Introduction
Total hip arthroplasty (THA) has been recognized as a reliable surgical treatment for osteoarthritis of the hip. While satisfactory clinical results have been reported all over the world, periprosthetic infection is still one of the unsolved complications. We applied $^{18}F$-fluorodeoxy glucose (FDG) and $^{18}F$-fluoride (fluoride) PET to diagnose painful THA, including infection cases. The purpose of this study was to reveal and compare the differences between FDG and fluoride PET findings in painful THA cases.

Materials and Methods
This prospective diagnostic study was approved by our institutional review board. A total of 8 patients who had undergone THA and were given FDG and fluoride PET scans were enrolled in this study. The primary diseases were osteoarthritis in 7 cases and rheumatoid arthritis in 1 case. These individuals were aged between 61 and 89 (mean: 73), and the mean period after primary surgery was 17 years (3-29). Six of 8 cases had radiological loosening of the prosthesis and underwent revision surgery.

PET scanning
Both FDG and fluoride PET images were obtained using an SET 2400W machine (Shimadzu, Kyoto, Japan).

1. FDG PET findings were defined as suggestive of infection if abnormally increased FDG uptake at the bone-implant interface was recognized, and not suggestive of infection if the uptake was limited to the soft tissues or only adjacent to the neck of the prosthesis (2).

2. Fluoride PET findings were defined as suggestive of infection if abnormally increased fluoride uptake was recognized over more than half of the bone-implant interface, and not suggestive of infection if the uptake was limited to less than half of the bone-implant interface.

The maximal standardized uptake values (SUV max) were measured in all PET images.

Tissue examinations
Intraoperative tissues were obtained and evaluated by histopathological examination, microbiological culture, and real-time polymerase chain reaction (PCR).

1. Histopathological examination: Infiltration of 10 or more neutrophils per high-power virtual field (×400) was defined as acute inflammation and was considered suggestive of infection.

2. Microbiological culture: All specimens were submitted to standard microbiological aerobic culture.

3. Real-time PCR: Bacterial DNA was extracted using a QIagen mini kit (Qiagen, Valencia, CA) and was then analyzed by quantitative real-time PCR using the LightCycler 2.0 system (Roche, Mannheim, Germany). A Methicillin-resistant Staphylococcus aureus (MRSA) detection kit (Roche, Mannheim, Germany) for MRS PCR and broad-range universal PCR (4) were used.

When one or more of these examinations showed a positive finding, a definitive diagnosis of periprosthetic infection was made. FDG and fluoride PET images were compared in all cases. In the 6 revision cases, diagnosis from FDG and fluoride PET and diagnosis from intraoperative tissue examinations were compared.

Results

Table 1: Results of PET, histopathology, culture, and PCR

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>SUV Suggestive of infection or not</th>
<th>FDG PET Suggestive of infection or not</th>
<th>Fluoride PET Suggestive of infection or not</th>
<th>Histopathology</th>
<th>Microbiological Culture</th>
<th>Real time PCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>70M</td>
<td>5.6 infection</td>
<td>12.3 infection</td>
<td>+ Non-hemolytic streptococcus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>70F</td>
<td>4.4 infection</td>
<td>13.5 infection</td>
<td>+ Staphylococcus warner</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>73F</td>
<td>12.3 infection</td>
<td>8.6 infection</td>
<td>+ Aerobic gram positive bacillus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>82F</td>
<td>6.0 infection</td>
<td>12.8 infection</td>
<td>+ Aerobic gram positive bacillus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>65M</td>
<td>6.6 infection</td>
<td>12.6 infection</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>69F</td>
<td>2.4 no infection</td>
<td>0.8 infection</td>
<td>+ Staphylococcus saprophytis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>61F</td>
<td>5.2 infection</td>
<td>15.4 infection</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>70F</td>
<td>2.4 no infection</td>
<td>7.3 no infection</td>
<td>N/A</td>
<td>N/A</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

From FDG PET findings, 6 cases were diagnosed as infections, while from fluoride PET findings, 7 cases were diagnosed as infections (Table 1). With a comparison of FDG and fluoride PET images, 6 cases (Cases 1, 2, 3, 4, 5, and 7) showed a similar uptake region (Figure 1, white arrow) and 4 cases (Cases 6, 8 and also 4 and 5) showed a different uptake region (Figure 1, red arrow). In tissue examinations, 6 of revision surgery cases were postoperatively revealed to be infections. In one revision surgery cases, the FDG PET findings were preoperatively diagnosed as no infection (Case 6). One case showed negative culture results despite the positive FDG and fluoride PET findings (Case 5). However, this case was diagnosed as infection by real time PCR.

Fig 1: Images of FDG and Fluoride PET.

The highest FDG uptake in Cases 4 and 5 is located around the neck, despite the highest fluoride uptake regions at the bone-implant interface (red arrow). In Case 6, although infection was diagnosed from the tissue examination, FDG PET does not show any abnormal uptake. However, in most cases, FDG and fluoride PET show a similar uptake region (white arrow).

Discussion
FDG is one of the most common tracers for PET imaging and has been widely applied in the diagnosis of periprosthetic infections of the hip (1,2). Chryssikos et al emphasized that optimal diagnostic criteria can differentiate septic from aseptic loosening in THA with a high degree of sensitivity and specificity (2). However, an optimal classification system for these two conditions has not yet been standardized, and evaluations using SUV max have been shown not to be significant in detecting regions of possible inflammation (1).

Fluoride PET has been applied for bone associated disease and recognized as a useful indicator for bone remodeling (3). Regardless of the similar dynamic capacity of fluoride PET and $^{99m}Tc$-labelled bone scintigraphy, which is also well known for its validity in the diagnosis of septic loosening in hip prostheses (5), fluoride has not been applied in the diagnosis of periprosthetic infections of the hip previously.

Therefore, we have applied fluoride PET to differentiate between septic and aseptic loosening, and to detect the inflammation focus in THA cases suggestive of infection.

In the present study, we compared two different tracers, FDG and fluoride, to visualize differential uptake patterns. Both images showed clearly visualized uptake regions. Their uptake indicates different molecular reactions, and some cases showed different uptake regions. However, both images pointed to a similar inflammation focus in most infection cases.

Because our results were from a small number of patients, and there were no aseptic loosening cases, it is difficult to evaluate the sensitivity and specificity of both tests. Nevertheless, this study indicated that combined FDG and fluoride PET findings may possibly improve the diagnostic accuracy in distinguishing between septic and aseptic loosening cases. To prove their usefulness, we need clearer definitions, type classifications, and quantitative criteria for positive uptake using SUV max, based on a study of more cases.

References