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Utility of FDG-PET in differential diagnosis of benign and malignant fractures in acute to subacute phase

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Objective: To evaluate the usefulness of positron emission tomography with [fluorine-18] 2-deoxy-2-fluoro-D-glucose (FDG-PET) for early differential diagnosis of benign and malignant fractures. ***Materials and Methods:*** Among 1,164 patients who had received FDG-PET between January 1999 and December 2000, 20 patients were found to have an acute fracture on review of clinical charts and/or radiologic images taken within one month before or after FDG-PET examination. The fractures were finally diagnosed by clinical follow up of at least five months duration. Standardized uptake values (SUV) for the benign and malignant bone lesions were calculated and compared. ***Results:*** Ten of the 20 patients were finally diagnosed to have a benign fracture, nine patients to have a malignant fracture, and one patient to have both a benign and a malignant fracture at different locations. A statistically significant difference in the SUV was found between the benign group (SUV: 1.36 ± 0.49) and the malignant group (SUV: 4.46 ± 2.12) ($p = 0.0006$, the nonparametric Mann-Whitney U test). ***Conclusions:*** FDG-PET can be a useful method for early differentiation between acute benign and metastatic fractures. Our retrospective study indicates that an acute benign fracture itself does not show significant FDG uptake.

Key words: emission CT (ECT); fluorine; fractures; fractures, pathologic; glucose

INTRODUCTION

POSITRON EMISSION TOMOGRAPHY (PET) with a glucose analogue tracer, 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (FDG), has been used extensively to differentiate malignant tumors from benign lesions in many organ systems.[1–3] As FDG accumulation reflects the rate of glucose metabolism in tissues, it has been expected that FDG-PET would be useful in detecting and grading aggressive tumors. Several reports have emphasized the utility of FDG-PET in the differential diagnosis and grading of primary musculoskeletal tumors,[4–7] but little is known about the contribution of FDG-PET to differentiating acute benign fractures from metastatic fractures. Determining whether fractures in patients with primary extraskeletal malignant tumors are benign or metastatic is a common problem in clinical practice.

The purpose of this study is to evaluate the usefulness of FDG-PET for early differential diagnosis of benign and metastatic fractures.

MATERIALS AND METHODS

We reviewed clinical charts and radiologic images of all patients who received FDG-PET (of the whole body, trunk or limbs) between January 1999 and December 2000 at our hospital, which amounted to a total of 1,164 cases. Among these 1,164 examinations, 20 patients were diagnosed as having an acute fracture on clinical symptoms and radiologic images, including plain radiography, computed tomography (CT), bone scintigraphy, and/or magnetic resonance imaging (MRI). The images were obtained within 1 month before or after FDG-PET examination.

Among 20 patients, 13 patients presented with distinct

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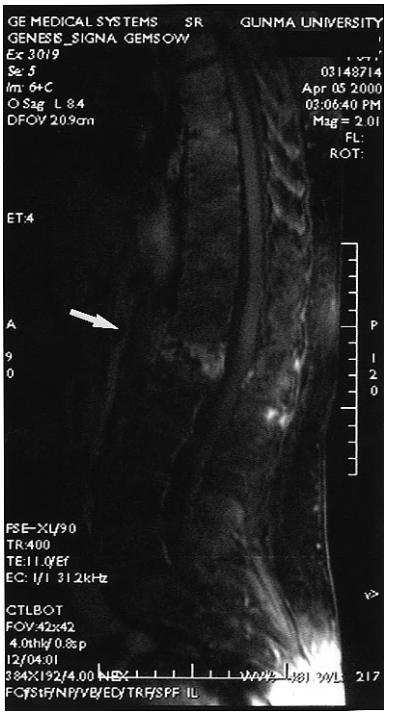

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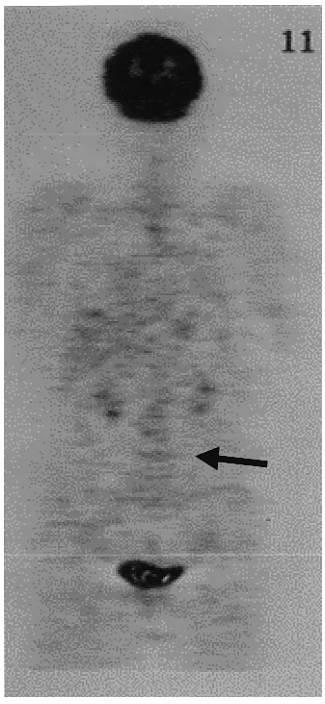

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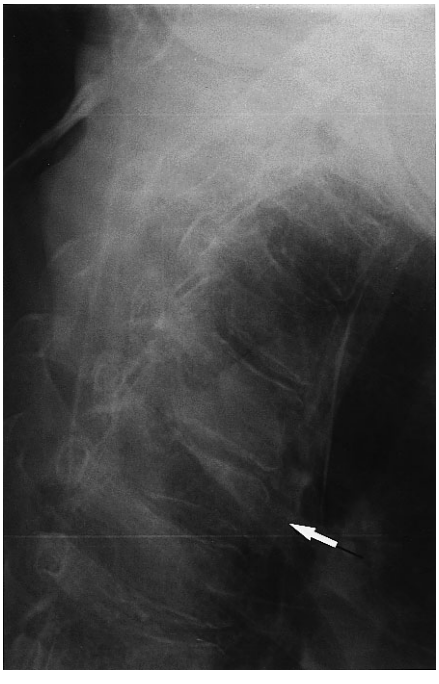
Fig. 1 Osteoporotic compression fracture of the 1st lumbar vertebra in a 64-year-old woman with lung carcinoma. Final diagnosis was made by clinical course of improved back pain and a X-ray of five months later which showed no progressive change. a) Sagittal T1-weighted MR image with gadolinium enhancement and fat suppression shows vertebral collapse and diffuse enhancement (*arrow*). b) Coronal PET image demonstrates a low accumulation of FDG (SUV = 1.57) in the fracture (*arrow*).

a



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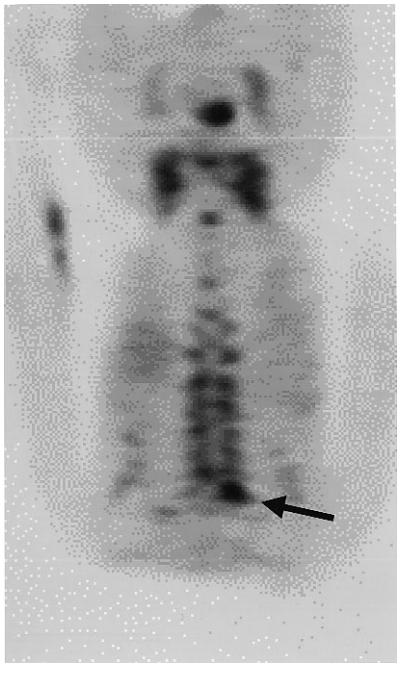

Fig. 2 Metastatic tumor of the 5th thoracic vertebra in a 65-year-old man with laryngeal carcinoma. Final diagnosis was made by increasing back pain and progressive destructive change on X-ray of six months later. a) Lateral radiograph shows a compression fracture in the 5th thoracic vertebra (*arrow*). b) Coronal PET image demonstrates a high accumulation of FDG (SUV = 4.99) in the tumor (*arrow*).

clinical symptoms associated with acute fracture, which included chest pain, shoulder pain, hip pain or back pain. In these patients, radiographic examination showed subtle or definite bone destruction at the location of the pain. Seven patients had subtle pain or no significant clinical symptoms. Among them, three patients had prostatic carcinoma, two patients had lung carcinoma, one patient had hypopharyngeal carcinoma, and one patient had

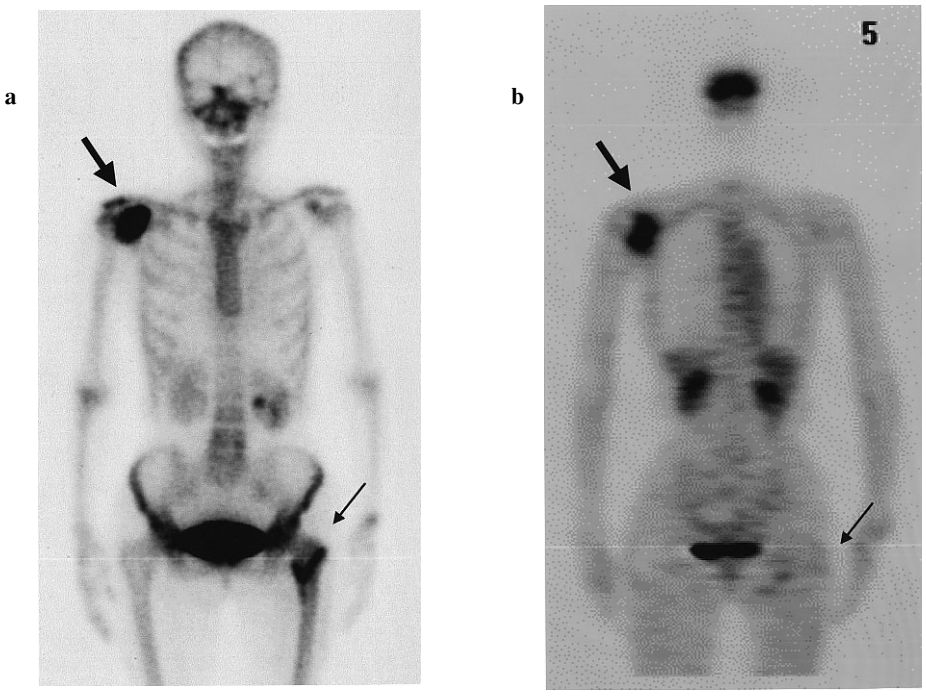

Fig. 3 Metastatic scapular fracture and benign (traumatic) femoral neck fracture in a 76-year-old woman with hepatocellular carcinoma. Final diagnosis was made by follow up CT and MRI findings which showed a mass lesion destructing the scapula and no mass in the femoral neck. a) Bone scan demonstrates high accumulation in both scapular fracture (*thick arrow*) and femoral neck fracture (*thin arrow*). b) Coronal PET image demonstrates a high accumulation of FDG in the scapular fracture (SUV = 3.30) (*thick arrow*) but a low accumulation in the femoral neck fracture (SUV = 0.66) (*thin arrow*).

Wegener's granulomatosis. All of them were examined by FDG-PET to screen for systemic metastasis. Among these seven patients, five were examined by MRI and diagnosed as having an acute or subacute fracture. Differentiating whether or not the fracture is acute on MRI, by means of the high signal intensity on a T2 weighted image (T2WI) or short TI inversion recovery (STIR) was relatively easy.[8]

In the two remaining patients with high FDG accumulation without suggestive clinical symptoms or MRI findings, the diagnosis of acute fracture was made because of a newly appeared fracture on X-ray, CT, or bone scintigraphy, and the diagnosis of metastasis was confirmed on follow-up images.

The maximum size of the lesions as measured on radiologic imaging ranged from 1.5 cm to 5.0 cm (average ± standard deviation; 3.95 ± 0.86 cm).

Pathologic proof of the diagnosis (benign or metastatic) was not available in the patients' bone lesions in this group. The final diagnosis was made by clinical and radiologic follow up of at least five months' duration (average ± standard deviation; 7.48 ± 2.20 months). Fractures with improving clinical symptoms and healing processes detected on radiologic imagings were determined to be benign. On the other hand, fractures with deteriorating pain and progressive bone destruction on imaging studies were considered malignant.

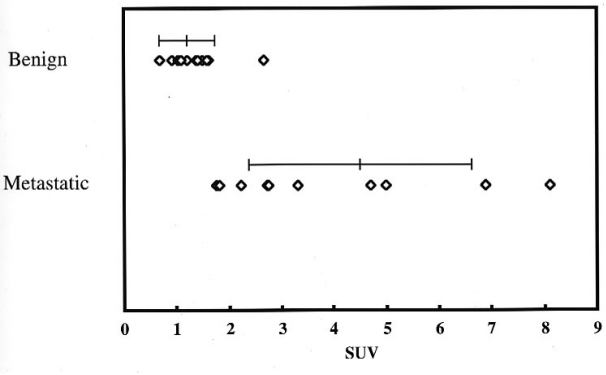

Fig. 4 Standardized uptake values of benign and metastatic fractures. SUV of benign lesions: 1.36 ± 0.49, SUV of metastatic lesions: 4.46 ± 2.12 (p = 0.0006)

PET studies were performed by using a whole-body positron camera (HEADTOME-V SET 2400W; Shimadzu, Kyoto, Japan). Axial and transverse fields of view were 59.5 and 20 cm, respectively. Transverse spatial resolution was 4.2 mm full width at half maximum at the center of the field of view, and axial spatial resolution was 5.0 mm full width at half maximum. FDG was synthesized by using a method modified from that of Hamacher et al.[9] The patients fasted for at least 4 hours and received injections of 185–250 MBq of FDG (5 MBq

per kilogram of body weight). Simultaneous emission-transmission whole-body scan was obtained at 40–50 minutes after the injection of FDG. It took 48 minutes to obtain a whole-body image, but automatic decay correction was done during the scanning. Attenuation-corrected images were reconstructed by using the ordered-subsets expectation maximization method.

By using the attenuation-corrected images, injection doses of FDG, patient's body weight, and cross-calibration factors between PET and the dose calibrators, functional images of the standardized uptake value (SUV) were produced. SUV was defined as follows[1,10]: SUV equals the radioactive concentration in tissue (in becquerels per gram) divided by the (injected dose [in becquerels] divided by the patient's body weight [in grams]).

The injected dose of radioactivity of FDG was measured by using a dose calibrator (IGS-3; Aloka, Tokyo, Japan). The cross-calibration factor for the dose calibrator and PET was measured with a cylindrical phantom containing gallium-68 solution.[11]

SUVs of the benign and malignant bone lesions were calculated and compared. The significance of difference between benign and malignant lesions in SUV was statistically analyzed by means of the nonparametric Mann-Whitney U test with multiple comparison. A p value < 0.05 was regarded as significant.

RESULTS

Among the 20 patients who were found to have acute fractures, 10 were diagnosed as having a benign fracture (Fig. 1), nine patients as having a fracture due to metastasis (Fig. 2), and one patient having both a benign and a metastatic fracture at different locations (Fig. 3). The interval between FDG-PET and the other radiological studies ranged from 0 (the same day) to 29 days (average ± standard deviation: 7.9 ± 8.5 days). No significant difference was noted in patients' age and sex between those with benign lesions (six men and five women; ranging from 51 to 80 years: mean 67.1 years) and malignant lesions (seven men and three women; from 20 to 79 years: mean 60.3 years).

SUVs of these patients are listed in Figure 4. A statistically significant difference was found between the benign group (SUV: 1.36 ± 0.49) and the malignant group (SUV: 4.46 ± 2.12) ($p = 0.0006$).

The causes of 11 benign fractures were diagnosed as osteoporosis in six lesions, and traumatic fracture in five lesions. Among these 11 lesions, seven were found in patients who had a history of a malignant tumor. Two of these patients had bone metastasis in other locations. Among the 11 benign fractures, only one costal traumatic fracture had relatively high SUV accumulation (2.64). This patient's CT and MR images showed a soft tissue mass surrounding the fracture without osteolytic nor sclerotic change. Metastasis was ruled out on the clinical and radiologic follow up images.

The other 10 lesions were eight vertebral compression fractures, one femoral neck fracture, and one costal fracture. All 10 metastatic fractures had high SUV. Among the 10 patients with metastatic fractures, the primary malignant tumors were prostate carcinoma in three patients (SUV: 1.76, 2.74, 6.88), lung carcinoma in two patients (SUV: 2.20, 8.11), hypopharyngeal carcinoma (SUV: 2.72), laryngeal carcinoma (SUV: 4.99), ameloblastoma (SUV: 1.81), hepatocellular carcinoma (SUV: 3.30), and malignant lymphoma (SUV: 4.70) in one patient each. No significant correlation was noted between the histologic type of primary malignant tumor and FDG accumulation of the metastatic lesion.

Vertebral compression fractures were noted in nine patients, and a scapular fracture in one patient. Six patients had bone metastasis in other locations.

DISCUSSION

The spine is a common site of metastatic disease, and vertebral metastases account for up to 39% of all bone metastases.[12]

Both osteoporotic and malignant vertebral collapse are frequent in elderly patients. In most cases, clinical evaluation, routine biologic tests, and plain radiographic examinations are sufficient for diagnosis of a benign or malignant condition. But in some cases, especially in the acute phase of vertebral fractures, differentiation of benign fractures from fractures caused by metastasis is difficult. It has been estimated that about one-third of vertebral compression fractures in patients with known malignancies are benign.[13] When the fractured site is solitary, differential diagnosis becomes more difficult. In the lesions in which involvement is limited to the vertebral body, the probability of malignancy is low, but still amounts to 26%.[14]

MR imaging is highly sensitive in the assessment of bone marrow changes due to traumatic, neoplastic, and inflammatory lesions. But signal intensity changes are mostly non-specific and may be quite similar in these conditions.[8,15–17] Four MRI findings for the differential diagnosis of bone marrow change have been investigated: 1) the margin of intravertebral abnormality between normal and abnormal bone marrow, 2) pedicle involvement, 3) enhancement pattern, and 4) paravertebral soft tissue (mass) lesion (PSL).[18]

The characteristic findings of malignant vertebral collapse include 1) ill-defined margin of abnormal signal; 2) signal change in the pedicle with an expansile lesion; 3) marked and heterogeneous pattern of contrast enhancement (due to uneven blood supply, necrosis and enhancing peritumoral edema); and 4) irregular nodular PSL.

On the other hand, a benign cause of vertebral collapse can be considered when lesions show any of the following findings: 1) well-defined margin of abnormal signal; 2)

mild and/or homogeneous enhancement (due to the blood supply in the healing bone); and 3) rim-shaped PSL. Among the above four signs, about 30% of cases of benign vertebral compression fractures had ill-defined margins, and about 25% of cases of malignant vertebral fractures had well-defined margins. About one-third of benign fractures showed signs of heterogeneous enhancement. Therefore, the specificity of MR imaging for differential diagnosis is not sufficiently high.

On T2-weighted MR images of benign fractures, a gradual decrease in high signal intensity is noted during transition from the acute phase to the chronic phase, and is helpful in differential diagnosis. Nevertheless, since it takes one to three months to switch over to the chronic phase, it has little to contribute to early differential diagnosis.[16]

For early differential diagnosis of benign and metastatic fractures, the usefulness of diffusion-weighted MR imaging (DWI) has been indicated in a recent report.[19] On DWI, benign vertebral compression fractures are hypo- or iso-intense compared with adjacent normal bone marrow, due to persistent mobility of free water protons in edema and hemorrhage. In malignant vertebral collapse, the replaced bone marrow is hyperintense compared with adjacent normal unaffected bone marrow, due to restricted mobility of water protons between tumor cells. But this report is not yet fully supported by subsequent investigations, which indicated the "T2 shine through effect" as a cause of false-positive cases.[20]

FDG-PET is a nuclear medicial technique that has recently been used in clinical oncology, and is promising as a tool for estimating the biologic activity of skeletal lesions, including metastases. Several reports reviewed comparison of FDG-PET with bone scans (Tc-99m MDP) in sensitivity and specificity for the detection of bone metastases. But the results are not constant, and the significant superiority of FDG-PET to bone scan is not yet defined.[21–24] Bone scan generally shows high sensitivity but low specificity for diagnosis of bone metastasis. The specificity of FDG-PET would be expected to be higher than that of bone scan in diagnosing bone metastasis. The result of this study show superior specificity of FDG-PET to previously reported bone scan results in diagnosing bone metastasis.

Studies on FDG accumulation in benign fracture have been very limited, and they are all case reports, including a case of high accumulation in a 2-week-old traumatic fracture or stress fracture. In one of these reports, the diagnosis of benign fracture was made due to the disappearance of FDG accumulation on a follow up study.[25–27]

To the best of our knowledge, there has been no report which focused on the utility of FDG-PET for early differentiation of acute benign fractures from metastatic fractures. In our study, there was a statistically significant difference between acute benign fracture and malignant pathologic fracture in the SUV of FDG-PET. When a previously suggested[7] cutoff point (2.0) was applied, we had 80.0% sensitivity, 88.9% specificity, and 85.7% accuracy in detecting metastatic fractures. This high specificity in differentiation between benign and malignant fractures has not been reported with other imaging methods.

Interestingly, some chronic fractures have been reported to show high accumulation of FDG due to infiltrating macrophages and granulation tissue.[28–30] Macrophages play a central role in the host response to injury and infection, and their energy is predominantly supplied by means of intracellular glucose metabolism.[31,32] High uptake of FDG has been reported in chronic osteomyelitis and rheumatoid arthritis.[28–30] In our study, one false positive case was considered likely to be due to subacute inflammation of surrounding soft tissue. In the future, serial change in FDG-PET during the fracture healing process should be investigated. This study was based on a broad retrospective survey of 1,164 FDG-PET studies. The patients were not referred with a fracture to evaluate benign vs. malignant causes, but just happened to have a fracture. Therefore, numerous variables which might have strong effects on the appearance of fractures were not controlled. Those factors were the site and timing of a fracture, stability of the fracture site, age of the patient, bone mineral content and mobile activity of the patient, and any drug therapies received by the patient. We believe that our results should be verified in future by a systematic study either of fracture findings with FDG-PET or with cases prospectively sent to evaluate pathological fractures on FDG-PET.

In conclusion, FDG-PET can be a useful method for early differentiation of acute benign and metastatic fractures. Our retrospective study indicates that acute benign fracture itself does not show any sign of significant FDG uptake. Prospective investigation of the utility of FDG-PET will be necessary in a larger series in the future.

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