Comparison of Positron Emission Tomography Diffusion-Weighted Imaging (PET/DWI) Registration Quality in a PET/MR Scanner: Zoomed DWI vs. Conventional DWI

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Title: Comparison of PET/DWI registration quality in PET/MR scanner: zoomed DWI vs. conventional DWI

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Running title: Zoomed DWI in PET/MR hybrid scans

Abstract

Purpose

To compare zoomed diffusion-weighted imaging (z-DWI) with reduced field of view (FOV) by spatially selective radiofrequency pulses and conventional EPI DWI (c-DWI) with regard to registration quality using PET/MR, in patients with malignant tumors.

Materials and Methods

Fludeoxyglucose (18[F]) PET imaging, c-DWI, and z-DWI were conducted simultaneously in 21 patients with known or suspected malignancy using a PET/MR system. A fusion image showing the largest tumor area was generated for analysis. Registration accuracy between PET and DWI was assessed based on the area of maximum overlap and central point displacement of the tumor. EPI factor, echo time (TE), matching area and displacement were compared between c-DWI and z-DWI by paired t-test. Agreement of apparent diffusion coefficient (ADC) acquired by the two sequences were also assessed with linear regression s and Bland–Altman plot analysis.

Results

Thirty-two lesions were detected on both PET and DWI (mean size 536.3±471.8 mm^2). At least one lesion was found in all subjects. In all cases, EPI factor

was smaller with z-DWI than c-DWI (43.1±15.6 vs. 62.0±10.0, P<0.0001), and TE was also shorter for z-DWI (53.6±3.6 ms vs. 65.2±3.6 ms, P<0.0001). Registration accuracy was better with z-DWI in 30 of 32 lesions (93.8%), and both average matching area and central point displacement were significantly improved (79.8±18.1% vs. 61.8±22.9%, P<0.0001 and 3.92±2.69 mm vs. 7.51±4.07 mm, P<0.0001). ADC values calculated with c-DWI and z-DWI showed good agreement.

Conclusion

Zoomed DWI reduces image distortion and provides better registration accuracy with PET images.

Keywords: PET/MR, image fusion, zoomed-EPI DWI, spatially selective RF pulse

INTRODUCTION

Positron emission tomography/magnetic resonance (PET/MR) systems combine

PET using fludeoxyglucose (^{18}F), or ^{18}FDG-PET, and diffusion-weighted imaging (DWI).

PET using fludeoxyglucose (^{18}F), a marker of glucose metabolism, is widely used to

detect, localize, and characterize tumors and to evaluate the effects of tumor treatment (1–

3). While its sensitivity and specificity for malignancy are high, false positives may be

observed with inflammation, and false negatives may be observed with some kinds of

malignant tumors (2,4). Diffusion-weighted imaging (DWI) is one of the most

representative methods of MR imaging and can be used to determine the apparent

diffusion coefficient (ADC), which reflects the motion of water molecules and the density

of cells in tissue. DWI in combination with ADC is now widely accepted for detecting

lesions, assessing malignancy, and evaluating treatment effect (5–8). Comprehensive

imaging using FDG-PET and DWI can help assess the internal structure of a malignant

tumor, and PET/MR systems with image fusion allow simultaneous and comparative

assessment of images taken using both methods, facilitating tumor diagnosis and

management (9). Indeed, this precise image coregistration enables detailed

voxel-by-voxel comparison. However, a single-shot echo planar imaging (EPI) sequence

may result in severe DWI distortion, degrading the fused image (5,10). Such a sequence

acquires all echoes in one excitation, and the long echo train length makes the sequence quite vulnerable to B0 (static magnetic field) inhomogeneity, which tends to be especially prominent in locations such as the head and neck, lungs, and extremities. Although many registration programs have been developed (11,12), precise registration between distorted DWIs is quite difficult, as such distortions are not rigid but nonlinear.

The recent development of parallel radiofrequency (RF) transmitters has enabled independent transmission of RF power over multiple channels, which allows the use of spatially selective RF pulses to excite only those protons inside the field of view (FOV), as well as permitting the FOV to be narrowed along the phase-encoding direction without the risk of aliasing artifacts (13–15). With this technique, called zoomed DWI, DWI distortion can be minimized with no influences from adjacent tissue along the phase-encoding direction (16–18).

The aim of this study was to compare zoomed DWI (z-DWI) with conventional DWI (c-DWI) with regard to registration quality of images produced by a PET/MR scanner in patients with malignant tumors.

MATERIALS AND METHODS

Participants

This study was approved by the hospital's institutional review board. Twenty-one patients with a known or suspected malignancy (mean age 62.2 ± 16.3, 13 men and 8 women) were prospectively enrolled in this study. The primary lesions were as follows: five soft tissue sarcomas, four head-and-neck cancers, four GI tract cancers, four pancreatic cancers, three lung cancers, and one mesothelioma. Written informed consent was obtained from all patients.

Image acquisition

All imaging was performed with the Ingenuity TF PET/MR system (Philips Healthcare, Cleveland, OH, USA). PET/MR imaging was started 2 h after administration of 4 MBq/kg of ^{18}FDG. After the scout image was taken and 3-dimensional T1-weighted image was acquired to correct attenuation, participants underwent PET imaging with 3-dimensional ordered subset expectation maximization (3D-OSEM) and time of flight (TOF). The sampling time was 2–5 min per station, and images were reconstructed with 2^3-mm voxels. After PET imaging, a series of diagnostic MR images were obtained. c-DWI was always acquired first, followed by

z-DWI. The FOV for c-DWI was set to cover the entire body along the phase-encoding direction with enough margin to avoid aliasing; the FOV for z-DWI was then set to cover the organ in which the lesion was located. Other parameters were identical between the two sequences (in-plane resolution, 1.2 to 2.0 mm, depending on the lesion; slice thickness, 5 or 7 mm; sensitivity encoding (SENSE) factor, 2.5; number of averages, 3 to 6; b value, 0 or 800 s/mm^2). Echo time (TE) was set to the shortest. All images were acquired under free breathing. Acquisition time of each sequence was from 2 min and 21 s to 4 min and 34 s depending on number of slices and averages.

Image evaluation

All imaging analysis was performed on an Intellispace Portal 6.0 workstation (Philips Healthcare). No image registration function was used in this study. Lesions appearing on both PET and DWI that were 50 mm^2 or larger in size were examined, with the single slice showing the largest area of each tumor being selected for analysis. The image analysis was performed by consensus of two board-certified radiologists (K.S. and Y.W., with 10 and 25 years of experience in radiology, respectively). For PET imaging, regions of interest (ROIs) for metabolic tumor volume included areas with standardized uptake values (SUVs) more than 40% of tumor SUV_{max}. On c-DWI and

z-DWI (b = 800 s/mm^2), ROIs were manually drawn (by K.S. or Y.W.) along the borders

of tumor areas with high signal intensity. The ROIs for both types of image were then

copied onto the fusion image, and semi-quantitative assessment of registration accuracy

was performed for the area of maximum overlap, using the following matching index:

[matching area (%) = overlapping area of PET and DWI/PET-positive areas] (Fig. 1). In

addition, displacement of the central point of the tumor between PET and DWI was

measured. The central point was manually determined by the readers as the point of

intersection of major and minor axes, which was equally distant from the tumor margin.

These measurements were repeated again to assess intra-observer agreement, and the

first measurement was used for further analysis. ADC maps were also generated from

c-DWI and z-DWI, and the same ROIs were mapped onto the lesions to quantify ADC

value for each sequence.

Statistical Analysis

EPI factor, TE, matching area, and central point displacement in all patients were

compared between c-DWI and z-DWI by using the paired *t*-test. Matching area and

central point displacement in patients with chest tumors was also compared between

c-DWI and z-DWI, and the same was done for patients with non-chest tumors.

Intra-observer agreement of matching area and central point displacement was evaluated

by intraclass correlation coefficient (ICC). Linear regression analysis was used to

determine the correlation of the matching area and the central point displacement with

tumor size for each sequence. We used linear regression and Bland–Altman plot analysis

to compare ADC values between c-DWI and z-DWI. In all statistical analyses, a P value

<0.05 was considered significant.

RESULTS

Thirty-two lesions of 50 mm^2 or larger were included in this study. There were

12 in the chest (6 lung, 3 chest wall, 3 mediastinum) and 20 outside the chest cavity,

including 4 in the head and neck (1 skull base, 3 cervical lymph nodes), 10 in the

abdomen (3 liver, 4 pancreas, 1 ileum, 1 rectum, 1 paraaortic lymph node), and 6 in the

musculoskeletal system (4 thigh, 2 foot). The mean size of the lesions was 536.3 ±

471.8 mm^2. In all cases, EPI factor was smaller for z-DWI than c-DWI (43.1 ± 15.6 vs.

62.0 ± 10.0, P < 0.0001). Effective TE was also shorter by 8 ms on average for z-DWI

than for c-DWI (53.6 ± 3.6 ms vs. 65.2 ± 3.6 ms, P < 0.0001).

Figure 1 shows a representative case; the patient had metastatic liver tumors. In

this case, distortion on the c-DWI image caused misregistration with the PET image.

The distortion was reduced on the z-DWI image in which the anterior abdominal wall and back muscles were excluded from the FOV, and registration accuracy was remarkably improved for both the small tumor and the large.

The ICCs for matching area and central point displacement were 0.984 and 0.999, respectively, and considered as excellent intra-observer agreement. Matching area and central point displacement was better with z-DWI than c-DWI in 30 of 32 lesions (93.8%), and average matching area was significantly higher with z-DWI (79.8 ± 18.1%) than c-DWI (61.8 ± 22.9%) (P value <0.0001) (Fig. 2A). Average central point displacement was also significantly smaller with z-DWI than c-DWI (3.92 ± 2.69 mm vs. 7.51 ± 4.07 mm, $P < 0.0001$) (Fig. 2B). The two lesions in which registration accuracy was worse with z-DWI were a cervical lymph node metastasis from thyroid cancer (72.5% vs. 79.2% and 6.32 mm vs. 5.72 mm) and a primary tumor in the left upper lobe of the lung (28.8% vs. 85.6% and 15.42 mm vs. 1.76 mm). When only chest tumors were considered, matching area or central point displacement did not improve with z-DWI (57.7 ± 21.6% vs. 71.6 ± 22.6%, $P = 0.08$ and 6.64 ± 4.34 mm vs. 4.32 ± 3.36 mm, $P = 0.13$, Fig. 3A and B). On the other hand, for non-chest tumors, registration accuracy was significantly better with z-DWI (64.2 ± 23.8 vs. 84.8 ± 13.0, $P < 0.001$ and 8.03 ± 3.92 mm vs. 3.68 ± 2.29 mm, $P < 0.0001$, Fig. 3C and D).

Figure 4A shows the correlation between the tumor size and matching area. For c-DWI, there was a weak positive correlation ($R^2 = 0.20$, P < 0.01); for z-DWI, the correlation was not significant ($R^2 = 0.11$, P = 0.06), and the matching area was constant regardless of tumor size. Displacement of the central point did not show any correlation with the tumor size either in c-DWI ($R^2 = 0.003$, P = 0.75) or z-DWI ($R^2 = 0.003$, P = 0.78) (Fig. 4B). Even for small tumors, z-DWI showed better coregistration with PET images than c-DWI.

ADC values obtained with c-DWI and z-DWI were nearly identical and showed a strong linear correlation (coefficient = 0.94, $R^2 = 0.95$, P < 0.0001). Figure 5 shows the Bland–Altman plot of ADC values obtained with c-DWI and z-DWI. The bias was small (-0.044 $\times$ 10^{-3} mm^2/s) and no systemic bias was observed. The 95% limits of agreement ranged from -0.36 to 0.27 $\times$ 10^{-3} mm^2/s, and all lesions except one (a lung metastasis) were within the limit.

DISCUSSION

In the present study, we found that zoomed DWI, a single-shot EPI sequence with spatially selective RF excitation for PET/MR systems, showed better registration quality with FDG-PET images than conventional DWI. The z-DWI sequence allowed

narrowing of the FOV along phase-encoding direction without any aliasing artifacts and shortening of the echo train length (EPI factor) while keeping in-plane resolution consistent with c-DWI. EPI factor was smaller for z-DWI than for c-DWI by approximately 30%, and the echo time was also shortened for z-DWI, potentially contributing to reduction in susceptibility and motion artifacts. Consistently with previous studies (16–18), our results suggested that z-DWI can provide high-resolution images with less distortion than c-DWI.

Registration accuracy of FDG-PET with DWI was better with z-DWI than c-DWI in all cases except two, apparently because z-DWI produced less image distortion. Other factors that might have affected registration quality included body movement and respiratory motion during the examination. The PET/MR system used in this study was a sequential type (19), and after PET image acquisition, the z-DWI scan was always performed immediately after the c-DWI to minimize potential differences resulting from body movement; if the patient moved during z-DWI acquisition, this might result in inferior images. However, z-DWI showed better registration quality with PET images than c-DWI. Both PET and DWI were performed under free breathing, and image blurring might result, especially in regions such as the chest and upper abdomen, although we instructed the patients to breathe in a regular manner.

Another factor that might have affected registration accuracy was lesion size. Matching areas for small lesions could have been underestimated in comparison with large lesions. Although very small lesions (less than 50 mm^2) were excluded from the study, a wide range of tumor sizes, from a 65-mm^2 lymph node tumor to a 1696-mm^2 soft tissue sarcoma, were included. For c-DWI, the matching area proved to be dependent on tumor size, while for z-DWI, it was shown to be constant regardless of tumor size. For z-DWI, area matching the PET image could be as high as 79.8%. On the other hand, central point displacement was independent of tumor size, while determination of the center point could be affected by distortion of tumor shape as well as shift.

Although no image registration function software was used in the present study, some misregistrations of PET and DWI images could not be completely corrected, either manually or using software; these may have been due to distortions of the tumor shape itself. In this regard, z-DWI could still be expected to show more accurate tumor registration than c-DWI, because these tumor shape distortions occurred in a similar manner to the distortions seen in c-DWIs.

This study also showed that the ADC values obtained with z-DWI seemed to be almost identical to those obtained with c-DWI, regardless of the tumors' locations.

Theoretically, reduced phase-encoding steps in z-DWI are expected to decrease the image signal-to-noise ratio (SNR), whereas the shorter TE in z-DWI might still work as the SNR increases. Regardless of these factors influencing the SNR of DWI, ADC measurements did not differ between Z-DWI and c-DWI, which means that the ADC values obtained with z-DWI are comparable to that obtained with c-DWI.

However, there are some limitations and tradeoffs of z-DWI sequence. The shorter TE reduces T2 contrast, which may make it harder to distinguish between lesions and background tissue. Moreover, the coverage area is so small that the structures outside the reduced FOV cannot be used as standard references for the signal intensities of the lesions, and lesions outside the FOV may be missed entirely. For these reasons, we consider z-DWI best used for targeted analysis of lesions detected using PET or other MR methods.

This study has some limitations. First, the acquisition parameters for DWI and PET needed to be modified among the patients owing to the different locations and sizes of the tumors. However, it should not majorly influence the results, because both c-DWI and z-DWI had been modified similarly and statistically compared (paired *t*-test). Second, the sample size is relatively small for further analysis. The influence of tumor location or respiratory motion on registration accuracy should be evaluated in future

work. Instead of performing inter-observer agreement, we carried out measurements by

consensus of two radiologists, and the intra-observer agreement was excellent; the

results proved reliability of our semi-quantitative measurements.

In conclusion, when PET/MR systems are used to examine tumors, z-DWI

provides better registration accuracy than c-DWI with less image distortion and

theoretically more precise ADC measurement, which might enable direct comparison of

ADC and FDG uptake in the tumor.

ACKNOWLEDGEMENT

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FIGURE LEGENDS

Figure 1. FDG-PET and DWI registration in a patient with metastatic liver tumors.

(A) A large tumor in the left lobe and a small tumor in the right lobe are shown (arrowhead) as round, hyperintense lesions on T2WI. (B) Increased FDG uptake is observable in both tumors on the PET image. (C,D) With c-DWI, image distortion caused misregistration with the PET image (C); with z-DWI, the result was better (D). (E,F) ROIs were mapped onto the metastatic lesion in the left lobe to quantify the matching area between PET and DWI, and c-DWI € showed worse registration with the PET image than z-DWI (F).

Figure 2. Comparison of matching area (A) and central point displacement (B) between c-DWI and z-DWI. Registration was better with z-DWI in 30 of 32 lesions, and the mean matching area and central point displacement improved significantly with z-DWI. ***P < 0.0001 by paired *t*-test.

Figure 3. Matching areas and central point displacements for chest tumors (A, B) and non-chest tumors (C, D). Registration was not better with z-DWI than with c-DWI for

chest lesions, but it was significantly improved for non-chest lesions. ***P <0.0001 by

paired *t*-test.

Figure 4. Correlations between tumor size and matching area (A) or central point

displacement (B) for c-DWI (circle and dashed line) and z-DWI (square and solid line).

On linear regression analysis, matching area showed a weak correlation with tumor size

for c-DWI, but with z-DWI, it did not show a significant correlation. Central point

displacement did not show any significant correlation with tumor size either with

c-DWI or with z-DWI.

Figure 5. Bland–Altman plot for ADC values calculated based on c-DWI and z-DWI.

Middle dashed line indicates mean difference and top and bottom dashed lines show

95% limits of agreement.