Evaluation of $^{18}$F-Fluoride PET/MR and PET/CT

in patients with unclear foot pain

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Short running title: $^{18}$F-Fluoride PET/MR and PET/CT

Word count: 5344
ABSTRACT

To evaluate the quality and diagnostic performance of $^{18}$F-Fluoride positron-emission tomography/magnetic resonance imaging ($^{18}$F-Fluoride PET/MR) compared to $^{18}$F-Fluoride positron-emission tomography/computed tomography ($^{18}$F-Fluoride PET/CT) imaging in patients with unclear foot pain.

Methods: Twenty-two patients (9 men, 13 women; mean age 48±18 years, range: 20–78 years) were prospectively included in this study and underwent a single injection dual imaging protocol with $^{18}$F-Fluoride PET/CT (Siemens Biograph mCT) and PET/MR (Siemens Biograph mMR). PET/MR protocol included at least T1w SE and PD fs sequences in two planes each with simultaneous acquisition of PET over 20min. PET/CT included a native isotropic (0.6mm) diagnostic CT (120kV, 90mAs) and a subsequent PET (2min per bed position (BP)). Two blinded readers assessed in consensus randomly both PET datasets for image quality (three-point scale) and for the presence of focal lesions with increased $^{18}$F-Fluoride uptake (maximum of 4 lesions). For each dataset (PET/CT vs. PET/MR) the diagnoses were defined by using both PET and morphological dataset. SUV values from the two devices were compared using linear correlation and Bland-Altman plots. Moreover we estimated the potential for dose reduction for PET/MR compared to PET/CT considering the longer acquisition time of PET/MR analyzing count rate statistics.

Results: Image quality was rated diagnostic for both PET datasets. However, with a mean rating of 3.0/3 for PET/MR and 2.3/3 for PET/CT, image quality was significantly superior for PET/MR (p<0.0001). Sensitivity of the PET datasets in PET/MR and PET/CT were equivalent with the same 42 lesions with focal $^{18}$F-Fluoride uptake. In PET/MR mean SUV$_{\text{mean}}$ was 10.4 [range 2.0-67.7] and mean SUV$_{\text{max}}$ 15.6 [range 2.9-94.1], corresponding mean SUV$_{\text{mean}}$ of PET/CT was 10.2 [range 1.8-55.6] and mean SUV$_{\text{max}}$ 16.3 [range 2.5-117.5], resulting in a high linear correlation...
coefficient (correlation coefficient r=0.96, p<0.0001 for SUV\textsubscript{mean} and for SUV\textsubscript{max}, respectively).

A final consensus reading revealed as most frequent main diagnoses, osteoarthritis, stress fracture and bone marrow edema (BME). Hereby, PET/CT was more precise in visualizing osteoarthritis, while PET/MR was more specific in non-degenerative pathologies due to the higher soft-tissue and bone marrow contrast. The longer acquisition time of MR compared to CT would potentially allow \(^{18}\)F-Fluoride dose reduction using hybrid \(^{18}\)F-Fluoride PET/MR imaging of at least 50% according to the count rate analysis.

**Conclusion:**

In patients with unclear foot pain \(^{18}\)F-Fluoride PET/MR is technical feasible and robust in terms of image quality and SUV quantification compared to \(^{18}\)F-Fluoride PET/CT. In a majority of patients \(^{18}\)F-Fluoride PET/MR provided more diagnostic information at a higher diagnostic certainty as compared to PET/CT. Thus PET/MR combines the high sensitivity of \(^{18}\)F-Fluoride PET to pinpoint areas with the dominant disease activity and the specificity of MRI for the final diagnosis with the potential for a substantial dose reduction compared to PET/CT.

**Keywords:** foot pain, PET/MR, \(^{18}\)F-Fluoride
INTRODUCTION

Foot pain is a common problem in daily routine of orthopaedic surgeons. It can be a clinical symptom of many different entities such as stress reactions or fractures, systemic disorders, foot deformation and osteoarthritis, osteochondral lesions, interdigital neuroma, synovitis, impingement, tendinopathy and tenosynovitis, or metatarsophalangeal joint instability. Incidence and prevalence of metatarsalgia and foot pain vary depending upon the causative condition. Multiple imaging modalities are available to evaluate foot pain including radiography, computed tomography (CT), magnetic resonance imaging (MRI), bone scintigraphy, and ultrasound. Radiography of the foot may reveal fractures, foot deformation, or arthritis whereas bone scans are helpful with an earlier diagnosing of stress fractures as well as some types of infections and tumors. MR imaging has shown to be useful and superior to CT in the assessment of soft tissue pathologies and abnormalities of bone marrow.

Another option to evaluate areas of bone remodelling is $^{18}$F-Fluoride PET imaging which mainly depicts osteoblastic activity. Several PET-only studies have shown that it is not possible to differentiate benign from malignant lesions based on the intensity of $^{18}$F-fluoride uptake and that diagnostic accuracy can be significantly improved by additional morphological CT and/or MR imaging (1-3). A recent study of Fischer et al. revealed that $^{18}$F-Fluoride PET/CT has a substantial therapeutic impact on management in patients with unclear foot pain (4). However, it is well known that for most musculoskeletal pathologies, MRI is superior to CT due to its increased soft tissue contrast and the possibility to image bone marrow edema (BME). In combination with the excellent lesion-to-background ratio of $^{18}$F-Fluoride PET, $^{18}$F-Fluoride PET/MR has the potential to further enhance the accuracy in the diagnosis of chronic foot pain. Thus, the purpose of our study was to compare the performance of $^{18}$F-Fluoride PET/MR to $^{18}$F-Fluoride PET/CT in 2 aspects: First, to evaluate the quality and performance of $^{18}$F-Fluoride PET
using PET/MR vs. PET/CT and second, to analyse the diagnostic performance of combined $^{18}$F-
Fluoride PET/MR vs. PET/CT in patients with unclear foot pain.

**MATERIAL AND METHODS**

**Patient Population**

Twenty-two patients (9 men, 13 women; mean age 48 ±18 years, range, 20–78 years) with
unclear foot pain were prospectively enrolled in this study between February 2012 and August 2013, routinely referred to our institute for clinical $^{18}$F-Fluoride PET/CT imaging. For these patients the specific diagnosis for this condition had remained inconclusive after clinical examination and radiography. The study was approved by the local institutional review board. Written informed consent was obtained from all patients. The inclusion criteria were: Informed consent and the ability to undergo a PET/MR following the PET/CT examination. Exclusion criteria were: Pregnancy, age under 18 years, and contraindications for MR imaging. All subjects underwent a single-injection/ dual-imaging protocol. After completion of the PET/CT scan patients were subsequently positioned on the PET/MRT scanner with the smallest possible temporal delay to utilize the remaining activity of the initial $^{18}$F-Fluoride injection. $^{18}$F-Fluoride was produced by proton irradiation of $^{18}$O-enriched water in a cyclotron (5).

**$^{18}$F-Fluoride PET/CT And PET/MR Imaging**

Scanning was started approximately 75±18 min after the i.v. injection of a dose of 133±68 MBq of $^{18}$F-Fluoride and performed on a clinical PET/CT system (Siemens Biograph mCT scanner, Siemens Healthcare). This scanner has an axial FOV of 21.8cm and a ring diameter of 84.2cm. The transverse spatial resolution of its PET detector assembly was measured to be 4.4mm near the center of the FOV, whereas the sensitivity in the center was found to be 9.7kcps/MBq (6). The patients were examined in a supine position. PET/CT included a native CT (field of view
(FOV) 780mm, tube voltage 80kV, tube current 165mAs, care dose 4D, rotation time 0.5s; collimation 0.6mm) and a subsequent PET (2min per bed position (BP)). Attenuation maps were obtained by bilinear transformation and were used for attenuation correction as previously described (7). The acquired images were post-processed on the Siemens Biograph mCT scanner providing multiplanar reformatted images for PET alone, CT alone (axial, coronal and sagittal reformation with slice thickness 2mm and axial reconstruction with slice thickness 0.6mm) and fused PET/CT.

All PET/MR examinations were performed using an integrated whole-body hybrid PET/MR system (Biograph mMR; Siemens Healthcare). Compared to the Biograph mCT, PET/MR has a larger axial FOV of 25.8cm and a smaller ring diameter of 65.6cm. The spatial resolution of 4.3mm is similar, but its sensitivity approximately 50% higher at 15.0kcps/MBq (8-10). PET data acquired on the Biograph mCT was reconstructed without using time-of-flight information to better match the reconstruction parameters of the Biograph mMR, which is not equipped with such a capability. On average, the PET/MR scan was started 107±26 min p.i.. Patients were positioned in the MR scanner as similar as possible to the PET/CT examination. Since the mean acquisition time in PET/MR was longer than in PET/CT, the patient was immobilized using cushions in various sizes around the coil to reduce motion artefacts during scan time. The combined PET/MR protocol was as follows: First, a coronal 2-point Dixon 3D volumetric interpolated examination (VIBE) T1 weighted (T1w) MR sequence was acquired, which was used for the generation of attenuation-maps as recently published (11). Together with the start of this Dixon MR sequence, the PET-acquisition (20 min) started simultaneously in the same BP, thus ensuring optimal temporal and regional correspondence between MRI and PET data.
Additionally, a dedicated MR protocol of the foot was defined depending on the localization of the maximum pain with the following parameters: slice thickness 3mm, field of view (FoV) 120-225 mm, matrix: 320x256-384x384. The protocol consisted of at least one intermediate-weighted fat-saturated (PDfs) sequence in 2 planes and one T1- and T2- weighted turbo spin echo (TSE) sequence. If clinically relevant, additional contrast-enhanced sequences were performed: T1-weighted TSE sequence before and after application of Gadolinium (Gd) in the best suitable plane and T1-weighted TSE fs sequence with Gd in a second plane.

**Data Processing And Image Analysis**

PET data obtained on the PET/CT and PET/MR scanners were processed with comparable reconstruction and correction algorithms. For both modalities, emission data were corrected for randoms, dead time, scatter, and attenuation. A 3-dimensional attenuation-weighted ordered-subsets expectation maximization iterative reconstruction algorithm (OSEM 3D) was applied with 3 iterations and 21 subsets, gaussian smoothing of 4mm in full width at half maximum, and a zoom of 1.

For image analysis all datasets were transferred to a dedicated postprocessing workstation (Syngo MMWP, Siemens Medical Solutions). PET/CT and PET/MR were analysed in consensus by a dual board certified radiologist and nuclear physician with several years of experience in PET/CT and PET/MR reading and a board certified radiologist with special training in musculoskeletal radiology. The readers were aware of the patients’ history, results of prior radiography and clinical examination. PET/MR and PET/CT were evaluated separately with at least 8 weeks difference.

**Visual Rating**
$^{18}$F-Fluoride PET data from both CT and MRI were rated for every patient with regard to overall image quality: 0–non diagnostic image quality, 1-low image quality (distinct artifacts, strong image noise), 2-good image quality (little artifacts, moderate image noise), 3-excellent image quality (no artifacts, low image noise).

**Lesion Identification And Classification**

Both PET datasets were evaluated for the presence of focal lesions with increased $^{18}$F-Fluoride uptake compared to normal bone. Data of CT and MR imaging were used for exact anatomic correlation with Fluoride uptake and were analysed for additional PET negative important morphological findings. After describing both findings in PET and morphological imaging one main diagnosis and up to two secondary diagnoses were determined for each PET/MR and PET/CT dataset. Depending on the readers’ certainty they were either judged as diagnostic (category 1) or suspicious (category 2).

The following criteria were used to define the most frequently observed pathologies:

- **osteoarthritis:** presence of osteophytes, joint space narrowing, subchondral cysts, subchondral sclerosis, or a combination of them on both sides of the articular joint in PET/CT with the $^{18}$F-Fluoride being centered along the joint space; additional finding in PET/MR:
  - BME, which was defined as an ill-defined area of increased signal intensity on intermediate-weighted images with fat suppression and corresponding hypointensity on T1w images not below the intensity of skeletal muscle.

- **stress reaction:** BME and absence of a fracture line; $^{18}$F-Fluoride uptake and if adjacent to a joint the absence of osteoarthritis on PET/CT

- **stress fracture:** BME with the presence of a fracture line on a T1-weighted MR image or a dense sclerotic line on CT; $^{18}$F-Fluoride uptake
Finally, a consensus reading was carried out based on all available data trying to define the modality (PET/CT vs. PET/MR) that provided the most specific and precise diagnosis.

**Quantitative Assessment**

For quantitative comparison between the PET data acquired in PET/CT and in PET/MR, a SUV-based analysis of mean and maximum tracer uptake in up to 4 focal lesions and in three representative, not pathological osseous structures (calcaneus, distal tibia and calcaneus) was performed. Volumes of interest (VOIs) were placed over matching corresponding Fluoride positive lesions. To calculate SUVs, the axial slice with the maximum SUV of the lesion was first located automatically, using standardized software for images of both scanners. An isocontour VOI including all voxels above 50% of the maximum was then created to calculate SUV\text{mean}. Within all VOI’s, mean and maximum standardized uptake values were measured.

**Count Rate Analysis On PET/CT and PET/MR With Regard To Scan Duration**

As image quality of PET/MR was suspected to be superior to that of PET/CT due to the longer acquisition time in PET/MR (20min compared to 2min in PET/CT), the theoretical $^{18}$F-Fluoride dose reduction in PET/MR was calculated that would yield equal numbers of detected true coincidences on both scanners. For this purpose, count rate statistics were analyzed for all 7 patient data sets, the PET raw data of which had been acquired in listmode format, by determining the number of trues in the first 120s of the PET/CT and PET/MR examinations as well as of the entire 1200s of the PET/MR scan. The obtained information was then corrected for decay to the start of the PET/CT scan. Since for one patient the PET/MR scan duration was only 600s, the number of trues in this case was extrapolated to an acquisition time of 1200s.

**Statistical Analysis**
Statistical analysis was performed using the MedCalc 12.3.0.0 software package for Windows. $P$ values of less than 0.05 were considered statistically significant. First, descriptive statistical evaluation was performed. Then, differences in image quality as well as $SUV_{\text{mean}}/SUV_{\text{max}}$ of focal foot lesions/normal bone between PET/MR and PET/CT were compared by using the Spearman rank correlation coefficient. The overall statistical differences in measured SUVs were tested using the nonparametric Wilcoxon matched-pairs signed rank test. Because a high degree of correlation does not necessarily imply good agreement between the 2 measurements, a Bland–Altman plot was constructed to assess this agreement (12). A Bland–Altman plot displays the difference between the 2 measurements versus their average as a scatterplot, on which each point represents 1 measurement.

RESULTS

Visual Rating

The results of overall image quality showed that PET/MR was superior to PET/CT with an overall excellent image quality score of 3.0/3 points in all PET/MR datasets while PET/CT achieved 2.3 out of 3 possible points (2/3 points in 15/22 patients and 3/3 points in 7/22 patients). Image quality of PET/MR was significantly superior to PET/CT ($p<0.0001$).

Quantitative Analysis

Both $SUV_{\text{mean}}$ and $SUV_{\text{max}}$ of PET/CT and PET/MR showed a highly statistical significant linear correlation ($R=0.96$; $p<0.0001$ for both $SUV_{\text{mean}}$ and $SUV_{\text{max}}$) for pathological foot lesions. Mean $SUV_{\text{mean}}$ and $SUV_{\text{max}}$ including standard deviation (SD) and range for pathological lesions and regions of normal bone in PET/MR and PET/CT are presented in table 1 including $p$-value, correlation coefficient ($R$) and 95% confidence interval (CI) for the correlation betweeen
PET/MR and PET/CT. Correlation analysis and Bland-Altman Plot for $SUV_{\text{mean}}$ and $SUV_{\text{max}}$ can be found in figure 1 and figure 1S, respectively.

**Findings And Diagnoses In PET/MR And PET/CT**

In total, the same 42 lesions with intense, focal $^{18}$F-Fluoride uptake were identified both in PET datasets of PET/MR and PET of PET/CT showing an equivalent sensitivity. A detailed presentation of patient characteristics including symptoms, findings and diagnoses in PET/MR and PET/CT is shown in table 1S. Note that one patient did not show any abnormal findings.

**Most Frequent Diagnoses** The three most frequent diagnoses were osteoarthritis, stress fracture and BME representing a stress reaction of bone. Osteoarthritis of one or several articular joints was diagnosed in 9 out of 22 patients. Note that in patients with osteoarthritis but no other concomitant findings PET/CT was favoured as modality of choice by the reading team. This was related to the higher image resolution and thus better depiction of anatomical findings including some additional minor findings like calcaneal spurs in CT. Nevertheless the certainty of diagnosing osteoarthritis as the main final pathology was rated as diagnostic (category 1) in both PET/CT and PET/MR.

Stress fractures were present in 4 out of 22 patients. Hereby, PET/MR was rated as modality of choice in all but one case. However, in one patient the depiction of PET/CT as most conclusive modality was only related to an additional sesamoid fracture whose displacement could be better visualized in CT. Otherwise the reviewer regarded PET/MR more conclusive for stress fractures due to the earlier depiction of the typical T1w hypointense line compared to a sclerotic line in CT providing a higher diagnostic confidence.
Six out of 22 patients showed stress reactions. Due to the visualization of BME, stress reactions could be classified in all presented cases more precisely in PET/MR, which was chosen as modality of choice by the reading team. In PET/CT this diagnosis could only be assumed indirectly due to the absence of any sclerotic bone changes and signs of osteoarthritis in a region of monofocal $^{18}$F-Fluoride uptake resulting in a lower diagnostic certainty (category 2).

*Modality Of Choice ($^{18}$F-Fluoride PET/MR Vs. $^{18}$F-Fluoride PET/CT)* With regard to the modality of choice PET/MR was rated in 13/22 patients to be more appropriate than PET/CT. Hereby the better specificity of PET/MR was related to its capability to visualize bone marrow or soft tissue pathologies. Besides stress reaction and stress fracture (see above) PET/MR enabled a more precise diagnosis in cases with an aneurysmatic bone cyst, soft tissue edema, tenosynovitis, large ganglion cysts or osteochondral lesions. Here, in 6 out of 22 patients the MR part of $^{18}$F-Fluoride PET/MR revealed 6 complete new findings with no correlate both in $^{18}$F-Fluoride PET and CT. PET/CT was regarded as modality of choice in cases in which the better anatomical depiction of morphological changes in the cortical bone (e.g. osteophytes, subchondral changes, calcaneal spur) was crucial (6 out of 22 patients). In detail, this were the patients with only osteoarthritis and no other pathological findings, a patient with an accessory navicular syndrome and one patient with a fracture of the sesamoid bone.

Figure 2 shows representative images of a patient with a stress fracture at the base of OMT I and figure 3 images of a patient with osteoarthritis and a ganglion originating from the dorsal upper ankle joint, which could only be depicted in MRI. Additional $^{18}$F-Fluoride PET/MR and PET/CT images of a patient with an aneurysmatic bone cyst and a stress reaction resolving on follow-up imaging are shown in figure 2S and 3S.
Assessment Of Potential Dose Reduction

The average number of true coincidences per injected dose detected in the first 120s of a scan was measured to be $(48928\pm31400)$ MBq$^{-1}$ on the PET/CT and on the PET/MR $(63599\pm44329)$ MBq$^{-1}$. The number of trues registered during the entire 1200s of the PET/MR scan was $(600405\pm419410)$ MBq$^{-1}$, i.e. on average 12 times higher than that of the PET/CT scan with a duration of 120s. This means that with equal scan duration approximately 80% of the dose administered for the PET/CT scan would have been required on the PET/MR to yield the same number of true coincidences. For a PET/MR scan duration of 20 minutes, only approximately 10% of the injected activity would have resulted in the same number of acquired trues.

Before conclusions can be drawn from count rate statistics with regard to image quality, effects of additional hardware in the PET/MR field of view have to be evaluated in this clinical setting (13). However, these first results hint at a possible dose reduction of at least 50% on the PET/MR compared to the PET/CT, if the corresponding scan duration is 10 times longer.

DISCUSSION

The results of this study indicate that $^{18}$F-Fluoride PET/MR is equivalent to $^{18}$F-Fluoride PET/CT concerning SUV-quantification and lesion detection in patients with unclear foot pain. Image quality of PET/MR was superior to PET/CT potentially due to longer acquisition time in PET/MR raising the possibility of $^{18}$F-Fluoride dose reduction. However, $^{18}$F-Fluoride PET/MR was more conclusive than PET/CT due to the higher soft tissue contrast and the visualization of bone marrow pathologies on MRI.
Our study indicates that $^{18}$F-Fluoride PET/MR is technically feasible and robust despite difference in attenuation correction which is concordant with other studies comparing $^{18}$F-FDG PET/CT and PET/MR in malignant bone lesions (14, 15). However, in both cited whole-body studies SUVs of bone lesions were substantially lower in PET/MR. In contrast, in our study, mean SUV$_{\text{mean}}$/SUV$_{\text{max}}$ of PET/CT and PET/MR were nearly similar. Two possible explanations could be the different radiotracer ($^{18}$F-Fluoride vs. $^{18}$F-FDG) and examination of a small peripheral part of the body instead of the central skeleton. Hereby, amongst other MR FOV-restrictions can lead to significant quantification error in large compared to small volumes (16). Furthermore, concerning attenuation correction in PET/MR other problems (e.g. treating bone as soft tissue, increased attenuation by cortical bone and calcified areas) are still unresolved. Compared to those potential confounders, our results indicate that for $^{18}$F-Fluoride PET/MR of the feet no relevant influence is present. From a clinical point-of-view this is supported by the fact that in our study the identical lesions were identified in both modalities by the reading team.

$^{18}$F-Fluoride PET/MR would allow substantial reduction in the applied activity due to the potential of longer PET-acquisition in parallel to the acquisition of MR. This would offer a substantial dose reduction of at least 50% in patients with no history of malignant disease and who often are of younger age (see table 1S). However, this has to be validated in further prospective studies.

For diagnostic purposes $^{18}$F-Fluoride PET is a highly sensitive but not very specific tool for the detection of metabolically active benign bone disease with the drawback of a low specificity (5). Thus, additional morphological imaging is recommended either using sequentially CT/MRI or by means of hybrid PET/CT and more recently PET/MR.
The results from our study show that $^{18}$F-Fluoride PET/MR was regarded as the modality of choice in a substantial higher number of cases (13/22) than $^{18}$F-Fluoride PET/CT. A majority of these cases were patients with stress fractures or BME and here the superiority of MR in the depiction of bone marrow pathologies is well known while the bony structures in these cases were still without any detectable changes in CT leading to a less reliable diagnosis in PET/CT (17).

$^{18}$F-Fluoride PET/CT was only superior in cases with osteoarthritis showing no additional findings/complications (4/22) and in cases (2/22) in which the superb image resolution of multi-slice CT was crucial (e.g. assessment of small bony structures). Hereby, the clinical preference of CT due to a more accurate anatomical depiction is related to an overall low signal of dense bony structures on all MR-sequences leading to a less distinct delineation and the usual lower spatial resolution of MR (18, 19). Nevertheless, even in complicated cases with osteoarthritis (5/9) by means of stress reaction in adjacent bone or concomitant soft-tissue pathologies (e.g. ganglion cyst) $^{18}$F-Fluoride PET/MR was regarded as equal or superior compared to $^{18}$F-Fluoride PET/CT.

A potential disadvantage of PET/MR is the use in patients with bilateral complaints as a simultaneous examination of both feet would lead to a tremendous loss in diagnostic quality of a PET/MR-study (use of body vs. dedicated surface coils). Thus, due to the natural history of osteoarthritis in elderly people $^{18}$F-Fluoride PET/CT most likely would fulfil the diagnostic needs in patients >60 years with pain in both feet and without a trauma history when primary osteoarthritis is more likely.

Compared to morphological imaging alone the specific value of hybrid $^{18}$F-Fluoride PET/CT or PET/MR imaging consists in the possibility to (semi)-quantitatively assess tracer uptake. Various reports have described the value of $^{18}$F-Fluoride to help in the therapeutic management to the
right regions due to a direct relation between the intensity of bone metabolism and the complaints
of the patient (4, 5). Especially in patients with multifocal disease the maximum of $^{18}$F-Fluoride
uptake can help the clinician to tailor the therapy to the region of most clinical relevance/highest
disease activity (e.g. the joint which is affected the most by osteoarthritis). A study by Fischer et
al. was showing that $^{18}$F-Fluoride PET in addition to sequentially performed MR offers additional
value information allowing a more specific therapy in 13 of 28 patients (4). Therefore, we
hypothesize that the use of $^{18}$F-Fluoride PET/MR can provide additional therapeutically relevant
information in patients with unclear foot pain. However, this has to be proven in prospective
studies also evaluating the contribution both of MR and $^{18}$F-Fluoride to the final diagnosis and
the therapeutic management in a large patient cohort.

Our study has some limitations. We did not examine the potential influence when performing
PET/CT and PET/MR in random order. However, despite reports for $^{18}$F-FDG PET leading to a
tendency to lower of SUV in benign lesions, such an effect is not known for $^{18}$F-Fluoride (20). In
addition, the rare number of studies comparing lesion-to-background-ratio of $^{18}$F-Fluoride and
skeletal scintigraphy both at an early and a later time-point do not indicate a relevant influence
(21). In addition, we have not specifically evaluated whether $^{18}$F-Fluoride PET/MR or PET/CT
lead to a difference in therapeutic management. However, as in many of our cases the final
diagnosis was the same in PET/MR and PET/CT differing only in the diagnostic certainty we
would not expect a substantial difference.

**CONCLUSION**

Despite different attenuation techniques $^{18}$F-Fluoride PET/MR can be regarded as technical
feasible and robust. In patients with unclear foot pain $^{18}$F-Fluoride PET/MR provided more
diagnostic information at a higher diagnostic certainty as compared to $^{18}$F-Fluoride PET/CT. Besides information on bone metabolism it provides additional diagnostic relevant findings from soft-tissue and bone marrow pathology compared to PET/CT. A further advantage of $^{18}$F-Fluoride PET/MR consists in the potential for additional dose reduction due to the longer acquisition time. Thus, larger prospective studies exploring the use of $^{18}$F-Fluoride PET/MR in patients with unclear foot pain when medical history, clinical, and radiographic examination remain inconclusive are warranted. These should also focus on the impact of this technique on patient management and cost-effectiveness.
References


Figure 1

Correlation analysis of tracer uptake between PET/CT and subsequent PET/MR as assessed by SUV\textsubscript{mean} in focal lesions reveals a high correlation ($R=0.96$) between both modalities (A). The difference between the two SUV measurements is shown by the Bland–Altman (B) on which the difference between 2 SUV measurements is plotted against their average: For SUV\textsubscript{mean} the mean difference is -0.2 SUV (95% CI are +6.0 and -6.4 SUV) indicating a nearly perfect quantitative agreement between SUV from both modalities.
Figure 2

Simultaneously acquired $^{18}$F-Fluoride PET/CT and PET/MR images in a 49-year-old female patient with pain over the left metatarsal foot since several months without history of trauma. Sagittal MR images show bone marrow edema (BME) in fat-saturated (fs) proton-density (PD) weighted images at the base of Os metatarsale I (OMT I) (red arrow A) with the presence of a hypointense fracture line on the T1-weighted image (red arrow B). In the corresponding PET of PET/MR (D), PET/MR (E) and PET/CT (F) an intense focal $^{18}$F-Fluoride uptake at the base of OMT I is shown (red arrow). However, in the area of the PET positive region, the corresponding CT scan shows only a slight sclerotic band (red arrow C).
Figure 3

Sagittal $^{18}$F-Fluoride PET/CT and PET/MR images of a 55-year-old male patient with persistent pain and swelling of the left foot since several years. There are advanced signs of osteoarthritis particularly in the tarsometatarsal joints and in the subtalar joint which can be observed on both MR imaging (sagittal T1 TSE sequence (A), sagittal PD fs sequence (B)) and sagittal CT (C) including joint space narrowing, osteophytes, subchondral cysts and subchondral bone marrow edema (only on MR imaging). Additionally, only MR imaging could detect the T1 hypointense, PD fs hyperintense ganglion cyst originating from the posterior subtalar joint (red arrows). Corresponding PET of PET/MR (D), PET/MR (E) and PET/CT (F) show intense focal $^{18}$F-Fluoride uptake on both sides of the tarsometatarsal and the subtalar joint; however in this case no additional information was provided by PET. Note the slight difference in slice positioning leading to a different impression of $^{18}$F-Fluoride uptake.
Table 1

Summary of mean SUVmean/SUVmax including standard deviation (SD) and range for pathological lesions and regions of normal bone in PET/MR and PET/CT including correlation coefficient (R) and 95% confidence interval (CI) for the correlation between PET/MR and PET/CT. * indicates a significant difference (p-value <0.0001)

<table>
<thead>
<tr>
<th></th>
<th>Mean SUV&lt;sub&gt;mean&lt;/sub&gt; ± SD [range]</th>
<th>R (95% CI)</th>
<th>Mean SUV&lt;sub&gt;max&lt;/sub&gt; ± SD [range]</th>
<th>R (95% CI)</th>
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<tbody>
<tr>
<td>Pathological lesions in PET/MR</td>
<td>10.4 ± 11.3 [2.0 - 67.7]</td>
<td>0.96 (0.93 - 0.98)*</td>
<td>15.6 ± 16.9 [2.9 - 94.1]</td>
<td>0.96 (0.93 - 0.98)*</td>
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<tr>
<td>Pathological lesions in PET/CT</td>
<td>10.2 ± 9.9 [1.8 - 55.6]</td>
<td></td>
<td>16.3 ± 19.2 [2.5 - 117.5]</td>
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<tr>
<td>Regions of normal bone in PET/MR</td>
<td>0.67 ± 0.36 [0.12 – 1.76]</td>
<td>0.75 (0.59 – 0.85)*</td>
<td>1.00 ± 0.62 [0.20 – 2.84]</td>
<td>0.84 (0.73 – 0.91)*</td>
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<td>Regions of normal bone in PET/CT</td>
<td>0.89 ± 0.53 [0.12 – 2.55]</td>
<td></td>
<td>1.17 ± 0.71 [0.21 – 2.76]</td>
<td></td>
</tr>
</tbody>
</table>
Evaluation of $^{18}$F-Fluoride PET/MR and PET/CT in patients with unclear foot pain

Isabel Rauscher, Ambros Beer, Christoph Schaeffeler, Michael Souvatzoglou, Moritz Crönlein, Chlodwig Kirchhoff, Gunther Sandmann, Sebastian Fürst, Robert Kilger, Michael Herz, Sybille Ziegler, Markus Schwaiger and Matthias Eiber

J Nucl Med.
Published online: February 12, 2015.
Doi: 10.2967/jnumed.114.150532

This article and updated information are available at:
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