Usefulness of ^{18}F-fluorodeoxyglucose Positron Emission Tomography–Computed Tomography in Monitoring Adhesive Capsulitis After Breast Cancer Treatment

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Objectives: We aimed to assess the usefulness of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography–computed tomography (PET/CT) in the monitoring of adhesive capsulitis (AC), a joint problem commonly observed in the upper arm after breast cancer treatment.

Methods: This retrospective study included 230 patients who underwent ^{18}F-FDG PET/CT before and after modified radical mastectomy of whom 22 patients were identified as having AC and categorized into 2 groups: with severely and mildly limited range of motion in the shoulder joint. The ^{18}F-FDG uptake patterns and mean and maximum standardized uptake values (SUVs) were analyzed.

Results: The overall incidence of AC after MRM was 9.57%. The SUVs were significantly higher in patients with severely limited range of motion compared with the other group. There was no association between the SUV and radiotherapy. The ^{18}F-FDG uptake pattern differed between the groups.

Conclusions: ^{18}F-fluorodeoxyglucose PET/CT is useful in evaluating AC after breast cancer treatment.

Key Words: adhesive capsulitis, ^{18}F-FDG, PET/CT, breast cancer

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Breast cancer is one of the most common malignancies in women. Although the survival rate has improved because of significant advancement in surgical technique and chemotherapeutic agents, a considerable number of patients had arm morbidity after the treatment.[1,2]

In most patients with breast cancer, except far advanced cases, surgery is the treatment of choice, with modified radical mastectomy (MRM) being the most common modality and chemotherapy (CTx) or radiotherapy (RTx) being complementary treatments depending on the disease status.[2] Although the most common complaint after MRM is edema related to axillary lymph node dissection, pain and limitation of the shoulder motion also affect patients after a multidisciplinary treatment for breast cancer.[3] Currently, arm morbidity is increasingly being recognized as a chronic problem after breast cancer surgery.[4] The etiology of arm pain related to breast cancer is diverse and includes musculoskeletal, neuromuscular, lymphovascular, and integumentary causes.[5]

Adhesive capsulitis (AC) is one of the musculoskeletal disorders causing pain and limited range of motion in the shoulder after breast cancer treatment. The disease has been reported to have a complex and varied course, and the pathological findings include inflammation and fibrosis of the joint capsule.[5] Therefore, early diagnosis and proper treatment are extremely important, but the disease has been differentiated from numerous other conditions with similar symptoms, such as incisional pain after axillary surgery, rotator cuff tendinitis, radiculopathy, bone metastasis, infections, and even lymphedema.[6] In the diagnosis of AC, arthrography, and plain radiography may be useful[7]; and currently, less invasive magnetic resonance arthrography and ultrasonography are also used.[8] However, these diagnostic tools are not commonly used for secondary AC after breast cancer treatment.

Recently, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography–computed tomography (PET/CT) has become increasingly useful in the evaluation of breast cancer before and after surgery. However, little emphasis has been placed on the examination of the shoulder joint during the interpretation of ^{18}F-FDG PET/CT in this patient group.[9–11] If secondary AC could be found incidentally in routine ^{18}F-FDG PET/CT for postoperative evaluation after breast cancer surgery, that would be helpful to improve the quality of lives of the patients. Therefore, the aim of this retrospective study was to analyze the metabolic pattern of shoulder in ^{18}F-FDG PET/CT of patients with breast cancer treated by MRM and to find how it related to the clinical symptom of AC; the pain and limited range of motion in the shoulder joint and the changes of the metabolic pattern of ^{18}F-FDG PET/CT over time were also evaluated.

MATERIALS AND METHODS

This research was approved by the institutional review board at Gangnam Severance Hospital of Yonsei University Medical College,

Patients

Between December 2007 and December 2013, 230 consecutive patients (mean age, 56.46 ± 10.3 years) were recruited into the study, who had breast cancer treated by MRM in a university hospital and underwent ^{18}F-FDG PET/CT before and after the surgery. Patients with secondary AC were defined as those who fulfill both criteria as follow: (1) those who complained of newly developed ipsilateral shoulder pain and a limited range of motion during follow-up PET/CT after MRM, and (2) those who showed a significantly increased or newly developed asymmetric ^{18}F-FDG uptake in the ipsilateral shoulder joint on follow-up PET/CT, with no or minimal symmetric ^{18}F-FDG uptake in bilateral shoulder joints on baseline PET/CT. Patients who showed joint space loss, osteophytosis, or calcification on radiography of the glenohumeral joint, and those who had narrow acromiohumeral space (<7 mm) on plain chest radiography were excluded.

The subjects were classified into 2 subgroups according to the degree to which the range of motion in the shoulder joint was limited. To obtain better ^{18}F-FDG PET/CT images for breast cancer, the arm should be fully lifted. Patients were classified into the group with severely limited range of motion (G1) or with

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mildly limited range of motion (G2) based on their ability to lift the arm during the first routine follow-up PET/CT study 1 year after the treatment. Group G1 included 12 subjects who could not lift the affected arm during PET/CT imaging, and group G2 included 10 subjects who could lift the arm incompletely and maintain this arm position during the test.

^{18}F-FDG PET/CT Imaging

The minimum fasting time for all patients was 6 hours before the injection of 5.18 MBq/kg (0.14 mCi/kg) of ^{18}F-FDG, and at the time of the injection, serum glucose levels in all patients were lower than 150 mg/dL. Whole-body PET with non–contrast-enhanced CT for attenuation correction was performed consecutively 60 minutes after the injection of ^{18}F-FDG by using a dedicated PET/CT system (Biograph TruePoint 40; Siemens Healthcare, Erlangen, Germany). The parameters for CT were 120 kilovolt (peak) (kV[p]), 170 effective mA s, 0.5-s gantry rotation, 1.2-mm collimation, and 0.05-mm intervals. ^{18}F-fluorodeoxyglucose PET images were reconstructed using the ordered-subset expectation maximization method under the condition of 2 iterations and 21 subsets. Reconstructed PET and CT data were fused to enable the interpretation of the images.

Image Analysis

Serial PET/CT images of 22 patients with increased ^{18}F-FDG uptake in the shoulder joint were evaluated using both the P-mod software (PMOD Technologies Ltd., Zurich, Switzerland) and PACS (GE Healthcare, Barrington, IL). A region of interest was drawn in each transaxial image showing ^{18}F-FDG uptake between the glenoid fossa and humeral head, including the rotator interval (RI), anterior joint capsule (AJC), axillary recess (AR) of the glenohumeral joint, and terminal tendon of the rotator cuff muscles at the greater tuberosity, according to the study by Kim et al.[11] Then, the areas were summed up, and the volume of the joint space was obtained. The mean and maximum standardized uptake values (SUV_{mean} and SUV_{max}) were obtained for each volume of interest. The volume of interest and both SUVs were automatically calculated using the P-mod software. The morphological patterns of ^{18}F-FDG uptake in the shoulder joint were classified into 4 types based on the study by Kim et al[11]: glenoid type I (high uptake in the RI, AJC, and AR); glenoid type II (high uptake in the AJC and AR); glenoid type III (high uptake in the RI and AJC); and focal type (high uptake in the RI or AR) (Fig. 1). Although there was difference in the arm position of a patient during PET/CT scanning between ours (mostly arm lifting) and the study by Kim et al study (arm lowering), we adopted this classification because we could not find significant changes in the location of target points of shoulder joint according to different arm position.

Changes in SUVs over time were evaluated by comparing the results of baseline PET/CT and follow-up PET/CT performed 1 and 2 years after the treatment. Four patients in group G1 underwent an additional PET/CT test between the baseline and first routine follow-up tests, and 6 patients in this group underwent the second follow-up PET/CT test. In contrast, all patients in group G2 underwent the second follow-up PET/CT test, but none of the patients in this group underwent an additional PET/CT test between the baseline and first follow-up tests.

Data Analysis

The *t* test was used to compare the differences in the SUVs in the first follow-up PET/CT between the groups and to compare the differences in the SUVs between the first and second follow-up PET/CT tests in each group. To determine the effect of RTx on AC, we also compared SUVs between patients who underwent MRM and CTx and those who underwent MRM, CTx, and RTx.

RESULTS

Incidence and Age Distribution in Patients With AC

The overall incidence of AC after breast cancer treatment, diagnosed on the basis of PET/CT findings and clinical manifestations, was 9.57% (22 of 230 patients). All 22 patients were treated by MRM and CTx. Additionally, 8 patients underwent RTx (4 of 12 patients in group G1 and 4 of 10 patients in group G2). The mean age of the 22 patients was 54.9 ± 8.2 years, which was not significantly different from the mean age of patients treated for breast cancer (56.5 ± 10.3 years) and showing no ^{18}F-FDG uptake in the shoulder joint. However, the mean age of group G1 was significantly lower than that of group G2 (51.8 ± 6.9 years and 58.6 ± 8.2 years, respectively; P = 0.0473). Measured joint space volume of the shoulder joint were mean 10.71 mL (range, 8.46-14.12 mL).

The first routine follow-up ^{18}F-FDG PET/CT test in groups G1 and G2 was performed 296 ± 76.7 and 365 ± 82.3 days after MRM, respectively. The *t* test revealed no significant differences between groups G1 and G2 ($P = 0.55$). Moreover, there were no significant differences in the time interval between MRM and the second follow-up PET/CT test in groups G1 and G2 (638 ± 65.7 and 723 ± 121.6 days, respectively). Hence, any bias related to the differences in the follow-up period could be excluded in the comparison of PET/CT data between groups G1 and G2. Four additional PET/CT tests in group G1 (between baseline and first follow-up tests) were performed 124 ± 50.3 days after MRM.

The SUV_{mean} and SUV_{max} in groups G1 and G2 in serial PET/CT are presented in Table 1 and Figure 2. Baseline SUV between the 2 groups revealed no significant difference. Group G1 showed significantly higher SUV_{mean} and SUV_{max} than group G2 (P = 0.015 and P = 0.018, respectively) in follow-up PET-CT at 1 year and which was significantly higher than those of baseline SUVs in both G1 and G2 ($P < 0.05$). Both groups showed a decrease in both SUVs in the second follow-up PET-CT, but the difference was not statistically significant. The SUV_{mean} and SUV_{max} in 4 additional PET/CT tests before routine first follow-up in group G1 (1.59 ± 0.25 and 2.53 ± 0.36, respectively) were not significantly different from those obtained in the first follow-up PET/CT test. This means that AC may develop early after MRM, even approximately 4 months (124 days) after the surgery. The SUV_{mean} and SUV_{max} of the patients who additionally underwent RTx were 1.48 ± 0.45 and 2.52 ± 0.80, respectively, and they were not significantly higher than those of the patients treated by MRM and CTx only (1.51 ± 0.35 and 2.34 ± 0.66, respectively).

The second follow-up PET/CT test, performed approximately 2 years after MRM, revealed slightly decreased SUVs in groups G1 and G2 compared with the test performed at 1 year; however, the difference was not statistically significant. Although the SUV_{mean} revealed a similar decreasing pattern in groups G1 and G2, the individual changes were quite different, although statistical evaluation was not possible in each case. For example, 6 of 10 second follow-up PET/CT tests in group G1 showed a decreased SUV (Fig. 1), except for 1 case (case 10) with systemic progression (Fig. 3) and the remaining 3 without significant changes. On the other hand, group G2 revealed a decreased SUV in 5 cases (Fig. 4), whereas the remaining 5 patients in this group showed a slightly increased and decreased SUV_{mean} or SUV_{max} (cases 1, 3, 5, 8, and 9).

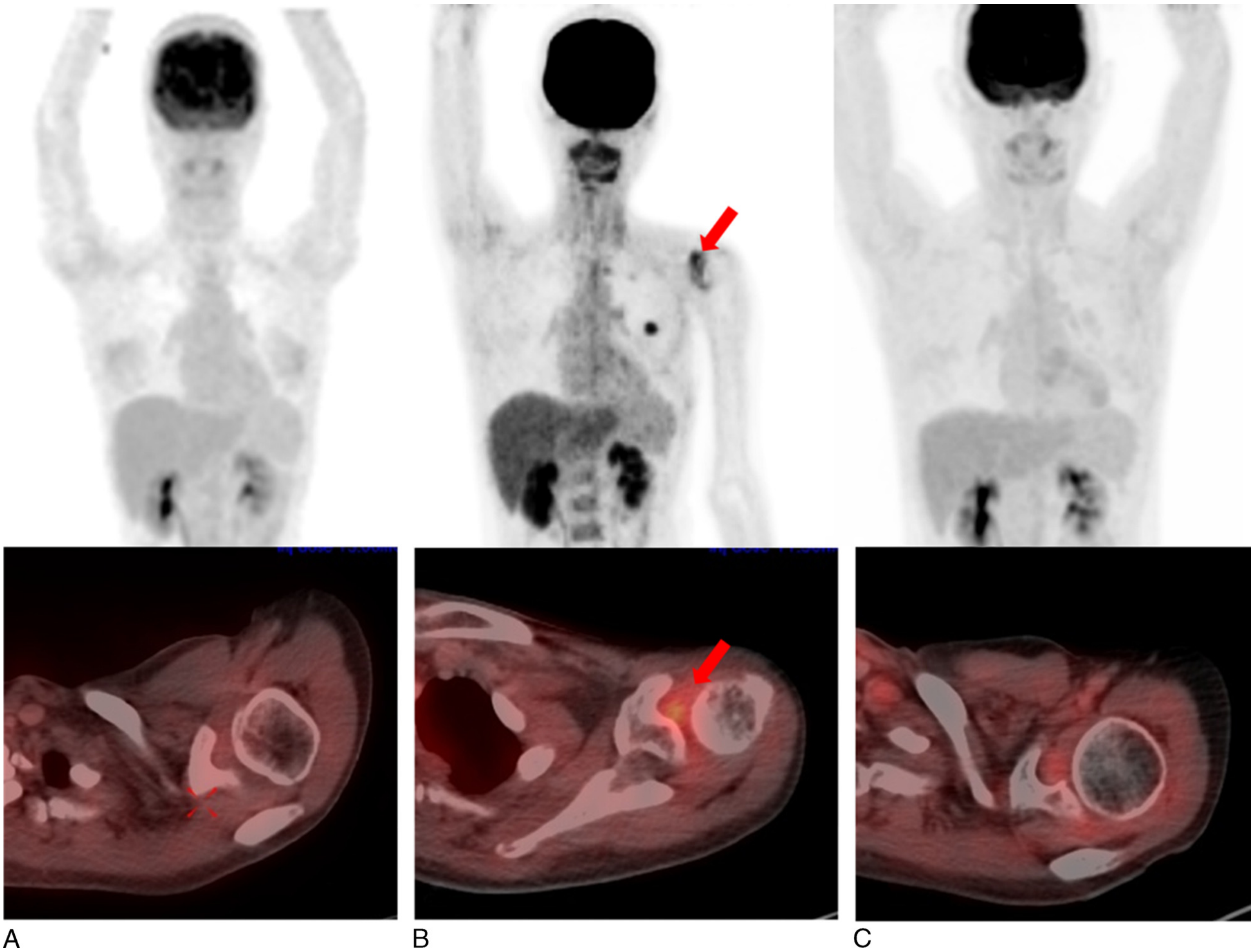


FIGURE 1. Patient with left breast cancer in group G1. A, Baseline PET/CT revealed no significant ^{18}F-FDG uptake in the shoulder joint. Follow-up PET/CT at 1 year showed asymmetric hot uptake in the left shoulder joint (arrow) with severely limited range of motion (B), and this patient showed a significantly decreased uptake with improved range of motion on second follow-up PET/CT at 2 years. Figure 1 can be viewed online in color at www.jcat.org.

With regard to the limited range of motion, it persisted only in 1 patient in group G1 with a further increase in the SUV, whereas it improved in the remaining 5 patients. Only 1 patient in group G1 showed a newly developed limited range of motion in the second follow-up PET/CT test.

The pattern of ^{18}F-FDG uptake in secondary AC after breast cancer treatment differed between groups G1 and G2. On the first follow-up PET/CT, all 12 patients in group G1 showed glenoid type I, whereas patients in group G2 showed various types of the uptake pattern: 2 patients showed type I, 6 patients showed type III, and 2 patients showed the focal type.

DISCUSSION

According to our retrospective study of PET/CT findings after breast cancer treatment, 9.6% of the patients with breast cancer showed increased ^{18}F-FDG uptake in the joint capsule of the shoulder 1 year after MRM compared with baseline. The incidence of AC in this population of patients cannot be neglected as it is significantly higher than that in the general population (2%-5%).[12] Despite such high incidence, AC tends to be underdiagnosed by breast cancer surgeons, and thus it may be attributed to the fact that the significance of the disease is slightly underrated, and its diagnosis after breast cancer treatment is commonly believed to be difficult. Recently ^{18}F-FDG PET/CT has begun to be widely used as baseline and follow-up imaging modality for staging workup and posttreatment evaluation in patients with breast cancer.[13–15] However, in most cases, both clinicians and nuclear medicine physicians have concentrated on cancer-related ^{18}F-FDG PET/CT findings in the torso and paid little attention to those in the shoulder joint after surgery. Considering that ^{18}F-FDG uptake is commonly used as a marker of inflammation,[16,17] ^{18}F-FDG PET/CT may be useful in the evaluation of the inflammatory process in the shoulder joint, such as that associated with AC. Therefore, routine ^{18}F-FDG PET/CT imaging may become a useful, noninvasive, and cost-effective method to evaluate the shoulder joint.

In our study, ^{18}F-FDG uptake measured by the SUV was significantly higher in patients with severely limited range of motion than in those with a mildly limited range of motion in the shoulder joint. In other words, there were more intense inflammatory processes in the shoulders of patients who could not raise their arms because of pain. Our study also showed that the SUV decreased in most of the patients over 2 years of follow-up. These results can be supported by a natural history of AC, which is believed to be a self-limiting condition, with complete pain relief and the range of motion in the shoulder joint fully restored within a maximum of 2 years from the onset of symptoms.[18,19] However, if proper

TABLE 1. Values in the SUV in the Shoulder Joint on Serial PET-CT Tests in All the Subjects of Groups G1 (n = 12) and G2 (n = 10)

			Baseline PET/CT		First F/U PET/CT (1 Year)		Second F/U PET/CT (2 Years)	
Group	Case #	MRM Site	SUV_{mean}	SUV_{max}	SUV_{mean}	SUV_{max}	SUV_{mean}	SUV_{max}
G1	1	Left	1.05	1.17	1.54	1.86	1.25	1.58
G1	2	Left	1.08	1.80	1.89	2.67	1.46	2.07
G1	3	Right	1.03	1.45	1.54	2.18	1.54	1.82
G1	4	Left	1.01	1.28	1.45	2.65	1.35	1.67
G1	5	Left	1.02	1.19	1.23	2.43	1.21	1.64
G1	6	Right	1.04	1.32	1.37	2.77	1.41	2.34
G1	7	Left	1.07	1.36	1.52	3.29	1.53	2.31
G1	8	Left	1.02	1.45	1.54	2.32	1.79	3.30
G1	9	Right	1.06	1.70	2.32	3.55	NA	NA
G1	10	Left	1.06	1.47	1.36	2.00	1.66	3.28
G1	11	Right	1.11	1.14	1.85	2.77	1.72	2.06
G1	12	Right	1.05	1.54	2.48	4.00	NA	NA
Mean			1.05	1.41	1.67	2.71	1.49	2.21
SD			0.03	0.21	0.39	0.64	0.20	0.63
G2	1	Right	1.01	1.12	1.32	1.71	1.58	2.31
G2	2	Left	1.03	1.13	1.25	1.68	1.01	1.42
G2	3	Left	1.10	1.18	1.38	1.66	1.04	2.03
G2	4	Left	1.06	1.57	1.37	2.52	1.01	1.15
G2	5	Right	1.09	1.35	1.30	2.00	1.36	2.20
G2	6	Left	1.08	1.29	1.21	1.85	1.18	1.62
G2	7	Left	1.09	1.41	1.31	2.35	1.05	1.58
G2	8	Right	1.05	1.54	1.34	2.30	1.61	2.17
G2	9	Left	1.05	1.18	1.48	2.26	1.20	2.34
G2	10	Right	1.07	1.59	1.59	1.95	1.57	1.63
Mean			1.06	1.34	1.35	2.03	1.26	1.85
SD			0.03	0.11	0.15	0.31	0.25	0.42

NA indicates not applicable.

treatment for AC is not introduced in a timely manner, patients may suffer from pain, poor quality of life, and possibly, arm disability. Considering these findings, the activity of AC can be monitored by routine follow-up PET/CT imaging after MRM in patients with breast cancer. If abnormal ^{18}F-FDG uptake is observed in the shoulder joint on follow-up PET/CT, the surgeon or nuclear medicine physician might diagnose AC and recommend proper treatment.

The effect of RTx on the shoulder joint in patients with breast cancer should also be considered because subcutaneous fibrosis is

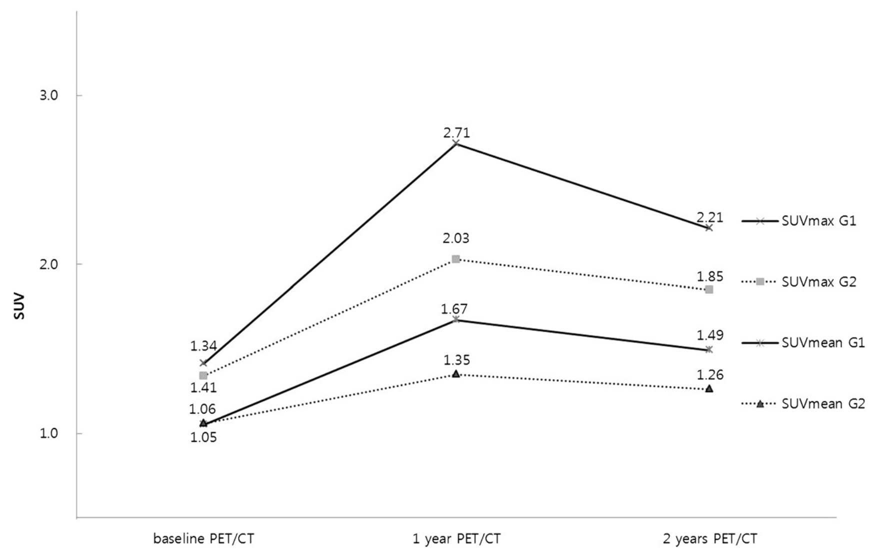
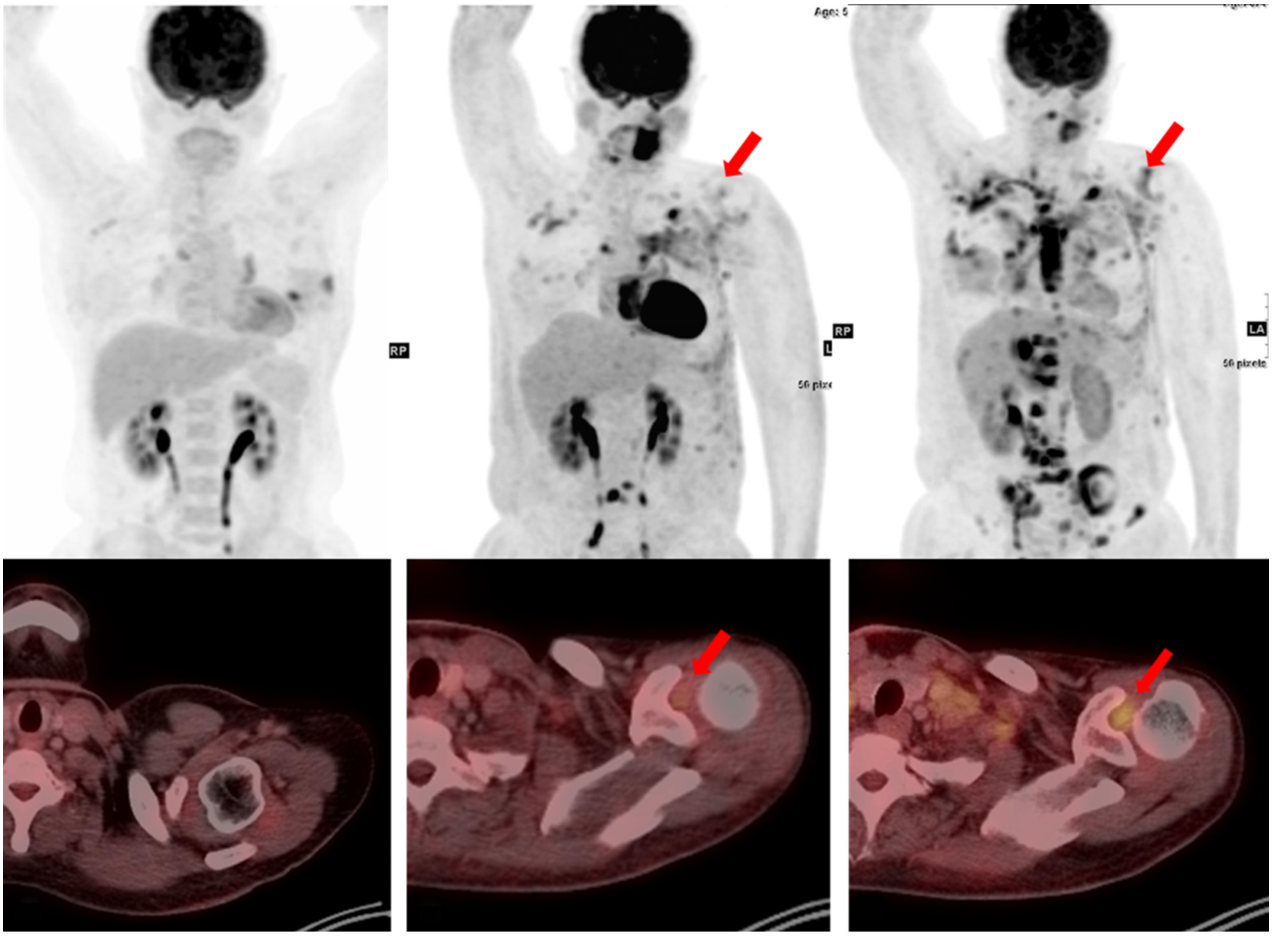


FIGURE 2. Changing trend of the SUV_{mean} and SUV_{max} on serial PET-CT tests in groups G1 and G2.



A B C

FIGURE 3. Patient with left breast cancer in group G1. A, Baseline PET/CT revealed negative ^{18}F-FDG uptake in the shoulder joint. B, Follow-up PET/CT at 1 year showed a mild ^{18}F-FDG uptake in the left shoulder joint (arrow) with severely limited range of motion. Increased ^{18}F-FDG uptake in the left shoulder joint (arrow) and persisting limited range of motion with progressive systemic metastases were noted on second follow-up PET/CT. Figure 3 can be viewed online in color at www.jcat.org.

a serious problem,[20] and radiation fibrosis in the axillary node dissection area can affect shoulder joint mobilization. However, our study did not show any significant correlations between RTx and the limited range of motion or SUV in the shoulder joint. Moreover, there were no significant differences in the SUV between patients who underwent RTx and those who did not. These results suggest that RTx in breast cancer management does not affect the inflammatory process in the shoulder joint. However, further studies on a larger population should be performed to obtain more reliable results.

The impairment of the upper limbs in patients with breast cancer may occur at various times,[3] but several studies reported the onset between 6 and 12 months after breast cancer treatment.[21–23] In our study, the exact onset of secondary AC after MRM could not be determined because a routine follow-up protocol at our institute was 1 year after MRM. However, 4 patients had undergone additional PET/CT earlier than at 1 year (between 79 and 196 days) after MRM, and they had increased ^{18}F-FDG uptake in the shoulder joint. There were no differences in the SUV between those tests and those performed at 1 year in any of the 4 patients. This suggests a strong possibility that secondary AC may develop earlier, even within 6 months after MRM and that it may persist at least for 1 year after the treatment. Moreover, some patients may reveal persistent ^{18}F-FDG uptake in the shoulder joint even at 2 years. Although the number of patients who underwent PET/CT earlier than at 1 year was small, the result suggests the possibility of long-standing inflammatory process in secondary AC in the shoulder joint after MRM, and further studies are needed to determine the association between the onset and persistence of the inflammation in the shoulder joint after MRM with due consideration for shoulder pain and limited range of motion.

In our study, patients differed with regard to the ^{18}F-FDG uptake pattern, which may support the hypothesis that the degree to which the range of motion is limited correlates with the progression or extent of AC. As previously mentioned, the SUV decreased in most of the patients in our study over 2 years of follow-up. Furthermore, in most of the patients with a mildly limited range of motion in the shoulder joint, the uptake pattern changed over time. The exact interpretation of these findings is not possible without additional histological and imaging studies, but the results clearly show that the pattern of disease progression differs between patients with a severely limited range of motion and those with a mildly limited range of motion and that it changes over time.

Our study has several limitations. First, this was a retrospective study, and no clinical diagnosis was established; the severity

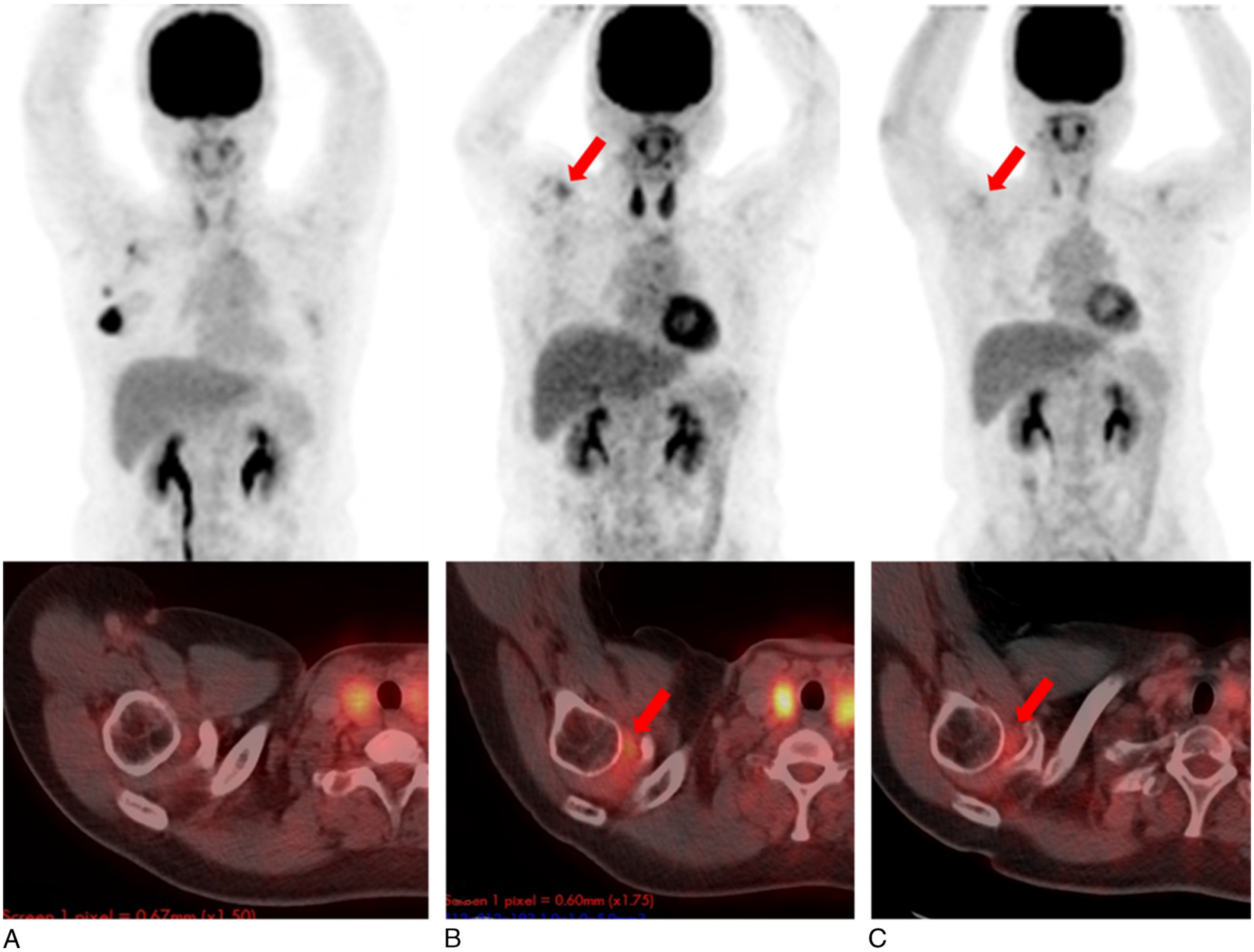


FIGURE 4. Patient with right breast cancer in group G2. Baseline PET/CT revealed negative ^{18}F-FDG uptake in the shoulder joint (A); follow-up PET/CT at 1 year showed several focal ^{18}F-FDG uptakes in the right shoulder joint (arrow) without limited range of motion (B). Second follow-up PET/CT revealed a significantly decreased ^{18}F-FDG uptake in the shoulder joint (arrow). Figure 4 can be viewed online in color at www.jcat.org.

of pain and the limited range of motion were not precisely measured; and additional imaging tests such as magnetic resonance imaging or ultrasonography were not performed. Second, only 4 patients underwent ^{18}F-FDG PET/CT imaging before a routine follow-up test at 1 year, so the exact onset of secondary AC cannot be established. However, this limitation cannot be resolved because running an additional PET/CT test 6 months after the surgery to evaluate the shoulder joint is not justified. Despite all those limitations, our study revealed an additional role of ^{18}F-FDG PET/CT in the evaluation of secondary AC, including the estimation of its overall incidence at 1 year after surgery. Moreover, it showed the relationship between the degree to which the range of motion is limited and the extent of AC, the effect of RTx on secondary AC, and the onset and pattern of disease progression over 2 years after the treatment. However, prospective study for this subject is essential for precise evaluation of correlation between clinical evaluation and radiological evaluation of secondary AC after MRM.

In conclusion, secondary AC after MRM for breast cancer is common and differs in severity and the progression pattern depending on whether the range of motion in the shoulder joint is mildly or severely limited. ^{18}F-fluorodeoxyglucose PET/CT of the torso can provide information on the activity of secondary AC, in addition to its primary aim of staging workup and evaluating the recurrence of breast cancer.

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