



Importance of Whole-Body Scintigraphy or Positron Emission Tomography for Early Detection of Femoral Lesions in Breast Cancer Patients Treated with Bisphosphonates

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Background: We hypothesized that most of the atypical femoral fractures (AFFs) associated with bisphosphonate treatment for breast cancer (BC) could be found before the fracture event in another radiological examination already performed by breast surgeons, rather than on simple radiographs (SRs).

Methods: We thoroughly inspected the clinical charts of BC patients treated at our institute between 2008 and 2017. In total, 228 patients were categorized into three groups based on SRs: complete AFF on at least one side (group 1); incomplete fracture on at least one side, but not any complete fracture (group 2); and no suspicious lesion (group X) on either femur. Then, we inspected whole-body scintigraphy (WBS) and positron emission tomography (PET)-computed tomography (CT) images in all groups. For group X, patients with radiological clues from at least one femur were categorized, ultimately, into final group 3 and the rest made up the normal group.

Results: About 35% of the patients showed AFFs (complete or incomplete) or suspicious lesions as AFFs, associated with the side effect of Bisphosphonate. In group 1, bilateral lesions (complete or incomplete fractures) were more frequently seen on SRs than unilateral lesions ($p = 0.008$). The initially identified findings in WBS and PET-CT for the respective complete and incomplete fractures on SRs of groups 1 and 2 were seen at a mean of 7 months previously. SRs did not reveal the lesions in group 3 until 5 months after the initial identification of the lesions in WBS and PET-CT.

Conclusions: Even before incomplete AFFs were detectable on SRs, they could be found at check-ups using WBS and PET-CT that had been previously examined by breast surgeons and radiologists for metastasis surveillance. Awareness of the lesions creates an opportunity for prophylactic surgery before complete fractures occur.

Keywords: Radionuclide imaging, Positron-emission tomography, Breast Neoplasms, Atypical fracture, Femur

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Bisphosphonate (BP) therapy has become the principal method for managing osteoporosis. BPs increase bone mineral density and prevent fragility fractures.¹⁻³⁾ However, atypical fractures, particularly of the femur, are a serious issue, so radiologic surveillance is essential. Long-term use of BPs carries a potential risk of severely suppressing bone turnover, which can paradoxically weaken the ability of the bone to remodel. This eventually leads to

accumulated microdamage, reduced bone toughness, and increased brittleness.⁴⁾ The lesions of atypical femoral fractures (AFFs) typically occur in the subtrochanteric area, and most of these fractures occur after the appearance of various prodromal symptoms, such as pain or discomfort around the hip. However, most patients are diagnosed after a complete fracture, and a bony insufficiency lesion is occasionally revealed in the contralateral femur during regular follow-up radiography.

High-dose BPs are administered to patients with solid malignancies such as breast cancer (BC) or multiple myeloma to prevent bony metastasis or hypercalcemia induced by existing metastatic lesions. High-dose BPs have been incorporated into standard postoperative treatment algorithms of early-stage BC without metastasis since 2000.⁵⁻⁸⁾ Although BP therapy reduces the risk of skeletal-related events (SREs) in diseases that metastasize to the bone and may improve quality of life, there is no effect on survival rate in metastatic BC.⁹⁾ Interestingly, most BPs are prescribed by breast surgeons, and the radiological surveillance of bony metastasis after breast surgery is performed by musculoskeletal radiologists and breast surgeons through whole-body scintigraphy (WBS) and positron emission tomography (PET)-computed tomography (CT).

These unique patient populations have had occasional AFFs and have been treated by orthopedic surgeons. However, most breast surgeons are unaware of the association between fractures and BP treatment and have little interest unless skeletal lesions occur due to metastasis. Interestingly, AFFs associated with BPs for osteoporosis show pathognomonic lesions (incomplete fracture) before a displaced fracture on simple radiographs, and some orthopedic surgeons suggest preventive fixation for these findings.¹⁰⁻¹³⁾ We have treated AFFs after patients are diagnosed with BC for a few decades and hypothesized that most of the fractures could be found earlier than the final fracture event in another radiological examination rather than on simple radiographs. Thus, we evaluated (1) the preceding lesions in WBS/PET-CT before actual development to complete/displaced AFFs or detection of incomplete AFFs on simple radiographs among the BC patients treated by BPs and (2) when these lesions are detectable on WBS/PET-CT before being evident on simple radiographs through a retrospective study.

METHODS

We conducted this study in compliance with the principles of the Declaration of Helsinki. The protocol of this study was reviewed and approved by the Institutional Review

Board of Chungnam National University Hospital (No. 2019-08-023), and all patients provided informed consent before study participation.

Patient Selection

We retrospectively inspected the clinical charts of BC patients treated at Chungnam National University Hospital between 2008 and 2017. Among the 304 patients screened, 228 were investigated. The patients were selected based on the following criteria: (1) history of BP therapy or ongoing administration for at least 1 year after surgery for early BC, (2) presence of simple radiographs of both femurs, (3) complete medical records and radiological data available, and (4) follow-up period > 5 years after breast surgery.

The exclusion criteria were (1) evidence of skeletal metastasis, as evidenced by a thorough inspection using WBS, PET-CT, or single-photon emission CT, (2) traumatic femoral fracture, (3) typical osteoporotic fracture in the femur with low bone mineral density estimated by dual-energy X-ray absorptiometry, and (4) pathological fracture or impending fracture due to metastasis.

Demographic and Clinical Characteristics

We evaluated demographic factors, including age. The clinical variables included in the analyses were the kind of BP agent used, period of administration, and total amount of dosage. Additional therapies received after BC surgery were also investigated.

Three Groups Classified According to the Femoral Lesion

We divided the 228 patients into three groups: complete AFF on at least one side, regardless of displacement (group 1); any pathognomonic lesion or incomplete fracture of the femur on at least one side on simple radiographs, but not any complete fracture (group 2); and no suspicious lesion on simple radiographs (group X) (Fig. 1). The group allocation was performed using the femoral status on one side in all patients. For example, a right-side complete fracture was designated as group 1, regardless of contralateral left femoral status. Group 3 means that both femurs had neither complete nor incomplete fractures on simple radiographs.

Retrospective Radiological Evaluation for the Final Three Groups

After the designation of groups based on the simple radiographs, we thoroughly reviewed all WBS/PET-CT images. Then, we checked for hotspot uptake by any lesion, increased metabolism, and increased radiopaque/sclerosis

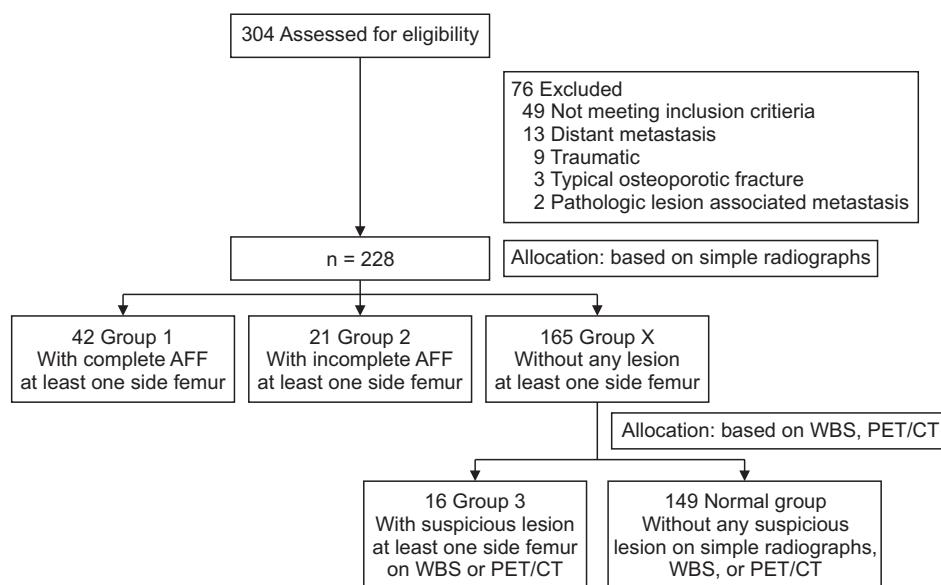


Fig. 1. Flowchart of this study. AFF: atypical femur fracture, WBS: whole-body scintigraphy, PET: positron emission tomography, CT: computed tomography.

of any lesion. In group 1, we evaluated the period from the initial detection of special radiological findings to a broken femur. Similarly, in group 2, we checked the period from the initial detection on special radiology images to the initial typical lesion (incomplete fracture) on simple radiographs. Group X was composed of patients without abnormal findings in either femur on the most recent simple radiographs. We sought to find lesions from a specific radiological study; thus, we ultimately designated the patients to final group 3. Then, we checked the period from the lesion on a specific study to the most recent simple radiograph seen as normal. The rest without any clue despite inspection for special radiology of both femurs were finally categorized as the normal group (Fig. 1).

Lesion Location

We categorized the locations of all lesions into the subtrochanteric, diaphyseal, and supracondylar areas. The subtrochanteric area included lesions below the lesser trochanter to 5 cm distal in the shaft of the femur. The supracondylar was defined from the metaphyseal-diaphyseal junction to the articular surface of the knee, involving approximately the distal 15 cm of the femur.¹⁴⁾ We checked lateral bowing using the Yau method.¹⁵⁾ According to this method, the lateral femoral bowing angle in the coronal plane is measured by dividing the femoral diaphysis into four equal parts. As Yau et al.¹⁵⁾ did not exactly describe the femoral diaphysis, we defined the femoral diaphysis from the lower border of the lesser trochanter to the upper border of the distal femoral segment, demarcated by a square whose sides had the same length as the widest part of the femoral condyle or the so-called rule of the square. Thus,

the overall lateral femoral bowing angle was measured as the angle between the proximal and distal quarters of the femoral diaphysis.¹⁶⁾

Patient's Awareness of the Association between BPs and Fracture Risk

A thorough investigation into the patient's medical records and counseling by the orthopedic surgeon (SMC) were used to evaluate the patient's awareness or knowledge of the purpose and effectiveness of BPs, the association between BPs and the patient's awareness or knowledge, and the occurrence of AFFs.

Statistical Analyses

One-way analysis of variance and Scheffé post hoc analyses were performed to compare variables among groups 1, 2, and 3. Student *t*-test was used to analyze continuous variables among the three groups and the normal group. The chi-square test or Fisher's exact test was used for categorical variables in the three groups. The sample size calculation was performed using the G*Power program (ver. 3.1.9.2; Franz Faul, Universität Kiel, Germany). Data were analyzed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA). A *p*-value < 0.05 was considered significant.

RESULTS

A total of 228 patients were analyzed, and 149 patients were not categorized into any of the three groups because they had no suspicious AFF lesions. Namely, 35% of patients (79 / 228) showed AFFs (complete or incomplete) or suspicious lesions as AFFs, associated with the side effect

of BPs. About 20% of the affected patients (16 / 79, three groups) had normal findings on simple radiographs, despite the fact that suspicious lesions were detected in WBS and PET-CT. Complete fractures occurred accidentally in group 1 without any awareness of their lower extremity condition. However, the concurrent incomplete fracture lesion on the contralateral side was preventively fixed in 13 patients after a previous complete fracture (Fig. 2). Among 21 patients in group 2, only 4 were managed by prophylactic fixation after incomplete AFFs, and they had little information about the femur before the advice from an orthopedic surgeon (Fig. 3).

The mean ages at the initial diagnosis of BC in groups 1, 2, and 3 were not significantly different ($p =$

0.863). The total amount of Zoledronate-injections was 46.76 ± 4.28 , 37.14 ± 3.61 , and 28.63 ± 2.03 gm in groups 1, 2, and 3, respectively ($p < 0.01$) (Table 1). The amount in the three groups was significantly higher than that in the 149 patients in the normal group ($p < 0.01$) (Table 2). The type of additional management after breast surgery was not different among the three groups ($p = 0.173$). The pathognomonic lesions in WBS and PET-CT before respective complete and incomplete fractures on simple radiographs in groups 1 and 2 were present at a mean of 7 ± 3 and 7 ± 1 months ago, respectively ($p > 0.05$). In group 3, simple radiographs did not show any lesions until the final 5 ± 2 months after the initial identification of the lesion in WBS and PET-CT (Table 1, Fig. 4). In group 1 only, the

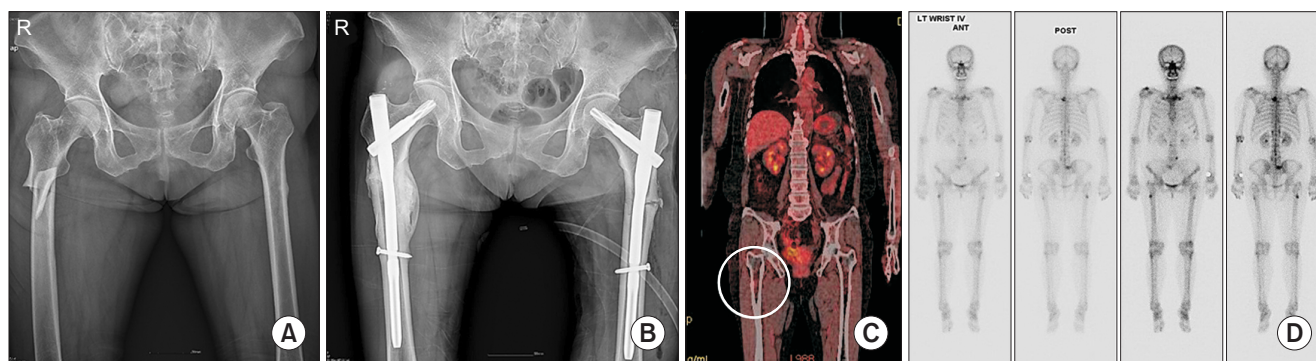


Fig. 2. (A) A 59-year-old woman (group 1) presented with a typical atypical femur fracture. The contralateral left side showed an incomplete atypical fracture. Prophylactic intramedullary nailing for the left side was refused by the patient at the time. The left side finally broke 4 months later. (B) Twelve months after surgery on the left side. Union was considerably delayed compared to an ordinary subtrochanteric fracture. (C) A hypermetabolic lesion of a right-sided complete fracture was detected retrospectively on positron emission tomography-computed tomography (PET-CT) image 12 months ago; however, the breast surgeon and radiologist were unaware of the lesion. (D) Both lesions were found in whole-body scintigraphy 8 months after the initial PET-CT findings (4 months before the right-side fracture), and unfortunately, no simple radiographs had been taken just before the right-side fracture.

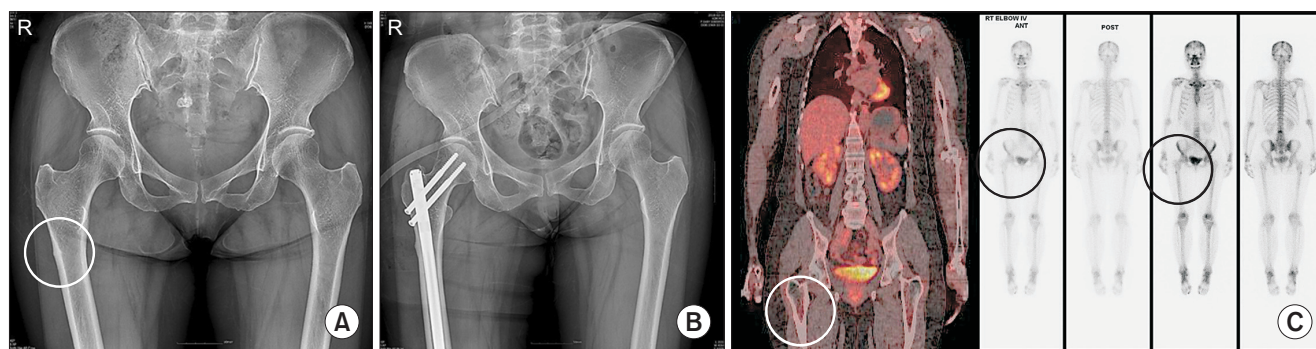


Fig. 3. (A) A 52-year-old woman was referred to us for vague discomfort around the right hip (group 2). She had not been screened with simple radiographs or counseled by an orthopedic surgeon during the 25 months of bisphosphonate administration after breast surgery. (B) Prophylactic intramedullary nailing was performed for the right femur 1 month later, and the final lesion improved 6 months later. (C) Increased uptake and a hypermetabolic lesion were detected in whole-body scintigraphy and positron emission tomography-computed tomography 5 months before the detection of a right-side incomplete fracture on simple radiographs.

Table 1. Clinical and Radiologic Data in Three Groups

Variable	Group 1 (complete fracture, n = 42)	Group 2 (incomplete fracture, n = 21)	Group 3 (no lesion on simple radiographs, n = 16)	p-value	Post hoc
Age at diagnosis of breast cancer (yr)	56 ± 5	55 ± 8	56 ± 5	0.863	
Total amount (gm)	46.76 ± 4.28	37.14 ± 3.61	28.63 ± 2.03	< 0.01	Group 1 > 2 > 3
Additional therapy after breast surgery					
Radiotherapy + chemotherapy	34	18	16	0.173	
Chemotherapy	8	3	0		
Radiologic period (mo)	7 ± 3*	7 ± 1*	5 ± 2 [†]	< 0.001	Group 1, 2 > 3

Values are presented as mean ± standard deviation.

*The period between the time of identified complete or incomplete fracture on simple radiographs and the time of first showing the lesions in whole-body scintigraphy (WBS)/positron emission tomography (PET)-computed tomography (CT) (group 1 or 2). [†]The period between the most recent time of normal finding on simple radiographs and the time of first showing the lesions in WBS/PET-CT (group 3).

Table 2. Clinical Data of Three Groups and Normal Group

Variable	Group 1, 2, 3 (n = 79)	Normal group (n = 149)	p-value
Age at diagnosis of breast cancer (yr)	56 ± 6	55 ± 3	0.757
Total amount (gm)	40.53 ± 8.18	18.78 ± 3.13	< 0.010

Values are presented as mean ± standard deviation.

bilateral lesions (complete or incomplete fractures) were more frequently seen on simple radiographs than unilateral lesions ($p = 0.008$). However, in groups 2 and 3, corresponding lesions on the contralateral limb were less prevalent than the absence of contralateral lesions ($p = 0.007$ and $p < 0.001$, respectively) (Table 3). Fractures in the diaphyseal area were seen in 8 patients (5 in group 1, 2 in group 2, and 1 in group 3), and the mean bowing angle was $8.62^\circ \pm 3.66^\circ$, which was significantly different from the angle for the subtrochanteric area ($2.27^\circ \pm 1.45^\circ$, $p = 0.002$).

DISCUSSION

BPs have routinely been utilized in patients with BC. BPs prevent or delay SREs and can improve pain control in patients with metastatic disease and bone involvement.¹⁷⁾ BPs significantly reduce distant recurrence, bone recurrence, and BC mortality, which is observed only in postmenopausal women. The relative benefit of BPs is not affected by receptor status, tumor grade, nodal involvement, or administration of adjuvant chemotherapy. Current guidelines support considering adjuvant zoledronic acid or oral clodronate for 3–5 years in postmenopausal women with

early-stage disease.¹⁷⁻²⁰⁾

Zoledronic acid is most commonly used in our institute for preventing distant metastasis or local recurrence by breast surgeons according to its protocol.^{7,8)} Surprisingly, 35% of the participants in the current study had opportunities for being diagnosed with AFF before a complete or incomplete fracture. The findings in WBS and PET-CT in these patients were not as interesting as a metastatic lesion for breast surgeons. Also, we discovered that breast surgeons and radiologists commonly rule out these lesions as “not serious” findings due to several reasons. First, subtrochanteric hot-uptake or hypermetabolism is not an ordinary location for a single distant metastasis. Most skeletal metastasis occurs initially at the spine or bony structures around the trunk. In addition, axillary lymph node involvement would be the primary predictor of bony metastasis at the time of breast surgery. Thus, most of the lesions in the current study were considered not serious and even benign bone lesions by breast surgeons and radiologists. Second, the degree of uptake and metabolism were relatively weak compared to those for metastases. Necrosis of the jaw is associated with BPs, but rarely in patients with AFFs.²¹⁻²³⁾ Ohbayashi et al.²¹⁾ reported that the degree of tracer uptake after long-term BP use is notably distinct in the jaw than other bones, including the femur and humerus and they regarded the uptake differences as differences in secondary turnover after primary excessive mineralization by BP and microcracks. Similarly, AFFs were finally considered only after consultation with an orthopedic surgeon due to patient discomfort in the lower extremity or even after sudden complete fractures, although the radiological clue was visible for several months, which was easily neglected (Table 4). Finally, even

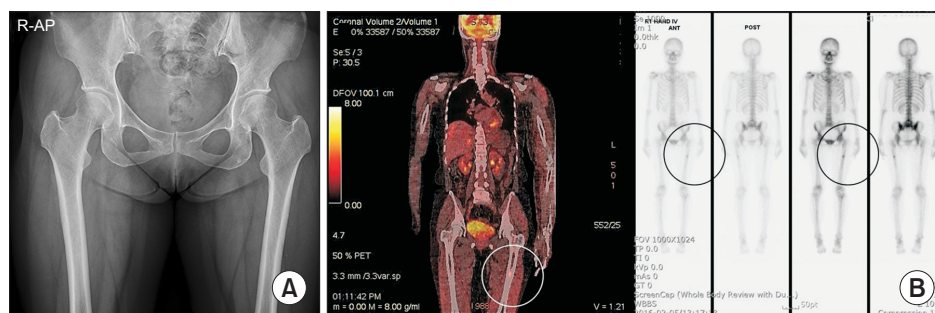


Fig. 4. (A) A 55-year-old woman presented with intermittent discomfort on the left side of the hip or knee (group 3). The patient had not recognized the possibility of an atypical femur fracture, even without any radiological workups for the lower extremities. Fortunately, no suspicious lesion was detected on simple radiographs. (B) However, whole-body scintigraphy and positron emission tomography-computed tomography had revealed the lesions 5 months previously but they were dismissed by the breast surgeon and radiologist as non-serious lesions.

Table 3. Lesions of Atypical Femoral Fractures in Three Groups

Variable	Bilateral lesion	Unilateral lesion	p-value
Group 1 (complete fracture, n = 42)	30*	12 [†]	0.008
Group 2 (incomplete fracture, n = 21)	4 [‡]	17 [§]	0.007
Group 3 (no lesion on simple radiographs, n = 16)	1	15	< 0.001

*Complete fracture at least on one side, complete or incomplete fracture on the contralateral side. [†]Only one side complete fracture, normal lesion in all radiologic examinations on the contralateral side. [‡]Incomplete fractures on both sides. [§]Incomplete fracture on only one side, normal lesion in all radiologic examinations on the contralateral side.

after complete AFFs, a few breast surgeons still use BPs as an important part of postoperative chemotherapy. Despite knowledge among orthopedic surgeons about the effects of BPs, the benefits of BP therapy could not be ignored by the breast surgeon. A drug holiday for BPs has been emphasized by established guidelines to prevent AFFs when treating osteoporosis; however, the dosages of BPs for BC are too high to be applied to the same guidelines.¹¹⁾

There are three reasons why we strongly suggest early detection of clues using advanced radiological tools. First, an incomplete fracture does not spontaneously heal due to compromised bone physiology, and several studies have supported the necessity of prophylactic fixation using simple intramedullary nailing.¹⁰⁻¹³⁾ Furthermore, complete displaced subtrochanteric fractures cannot always be fixed easily. In addition, noninvasive intramedullary nailing for displaced/complete fractures requires a prolonged period for final bone healing and has an increased risk of delayed union or nonunion, which demands secondary surgery rather than prophylactic fixation. Second, considering the mean 7.36 and 7.29 months from the identifiable lesions

in WBS and PET-CT to complete fractures and incomplete fractures on simple radiographs in groups 1 and 2, respectively, the calculated differences between the time periods mean that incomplete fractures found on simple radiographs would soon proceed to complete displaced fractures with vulnerability to minor trauma. Finally, most of the patients were immunocompromised under regular cycles of chemo-radiotherapy. Thus, another surgery after a complete fracture and prolonged immobilization, if necessary, would increase the risk of mortality compared to prophylactic fixation with least immobilization.

In the current study, the mean total amount of BPs administered to the overall three groups was significantly greater than that in the normal group. Once attached to the bony surface, BPs are not eliminated for a few years until transcytosis into osteoclasts; thus, the total times for the BP injections would properly reflect the total accumulated amount, if there were a non-injection period within 3 years. In addition, a few lesions were found in the diaphyseal area, and the locations were well correlated with increased lateral bowing, as described previously (Fig. 5).^{14,15)} Thus, it is worth noting that breast surgeons and radiologists can use the total number of BP injections and the degree of bowing to identify the lesions with a detailed suspicion based on WBS and PET-CT findings.

There were some limitations in this study. First, our report was based just on clinical/radiologic data from a single institute, thus the evidence was too weak to answer several questions about the overwhelming efficacy for bony metastasis, the proper period of BP injections after breast surgery, or the cessation and restart after diagnosis and surgical intervention of AFFs. For the management of postmenopausal osteoporosis, BP treatment was under the well-established guideline; however, in our study, the same agent was applied at a high dose to different patient groups

Table 4. Period of Pain Recognition in Three Groups

Variable	Bilateral lesion	Unilateral lesion	p-value
Group 1 (complete fracture, n = 42)	30	12	0.008
Both complete : complete + incomplete : only one side complete	13 : 17 : 0	0 : 0 : 12	
Period of pain recognition in both complete (n = 13) (right : left)	Null* : Null (12 patients) Null : 2 mo (1 patient)	-	
Period of pain recognition in complete + incomplete (n = 17) (right : left)	Null : 2.18 mo [†]	-	
Period of pain recognition in only one side complete (n = 12)	-	Null	
Group 2 (incomplete fracture, n = 21)	4	17	0.007
Period of pain recognition in both incomplete (right : left)	2.25 mo [†] : 3 mo [†]	-	
Period of pain recognition in only one side incomplete	-	3.2 mo [†]	
Group 3 (no lesion on simple radiographs, n = 16)	1	15	< 0.001
Period of pain recognition in both lesions (right : left)	2 mo : Null	-	
Period of pain recognition in only one lesion	-	Null (9 patients) 1.33 mo (6 patients) [†]	

*Null: there was no clinical data on the pain around the fracture or corresponding lesion. [†]Mean data.

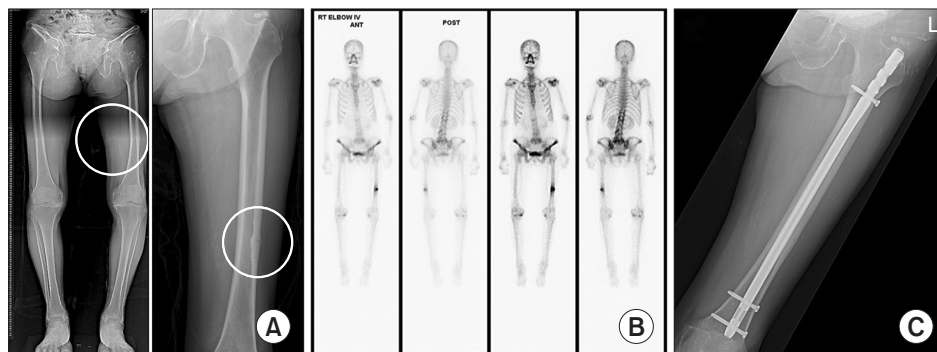


Fig. 5. (A) A 65-year-old woman presented with intermittent discomfort around the left knee. A simple radiograph showed an incomplete atypical femur fracture at the diaphysis. The lateral bowing angle was 6.4°. (B) The patient had not recognized the possibility of an atypical femoral fracture, even after a suspicious lesion had been detected in whole-body scintigraphy 4 months previously. (C) Complete union was acquired 8 months after prophylactic nailing.

by different surgeons. Thus, a well-designed, prospective, multicenter trial is needed. Second, the patients in group 3 could have the potential to move toward group X. During the treatment of osteoporosis using BP, the radiologic reversibility of incomplete AFFs after cessation of the agent was recently reported.²⁴⁾ However, breast surgeons argue that anti-metastatic treatment still has a priority rather than the prevention of fracture events, if there were no guidelines. Thus, through regular check-ups, prophylactic fixation for patients in group 2 may be a reasonable option.

In conclusion, about one-third (35%) of the patients had at least one femur affected under high-dose BP therapy after surgery for early-stage BC. Even before incomplete AFFs were detectable on simple radiographs, they could be found at check-ups using WBS and PET-CT that had been previously examined by breast surgeons and radiolo-

gists for metastasis surveillance. Awareness of the lesions creates an opportunity for prophylactic surgery before a complete fracture occurs.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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