18F-Fluoride Positron Emission Tomography and Positron Emission Tomography/Computed Tomography

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18F-Fluoride is a positron-emitting bone-seeking agent, the uptake of which reflects blood flow and remodeling of bone. Assessment of 18F-fluoride kinetics using quantitative positron emission tomography (PET) methods allows the regional characterization of lesions of metabolic bone diseases and the monitoring of their response to therapy. It also enables the assessment of bone viability and discrimination of uneventful and impaired healing processes of fractures, bone grafts and osteonecrosis. Taking advantage of the favorable pharmacokinetic properties of the tracer combined with the high performance of PET technology, static 18F-fluoride PET is a highly sensitive imaging modality for detection of benign and malignant osseous abnormalities. Although 18F-fluoride uptake mechanism corresponds to osteoblastic activity, it is also sensitive for detection of lytic and early marrow-based metastases, by identifying their accompanying reactive osteoblastic changes, even when minimal. The instant fusion of increased 18F-fluoride uptake with morphological data of computed tomography (CT) using hybrid PET/CT systems improves the specificity of 18F-fluoride PET in cancer patients by accurately differentiating between benign and malignant sites of uptake. The results of a few recent publications suggest that 18F-fluoride PET/CT is a valuable modality in the diagnosis of pathological osseous conditions in patients also referred for nononcologic indications. 18F-fluoride PET and PET/CT are, however, not widely used in clinical practice. The limited availability of 18F-fluoride and of PET and PET/CT systems is a major factor. At present, there are not enough data on the cost-effectiveness of 18F-fluoride PET/CT. However, it has been stated by some experts that 18F-fluoride PET/CT is expected to replace 99mTc-MDP bone scintigraphy in the future. 18F-fluoride PET and PET/CT are, however, not widely used in clinical practice. The limited availability of 18F-fluoride and of PET and PET/CT systems is a major factor. At present, there are not enough data on the cost-effectiveness of 18F-fluoride PET/CT. However, it has been stated by some experts that 18F-fluoride PET/CT is expected to replace 99mTc-MDP bone scintigraphy in the future.

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18F-Fluoride is a positron-emitting bone-seeking agent that was introduced by Blau and coworkers in 1962. Its uptake mechanism resembles that of 99mTc-MDP. After intravenous administration, 18F-fluoride diffuse through the bone capillaries into the bone extracellular fluid (ECF). Its plasma clearance is more rapid than that of 99mTc-MDP, and its single-pass extraction efficiency is higher because of its smaller molecular weight and the fact that its protein binding is negligible whereas binding of 99mTc-MDP to plasma proteins varies from 25% after injection to 70%, 12 hours after injection. In the blood, approximately 30% of 18F-fluoride is transported by erythrocytes. The single-pass extraction of 18F-fluoride is, however, almost 100% as the red blood cell 18F-fluoride, is available for clearance to bone. The fast blood clearance of 18F-fluoride results in a better target-to-background ratio. From the bone ECF, 18F-fluoride ions exchange with hydroxyl groups in the hydroxyapatite at the surface of bone crystals forming fluoroapatite mainly at sites of bone remodeling with high turnover. Therefore, uptake of 18F-fluoride reflects blood flow and osteoblastic activity. Bone uptake of 18F-fluoride is 2-fold greater than that of 99mTc-MDP.

Combining the favorable pharmacokinetic characteristics of 18F-fluoride with the high performance of positron emission tomography (PET) technology, 18F-fluoride is a valuable imaging modality of the skeleton. Quantitative methods of
18F-fluoride PET imaging allow dynamic measurement of the tracer uptake and regional characterization of metabolic bone lesions, monitoring their response to therapy, and separation between uneventful and impaired healing processes of bone fracture, osteonecrosis and graft incorporation.10-26 Static 18F-fluoride PET is highly sensitive for detection of malignant and benign bone abnormalities.27-45 As various pathological bone conditions are associated with increased uptake of 18F-fluoride, PET findings often require morphological characterization for accurate diagnosis. This is now easily achieved by using hybrid PET/computed tomography (CT) systems.36,41,43

18F-Fluoride PET/CT: Technical Notes

18F-Fluoride Preparation

18F-Fluoride was produced by the 18O(p,n)18F nuclear reaction in 2 mL of enriched 18O water as a target and then transferred into a fluorination module by a flow of argon. After trapping, it was loaded on an anion exchange column, dried, eluted with 1 mL of K2CO3 solution (5 mg/mL), and transferred to the reactor. After the addition of 1 mL of sterile water, the solution was heated to 120°C (2 minutes), followed by evaporation under reduced pressure. After the temperature of the solution was lowered to 30°C, 10 mL of saline and 4 mL of phosphate buffer (pH = 7) were added and transferred into a product vial through a 0.22-μm sterile filter. Chemical and radiochemical purity were analyzed by anion exchange high-performance liquid chromatography on an IC-PAKT anion HR (4.6*75 mm, Waters) and eluted with sodium borate/gluconate solution and acetonitrile (20 mL borate gluconate concentrate, 20 mL n-butanol, 120 mL acetonitrile, and 860 mL deionized water) at a flow of 0.8 mL/min.36

PET/CT Imaging

No special preparations are needed before the performance of 18F-fluoride PET/CT study. In most centers, scanning takes place approximately 60 minutes after injection. High-quality PET images can be acquired, however, within a very wide time-interval from 30 minutes to 4 hours after injection. The 18F-fluoride administered dose is usually 370 MBq (10 mCi). To reduce the radiation dose, mainly in patients referred for nononcologic indications, it is possible to inject only 185 MBq (5 mCi) of 18F-fluoride and increase acquisition time, maintaining the high quality of the images. The CT can be a full-dose CT or, as used in our center, reduced-dose CT with 140 kV, 80 mA, 0.8 seconds per CT rotation, a pitch of 6, and a table speed of 22.5 mm/s, without any specific holding instructions. A PET emission scan is performed immediately after the acquisition of CT, without changing the patient’s positioning. A total of 5 to 9 bed positions are performed with acquisition time of 3 minutes for each one (5 minutes when administered dose has been reduced), imaging the skeleton from skull to femurs. If lesions are suspected to be located at the distal peripheral bones, PET/CT acquisition includes these areas.36,41 In addition to morphological data, the CT part of the study is used for attenuation correction. The need to perform attenuation correction in 18F-fluoride PET is yet to be determined. Tayama and coworkers46 calculated bone-to-muscle ratios for 18F-fluoride PET images with and without attenuation correction. Their conclusion was that attenuation correction is not necessary for accurate visual interpretation of 18F-fluoride PET images. Lim and coworkers47 assessed the role of 18F-fluoride PET in young patients with back pain. In some cases, high tracer uptake in the renal collecting systems led to streak artifacts in the reconstructed PET images, which caused low tracer uptake and poor visualization of the adjacent spine. In these cases, calculated attenuation correction eliminated the artifact. The latter correction can be applied retrospectively.

Radiation Exposure

Radiation exposure of 18F-fluoride resembles that of 99mTc-MDP. Injection of 185 MBq (5 mCi) 18F-fluoride in an adult patient is associated with effective dose of 4.25 mGy, which is comparable with 4.75 mGy when 740 MBq (20 mCi) of 99mTc-MDP is injected.44,47,48 Although on oncologic patients CT is a routine imaging procedure, the additional radiation exposure of CT should be considered with caution in patients who are referred for nononcologic indications. The CT acquisition protocol used in our department is associated with radiation exposure of 7.3 mGy in an adult patient and 10.5 mGy in a 10-year-old-patient. Reduction from 140 kV to 120 kV may achieve reduction in radiation exposure to 5.1 mGy and 7.35 mGy, respectively, and reduction of mAs to 40 may result in exposure of the child to 3.7 mGy.48 It is also possible to alter the workflow so that, instead of whole-body CT, only regional CT will be added after PET, based on the scintigraphic findings.

Quantitative Assessment of 18F-Fluoride Uptake

Quantitative assessment of 18F-fluoride uptake and its change over time has been used for assessment of normal bone physiology, characterization of bone pathology, and monitoring response to therapy. A method for assessing the full kinetics of 18F-fluoride has been described by Hawkins and coworkers. The technique is a nonlinear regression (NLR) method composed of 3 compartments, and 4 rate constants.3 With this technique, data are obtained by combining dynamic PET acquisition and arterial blood sampling. The 3 compartments are plasma, bone ECF, and bone mineral. The 4 rate constants are k1; clearance of 18F-fluoride from the plasma to the total bone, k2; reverse transfer from the ECF to plasma, k3; incorporation of 18F-fluoride into the bone mineral, and k4; release of 18F-fluoride from the mineral. K, calculated as (k1×k2)/((k3+k4)k1) is the net uptake of 18F-fluoride to bone mineral. The parameters obtained by the NLR method were found by Piet and coworkers in porcine model to correlate with histomorphologic findings of bone formation.16 As an alternative to NLR method, K, can be estimated by Patlak graphical analysis, which applies to the linear part of the time–activity

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curve. In can be performed more easily and robustly than NLR method but still, it requires blood sampling and dynamic PET imaging and therefore is also not used on a regular basis. Standardized uptake value (SUV), which averages tracer uptake with respect to the injected dose and body weight, is the most widely used PET index for assessment of tracer uptake in routine clinical practice because it does not require blood sampling and is obtained by static PET acquisition. SUV was found to correlate with the full kinetic 18F-fluoride modeling in both normal and pathological bone and can therefore substitute NLR and Patlak analysis, although one should keep in mind that SUV may be less reliable, particularly in areas with low metabolic activity, such as the long bones of the peripheral skeleton.

There is a large variability in the normal values of 18F-fluoride uptake in different skeletal regions. The highest values are found in trabecular bones, as in the vertebrae, characterized by greater bone turnover compared with long bones of the peripheral skeleton, which are predominately cortical.

The Clinical Role of 18F-Fluoride Imaging

Assessment of Metabolic Bone Diseases and Other Pathological Bone Conditions Using Quantitative 18F-Fluoride Imaging

In vivo assessment of 18F-fluoride kinetics allows characterization of bone disease as well as monitoring response to therapy. Specific regions in the skeleton can be individually assessed. This section will address the clinical role of quantitative 18F-fluoride PET.

Metabolic Bone Disease: Paget, Osteoporosis, and Renal Osteodystrophy

Several groups have investigated the kinetics of 18F-fluoride in Paget’s disease. In Pagetic bones, Ki values were increased more than 3-fold increased and k1 values were increased more than 2-fold, reflecting increased regional bone formation and plasma clearance to the total bone, respectively. The value of k2 was reported to be lower in Pagetic bones, perhaps as result of the fact that the marrow is often replaced by fibrous tissue and therefore 18F-fluoride is less available for return to plasma. The value of k4v was also found lower in Pagetic bones, suggesting that 18F-fluoride is more tightly bound to bone. Characterizing the kinetics of 18F-fluoride allows objective monitoring of the response of Paget therapy. Blockers of bone remodeling, the bisphosphonates, are currently used for treatment of patients with Paget’s disease. A month after initiation of therapy, Installe and co-workers observed a decrease in Ki and k1 values, although 18F-fluoride uptake remained greater than in normal bone. Six months after successful treatment, there was a further decreased in 18F-fluoride uptake, and k1 values reached those values measured in normal bones. There was no significant change in k2, k3, and k4 values. Nonresponse was associated with no change in Ki values and an increase in SUV. These findings suggest that the decrease of 18F-fluoride in Pagetic bones after treatment with bisphosphonates is related to decrease in the clearance of 18F-fluoride from the blood to bone, although mineralization may remain unaffected. Although full kinetic evaluation is more accurate, it appears that SUV measured 60 minutes after injection may be suitable for monitoring the response of Pagetic bones to therapy and separation between responders and nonresponders in clinical practice. Clinical assessment of the response to bisphosphonates therapy relies on measurement of blood and urine markers of bone resorption and formation. This approach may be of limited value in monostotic disease. When comparing the change in 18F-fluoride uptake with biochemical markers during treatment, the latter were found to normalize a month after initiation of therapy whereas 18F-fluoride uptake remained high in Pagetic bones. It is yet to be seen, however, whether this discrepancy has any practical implication on treatment approach.

Cook and coworkers investigated the regional differences in 18F-fluoride kinetics between lumbar vertebrae and the humerus of postmenopausal women using the NLR 3-compartmental modeling. Mean vertebral values were significantly greater than humeral Ki values. These observations allow a better understanding of the differences in the pathophysiology of metabolic impairment in different skeletal regions consisting of different bone type (trabecular or cortical), as well as the regional difference in response to treatment. In another study by this group, the regional skeletal kinetics measured by dynamic 18F-fluoride PET and biochemical markers of bone formation and resorption, were measured in 72 postmenopausal women classified as normal, osteopenic, or osteoporotic according to bone mineral densitometric score at the lumbar spine. Lower values of Ki were found in women classified as osteoporotic, whereas levels of bone-specific alkaline phosphatase, a measure of global bone formation, were significantly increased indicating that in postmenopausal osteoporosis, the global skeletal bone turnover is increased whereas the regional bone formation at the lumbar spine composed of predominately trabecular bone, is reduced.

Monitoring the response to antiresorptive therapy by the quantitation of 18F-fluoride uptake also was found valuable in osteoporosis. High values of Ki and k1 were found in both juvenile and postmenopausal osteoporosis. Measuring the change in bone metabolism and blood flow by 18F-fluoride PET of the lumbar spine after Risedronate therapy, Frost and coworkers found successful response to be associated with decrease in Ki values and decrease in k1 values, suggesting an increase in the reverse transfer of 18F-fluoride from the bone ECF to the blood and decrease in k4/k3, indicating a decrease in the fraction of tracer found in the ECF, which undergoes specific binding to the bone matrix.

When performed in patients with renal osteodystrophy, quantitative 18F-fluoride assessment separated lesions with low turnover from lesions of secondary hyperparathyroidism, which showed greater Ki values. These values decreased when patients underwent parathyroidectomy.
Bone Grafts, Healing Fractures, and Osteonecrosis

18F-fluoride uptake is a valuable diagnostic tool for assessment of the viability of bone grafts, early prediction of fracture nonunion and diagnosis of osteonecrosis. Brenner and coworkers have performed serial 18F-fluoride imaging in 34 patients with cancellous and full bone grafts. In general, both types of grafts showed decrease in uptake 2 years after surgery but uptake was still significantly higher in cancellous grafts and in the border zone of full bone grafts compared with normal limb bones. The time-course of changes in metabolism reflected by the change in uptake values measured at different time points was different for the two graft types. Although cancellous grafts were characterized by a stepwise decrease in bone metabolism, full-bone grafts have showed initial increase in 18F-fluoride uptake with a subsequent decrease. In cancellous grafts, the decrease in 18F-fluoride uptake between 6 to 24 months after surgery, correlated with a relatively fast healing of the small bone chips with formation of stable union within a year after surgery. In full bone grafts, healing is usually delayed and complications and nonunion tend to occur more frequently being diagnosed clinically and radiologically as late as 18-24 months after surgery. There is agreement between 18F-fluoride uptake of different parts of full-bone grafts and the histopathologic findings in the corresponding areas. In the contact zones, histopathologic assessment shows ongoing graft remodeling up to 48 months after surgery and correspondingly, 18F-fluoride uptake increases reaching a peak at about one year after surgery with subsequently decreasing bone activity. In contrast, the central parts of full-bone grafts show no remodeling and low 18F-fluoride uptake. Nonunion of the graft, which requires surgical intervention is characterized by increased 18F-fluoride uptake reflecting the ongoing repair mechanisms which involves increased blood flow, vascular permeability, and high bone turnover.

Piert and coworkers observed a prolonged increased bone 18F-fluoride uptake in patients after hip augmentation surgery with allogenic acetabular grafts compared with genuine cortical bone. Their hypothesis was that the increased bone metabolism in allogeneic bone graft was caused by a reduced ability to respond to the same extent as genuine bone to increased metabolic demands after surgery, with continuous stress to the normal surrounding bone, which corresponded with histopathologic findings of prolonged new bone formation in peripheral areas.

In a small number of patients, the quantitation of 18F-fluoride uptake has been used for evaluation of new bone formation around a femoral allograft inserted for treatment of prosthetic loosening. During the first year, uptake was increased. It decreased to that measured in the contralateral femur when measured 6 years after successful surgery. In another pilot study, 8 patients who underwent anterior cruciate ligament reconstruction by incorporation of a tendon graft in a bone tunnel underwent quantitative 18F-fluoride PET to follow the regional bone turnover starting a day after surgery until 22 months later. The highest uptake value was measured 3 weeks after surgery and remained high until 7 months after surgery. It was almost normal at 22 months after surgery. Quantitative 18F-fluoride PET imaging also has been used for the assessment of perfusion and osteoblastic activity of revascularized fibular grafts for mandibular reconstruction. The technique was found valuable in separating between uneventful graft healing, early failure and nonunion.

Early diagnosis of delayed union or nonunion of fractures is a challenging imaging task. Such diagnosis by conventional imaging is still suboptimal resulting in delay in 9 to 12 months with a consequent poor outcome. Serial plain radiographs are being used to follow callus formation. CT allows one to reconstruct bony architecture in 3-dimensions. However, both modalities detect mineralized bone formation, which is the late manifestation of the fracture healing process. Magnetic resonance imaging (MRI) is a valuable diagnostic tool for the assessment of fracture healing, although it is less sensitive in identifying impaired fracture healing when located in long bones. The role of quantitative 18F-fluoride PET in early identification of impaired fracture healing was investigated in rat model by Hsu and coworkers. Although the union site was characterized by a progressive increase in uptake up to the 3-week time point and then stabilization, only minimal uptake was constantly observed in impaired healing. These findings suggest that 18F-fluoride PET can potentially predict the development fracture nonunion earlier than other imaging techniques. The role of 18F-fluoride PET in this clinical setting in humans is, however, yet to be determined.

Osteonecrosis of the femoral head may be a serious complication of fracture, treatment with high-dose steroids, or idiopathic treatment. In a pilot study in 5 patients with osteonecrosis, quantitative 18F-fluoride PET was found valuable for in vivo assessment of the regional blood supply of the femoral head as well as in monitoring the changes over time and prediction of outcome.

Detection of Malignant and Benign Lesions by Static 18F-Fluoride PET and PET/CT

18F-fluoride PET is the most sensitive imaging modality for detection of malignant bone involvement. The regional clearance of 18F fluoroide from plasma to bone is 3-fold or greater in metastatic lesions than in normal bone. Schirmeister and coworkers have shown, in several reports, the superiority of 18F-fluoride–PET for the detection of metastatic skeletal involvement compared with 99mTc-MDP bone scintigraphy (BS). In 34 patients with breast cancer, 18F-fluoride PET identified the presence of small bone marrow metastases. In a prospective study in 53 patients with small cell lung cancer or locally advanced nonsmall-cell lung cancer, the detection of bone metastases by planar BS, SPECT of the vertebral column, and 18F-fluoride PET were compared. Sensitivity of the 3 modalities was 78%, 94%, and 99%, respectively. Scintigraphic findings were associated...
with change in patient management in 9% of patients based on SPECT findings and in 11% of patients based on the findings of 18F-fluoride PET. However, 18F-fluoride is not tumor-specific and also accumulates excessively in benign bone abnormalities. As a matter of fact, because of its high sensitivity, 18F-fluoride PET performed for assessment of malignant bone involvement is prone to a high rate of false-positive interpretations by detecting nonmalignant lesions, including lesions that are usually not detected with 99mTc-MDP-BS, such as uncomplicated small cysts. It is not possible to differentiate benign from malignant lesions based on the intensity of 18F-fluoride uptake. Lesions detected on 18F-fluoride PET, therefore, often require correlation with CT and/or MRI. The use of hybrid PET/CT has improved significantly the limited specificity of 18F-fluoride PET because the morphologic CT appearance of the scintigraphic lesion achieves accurate differentiation between benign lesions and metastases. To evaluate the diagnostic accuracy of 18F-fluoride PET/CT in assessing malignant osseous involvement and in differentiating malignant from benign bone lesions, we performed 18F-fluoride PET/CT studies in 44 cancer patients and found a statistically significant improvement in the specificity of 18F-fluoride PET/CT (97%) compared with 18F-fluoride-PET alone (72%) on a lesion-based analysis and 88% versus 56% on a patient-based analysis. In another study in a more selective patient population, high-risk prostate cancer patients, we compared the detection of bone metastases by planar BS, multifield of view SPECT of the axial skeleton, 18F-fluoride PET, and 18F-fluoride PET/CT. 18F-Fluoride PET/CT was statistically more sensitive and more specific than planar and/or SPECT BS and more specific than 18F-fluoride PET. On a patient-based analysis, the sensitivity of planar BS, SPECT, and 18F-fluoride PET/CT was 70%, 92%, 100%, respectively. Specificity of planar BS, SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT was 57%, 82%, 62%, and 100%.

On fused images of PET/CT, the morphology of all lesions showing increased 18F-fluoride uptake is instantly provided. Although 18F-fluoride uptake mechanism corresponds to osteoblastic activity, it is highly sensitive for detection of lytic and early marrow-based metastases and not only osteoblastic ones. The reactive osteoblastic activity, which accompanies lytic lesions and malignant marrow deposits, is reflected by increased uptake of 18F-fluoride in the periphery of the lesions, even when minimal. PET/CT images allow a direct comparison between the diagnostic accuracy of 18F-fluoride PET and that of CT. 18F-Fluoride PET appears to be more sensitive in detecting bone abnormalities. Of 111 metastases identified by increased 18F-fluoride uptake, the appearance of bone CT was normal in 16 (14%). PET/CT is beneficial in ruling out metastatic spread when nonspecific lesions are reported on CT. In patients with prostate cancer, a tumor type with predominately osteoblastic metastases, the presence of nonspecific sclerotic lesions on CT pose dilemma as they may represent metastatic spread or be bone islands with no clinical relevance. Although the former show increased 18F-fluoride, the latter lesions are negative on PET. Most data on the role of 18F-fluoride PET in benign conditions address the use of quantitative PET and evaluation of 18F-fluoride kinetics. There are only few studies on the role of
static $^{18}$F-fluoride PET for the detection of lesions in patients referred for nononcologic indications. With the evolving use of PET and PET/CT technology in routine clinical practice, data on the clinical use of $^{18}$F-fluoride for detection of benign bone abnormalities are being accumulated. In a pilot study in a small group of patients with painful knee after arthroplasty, $^{18}$F-fluoride PET was found valuable in detecting aseptic loosening and differentiating loosening from simple synovitis.45 Two manuscripts were published recently on the role of $^{18}$F-fluoride imaging in assessment of back pain in children and young adults, one using PET and the other using hybrid PET/CT.43,44 Performance of $^{18}$F-fluoride PET/CT in this clinical setting allowed accurate diagnosis of various etiologies of back pain including pars interarticularis stress, spinous process injury, sacroiliac joint inflammation or stress, and osteoid osteoma. An important observation was the high negative predictive value of a normal study. Patients who had a negative $^{18}$F-fluoride PET/CT did not need any medical intervention and the pain resolved spontaneously.43

We have performed $^{18}$F-fluoride PET/CT in 82 patients referred for nononcologic indications, including acute back pain (n = 36), chronic back pain (n = 18), hip joint pain (n = 16), acute knee pain (n = 6), assessment of vertebral fusion mass (n = 3), and assessment of the viability of free fibular flaps (n = 3) (unpublished data). The instant fusion of scintigraphic findings with CT was beneficial in body regions

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**Figure 2** Multiple myeloma. Shown is a 54-year-old female patient with multiple myeloma. (A) MIP image. Before $^{18}$F-fluoride PET/CT imaging, she had known lesions only in a rib (B) and in a vertebra (C). $^{18}$F-fluoride PET/CT identified multiple unexpected lesions. Two such lesions located in the left humerus are presented, lytic (D), and intramedullary (E). Each row represents, from left to right, CT, PET, and fused PET/CT data of a myeloma lesion, noted by an arrow.

**Figure 3** Osteoid osteoma. A 24-year-old female patient with severe right hip joint pain and negative conventional imaging workup is shown. (A) MIP image. (B) Focal increased uptake of $^{18}$F-fluoride is detected in the periphery of the left femur found to correspond in location with a small osteoid osteoma (arrow). From left to right, CT, PET, and fused PET/CT data are illustrated. This abnormality was overlooked when CT was read alone. The patient underwent successful radiofrequency ablation. The uptake seen in the left pelvis is radioactive urine in the collecting system of a pelvic kidney.
with a complicated 3-dimensional structure such as the hip joint and allowed the identification of relevant lesions, which were overlooked when CT was interpreted alone (Fig. 3). In some cases, bone abnormality suggested by CT to cause the patient symptoms was negative on PET, whereas other relevant lesion associated with increased $^{18}$F-fluoride uptake was identified (Fig. 4).

Despite the high performance of $^{18}$F-fluoride PET/CT, it is not widely used. The tracer is not always commercially available, and the number of PET/CT systems is smaller than the number of gamma cameras. $^{18}$F-fluoride PET or PET/CT is reserved for selected patients, either high-risk cancer patients or patients who are suspected clinically to have malignant or benign skeletal problems even though conventional imaging modalities and/or BS are negative or nonconclusive. It has been stated already by some authors that $^{18}$F-fluoride imaging is expected to replace bone scintigraphy completely within several years. However, the decision to use of $^{18}$F-fluoride PET or PET/CT routinely warrants meticulous cost-effectiveness analysis. In a report by Hetzel and coworkers on 103 patients with lung cancer, the cost-effectiveness of $^{18}$F-fluoride PET was compared with that of bone scintigraphy completely within several years. However, the decision to use of $^{18}$F-fluoride PET or PET/CT routinely warrants meticulous cost-effectiveness analysis. In a report by Hetzel and coworkers on 103 patients with lung cancer, the cost-effectiveness of $^{18}$F-fluoride PET was compared with that of bone scintigraphy completely within several years.

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