phase. Further experience and research will also be needed to identify if certain MR sequences are redundant when the molecular information provided by PET is available.

Second, the quantification issue, with respect to MR-guided attenuation correction, still needs further validation. This might be critical for neuroreceptor studies where absolute quantification is needed, and differences between healthy subjects and patient populations are often subtle. In this respect, ongoing studies, also by our group, are focusing on the validation of MR versus CT-based attenuation correction.[26] For this reason, we focused our clinical practice with this new modality on studies whose interpretation was mostly based on qualitative or semiquantitative PET assessment, rather than quantitative measures.

CONCLUSIONS

The possibility to combine PET with a large variety of MR sequences opens new horizons for bimodal multiparametric imaging of the human brain. Acquiring both PET and MR in a single session on a hybrid tomograph minimized patient discomfort while maximizing clinical information and optimizing registration of both modalities.

Simplification of imaging protocols allowed keeping the total duration of the examination within a tolerable range (<2 hours), with an important impact on MR image quality.

In addition, in comparison to PET/CT, the effective dose (CT related) could be reduced, and this is particularly beneficial in the pediatric population.

REFERENCES

1. Ratib O, Beyer T. Whole-body hybrid PET/MRI: ready for clinical use? *Eur J Nucl Med Mol Imaging*. 2011;38:992–995.
2. Boss A, Stegger L, Bisdas S, et al. Feasibility of simultaneous PET/MR imaging in the head and upper neck area. *Eur Radiol*. 2011;21:1439–1446.
3. Schlemmer HP, Pichler BJ, Schmand M, et al. Simultaneous MR/PET imaging of the human brain: feasibility study. *Radiology*. 2008;248:1028–1035.
4. Beyer T, Pichler B. A decade of combined imaging: from a PET attached to a CT to a PET inside an MR. *Eur J Nucl Med Mol Imaging*. 2009;36(suppl 1): S1–S2.
5. Zaidi H, Del Guerra A. An outlook on future design of hybrid PET/MRI systems. *Med Phys*. 2011;38:5667–5689.
6. Herzog H, Langen KJ, Weirich C, et al. High resolution brain PET combined with simultaneous MRI. *Nuklearmedizin*. 2011;50:74–82.
7. Herzog H, Pietrzyk U, Shah NJ, et al. The current state, challenges and perspectives of MR-PET. *Neuroimage*. 2010;49:2072–2082.
8. Zaidi H, Ojha N, Morich M, et al. Design and performance evaluation of a whole-body Ingenuity TF PET-MRI system. *Phys Med Biol*. 2011;56: 3091–3106.
9. Ratib O, Lord M, Becker M, et al. Clinical applications of hybrid PET-MR. Med Nucl. 2012. Epub ahead of print.
10. Wissmeyer M, Heinzer S, Majno P, et al. Time-of-flight PET/MR on a hybrid scanner following liver radioembolisation (SIRT). *Eur J Nucl Med Mol Imaging*. 2011;38:1744–1745.
11. Lord M, Ratib O, Vallee JP. (18)F-fluorocholine integrated PET/MRI for the initial staging of prostate cancer. *Eur J Nucl Med Mol Imaging*. 2011;38:2288.
12. Garibotto V, Vargas MI, Lovblad KO, et al. A PET-MRI case of corticocerebellar diaschisis after stroke. *Clin Nucl Med*. 2011;36:821–825.
13. Vargas MI, Garibotto V, Viallon M, et al. Peripheral nerves, tumors and hybrid PET-MRI. *Clin Nucl Med*. In press.
14. Lassmann M. The new EANM paediatric dosage card. *Eur J Nucl Med Mol Imaging*. 2008;35:1748.
15. Slates RB, Farahani K, Shao Y, et al. A study of artefacts in simultaneous PET and MR imaging using a prototype MR compatible PET scanner. *Phys Med Biol*. 1999;44:2015–2027.
16. Judenhofer MS, Wehrl HF, Newport DF, et al. Simultaneous PET-MRI: a new approach for functional and morphological imaging. *Nat Med*. 2008;14: 459–465.
17. Catana C, Wu Y, Judenhofer MS, et al. Simultaneous acquisition of multislice PET and MR images: initial results with a MR-compatible PET scanner. *J Nucl Med*. 2006;47:1968–1976.
18. Varrone A, Asenbaum S, Vander Borght T, et al. EANM procedure guidelines for PET brain imaging using [^{18}F]FDG, version 2. *Eur J Nucl Med Mol Imaging*. 2009;36:2103–2110.
19. Vander Borght T, Asenbaum S, Bartenstein P, et al. EANM procedure guidelines for brain tumour imaging using labelled amino acid analogues. *Eur J Nucl Med Mol Imaging*. 2006;33:1374–1380.
20. Kleis M, Daldrup-Link H, Matthay K, et al. Diagnostic value of PET/CT for the staging and restaging of pediatric tumors. *Eur J Nucl Med Mol Imaging*. 2009;36:23–36.
21. Punwani S, Taylor SA, Bainbridge A, et al. Pediatric and adolescent lymphoma: comparison of whole-body STIR half-Fourier RARE MR imaging with an enhanced PET/CT reference for initial staging. *Radiology*. 2010;255:182–190.
22. Dukart J, Mueller K, Horstmann A, et al. Combined evaluation of FDG-PET and MRI improves detection and differentiation of dementia. *PLoS ONE*. 2011;6:e18111.
23. Kantarci K, Lowe VJ, Boeve BF, et al. Multimodality imaging characteristics of dementia with Lewy bodies. *Neurobiol Aging*. 2012;33:2091–2105.
24. Salamon N, Kung J, Shaw SJ, et al. FDG-PET/MRI coregistration improves detection of cortical dysplasia in patients with epilepsy. *Neurology*. 2008;71: 1594–1601.
25. Madan N, Grant PE. New directions in clinical imaging of cortical dysplasias. *Epilepsia*. 2009;50(suppl 9):9–18.
26. Catana C, van der Kouwe A, Benner T, et al. Toward implementing an MRI-based PET attenuation-correction method for neurologic studies on the MR-PET brain prototype. *J Nucl Med*. 2010;51:1431–1438.