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FULL PAPER

Initial experience with ^{18}F-sodium fluoride (NaF) PET-CT: a viable functional biomarker in symptomatic Os acromiale

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Objective: Os acromiale (OA) is a failure of complete fusion of the acromial process. It is usually asymptomatic and discovered incidentally. OA can contribute to shoulder impingement symptoms and rotator cuff tears. ^{18}F Sodium Fluoride (NaF) Positron Emission Tomography -CT (PET-CT) is an emerging and highly sensitive modality for oncological skeletal staging, and can show a variety of non-malignant uptake. We have analysed the relationship between ^{18}F-NaF uptake in OA and associated symptoms of shoulder pain.

Methods: Study population included 21 patients (mean age 60.2 ± 12 years; 13 females and 8 males) with OA who underwent PET-CT scan by injecting 2.22 MBq kg^{-1} of ^{18}F-NaF. The relationship between ^{18}F-NaF uptake and OA as a cause of pain was analysed. A 3-point grading system was used to evaluate uptake of ^{18}F-NaF.

Results: In total 27 OA (12 symptomatic and 15 asymptomatic) were enrolled. All symptomatic OA showed focal increase tracer uptake of Grade 2, while asymptomatic OA did not have significant activity Grade 0 (n = 11) and Grade 1 (n = 4).

Conclusion: ^{18}F-NaF PET-CT appears to be a useful adjunct in the assessment of symptomatic OA with its particular strength being its high negative predictive value.

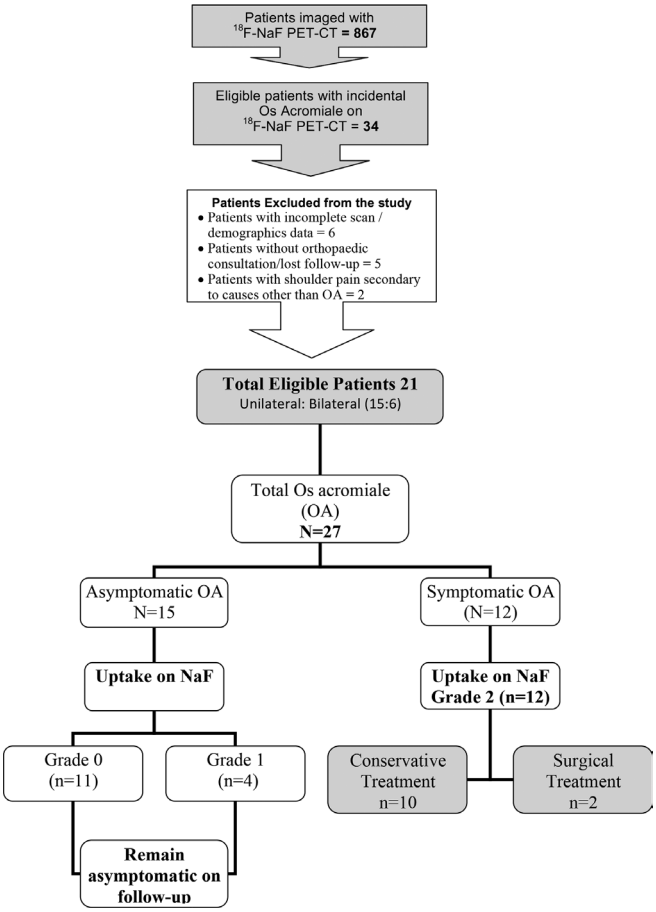
Advances in knowledge: ^{18}F-NaF PET-CT may be used as an ancillary tool for identifying symptomatic OA as a cause of shoulder pain in cases where other obvious causes of shoulder pain have been excluded.

INTRODUCTION

Os acromiale (OA) is the unfused epiphysis of the anterior part of the acromion that can be a potential source of shoulder pain.[1] OA is typically an incidental finding with reported incidence of about 8% in the population.[2,3] Symptomatic OA, can present as classic outlet impingement syndrome. In other patients, pain can be located directly over the superior acromion, especially when the fragment becomes more unstable.[4] OA can be missed on anteroposterior or y-view scapular radiographs but readily seen on CT with three-dimensional reconstructions.[5] MRI is a helpful adjunct in radiographic evaluation of indeterminate shoulder pain. In most patients, the OA defect appears as a vertical band of low signal intensity best seen posterior to a line bisecting the humeral head on oblique sagittal images. MRI may also detect oedema, or widening at the site of non-union, indicative of instability of OA.[6] Bone scanning, when positive, can be useful in assessing OA as a contributing factor in a painful shoulder, especially in patients at the cusp of skeletal maturity[7] with some reported cases of potential role of SPECT/CT (single photon emission CT) in painful OA.[8]

^{18}F Sodium Fluoride (NaF) Positron Emission Tomography -CT (PET-CT) hybrid imaging is an established imaging tool for skeletal oncological staging, which may be useful in the evaluation of benign bone and joint conditions.[9] However, given its high sensitivity, uptake on NaF PET can occasionally be non-specific. In a similar vein, the significance of focal uptake in ossicles is also not clear. Our institution has a high throughput of ^{18}F-NaF scans and our group noticed a variable degree of NaF uptake in incidentally detected uptake in ossicles, including OA. We therefore decided to assess the clinical significance of this observation by performing a study analysing if presence or absence of uptake can be a biomarker of symptomatic OA as a cause of shoulder pain.

Figure 1. Patient flow chart.



METHODS AND MATERIALS

The patient cohort was established by recruiting patients between October 2016 and July 2017. We prospectively identified incidental OA in patients undergoing ^{18}F-NaF PET-CT at Kuwait Cancer Control Center for oncological skeletal staging. When an incidental OA was identified, the Nuclear Medicine physician recorded if there was any ipsilateral shoulder pain and its relevant history either at the time of imaging or on telephone consultation. In addition, the following data were recorded for all patients: age, sex, study indication, symptomatic site, results of ^{18}F-NaF PET-CT and any other radiological studies. Patients with pain ipsilateral to the side of NaF uptake and no established diagnosis at the time of PET-CT were referred for formal orthopaedic review. The final diagnosis was based on findings on clinical follow-up and contemporaneous radiology (in symptomatic patients, formal orthopaedic assessment and clinical follow-up of at least 6 months after definitive treatment for example surgery and in asymptomatic patient's clinical follow-up of at least 4 months). The relationship between ^{18}F-NaF uptake and OA as a cause of shoulder pain was established based on this composite follow-up data. Cases with missing clinical and follow-up data, or already established cause for chronic shoulder pain were excluded from the study. A total of 34 patients were identified. Of these 6 patients were excluded due to inability to obtain complete clinical history, 5 patients were lost to orthopaedic follow-up (Figure 1) and 2 patients with mild focal uptake in the OA were excluded after competing cause for shoulder pain were identified in clinical history making assessment of the true significance of OA activity difficult (1 patient with a chronically unstable shoulder joint, and 1 patient with prior history of trauma to the left proximal humerus).

Hospital research and ethics committee approved this analysis and informed consent was waivered.

^{18}F-NaF PET-CT

Images were acquired after intravenous injection of 0.06 mCi kg^{-1} (2.22 MBq kg^{-1}) ^{18}F-NaF and a 60–90 min uptake period.[10] PET emission images were obtained in a three-dimensional mode at 2–3 min per bed position according to patient BMI [2 min for BMI <35 kg m^{-2}; 2.5 min (35.0–39.9 kg m^{-2}) and 3 min for BMI >40 kg m^{-2}] from vertex to toes and reconstructed with a standard iterative algorithm (ordered-subset expectation maximization, 3 iterative steps and 32 subsets) and filter cut-off 6.4 mm as recommended by the manufacturer. A non-contrast CT was performed using auto tube current of 50–120 mA determined by an automated algorithm based on the planar view to achieving a noise index of 20, 120 kVp and pitch 1.3. The CT axial images were reconstructed in a 512 × 512 matrix, with a thickness of 3.75 mm. PET, CT and fusion images were reviewed on a workstation integrated with a picture archiving and communication system on Hermes (Stockholm, Sweden) Hybrid viewer v. 2.2.

Image interpretation and data analysis

The ^{18}F-NaF PET-CT studies were independently analysed by two nuclear medicine specialists, who were blinded to all clinical details (including whether the patient had any symptoms or not) and results of other imaging methods. The degree of ^{18}F-NaF uptake in the accessory bone was graded on a 3-point scale by two nuclear physicians and any discrepancies were resolved by consensus reading. The 3-point scale was scored as follows: Grade 0, no uptake; Grade 1, mild uptake; and Grade 2, marked increase uptake. Mild uptake (Grade 1) was defined as activity similar or just above the adjacent coracoid bone. Marked increased uptake (Grade 2) was defined as markedly above the adjacent coracoid bone. Each site of abnormal radiotracer uptake and its morphological characteristics on CT were recorded.

RESULTS

In total 27 OA (12 symptomatic and 15 asymptomatic) were enrolled in 21 patients with mean age 60.2 years (13 females and 8 males). There were bilateral OA in 6 (29%) and unilateral in 15 patients (71%). General characteristics of the patients are described in Table 1.

All symptomatic OA showed focal increase tracer uptake of Grade 2 (Figures 2 and 3), while asymptomatic had either no uptake or mild activity *i.e.* Grade 0 (n = 11) and Grade 1 (n = 4) (Figure 4).

All symptomatic tracer avid OA referred to orthopaedics showed improvement in symptoms after treatment (conservative management in 10 patients and surgery in 2 patients). No asymptomatic or quiescent OA became symptomatic during

Table 1. Summary of patient characteristics

	Mean (SD)/Frequency
Mean age	60.2 ± 12
Dose (MBq)	145 ± 41
Gender Female:Male	13:8
Os acromiale (OA)	
Unilateral:Bilateral	15:6
Total OA	27
Symptomatic OA	
Number of OA	12
Laterality right:left	7:5
Grade on ^{18}F NaF	Grade 2 (n = 12)
Asymptomatic OA	
Number of OA	15
Laterality right : left	6:9
Grade on ^{18}F NaF	Grade 0 (n = 11) Grade 1 (n = 4)

OA, os acromiale.

Figure 2. A 42-year-old female with right-sided breast cancer and severe left shoulder pain. (a) MIP and (b) axial NaF image show increase tracer activity in the left acromioclavicular region (arrow), right knee, left ankle and both mid foot region. (c) CT images show unfused left anterior acromial ossification centre (OA) with sclerosis along the acromion-acromion articulation. (d) NaF fused axial images show increase tracer uptake at the articulation site (dotted arrow); findings are consistent with pathological uptake in a painful left OA. MIP, maximum intensity projections; NaF, Sodium Fluoride; OA, os acromiale.

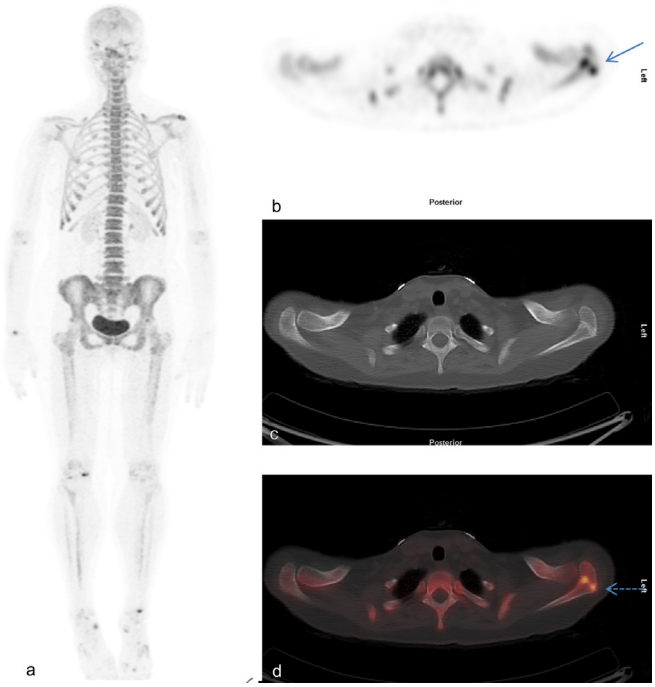
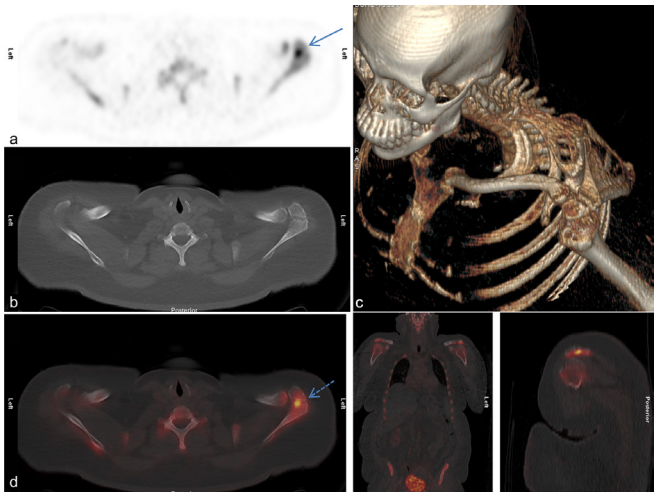


Figure 3. A 52-year-old female with left breast cancer, complaining of left shoulder pain. (a) Axial NaF shows increase tracer activity in the left acromial region (arrow). (b and c) CT and volume rendering CT images show unfused left anterior acromial ossification centre with an irregular border. (d) NaF Fused axial, coronal and sagittal images show focal increase tracer uptake at this articulation site (dotted arrow). Findings are consistent with osteoblastic activity in the left OA, which was congruent with symptoms on clinical review. NaF, Sodium Fluoride; OA, os acromiale.



clinical follow-up period. If increased radiotracer uptake is used as a diagnostic criteria for symptomatic OA in patients with no other obvious cause for pain, ^{18}F-NaF has a sensitivity, specificity, positive predictive value and negative predictive value of 100%

Figure 4. A 65-year-old male with a known case of rectal cancer. ^{18}F-NaF PET-CT is done to rule out bone metastasis. CT images show unfused accessory centre of ossification on the left side (middle row) in an asymptomatic patient. NaF PET and Fused PET-CT (upper and lower row) images show no significant tracer uptake at the articulation site. F-NaF, F Sodium Fluoride; PET, positron emission tomography.

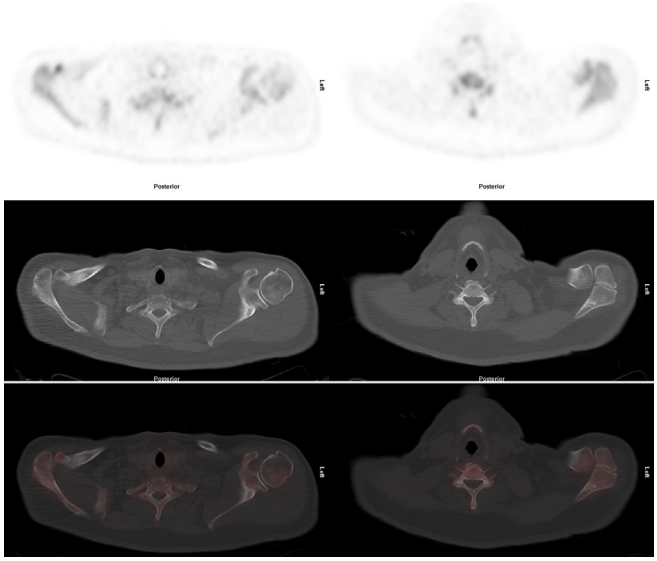
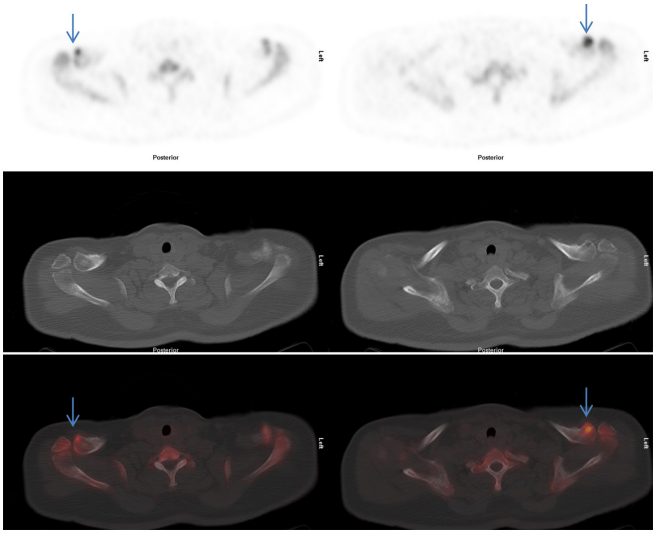


Figure 5. A 63-year-old female with right-sided breast cancer. Axial CT and fused PET-CT images show bilateral OA with no tracer uptake at articulation site. However, there is focal increased tracer uptake noted (arrow) along the left acromioclavicular joints (left more than right). Weight bearing stress radiographs demonstrated left ACJ instability. ACJ, acromio-clavicularjoint; OA, os acromiale; PET, positron emission tomography.



(95% Confidence Interval); however, our experience would suggest that the main utility would be in patients where OA as a cause of pain can be confidently excluded if there is no uptake. In 2 patients with pain ipsilateral to the uptake, NaF successfully identified quiescent OA, with activity centred on the acromio-clavicular joint (ACJ) and ACJ instability/arthropathy was thought to be the most likely cause of the pain (Figure 5).

DISCUSSION

OA is often an incidental radiographic finding discovered while examining a patient with shoulder pain. It is hypothesized to develop when one or more of the acromion ossification centres fail to unite with the others. The size and shape of the free acromial fragment is thought to depend on which of the ossification centres do not unite. Whilst OA may be completely unrelated to the true source of the patient's discomfort[11] it has been described as a potential source of impingement, either as a mobile fragment or from osteophytic lipping of the joint between the free fragment and the scapula. CT and MRI have been used in the identification of OA and could potentially be used to characterize the articulation;[12] however, it is usually difficult to predict whether OA is the dominant cause for the patient's symptoms, based entirely on the radiographic morphology with the main utility of these modalities being exclusion of competing causes.[13]

^{18}F-NaF PET-CT is a sensitive tool for detecting skeletal metastases[14] and has been found to be more sensitive and specific than ^{99m}Tc-MDP (99m-methyl diphosphonate) SPECT in the evaluation of osteoblastic metastases.[15,16] Compared with ^{99m}Tc-MDP, the bone uptake of ^{18}F-NaF is twice as great with minimal binding to serum proteins, allowing rapid single-pass extraction and fast clearance from the soft tissues.[17,18] This greater bone uptake and the faster soft-tissue clearance lead to shorter ^{18}F-NaF imaging time.[19] Lim et al[20] reported that the radiation dosimetry of ^{18}F-NaF PET is similar to that with ^{99m}Tc-MDP imaging. Encouraging results have also been reported for the use of ^{18}F-NaF in benign bone disease for example evaluation of back pain in adolescents, imaging of condylar hyperplasia and evaluation of suspected child abuse.[21,22] Few case reports also highlight the significance of ^{18}F-NaF PET-CT in symptomatic accessory bones.[23]

A functional biomarker to assess the clinical relevance of OA as a cause of pain in the shoulder would be beneficial given that some patients with intractable pain originating from the OA can be treated surgically and a reliable biomarker would make risk stratification and surgical planning easier. In our study, symptomatic patients with no other obvious cause of shoulder pain demonstrated increase ^{18}F-NaF uptake in the OA , while asymptomatic patients did not show any incidental significant activity *i.e* our results suggests that higher grade of ^{18}F-NaF uptake can predict OA as a cause of pain. To the best of our knowledge, this is the first report identifying qualitative ^{18}F-NaF assessment as a useful biological marker for symptomatic OA.

In our study, the localization of pain generating site was changed from OA to ACJ instability/arthropathy predominantly due to absence of osteoblastic activity in a quiescent OA and these findings were later confirmed with contemporaneous radiology (Figure 5). The interpretation of ^{18}F-NaF with fused CT images allows better morphological characterization, which improves the specificity. Recent studies in oncological settings show that ^{18}F-NaF PET-CT is more specific, accurate and has less equivocal findings.[24,25]

Our study had some limitations including its single institutional recruitment and relatively small numbers of patients. The relationship between uptake grade and clinical factors such as, degree of pain and amount of physical activity could also not be analysed due to lack of information. Nonetheless we set out to characterize our initial experience, which has shown that ^{18}F-NaF PET-CT is a useful imaging tool in the assessment of symptomatic OA. Indeed, increased bone turnover (high activity) may correlate better with sites of active pathology. The modality may be particularly useful in patients with an OA and the exact cause of pain being indeterminate. Similarly if uptake is incidentally detected in an OA, every attempt should be made to correlate this clinically and if appropriate, specialist orthopaedic opinion should be sought. More prospective studies with large cohort are needed to further clarify the clinical implications of these results.

CONCLUSIONS

^{18}F-NaF uptake in OA can be a clinically relevant finding, and in some patients, can provide valuable functional information with significant implications on management. We recommend ^{18}F-NaF PET-CT as a modality which can be helpful in establishing the true role of OA in patients with difficult to manage shoulder pain where other common and competing causes have been excluded.

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ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standard of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

The institutional review board of our institute approved this study and informed consent was waivered.

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