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Added value of 18F-FDG PET/CT in diagnosing infected hip prosthesis

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Abstract

Background: The diagnosis of infected hip prosthesis is frequently not straightforward yet very important as it changes treatment.

Purpose: To retrospectively investigate the added value of 18F-FDG PET/CT to conventional tests including radiography, erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP) testing, and joint aspiration, in diagnosing infected hip prosthesis.

Material and Methods: Seventy-eight hip prostheses of 78 patients (55% men; mean age = 66.5 years; age range = 30–85 years) with non-specific clinical presentation, i.e. no abscess or sinus tract communicating with the joint space at clinical examination, were analyzed. Cultures of intra-articular fluid and peri-implant tissues after revision surgery or clinical follow-up ≥6 months served as gold standard. Areas under the receiver operating characteristic curves (AUCs) of radiography, ESR/CRP testing, aspiration culture, and white blood cell (WBC) count without and with the addition of 18F-FDG PET/CT were compared.

Results: The addition of 18F-FDG PET/CT increased AUCs: for radiography with 0.212, $P = 0.001$; for ESR/CRP testing with 0.076, $P = 0.072$; for aspiration culture with 0.126, $P = 0.032$; and for aspiration WBC count with 0.191, $P = 0.035$.

Conclusion: This study shows that 18F-FDG PET/CT adds to individual conventional tests in diagnosing infected hip prosthesis. It may improve the preoperative planning and should therefore be considered in the diagnostic work-up. Future studies should define the exact place of 18F-FDG PET/CT in the diagnostic work-up of periprosthetic joint infection.

Keywords

Prosthesis, arthroplasty, hip joint, infection, 18-fluoro-deoxyglucose positron emission tomography (18F-FDG PET)

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Introduction

Approximately 0.8% of all Americans (2.5 million people) have a hip prosthesis (1). The prevalence is 2.3% among adults aged 50 years and rises to 6% by the age of 80 years (2). With aging and increased life expectancy of the general population, the incidence of hip arthroplasty procedures has increased substantially in recent decades (1,2). A major drawback is that approximately 6.5% of all hip prostheses need to be revised after five years, which rises to as much as 12.9% after ten years (3). The most common causes for revisions are aseptic loosening (55.2%), dislocation (11.8 %), septic loosening (7.5%), and periprosthetic fractures (6%) (4). While dislocations and periprosthetic fractures can be readily diagnosed, it is often a challenge to differentiate aseptic from septic loosening. Yet this differentiation is clinically very important, since aseptic loosening can be treated in a

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single-stage revision, whereas the standard treatment of septic loosening is a two-stage revision, using an interstage antibiotic-loaded spacer or beads (5).

The American Academy of Orthopaedic Surgeons' (AAOS) guideline on the diagnosis of periprosthetic joint infection (PJI) was published in 2010. Radiographs are routinely obtained in the work-up of suspected PJI (6). The AAOS guideline recommends erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) testing in all patients (6). The decision to perform joint aspiration is based on the probability of PJI and the results of ESR and CRP testing (6). The AAOS guideline also states that 18F-fluoro-2-deoxy-D-glucose positron emission tomography (18F-FDG PET) is an option in certain patients (6). The Musculoskeletal Infection Society (MSIS) defines PJI when one of the following criteria are present (7): (i) a sinus tract communicating with the prosthesis; (ii) a pathogen is isolated by culture from two separate tissue or fluid samples obtained from the affected prosthetic joint; (iii) four of the following six criteria exist: (a) elevated ESR and CRP, (b) elevated synovial fluid WBC count, (c) elevated synovial fluid neutrophil percentage, (d) presence of purulence in the affected joint, (e) isolation of a microorganism in one periprosthetic tissue or fluid culture, and (f) neutrophils per high-powered field in five high-power fields observed from histologic analysis of periprosthetic tissue at 400 times magnification. In contrast to the AAOS guideline, the MSIS does not mention the use and potential value of 18F-FDG PET in diagnosing PJI (7). Therefore, to elucidate this issue, the purpose of the present study was to retrospectively investigate the added value of 18F-FDG PET/CT to conventional tests including radiography, ESR/CRP testing, and joint aspiration in diagnosing infected hip prosthesis.

Material and Methods

Initial patient selection

Our study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Institutional ethics committee board approval was obtained and patients' consents were waived for this retrospective study. In our hospital, a tertiary referral hospital in the South of the Netherlands, patients with non-specific clinical presentation, i.e. those without an abscess or sinus tract communicating with the joint space at clinical examination, undergo 18F-FDG PET/CT as part of the diagnostic work-up of PJI. We performed a search in our institution's database for patients who had undergone 18F-FDG PET/CT in the evaluation of infected hip prosthesis between May 2007 and October 2014. This search resulted in 80 consecutive patients, with 82 hip prostheses suspected for PJI. Inappropriate use of multiple observations from single individuals may potentially bias results: when observations are not independent, the dependency between them has the potential to increase or decrease variance within that group (8). Thus, when two hips from a single patient are counted as independent observations without proper methodological considerations within the study design or adjustment in the analysis to account for within-observation correlation, the precision of the estimate may be falsely improved and the potential for a biased estimate increases (8). Therefore, to avoid potential bias, we choose to exclude one randomly selected hip from each of the two patients with bilateral suspected PJI (Fig. 1).

Finally, 78 hip prostheses of 78 Caucasian patients (55% men; mean age = 66.5 years; age range = 30–85 years) were analyzed.

Diagnostic tests

Radiography: Standard hip radiographs were obtained in anteroposterior and axial views. All radiographs were analyzed and compared to prior radiographs by a musculoskeletal radiologist (REW) who was aware of the purpose of this study but blinded to the results of all other diagnostic tests. PJI was defined as the presence of ill-defined and/or rapidly progressive lucencies > 2 mm at the acetabular zones according to DeLee and Charnley (9) and femoral zones according to Gruen et al. (10), or as the presence of periosteal reaction not deemed to be caused by mechanical stress (11–13).

ESR/CRP testing: Venous blood samples were drawn from the cubital vein. ESR and serum CRP levels were determined by our hospital's clinical laboratory according to accepted standards and controls. Predefined preoperative ESR values $\geq$ 31 mm/h or CRP values $\geq$ 20.5 mg/L were considered diagnostic for PJI (14). ESR and CRP test results were combined as this has shown to increase sensitivity (14).

Joint aspiration: Hip joint aspiration was performed under fluoroscopic guidance using a standardized technique (15). If no intra-articular fluid could be aspired initially (''dry tap''), the needle was repositioned. If still no intra-articular fluid could be aspired, 10 mL of saline was injected and the aspiration was repeated.

To cultivate microorganisms blood and chocolate agar plates (incubation for up to five days), Schaedler and nalidixic acid tween agar plates (incubation for up to ten days), and Thioglycollate medium (incubation for up to ten days) were used.

White blood cell (WBC) count was performed after Gram's staining. WBC count was categorized as

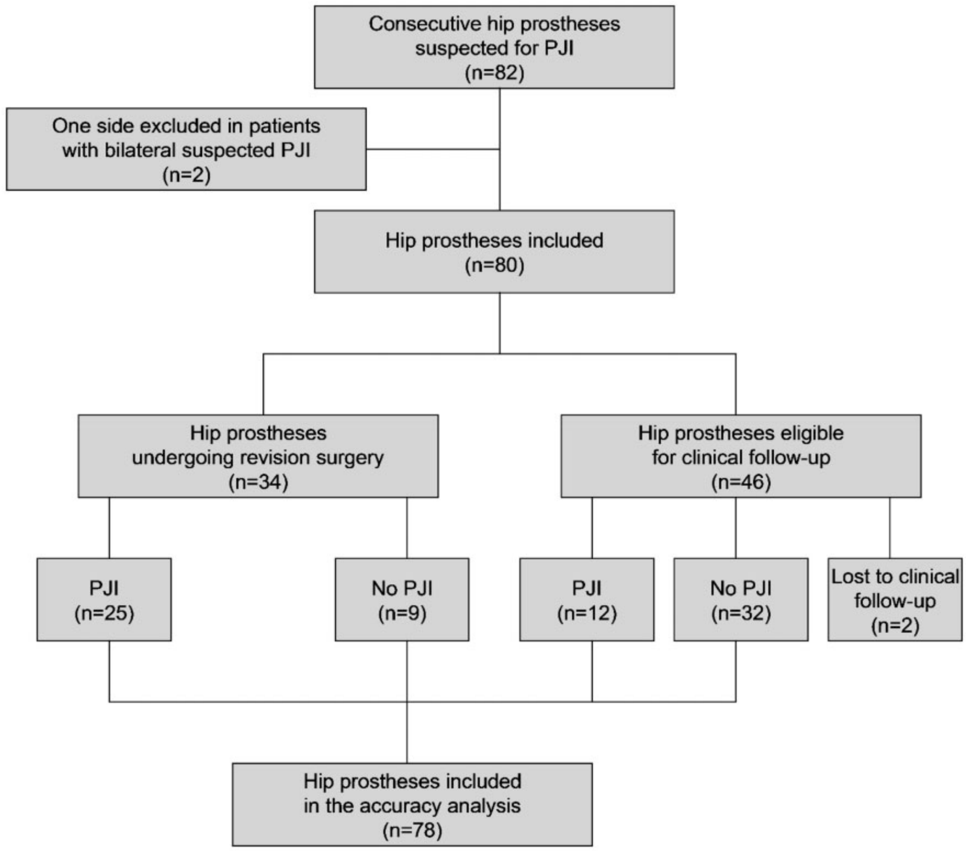

Fig. 1. Flowchart of the selection process and hip prostheses included in the accuracy analysis.

sporadic (0–1 leukocytes per high-power field [hpf]), little (1–5 leukocytes per hpf), moderate (6–10 leukocytes per hpf), and many (>10 leukocytes per hpf). Positive culture and predefined WBC count >10 per hpf were considered diagnostic for PJI.

18F-FDG PET/CT: 18F-FDG PET/CT was performed on a time-of-flight PET/CT scanner (Gemini TF 64; Philips Healthcare, Best, The Netherlands) using a standardized protocol (16). All patients had a blood glucose level under 11 mmol/L during scanning. Low-dose CT with a reconstructed slice thickness of 4 mm was used for attenuation correction and localization of 18F-FDG uptake. All 18F-FDG PET/CT scans were analyzed in consensus by a fourth-year nuclear medicine resident and a nuclear medicine physician (WAMB and BB) who were aware of the purpose of this study but blinded to the results of all other diagnostic tests. Visually increased 18F-FDG uptake at the bone-prosthesis interface at the central portion of the acetabular cup or at the middle portion of the femoral shaft were regarded as positive findings (Fig. 2), whereas 18F-FDG uptake limited to the soft tissues, synovium, or adjacent to the prosthesis neck was regarded as negative findings for PJI (Fig. 3) (17–19). Alternatively, maximum standardized uptake value (SUV_{max}) at the bone–prosthesis interface at the central portion of the acetabular cup and at the middle portion of the femoral shaft were assessed. To our knowledge, there is no uniformly accepted SUV_{max} threshold for diagnosing PJI. Using receiver operating characteristic (ROC) analysis (20), the optimal SUV_{max} threshold (i.e. with maximum sensitivity and specificity) for diagnosing PJI in our study population was 3.2. This threshold was used in further analysis.

Gold standard and further patient selection

One orthopedic surgeon specialized in hip arthroplasty and treatment of PJI (JG) reviewed the medical history of all patients. In 34 patients who underwent hip revision surgery, the results of cultures of material obtained at revision surgery were used as gold standard for PJI; in the first 12 patients, conventional cultures were obtained, whereas in the later 22 patients sonication cultures (21) were obtained. In 42 patients who did not undergo revision surgery, clinical follow-up data of a minimum of six months up to a maximum of eight years (mean = 2 years 11 months) consisting of close clinical observation for the presence of PJI and eventual hip prosthesis failure, was used as gold

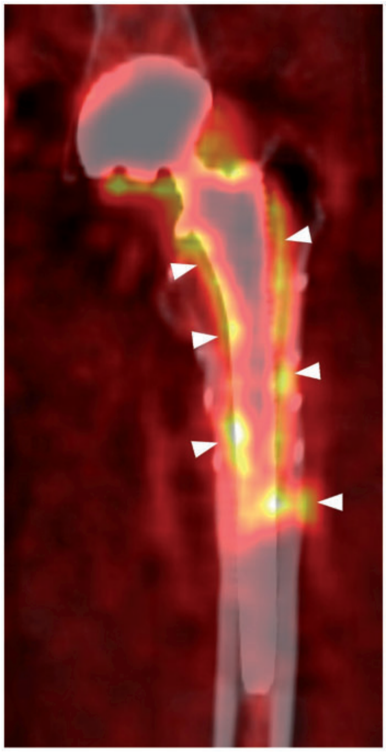

Fig. 2. Coronal reformatted 18F-FDG PET/CT image shows increased 18F-FDG uptake at the bone–prosthesis interface at the middle portion of the femoral shaft (arrowheads), which is regarded as a positive finding for PJI.

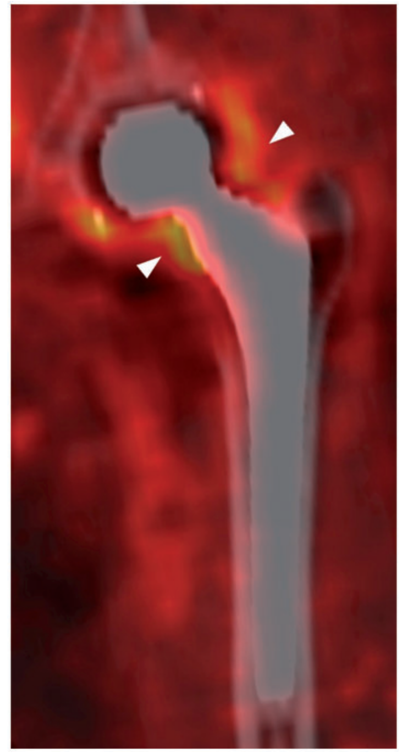

Fig. 3. Coronal reformatted 18F-FDG PET/CT image shows 18F-FDG uptake limited to the synovium adjacent to the prosthesis neck (arrowheads), which is regarded as a negative finding for PJI.

standard for PJI. The standard criteria were close observation for presence of infection and eventual prosthesis failure (19). The lack of such outcomes was considered as evidence for other causes than PJI as the underlying etiology of pain in these 42 patients (19). Two patients who did not undergo revision surgery were lost to follow-up and excluded from further analysis (Fig. 1).

Statistical analysis

The test results of radiography, ESR/CRP testing, joint aspiration culture, joint aspiration WBC count, and 18F-FDG PET/CT were dichotomized using the criteria as mentioned above. To a positive test result, a score of "1" was assigned, whereas to a negative test result, a score of "0" was assigned. The scores of each individual conventional test (radiography, ESR/CRP testing, joint aspiration culture, and joint aspiration WBC count), both without and with the score of 18F-FDG PET/CT, were determined. In addition, for patients in whom results of all diagnostic tests were available, the sum of scores for each patient was determined, both without and with the score of 18F-FDG PET/CT added. Sensitivity and specificity are the basic measures of accuracy of a diagnostic test; however, they depend on the cut point used to define "positive" and "negative" test results. As the cut point shifts, sensitivity and specificity shift (21). Therefore, we constructed ROC curves. An ROC curve is a plot of the sensitivity of a test versus its false-positive rate for all possible cut points (20). The area under the ROC curve (AUC) is a measure of how well a parameter can distinguish between two diagnostic groups (in our study PJI/no PJI). The AUC can take on values in the range of 0.0–1.0. A test with an AUC of 1.0 is perfectly accurate, whereas a test with an AUC of 0.0 is perfectly inaccurate (20). The areas AUCs, without and with the 18F-FDG PET/CT scores added, were compared using the method of Hanley and McNeil (22). Statistical analyses were executed using MedCalc statistical software version 12.6.0 (MedCalc Software, Ostend, Belgium).

Results

Seventy-eight hips of 78 patients (55% men; mean age = 66.5 years; age range = 30–85 years) were included in the accuracy analysis (Fig. 1, Table 1). Of the 78 patients, 54 (69%) were referred from other

Table 1. Characteristics of the 78 hip prostheses included in the analysis.

	n
• From our own hospital	24
• Referred from another hospital for evaluation of PJI	54
• Previously treated for PJI	18
• Left-sided prosthesis	41
• Right-sided prosthesis	37
• No previous revision surgery	52
Time after hip arthroplasty	Mean = 5.2 years, range = 0.05–27.0
• Previous revision surgery	26
Time after revision hip arthroplasty	Mean = 5.1 years, range = 0.2–21.3
• Cementless cup + cementless femoral stem	39
• Cemented cup + cementless femoral stem	17
• Cemented cup + cemented femoral stem	17
• Cementless cup + cemented femoral stem	3
• Cemented femoral stem (hemiprosthesis)	2

Table 2. Distribution of the data of all 78 patients that were included in the analysis. In 37 patients, results of all diagnostic tests were available.

	Radiography	ESR/ CRP	Culture	WBC count	18F-FDG PET/CT
Negative test result	73	43	18	33	35
Positive test result	5	30	21	5	43
Missing data	0	5	39	40	0

hospitals and 28/78 hips (36%) were previously treated for PJI (Table 1).

All 78 patients underwent radiography and 18F-FDG PET/CT. ESR/CRP testing, joint aspiration culture, and WBC count results were not available in all patients (Table 2). In 37 patients, results of all diagnostic tests were available.

Using visual assessment of 18F-FDG uptake, sensitivity and specificity of 18F-FDG PET/CT, excluding other tests, were 0.81 and 0.68, respectively. For all individual conventional tests, AUCs increased with the addition of 18F-FDG PET/CT (P values in the range of 0.001–0.072) (Figs 4a–d, Table 3). Of note, retrospective review of our available data revealed that one patient had an infected knee prosthesis and ESR and CRP values of 67 mm/h and 156 mg/L, respectively (indicating a positive test result). Exclusion of this patient did not have a significant impact on the results. Chart review did not reveal any other potential confounding factors such as systemic diseases including inflammatory arthropathies or more acute conditions such as pneumonia. The AUC of the sum of scores of all conventional tests in the 37 patients (radiography, ESR/CRP testing, joint aspiration culture, and WBC count results) did not significantly increase with the addition of 18F-FDG PET/CT ($P = 0.139$) (Fig. 4e, Table 3). Using SUV_{max} measurements with an optimized threshold, sensitivity and specificity of 18F-FDG PET/CT, excluding other tests, were 0.71 and 0.78, respectively. Analyses using SUV_{max} measurements were in accordance to the analyses using visual assessment of 18F-FDG uptake (Table 4).

Discussion

The aim of our study was to investigate the added value of 18F-FDG PET/CT in diagnosing infected hip prosthesis. We found that 18F-FDG PET/CT adds to conventional tests including radiography, ESR/CRP testing, and joint aspiration.

The diagnosis of PJI is frequently not straightforward and in many cases the diagnosis has not been established yet before revision surgery is planned. In the present study, we only included patients with non-specific clinical presentation. Patients with evident PJI, such as those with a sinus tract communicating with the joint, were not part of this study. Thus, from a diagnostic point of view, these patients can overall be regarded as "difficult cases." Indeed, there were a relatively large number of patients referred from other hospitals (69%) and a large proportion of the reoperated patients with PJI was infected with coagulase-negative staphylococcus (60%), a low-virulent bacterium, which usually only causes subtle clinical abnormalities (23,24). In these patients, diagnostic tests can be most helpful in clinical decision-making. In patients with frank clinical signs of PJI, it will merely confirm the clinical diagnosis.

Using the accepted criterion of visually increased 18F-FDG uptake at the bone–prosthesis interface at the central portion of the acetabular cup or at the middle portion of the femoral shaft as being consistent with PJI (17–19), sensitivity of 18F-FDG PET was good (0.81), whereas specificity was moderate (0.68) and a little lower than previously reported in the literature (19,25). In our comparative analyses, the weighting of the 18F-FDG PET/CT result was set equally to

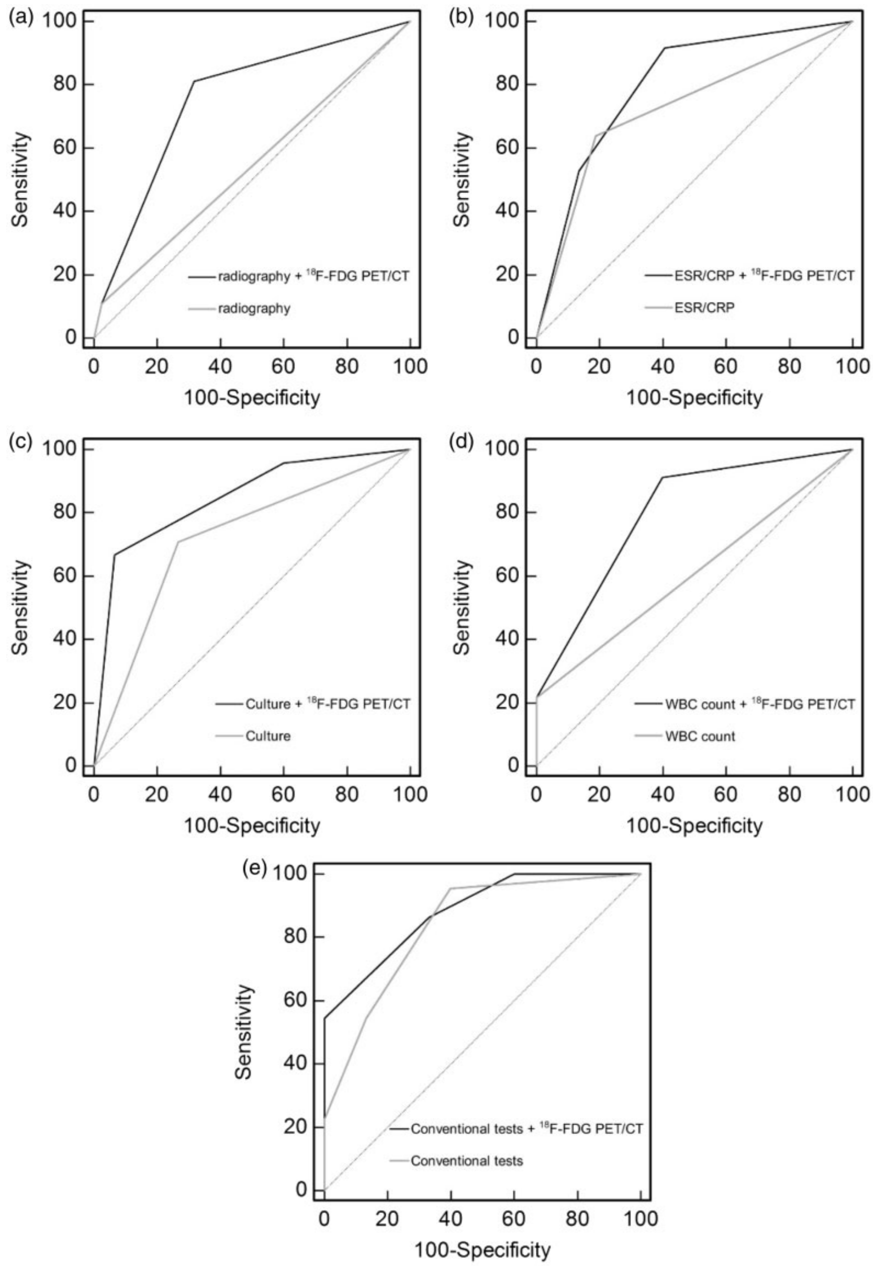

Fig. 4. ROC curves of individual conventional tests: (a) radiography, (b) ESR/CRP testing, (c) aspiration culture, (d) WBC count, and (e) conventional tests combined; without and with the addition of 18F-FDG PET/CT.

those of all individual conventional test results. Our study shows that 18F-FDG PET/CT adds to individual conventional tests in diagnosing PJI. However, the addition of 18F-FDG PET/CT did not significantly increase the diagnostic performance of all conventional test results combined. The analyses using an optimized SUV_{max} of 3.2 as threshold were in accordance to the analyses using visual assessment. It should be noted that the analysis with all test results combined was performed in only 37 of the 78 included patients, because in these 37 patients all diagnostic tests were available. We cannot rule out a type II error. Although 18F-FDG PET/CT may help diagnosing PJI, it is a relatively expensive, radiation-based, and time-consuming test. Future studies should define the exact place of 18F-FDG PET/CT in the diagnostic work-up of PJI.

Our study has several limitations. First, our study had a retrospective design, with inherent risk of selection bias. In particular, only half of the included patients (39/78) underwent joint aspiration. Second, there is no perfect gold standard for PJI available (26). In 44 patients who did not undergo revision

Table 3. Areas under the receiver characteristic operating curves of conventional tests (radiography, ESR/CRP testing, joint aspiration culture, and joint aspiration WBC count) without and with the addition of 18F-FDG PET/CT, using visual assessment of 18F-FDG uptake.

Diagnostic test(s)	Sample size	AUC	AUC difference	*P* value
Radiography	78	0.542	0.212	0.001
Radiography + 18F-FDG PET/CT		0.754		
ESR/ CRP	73	0.725	0.076	0.072
ESR/ CRP + 18F-FDG PET/CT		0.801		
Culture	39	0.721	0.126	0.032
Culture + 18F-FDG PET/CT		0.847		
WBC count	38	0.609	0.191	0.035
WBC count + 18F-FDG PET/CT		0.800		
Radiography, ESR/ CRP, culture, and WBC count	37	0.838	0.045	0.139
Radiography, ESR/ CRP, culture, and WBC count + 18F-FDG PET/CT		0.883		

AUC, area under the receiver characteristic operating curve.

Table 4. Areas under the receiver characteristic operating curves of conventional tests (radiography, ESR/CRP testing, joint aspiration culture, and joint aspiration WBC count) without and with the addition of 18F-FDG PET/CT, using SUV_{max} measurement.

Diagnostic test(s)	Sample size	AUC	AUC difference	*P* value
Radiography	76*	0.545	0.206	0.002
Radiography + 18F-FDG PET/CT		0.751		
ESR/ CRP	71*	0.714	0.080	0.057
ESR/ CRP + 18F-FDG PET/CT		0.795		
Culture	39	0.721	0.100	0.103
Culture + 18F-FDG PET/CT		0.821		
WBC count	38	0.609	0.172	0.087
WBC count + 18F-FDG PET/CT		0.781		
Radiography, ESR/ CRP, culture, and WBC count	37	0.838	0.046	0.177
Radiography, ESR/ CRP, culture, and WBC count + 18F-FDG PET/CT		0.879		

*Two hips were not included because SUV_{max} measurements were not reliable due to technical error.
AUC, area under the receiver characteristic operating curve.

surgery, we used clinical follow-up ≥ 6 months as gold standard. Although this is an accepted method, used in a previous study (19), cultures of material obtained at revision surgery may have been a better gold standard. Of note, in the first 12 of 34 patients who did undergo revision surgery, only conventional cultures of material obtained at revision surgery were performed, because the sonication culture technique was not yet available in our hospital at that time. Although the sonication culture technique is more sensitive (20), we believe that the use of conventional cultures in these 12 patients had, if any, negligible impact on our results, since only two patients could have had a (possibly false) negative culture. Furthermore, it may be worth considering that some patients without prosthesis failure may have had successful antibiotic treatment and could have been incorrectly categorized as non-infected. Third, we did not correct for multiple (n = 5) comparisons (Table 3). A Bonferroni correction might have been appropriate, but a disadvantage of Bonferroni correction is that it tends to be too conservative (27). Fourth, we only evaluated the inflammation markers ESR and serum CRP. A recent meta-analysis showed that the diagnostic accuracy of serum interleukin-6 for PJI may be higher than ESR and serum CRP (28). However, serum interleukin-6 values were not available in our study population. It should also be stressed that the results of our study do not imply that 18F-FDG PET/CT is the best nuclear imaging test to be used in the work-up of suspected PJI. The value of other nuclear imaging tests, such as combined labeled leukocyte/bone marrow scintigraphy (29), were not evaluated in our study.

In conclusion, this study shows that 18F-FDG PET/CT adds to individual conventional tests in diagnosing infected hip prosthesis. It may improve the preoperative planning and should therefore be considered in the diagnostic work-up. Future studies should define the exact place of 18F-FDG PET/CT in the diagnostic work-up of PJI.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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