PET/CT Shows Subjective Pain in Shoulder Joints is Associated with Uptake of ^{18}F-FDG

Toshihiko Kamasaki[1,3], Naomi Hayashida[1], Izumi Miyamoto[4], Toshiya Usui[4], Kenya Chiba[4], Takashi Kudo[2], Noboru Takamura[1]

[1]Department of Global Health, Medicine and Welfare and [2]Department of Radioisotope Medicine, Atomic Bomb Disease Institute, Nagasaki University, 1-12-4 Sakamoto, Nagasaki 852-8523, Japan

[3]Department of Rehabilitation, Nishi-Isahaya Hospital, 3015 Kaizumachi, Isahaya-city, Nagasaki 854-0063, Japan

[4]Nishi-Isahaya Hospital PET/CT Diagnostic Imaging Center, 3015 Kaizumachi, Isahaya-city, Nagasaki 854-0063, Japan

Correspondence author:

Naomi Hayashida, M.D., Ph.D.

Lecturer, Department of Global Health, Medicine and Welfare

Atomic Bomb Disease Institute, Nagasaki University

1-12-4 Sakamoto, Nagasaki 852-8523, Japan

Tel: +81-95-819-7171; Fax: +81-819-7172

E-mail: naomin@nagasaki-u.ac.jp

Running head: Subjective Shoulder Joints Pain is Associated with Uptake of ^{18}F-FDG

Conflicts of Interest: None declared.

Abstract

Objectives The aim of the study was to evaluate the capability of ^{18}F-FDG-PET/CT for the screening of musculoskeletal inflammation and injury of shoulder region.

Materials and Methods The study included 122 participants (69 men, 53 women) who complained of shoulder pain at rest, and 122 age- and sex-matched controls who did not experience pain at rest. SUV values were calculated for both left and right shoulders and compared via a 4-point visual analog scale of subjective shoulder pain. Correlations between SUV values and uric acid (UA) and C-reactive proteins (CRP) were also evaluated.

Results SUV values for shoulder joints with rest and/or motion pains were significantly higher than those of pain-free shoulder joints. SUV values associated with mild and severe pain at rest were significantly higher than those without resting pain, and SUV values associated with moderate and severe pain on motion were significantly higher than that those without motion pain. Furthermore, SUV values were significantly correlated with UA in men ($\beta = 0.21$, $p = 0.02$) and in all participants ($\beta = 0.22$, $p < 0.001$).

Conclusion ^{18}F-FDG-PET/CT may be useful for the screening of musculoskeletal inflammation and injury of shoulder region. Since shoulder pain is common, especially among elderly individuals, we should carefully consider the necessity of further examination when identifying the uptake of ^{18}F-FDG in shoulder joints.

Key words: ^{18}F-FDG-PET/CT; shoulder joint; pain; SUV

Introduction

Shoulder pain is a common musculoskeletal problem that was reported in 7 % to 20 % of the adult population [1]. Shoulder pain is also one of the most common disorders affecting the musculoskeletal system and is becoming more common in today's aging society [2]. It is also reasonable to think that the incidence of other shoulder conditions is increasing with the growth of the geriatric population. Generally, in the early stage, simple physical examination and radiographs are commonly used to analyze shoulder disorders. Nowadays, these simple examinations are complemented by ultrasound and magnetic resonance imaging (MRI), which both enable more detailed evaluation [2–8].

Recently developed fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) is an imaging modality that can detect the rate of glucose metabolization [9, 10], which is especially high in tumor [11–13] and inflammatory cells [14–16]. Furthermore, ^{18}F-FDG PET/computed tomography (^{18}F-FDG PET/CT) is a single imaging technique that provides both morphological and metabolic features of neoplastic lesions. This technique performs better than MRI for differentiating symptomatic lesions among the various lesions that present simultaneously within a particular region. This is because ^{18}F-FDG PET reflects the difference in the uptake of FDG between the various tissues and bones based on their activity, and can therefore detect osteoblast activity or increased vascularity of clinically abnormal tissue. The technique also has the advantage of detecting any pathological lesion at a very early stage [17–20].

Furthermore, it has been suggested that incidental uptake of FDG may also represent musculoskeletal inflammation and/or injury and may be a marker for joint disease [1].

Since shoulder pain frequently indicates musculoskeletal inflammation and injury, we recruited from a general population who participated in an ^{18}F-FDG-PET/CT screening program; and evaluated the relationship between clinical symptoms, laboratory findings and the standardized uptake values (SUV: semi-quantitative parameter of ratio tracer uptake; regional FDG concentration normalized with the injected tracer dose and patient body weight) of shoulder joints. The aim of the study was to evaluate the capability of ^{18}F-FDG-PET/CT for the screening of musculoskeletal inflammation and injury of the shoulder region.

Materials and Methods

Study participants and questionnaire

We initially included 621 consecutive non-cancer subjects who underwent PET/CT screening for a cancer check-up at the Nishi-Isahaya Hospital PET/CT Diagnostic Imaging Center (Isahaya, Japan) between December 2010 and September 2011. The age of participants ranged from 25 to 87 (mean age: 59 years). Written informed consent was obtained from all 621 subjects.

The demographic characteristics of each study participant (e.g., gender, age, medical history, etc.) were obtained by self-reported questionnaires. Participants also answered questions regarding pain (resting pain and motion pain) in right and left shoulders.

Of the 621 study participants, 122 (69 men and 53 women) who complained of joint pain at rest were assigned to the “rest pain (+) group”, and 122 age- and sex-matched participants without resting pain were assigned to the “rest pain (−) group”. These participants assigned to the “rest pain (+) group” or “rest pain (−) group” were not asked whether they had motion pain. These 244 participants (488 shoulders) were included for further studies.

Among these 244 participants, 85 individuals (51 men and 34 women) who complained pain on joint movement were assigned to the “motion pain (+) group”, and 146 participants (79 men and 67 women) without motion pain were assigned to the “motion pain (−) group”. These participants assigned to the “motion pain (+) group” or “motion pain (−) group” were not asked whether they had resting pain. Among the 244 participants, 131 participants (73 men and 58 women) with rest pain and/or motion pain were assigned to the “rest and/or motion pain (+) group”. This “rest and/or motion pain

(+) group" contained the participants with resting pain only, motion pain only, or both pain. In addition, 113 participants (65 men and 48 women) with neither resting nor motion pain were assigned to the "rest and/or motion pains (−) group".

Among 488 shoulders, 141 shoulders showed resting pain (rest pain (+) shoulder), whereas 347 shoulders did not (rest pain (−) shoulder); 54 shoulders showed motion pain (motion pain (+) shoulder), whereas 434 shoulders did not (motion pain (−) shoulder). Furthermore, 150 shoulders showed rest pain and/or motion pain (rest and/or motion pains (+) shoulder), whereas 338 shoulders showed neither rest nor motion pain (rest and/or motion pains (−) shoulder).

Each participant who complained of shoulder pain was asked to indicate their perceived degree of pain via a 10-point visual analog scale (VAS) comprising 4 categories, as follows: none (VAS 0); mild (VAS 1-3); moderate (VAS 4-6) and severe (VAS 7-10).

Prior to the study, ethical approval was obtained from the ethics committee of Nagasaki University (project registration number 10121010). The study was conducted during a cancer screening program at the Nishi-Isahaya Hospital PET/CT Diagnostic Imaging Center, Nagasaki Prefecture, Japan.

FDG-PET/CT

The PET/CT imaging study was performed on a PET/CT scanner (Discovery ST; GE Healthcare [WI. USA]). Imaging was started 50 min after intravenous injection of ^{18}F-FDG through an anterior cubital vein. Injected FDG doses were determined according to each subject's weight (4 MBq/kg), with individual doses ranging from

182.1 to 400 MBq. The subjects fasted at least 6 hours before FDG injection and the glucose level of each subject was measured by a quick and easy method before FDG injection. When the glucose levels were > 200 mg/dl, the participants were excluded from this study. In 244 participants included in the study, the glucose level was 93 (71‑196) mg/dl [median (min‑max)]. All patients were scanned in the turning up position with the arms down along the sides of the body. The image acquisition time was 2.5 min per bed position, with 7-8 bed positions, covering the whole body in a three-dimensional (3D) mode. The acquisition parameters for dual-detector helical CT were 140 kV, 30 mA, 3.75-mm slice thickness, and a pitch of 1.5. Attenuation correction was performed with acquired CT data. The PET/CT images displayed as coronal, sagittal, and transaxial slices were viewed on an Xeleris workstation (GE Healthcare). Details of this procedure are described elsewhere [21, 22].

Data collection and laboratory measurements

Blood samples were collected from each subject after fasting overnight. High-sensitivity C-reaction protein (hs-CRP) and uric acid (UA) were measured using standard laboratory procedures.

Evaluation of uptake ^{18}F-FDG in shoulder joints

The PET and CT images for each subject were analyzed using dedicated image analysis program on a personal computer. PET and CT images were superimposed as a fused PET/CT image using program, pMOD® (PMOD Technologies Ltd., Zürich, Switzerland). As the index of glucose metabolic activity in shoulder joints, SUVs in each volume of interest (VOI) were automatically calculated to quantitatively examine

the ^{18}F-FDG uptake. FDG uptake in bilateral shoulder joints was evaluated using a dedicated workstation to draw VOI covering each joint and calculate the SUVmax (maximum SUV value within each VOI) of each joint (Fig. 1). SUVmax was evaluated in right and left shoulder joints, respectively (Fig. 2). Mean-SUV was the average of SUVmax values in right and left shoulder joints; Max-SUV was the higher value of either right or left SUVmax.

Statistical analysis

Results are expressed as mean ± standard deviation or median (25^{th}-75^{th} quartiles). Differences in continuous values between men and women were compared using the *t*-test or Mann-Whitney *U*-test, and differences between categorized values such as frequency of joint pain were evaluated using the χ^2 test. Correlations of SUV with age were evaluated by univariate linear regression analysis. SUV values of resting and motion pains were adjusted for age and compared by analysis of covariance (ANCOVA). The correlations of SUV values with UA and log hs-CRP adjusted for age were evaluated by multivariate linear regression analysis. As hs-CRP levels showed a skewed distribution, logarithmic transformation was performed for multivariate linear regression analysis. SUV values for each pain score were evaluated via the Kruskal-Wallis test. A p-value < 0.05 was considered to indicate statistical significance. All statistical analysis was performed using SPSS software (v. 18.0 for Windows; SPSS Japan, Tokyo, Japan).

Results

The characteristics of the study participants are shown in Table 1.

The average age was not significantly different between men and women (58.8 ± 9.4 years vs. 59.3 ± 11.5 years, $p = 0.72$). Frequencies of resting pain and motion pain were not significantly different between men and women (69 / 138 (50.0 %) vs. 53 / 106 (50.0 %), $p = 1.00$; and 51 / 138 (39.2 %) vs. 34 / 106 (33.7 %), $p = 0.38$, respectively). Numbers of shoulder joints with both resting pain and motion pain were not significantly different between men and women (77 / 276 (27.9 %) vs. 64 / 212 (30.2 %), $p = 0.58$; and 27 / 276 (12.9 %) vs. 27 / 212 (15.0 %), $p = 0.54$, respectively). Also, numbers of shoulder joints with rest and/or motion pain were not significantly different between men and women (81 / 276 (29.3 %) vs. 69 / 212 (32.5 %), $p = 0.45$).

Univariate linear regression analysis showed that SUV of right joints (R-SUV), SUV of left shoulder joints (L-SUV), Mean-SUV and Max-SUV of shoulder joints were positively correlated with age in men, women and all participants (Table 2). L-SUV and Mean-SUV were significantly higher in men than in women (1.36 (1.19-1.63) vs. 1.26 (1.10-1.51), $p = 0.02$; and 1.39 (1.23-1.59) vs. 1.34 (1.17-1.47), $p = 0.03$, respectively), whereas R-SUV and Max-SUV were not significantly different between men and women (1.35 (1.20-1.59) vs. 1.28 (1.16-1.57), $p = 0.14$; and 1.51 (1.30-1.80) vs. 1.42 (1.25-1.70), $p = 0.056$, respectively).

SUV values of shoulder joints with rest and/or motion pain were significantly higher than those of shoulder joints without rest and/or motion pain. The difference remained significant even after adjustment for age. In addition, SUV values of shoulder joints with rest pain were significantly higher than those of shoulder joints without rest pain,

and SUV values of shoulder joints with motion pain were significantly higher than those of shoulder joints without motion pain (Table 3). There was no significant difference in SUV value between the rest pain (+) and motion pain (+) groups ($p = 0.156$).

When rest pain and motion pain were assessed according to perceived severity (none, mild, moderate and severe), SUV values were significantly higher in joints with mild and severe rest pain than those without rest pain. SUV values in joints with moderate and severe motion pain were significantly higher than those without motion pain (Table 4 and Fig. 3).

UA was significantly higher in men than in women (5.7 (5.1-6.6) g/l vs. 4.3 (3.7-5.0) g/l, $p < 0.001$). On the other hand, hs-CRP was not significantly different between men and women. Multivariate linear regression analysis adjusted for age revealed that Mean-SUV was significantly correlated with UA in men ($\beta = 0.21$, $p = 0.02$) and in all participants ($\beta = 0.22$, $p < 0.001$). On the other hand, Mean-SUV was not significantly correlated with log hs-CRP in men, women or in all participants (Table 5).

Discussion

In this study, we showed that R-SUV, L-SUV, Mean-SUV and Max-SUV of shoulder joints were positively correlated with age in men, women and all participants. Wandler et al. reported that, in patients undergoing ^{18}F-FDG PET for clinical oncologic assessment, the maximum SUV over the entire shoulder joint showed a significant positive correlation with age, increasing by an average of 0.023 units for each 1-year increase in subject age [18]. Takiguchi et al. found a significant positive correlation between the mean SUVmax of trapezius muscle and subject age in individuals with chronic neck/shoulder pain [23]. Our current results are consistent with such previous studies.

Our study also demonstrated that SUV values of shoulders with rest and/or motion pain were significantly higher than those of shoulders without rest and/or motion pain. Previously, Kubota et al. demonstrated that, in patients with rheumatoid arthritis (RA), SUVmax for large painful/swollen joints throughout the whole body were significantly higher than those of non-painful/swollen joints [17]. As far as we know, our study is the first to show the uptake of ^{18}F-FDG in shoulder joints in subjects with shoulder pain without rheumatic disorders. This uptake probably reflects local inflammation and its metabolic activity. When identifying uptake of ^{18}F-FDG in subjects with non-rheumatic disorders, we should carefully consider the necessity of further examination, including the collection of clinical symptoms and signs, X-ray, ultrasound and magnetic resonance imaging (MRI).

Using VAS values, we showed that, to some extent, SUV values reflect patients' perception of shoulder pain, which suggests that the degree of subjective pain may be

evaluated by the uptake of ^{18}F-FDG in shoulder regions. Recently, Masala et al. reported that, in bone lesion with metastases of bone tumor, changes in SUVmax and VAS values were not significantly correlated [24]; however, all subjects in that study were cancer patients and the number of participants (n = 20) was much smaller than in the present study. Further studies are needed to clarify the relationship between the perceived degree of shoulder pain and SUV values.

Interestingly, we found that FDG uptake in shoulder joints was significantly correlated with UA level in males and in all participants, even after adjustment for age. It is well known that gout due to hyperuricemia frequently affects the feet, hands, wrists, elbows and knees, whereas gout of the shoulder is rare [25, 26]. However, our current results suggest that — especially in males — relatively high UA level may be a risk factor for inflammation of the shoulder joint and, subsequently, shoulder pain. Since it is possible to collect information on SUV in other joints, including metatarsophageal joints that are frequently affected by gout, further investigations are warranted to clarify the involvement of uric acid in the development of shoulder pain.

On the other hand, we could not clarify the association between FDG uptake in shoulder joints and CRP. In patients with rheumatoid arthritis (RA), it has been reported that FDG uptake in inflamed RA joints may reflect disease activity [27]. Beckers *et al.* used ^{18}F-FDG PET to assess synovitis in patients with RA and showed that cumulative SUV and the number of PET-positive joints were significantly correlated with CRP [28]. They also showed that change in SUV due to initiation of anti-TNF-α treatment was correlated with changes in serum CRP, as well as MRI parameters and metalloproteinase-3 (MMP-3) levels [29]. Since our subjects were not patients with RA but general subjects for cancer screening, CRP concentrations were comparatively lower

than in patients with RA. Such differences in baseline CRP levels may account for the difference in the results compared with other studies involving RA patients.

Several limitations of this study warrant mention. Since we enrolled subjects who participated in cancer screening by PET/CT, selection bias might occur at this stage. We could not obtain final diagnosis of shoulder pain by further examination, such as shoulder X-ray and MRI. Also, since we used VAS values to evaluate severity of shoulder pain, the data are subject to differing perceptions between individuals. Furthermore, we could not evaluate inflammation markers (such as MMP-3, TNF-α) other than CRP. Further studies are needed to clarify the mechanism of ^{18}F-FDG uptake in shoulder joints.

Conclusions

The findings suggest that FDG-PET/CT might be useful in screening musculoskeletal inflammation and injury of the shoulder region. Since shoulder pain is common, especially among elderly individuals, we should carefully consider the necessity for further examination when identifying the uptake of ^{18}F-FDG in shoulder joints, even in subjects with non-rheumatic disorders.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Table 1 Characteristics of study participants

Variables	Men	Women	All	*p*
Age (y)	58.8 ± 9.4	59.3 ± 11.5	59.0 ± 10.4	0.72
Number with resting pain, n (%)	69 (50)	53 (50)	122 (50)	1.00
Number of shoulder joints with rest pain, n (%)	77 (27.9)	64 (30.2)	141 (28.9)	0.58
Number with motion pain, n (%)	51 (39.2)	34 (33.7)	85 (36.8)	0.38
Number of shoulder joints with motion pain, n (%)	27 (12.9)	27 (15.0)	54 (13.8)	0.54
Number with rest and/or motion pains, n (%)	73 (52.9)	58 (54.7)	131 (53.7)	0.78
Number of shoulder joints with rest and/or motion pains, n (%)	81 (29.3)	69 (32.5)	150 (30.7)	0.45
R-SUV (max)	1.35 (1.20-1.59)	1.28 (1.16-1.57)	1.33(1.18-1.58)	0.14
L-SUV (max)	1.36 (1.19-1.63)	1.26 (1.10-1.51)	1.31 (1.16-1.54)	0.02
Mean-SUV	1.39 (1.23-1.59)	1.34 (1.17-1.47)	1.37 (1.21-1.56)	0.03
Max-SUV	1.51 (1.30-1.80)	1.42 (1.25-1.70)	1.48 (1.27-1.75)	0.056
UA (g/l)	5.7 (5.1-6.6)	4.3 (3.7-5.0)	5.2 (4.2-6.0)	< 0.001

hs-CRP (g/l)	0.045 (0.019-0.110)	0.033 (0.017-0.065)	0.039 (0.018-0.087)	0.054

Values are mean ± standard deviation, number (percentage), or median (25^{th}-75^{th} percentile).

SUV, standardized uptake value; R-SUV, right-standardized uptake value; L-SUV, left-standardized uptake value; UA, uric acid; hs-CRP, high-sensitivity C-reaction protein.

Table 2 Correlation coefficients for univariate regression analysis of SUV with age

Variables	Men	Women	All participants
R-SUV (max)	0.16	0.43**	0.29**
L-SUV (max)	0.24**	0.44**	0.33**
Mean-SUV	0.22*	0.48**	0.34**
Max-SUV	0.15	0.43**	0.28**

*$p < 0.05$ and **$p < 0.01$.

SUV, standardized uptake value; R-SUV, right-standardized uptake value; L-SUV, left-standardized uptake value.

Table 3 Types of shoulder pain and SUV values

Types of pain	SUV values*	*p*	*p*, Age-adjusted		
			Men	Women	All participants
Rest and/or motion pains					
(+)	1.42 (1.23-1.74)	< 0.001	0.02	< 0.001	< 0.001
(−)	1.29 (1.16-1.51)				
Rest pain					
(+)	1.41 (1.23-1.73)	< 0.001	0.02	< 0.001	< 0.001
(−)	1.29 (1.16-1.51)				
Motion pain					
(+)	1.51 (1.26-1.91)	< 0.001	0.1	< 0.001	< 0.001
(−)	1.29 (1.16-1.51)				

*median (25^{th}-75^{th} percentiles)

SUV, standardized uptake value.

Table 4 Perceived degree of rest and motion pains and SUV values

	None	Mild	Moderate	Severe	*p*
Rest pain scale	1.29 (0.89-3.29)	1.43 (0.93-2.67) **	1.35 (0.90-2.83)	1.58 (1.04-2.36) *	0.005
Motion pain scale	1.29 (0.89-3.29)	1.41 (1.02-2.06)	1.54 (1.02-2.83) ***	1.80 (1.13-2.36) *	< 0.001

Values are median (min-max).

*v.s. “None” ($p < 0.05$); **v.s. “None” ($p < 0.01$); ***v.s. “None” ($p < 0.001$), respectively

Table 5 Multivariate regression analysis of Mean-SUV adjusted by age and sex

Variables		β	95% CI	*p*
UA				
	All	0.22	0.022, 0.076	< 0.001
	Men	0.21	0.009, 0.092	0.02
	Women	0.14	− 0.010, 0.088	0.12
log hs-CRP				
	All	0.09	− 0.018, 0.107	0.16
	Men	0.07	− 0.049, 0.122	0.41
	Women	0.10	− 0.045, 0.145	0.30

β, Standardized regression coefficient; CI, Confidence interval; UA, uric acid; hs-CRP, high-sensitivity C-reaction protein.

Figure Captions

Fig. 1 The volume of interest (VOI) covering each joint at the coronal, sagittal, and transaxial slices of fused PET/CT images and the SUVmax (maximum SUV value within each VOI) of each joint were automatically calculated.

Fig. 2 Typical finding of cases that showed total (a) (SUV = 2.36) and partial (b) uptakes of ^{18}F-FDG in shoulder joints (SUV = 3.27). Shoulder joint without uptake of ^{18}F-FDG (SUV = 0.89) (c).

Fig. 3 Perceived severity of pain and uptake of ^{18}F-FDG. Severe shoulder joint pain at rest and motion, and SUV was 2.36 (a). Mild shoulder rest and motion joint pain, and SUV was 0.93 (b).

Fig. 1

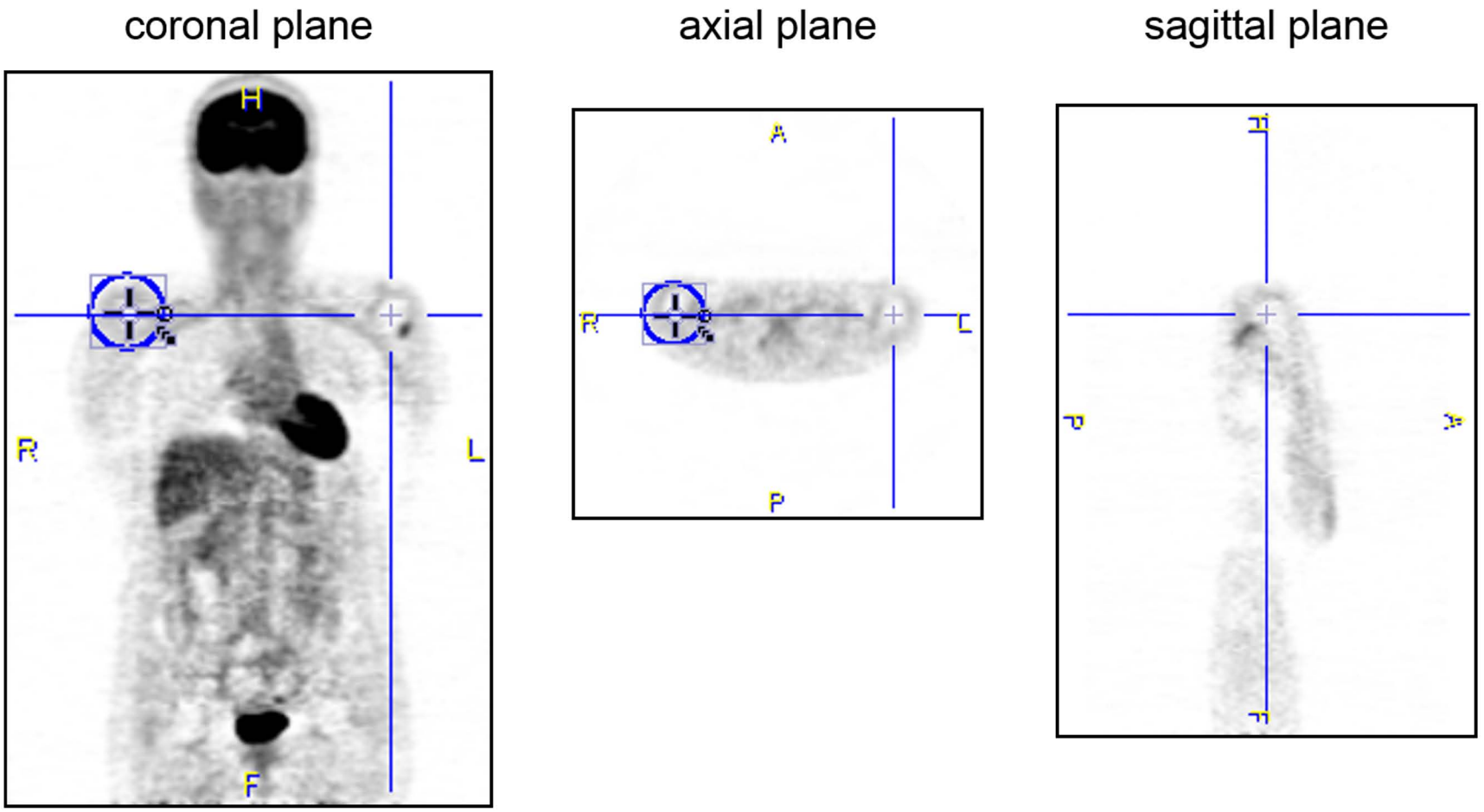

Fig. 2

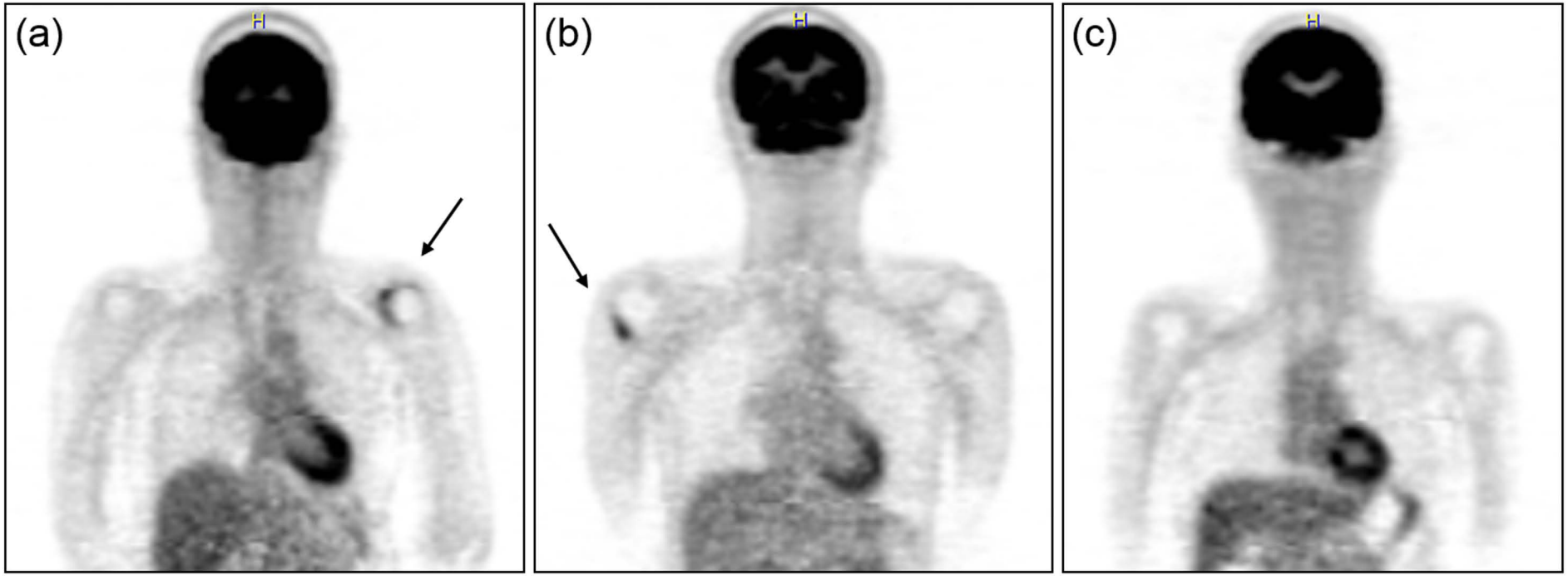

Fig. 3