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Clinical Study

Evaluation of the diagnostic performance of ^{18}F-NaF positron emission tomography/computed tomography in patients with suspected ankylosing spondylitis according to the Assessment of SpondyloArthritis International Society criteria

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Abstract

BACKGROUND CONTEXT: Positron emission tomography (PET) is a potential imaging technique for the diagnosis of AS. The visualization of physiological change makes PET potentially suitable for early detection of inflammatory processes, even before anatomical changes occur. Thus, PET might provide specificity via the use of receptor targeting tracers and allows quantification of disease activity in order to accurately monitor therapeutic effects.

PURPOSE: To examine fluorine-18 sodium fluoride (^{18}F-NaF) PET/computed tomography (PET/CT) findings in patients with inflammatory low back pain and evaluate the utility of this modality in the diagnosis of ankylosing spondylitis (AS) according to the Assessment of SpondyloArthritis International Society (ASAS) criteria.

STUDY DESIGN: Retrospective cohort study.

PATIENTS SAMPLE: Sixty-eight patients who underwent ^{18}F-NaF PET/CT imaging between April 2015 and April 2017 for evaluation of inflammatory low back pain.

OUTCOME MEASURES: We defined AS-positive lesions on PET/CT as symmetric sacroiliac joint uptake that suggests sacroiliitis, syndesmophytes on the spine, and enthesopathy at any site.

METHODS: All patients were evaluated using the ASAS criteria and assigned to either the AS or the control group. The diagnostic criteria of AS on PET/CT images were defined as ^{18}F-NaF PET/CT images with at least one of AS-positive findings.

RESULTS: The diagnostic rate of AS was 72.1% among the 68 patients according to the ASAS criteria. The baseline characteristics between the two groups differed significantly in terms of serum C-reactive protein levels and the presence of human leucocyte antigen-B27. Compared to the control group, in the AS group, 39 patients (79.5%) exhibited typical ^{18}F-NaF PET/CT-positive

Abbreviations: AS, ankylosing spondylitis; ASAS, Assessment of SpondyloArthritis International Society; AUC, area under the curve; BASDAI, Bath AS Disease Activity Index; BASFI, Bath AS Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA, human leucocyte antigen; IQR, interquartile range; MRI, magnetic resonance imaging; NaF, sodium fluoride; PET, positron emission tomography; ROC, receiver operating characteristic; SI, sacroiliac; SUV, standardized uptake value; SUVR, SUV ratio

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findings, such as enthesopathy (65.3%, p=.003), syndesmophytes (61.2%, p=.006) and symmetric sacroiliitis (67.3%, p=.001). PET-positive findings had significantly higher area under the curve values than did single ^{18}F-NaF PET/CT- positive findings, and they had the best performance for concordant diagnosis according to the ASAS criteria.

CONCLUSIONS: ^{18}F-NaF PET/CT yielded significantly different findings between the two groups according to the ASAS criteria and is useful for diagnosing AS.

Keywords: Positron emission tomography/computed tomography; Ankylosing spondylitis; Assessment of SpondyloArthritis International Society criteria; Diagnosis; Sacroiliitis; Enthesopathy; Syndesmophyte

Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory disease that typically shows onset at an early age and can result in irreversible bone deformation and long-term disability. AS is characterized by back pain, limited motion of the spine, and sacroiliitis on plain radiography. Peripheral arthritis and enthesitis may also be prominent features [1]. Entheses are sites at which tendons, ligaments, or joint capsules attach to the bone, and enthesitis is another characteristic feature of axial spondylo-arthropathy. Enthesitis results in new bone proliferation, providing the basis for eventual bony ankyloses [2].

Until recently, plain radiographs were required for the diagnosis of AS, according to the modified New York criteria [3]. The disadvantage of this imaging technique is that the disease typically develops over many years before definite radiographic sacroiliitis appears [4].

The Assessment of SpondyloArthritis International Society (ASAS) has published new classification criteria for the assessment of axial spondyloarthritis (Fig. 1) [5]. The development of these criteria was necessary because the older modified New York criteria for AS did not allow identification early in the course of the disease in the absence of radiographic changes in the sacroiliac (SI) joints, which can take years to manifest. To enable earlier diagnosis, highly reliable and sensitive imaging techniques are needed.

Currently, magnetic resonance imaging (MRI) is believed to be a sensitive imaging modality for the detection of sacroiliitis and inflammation of the spine in early AS. MRI detects early inflammation by visualization of tissue edema, enhanced gadolinium contrast uptake, or both of these. However, these imaging findings are nonspecific indicators of increased free water content and increased vascularization, respectively [6,7]. Moreover, chronic AS changes, such as new bone formation in the spine (eg, syndesmophyte formation), tend to be less well visualized on MRI than on radiographs [8]. Therefore, the precise role of MRI in visualizing the disease activity of AS has not yet been fully elucidated. Despite the use of MRI for the diagnosis of AS, the imaging arm alone of the ASAS classification criteria has 66.2% sensitivity and 97.3% specificity [5].

Positron emission tomography (PET) is another interesting imaging technique for the diagnosis of AS. PET allows sensitive imaging of functional tissue changes in the whole body by targeting binding sites [9]. The visualization of pathophysiology makes PET potentially suitable for early detection of inflammatory processes, even before anatomical changes occur. Because the hydroxyapatite matrix ($Ca_{10}(PO_4)_6OH_2$) forms fluorapatite ($Ca_{10}(PO_4)_6F_2$) before the occurrence of anatomical change in both osteoblastic and osteolytic lesions, PET has a potential role as a functional imaging technique that might allow sensitive imaging of functional tissue changes in the whole body, where the regional blood flow and bone turnover is changing, before anatomical change occurs [10,11]. The bone tracer fluorine-18 sodium fluoride (^{18}F-NaF) may have potential for AS imaging since AS is characterized by syndesmophyte formation and ankylosis in the vertebral column and SI joints. [12,13]. Thus, PET provides specificity via the use of receptor targeting tracers and allows quantification of disease activity in order to accurately monitor therapeutic effects [14]. Recently, PET/computed tomography (PET/CT) scanning was introduced as a hybrid imaging technique that combines the unique properties of sensitive imaging of pathophysiology and anatomical CT imaging as a reference [15]. In this manner, PET/CT offers the opportunity to visualize early inflammatory changes as well as early structural changes, such as new bone formation, which is difficult to detect on MRI.

The purpose of this study was to evaluate the diagnostic value of ^{18}F-NaF PET/CT in patients with suspected AS.

Material and methods

Patient population

Sixty-eight consecutive patients underwent ^{18}F-NaF PET/CT studies between April 2015 and April 2017 for the evaluation of inflammatory low back pain; their data were retrospectively reviewed. The primary features of inflammatory back pain include relatively young age of onset (<45 years), morning stiffness, back pain present for ≥3 months, and pain relieved by movement [16]. The study inclusion criteria included complaints of inflammatory back pain and limited lumbar movement. All patients underwent conventional radiography of the entire spine, lumbar spine including anterior/posterior and lateral views, and both sacroiliac joint oblique views for screening. Among the 68 patients, 49 patients (72.1%) who met the ASAS diagnostic

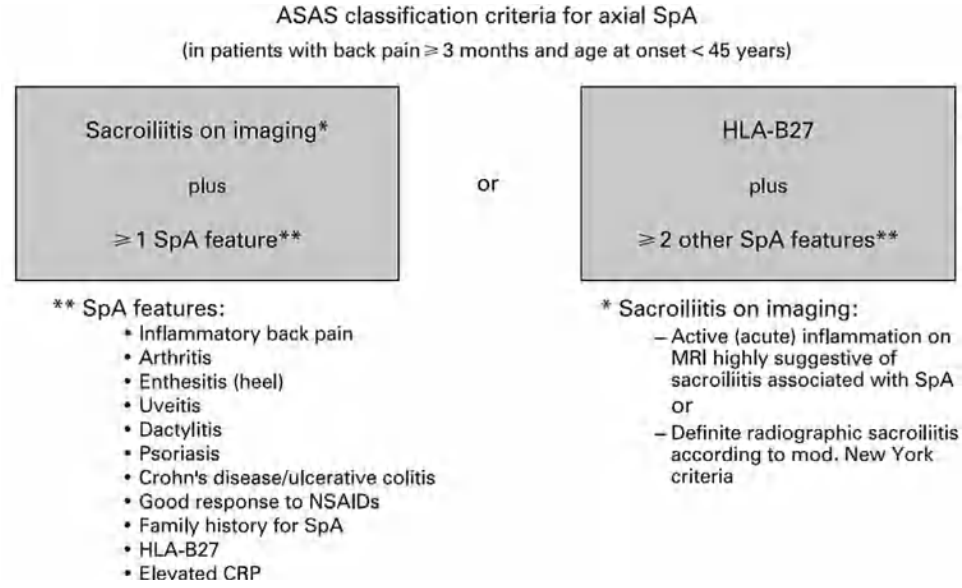

Fig. 1. The Assessment of SpondyloArthritis International Society criteria for diagnosing axial spondyloarthritis. Adapted from Rudwaleit M, van der Heijde D, Landewe R, et al. According to the New York criteria, sacroiliitis is scored, ranging from 0 to 4 per reading: grade 0=normal; grade 1=suspicious changes; grade 2=minimum abnormality (small localized areas with erosion or sclerosis without alteration in joint width); grade 3=unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing, or partial ankyloses); grade 4=severe abnormality (total ankyloses). In the modified New York criteria for ankylosing spondylitis, the radiologic criterion was defined as sacroiliitis of grade ≥2 bilaterally or grade 3 to 4 unilaterally. SpA, Spondyloarthritis.

criteria [5] were included as the AS group. Nineteen patients (27.9%) who did not satisfy the ASAS criteria were allocated to the control group. After evaluation, the patients in the control group were diagnosed with lumbar strain, facet joint syndrome, etc. Patients with pain originating from the spine owing to other medical conditions, such as pregnancy were excluded. Previous or concurrent diseases of the spine (eg, spinal deformities, vertebral fracture, spinal stenosis, degenerative intervertebral disc disease, or spinal surgery) or concomitant neurological or psychiatric diseases were also excluded. For assessment of the disease status, the Bath AS Disease Activity Index (BASDAI) score [17] and Bath AS Functional Index (BASFI) [18] were determined. Furthermore, laboratory tests including the presence of human leucocyte antigen (HLA)-B27, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level were also measured since hematologic factors such as ESR or CRP levels can reflect the level of AS disease activity. The present study was approved by the Research and Ethical Review Board of Pusan National University Hospital.

PET-CT scan

All ^{18}F-NaF PET/CT scans were acquired with a high-resolution PET/CT scanner, Gemini TF or Ingenuity TF (Philips Healthcare, Andover, MA). Per patient, a mean of 370 MBq of ^{18}F-NaF was injected. At 60 minutes postinjection, 30 minutes whole body scans were performed using an axial field of view of 18 cm. A low-dose noncontrast CT scan (30 mA, 120 kV, 512×512 matrix, slice thickness 3 mm) was performed for attenuation correction and to obtain anatomical information after the PET scan. The acquired PET images were reconstructed using the three-dimension row-action maximum likelihood iterative reconstruction algorithm. The reconstructed static PET images were converted to standardized uptake value (SUV) images and ^{18}F-NaF uptake was measured using the Philips Extended Brilliance Workspace version 4.5.3.40140 (Philips Healthcare, Best, The Netherlands) using the maximum SUV.

Imaging analysis

For imaging assessment, all patients underwent conventional radiography for sacroiliitis and ^{18}F-NaF PET/CT. Twelve patients who had typical clinical features of AS but no definite evidence of sacroiliitis on conventional radiography underwent MRI for evaluation of acute inflammation of the SI joint. Sacroiliitis was evaluated twice via conventional radiography and MRI independently by two spinal surgeons (S.M.S and J.S.L) with an interval of 2 weeks. Furthermore, all PET/CT images were reviewed by a nuclear medicine physician (K.K), who was blinded to the patients' details and clinical characteristics.

Based on a literature review [8,19–22], we defined AS-positive lesions on PET/CT as symmetric SI joint uptake that suggests sacroiliitis (Fig. 2), syndesmophytes on the spine (Fig. 3a–c), and enthesopathy at any site (Fig. 3a, d, e) such as the spinous process, interspinous ligament, attachment site of the hip or shoulder articular capsules,

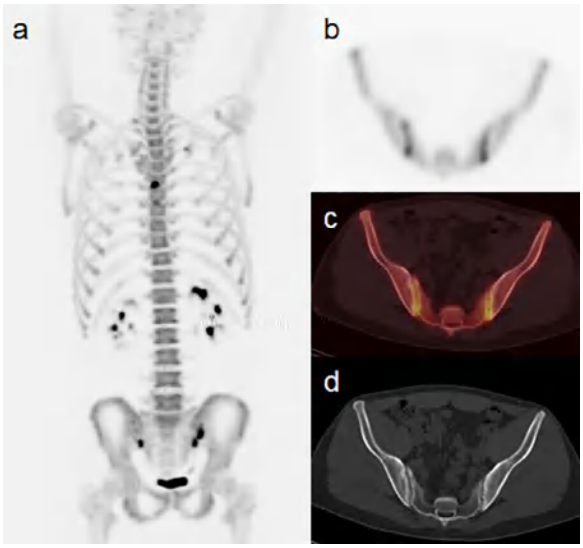

Fig. 2. ^{18}F-NaF positron emission tomography image of a 25-year-old patient who was diagnosed with ankylosing spondylitis according to the Assessment of SpondyloArthritis International Society criteria. The maximum intensity projection image (a) and axial images indicates predominant F-18 NaF uptake at the bilateral sacroiliac joint (right maximum standardized uptake value [SUVmax]=9.67 and left SUVmax 21.41; b–d).

costovertebral joint, or pubic ramus. AS-positive lesions were distinguished from osteoarthritis lesions by two orthopedic experts on conventional X-ray and/or low-dose CT. Lesions were regarded as degenerative if no signs of AS were present close to the lesions.

The diagnostic criteria of AS on PET/CT images were defined as ^{18}F-NaF PET/CT images with at least one of the positive findings described above without other distinguishable etiologies of low back pain, such as compression fracture, degenerative osteophyte, or Schmorl's nodule (Fig. 4).

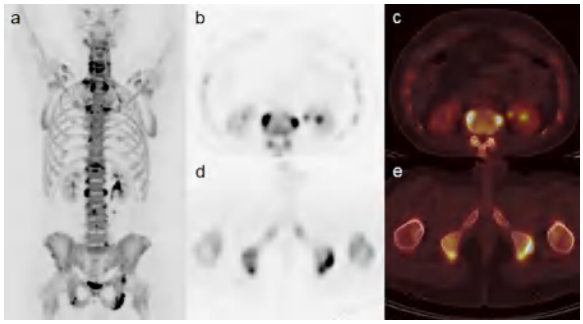

Fig. 3. ^{18}F-NaF positron emission tomography image of a 33-year-old patient who was diagnosed with ankylosing spondylitis according to the Assessment of SpondyloArthritis International Society criteria. The maximum intensity projection image (a) reveals several positive findings including syndesmophytes of T-, L- spines, particularly at L1 with a maximum standardized uptake value (SUVmax) of 8.76 (b, c), and enthesopathies of the bilateral ischial tuberosity (right SUVmax=6.37 and left SUVmax=7.02; d, e).

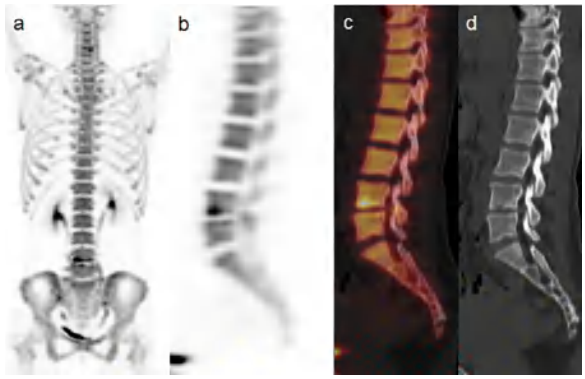

Fig. 4. ^{18}F-NaF positron emission tomography image of a 38-year-old patient who was diagnosed with ankylosing spondylitis according to the Assessment of SpondyloArthritis International Society criteria and tested positive for serological human leucocyte antigen-B27. However, significant ^{18}F-NaF uptake was observed at the lower end plate of L4 (maximum standardized uptake value [SUVmax]=8.53) and upper end plate L5 (SUVmax=6.92; a), which is suggestive of degenerative changes in the L-spines. Diagnosis of degenerative change in the lower back was made; this diagnosis was supported by the presence of Schmorl's nodes, which were found on the sagittal plane images of both positron emission tomography and nonenhanced computed tomography (b–d). This case was considered to be false positive.

Statistical analysis

All variables with non-normal distributions are expressed as medians and interquartile ranges (IQRs; 25%–75%). The Mann-Whitney *U* test was used to compare continuous variables between the two groups. The chi-square test was used to compare the two groups of categorical data. Receiver operating characteristic curves were plotted to determine the most rational optimal cut-off values of continuous data for logistic regression analysis for predicting the responders. Statistical analyses were performed using MedCalc software (MedCalc, Mariakerke, Belgium), version 16.4.3, and a p value of $<.05$ was considered indicative of significance.

Results

Patient characteristics

The baseline characteristics of the 68 patients who underwent ^{18}F-NaF PET/CT imaging are summarized in Table 1. Overall, the median age was 35 years (range 19–58 years) and 59.3 % (n=43) of the patients were male. The average disease duration was shorter in the AS group (mean 11 months) than in the control group (mean 17 months). However, there was no significant difference between the two groups. The median age, gender, duration of disease, BASDAI score, BASFI score, and ESR level at diagnosis did not significantly differ between the groups. However, the CRP level at diagnosis (median, 0.070; [IQR, 0.020–0.185] vs. 0.030 [IQR, 0.000–0.050], $p<.0127$) was higher in the AS group than in the control group. The

Table 1
Baseline characteristics of the participants

Characteristics	No. of patients (%) & median values (IQR)*		p Value
Total no. of patients with ≥ 3 mo back pain	68		
ASAS criteria	Positive	Negative	
	49 (72.1%)	19 (27.9%)	
Gender (M:F)	30:19	13:6	.5836
Age	37 (29.8–50.3)	30 (26.5–46.8)	.4278
Duration of disease (mo)	11.433 (4.808–19.992)	17.100 (9.6333–22.375)	.1630
Positive HLA-B27	41 (83.7%)	2 (10.5%)	<.0001
BASDAI score	4.300 (3.300–5.625)	4.000 (3.0750–5.2750)	.5845
BASFI score	0.800 (0.275–2.075)	0.700 (0.000–1.275)	.5587
CRP level at diagnosis	0.070 (0.020–0.185)	0.030 (0.000–0.050)	<.0127
ESR level at diagnosis	3.000 (2.000–9.250)	2.000 (2.000–4.250)	.1458

* Variables are expressed as the median (interquartile range; IQR).ASAS, The Assessment of SpondyloArthritis International Society; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, The Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HLA-B27, Human leukocyte antigen subtype B27.

presence of HLA-B27 was also more common in the AS group (83.7% vs. 10.5%, p<.001).

Characteristic findings of F-18 NaF PET/CT

Compared to the control group (Figs. 5 and 6), among the 49 patients in the AS group, 39 (79.5 %) exhibited typical ^{18}F-NaF PET/CT-positive findings, such as enthesopathy (65.3%, p=.0033), syndesmophytes (61.2%, p=.0069), and symmetric sacroiliitis (67.3%, p=.0001) (Table 2). Combining the ^{18}F-NaF PET/CT findings, 79.6% of patients who were diagnosed as PET-positive were

Table 2
Characteristic finding of ^{18}F-NaF PET/CT according to ASAS criteria

ASAS criteria	Positive (n=49)	Negative (n=19)	p Value
Enthesopathy	32:17	0:19	.0033
Syndesmophyte	30:19	1:18	.0069
Symmetric sacroiliitis	33:16	3:16	.0001
PET positive	39:10	3:16	<.0001
SUVR of SIJ	0.842 (0.756–1.021)	0.725 (0.654–0.824)	.0035

ASAS, The Assessment of SpondyloArthritis International Society; NaF, sodium fluoride; PET/CT, positron emission tomography/computed tomography; ; SIJ, sacroiliac joint; SUVR, standard uptake value ratio.

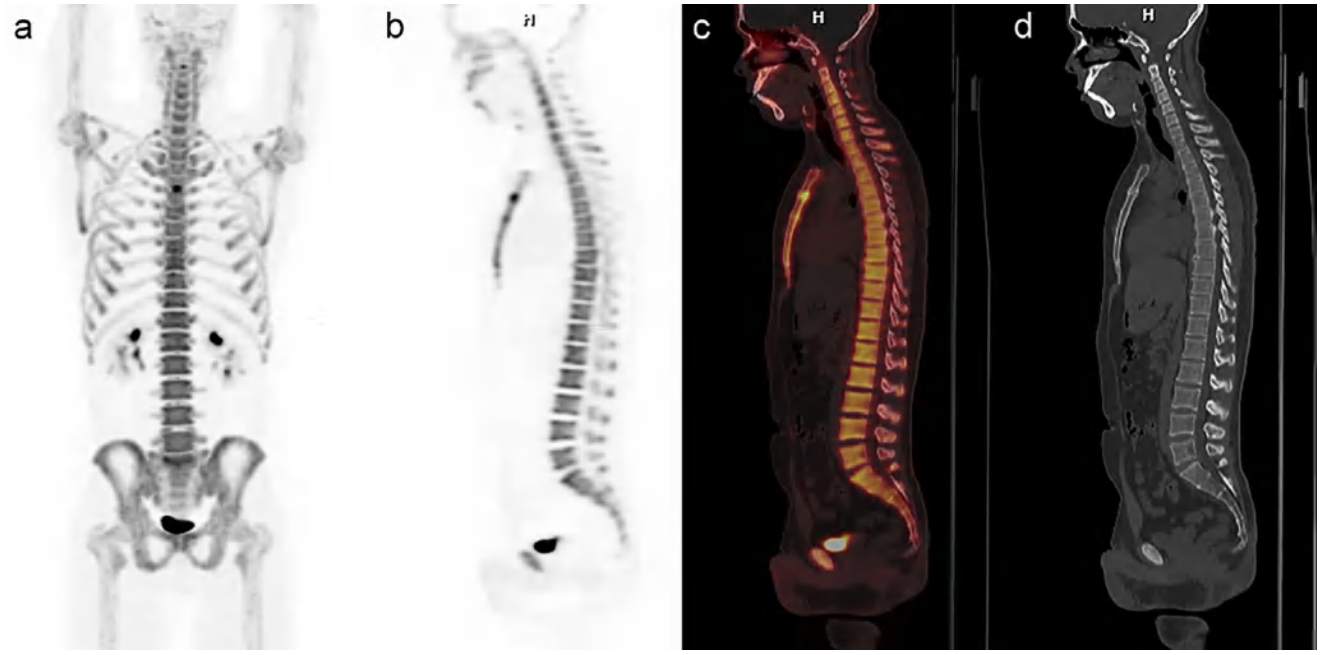

Fig. 5. ^{18}F-NaF positron emission tomography image of a 29-year-old patient with chronic lower back pain who tested negative for serological human leucocyte antigen B27 and did not meet the Assessment of SpondyloArthritis International Society criteria for ankylosing spondylitis. The maximum intensity projection image (a) and sagittal plane images of both positron emission tomography and nonenhanced computed tomography (b–d) are represented as a normal scan.

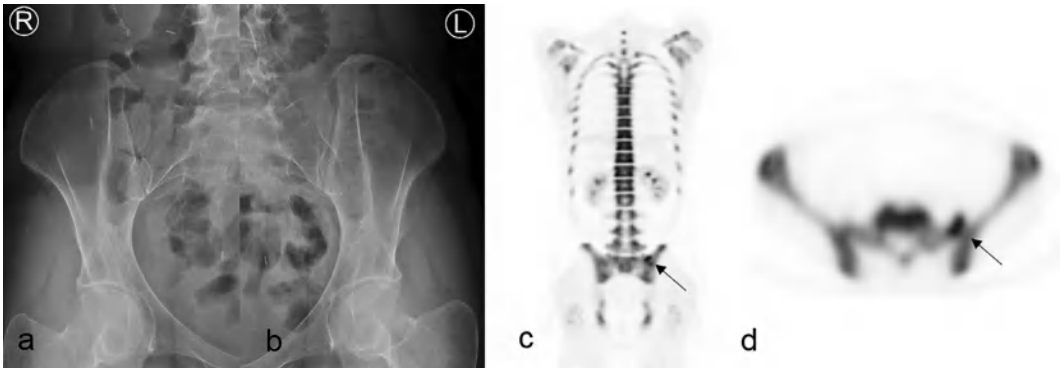

Fig. 6. Sacroiliac joint oblique X-ray and ^{18}F-NaF positron emission tomography/computed tomography images of a 48-year-old patient with chronic lower back pain who tested negative for serological human leucocyte antigen B27 and did not meet the Assessment of SpondyloArthritis International Society criteria for ankylosing spondylitis. Conventional X-ray was not indicative of sacroiliitis (a, b). However, increased uptake at the left sacroiliac joint on the F-18 NaF positron emission tomography/computed tomography image was observed (c, d) and the patient was considered false negative according to Assessment of SpondyloArthritis International Society criteria.

concordant with the ASAS criteria. The SUV ratio (SUVR) of both SI joints was also significantly higher in the AS group (median, 0.842; [IQR, 0.756−1.021] vs. 0.725 [IQR, 0.654−0.824], p<.0035).

Diagnostic accuracy of F-18 NaF PET/CT

The presence of symmetric sacroiliitis (72.1 %) on ^{18}F-NaF PET/CT exhibited the highest diagnostic accuracy among the ^{18}F-NaF PET/CT findings. The ^{18}F-NaF PET/CT could discriminate the patients in the AS group from those in the control group by utilizing the presence of enthesopathy, syndesmophytes on the spine, sacroiliitis, SUVR, and PET-positive criteria with sensitivities of 65.3, 61.2, 67.4, 71.4 and 79.6%; specificities of 100, 94.7, 84.2, 68.4, and 84.2%; positive predictive values of 100, 96.8, 91.7, 85.4, and 92.9%; and negative predictive values of 52.8, 48.7, 50.0, 48.2, and 61.5%, respectively (Table 3). The ability of PET/CT-positive findings including the SUVR, sacroiliitis, enthesopathy, and syndesmophytes on the spine, along with combined diagnostic criteria using PET/CT to diagnose the ASAS-positive patients, was depicted by an receiver operating characteristic curve. The PET-positive criteria, which were composed of findings of enthesopathy, syndesmophytes on the spine, and symmetric sacroiliitis had a significantly higher area under the curve (AUC) value than did single ^{18}F-NaF PET/CT-positive findings, and they had the best performance for concordant diagnosis according to the ASAS criteria (Fig. 7).

Discussion

For the diagnosis of AS, conventional radiography for sacroiliitis was considered the gold standard until now. However, diagnosis is often delayed by 5 to 10 years, particularly in patients with an early or incomplete clinical record [1,23]. To enable earlier diagnosis, highly reliable and sensitive imaging techniques are needed.

It is well known that MRI is highly sensitive for the detection of sacroiliitis in patients at the early stage of the disease. Nonetheless, conflicting data regarding the sensitivity and specificity of MRI in patients with suspected AS have been reported [5,19,24,25]. Therefore, the precise role of MRI in visualizing the disease activity of AS has not yet been fully elucidated.

Recently, PET/CT scanning that combines the unique properties of sensitive imaging of pathophysiology and anatomical CT imaging as a reference has been introduced [13]. Nuclear imaging techniques may detect increased bone turnover not only during inflammation, but likely also paralleling postinflammatory reparative changes at the start of new bone formation [20]. In this manner, PET/CT offers

Table 3
Diagnostic results of ^{18}F-NaF PET/CT

Characteristics	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Enthesopathy	65.3	100	100	52.8	47.0
Syndesmophyte	61.2	94.7	96.8	48.7	54.4
Symmetric sacroiliitis	67.4	84.2	91.7	50.0	72.1
SUVR of SIJ	71.4	68.4	85.4	48.2	63.2
PET positive	79.6	84.2	92.9	61.5	80.9

NaF, sodium fluoride; NPV, negative predictive value; PET/CT, positron emission tomography/computed tomography; PPV, positive predictive value; SIJ, sacroiliac joint; SUVR, standard uptake value ratio.

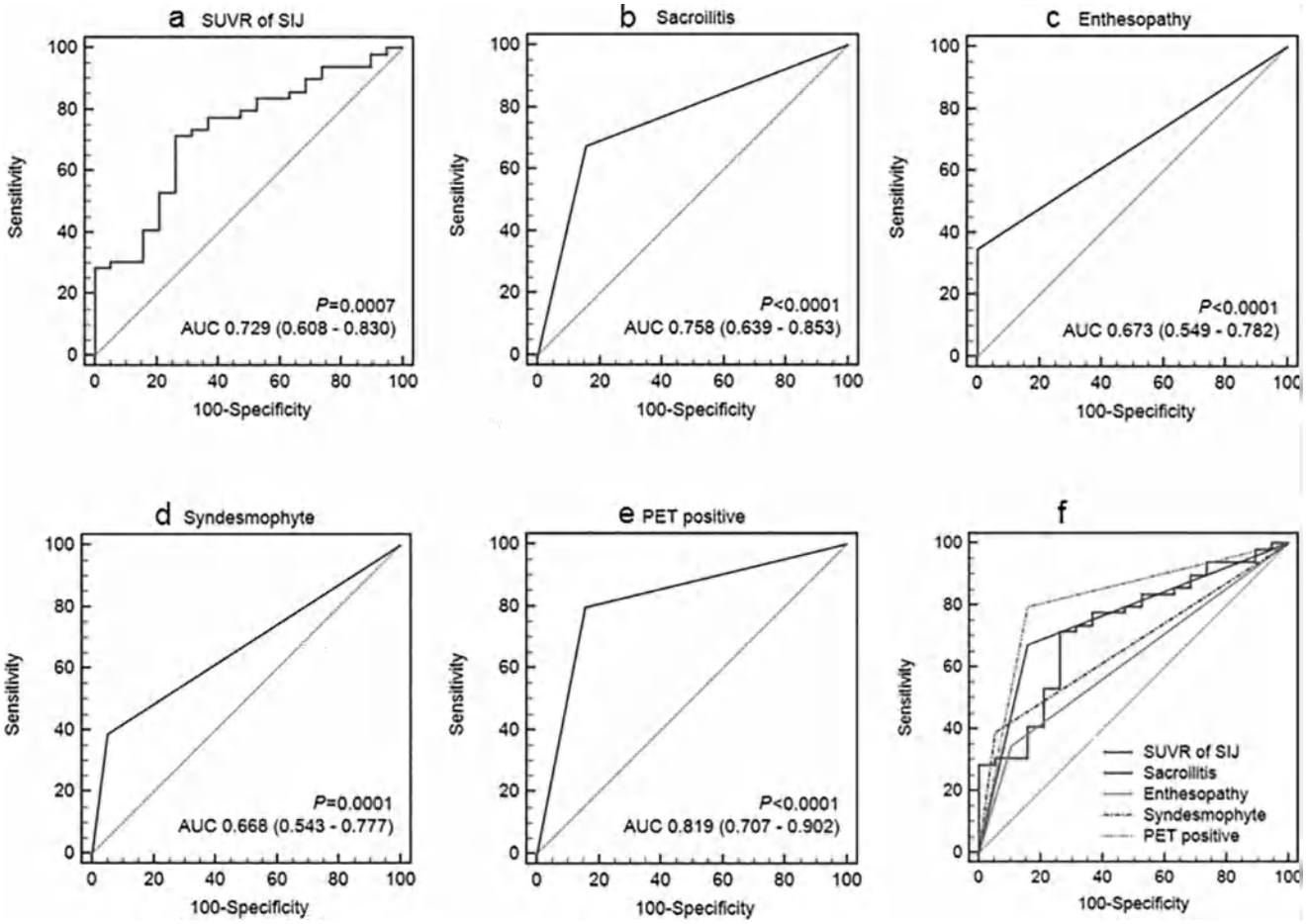

Fig. 7. R eceiver-operating characteristic curves. Receiver-operating characteristic (ROC) curves of the findings of ^{18}F-NaF positron emission tomography (PET)/computed tomography including the standardized uptake value ratio (SUVR) of the sacroiliac joint (SIJ) (a), presence of sacroiliitis (b), enthesopathy (c), syndesmophytes (d) and a combination of positive findings of PET images (e) for the diagnosis of Assessment of SpondyloArthritis International Society criteria positive spondylo-arthopathy. Comparison ROC analysis indicated that the combination of positive PET findings offer the best diagnostic performance compared to other findings (f). ROC curve analysis provides a complete sensitivity/specificity report and the comparative ROC curves illustrate the difference between the area under dependent ROC curves. AUC, area under the curve.

the opportunity to visualize early inflammatory changes as well as early structural changes such as new bone formation, which are difficult to detect on MRI.

The definite pathogenesis of AS is still unclear, and different joint structures may be involved in inflammatory sites in AS [21]. Therefore, different targets for the PET tracers must be considered. Synovial tissue, bone marrow, entheses, and ligaments can be affected in AS [22,26,27] and may need different tissue-specific PET tracers. The bone tracer ^{18}F-NaF may have potential for AS imaging since AS is characterized by syndesmophyte formation and ankylosis in the vertebral column and SI joints. Furthermore, ^{18}F-NaF uptake in active bone reflects local blood flow and regional osteoblastic activity [9,15].

Several studies have reported specific PET-positive lesions in patients with AS. Taniguchi et al. [28] reported significantly high fluorodeoxyglucose uptake in the sternoclavicular joints, lumbar spinous processes, SI joints, pubic symphysis, and ischial tuberosity in patients with spondyloarthritis. Bruijnen et al. [29] reported that PET-positive lesions were found in the costovertebral joints (43%), facet joints (23%), bridging syndesmophytes (20%), and nonbridging vertebral lesions (14%). The greatest number of PET-positive lesions was found in the thoracic spine. The SI joints were ^{18}F-NaF PET-positive in at least one SI joint in 9 of 10 (90%) patients.

Our findings suggest that ^{18}F-NaF PET/CT may be a useful procedure for the diagnosis of AS. The PET-positive criteria had a significantly higher AUC value than when compared with single positive findings and had the best performance for concordant diagnosis according to the ASAS criteria. PET/CT provides an excellent resolution of both inflammatory and osteoblastic sites. In a single exam, the entire skeleton may be examined, with a remarkable advantage over MRI.

Previous studies have attempted to evaluate the diagnostic performance of ^{18}F-NaF PET/CT in patients with AS. Bruijnen et al. [4] showed that targeting of bone formation

using ^{18}F-NaF tracer may be the most promising approach to visualize AS activity, and inflammatory tracers, such as ^{18}F-FDG and ^{11}C-PK11195, seem to be less useful for AS imaging. In addition, most MRI lesions corresponded to lesions with ^{18}F-NaF uptake on the PET scan. Raynal et al. [30] reported that ^{18}F-NaF PET/CT may be more sensitive than MRI or CT scans for the detection of inflammatory and/or structural sacroiliitis by detecting early lesions or scar lesions that are not visible on CT scans or MRI in patients with spondyloarthritis. In addition, the PET activity score and SUVmax had good correlations with inflammatory scroiliitis but not with structural lesion on CT scan. Fischer et al. [31] compared the distribution of the lesion with inflammation detected as bone marrow edema on whole-body MRI in patients with AS. They concluded that increased ^{18}F-NaF uptake in PET/CT is only modestly associated with bone marrow edema on MRI. However, they conducted ^{18}F-NaF PET/CT in a small number of patients [4,30,31]. In addition, they identified suspected peripheral lesions associated with AS in the sternum and shoulder but did not perform further evaluation [4], and there was no control group [30].

This study has several limitations that require consideration. First, the present study shows that patients can be heterogeneous in terms of disease activity, treatment periods, and treatment agents. The patients in our study underwent PET/CT during treatment. In comparing the BASDAI and BASFI scores between groups, there were no significant differences. We consider that the results may have originated from the heterogeneity of these patients. In the future, PET/CT image analysis according to homogenous disease status will be necessary. Second, the difference in the number of patients between the AS and control groups was significant, which may have affected the statistical significance. Third, in order to compare the diagnostic value of ^{18}F-NaF PET/CT and MRI, it is necessary for all patients to undergo the both imaging modalities. However, in the present study, MRI was performed for only 12 patients with clinically suspected AS who did not exhibit significant sacroiliitis on X-ray. Lastly, conventional radiography and pelvic MRI were used as imaging modalities for the diagnosis of AS. Therefore, it is possible that patients, such as those with spinal stenosis or degenerative intervertebral disc disease, whose condition was difficult to diagnose with the imaging modalities, may not have been completely excluded.

Despite these limitations, this study was conducted on a large number of patients who were unable to undergo previous studies, and it identified the specific characteristics of PET/CT images of AS patients. In addition, comparative study was possible because the patients could be evaluated together as a control group and an AS group. Furthermore, we assessed PET/CT imaging features using both quantitative and qualitative evaluations, and we found that these features had high diagnostic value when both modalities were conducted in a combined assessment. Qualitative evaluation is meaningful in that it is easily applicable in clinical practice.

Conclusions

In diagnosing AS, ^{18}F-NaF PET/CT had 79.6% sensitivity and 84.2% specificity. This demonstrates the diagnostic value of ^{18}F-NaF PET/CT, which may be a good alternative modality in the diagnosis of early AS, and is capable of evaluating whole body lesions in a single session. ^{18}F-NaF PET/CT had significant diagnostic value.

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References

[1] Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. Ann Rheum Dis 2002;61(Suppl 3):iii8–18.
[2] El-Khoury GY, Kathol MH, Brandser EA. Seronegative spondyloarthropathies. Radiol Clin North Am 1996;34:343–57.
[3] van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361–8.
[4] Bruijnen ST, van der Weijden MA, Klein JP, Hoekstra OS, Boellaard R, van Denderen JC, et al. Bone formation rather than inflammation reflects ankylosing spondylitis activity on PET-CT: a pilot study. Arthritis Res Ther 2012;14:R71.
[5] Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2009;68:777–83.
[6] Maksymowych WP, Lambert RG. Magnetic resonance imaging for spondyloarthritis—avoiding the minefield. J Rheumatol 2007;34(2):259–65.
[7] Rudwaleit M, Jurik AG, Hermann KG, Landewe R, van der Heijde D, Baraliakos X, et al. Defining active sacroiliitis on magnetic resonance imaging (MRI) for classification of axial spondyloarthritis: a consensual approach by the ASAS/OMERACT MRI group. Ann Rheum Dis 2009;68:1520–7.
[8] Braun J, Baraliakos X, Golder W, Hermann KG, Listing J, Brandt J, et al. Analysing chronic spinal changes in ankylosing spondylitis: a systematic comparison of conventional x rays with magnetic resonance imaging using established and new scoring systems. Ann Rheum Dis 2004;63:1046–55.
[9] Jones T. The role of positron emission tomography within the spectrum of medical imaging. Eur J Nucl Med 1996;23:207–11.
[10] Hawkins RA, Choi Y, Huang SC, Hoh CK, Dahlbom M, Schiepers C, et al. Evaluation of the skeletal kinetics of fluorine-18-fluoride ion with PET. J Nucl Med 1992;33:633–42.
[11] Piert M, Zittel TT, Becker GA, Jahn M, Stahlschmidt A, Maier G, et al. Assessment of porcine bone metabolism by dynamic. J Nucl Med 2001;42:1091–100.
[12] Cook GJ, Fogelman I. The role of positron emission tomography in the management of bone metastases. Cancer 2000;88:2927–33.
[13] Fischer DR, Maquieira GJ, Espinosa N, Zanetti M, Hesselmann R, Johayem A, et al. Therapeutic impact of [(18)F]fluoride positron-emission tomography/computed tomography on patients with unclear foot pain. Skeletal Radiol 2010;39:987–97.

[14] Elzinga EH, van der Laken CJ, Comans EF, Boellaard R, Hoekstra OS, Dijkmans BA, et al. 18F-FDG PET as a tool to predict the clinical outcome of infliximab treatment of rheumatoid arthritis: an explorative study. J Nucl Med 2011;52:77–80.
[15] von Schulthess GK, Steinert HC, Hany TF. Integrated PET/CT: current applications and future directions. Radiology 2006;238:405–22.
[16] Braun J, Inman R. Clinical significance of inflammatory back pain for diagnosis and screening of patients with axial spondyloarthritis. Ann Rheum Dis 2010;69:1264–8.
[17] Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286–91.
[18] Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281–5.
[19] Sieper J, Appel H, Braun J, Rudwaleit M. Critical appraisal of assessment of structural damage in ankylosing spondylitis: implications for treatment outcomes. Arthritis Rheum 2008;58:649–56.
[20] Rostom S, Dougados M, Gossec L. New tools for diagnosing spondyloarthropathy. Joint Bone Spine 2010;77:108–14.
[21] Rudwaleit M, Landewe R, van der Heijde D, Listing J, Brandt J, Braun J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part I): classification of paper patients by expert opinion including uncertainty appraisal. Ann Rheum Dis 2009;68:770–6.
[22] Weber U, Hodler J, Kubik RA, Rufibach K, Lambert RG, Kissling RO, et al. Sensitivity and specificity of spinal inflammatory lesions assessed by whole-body magnetic resonance imaging in patients with ankylosing spondylitis or recent-onset inflammatory back pain. Arthritis Rheum 2009;61:900–8.
[23] Maksymowych WP. MRI in ankylosing spondylitis. Curr Opin Rheumatol 2009;21:313–7.
[24] Maksymowych WP. Disease modification in ankylosing spondylitis. Nat Rev Rheumatol 2010;6:75–81.
[25] Frost ML, Cook GJ, Blake GM, Marsden PK, Benatar NA, Fogelman I. A prospective study of risedronate on regional bone metabolism and blood flow at the lumbar spine measured by 18F-fluoride positron emission tomography. J Bone Miner Res 2003;18:2215–22.
[26] Muche B, Bollow M, Francois RJ, Sieper J, Hamm B, Braun J. Anatomic structures involved in early- and late-stage sacroiliitis in spondylarthritis: a detailed analysis by contrast-enhanced magnetic resonance imaging. Arthritis Rheum 2003;48:1374–84.
[27] Tam LS, Gu J, Yu D. Pathogenesis of ankylosing spondylitis. Nat Rev Rheumatol 2010;6:399–405.
[28] Taniguchi Y, Arii K, Kumon Y, Fukumoto M, Ohnishi T, Horino T, et al. Positron emission tomography/computed tomography: a clinical tool for evaluation of enthesitis in patients with spondyloarthritides. Rheumatology (Oxford) 2010;49:348–54.
[29] Bruijnen STG, Verweij NJF, van Duivenvoorde LM, Bravenboer N, Baeten DLP, van Denderen CJ, et al. Bone formation in ankylosing spondylitis during anti-tumour necrosis factor therapy imaged by 18F-fluoride positron emission tomography. Rheumatology (Oxford) 2018;57:770.
[30] Raynal M, Bouderraoui F, Ouichka R, Melchior J, Morel O, Blum A, et al. Performance of ^{18}F-sodium fluoride positron emission tomography with computed tomography to assess inflammatory and structural sacroiliitis on magnetic resonance imaging and computed tomography, respectively, in axial spondyloarthritis. Arthritis Res Ther 2019;21:119.
[31] Fischer DR, Pfirrmann CW, Zubler V, Stumpe KD, Seifert B, Strobel K, et al. High bone turnover assessed by 18F-fluoride PET/CT in the spine and sacroiliac joints of patients with ankylosing spondylitis: comparison with inflammatory lesions detected by whole body MRI. EJNMMI Res 2012;2:38.