Imaging of Urethroprostatic Reflux mimicking Prostate Cancer on FDG-PET/CT

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Purpose

INTRODUCTION

In the evaluation of prostate cancer, the usefulness of $^{18}$F-FDG PET for tumor detection has been regarded as limited [1]. It has been reported that there is no difference in FDG uptake between benign prostate hyperplasia and prostate carcinoma [2-5]. Furthermore, FDG-PET is limited in the identification of prostate tumors, as normal urinary excretion of radioisotope can mask pathological uptake [6, 7]. Streak artifacts arising from the FDG-filled bladder can be caused by filtered back projection algorithms for image reconstruction. Recently, with the use of iterative image reconstruction technique, combined PET/CT units have been reported to improve image quality and facilitate better localization of abnormal uptake in the prostate [1, 8].

Despite the usefulness of FDG in PET/CT imaging, FDG has still limitations with regard to distinguishing tumors from inflammation [9]. Urethropsrostate reflux of urine may also cause increase in FDG uptake of the prostate [10-12].

MR imaging of the prostate gland with endorectal coil or pelvic phased array coil has been widely used to detect and localize malignant lesions [13-15]. Recently, a number of investigators have reported the potential usefulness of diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) map for detecting prostate cancer, which shows lower ADC than a normal peripheral zone and a non-malignant transition zone [14, 16-20]. However, differentiation between benign and malignant lesions seems to be limited on the basis of ADC value alone, though there was a tendency that cancer lesions showed lower ADC values than non-malignant lesions including hyperplastic nodules[21]. As shown in the previous reports, a combination with T2-weighted imaging and dynamic contrast-enhanced imaging could yield higher sensitivities and specificities in the detection of prostate cancer by incorporating information from different aspects such as morphology, T2 value and vascular properties [1, 17, 18, 22-25].

The hypothesis is that combination of FDG-PET/CT and MR imaging could help to characterize FDG-avid lesions as malignant or non-malignant such as inflammation and urethroprostatic reflux of urine. Therefore, we compare PET/CT and MRI in the detection and localization of prostate cancer and put emphasis on urethroprostatic reflux as a cause of false positives in PET/CT imaging.

Methods and Materials

Patient Population
From the database of radiological information in our hospital, 89 patients who underwent both prostatic MRI and whole-body FDG-PET/CT examinations within two months between November 2006 and October 2011 were nominated in this retrospective study. Excluded were patients who underwent prostate biopsies or cancer treatment in the interval between the MRI and PET/CT examinations. Thus, this retrospective study included 76 patients. Among them, the preceding examination was MRI for 30 and PET/CT for 46 patients. The malignant diseases which the patients had or were suspected to have at the FDG-PET/CT examinations were lung cancer (n=28), prostate cancer (n=8), malignant lymphoma (n=7), colorectal cancer (n=5), laryngo-pharyngeal cancer (n=4), lung metastases (n=4), gastric cancer (n=3), bladder cancer (n=3), tumor of unknown origin (n=3), thyroid cancer (n=2), mediastinal tumor (n=2), hepatocellular cancer (n=2), pancreatic cancer (n=1), and so on. Serum PSA level at the MR examination ranges from 0.4 to 124 ng/ml (mean + SD: 17.1 + 27.8 ng/ml).

The written informed consent from the patients was waived owing to the retrospective design of this study.

**FDG-PET/CT imaging**

After fasting for at least four hours, serum glucose level was measured to confirm normoglycemia in each patient. Patients received an intravenous injection of 300-370MBq of $^{18}$F-FDG (FDGscan inj., Nihon-Mediphysics, Tokyo, Japan). Patients were encouraged to void before scan. Sixty minutes after injection, PET/CT images were acquired with a dedicated PET/CT scanner Aquiduo (PCA-7000B)(Toshiba Medical Systems, Otawara, Japan). CT images were acquired immediately before the PET scan without the use of contrast media.

All PET scans were acquired in 3-dimensional (3D) mode with an acquisition time of 2 minutes per bed position. PET images were reconstructed into a 128 x 128 matrix with 1.34 zooming, using interactive algorithms (orderedsubset expectation maximization, 4 iterations, 14 subsets) and the CT-based attenuation map, and noise was reduced by smoothing the images with an 8-mm full width at half maximum (FWHM) Gaussian filter. The attenuation maps were calculated from CT images of 512 x 512 matrix by Aquiduo PCA-7000B software. The CT images were reduced to the 128 x 128 matrix of the PET images by a linear interpolation. The attenuation maps were smoothed with a Gaussian filter to match the resolution to the PET images.

Regions of interest (ROIs) were placed over FDG-avid foci in the prostate gland. Standardized uptake value (SUV) was calculated by the following formula:

$$SUV = \frac{\text{tissue activity [Bq/ml]} \times \text{body weight [g]}}{\text{injected radioisotope activity [Bq]}}$$
The maximum value of SUV (SUVmax) in each ROI was measured. A 3-dimentional PET/CT workstation (VOX-BASE II; J-MAC System, Inc., Sapporo, Japan) was used for image analysis.

**MR Imaging**

MR imaging was performed on a 1.5 Tesla super-conductive magnet system (Gyroscan Achieva; Philips Medical systems, Best, the Netherlands) with the synergy cardiac coil. After initial T1-weighted localizing images were obtained, MR images of the entire prostate gland and the seminal vesicle in the transaxial direction were acquired with DWI, three-dimensional T2-weighted turbo spin echo (TSE) imaging and dynamic contrast-enhanced imaging.

DWI was performed with spin-echo echo-planar-imaging sequence in the straight transaxial direction. The scan parameters were b values of 0 and 600 s/mm$^2$, TR/TE 6300/50, section thickness of 2.5 mm without intersection gap, field of view of 350mm, matrix of 144 x 256 that was interpolated to 256 x 256, voxel size of 1.37 x 1.37 x 2.5 mm$^3$, seven signal acquisition, and scan time of 5 min 21 sec. The ADC maps with 2.5 mm-thick sections without intersection overlap were constructed from ADC values calculated from signal intensity data obtained in the diffusion weighted images with b values 0 and 600 s/mm$^2$. Then, by using the 2.5 mm-thick ADC maps, the transaxial, coronal and sagittal ADC-maps were reconstructed with 4mm-thick gapless sections to match 4mm-thick sections of the following T2-weighted images.

For T2-weighted imaging, thin-section high-spatial-resolution three-dimensional T2-weighted TSE images were obtained in the straight transaxial plane with the following parameters: TR/TE 1500/150 msec; echo train length of 61, section thickness of 1.4 mm with intersection overlap of 0.7 mm; field of view of 200 mm; matrix of 224 x 512 that was interpolated to 512 x 512; reconstructed voxel size of 0.4 x 0.4 x 0.7 mm$^3$; and number of excitation of two. Total acquisition time was 7 minutes 27 seconds. Then, transaxial, coronal and sagittal images were reconstructed with 4 mm-thick gapless sections, which provided anatomical details of the prostate gland.

Dynamic contrast-enhanced TSE T1-weighted images were obtained before and after a rapid intravenous bolus injection of 0.1 mmol/kg of gadopentetate dimeglumine (Magnevist: Nihon Bayer, Tokyo, Japan) with injection rate of 3ml/sec. Five consecutive imaging sets were obtained at the time points of 20, 40, 60, 90, 120 seconds after injection of contrast material.

**Image Analysis**
All images were analyzed and reviewed by the three radiologists (yw, ti, mn) with use of soft-copy reading on an electronic workstation (ShadeQuest; Yokogawa Medical Solutions Co, Tokyo, Japan).

In the detection and localization of prostate cancer, FDG-PET/CT and MR images were evaluated as follows. For FDG-PET/CT images, FDG-avid focal lesions in the prostate gland discovered on PET/CT were interpreted as suggestive of prostate cancer. The SUVmax of 3.0 or more for the prostate was defined as positive.

For MR images, low-ADC lesions with the following features were interpreted as suggestive of prostate cancer: nodular and homogeneous appearance of round, oval or crescent shape, short diameter of 5mm or greater, ADC value of $1.35 \times 10^{-3} \text{ mm}^2/\text{second}$ or less, and either of low signal intensity on T2-weighted image or high signal intensity on the early phase of dynamic contrast-enhanced image [16-21, 25]. The exclusion criteria to eliminate benign lesions were applied for the low-ADC lesions described above, by using the characteristics on T2-weighted images indicative of hyperplastic nodules: inhomogeneous round signal intensity with high-intensity spots, smooth margin and hypointense pseudocapsule [22, 23].

These abnormal findings were compared with the final diagnosis obtained from the medical records including FDG-PET/CT, MR examinations and pathologic reports.

In the patients with the false positives of FDG-PET/CT findings, MR findings and pathological reports were also assessed to determine the cause of the false positive results. The diagnostic criteria of urethroprostatic reflux of urine were cystic lesion on MR images corresponding with FDG-avid focal areas in the prostate gland; remarkably high signal intensity on T2-weighted imaging, high ADC value on ADC map, and no contrast-enhancement on dynamic contrast-enhanced MR image. The criteria for prostatitis were: the wedge-shape inhomogeneous T2-hypointensity area showing hyperintensity on dynamic contrast-enhanced MR imaging which corresponds with FDG-avid focal areas in the prostate gland, and hypertrophy and/or atrophy of glands with lymphocytic infiltration on pathologic reports. The criteria for hyperplastic nodule were: inhomogeneous round signal intensity lesion with smooth margin and hypointense pseudocapsule on T2-weighted MR image [22, 23].

**Statistical analysis**

Histopathology was the standard of reference in the diagnosis of prostate cancer. Sensitivity, specificity, and accuracy of MRI and PET/CT were calculated for the detection of prostate cancer. Agreement with MRI and PET/CT was also calculated. Causes of false positive results in FDG-PET/CT were determined and counted according to diagnostic
criteria for urethroprostatic reflux of urine: cystic lesion on MR images corresponding with FDG-avid focal areas in the prostate gland.

Statistical analysis was performed with Fisher's exact test. In every statistical analysis, significance was considered to exist when the p-value was less than 0.05.

Results

RESULTS

Final diagnosis of prostate cancer (n=33) was made histologically by prostate biopsy (n=26) and prostatectomy (n=7). Diagnosis of no malignancy (n=43) was made by 8-core systematic prostate biopsy (n=29) and follow-up for one and a half year or longer (n=14).

Among the 33 patients with prostate cancer, PET/CT and MRI showed positive findings in 22 and 27 patients, respectively (Table 1)(Fig.1-3). The number of patients with false positive results was 15 for PET/CT and 6 for MRI (Table 1)(Fig.4-7). Sensitivities, specificities, and accuracies in the detection of prostate cancer were 70% (95%CI: 54-85), 67% (95%CI: 53-81) and 68% (95%CI: 58-79) for PET/CT, and 82% (95%CI: 69-95), 86% (95%CI: 76-96), and 84% (95%CI: 76-92) for MRI, respectively (Table 2). The specificity and accuracy were significantly higher for MRI than for PET/CT (p<0.05).

Among the 22 patients in whom PET/CT detected prostate cancer, 8 patients (36%) had history of prostate cancer at the time of PET/CT examination. Thus, in 14 patients (64%), prostate cancer was unexpectedly detected with PET/CT.

Among all the 76 patients, the positive and negative results agreed between PET/CT and MRI in 20 and 26 patients, respectively (Table 3). Disagreement between PET/CT and MRI was found in 30 patients. Thus, the agreement ratio between MRI and PET-CT was 61% (95%CI: 50-72).

The false positives of PET/CT (n=15) were diagnosed as urethroprostatic reflux (Fig.4,5) in 33% (95%CI: 9-57) (n=5), prostatitis (Fig.6) in 40% (95%CI: 15-65) (n=6) and hyperplastic nodule (Fig.7) in 27% (95%CI: 4-49) (n=4) with MRI and/or pathologic reports (Table 4).

Images for this section:
Fig. 1: Prostate Cancer: T3a, well-differentiated adenocarcinoma, GS8=4+4; PET/CT-true positive, MR-true positive SUVmax=5.97, ADC0.85, PSA 73.026 a:FDG-PET/CT, b:ADC map, c:T2-weighted image, d: dynamic contrast-enhanced image Focal FDG uptake in the prostate gland corresponded with ADC-low area on MR. Well-differentiated adenocarcinoma was proven by biopsy.
**Fig. 2:** Prostate Cancer (multiple): well-differentiated adenocarcinoma, GS7=4+3; PET/CT-true positive, MR-false negative SUVmax=3.55, ADC-negative, PSA 4.23 a:FDG-PET/CT, b:ADC map, c:T2-weighted image, d: dynamic contrast-enhanced image

Multiple focal FDG uptake in the prostate gland was found, though MR images showed no ADC-low areas. On T2-weighted images, the peripheral zone showed diffuse hypointensity areas with intense contrast enhancement. Well-differentiated adenocarcinoma was detected by biopsy.
Fig. 3: Prostate Cancer: mod-differentiated adenocarcinoma, GS7=3+4; PET/CT-false negative, MR-true positive ADC 0.91, PSA 18.893 a:FDG-PET/CT, b:ADC map, c:T2-weighted image, d: dynamic contrast-enhanced image No focal FDG uptake in the prostate gland was found. MR images showed ADC-low lesion in the transition zone with T2-hypointensity and early contrast enhancement. Moderately-differentiated adenocarcinoma was proven by surgery.
Fig. 4: Urinary Reflux in a Patient with Neurogenic Bladder Caused by Cord Contusion; PET/CT-false positive, MR-true negative SUVmax=21.8, MR: cyst formation, ADC=3.0

a:FDG-PET/CT, b:ADC map, c:T2-weighted image, d: dynamic contrast-enhanced image

Intense FDG uptake in the prostate gland corresponded with cystic lesion on MR. The cyst formation was caused by urethroprostatic reflux related to known previous history of spinal cord contusion.
Fig. 5: Urinary Reflux associated with cystic dilatation of ductules; PET/CT-false positive, MR-true negative SUVmax=3.93, ADC-negative a:FDG-PET/CT, b:ADC map, c:T2-weighted image, d: dynamic contrast-enhanced image Intense FDG uptake in the prostate gland corresponded with cystic lesion on MR. The cyst formation was associated with urethroprostatic reflux.
Fig. 6: Chronic prostatitis: PET/CT-false positive, MR-true negative SUVmax=5.15, ADC-negative, PSA=10.697  

a:FDG-PET/CT, b:ADC map, c:T2-weighted image, d: dynamic contrast-enhanced image  

Focal FDG uptake in the prostate was seen although no apparent focal lesion was detected on MR images. Inflammatory change with lymphocytic infiltration was proven by biopsy.
Fig. 7: Hyperplastic nodule: PET/CT-false positive, MR-true negative SUV\textsubscript{max}=4.51, ADC 1.13, PSA 3.6  a:FDG-PET/CT, b:ADC map, c:T2-weighted image, d: dynamic contrast-enhanced image  Focal FDG uptake in the prostate corresponded with ADC-low nodule in the transition zone. On T2-weighted image, the nodule showed heterogenous hypointensity with hypointense pseudocapsule, indicative of exclusion criteria. Hyperplastic nodule was proven by biopsy.
Table 1
Results of PET-CT, MRI and pathologic results in the detection of prostate cancer

<table>
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<tr>
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<th>PET-CT</th>
<th>MRI</th>
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<tbody>
<tr>
<td></td>
<td>positive (n)</td>
<td>negative (n)</td>
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<tr>
<td>pathologic results</td>
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<td></td>
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<tr>
<td>positive (n)</td>
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<td>10</td>
</tr>
<tr>
<td>negative (n)</td>
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n: number of patients
Table 2
Sensitivity, specificity and accuracy of PET-CT and MRI in the detection of prostate cancer

<table>
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<th></th>
<th>Sensitivity (%)</th>
<th>95% CI</th>
<th>Specificity (%)</th>
<th>95% CI</th>
<th>Accuracy (%)</th>
<th>95% CI</th>
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<tbody>
<tr>
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<td>53-85</td>
<td>66</td>
<td>52-80</td>
<td>67</td>
<td>57-78</td>
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<tr>
<td>MRI</td>
<td>82</td>
<td>69-95</td>
<td>86</td>
<td>76-96</td>
<td>84</td>
<td>76-92</td>
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<tr>
<td>p-value</td>
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<td>0.0282</td>
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<td>0.0140</td>
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Table 2
Table 3
Agreement between PET-CT and MRI in the detection of prostate cancer

<table>
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<tr>
<th>MRI</th>
<th>PET-CT</th>
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<th>Agreement (%, 95%CI)</th>
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<tr>
<td></td>
<td>positive (n)</td>
<td>negative (n)</td>
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</tr>
<tr>
<td>positive (n)</td>
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<td>13</td>
<td></td>
</tr>
<tr>
<td>negative (n)</td>
<td>17</td>
<td>26</td>
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<tr>
<td>MRI-PET agreement (%, 95%CI)</td>
<td></td>
<td></td>
<td>61% (50-72)</td>
</tr>
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</table>

n: number of patients
Table 4
Causes of false positives in FDG-PET/CT

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>%</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Cyst formation</td>
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<td>33</td>
<td>9.57</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>6</td>
<td>40</td>
<td>15-64</td>
</tr>
<tr>
<td>Hyperplastic nodule</td>
<td>4</td>
<td>27</td>
<td>4.49</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>100</td>
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</table>
Conclusion

DISCUSSION

As prostate cancer detection with \( ^{18} \)F-FDG PET/CT was reported to be disappointing [1-5], the sensitivity, specificity and accuracy in the detection of prostate cancer was lower with FDG-PET/CT than with MRI in this study. However, considering that there was no significant difference in the sensitivity between PET/CT and MRI, PET/CT showed the sensitivity of 70% high enough for the clinical application. Furthermore, PET/CT could detect prostate cancer unexpectedly in patients who are not suspected of having it, while the population of patients who undergo MR examination is suspected of having prostate cancer at the time of examination. Therefore, our data suggests FDG-avid focal prostate lesion incidentally found on FDG-PET/CT might require further evaluation with MRI because of the substantial rate of malignancy.

The specificity in the detection of prostate cancer with PET/CT was significantly lower than with MRI, which resulted from quite a few false positives. It has been reported that there is no difference in tracer uptake between benign prostate hyperplasia and prostate carcinoma [3-5]. In this study, the causes of false positives of PET/CT included not only hyperplastic nodule but chronic prostatitis and urethoprostatic reflux of urine. These causes of false positives can be differentiated from prostate cancer with MRI. The typical MR features of prostate cancer are low-ADC lesions with nodular and homogeneous appearance of round, oval or crescent shape, ADC value of \( 1.35 \times 10^{-3} \) mm\(^2\)/second or less, and either of low signal intensity on T2-weighted image or high signal intensity on the early phase of dynamic contrast-enhanced image [16-22, 25]. In contrast, the MR findings indicative of hyperplastic nodules on T2-weighted image appear as inhomogeneous round low-signal intensity lesion with high-intensity spots in it, and also show smooth margin and hypointense pseudocapsule [22, 23]. Chronic prostatitis typically appears as wedge-shaped T2-low intensity area with intermediate ADC value, and also show intense and prolonged contrast enhancement [26]. Cystic lesions caused by urinary reflux to the prostate appear as high intensity area on both T2-weighted image and ADC map, and do not show contrast enhancement.

Urethoprostatic reflux of urine is a pathological phenomenon which occurs during urinary voiding [27]. PET/CT can have a chance to detect this phenomenon as follows; Image acquisition of FDG-PET/CT is performed 60minutes after FDG-administration. Immediately before PET/CT scan, a patient is instructed to void urine, which may happen to make urine with high FDG content go back into prostate gland, preferentially in the peripheral zone [10, 12]. In contrast, it is difficult to observe urinary reflux into prostate during MR examination, because MR scan is usually performed at rest and not during urination. However, MR image can readily reveal cystic dilatation or formation of peripheral zone caused by urinary reflux into prostate gland. Frequent urethoprostatic
reflux of urine can cause inflammation in the peripheral zone [11, 28], which may subsequently lead to devastate original tissue of peripheral zone, dilate ductal structure and form large cysts as shown in Fig.4. Thus, combination of typical PET/CT and MRI findings, cystic lesion on MR images corresponding with FDG-avid focal area in the prostate gland, can lead to diagnose urethroprostatic reflux of urine.

Although new PET agents including \(^{11}\)C-methionine, \(^{11}\)C-acetate, \(^{11}\)C-choline, and \(^{18}\)F-fluorodihydrotestosterone can hold great promise for the metabolic evaluation of prostate cancer [1, 29], even a new PET agent, when it could be excreted from the kidney into urine, would have similar limitation to the \(^{18}\)F-FDG PET/CT in the detection of prostate cancer because of a risk of urethroprostatic reflux.

In summary, FDG-PET/CT and MR imaging can play a complementary role in the detection of prostate cancer, and a combination of PET/CT with MRI could reveal urethroprostatic reflux.

References


Personal Information