Review of Published Literature on the Use of Sodium Fluoride F 18 (^{18}F-NaF) Positron Emission Tomography (PET) in the Evaluation of Altered Osteogenic Activity

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List of Abbreviations

LIST OF ABBREVIATIONS

^{18}F-NaF	Sodium fluoride F 18
AUC	Area under the plasma concentration curve
BBF	Bone blood flow
BMD	Bone mineral density
BS	Bone scintigraphy
BSALP	Bone-specific alkaline phosphatase
CI	Confidence interval
CML	Classic metaphyseal lesion
CT	Computerized axial tomography
DXA	Dual-energy x-ray absorptiometry
ECF	Extracellular fluid
EDTA	Ethylenediaminetetraacetic acid
FCH	Fluorocholine
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
GFR	Glomerular filtration rate
HPT	Hyperparathyroidism
HRT	Hormone replacement therapy
HSA	Human serum albumin
HU	Hounsfield unit
IF	Input function
K_1	Bone blood flow
k	Rate constant
kEV	Kiloelectron volt
K_{bone}	Net plasma clearance of tracer to bone mineral
K_{MLF}	Bone uptake constant determined by multilinear least squares fitting
K_{NLR}	Bone uptake constant determined using non-linear regression
K_{PAT}	Bone uptake constant determined using Patlak graphical analysis
LBT	Low-turnover bone disease
MBq	Megabecquerel
mCi	Millicurie
MDP	Methylene diphosphonate
MRI	Magnetic resonance imaging
mSv	Millisievert
NaF	Sodium fluoride
NDA	New Drug Application
NLR	Non-linear regression
NSCLC	Non-small cell lung cancer
PET	Positron emission tomography
PK	Pharmacokinetic
PTH	Parathyroid hormone

ROC	Receiver operating characteristic
ROI	Region of interest
SCLC	Small cell lung cancer
SPECT	Single photon emission computerized tomography
SUV	Standardized uptake value
TAC	Time-activity curve
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
UK	United Kingdom
VOI	Volume of interest
WBI	Whole-body iodine scintigraphy
WHO	World Health Organization

1. Introduction

This is a review of the recent published literature reporting efficacy and safety of sodium fluoride F 18 (^{18}F-NaF) positron emission tomography (PET) for the evaluation of altered osteogenic activity.

Stable fluoride is a natural trace element. Diffusion through capillaries into bone extracellular fluid leads to a slow exchange of fluoride ions with hydroxyapatite crystals, forming fluoroapatite [1]. At least 99% of whole-body fluoride is thought to be present in the skeleton, primarily as fluoroapatite [2]. ^{18}F-NaF was initially introduced by Blau *et al*. [3] in 1962 as an imaging agent for bone lesions. ^{18}F-fluoride has favorable tracer kinetics as a radiopharmaceutical for bone imaging: it accumulates in bone rapidly to a high concentration and clears quickly from the circulation, allowing a high bone-to-background uptake ratio within a short time [2]. As a result, exposure of patients to radiation is low, and imaging can be obtained within a short time after intravenous administration. Fluoride ^{18}F ions normally accumulate in the skeleton in an even fashion, with greater deposition in the axial skeleton (*e.g.*, vertebrae and pelvis) than in appendicular skeleton, and greater deposition in the bones around joints than in the shafts of long bones [4]. Uptake of ^{18}F is higher in areas of increased osteogenic activity (reviewed in [5]). The use of ^{18}F-NaF to define areas of altered osteogenic activity was approved by FDA in 1972 (NDA 17-42). The approved dose is 0.5−2 mCi (18.5−74 MBq), maximum 4 mCi (148 MBq) administered as an intravenous injection.

^{18}F-fluoride was replaced by ^{99m}Tc-labeled diphosphonates in 1970s as the standard imaging agents for bone scintigraphy (BS) because of the convenience in producing ^{99m}Tc on site from ^{99}Mo/^{99m}Tc generators. In addition, gamma cameras are optimally designed for detecting 140 keV photons from ^{99m}Tc rather than higher energy 511 keV photons from ^{18}F-fluoride. Therefore, the decline in use of ^{18}F-fluoride in BS was due to technical and logistic issues other than the limitations of fluoride ion as a radiotracer.

The interest in ^{18}F-fluoride as a bone imaging agent was renewed in 1990s owing to a wider availability and improved technology of PET scanners, which offer higher spatial resolution and sensitivity than conventional gamma cameras used in planar scintigraphy or single photon emission computerized tomography (SPECT). Since that time, ^{18}F-fluoride has been used clinically for PET imaging of primary and metastatic bone cancers as well as in benign skeleton diseases. Results from 41 clinical trials investigating the use of ^{18}F-NaF PET as a bone imaging agent have been published since 1992 and are summarized in this report. The majority of trials used a dose of ^{18}F-fluoride that is substantially higher than the approved dose of 0.5−2 mCi. In most cases where different imaging modalities were compared, ^{18}F-NaF PET proved to be more sensitive and specific than other techniques, though also more expensive. No safety issues have been reported. Effectiveness and safety information available in the published literature are summarized in the next section.

2. Evaluation of the Safety and Effectiveness Data for Sodium Fluoride F 18 PET Imaging in Altered Osteogenic Activity

2.1 Data Sources

A search of the recent peer-reviewed journal literature was conducted to identify original clinical studies and case reports using ^{18}F-fluoride PET. The initial search of Medline through PubMed included the search terms: "Sodium Fluoride / diagnostic use" [MESH]; all permutations of "18F-NaF" as a free text term; and "18F-fluoride" as a free text term limited to humans, clinical trial, randomized controlled trial and case reports. A search was then done in the Embase database on Dialog with the free text term "18F-fluoride" limited to clinical studies and case studies. Review articles were identified using the same criteria; however, review articles are not included in this summary.

The search generated 41 articles of interest. Fourteen of these involved the use of ^{18}F-fluoride PET to identify bone metastases in adults, three evaluated use of ^{18}F-fluoride PET to diagnose benign skeletal disorders in adults, four were conducted in a pediatric population (two prospective studies evaluating back pain, one case report evaluating bone metastases, and one case report evaluating skeletal injuries), 19 were investigations of normal and/or abnormal bone healing, metabolism and kinetics, and one evaluated accuracy of PET imaging with and without attenuation correction in subjects with a variety of skeletal conditions. The findings in each article, grouped by application, are summarized in the following sections. Well-controlled studies demonstrate the effectiveness and safety of ^{18}F-fluoride PET by having all or most of the following components in the trial design: there was a comparison between ^{18}F-fluoride PET and a "truth" standard for disease, namely conventional diagnostic or pathology results; the study population was prospectively controlled; the entry criteria defined the target clinical population in which ^{18}F-fluoride was intended to be used; there were clearly defined endpoints; detailed data on findings were presented; and there were procedures to minimize interpretation bias, such as masking (also referred to as blinding), randomization or multiple independent readers. Additional studies examined the effectiveness and utility of ^{18}F-fluoride PET imaging to detect abnormal osteogenic activity under a variety of circumstances, but may not have incorporated the elements of a well-controlled study (*e.g.*, the patient cohort was not prospectively controlled; comparison to "truth" standard was not possible or not done; procedures to minimize interpretation bias were not disclosed, *etc*.). Four publications using ^{18}F-fluoride PET in the pediatric population were identified (two well-controlled studies and two case studies). These publications are discussed separately, and all of the publications reviewed in this summary are also listed in Table 1 for reference.

FDA's Adverse Event Reporting System (AERS) database was also searched for adverse events associated with use of ^{18}F-NaF. All quarterly files currently available on the AERS

website were accessed (January 2004–September 2008). A search using the term "NaF18" identified the following drug synonyms:

ZYMAFLUOR D (COLECALCIFEROL, SODIUM FLUORIDE)
2.0% SODIUM FLUORIDE (0.9% FLUORIDE ION)
CALCIUM ^NAF^
ERGOCALCIFEROL, CALCIUM PHOSPHATE, CYANOCOBALAMIN, SODIUM FLUORIDE, NU
FLUDEOXYGLUCOSE (18F) (FLUDEOXYGLUCOSE (18F))
FLUDEOXYGLUCOSE F 18
FLUORETTE (SODIUM FLUORIDE)
FLUORODEOXGLUCOSE F 189 (FLUDEOXYGLUCOSE (18F) (INJECTION FOR INFUSION
FLUORODEOXYGLUCOSE F 18 (FLUDEOXYGLUCOSE (18F) (INJECTION FOR INFUSION
FLUORODEOXYGLUCOSE F 18 (FLUDEOXYGLUCOSE (18F))
FLUORODEOXYGLUCOSE F 18 (FLUDEOXYGLUCOSE (18F))
FLUORODEOXYGLUCOSE F 18 (FLUDEOXYGLUCOSE (18F)) (INJECTION FOR INFUSIO
FLUOROTHYMIDINE F 18 (INJECTION FOR INFUSION)
FOLSYRE NAF
LIDOCAINE 'NAF^
LURIDE 0.5 MG (1.1 MG NAF)
OSSIPPLEX-SLOW RELEASE (SODIUM FLUORIDE, ASCORBIC ACID)
PROCAL (SODIUM FLUORIDE)
SODIUM FLUORIDE
SODIUM FLUORIDE (SODIUM FLUORIDE)
SODIUM FLUORIDE (SODIUM FLUORIDE)
SODIUM FLUORIDE (SODIUM FLUORIDE)
SODIUM FLUORIDE (FORMULATION UNKNOWN) (SODIUM FLUORIDE)
SODIUM FLUORIDE (NCH) (SODIUM FLUORIDE)
SODIUM FLUORIDE (NCH)(SODIUM FLUORIDE) UNKNOWN
SODIUM FLUORIDE (SODIUM FLUORIDE)
SODIUM FLUORIDE (SOLDIUM FLUORIDE)
SODIUM FLUORIDE + POTASSIUM NITRATE (FORMULATION UNKNOW) (SODIUM FLUO
SODIUM FLUORIDE 1.1%
SODIUM FLUORIDE CHEW
SODIUM FLUORIDE GEL
SODIUM-FLUORIDE GEL (SODIUM FLUORIDE)
TRIMETOPRIM ^NAF^
ZYMAFLUOR (SODIUM FLUORIDE)
NAF18

Of the 79 cases identified, none listed ^{18}F-NaF or sodium fluoride F18 as the associated drug. For sodium fluoride cases, the fields for route, dose and NDA number were reviewed to verify that the injectable imaging agent had not been administered. No additional adverse events related to ^{18}F-NaF were identified; however, the dosing and NDA fields were empty for the majority of cases.

2.2 Published Literature

2.2.1 Studies of Bone Metastases

2.2.1.1 Well-controlled Studies

2.2.1.1.1 Prostate Cancer

Beheshti, M., et al. Detection of bone metastases in patients with prostate cancer by ^{18}F fluorocholine and ^{18}F fluoride PET-CT: a comparative study. Eur J Nucl Med Mol Imag. 35:1766–1774, 2008 [6]

The aim of this prospective trial was to compare the potential value of ^{18}F-fluorocholine (FCH) PET-computerized tomography (CT) and ^{18}F-fluoride PET-CT for the detection of bone metastases in subjects with prostate cancer. The study was conducted at St. Vincent's Hospital (Linz, Austria) and Guy's and St. Thomas' NHS Foundation Trust (London, UK).

Inclusion Criteria: Men with biopsy-proven prostate cancer. Subjects were assessed either pre-operatively (untreated patients with high Gleason score and/or elevated prostate specific antigen levels) or post-operatively (evidence of disease progression or suspicious bone metastases based on clinical signs or other imaging modalities); patients with low-risk prostate cancer or a history of a second cancer were excluded. A total of 38 subjects were enrolled (mean age 69 ± 8 years).

Dose: Image acquisition began 60 minutes after intravenous administration of 370–555 MBq (10–15 mCi) ^{18}F-NaF, or one minute after intravenous injection of 4.07 MBq/kg-bw ^{18}F-FCH.

Schema of Trial: Comparison of visual interpretation of ^{18}F- FCH and ^{18}F-fluoride PET-CT scans; all participants were scanned by both imaging techniques, with a maximum interval of two weeks between scans. The final diagnoses of bone metastases were established by histopathological findings or follow-up studies (*e.g.*, FCH and/or ^{18}F-fluoride PET-CT and clinical follow-up for at least six months).

Image Protocol: PET image acquisition and reconstruction information is presented; CT data were used for attenuation correction; selection of regions of interest (ROI) and determination of maximum standardized uptake value (SUV_{max}) was described.

The interpretation of PET-CT studies was made as a consensus reading of two nuclear medicine physicians and a radiologist who had access to clinical, as well as previous radiological imaging information. For anatomical analysis, the skeleton was divided into sections: cervical; upper thoracic (T1−T6); lower thoracic (T7−T12) and lumbar spine;

ribs and sternum; upper and lower extremities; and other (*e.g.,* scapula). In patients with general bone metastases, only one dominant lesion in each anatomical section was selected for semi-quantitative analysis. Since the ^{18}F-FCH PET-CT scans were obtained from the base of the skull to the level of the upper thighs, lesions in the skull, distal femurs and both feet were excluded from the study.

Lesions were diagnosed as benign when unsuspicious morphological alterations located around the joints, degenerative changes, osteoporotic patterns, and/or fractures were detected. Lesions were considered malignant depending on anatomical localization and/or considerable morphological changes. Lesions neither malignant nor benign were classified as equivocal. Positive lesions by ^{18}F-FCH or ^{18}F-fluoride PET with negative CT were considered likely to be bone marrow metastases or "micro-scleroses", respectively. The quantitative radiodensity of sclerotic lesions was measured by Hounsfield unit (HU) using a standard spherical region of ROI (maximum diameter 6.5 mm).

Primary Endpoints: Comparison of two techniques based on visual interpretation of number, sites, and morphological pattern of bone lesions; radiodensity of lesions; semi-quantitative analysis by means of maximum standardized uptake value (SUV_{max}); comparison to histopathological and/or follow-up findings.

Results: Overall, 321 lesions (151 malignant, 155 benign and 15 equivocal) were evaluated in the study. Fifteen equivocal lesions without final diagnosis were excluded from the analysis. ^{18}F-FCH PET-CT showed 106 sites with increased tracer uptake (100 malignant, 6 benign), while ^{18}F-fluoride PET-CT detected 200 bone lesions (116 malignant, 84 benign). The sensitivity, specificity and accuracy, respectively, for detection of bone metastases was 74%, 99% and 85% for ^{18}F-FCH PET-CT, and 81%, 93% and 86% for ^{18}F-fluoride PET-CT. ^{18}F-FCH PET-CT showed significantly higher specificity ($p=0.01$) than ^{18}F-fluoride PET-CT. Mean SUV_{max} in malignant lesions detected by ^{18}F-FCH PET-CT was 7.8±3.2; mean SUV_{max} detected by ^{18}F-fluoride PET-CT was 57±43 in malignant lesions, and 20±7 for benign lesions. Lytic lesions showed more intense uptake than sclerotic lesions by both imaging modalities. Relatively close agreement was found between the two procedures for detection of malignant bone lesions in lesion-based ($\kappa=0.57$) and patient-based ($\kappa=0.76$) analyses. For 80% of lesions, ^{18}F-FCH PET-CT and ^{18}F-fluoride PET-CT showed similar findings. There was significant correlation between tracer intensity by SUV and density of sclerotic lesions by HU both in ^{18}F-FCH PET-CT ($r=-0.28$; $p<0.006$) and ^{18}F-fluoride PET-CT ($r=-0.20$; $p<0.05$). ^{18}F-fluoride PET-CT identified more lesions in some patients compared with ^{18}F-FCH PET-CT; however, it did not change patient management. ^{18}F-FCH PET-CT led to a change in management in two of 38 patients in preoperative evaluation due to early detection of bone metastases; in both of these patients, CT as well as ^{18}F-fluoride PET scans were negative, but malignancy was confirmed in follow-up examinations.

Safety Issues: No safety issues were identified in the study.

2.2.1.1.2 Breast Cancer

Petren-Mallmin, M., et al. Skeletal metastases from breast cancer: uptake of ^{18}F-fluoride measured with positron emission tomography in correlation with CT. Skeletal Radiol. 27(2):72–76, 1998 [7]

Uptake of ^{18}F-fluoride in skeletal metastases was characterized by performing PET in five breast cancer patients, and comparing these findings to CT. The study was conducted at University Hospital, Uppsala, Sweden.

Inclusion Criteria: Five women with histologically proven breast cancer and skeletal metastases participated in the study (age range 50−70 years); four patients had received oncologic treatment prior to participation.

Dose: 200−400 MBq (5.4−10.8 mCi) ^{18}F-fluoride by rapid intravenous injection; dynamic PET imaging began immediately after injection and continued for 50 minutes.

Schema of Trial: Subjects underwent both CT and dynamic ^{18}F-fluoride PET imaging, with an average of five days (range 0−9 days) between imaging modalities. Plasma samples were collected during the PET imaging period for analysis of plasma ^{18}F concentration. Areas of sclerotic or lytic lesions detected by CT and ^{18}F-fluoride PET were compared.

Image Protocol: PET and CT image acquisition and reconstruction information is presented. CT was considered positive for metastases when osteolytic lesions, osteosclerosis without degenerative joint disease, or mixed lytic and sclerotic lesions were present. For PET, potential metastases or other pathological processes were considered when there were areas with a focal increase or decrease in the uptake of ^{18}F compared with surrounding normal bone. ROIs were drawn for lesions and normal bone. For each ROI, the mean value of the transport rate constant was calculated. The four contiguous pixels with the highest levels of activity within the tumor ROIs were also identified, and the corresponding transport rate constants were estimated.

Corresponding PET and CT sections were identified by visual inspection, and scans were anatomically correlated. The outlines of bones seen in the CT images were drawn onto the PET images. From these anatomically matched images, the relationships between ^{18}F uptake and areas of sclerotic or lytic lesions as seen on CT were determined.

Primary Endpoints: Visual correlation of location and diagnosis of lesions observed by CT and PET.

Results: All patients had multiple skeletal metastases. Kinetic analysis indicated that the regional clearance of ^{18}F-fluoride from blood to bone metastases was 5−10 times greater than to normal bone. Focally increased uptake of ^{18}F-fluoride was seen in both

osteolytic and osteoblastic bone lesions as defined by CT; however, lesions less than 3 mm on CT were not detected by ^{18}F-fluoride PET. Overall, the areas of abnormal high accumulation of ^{18}F correlated well with the pathological appearance on CT.

Safety Issues: No safety issues were mentioned in the study.

Schirrmeister, H., et al. Early detection and accurate description of extent of metastatic bone disease in breast cancer with fluoride ion and positron emission tomography. J Clin Oncol. 17(8):2381–2389, 1999 [8]

This is a prospective trial to evaluate the sensitivity and specificity of ^{18}F-fluoride PET to detect bone metastases in patients with breast cancer. The study was conducted at University Hospital in Ulm, Germany.

Inclusion Criteria: This trial enrolled 34 women (age range 37−75 years, mean age 52.3 years) with confirmed breast cancer and known (n=6) or suspected (n=28) metastatic bone involvement.

Dose: PET scanning of the skeletal trunk was performed one hour after intravenous injection of 370 mBq (10 mCi) of ^{18}F-fluoride.

Schema of Trial: Comparison of visual interpretation of ^{18}F-fluoride PET and conventional ^{99m}Tc-methylene diphosphonate (MDP) planar BS. A panel of reference methods was used, including magnetic resonance imaging (MRI; n=28), planar x-ray (n=17), and spiral CT (n=4).

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was not performed. Parameters used for reference methods were stated or referenced.

PET and BS were compared using patient-by-patient and lesion-by-lesion analysis. All lesions and all diseases were rated using a five-point scale (definitely metastatic=1, definitely not metastatic=5) for receiver operating characteristic (ROC) curve analysis

Two experienced nuclear medicine physicians interpreted bone scans and two other nuclear medicine physicians interpreted PET scans, independently and blinded to the results of the other imaging modalities. Extravertebral lesions detected by PET or BS were confirmed by planar x-ray, MRI or spiral CT; images produced by these reference methods were interpreted by two diagnostic radiologists. The locations of lesions as determined by ^{18}F-fluoride PET and/or BS were given to two readers. If the two readers did not agree on the grading of a lesion, they discussed their differences until reaching a consensus. Patients were considered to have no bone metastases when BS, ^{18}F-fluoride PET and the reference methods did not reveal any suspicious lesions. Lesions were considered metastases when they increased in number over one year, when they

appeared osteolytic on spiral CT scans or x-rays, or when there was a typical gadolinium enhancement or hyperintense lesion in fat-suppressed T2-weighted MRI. All lesions not having characteristic features of degenerative disease or trauma were considered metastases.

Primary Endpoints: Visual interpretation; extraverterbal lesions detected by PET or BS were confirmed by planar x-ray, MRI or spiral CT.

Results: ^{18}F-fluoride PET out-performed ^{99m}Tc-MDP BS by both patient-based and lesion-based analyses. ^{18}F-fluoride PET detected 64 bone metastases in 17 patients, whereas bone scan only identified 29 metastases in 11 patients. All lesions detected by bone scan were also identified by ^{18}F-fluoride PET. The full extent of metastatic bone disease was correctly characterized by ^{18}F-fluoride PET in all patients, but in only 6 patients (35.3%) with ^{99m}Tc-MDP. ^{18}F-fluoride PET resulted in restaging of disease in three patients and subsequent change in the disease management of four patients (11.7%). Nine equivocal or benign lesions on ^{99m}Tc-MDP were later shown to be metastatic, but only one metastatic lesion was misinterpreted as equivocal by ^{18}F-fluoride PET; there were no false-negative or false-positive results with ^{18}F-fluoride PET. ^{99m}Tc-MDP SPECT was also performed in 12 patients in this series and revealed no additional metastases as compared with planar imaging. On a patient basis, the area under the ROC curve was 1.00 for ^{18}F-fluoride PET and 0.82 for BS ($p<0.05$); on a lesion basis, the area under the ROC curve was 0.99 for ^{18}F-fluoride PET and 0.72 for BS ($p<0.05$). There was excellent agreement for area under the ROC curve for both analyses with ^{18}F-fluoride PET.

Safety Issues: No safety issues were mentioned in the study.

2.2.1.1.3 Lung Cancer

Hetzel, M., et al. F-18 NaF PET for detection of bone metastases in lung cancer: accuracy, cost-effectiveness, and impact on patient management. J Bone Miner Res. 18(12): 2206–2214, 2003 [9]

A prospective study to evaluate the use of ^{18}F-fluoride PET, SPECT and ^{99m}Tc-MDP planar BS for detection of bone metastases in patients with lung cancer. The study was conducted at The University of Ulm in Ulm, Germany.

Inclusion Criteria: Patients with newly diagnosed lung cancer established by bronchoscopic or percutaneous biopsy. Patient selection was independent of the histological subtype or suspected stage of disease. A total of 103 patients were enrolled (72 male, 31 female, age range 38−81 years, median age 62 years); 73 had non-small cell lung cancer (NSCLC) and 30 had small cell lung cancer (SCLC). Patients less than 18 years of age, pregnant, or with a history of extrapulmonary disease were excluded.

Dose: 261−740 MBq (7−20 mCi) ^{18}F-NaF administered intravenously; the emission scan was initiated 75−180 minutes after administration.

Schema of Trial: Each patient was analyzed by ^{18}F-fluoride PET, SPECT and ^{99m}Tc-MDP planar BS. ROC curve analysis was used for determination of diagnostic accuracy. Whole spine MRI, sometime in conjunction with ^{18}F-fludeoxyglucose (FDG) PET or spiral CT, was used as the standard reference to define bone metastases.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was not performed. ^{99m}Tc-MDP, SPECT, and MRI parameters are provided.

Two experienced nuclear medicine physicians interpreted bone scans in a first reading. In a second reading, the bone scans were interpreted in combination with SPECT images of the vertebral column. Finally, the ^{18}F-fluoride PET scans were interpreted. Both readers were blinded to the results of the reference methods. The results of all available reference methods (plain radiographs, CT, ^{18}F-FDG PET, clinical follow-up) were made available to the two diagnostic radiologists who interpreted the MRIs.

Patients were defined as having no bone metastases when ^{99m}Tc-MDP BS, SPECT, ^{18}F-fluoride PET, and MRI showed no metastases. Lesions with typical gadolinium enhancement in hyperintense regions in fat-suppressed T2-weighted MRI were defined as bone metastases. ^{18}F-fluoride PET and ^{99m}Tc-MDP BS with and without SPECT were compared on a patient basis using ROC curve analysis. Readers also described the extent of metastatic disease by counting the number of metastases. Two oncologists experienced in the management of lung cancer defined the treatment strategy based on results obtained from ^{18}F-fluoride PET and ^{99m}Tc-MDP BS with and without SPECT. Effectiveness was defined as the proportion of correctly diagnosed patients, comprised of true positives and true negatives. Average cost-effectiveness ratios were calculated for each diagnostic strategy by dividing the expected costs by the expected effectiveness.

Primary Endpoints: Specificity and sensitivity by visual interpretation, comparison to reference methods, and ROC curve analysis; cost effectiveness.

Results: Of the 103 patients, bone metastases were present in 33 patients as determined by reference methods. ^{18}F-fluoride PET correctly identified bone metastases in 31 of these patients compared with 20 by planar ^{99m}Tc-MDP scan and 29 by SPECT. In addition, two patients with negative ^{18}F-fluoride PET scan but positive MRI were later confirmed to have no bone metastases by clinical follow-up or autopsy. Compared with ^{18}F-fluoride PET, the extent of bone metastases was underestimated in 23 (69.7%) patients with ^{99m}Tc-MDP BS and in 16 (48.5%) of 33 patients with SPECT. The area under the ROC curve was 0.771 for ^{99m}Tc-MDP BS, 0.875 for SPECT, and 0.989 for ^{18}F-fluoride PET. As a result of identifying additional patients with bone metastases by ^{18}F-fluoride

PET compared with ^{99m}Tc-MDP BS and SPECT, the clinical management was changed for two patients. Compared with ^{99m}Tc-MDP BS, the costs per additional correctly diagnosed patients were 1272 Euro with SPECT and 2861 Euro with ^{18}F-fluoride PET. The threshold for the cost of ^{18}F-fluoride PET being more cost-effective than SPECT was 345 Euro.

Safety Issues: No safety issues were mentioned in the study.

Schirrmeister, H., et al. Prospective evaluation of the clinical value of planar bone scans, SPECT, and (18)F-labeled NaF PET in newly diagnosed lung cancer. J Nucl Med. 42(12):1800–1804, 2001 [10]

This is a prospective study designed to compare the sensitivities and specificities of ^{18}F-fluoride PET and BS with and without and SPECT to detect bone metastases in subjects with newly diagnosed SCLC or advanced NSCLC. The study was conducted at University Hospital in Ulm, Germany.

Inclusion Criteria: Patients with SCLC or locally advanced NSCLC diagnosed through bronchoscopy and CT were enrolled (53 total subjects, 42 men, 11 women, age range 43–78 years, median age 63 years). Patients with a history of extrapulmonary cancer, known metastatic bone disease, NSCLC at stages lower than Stage III of the Union Internationale Contre le Cancer, <18 years of age, or pregnant were excluded.

Dose: PET imaging was initiated 75−180 minutes after intravenous injection of 370–555 MBq (10–15 mCi) ^{18}F-labeled NaF.

Schema of Trial: Comparison of visual interpretation of ^{18}F-fluoride PET and conventional ^{99m}Tc-MDP planar BS with SPECT. MRI and all available imaging methods were used as reference methods.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was not performed. Parameters used for BS, SPECT, and MRI were stated or referenced.

PET and BS with and without SPECT were compared on a patient basis. All patients were rated using a five-point scale (definitely having bone metastases=1, definitely not having bone metastases=5) for ROC curve analysis. The area under the ROC curve was used to test for statistically significant differences ($p<0.05$) between BS, SPECT and ^{18}F-fluoride PET.

Two nuclear medicine physicians interpreted ^{18}F-fluoride PET, and two other nuclear medicine physicians interpreted BS complemented by SPECT. Planar BS was interpreted without SPECT by two other nuclear medicine physicians. The readers of BS, SPECT and ^{18}F-fluoride PET were unaware of the other's findings. The results of all imaging methods were made available to the two diagnostic radiologists who interpreted MRI

results. Patients were considered to have no bone metastases when BS, SPECT, ^{18}F-fluoride PET and MRI did not reveal any suspicious lesions. Typical gadolinium enhancement at hyperintense lesions in fat-suppressed T2-weighted MRI, or lesions not detectable on planar BS but showing the typical patterns of bone metastases from SPECT or ^{18}F-fluoride PET and MRI were defined as metastases. Lesions that were unclear at MRI but negative according to the scintigraphic methods were assessed with ^{18}F-FDG PET and spiral CT.

Primary Endpoints: Comparison of sensitivity and selectivity of test methods based on visual interpretation and comparison with reference methods.

Results: Of the 53 patients, 12 (23%) had metastatic bone disease as determined by a whole spine survey of MRI, which served as a standard reference method. ^{18}F-fluoride correctly detected bone metastases in 11 patients, correctly diagnosed 41 subjects as not having bone metastases, and interpreted one patient with a single rib metastases as equivocal. With planar BS, only five patients were classified correctly as having bone metastases, six patients were falsely interpreted as negative, five patients were equivocal (two of whom had bone metastases), and two patients with degenerative lesions were falsely interpreted as having bone metastases. By combining ^{99m}Tc-MDP planar scan with SPECT findings, the detection accuracy was improved markedly: an additional five patients with bone metastases were identified. The combination of planar scan and SPECT, however, missed bone metastases in one patient and underestimated the extent of bone involvement in seven of 12 patients (58%) as compared with ^{18}F-fluoride PET. All metastases that were detected by ^{99m}Tc-MDP planar scan and SPECT were identified by ^{18}F-fluoride PET. For the patient whose bone metastases were missed by both planar scan and SPECT, the clinical management was changed as a result of ^{18}F-fluoride PET findings.

The areas under the ROC curve were 0.779±0.078 for planar BS, 0.944±0.043 for planar BS plus SPECT, and 0.993±0.008 for ^{18}F-fluoride PET. The diagnostic accuracy of both tomographic imaging modalities was significantly higher than that of BS alone.

Safety Issues: No safety issues were mentioned in the study.

2.2.1.1.4 Thyroid Cancer

Schirrmeister, H., et al. Anatomical distribution and sclerotic activity of bone metastases from thyroid cancer assessed with F-18 sodium fluoride positron emission tomography. Thyroid. 11(7):677–683, 2001 [11]

A prospective study to evaluate the anatomical distribution and metabolic behavior of bone metastases in subjects with thyroid cancer using a variety of imaging techniques. The study was conducted at the University of Ulm (Ulm, Germany) between December 1995 and March 2000.

Inclusion Criteria: Subjects with thyroid cancer who had undergone thyroidectomy (35 total subjects; nine male, 26 female, mean age 62 years, age range 36−89 years) and met at least one of the following criteria: known distant metastases from papillary of follicular thyroid carcinoma; elevated Tg-serum levels; or newly diagnosed bone pain. All subjects had either follicular (26) or papillary (9) carcinoma. Twenty-two bone metastases were previously known in 14 subjects (12 follicular, two papillary cancers).

Dose: 370−555 MBq (10−15 mCi) ^{18}F-NaF administered intravenously; PET imaging began 75-90 minutes after administration.

Schema of Trial: Comparison of visual interpretation of conventional ^{99m}Tc-MDP planar BS with and without whole-body iodine scintigraphy (WBI); SPECT was carried out in indeterminate vertebral lesions in five patients. ^{18}F-fluoride PET and MRI were used as the primary reference method. The degree of sclerotic activity and the diagnosis of metastatic bone disease were verified by planar radiographs in all metastases. Additional CT scans were performed in nine patients with 18 metastases. T1 weighted images with and without gadolinium enhancement as well as fat-suppressed T2 weighted sagittal MRI of the entire vertebral column were used to exclude further small metastases probably not detected with BS or ^{18}F-fluoride PET (13 patients). Whole body ^{18}F-FDG-PET was carried out to exclude iodine negative metastases in 15 subjects. The clinical course (mean follow-up period 3.2 years) and results of all imaging modalities were used to confirm the diagnosis and to define the exact extent of metabolic disease.

Image Protocol: Image acquisition and reconstruction information is presented for BS, WBI and ^{18}F-fluoride PET; for ^{18}F-fluoride PET, attenuation correction was not performed.

BS and WBI were evaluated by two experienced nuclear medicine physicians who were blinded to the results of the other imaging modalities; BS was evaluated first, and a second evaluation was performed for the combination of BS and WBI. Lesions detected on BS were interpreted as metastases when: they appeared as cold lesions or as hot spots not located at articulations and did not show the typical linear tracer uptake of end plate fractures; increased tracer uptake on WBI or ^{18}F-FDG-PET persisted on follow-up examinations and correlated with osteolytic lesions on x-ray or CT; or hyperintense signals on fat-suppressed T2 combined with increased gadolinium uptake on T1 MRI corresponded to alterations in tracer uptake on ^{18}F-fluoride PET.

Primary Endpoints: Accuracy, sensitivity and specificity of ^{99m}Tc-MDP BS with and without WBI on a patient basis.

Results: Twenty-two metastases in 14 patients were previously known. The study identified 18 patients with metastases (nine single, nine multiple). At initial diagnosis, 41 metastases were osteolytic on x-ray or CT and two rib metastases were mixed

osteolytic/osteosclerotic. With ^{18}F-fluoride PET, 21 previously unknown metastases appeared (13 with very low sclerotic activity and eight with increased sclerotic activity). The anatomical distribution of bone metastases was as follows: spine, 42%; skull, 2%; thorax, 16%; femur, 9%; pelvis, 26%; and humerus and clavicle, 5%. With BS, nine subjects were true positive, 17 were true negative, one was false positive, two were false negative, and six were indeterminate (three degenerative lesions and three bone metastases). The combination of BS and WBI was true positive in all 14 patients with metastatic bone disease and true negative in 20 of 21 subjects without bone metastases. The sensitivity, specificity and accuracy of BS alone was 64−85%, 81−95%, and 83%, respectively; corresponding values for BS and WBI were 100%, 95%, and 97%, respectively. The sensitivity of the combination of BS and WBI was as high as that obtained with ^{18}F-fluoride PET and MRI, which were used as the primary reference methods.

Safety Issues: No safety issues were mentioned in the study.

2.2.1.1.5 Multiple Cancer Types

Even-Sapir, E., et al. Assessment of malignant skeletal disease: Initial experience with ^{18}F-fluoride PET/CT and comparison between ^{18}F-fluoride PET and ^{18}F-fluoride PET-CT. J Nucl Med. 45(2):272–278, 2004 [12]

This prospective study was conducted to evaluate the diagnostic accuracy of ^{18}F-fluoride PET and ^{18}F-fluoride PET-CT in assessing malignant osseous involvement and in differentiating malignant from benign bone lesions in oncologic patients. The study was conducted at the Tel-Aviv Sourasky Medical Center (Tel-Aviv, Israel).

Inclusion Criteria: Consecutive patients who met the following criteria were enrolled after providing informed consent: ^{18}F-fluoride PET indicated as an alternative to ^{99m}Tc-MDP BS for performing a metastatic survey; to investigate skeletal pain for which the results from BS were normal; and to investigate bone suggestive of tumoral involvement because of abnormal laboratory findings such as elevated blood tumor markers or unclear findings on other imaging modalities. A total of 44 subjects were enrolled (20 male, 24 female, mean age 52±17 years, age range 15–81 years). Subjects had various oncologic diseases, including cancer of the breast (10), prostate (6), lung (4), colon (4), ovary (1), nasopharynx (1), and testes (1); gastrointestinal stromal tumor (2); lymphoma (4); malignant melanoma (2); multiple myeloma (4); Ewing's sarcoma (3); soft-tissue sarcoma (1); chondrosarcoma (1); metastatic giant cell tumor (1); and carcinoid (1). Two patients had double primary tumors.

Dose: 296–444 MBq (8–12 mCi) of ^{18}F-fluoride administered intravenously; scanning began 45 minutes after administration.

Schema of Trial: Visual interpretation of PET and PET-CT scans performed on the same subject, with lesion-based and patient-based analyses. The final diagnosis of lesions was based on histopathology, correlation with contemporaneous diagnostic CT or MRI, or clinical follow-up of at least six months.

Image Protocol Image acquisition and reconstruction information is presented for PET and PET with low-dose CT. CT data were used for attenuation correction.

Low-dose CT was performed first, without any specific breath-holding instructions. A PET emission scan was obtained immediately after acquisition of the CT scan without changing the patient's position. The skeleton was imaged from the skull to the femurs. If lesions at the distal regions of the limbs were suspected before the PET-CT study, a second PET-CT scan was performed to include these areas.

PET and PET-CT images were interpreted on two separate days in a consensus reading by two individuals; the order of the reports was changed before the second interpretation. Readers were unaware of clinical data and findings from other imaging modalities. Lesions showing increased ^{18}F-fluoride uptake were categorized as malignant, benign or inconclusive. On the PET images, only sites of increased uptake that could be either benign or malignant were included in the analysis; clearly benign lesions were not included. On PET-CT images, lesions were categorized as benign if increased ^{18}F-fluoride uptake correlated in location with a benign CT finding. Malignancy was suggested if increased uptake correlated in location with lytic, sclerotic, mixed lytic-sclerotic, or intramedullary changes on CT. The final diagnosis of lesions was based on histopathology, correlation with contemporaneous diagnostic CT or MRI, or clinical follow-up of at least six months. The sensitivity and specificity of ^{18}F-fluoride PET and ^{18}F-fluoride PET-CT for the differentiation of benign and malignant lesions were assessed and compared in lesion-based and patient-based analyses using the McNemar test; $p<0.05$ was considered significant.

Primary Endpoints: Lesion-based and patient-based correlation of sensitivity and specificity of PET and PET-CT compared with final diagnoses based on histopathology, contemporaneous imaging, or clinical follow-up.

Results: The results analysis included 212 sites of increased ^{18}F-fluoride uptake. There were 111 malignant lesions and 89 benign lesions based on histopathology (9), contemporaneous diagnostic CT or MRI (64), or imaging and clinical follow-up (125). The final diagnosis of the remaining 12 lesions could not be established; these represented inconclusive findings on PET-CT that were not further assessed because the patients had proven metastases elsewhere. In a lesion-based analysis, the sensitivity of PET alone in differentiating benign from malignant bone lesions was 72% when inconclusive lesions were considered false negative and 90% when inconclusive lesions were considered true positive. On PET-CT, 94 of 111 metastases (85%) presented as sites of increased uptake with corresponding lytic or sclerotic changes, and 16 of the 17 remaining metastases

showed normal-appearing bone on CT, for an overall sensitivity of 99% for tumor detection. In only one of the 111 malignant lesions were the CT findings misleading, resulting in a benign diagnosis. The specificity of PET-CT was significantly higher than that of PET alone (97% *vs*. 72%, p<0.001). In a patient-based analysis, the sensitivity of PET and PET-CT was 88% and 100%, respectively (p<0.05), and the specificity was 56% and 88%, respectively (difference not statistically significantly). In 12 patients referred for ^{18}F-fluoride assessment due to bone pain despite negative findings with ^{99m}Tc-MDP bone scintigraphy, ^{18}F-fluoride PET/CT suggested malignant bone involvement in all four patients with proven skeletal metastases, a potential benign cause in four of seven patients who had no evidence of metastatic disease, and a soft-tissue tumor mass invading a sacral foramen in one patient.

Safety Issues: No safety issues were mentioned in the study.

Hoegerle, S., et al. Combined FDG and [F-18]Fluoride whole-body PET: a feasible two-in-one approach to cancer imaging? Radiology. 209(1):253–258, 1998 [13]

This is a prospective trial conducted to determine the feasibility of conducting combined ^{18}F-FDG and ^{18}F-fluoride PET for cancer imaging, and to evaluate the utility of this approach for detecting, localizing, and staging disease. The study was conducted at the Albert Ludwigs University Center for Health Science (Freiburg, Germany).

Inclusion Criteria: Sixty consecutive patients referred for clinically indicated PET were enrolled (23 women, 37 men, mean age 51±14 years, age range 13 –76 years). Patients with known metastatic bone disease or with elevated blood glucose measured prior to radiopharmaceutical injection were excluded.

Dose: 100±10 MBq (2.7 mCi) ^{18}F-fluoride and/or 300±20 MBq ^{18}F-FDG were injected into a peripheral vein after fasting for at least 12 hours. Imaging began 90 minutes after injection.

Schema of Trial: Thirty patients were imaged only with ^{18}F-FDG (control group) and 30 patients were imaged with both ^{18}F-FDG and ^{18}F-fluoride (study group). Topographical location and classification of total, soft-tissue and skeletal lesions in study and control groups were determined by two independent readers; results between readers and between study and control groups were compared. PET findings were correlated with findings from other imaging modalities (CT, plain radiography, BS, CT); histopathology was not performed, and specificity and sensitivity were not calculated.

Image Protocol: PET image acquisition and reconstruction information is presented. Whenever the abdomen or pelvis was imaged, fluids were administered and a urinary bladder irrigation catheter was used to minimize scaling problems caused by intense activity in the kidneys or bladder.

PET images were interpreted by two experienced, blinded, independent investigators. A slight difference in topographical localization within the same organ was not considered a disagreement; however, if the readers related a specific lesion to a different tissue or organ, this was counted as a disagreement. In the control group, soft-tissue and bone lesions were classified as potentially malignant if there was focally increased radiotracer uptake that exceeded the normal limits of regional uptake in the area, if the lesion was located in a typical metastatic site, and if there was a standardized uptake value greater than 4. The same criteria for soft-tissue lesion designation were used for the study group. The diagnostic criteria for potential bone cancers in the study group were based on standard criteria for BS, and included intensity of radiotracer uptake (low, medium, high), location of the lesion in the skeleton, and the number of lesions (a high number of lesions being indicative of malignancy). Interobserver agreement was calculated with the use κ statistics and 95% confidence intervals (CI); a κ of 1 indicates perfect agreement, while a κ of 0 indicates chance agreement.

Primary Endpoints: Visual interpretation; comparison of findings between methods and agreement between observers for number, status, and topographical localization of total, soft-tissue and skeletal lesions in control and study groups.

Results: In the control group, 69 lesions were diagnosed; 54 (78%) of these were confirmed with other imaging modalities. Discrepancies between PET and morphological imaging findings were mainly evident in the detection of intestinal lesions, regional lymph node lesions, and skeletal lesions. Interobserver agreement for the localization of all lesions was 0.74 (95% CI=0.64 to 0.84). Discrepancies between observers were mainly in the localization of nine of 18 probable skeletal lesions; some discrepancies were also noted in the localization of mediastinal *vs*. central lung lesions, intestinal *vs*. peripheral liver lesions, and intestinal *vs*. retroperitoneal lymph node lesions. In the study group, 73 lesions were diagnosed (41 soft-tissue and 32 skeletal), and 64 of these (88%; 36 soft-tissue and 32 skeletal) were confirmed with morphologic imaging. The interobserver agreement for the differentiation between soft-tissue and skeletal lesions was 1.00. Interobserver agreement for the localization of all lesions was 0.95 (95% CI=0.81 to 1.00). The improvement in interobserver agreement for localization from 0.74 to 0.95 was significant (p=0.007). Twenty-one PET lesions were diagnosed as malignant. Degenerative disease was misinterpreted as metastatic disease in two cases. In another two cases, morphologic imaging techniques revealed no sign of degenerative or malignant disease. The interobserver agreement for differentiation of malignant from benign disease was 0.86 (95% CI=0.52 to 1.00); discrepancies were observed in classification of two solitary hypermetabolic spinal lesions.

Safety Issues: No safety issues were mentioned in the study.

Hoh, C.K., et al. Whole body skeletal imaging with [18F]fluoride ion and PET. J Comput Assist Tomogr. 17(1):34–41, 1993 [14]

This is a prospective trial to evaluate the sensitivity and specificity of ^{18}F-fluoride PET to detect areas of altered osteogenic activity in patients with a range of malignant and benign skeletal conditions. Results from these patients were compared with results from normal volunteers. The study was conducted at the UCLA School of Medicine.

Inclusion Criteria: A total of 38 subjects were enrolled; 19 had benign or malignant skeletal conditions (age range 24−87 years), and 19 were normal volunteers with no previous history of skeletal pathology or any other significant medical disorders (age range 19−56 years). Of the 19 subjects with skeletal conditions, 13 had histologically documented malignant bone lesions (primary and/or metastatic tumors); five had benign bone lesions (osteoporotic compression fractures (2), unicameral bone cyst, degenerative disc disease, idiopathic diaphyseal sclerosis); and one had colorectal carcinoma and no known bone lesions.

Dose: Image acquisition was started one hour after intravenous administration of 185−370 MBq (5−10 mCi) ^{18}F-fluoride.

Schema of Trial: Visual comparison of ROIs seen in patients with known skeletal lesions compared with the normal pattern of ^{18}F-fluoride uptake in whole body scans from normal volunteers.

Image Protocol: PET image acquisition and reconstruction information is presented; no attenuation correction was used. To compare the utility of projection and tomographic images, the total number of lesions visualized on projection images and their activity ratios were compared with those seen on the tomographic images. Activity ratios were obtained by drawing a ROI around a focal increase in ^{18}F activity in the bone lesions and in a contralateral region on the opposite side of the body. For midline structures, reference ROIs were drawn on normal adjacent vertebral bodies above and/or below the involved level. To evaluate the range of relative ^{18}F-fluoride uptake levels in malignant and benign bone lesions, the average projection and coronal tomographic activity ratios were determined. Procedures to minimize interpretation bias were not discussed.

Primary Endpoints: Visual interpretation, activity ratio, localization potential of projection and tomographic images.

Results: In the 19 normal volunteers, no unexpected sites of uptake of ^{18}F-fluoride were evident. In subjects with malignant or benign skeletal lesions, a total of 101 bone lesions (94 malignant and seven benign) were analyzed. Both malignant and benign skeletal lesions were correctly identified in 18 patients by two-dimensional projection imaging and tomography. One patient with colorectal carcinoma had a normal skeleton scan,

consistent with results from local bone biopsies which showed no histological evidence of bone involvement. The ratio of tracer uptake in abnormal-to-normal bone in the projection images (2.02±1.31) was significantly lower than ratios for the same lesions in the coronal images (4.93±8.19; $p<0.00025$). Of the 101 lesions, 13 (12.9%) were visually detected on the coronal images that were not evident on the projection images. Overall, the tomographic imaging technique produced improved lesion contrast and anatomical localization compared with planar imaging methods.

Safety Issues: No safety issues were mentioned in the study.

Schirrmeister, H., et al. Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus ^{18}F PET. J Nucl Med. 40(10):1623–1629, 1999 [8]

A prospective study was conducted to evaluate the accuracy of planar radionuclide bone scanning *vs*. tomographic bone imaging with ^{18}F-NaF PET for detection of osteolytic and osteoblastic bone metastases, as well as to examine dependence on anatomic localization. The study was conducted at University Hospital in Ulm, Germany between March 1996 and August 1997.

Inclusion Criteria: Forty-four patients with histologically proven, clinical Stage III or IV cancer of the prostate (20), lung (5) or thyroid (19), and known (9) or suspected (35) bone metastases were enrolled. Pregnant patients, and patients with previously known disseminated metastatic bone disease (five or more metastases), medullary or anaplastic thyroid cancer, or an unknown clinical stage of cancer were excluded.

Dose: 370 mBq (10 mCi) ^{18}F-NaF administered by intravenous injection; data acquisition began one hour after administration. 740 mBq of ^{99m}Tc-MDP was administered by intravenous injection; data acquisition began three hours following administration.

Schema of Trial: All patients were examined with ^{18}F-fluoride PET and ^{99m}Tc-MDP BS. MRI, spiral CT, WBI, ^{18}F-FDG PET, radiography, or clinical follow-up of at least one year were used as reference methods for confirmation of lesions diagnosed by ^{18}F-fluoride PET.

Image Protocol: PET image acquisition and reconstruction information is presented. Experienced nuclear medicine physicians independently interpreted BS and ^{18}F-fluoride PET results; all reviewers were unaware of the results of the reference methods. Two diagnostic radiologists reviewed each MRI, spiral CT scan, WBI scintigram and radiograph. The reviewers of MRI or spiral CT scans were provided with the additional reference methods but were unaware of the results of ^{18}F-fluoride PET or BS. Discrepant interpretations of the readers were resolved by consensus. Results from ^{18}F-fluoride PET and ^{99m}Tc-MDP BS were compared in a lesion-by-lesion analysis. In 42 patients, every lesion was judged on a five-point scale (1=definitely metastatic, 5=definitely not

metastatic); a modified five-point scale was used for two subjects with disseminated metastatic bone disease. Lesions on ^{18}F-fluoride PET that were not visible on ^{99m}Tc-MDP BS were defined as benign on ^{99m}Tc-MDP BS. ROC curve analysis was performed, and the area under the curve was used to test for statistically significant differences between the two imaging modalities.

Primary Endpoints: Comparison of sensitivity and specificity of ^{18}F-fluoride PET and ^{99m}Tc-MDP BS by visual interpretation (lesion-by-lesion analysis) and differentiation of benign and malignant lesions (ROC curve fitting).

Results: Fifteen of the 44 patients were determined to have bone metastases by the reference methods. All 15 were identified by ^{18}F-fluoride PET and 13 were identified by BS ^{18}F-fluoride PET detected two-fold more lesions, both benign and malignant, than planar ^{99m}Tc-MDP scan. ^{18}F-fluoride PET was equally sensitive in detecting osteoblastic metastases and osteolytic metastases with a 100% detection rate, whereas planar ^{99m}Tc-MDP scan detected 49.3% of osteoblastic and 44.8% of osteolytic lesions. The detection sensitivity of planar ^{99m}Tc-MDP scan depended highly on anatomic location of the lesion: in the thorax, skull and extremities, the detection rate was 80–90%, but only 40–42% of the lesions were detected in the spine and pelvis. In contrast, ^{18}F-fluoride PET detected all lesions regardless of their anatomic location. It was also more accurate than ^{99m}Tc-MDP in differentiating benign from malignant lesions. In patient-based analysis, two patients with undetectable bone metastases on ^{99m}Tc-MDP scan were later proven false negative, and the extent of bone metastases was underestimated in eight patients (53%). In contrast, no patient was false negative with ^{18}F-fluoride PET, and the extent of bone metastases was accurately assessed by ^{18}F-fluoride PET in all 15 patients. The area under the ROC curve was 0.99 for ^{18}F-fluoride PET and 0.64 for ^{99m}Tc-MDP BS.

Safety Issues: No safety issues were mentioned in the study.

2.2.1.2 Other Studies of Bone Metastases

The following is a review of published case studies, plus one publication for a study that was not considered well-controlled (details on how results were obtained were not included).

Bhargava, P. et al. Whole-body F-18 sodium fluoride PET-CT in a patient with renal cell carcinoma. Clin Nucl Med. 33(12):894–895, 2008 [15]

A published case report describes the use of ^{18}F-fluoride PET-CT to locate a lytic lesion in the right calcaneus of a 59-year-old male patient with metastatic renal cancer.

Inclusion Criteria: Not applicable.

Dose: 363 MBq (9.8 mCi) ^{18}F-NaF

Schema of Trial: Not applicable.

Image Protocol: Detailed PET image acquisition and reconstruction information is not presented. A low dose non-contrast enhanced CT scan was acquired for attenuation correction and anatomic localization.

Primary Endpoints: Not applicable.

Results: A 59-year-old male patient with metastatic renal cell cancer presented with pain in the right heel. Radiographs showed a large lytic lesion in the right calcaneus, suspicious for bone metastasis. A whole-body ^{18}F-fluoride PET-CT was acquired. All lytic lesions seen on the CT showed intense peripheral fluoride uptake; in addition, five lesions were seen by ^{18}F-fluoride PET-CT that were not seen on CT. Eight foci of mild to moderate activity on the fluoride scan were correctly identified as degenerative joint disease on the CT scan. Intense peripheral fluoride uptake was seen in the right calcaneus, which was later proven by needle biopsy to be metastasis from renal cell cancer. ^{18}F-fluoride PET identified more metastatic lesions than CT.

Safety Issues: No safety issues were mentioned in the study.

Langsteger, W. The role of fluorodeoxyglucose, 18F-dihydroxyalanine, 18F-choline, and 18F-fluoride in bone imaging with emphasis on prostate and breast. Semin Nucl Med. 36:72–96, 2006 [1]

This publication reviews the role of diagnostic imaging in the evaluation of patients with bone metastases. In addition, some previously unpublished results are presented; however, no details on how the results were obtained are included.

Inclusion Criteria: Not applicable. The author describes ^{18}F-fluoride PET-CT experience from evaluations performed in Linz, Austria within the prior two years on more than 100 patients with different malignant tumors or disease. Twenty cancer patients were imaged using both ^{18}F-fluoride and ^{18}F-FDG PET-CT. The types of cancers in these 20 subjects were: breast (6), medullary thyroid (2), prostate (2), unknown primary (2), anorectal (2), ovarian (2), lung (1), follicular thyroid (1), renal cell (1), and urinary bladder (1).

Dose: Not specified.

Schema of Trial: Not applicable.

Image Protocol: Not provided

Primary Endpoints: Not specified; presumably, diagnostic ^{18}F-fluoride PET-CT was for identification and localization of sites of metastases.

Results: In the 20 patients who underwent both ^{18}F-fluoride and ^{18}F-FDG PET-CT, 150 lesions were detected. These represented lesions detected by both modalities (72), lesions detected only by ^{18}F-fluoride PET-CT (34), and lesions that were detected only by ^{18}F-FDG PET-CT (44). Lesions that were detected by ^{18}F-FDG PET-CT but not ^{18}F-fluoride were mostly small osteolytic metastases or located in bone marrow; lesions that were detected by ^{18}F-fluoride PET-CT but not by ^{18}F-FDG PET-CT were mostly tumors known to have less FDG avidity (medullary thyroid carcinoma, renal call carcinoma, or thyroid cancer). No other information on imaging techniques or results was presented.

Safety Issues: No safety issues were mentioned in the study.

Tse, N. et al. Positron emission tomography diagnosis of pulmonary metastases in osteogenic sarcoma. J Am J Clin Oncol. 17(1):22–25, 1994 [16]

This is a case report of a patient with polyostotic fibrous dysplasia, metastatic osteogenic sarcoma and a breast mass, who presented with pulmonary nodules. CT of the chest revealed multiple contrast-enhancing masses in both the lungs and mediastinum. ^{18}F-fluoride PET imaging was used to confirm the nature of the pulmonary nodules.

Inclusion Criteria: Not applicable.

Dose: Not specified.

Schema of Trial: Visual interpretation of ^{18}F-fluoride PET. No reference methods were used to confirm the PET findings.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was not performed.

Primary Endpoints: Not applicable.

Results: A PET scan revealed multiple areas of abnormal localized ^{18}F-fluoride uptake in the lungs. The PET finding was interpreted as diagnostic of metastatic disease from an osteogenic source. The diagnosis could not be confirmed because the patient died six months later and autopsy permission was not granted by the patient's family.

Safety Issues: No safety issues were mentioned in the report.

Wade, A.A., et al. Flare response in ^{18}F-fluoride ion PET bone scanning. Am J Roentgenol. 186(6):1783–1786, 2006 [17]

This is a case report on a 27-year-old woman initially diagnosed with infiltrating ductal carcinoma of the right breast. At surgery, axillary lymph node involvement was confirmed. ^{18}F-FDG PET-CT revealed multiple foci of elevated FDG uptake corresponding with mediastinal and hilar adenopathy. A focus of elevated fluoride ion and FDG uptake in the T7 vertebral body was confirmed by MRI. An evaluation was performed to compare the appearance of osseous flare in the thoracic spine by ^{18}F-FDG PET-CT, ^{18}F-fluoride PET, ^{99m}Tc-MDP BS, and gadolinium-enhanced MRI.

Inclusion Criteria: Not applicable.

Dose: Not specified.

Schema of Trial: Visual interpretation of ^{18}F-fluoride PET. A panel of reference methods was used, including ^{18}F-FDG PET-CT, MRI, and ^{99m}Tc-MDP bone scanning.

Image Protocol: Not specified.

Primary Endpoints: Not applicable.

Results: ^{18}F-fluoride PET showed increased uptake in T7, which was photopenic on ^{18}F-FDG PET and sclerotic on CT. MRI of the spine confirmed a decrease in enhancement at this location. There was also a subtle interval increase in uptake at T7 on the ^{99m}Tc-MDP bone scans.

Safety Issues: No safety issues were mentioned in the report.

2.2.2 Well-controlled Studies of Benign Bone Disease

Gamie S. and El-Maghraby T. The role of PET/CT in evaluation of facet and disc abnormalities in patients with low back pain using ^{18}F-Fluoride. Nucl Med Rev Cent East Eur. 11(1):17–21, 2008 [18]

This study evaluated the use of ^{18}F-fluoride PET-CT in patients with back pain and suspected facetogenic pain when a clear cause could not be identified by x-ray, CT and/or MRI. The study took place at the Palo Alto Veteran Affairs Hospital/Stanford University Medical Center (Palo Alto, CA).

Inclusion Criteria: Patients with back pain with no clear cause detected by x-ray, CT and/or MRI. A total of 67 patients participated (63 males, 4 females, age range 40−85 years, mean age 60 years); 25 of these had previous lumbar spine surgery consisting of laminectomy or discectomy (17) and lumbar fusion (8).

Dose: 444−555 MBq (12−15 mCi) ^{18}F-fluoride administered intravenously.

Schema of Trial: Patients were initially seen in the neurosurgery clinic at the Palo Alto Veteran Affairs Hospital/Stanford University Medical Center for x-rays, CT and/or MRI. When these methods failed to identify obvious causes of back pain, such as herniated discs, spondylolistheses or lumbar stenosis, the patients were referred to the Nuclear Medicine Lab for ^{18}F-fluoride PET-CT.

Image Protocol: PET image acquisition and reconstruction information was presented; low resolution, non-contrast CT was used for anatomic localization and attenuation correction. Parameters used for initial x-ray, CT and/or MRI were not provided. Image interpretation was carried out after reviewing all images in the transaxial, coronal and sagittal planes. Methods for minimizing interpretation bias were not presented.

Primary Endpoints: Visual interpretation to identify abnormal foci of uptake.

Results: ^{18}F-fluoride PET-CT showed abnormal foci of uptake in the spine in 56 of 67 patients (84%). Abnormal tracer uptake in facet joints was seen in 25 patients, while abnormal uptake in discs lesions was seen in 11 patients; 20 additional subjects showed abnormal uptake in both facet joints and discs. ^{18}F-fluoride PET-CT showed positive areas of uptake in 100% of patients with a history of lumbar fusion, in 65% of subjects with a history of laminectomy, and in 88% of subjects with no history of lumbar surgery. Overall, focal abnormalities in discs or facets were seen in 84% of patients that had negative diagnoses after standard x-ray, CT and/or MRI procedures.

Safety Issues: No safety issues were mentioned in the study.

Laverick S, et al. [^{18}F]-fluoride positron emission tomography for imaging condylar hyperplasia.Br J Oral Maxillofac Surg Oct 14. [Epub ahead of print], 2008 [19]

This is a prospective trial to investigate the ability of ^{18}F-fluoride PET to identify condylar hyperplasia.

Inclusion Criteria: This study enrolled five patients with suspected condylar hyperplasia (three women, two men, age range 19−33 years, mean age 23 years).

Dose: PET scanning of the entire mandible and skull base was performed one hour after intravenous administration of 150 MBq (4 mCi) of ^{18}F-fluoride.

Schema of Trial: ^{18}F-fluoride PET was used to establish the presence of continued active hyperplastic growth in the affected condyle. Diagnoses were confirmed by histological findings.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was not performed.

The scans were reviewed by one observer who was experienced in PET, independently of the clinical findings, and he was unaware of the final outcome. Condylar hyperplasia was characterized by visible focal asymmetric uptake of ^{18}F-fluoride in the region of the mandibular condyle. ^{18}F-fluoride PET diagnosis was correlated with the histological findings.

Primary Endpoints: Correlation between ^{18}F-fluoride PET diagnosis and histological findings.

Results: All five patients had asymmetrical uptake of ^{18}F-fluoride within the mandible with focal increased uptake seen within the condyle, which correlated to the site of suspected disease identified by clinical examination and plain radiographs. The mandibular condyle that showed increased ^{18}F-fluoride uptake correlated with the histological diagnosis of condylar hyperplasia in all patients.

Safety Issues: The radiation burden to the patient using ^{18}F-fluoride is comparable to that of ^{99m}Tc-MDP bone scanning, and is less than that of SPECT.

Sterner, T., et al. The role of [^{18}F]fluoride positron emission tomography in the early detection of aseptic loosening of total knee arthroplasty. Int J Surg. 5(2):99–104, 2007 [20]

This is a prospective trial to evaluate the value of ^{18}F-fluoride PET in the early diagnosis of aseptic loosening after total knee arthroplasty (TKA).

Inclusion Criteria: This trial enrolled 14 patients (mean age 70.5 years, age range 63.8−81.8 years) with painful TKA and suspected aseptic loosening diagnosed by intraoperative findings (6) or by long-term clinical evaluation (8).

Dose: PET scanning was performed one minute after intravenous administration of 350 MBq (9.4 mCi) of ^{18}F-fluoride and again at 60 minutes.

Schema of Trial: Comparison of visual interpretation of ^{18}F-fluoride PET and conventional x-rays. Intraoperative findings or long-term clinical evaluation (≥6 months) were used as reference methods to confirm the diagnosis.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was performed, but results are presented without correction. Parameters used for conventional x-rays were stated.

The scans were visually classified by two independent experienced nuclear medicine physicians who were blinded to the clinical, biochemical and radiological findings. The evaluation criteria were based on the pattern and location of the ^{18}F-fluoride uptake at

the prosthesis/bone interface or cement/bone interface in the case of cemented knee prosthesis. Established TKA criteria were followed for diagnosis of aseptic loosening.

Results: For ^{18}F-fluoride PET, the sensitivity, specificity and accuracy were 100%, 56% and 71%, respectively. No false-negative results were detected; in 4 patients one component (tibial or femoral) was diagnosed as false positive. The sensitivity, specificity and accuracy for the plain radiograph of the same patients were 43%, 86% and 64%, respectively. ^{18}F-fluoride PET scans showed excellent spatial resolution and allowed detection of aseptic loosening with differentiation from simple synovitis.

Safety Issues: No safety issues were mentioned in the study.

2.2.3 Well-controlled Studies of Bone Metabolism and Repair

Several published articles used ^{18}F-PET to assess and monitor changes in bone metabolism associated with disease or repair. While in many cases these were feasibility evaluations, the studies were reasonably well-controlled in that the subject population was controlled, study endpoints were defined, and results were clearly presented.

Berding, G. et al. Evaluation of the incorporation of bone grafts used in maxillofacial surgery with [^{18}F]fluoride ion and dynamic positron emission tomography. Eur J Nucl Med. 22(10):1133–1140, 1995 [21]

This is a prospective trial using dynamic ^{18}F-fluoride PET to evaluate the incorporation of bone grafts used in maxillofacial surgery.

Inclusion Criteria: This trial enrolled nine subjects (four female and five male, age range 21−68 years) who had received pedicle grafts for mandibular reconstruction or onlay grafts for alveolar ridge augmentation.

Dose: Dynamic PET imaging was started immediately after administration of 370 MBq (10 mCi) of ^{18}F-fluoride and continued for 60 minutes

Schema of Trial: Estimation of blood flow and osteoblastic activity using dynamic ^{18}F-fluoride PET combined with a three-compartment model and multilinear least squares fitting.

Image Protocol: Dynamic PET image acquisition and reconstruction information is presented; attenuation correction was performed. Blood sampling occurred during PET image acquisition.

Data processing was described. Cervical vertebral bodies were used as the reference region. For tracer kinetics, a three-compartment model was assumed, consisting of fluoride ion: in vascular space; in extravascular space of bone; and bound to bone. Rate

constants of fluoride transport between compartments were determined by multilinear least squares fitting.

Primary Endpoints: Blood flow and osteoblastic activity in onlay grafts and regions of osteosyntheses as an indication of graft incorporation.

Results: Assuming a three-compartment model and applying multilinear least squares fitting, bone blood flow (K_1) and fluoride influx (K_{MLF}) were determined. Additionally Patlak plot analysis was used to calculate fluoride influx (K_{PAT}). In cervical vertebral bodies as the reference region, mean values for flow of K_1=0.1162±0.0396 ml/min/ml and influx of K_{MLF}=0.0508±0.0193 and K_{PAT}=0.0385±0.0102 ml/min/ml were found. These figures are stated to be comparable with physiological values in animal and man reported in the literature. Early after surgery, a significant increase in flow and influx compared to vertebral bodies was observed in the regions of osteosyntheses between grafts used for reconstruction and recipient bone (K_1=0.2181, K_{MLF}=0.1000 and K_{PAT}=0.0666 ml/min/ml) and in onlay grafts (K_1=0.2842, K_{MLF}=0.1637 and K_{PAT}=0.0827 ml/min/ml). At the same time, pedicle grafts showed a significant increase in flow but not in influx (K_1=0.2042, K_{MLF}=0.0774 and K_{PAT}=0.0529 ml/min/ml). Furthermore, K_{PAT} was significantly lower in pedicle grafts than in onlay grafts. In follow-up studies, a significant decrease in flow occurred in pedicle grafts and the regions of osteosyntheses. Moreover the latter showed a significant decrease in K_{MLF} as well. ^{18}F-fluoride PET depicted increased blood flow and osteoblastic activity in onlay grafts and regions of osteosyntheses, indicating bone repair in the graft and adjacent host bone early after surgery. For the regions of osteosyntheses, the decrease in both parameters corresponded to uncomplicated healing. The lack of increased influx in pedicle grafts, although flow was increased, most likely indicates that some necrosis occurred in these grafts despite patency of anastomoses. ^{18}F-fluoride PET was useful in providing further insight into the biology of graft incorporation.

Safety Issues: No safety issues were mentioned in the study.

Brenner, W., et al. Assessment of the metabolic activity of bone grafts with 18F-fluoride PET. Eur J Nucl Med Mol Imag. 31(1):1291–1298, 2004 [22]

This prospective study was conducted to evaluate the use of dynamic ^{18}F-fluoride PET to assess the time course and characteristic pattern of normal and impaired healing during the first two years after full and cancellous bone graft surgery. The study was conducted at the University of Washington Medical Center (Seattle, WA). Due to the lack of an established standard of truth in this setting, no reference method was used. This study appears to use some or all of the same subjects evaluated in the publication below by the same author [23].

Inclusion Criteria: Thirty-four consecutive patients presenting for regular follow-up examinations after bone graft surgery, with no evidence of residual tumor tissue or local

relapse at the time of initial scanning and serum creatinine levels within normal limits, were selected for imaging. No other criteria contributing to selection were presented. Participating patients had a wide range of benign (19) or malignant (15) tumors of limb bones leading to cancellous chips (23) or full bone grafts (11) located in the humerus (13), femur (12), tibia (6), fibula (1) or bones of the foot (2). Subjects ranged in age from 18 to 66 years.

Dose: 3.7 MBq (0.1 mCi) ^{18}F-fluoride ion/kg body weight dissolved in 10 mL of 0.9% saline solution and infused over two minutes with a syringe pump; dynamic PET imaging began simultaneously with intravenous administration and continued for 60 minutes.

Schema of Trial: Imaging was performed between two and 51 months after surgery; seven patients were imaged three times, and four patients were imaged twice during that time frame, resulting in a total of 52 ^{18}F-fluoride PET scans.

Image Protocol: PET image acquisition and reconstruction information is presented; all images underwent corrections for random and scattered coincidence events, and each image was corrected for attenuation and physical decay of ^{18}F-fluoride.

Primary Endpoints: Comparison of tissue time-activity curves (TAC) in graft and normal contralateral bone processed using both non-linear regression and Patlak graphical analysis, SUV analysis.

Results: Significantly elevated values in bone grafts *vs*. normal bone were observed for SUV, fluoride bone influx rate, fractional blood volume, and for all studied rate constants except for the rate of release of fluoride from the bone mineral compartment. In patients imaged more than once, there was no major shift in normal bone activity over time. In contrast, ^{18}F-fluoride uptake in cancellous bone grafts decreased by approximately 25% between six and 12 months after surgery, and there was a total decrease of 60–65% for SUV and fluoride bone influx rate after two years. In full bone grafts, there was an increase in bone metabolism by approximately 20% between month six and 12 after surgery, and then bone metabolism decreased to 70% of the initial activity at the end of two years. In cancellous bone grafts, there was a significant decrease in the graft-to-normal ratio of bone activity from month six to month 12; in full bone grafts, there was an increase in the graft-to-normal ratio of bone activity from month six to month 12 after surgery. Non-union of the grafts was diagnosed in two patients with full bone grafts at 13 and 19 months after surgery; both patients showed inconsistent patterns in graft-to-normal ratios of bone activity by ^{18}F-fluoride PET compared to those associated with normal bone healing.

Safety Issues: No safety issues were mentioned in the study.

Cook, G.J.R., et al. Quantification of skeletal kinetic indices in Paget's disease using dynamic ^{18}F-fluoride positron emission tomography. J Bone Miner Res. 17:854–859, 2002 [24]

This is a prospective study designed to quantify regional bone metabolism in Paget's disease and to compare these indices with normal bone using dynamic ^{18}F-fluoride PET. The study was conducted at Royal Marsden Hospital (Surrey, UK), and Guy's and St. Thomas' Hospitals (London, UK).

Inclusion Criteria: Subjects with Paget's disease confirmed by radiographic and scintigraphic signs, and known to have vertebral involvement. A total of seven subjects were enrolled (four female, three male, mean age 70.7 years). All subjects had polyostotic disease with a mean of 6.6 bones affected (range 2−14) and evidence of current abnormal activity.

Dose: 180 MBq (4.9 mCi) ^{18}F-fluoride injected intravenously and flushed with 10 ml saline; dynamic PET images were collected over 60 minutes beginning at the time of ^{18}F-fluoride administration.

Schema of Trial: ^{18}F-fluoride PET scans and arterial plasma ^{18}F-fluoride activity were determined for each subject; scans included a diseased vertebra and an adjacent, normal vertebra. Data were fitted to a three-compartment model (plasma, extravascular bone compartment, and bone mineral compartment). Time-activity curves were produced for individual vertebrae. Individual kinetic parameters were estimated from bone and arterial plasma curves using standard non-linear regression/least-squares iterative analysis. Statistical differences were sought using Wilcoxon signed rank sum test, and the Spearman rank correlation test for correlations between plasma clearance to bone (K_{bone}) and mean serum bone specific alkaline phosphatase (BSALP).

Image Protocol: PET image acquisition and reconstruction information, and parameters used to define ROIs, is presented; attenuation correction was performed.

Primary Endpoints: Influx and flow of ^{18}F-fluoride in pagetic *vs.* adjacent normal bone.

Results: A correlation was found between BSALP and K_{bone} ($r=0.96$; $p<0.001$), supporting the use of K_{bone} as a marker of regional bone formation. Compared with normal bone, pagetic bone demonstrated higher values of plasma clearance to bone mineral ($p=0.018$) and clearance to total bone tissue ($p=0.018$), reflecting increased mineralization and blood flow, respectively. Release of ^{18}F-fluoride from bone mineral was lower in pagetic bone ($p=0.022$), suggesting tighter binding of ^{18}F-fluoride to bone mineral. The notional volume of the extravascular bone compartment was greater ($p=0.018$), and the unidirectional extraction efficiency from the extravascular space to bone mineral was greater ($p=0.018$) in pagetic bone. A lower rate of transfer from the bone extravascular compartment to plasma in pagetic bone suggests that the ^{18}F-

fluoride that enters pagetic bone may be less accessible for return to plasma. Results are consistent with the known pathophysiology of Paget's disease.

Safety Issues: No safety issues were mentioned in the study.

Forrest, N., et al. Femoral head viability after Birmingham resurfacing hip arthroplasty: assessment with use of [^{18}F] fluoride positron emission tomography. J Bone Joint Surg Am. 88 Suppl 3:84–89, 2006 [25]

This prospective trial used ^{18}F-fluoride PET to examine femoral head viability following hip resurfacing through a modified anterolateral approach. The study was conducted at University of Aberdeen, Scotland.

Inclusion Criteria: Patients with diagnoses of primary and secondary osteoarthritis. The study enrolled 10 patients, including six women (age range 3–55 years, mean age 44 years) and four men (age range 50–57 years, mean age 54 years). For all patients, Birmingham resurfacing was performed by one surgeon using a specific routine anterolateral approach. All patients were functioning well clinically with no evidence of loosening on radiographic evaluation at the time of the study.

Dose: PET scanning was performed 40 minutes after intravenous administration of 250 MBq (6.8 mCi) ^{18}F-fluoride.

Schema of Trial: The viability of the femoral heads of 10 patients who had undergone successful unilateral Birmingham hip resurfacing was assessed by ^{18}F fluoride PET at a mean of 20 months after surgery. Activity was measured in four regions of interest in both the hip that had undergone resurfacing and the contralateral, nonresurfaced hip: the lateral aspect of the femoral head; the medial aspect of the femoral head; the lateral aspect of the femoral neck; and the proximal aspect of the femur. SUVs were determined for each area.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was performed; selection of ROIs was described.

All images were examined visually for photopenic areas that would represent areas of necrosis, and uptake values were calculated for each ROI. An initial analysis was carried out using uptake values from the normal hip for comparison, with differences in uptake examined statistically. The uptakes were then expressed as ratios. SUVs were also calculated from the static images for each of the regions of interest. Data sets for the nonresurfaced and resurfaced regions were examined with use of a Kruskal-Wallis test. Paired data at each region were then examined, comparing resurfaced and nonresurfaced SUVs, with use of a Mann-Whitney U test. A p value of <0.05 was considered significant.

Primary Endpoints: The usefulness of ^{18}F fluoride PET in evaluating femoral head viability after hip resurfacing.

Results: No areas of osteonecrosis were seen in the femoral head of any patient. There were no significant differences in the SUVs as measured in the four regions of the nonresurfaced hips, whereas the median values were higher in all four regions of the resurfaced hips. The difference between the values in the resurfaced hips compared with those in the nonresurfaced hips was only significant ($p<0.05$) in the lateral aspect of the femoral head.

Safety Issues: No safety issues were mentioned in the study.

Frost, M.L. et al. A prospective study of risedronate on regional bone metabolism and blood flow at the lumbar spine measured by ^{18}F-fluoride positron emission tomography. J Bone Miner Res. 18(12):2215–2222, 2003 [26]

This is a prospective study to compare skeletal kinetics in the lumbar vertebrae in postmenopausal osteoporotic women measured by ^{18}F-fluoride PET before and after six months of bisphosphonate therapy. The study was conducted at the Guy's, King's and St. Thomas School of Medicine (London, UK).

Inclusion Criteria: This trial enrolled 18 postmenopausal women (mean age of 67 years, age range 59–75 years) with a bone mineral density (BMD) T-score of less than 2 at the spine or hip and were therefore diagnosed as having osteoporosis or significant osteopenia according to the World Health Organization (WHO) criteria for diagnosing osteoporosis.

Dose: 90 MBq (2.43 mCi) of ^{18}F-fluoride injected intravenously and simultaneously with the initiation of a dynamic 60 minute PET scan. Patients were scanned at baseline and 6 months after commencing risedronate therapy.

Schema of Trial: The arterial plasma input function was derived using aorta arterial activity from the PET image. Time-activity curves were measured by placing ROI over the lumbar vertebrae. A three-compartmental model was used to calculate bone blood flow (K_1) and the net plasma clearance of tracer to bone mineral (K_{bone}). Rate constants k_2, k_3, and k_4, which describe transport between plasma, the extracellular fluid (ECF) compartment, and the bone mineral compartment, respectively, were also measured.

The use of dynamic ^{18}F-fluoride PET scanning to obtain regional rate constants reflecting bone blood flow and metabolism was previously validated by other studies. In this study, no reference methods were used for comparison of results. In addition, as this was the first study to examine changes in fluoride kinetics at the lumbar vertebrae after antiresorptive therapy, these results could not be directly compared with others.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was performed; and selection of ROI was described.

The plasma arterial IF was derived by measuring ^{18}F-fluoride counts over the aorta. Power calculations were performed before setting up the study using data from previous PET studies of skeletal fluoride clearance. Nonlinear regression analysis of the tissue and plasma time-activity curves was used to estimate the rate constants described above. Values for each parameter were derived for each vertebra and averaged to give regional kinetic parameters for each subject. Tests for normality were performed, and statistical tests for parametric and nonparametric were used accordingly. Differences in BMD, biochemical markers of bone turnover, and kinetic parameters before and after risedronate therapy were compared using a paired Student t-test or Wilcoxon signed rank sum test. Correlations between changes in the kinetic parameters and changes in BMD and biochemical markers were assessed using the Spearman rank correlation test. Statistical significance was set at $p<0.05$.

Primary Endpoints: Osteoblastic activity at the lumbar spine after risedronate therapy, as measured by dynamic PET and estimated by a three-compartmental kinetic model.

Results: Mean vertebral K_{bone} decreased significantly by 18.4% from baseline (3.32 ± 10^{-2} ml/min/ml) to six months post-treatment (2.71 ± 10^{-2} ml/min/ml; p=0.04). This decrease was similar in magnitude to the decrease observed for BSALP, a marker of bone formation. There was no significant difference in K_1 from baseline (1.49 ± 10^{-1} ml/min/ml) to six months after treatment (1.38 ± 10^{-1}ml/min/ml; p>0.05). There was a significant increase in k_2, reflecting the reverse transport of fluoride from the extravascular tissue compartment to plasma, after six months of treatment (2.90 ± 10^{-1}/min versus 4.43 ± 10^{-1}/min; p=0.01). No significant changes were seen for k_3 or k_4. There was a significant decrease of 18.1% (p=0.02) from baseline in the fraction of tracer in the extravascular tissue space that underwent specific binding to the bone matrix ($k_3/[k_2 + k_3]$). No significant correlations between changes in BMD and biochemical markers of bone turnover were observed. Neither changes in BMD nor changes in biochemical markers correlated with changes in the ^{18}F-fluoride kinetic parameters. In summary, K_{bone}, the net plasma clearance to bone mineral reflecting regional osteoblastic activity, displayed a significant decrease after six months of antiresorptive therapy.

Safety Issues: No safety issues were mentioned in the study.

Frost M.L. et al. Dissociation between global markers of bone formation and direct measurement of spinal bone formation in osteoporosis. J Bone Miner Res. 19(11):1797–1804, 2004 [27]

This is a prospective study to compare regional skeletal kinetics using ^{18}F-fluoride PET in postmenopausal women classified as normal, osteopenic, or osteoporotic according to their BMD T score at the lumbar spine.

Inclusion Criteria: This trial enrolled 72 postmenopausal women (mean age 61 years) in one of three groups according to their BMD T score at the lumbar spine using the WHO criteria for diagnosing osteoporosis: women with a T score ≥ -1 (normal); women with a T score between -1 and -2.5 (osteopenic); and women with a T score ≤ -2.5 (osteoporotic). None of the subjects had diseases or took medications that affected bone metabolism.

Dose: 90 MBq (2.43 mCi) of ^{18}F-fluoride injected intravenously and simultaneously with the initiation of a dynamic PET scan.

Schema of Trial: The arterial plasma input function was derived using aorta arterial activity from the PET image. Time-activity curves were measured by placing ROI over the lumbar vertebrae. A three-compartmental model was used to calculate bone blood flow (K_1) and the net plasma clearance of tracer to bone mineral (K_{bone}). Rate constants k_2, k_3, and k_4, which describe transport between plasma, the ECF compartment, and the bone mineral compartment, respectively, were also measured.

The use of dynamic ^{18}F-fluoride PET scanning to obtain regional rate constants reflecting bone blood flow and metabolism was previously validated by other studies. In this study, no reference methods were used for comparison of results.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was performed; and selection of ROI was described.

The plasma arterial IF was derived by measuring ^{18}F-fluoride counts over the aorta. Nonlinear regression analysis of the tissue and plasma time-activity curves were used to estimate the rate constants described above. Values for each parameter were derived for each vertebra and averaged to give regional kinetic parameters for each subject. Tests for normality were performed, and statistical tests for parametric and nonparametric used accordingly. Differences in BMD, biochemical markers of bone turnover, and kinetic parameters between groups were compared using a paired Student's t-test or Wilcoxon signed-rank sum test. Analysis of covariance was used to compare differences in the parameters with age as the covariate. Data for the three groups were pooled and correlations between the PET kinetic parameters, and BMD and biochemical markers were assessed using Spearman rank correlation test; $p<0.05$ was considered statistically significant.

Primary Endpoints: Osteoblastic activity at the lumbar spine as measured by dynamic PET and estimated by a three-compartmental kinetic model.

Results: The net uptake of fluoride to the bone mineral compartment was significantly lower in the osteoporotic group compared with both the osteopenic and normal groups, with a mean difference of 0.005 ml/min/ml (16.7%). The fraction of tracer in the

extravascular tissue space that underwent specific binding to bone mineral ($k_3/k_2 + k_3$) was also significantly reduced in the women classified as osteoporotic. In contrast, levels of BSALP were significantly higher in the osteoporotic group compared with the normal and osteopenic groups by 35% and 27%, respectively. A significant negative correlation (r=0.41) was observed between levels of BSALP and the fraction of the tracer that underwent specific binding to bone mineral. In short, lower values of K_{bone}, a measurement of regional bone formation activity, were seen in women classified as osteoporotic, whereas levels of BSALP, a measure of global bone formation, were significantly increased.

Safety Issues: No safety issues were mentioned in the study.

Installe, J., et al. ^{18}F-fluoride PET for monitoring therapeutic response in Paget's disease of bone. J Nucl Med. 46(10):1650–1658, 2005 [28]

This prospective study was conducted to evaluate PET with ^{18}F-fluoride for monitoring the response to bisphosphonates in Paget's disease of bones.

Inclusion Criteria: This trial enrolled 14 patients with Paget's disease of bones (five women, nine men, age range 41–84 years, mean age 66.5 years). Patients presented with either a monostotic form (9) or a polyostotic form (5) of Paget's disease, as demonstrated by BS and radiographic studies.

Dose: A mean dose of 397±40.7 MBq (10.75±1.1 mCi) of ^{18}F-NaF diluted in 5 ml of saline solution was injected over 30 seconds with an infusion pump. Dynamic acquisition was started midinjection.

Schema of Trial: Patients were scanned at baseline and at one and six months after the beginning of treatment with bisphosphonates. Dynamic acquisition and arterial blood sampling were used to calculate the influx constant by both the Patlak (K_{PAT}) and the nonlinear regression (K_{NLR}) methods. Kinetic modeling using a three-compartment model was compared with SUV_{max} and biochemical markers of bone remodeling.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was performed; selection of ROIs was described.

Primary Endpoints: The feasibility and accuracy of ^{18}F-fluoride PET to monitor the response to bisphosphonates; feasibility of using SUV to supersede kinetic modeling in this indication.

Results: Baseline uptake of ^{18}F-fluoride by pagetic bones was significantly higher than in normal bones ($p<0.05$). One month after the start of treatment, SUV_{max}, K_{PAT}, K_{NLR}, and K_1 (the unidirectional clearance of fluoride from plasma to the whole of the bone tissue) decreased significantly by 27.8%, 27.9%, 27.5%, and 23.6%, respectively. Biochemical

markers were already normalized in six of nine patients with monostotic disease, although all had high ^{18}F-fluoride SUVs. Six months after the start of treatment, ^{18}F-fluoride uptake further diminished by 22.3–25.6%. Biochemical markers were normal in all but two patients, although 10 of 14 patients still showed high ^{18}F-fluoride uptake. One patient did not respond to treatment and maintained high uptake of ^{18}F-fluoride throughout the study. SUV_{max} correlated with both K_{PAT} and K_{NLR} at baseline, one month, and six months ($p<0.05$). Moreover, the change in SUV_{max} between baseline and one month, as well as between baseline and sic months, correlated with the change of K_{PAT} and K_{NLR} ($p<0.05$). Results show that ^{18}F-fluoride PET can be used to monitor the efficacy of treatment with bisphosphonates in Paget's disease. SUV_{max} correlates with K_{PAT} and K_{NLR}; the use of SUV_{max} could avoid the need for dynamic acquisition and arterial blood sampling and would facilitate the use of whole-body PET in a clinical setting.

Safety Issues: No safety issues were mentioned in the study.

Messa, C., et al. Bone metabolic activity measured with positron emission tomography and [^{18}F]fluoride ion in renal osteodystrophy: correlation with bone histomorphometry. J Clin Endocrinol Metab. 77(4):949–955, 1993 [29]

This is a prospective study to evaluate the bone activity in patients with renal osteodystrophy using dynamic ^{18}F-fluoride PET.

Inclusion Criteria: The study enrolled 11 patients with end-stage renal disease (eight women, three men, mean age 29.8 years, age range 16–52 years) and 11 age-matched normal male subjects (mean age 33.9 years, age range 23–59 years). Patients with end-stage disease had an established diagnosis of renal osteodystrophy, and either secondary hyperparathyroidism (HPT; 8) or low-turnover bone disease (LTB; 3).

Dose: Dynamic PET acquisition was started after intravenous administration of 370 MBq (10 mCi) ^{18}F-fluoride. The scan lasted for one hour.

Schema of Trial: Quantitative PET was performed and results were evaluated for correlation with serum biochemical markers and bone histomorphometry. A rate constant (K) describing the net transport of ^{18}F-fluoride ion into a bound compartment in bone was calculated using both a three-compartment model and Patlak graphical analysis. Values of K were compared with biochemical data and with histomorphometric indices.

The patients with secondary HPT were compared with patients with LTB and with normal subjects using the Wilcoxon test. In all patients, K_{PAT} values were correlated with K_{NLR} and K_1 values and with alkaline phosphatase and parathyroid hormone (PTH) levels using simple linear regression. In the eight patients who had bone histomorphometry, K_{PAT} values were correlated with histomorphometric indices using multiple regression analysis.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was performed.

Primary Endpoints: Correlation of quantitative PET results and bone histomorphometry.

Results: K was significantly higher ($p<0.01$) in HPT patients than in normal subjects and patients with LTB. Values of K correlated with serum alkaline phosphatase ($r=0.81$) and PTH ($r=0.93$) levels and with histomorphometric indices of bone formation rate ($r=0.84$; $p<0.01$) and eroded perimeter ($r=0.77$; $p<0.05$). Values of K decreased by 30–40% in two of the three patients who underwent parathyroidectomy and medical therapy, corresponding to clinical and biochemical improvement. These results indicate that PET studies of bone using ^{18}F-fluoride can differentiate low-turnover from high-turnover lesions of renal osteodystrophy, and can provide quantitative estimates of bone cell activity that correlate with histomorphometric data.

Safety Issues: No safety issues were mentioned in the study.

Piert, M., et al. Allogenic bone graft viability after hip revision arthroplasty assessed by dynamic [^{18}F]fluoride ion positron emission tomography. Eur J Nucl Med. 26(6):615–624, 1999 [30]

This is a prospective study to evaluate allogenic bone graft viability after hip revision arthroplasty using dynamic ^{18}F-fluoride PET. The study was conducted at University of Tubingen, Germany.

Inclusion Criteria: Sixteen patients (nine female, seven male, age range 56–82 years) who had hip revision arthroplasty with allogenic bank bone on one or both sides of the pelvis were enrolled; imaging was performed no less than three weeks post-operation.

Dose: Dynamic PET acquisition was started simultaneously with intravenous administration of 160–370 MBq (4.8–10 mCi) of ^{18}F-fluoride diluted in 10 ml of 0.9% saline solution.

Schema of Trial: Dynamic ^{18}F-fluoride PET was used to measure the metabolic activity of acetabular allogenic bone grafts and genuine bone, either 3–6 weeks (short-term group; 9) or five months to nine years (long-term group; 10) after hip revision arthroplasty.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was performed; selection of ROIs was described. Phantom measurements were made to quantify errors due to the influence of the metal implants.

A three-compartment model was applied to calculate the fluoride influx constant from individually fitted rate constants (K_{NLF}) and by Patlak graphical analysis (K_{PAT}). The results

were compared with genuine cancellous and cortical acetabular bone of contralateral hips without surgical trauma (n=7).

Primary Endpoints: ^{18}F-fluoride uptake in allogenic bone grafts as an indication of bone metabolic activity; transport and incorporation of ^{18}F-fluoride ion after bone grafting; comparison between genuine acetabular bone of operated and non-operated contralateral hips.

Results: In genuine cortical bone, K_{NLF} was significantly increased in short- and long-term groups (+140.9% and +100.0%, respectively) compared with contralateral hips. Allogenic bone grafts were characterized by a significantly increased K_{NLF} in the short-term group (+190.9%) compared with contralateral hips, but decreased almost to the baseline levels of contralateral hips (+45.5%) in the long-term group. Values of K_{NLF} correlated with the rate constant K_1 in genuine ($r=0.89$; $p<0.001$) and allogenic bone regions ($r=0.79$; $p<0.001$), indicating a coupling between bone blood flow and bone metabolism in genuine bone as well as allogenic bone grafts. K_{PAT} values were highly correlated with K_{NLF} measurements in all regions. In conclusion, ^{18}F-fluoride ion PET revealed the presence of an increased host bone formation in allogenic bone grafts early after hip revision arthroplasty. In contrast to genuine cortical bone, allogenic bone graft metabolism decreased over time, possibly due to a reduced ability to respond to the same extent as genuine bone to elevated metabolic demands after surgery.

Safety Issues: No safety issues were mentioned in the study.

Schiepers, C., et al. Measurement of skeletal flow with positron emission tomography and ^{18}F-fluoride in femoral head osteonecrosis. Arch Orthop Trauma Surg. 118:131–135, 1998 [31]

This is a pilot study to evaluate regional blood flow to the femoral head in early osteonecrosis using ^{18}F-fluoride PET. The study was conducted at University Hospital Gasthuisberg (Leuven, Belgium) in 1993.

Inclusion Criteria: Subjects with a history of unilateral hip trauma with a suspicion of osteonecrosis and a normal contralateral side; five patients enrolled (three male, two female, age range 19−51 years). None of the subjects had osteosynthesis material in place at the time of imaging.

Dose: 300−370 MBq (8.1−10 mCi) ^{18}F-fluoride injected intravenously; dynamic PET images were acquired for one hour after ^{18}F-fluoride administration.

Schema of Trial: Dynamic PET imaging and blood sampling were initiated simultaneously with ^{18}F-fluoride injection. The clearance of ^{18}F-fluoride from plasma was determined by sampling from the radial artery. Flow and influx rate in abnormal bone were compared with these values in the contralateral normal bone in the same patient.

Image Protocol: Subjects were referred after a thorough clinical assessment, evaluation of pain and functioning, and radiologic imaging resulting in a diagnosis of suspected osteonecrosis. PET image acquisition and reconstruction information is presented; attenuation correction was performed. ROIs were drawn over the femoral heads, and time activity curves were generated. Flow and influx rate were calculated using a three-compartment model. The extent of viable bone tissue in the femoral head was assessed visually on the transverse, coronal and sagittal PET slices, and classified as: <25%, <50%, or >50% compared with the contralateral side. A two-sample t-test was used to compare subgroups of patients. Hotelling's T^2 test, a multivariate T statistic, was applied to compare the joint effect of flow and influx rate in the subgroups.

Primary Endpoints: Regional bone blood flow (BBF) and influx rate, with comparison between normal and abnormal side; relation between blood flow and final outcome (*e.g.,* surgical replacement or conservative treatment).

Results: The ratio of abnormal to normal BBF was variable, with an observed range of 1.6−2.6. Similar results were obtained for influx rate, with a tendency for higher abnormal to normal values (range 1.3−3.4), reflecting the increased absorption of fluoride to newly formed bone in active remodeling zones. Two subgroups could be identified: those with both abnormal to normal BBF and influx rate ratios <2, and those with ratios >2. The difference in flow between the two groups was significant ($p<0.01$), whereas the difference in influx rate was not significantly different. A flow ratio of at least 2 between normal abnormal and normal femoral head was necessary to predict a successful outcome with a conservative regimen. A minimum flow of 0.04 ml/min/ml was measured in one patient whose affected femoral head healed conservatively. Hotelling's T^2 statistic was significant at the $p<0.005$ level, indicating that the joint effect of BBF and influx rate can be used to distinguish subgroups for conservative *vs*. surgical management.

Safety Issues: No safety issues were mentioned in the study.

Sorensen, J., et al. Rapid bone and blood flow formation in impacted morselized allografts: positron emission tomography (PET) studies on allografts in 5 femoral component revisions of total hip arthroplasty. Acta Orthop Scand. 74(6):633–643, 2003 [32]

This prospective trial used PET (^{18}F-fluoride PET, ^{15}O-water PET and ^{15}O-carbon monoxide PET) to evaluate rapid bone and blood flow formation in impacted morselized allografts in femoral component revisions of total hip arthroplasty (THA). The study was conducted at Uppsala University in Sweden.

Inclusion Criteria: Five patients (age range 54–77 years) were enrolled who were previously treated with a revision THA and impaction bone allografting due to mechanical loosening of a primary THA together with loss of bone.

Dose: ^{15}O-labeled water (15–20 MBq/kg) was injected into an antecubital vein as a rapid bolus. ^{15}O-labeled carbon monoxide was administered by inhalation (dose not specified). When ^{15}O-tracers had decayed to background levels and no distorting radioactivity remained in the tissue, 180–380 MBq (4.8–10.3 mCi) of ^{18}F-fluoride in 5 ml saline was injected intravenously as a bolus with a subsequent saline flush; dynamic PET scanning began at the time of ^{18}F-fluoride injection.

Schema of Trial: PET was used to evaluate vascularization and new bone formation in the allograft. Kinetic ^{18}F-fluoride PET was used to produce quantitative images, interpreted as new bone formation in the allograft surrounding the femur stem; ^{15}O-water PET was used to quantify bone blood flow; and ^{15}O-carbon monoxide PET was used to determine blood volume. After surgery, all patients were evaluated twice: at 1–8 days and 12 months; three patients were also studied at four months.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was performed; selection of ROIs was described, where femoral diaphysis contralateral to the graft bed was used as a reference region for imaging analysis.

Quantification methods (*i.e.*, mathematical models) used for analyzing and interpreting dynamic ^{18}F-fluoride PET, ^{15}O-water PET, and ^{15}O-carbon monoxide PET were referenced and described.

Primary Endpoints: The usefulness of quantitative PET in evaluating neovascularization and bone formation in graft bed.

Results: As early as at eight days after surgery, blood flow and bone formation had increased greatly adjacent to the allograft. At four months, blood flow and bone formation were about the same, but activity was highest in the graft material. At one year after surgery, blood flow had declined to the levels of the contralateral femur diaphysis in most of the graft bed. Results show that angiogenesis and new bone formation occur early after impaction of morselized bone allografts around the femoral component in revision THA.

Safety Issues: No safety issues were mentioned in the study.

2.2.4 Studies of Bone Pharmacokinetics

Blake, G.M., et al. Quantitative studies of bone in postmenopausal women using ^{18}F-fluoride and ^{99m}Tc-methylene diphosphonate. J Nucl Med. 43(3):338–345, 2002 [33]

This is a prospective trial to evaluate skeletal kinetics of ^{99m}Tc-MDP and ^{18}F-fluoride using plasma clearance methods. The study was conducted at Guy's Hospital, United Kingdom, in postmenopausal women. NOTE: these are the same patients as Park-Holohan.

Inclusion Criteria: The study enrolled 69 healthy postmenopausal women (age range 45–79 years, mean age 60.4 years) who were taking hormone replacement therapy (HRT) for at least six months (26), or were not taking any treatment that might affect bone turnover (43).

Dose: A mixture of trace amounts of ^{18}F-fluoride (1 MBq), ^{99m}Tc-MDP (1 MBq), ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA; 3 MBq) and ^{125}I-human serum albumin (^{125}I-HAS; 0.25 MBq) injected intravenously.

Schema of Trial: Multiple blood and urine samples were collected up to four hours after injection, and used to determine the renal and whole-blood kinetics of ^{18}F-fluoride and ^{99m}Tc-MDP; glomerular filtration rate (GFR) and plasma volume were estimated by measuring ^{51}Cr-EDTA and ^{125}I-HSA levels, respectively.

The clearance to bone mineral K_{bone} was first evaluated using the area under the plasma concentration curve (AUC) using the assumption that the rate constant k_4 for the outflow of tracer from bone was negligibly small. AUC values of K_{bone} were then compared with those found using a compartmental model method that allowed rate constant k_4 to be fitted as a free parameter.

Image Protocol: The study had no imaging component.

Primary Endpoints: Difference in skeletal turnover between women receiving antiresorptive therapy and age-matched control subjects; comparison of the relative merits of ^{18}F-fluoride and ^{99m}Tc-MDP as suitable tracers.

Results: Using the AUC method, mean K_{bone} with ^{18}F-fluoride was 61.8±12.0 ml/min and 67.2±12.6 ml/min for the HRT and control groups, respectively ($p=0.045$); corresponding values for ^{99m}Tc-MDP were 40.3±8.2 ml/min and 44.2±7.6 ml/min for the HRT and control groups, respectively ($p=0.024$). Values for the two tracers in individual patients were moderately well correlated ($r=0.76$; $p<0.001$). Using the compartmental model method, k_4 for ^{18}F-fluoride was shown to lie in the range 0–0.0025 min^{-1} with a best-fit value of 0.0018 min^{-1}. Values of K_{bone} determined using k_4=0.0018 min^{-1} were highly correlated with the AUC values ($r=0.989$) with numeric values that were larger by a factor of 1.53. Analysis of the ^{99m}Tc-MDP data was more difficult because of uncertainties in protein binding in the extracellular fluid compartment space. The best fit for k_4 was in the range 0.0010–0.0014 min^{-1} with values of K_{bone} similar to those found using the AUC method. In conclusion, values of K_{bone} determined using the AUC

method were able to differentiate between HRT-treated women and postmenopausal women who were not treated and were highly correlated with those determined using a compartmental model method with nonzero values of k_4.

Safety Issues: No safety issues were mentioned in the study.

Brenner, W., et al. Comparison of different quantitative approaches to 18F-fluoride PET scans. J Nucl Med. 45:1493–1500, 2004 [23]

This study was conducted to evaluate the relationship between ^{18}F-fluoride bone metabolic parameters obtained by nonlinear regression (NLR), Patlak analysis, and SUV for a wide range of normal and pathological bone conditions. The study was conducted at the University of Washington Medical Center (Seattle, WA). This study appears to use some or all of the same subjects evaluated in the above publication by the same author [22].

Inclusion Criteria: Thirty-three consecutive patients with tumors of the bone presenting for regular follow-up exams after tumor resection and bone graft surgery were enrolled (age range 18−65 years). Subjects had a wide range of benign (18) and malignant (15) bone tumors. Nine patients were imaged twice. Imaging was performed 2−51 months (mean 12 months) after primary or revision graft surgery. Grafts were located in the humerus (15), femur (16), tibia (7), fibula (2), or bones of the foot (2).

Dose: 250−370 MBq (6.8−10 mCi) ^{18}F-fluoride (3.7 MBq/kg-bw; 0.1 mCi/kg-bw) in 10 ml 0.9% saline infused over one minute with a syringe pump. Dynamic PET images began simultaneously with the initiation of tracer infusion and continued for 60 minutes.

Schema of Trial: Dynamic PET scans were performed 2−51 months after resection of bone tumor of the limbs. SUV, K_{PAT} and K_{NLR} were calculated in each subject for the bone graft, the contralateral normal side, and the spine if in the field of view. In subjects imaged twice, changes in metabolic rates were determined.

Image Protocol: An intravenous line was placed in each arm; one for tracer injection and the other for venous blood sampling. Dynamic PET images began simultaneously with the initiation of tracer infusion. PET image acquisition and reconstruction information is presented; all images underwent corrections for random and scattered coincidence events, and each image was corrected for attenuation and physical decay of ^{18}F-fluoride.

Blood samples were centrifuged, and radioactivity in plasma was determined. PET data were analyzed by an ROI approach; procedures used to define ROIs and volumes of interest (VOIs) were provided. Tissue TACs of the graft, contralateral normal bone, and a thoracic vertebra, if within the field of view, were generated from the ROI for each image in the dynamic dataset. Data were processed by three different techniques: NLR and Patlak graphical analysis, both using a three-compartment model, and SUV. For

each patient graft, values for SUV and K_{PAT} were plotted against K_{NLR}, and the correlation coefficient was calculated. The student t-test or ANOVA was used to evaluate statistical differences ($p<0.05$) between subgroups.

Primary Endpoints: Correlation between K_{PAT}, K_{NLR} and SUV in abnormal and normal bone in each subject; change in parameters over time for those subjects imaged more than once.

Results: Metabolic measures for ^{18}F-fluoride were obtained in a total of 98 bone sites (42 graft, 42 contralateral normal bone sites, 14 thoracic vertebrae). Significant linear correlations were observed between K_{PAT} and K_{NLR} (r=0.99), K_{PAT} and SUV (r=0.95) and K_{NLR} and SUV (r=0.93). Changes in metabolic values of grafts in subjects imaged twice (at approximately six and 12 months after surgery) were significantly correlated for K_{PAT} and K_{NLR} (r=0.96), K_{PAT} and SUV (r=0.88) and K_{NLR} and SUV (r=0.79). The high 95% range or normal change of SUV in limb bones indicates that this parameter is of limited value in areas with low metabolic activity.

Safety Issues: No safety issues were mentioned in the study.

Cook, G.J., et al. Non-invasive assessment of skeletal kinetics using fluorine-18 fluoride positron emission tomography: evaluation of image and population-derived arterial input functions. Eur J Nucl Med. 26(11):1424–1429, 1999 [34]

This is a prospective trial to compare a population approach and an image-derived method with direct arterial sampling in the measurement of ^{18}F fluoride kinetics in the lumbar spine.

Inclusion Criteria: This trial enrolled 10 normal postmenopausal women (mean age 54.8 years) who did not have a metabolic bone disorder, and were not receiving drugs known to affect skeletal metabolism.

Dose: Dynamic PET acquisition of the lumbar spine was initiated after intravenous administration of 180 MBq (4.86 mCi) of ^{18}F-fluoride and continued for 60 minutes.

Schema of Trial: Comparison of a scaled population input function (IFp) and a corrected image-derived input function from the aorta (IFi) with an arterial input function (IFa) directly measured from a radial artery line.

Image Protocol: Dynamic PET image acquisition and reconstruction information is presented; attenuation correction was performed.

Primary Endpoints: The IFp and the IFi were compared with the IFa in terms of the accuracy of determination of six parameters. These were: plasma clearance of fluoride to bone mineral (K_{bone}), unidirectional plasma clearance to total bone tissue (K_1) and

individual rate constants k_2, k_3 and k_4, calculated using non-linear regression with a three-compartment model, and the plasma clearance to bone mineral calculated using the Patlak method (K_{PAT}).

Results: For both the IFp and the IFi methods, the root mean square errors for K_{PAT} and K_{bone} were similar and small (<8.2%). The errors in determining K_1 and the rate constants k_2 to k_4 are larger by either method, but with a small advantage using the IFp method. It is concluded that the use of either non-invasive method for determining the arterial plasma input function is suitable for the measurement of the most important parameters, K_{bone} and K_{PAT}, in these subjects.

Safety Issues: No safety issues were mentioned in the study.

Frost, M.L., et al. The relationship between regional bone turnover measured using ^{18}F-fluoride positron emission tomography and changes in BMD is equivalent to that seen for biochemical markers of bone turnover. J Clin Densitom. 10(1):46–54, 2007 [35]

This follow-up study of postmenopausal women participating in studies to evaluate regional bone turnover was conducted to examine the relationship between regional bone turnover measured using ^{18}F-fluoride PET and changes in BMD, and compare this to measurements of biochemical markers of bone turnover and resorption.

Inclusion Criteria: Postmenopausal women who had an ^{18}F-fluoride PET scan of the lumbar spine, measurements of biochemical markers of bone turnover, and a dual-energy x-ray absorptiometry (DXA) scan of BMD at the lumbar spine and hip within the prior three to eight years were invited to participate. At the time of the initial assessments, routine blood chemistry test results were with the normal limits, and none of the subjects were taking treatments for osteoporosis. A total of 43 women enrolled: 22 who began treatment for osteoporosis within two months of baseline assessments (mean age 64.4 years), and 21 not being treated for osteoporosis (mean age 57.1 years).

Dose: PET scanning of the lumbar spine was performed after intravenous administration of 90 or 180 MBq (2.4 or 4.9 mCi) of ^{18}F-fluoride.

Schema of Trial: Global (biochemical markers) and regional (^{18}F-fluoride PET) measurements of bone turnover were compared with subsequent changes in BMD at lumbar spine and hip occurring over a median follow-up time of 4.1 years. Since their initial assessment, subjects had between two and five BMD scans to estimate the annual percentage change in BMD. The relationship between the ^{18}F-fluoride PET regional bone turnover parameter, K_{bone}, and annual changes in lumbar spine and hip BMD was compared to the relationship between **biochemical** markers of bone formation (BSALP) and bone resorption (urinary deoxypyridinoline).

Image Protocol: PET image acquisition, reconstruction, and attenuation correction information is referenced and briefly summarized; selection of ROIs is described.

A three-compartment model was used to derive the ^{18}F-fluoride kinetic parameters that reflect regional bone turnover.

Primary Endpoints: Correlation among biochemical markers of bone formation and resorption, ^{18}F-fluoride PET measurements of bone turnover, and BMD at lumbar spine and hip in postmenopausal women; comparison of results in women who were or were not receiving treatment for osteoporosis.

Results: Treated women in the highest tertile of bone turnover as measured by ^{18}F-flouride PET and global biochemical markers showed the greatest annual percentage increases in lumbar spine BMD. The annual increase in lumbar spine BMD was 1.8%, 2.2%, and 3.2% for women in the lowest, middle, and highest tertile of BSALP levels, respectively; similar annual increases were seen for women in the lowest, middle, and highest tertile of measured K_{bone} (1.7%, 2.2%, and 2.7% respectively). Untreated women in the highest tertile of regional (as measured by ^{18}F-fluoride PET) and global bone turnover had larger decreases in lumbar spine BMD compared to those women in the lowest tertile, with a 1.4- to 4.8-fold difference in the annual decrease in BMD between the two. Less consistent patterns were observed when assessing the relationship between regional and global bone turnover with changes in hip BMD. This study showed that regional bone turnover measured directly at the lumbar spine, and global skeletal bone turnover measured by biochemical markers, have a similar relationship to changes in BMD.

Safety Issues: No safety issues were mentioned in the study.

Hawkins, R.A., et al. Evaluation of the skeletal kinetics of fluorine-18-fluoride ion with PET. J Nucl Med. 33(5):633–642, 1992 [36]

The skeletal kinetics of ^{18}F-fluoride ion was evaluated using dynamic PET imaging. The study was conducted at the UCLA School of Medicine (Los Angeles, CA).

Inclusion Criteria: Provision of informed consent. Eleven healthy male volunteers (age range 23 to 59 years) were imaged once; one female breast cancer patient was imaged on three separate occasions.

Dose: Approximately 185−370 MBq (5−10 mCi) ^{18}F-fluoride ion diluted in 10 ml saline solution and injected intravenously over 30 seconds; image acquisition began simultaneously with intravenous administration and continued for 60 minutes.

Schema of Trial: Dynamic PET imaging and blood sampling were initiated simultaneously with ^{18}F-fluoride injection. Total imaging time was one hour; blood sampling continued for the duration of the imaging period.

Image Protocol: PET image acquisition, reconstruction and attenuation correction information is presented. ROIs were selected over the vertebral body in each image of each dynamic set. In the cancer patient, additional ROIs were constructed corresponding to focal metastatic disease characterized by zones of increased ^{18}F-fluoride uptake. In a subset of three volunteers, rapid initial scan sequences and blood samples were collected; ROIs in the left ventricular cavity were chosen for focused evaluation of ventricular activity. Input functions (plasma ^{18}F-fluoride time-activity curves) were measured directly from arterialized blood and determined from image-derived left ventricular cavity activity measurements. Pharmacokinetic data were evaluated using two- and three-compartment model configurations to find the model that best fit the data.

Primary Endpoints: Distribution between whole blood and plasma, bone and plasma pharmacokinetics.

Results: Linear regression analysis yielded an initial (time zero) ratio of 1.44 for plasma-to-left ventricular ^{18}F-fluoride distribution, and a ratio of 1.23 for plasma-to-whole blood ^{18}F-fluoride distribution; the ratios were fairly constant, although a slight decrease as a function of time was evident. The data fit a three-compartment model better than a two-compartment model ($p<0.01$); an even better fit was achieved when using a three-component model with a tissue vascular space component, but this difference was not statistically significant. Rate constants determined in the study are consistent with the relatively rapid uptake of ^{18}F-fluoride in the bound space within the bone, and a slow rate of release from that compartment. Estimates of the uptake constant for fluoride in bone using non-linear regression (K_{NLR}) and Patlak graphical analysis (K_{PAT}) were in very good agreement.

Safety Issues: No safety issues were mentioned in the study.

Hirata T, et al. Reliability of one-point blood sampling method for calculating input function in Na18F PET. Nucl Med Commun. 26(6):519–525, 2005 [37]

This is a prospective study to test the reliability of a one-point arterial blood sampling method for calculating input function in quantitative ^{18}F-fluoride PET. The study took place in Japan.

Inclusion Criteria: This trial enrolled patients with osteoporosis (5), patients with spondylosis deformans (5), and health volunteers (3). A total of 12 subjects were enrolled (5 men, 7 women, age range 25–88 years, mean age 66.6 years). Subjects had

blood urea nitrogen lower than 20 mg/dl, creatinine lower than 1.5 mg/dl, and no electrocardiogram abnormalities.

Dose: Dynamic PET dynamic imaging began 20 seconds after the initiation of intravenous injection of 10 mL of ^{18}F-NaF (185–296 MBq; 5−8 mCi) and continued for 42 minutes. The injection was completed in 40 seconds.

Schema of Trial: The input function was estimated by the one-point venous blood sampling technique using ^{18}F-fluoride PET. The input function obtained from conventional, consecutive arterial blood sampling was used a reference.

Image Protocol: PET image acquisition information is presented. Other details are not described.

Primary Endpoints: Accuracy of the input function obtained by the one-point blood sampling technique; correlation between the estimated integrated value obtained from one-point blood sampling and the real integrated value.

Results: The optimal timing for one-point sampling was 12 min after intravenous injection of ^{18}F-fluoride. The estimated integrated value obtained from arterial blood sampling at 12 min and the reference table was highly correlated with the real integrated value ($p<0.001$). Levels of plasma radioactivity of arterial blood and venous blood were almost the same at 12 and 40 min after ^{18}F-fluoride injection. Percent errors in the estimation of the integrated values were 2.63% (n=12) for the arterial blood collected at 12 min and 4.14% (n=12) for the venous blood collected at 30 min. Results indicate that this simplified method is clinically applicable and may replace traditional methods that require multiple blood sampling.

Safety Issues: No safety issues were mentioned in the study.

Park-Holohan, S.J., et al. Quantitative studies of bone using (18)F-fluoride and (99m)Tc-methylene diphosphonate: evaluation of renal and whole-blood kinetics. Nucl Med Commun. 22(9):1037–1044, 2001 [38]

This is a prospective trial to evaluate the renal and whole-blood kinetics of ^{99m}Tc-MDP and ^{18}F-fluoride in postmenopausal women treated with HRT compared with untreated, age-matched women. NOTE: these are the same patients as Blake.

Inclusion Criteria: The study enrolled 70 healthy, postmenopausal women (mean age 60.4 years, range 45−79 years) who were (n=26) or were not (n=44) on HRT.

Dose: A mixture of trace amounts of ^{18}F-fluoride (1 MBq), ^{99m}Tc-MDP (1 MBq), ^{51}Cr-ethylenediaminetetraacetic acid (^{51}Cr-EDTA; 3 MBq) and ^{125}I-human serum albumin (^{125}I-HAS; 0.25 MBq) injected intravenously.

Schema of Trial: Multiple blood and urine samples were collected up to four hours after injection, and used to determine the renal and whole-blood kinetics of ^{18}F-fluoride and ^{99m}Tc-MDP; GFR and plasma volume were estimated by measuring ^{51}Cr-EDTA and ^{125}I-HSA levels, respectively.

Image Protocol: The study had no imaging component.

Primary Endpoints: Renal and whole-blood kinetics of ^{99m}Tc-MDP and ^{18}F-fluoride.

Results: At four hours, the cumulative excretion in urine was 58.2±4.8%, 36.1±5.7%, and 81.5±4.5% for ^{99m}Tc-MDP, ^{18}F-fluoride, and ^{51}Cr-EDTA, respectively. Plots of the renal clearance of ^{18}F-fluoride against urine volume showed that urine flow rates greater than 5 ml/min were necessary to ensure a constant renal clearance of ^{18}F and hence stable conditions for the evaluation of bone tracer kinetics. In contrast, a low urine flow rate had no effect on the renal kinetics of ^{99m}Tc-MDP. For MDP, the evaluation of skeletal kinetics requires data on protein binding so that calculations can be performed for free MDP. In the present study, protein binding of MDP was evaluated from the ratio of total ^{99m}Tc-MDP renal clearance to GFR based on the principle that free ^{99m}Tc-MDP is a GFR tracer. Between zero and four hours after injection, the fractional protein binding of MDP increased linearly with time, changing from 21±5% immediately after injection to 58±5% at four hours. Although red cell uptake of ^{99m}Tc-MDP was negligible, around 30% of circulating ^{18}F-fluoride was transported in red cells. In view of the data showing rapid transport of ^{18}F-fluoride across the red cell membrane, bone kinetic data for ^{18}F are more accurately reported as whole-blood clearance rather than plasma clearance.

Safety Issues: No safety issues were mentioned in the study.

Schiepers, C. et al. Fluoride kinetics of the axial skeleton measured in vivo with fluorine-18-fluoride PET. J Nucl Med. 38(12)1970–1976, 1997 [39]

This is a pharmacokinetic investigation quantifying regional blood flow and influx rate using ^{18}F-fluoride PET in subjects with metabolic bone disorders. The study was conducted at University Hospital Gasthuisberg (Leuven, Belgium)

Inclusion Criteria: Nine subjects with various skeletal disorders were enrolled. These included four subjects with involutional osteoporosis (one male, three females, age range 52−78 years), one subject with juvenile osteoporosis (male, age 30 years), two subjects with Paget's disease (one male, age 68 years; one female, age 69 years), and two subjects with hyperparathyroidism (one male, age 52 years; one female, age 56 years).

Dose: 300−370 MBq (8.1−10 mCi) ^{18}F-fluoride injected intravenously; dynamic PET images were acquired for 1−2 hours after ^{18}F-fluoride administration.

Schema of Trial: Dynamic PET imaging and blood sampling were initiated simultaneously with ^{18}F-fluoride injection. Imaging and blood collection continued for 1 –2 hours after ^{18}F-fluoride administration.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was performed. Tracer plasma clearance was determined by sampling blood from the radial artery. Gas chromatography was used to determine fluoride concentration; both whole-blood and plasma fluoride concentrations were analyzed.

PET images were used to define ROIs and generate and time-activity curves for skeletal regions of interest. Mathematical modeling with a three-compartment model was used to estimate the influx rate (K) and rate constants between the different compartments (vascular, extracellular and bone). Rate constants k_1 and k_2 represent forward and reverse transport from plasma, respectively, and rate constants k_3 and k_4 represent uptake and release from bone, respectively.

Primary Endpoints: Fluoride kinetics (regional flow and influx rate) calculated using a three-compartment model. Results in subjects with skeletal disorders were compared with published results from healthy male volunteers [36]

Results: The plasma-to-whole-blood ratio of ^{18}F-fluoride stabilized within approx. 20 seconds of injection, and averaged 1.30±0.09. Detailed analysis began with blood samples collected 30 seconds after injection. Fluoride flux was consistent with the pathophysiology of the studied metabolic disorders. Low flow and influx rate were observed in elderly subjects with osteoporosis, whereas the reverse pattern was seen in juvenile osteoporosis and Paget's disease. In the subjects with Paget's disease, abnormal bone showed a 3- to 5-fold increased flow and a 2- to 3-fold increased influx rate compared with contralateral control areas. Subjects with hyperparathyroidism showed similar values for flow and influx rate compared with published values for normal controls; however, clearance half-time of the bone compartment was lower, suggesting increased turnover. BMD was most decreased in the subjects with osteoporosis. Flux appeared to have the highest power to distinguish disorders.

Safety Issues: No safety issues were mentioned in the study.

2.2.5 Studies in the Pediatric Population

2.2.5.1 Prospective Studies in the Pediatric Population

Lim, R., et al. Early experience with fluorine-18 sodium fluoride bone PET in young patients with back pain. J Pediatr Orthop. 27(3):277–282, 2007 [40]

The purpose of this prospective trial was to evaluate the effectiveness of ^{18}F-fluoride PET in determining the cause of back pain in young patients. The study was conducted by doctors at Children's Hospital Boston, Harvard Medical School, Boston (Boston MA) and The Hospital for Sick Children, University of Toronto (Toronto, Ontario, Canada) during the interval from October 2004 through March 2005.

Inclusion Criteria: Patients referred for evaluation of back pain (94 total; 27 male, 67 female, age range 4–26 years, mean age 15 years, median age 16 years).

Dose: 2.1 MBq (0.06 mCi) ^{18}F-NaF/kg-bw [maximum 148 MBq (4 mCi)] administered intravenously. PET scans were initiated 30 minutes after administration.

Schema of Trial: All subjects underwent ^{18}F-fluoride PET; results were examined in attempt to identify causes of back pain. Advantages and disadvantages compared with ^{99m}Tc-MDP BS experience are discussed; however, ^{99m}Tc-MDP BS scans were not performed as part of the trial.

Image Protocol: PET image acquisition and reconstruction information is presented; attenuation correction was not performed unless high activity accumulation in the renal system would have led to artifacts.

Scans were interpreted by one of three pediatric nuclear medicine staff physicians; images and reports were then reviewed retrospectively by a fourth nuclear medicine physician, who tabulated abnormal findings.

Primary Endpoints: Visual interpretation and correlation to findings from conventional diagnostic measures.

Results: Increased focal uptake, indicative of a possible cause for back pain, was seen in 52 patients (55%) with a total of 70 sites of focal abnormal uptake. Among these patients, 15 had more than two sites of abnormal uptake. ^{18}F-fluoride PET suggested pars interarticularis/pedicle stress in 32 patients, spinous process injury in 15 patients, vertebral body ring apophyseal injury in 13 patients, stress at the articulation between a transitional vertebra and sacrum in 7 patients.

Safety Issues: Comparing dosimetry data derived for ^{18}F-fluoride and ^{99m}Tc-MDP, the effective dose is similar (3.5 mGy for ^{18}F-NaF *vs*. 2.8 mGy for ^{99m}Tc-MDP), bone surface dose was higher for ^{99m}Tc-MDP (33.4 mGy *vs*. 6.0 mGy for ^{18}F-NaF), and bladder wall dose is slightly higher for ^{18}F-NaF (32.4 mGy *vs*. 24.4 mGy for ^{99m}Tc-MDP).

Ovadia D., et al. Back pain in adolescents: assessment with integrated 18F-fluoride positron-emission tomography-computed tomography. J Pediatr Orthop. 27(1):90–93, 2007 [41]

A prospective study to evaluate the use of ^{18}F-fluoride PET-CT for diagnosis of the cause for back pain as an isolated and presenting complaint in adolescents. The study was conducted at Dana Children's Hospital in Tel Aviv, Israel, between November 2002 and June 2005.

Inclusion Criteria: Fifteen consecutive patients (11 male, four female, mean age 14 years, age range 9−19 years) were enrolled after being referred to the tertiary medical center for isolated and subjectively severe complaints of back pain. Patients were referred when routine assessments, including anteroposterior and lateral plain radiographs of the spine, and sometimes SPECT and/or CT, were unable to identify or fully diagnose the cause of pain.

Dose: 5−10 mCi (185-370 MBq) ^{18}F-fluoride administered intravenously; PET image acquisition began 45 minutes after injection.

Schema of Trial: All subjects underwent ^{18}F-fluoride PET with low-dose CT; resulting images were examined in attempt to identify causes of back pain.

Image Protocol: PET image acquisition and reconstruction information is presented; CT data were used for attenuation correction.

Low-dose CT acquisition was performed first, and PET scanning was performed immediately after, without changing the patient's positioning. The interpretation of PET-CT fused images was based on increased ^{18}F-fluoride uptake and the corresponding CT-located abnormality. Methods to reduce interpretation bias were not described.

Primary Endpoints: Visual interpretation of abnormal areas of ^{18}F-fluoride uptake on fused PET-CT images.

Results: Ten patients had positive findings that included four cases of spondylosis, three frank fractures, two osteoid osteomas, one osteitis pubis, one sacroiliitis, and two herniated discs; three patients presented with two coexisting pathologies. In the five patients in whom no abnormality was identified by ^{18}F-fluoride PET-CT, the back pain resolved spontaneously.

Safety Issues: No safety issues were mentioned in the study other than radiation exposure. In consideration of cost and radiation exposure, it is suggested that the use of ^{18}F-fluoride PET diagnosis of back pain in adolescents be reserved for cases of long-standing and disabling back pain in which other modalities were inconclusive.

2.2.5.2 Case Reports in the Pediatric Population

Brunkhorst, T. et al. Pretherapeutic assessment of tumour metabolism using a dual tracer PET technique. Eur. J Nucl Med. 29(10):1416, 2002 [42]

A published case study describes the use of whole-body ^{18}F-fluoride PET and ^{18}F-FDG PET to evaluate the extent of metastatic disease in a 15-year-old female with bone metastases associated with osteosarcoma.

Inclusion Criteria: Not applicable.

Dose: Not provided.

Schema of Trial: Not applicable.

Image Protocol: PET image acquisition and reconstruction information is not presented.

Primary Endpoints: Not applicable.

Results: ^{18}F-fluoride PET demonstrated bone metastases, and ^{18}F-FDG PET revealed additional soft tissue metastases in the mediastinum and lungs. The fused images of ^{18}F-fluoride PET and ^{18}F-FDG PET showed an extent of soft tissue disease unknown from previous structural imaging (CT and MRI). The primarily curative intent had to be abandoned in favor of pain palliation only.

Safety Issues: No safety issues were mentioned in the study.

Drubach, L., et al. Fluorine-18 NaF PET imaging of child abuse. Pediat. Radiol. 38: 776–779, 2008 [43]

A published case study describes the use of whole-body ^{18}F-fluoride PET in a four-month-old boy for the evaluation of skeletal trauma in a case of suspected child abuse.

Inclusion Criteria: Not applicable.

Dose: 18 MBq (0.5 mCi) ^{18}F-NaF administered intravenously

Schema of Trial: Not applicable.

Image Protocol: PET image acquisition information, but not reconstruction information, is presented.

Primary Endpoints: Not applicable.

Results: A skeletal survey performed according to American College of Radiology guidelines employing a high-resolution computer radiography system showed multiple rib fractures at different stages of healing. There was also an acute left mid-shaft tibial spiral fracture and a metaphyseal fracture with epiphyseal separation of the right

proximal humerus. A classic metaphyseal lesion (CML) of the left proximal humerus was suspected. The ^{18}F-fluroide PET scan clearly demonstrated all fractures shown on the initial skeletal survey. In addition, a left iliac crest injury and posteromedial fracture of the left 8th rib not shown on the initial skeletal survey were identified. A follow-up skeletal survey performed two weeks after the initial survey confirmed healing fractures of the right proximal humerus, left iliac crest and the 8th rib, and also demonstrated a healed left proximal CML

Safety Issues: No safety issues were mentioned in the study.

2.2.6 Studies Assessing PET Technique Variables

Tayama, Y. et al. Clinical evaluation of the effect of attenuation correction technique on 18F-fluoride PET images. Ann Nucl Med. 21(2):93–99, 2007 [44]

This is a prospective study evaluating the effect of attenuation correction on ^{18}F-fluoride PET. Subjects were evaluated between October 2004 and April 2005 at the Yokohama University School of Medicine (Yokohama, Kanagawa, Japan).

Inclusion Criteria: Thirty-two consecutive subjects who underwent ^{18}F-fluoride PET scans were enrolled (21 female, 11 male, age range 20−86 years, mean age 54 years). Reasons for undergoing ^{18}F-fluoride PET included: suspicion of a tumor (17); bone necrosis (5); bone fractures (2); Paget's disease (1); osteoarthritis (2); and rheumatoid arthritis (5). Of the subjects suspected of having a tumor, four had sarcoma, two had giant cell tumor, four had metastases, one had suspected hemangioma, and six were tumor free.

Dose: 185 MBq (5 mCi) ^{18}F-fluoride in 10 ml saline by intravenous administration; PET imaging began 40 minutes after administration.

Schema of Trial: Whole-body images were obtained for each subject, and tracer uptake in normal and abnormal bone was compared with uptake in the gluteus muscle. ROIs were used to evaluate normal bone accumulation in skull, cervical vertebra, mandible, scapula, thoracic vertebra, rib, humerus, lumbar vertebra, radius, ulna, pelvis, femoral head, femoral shaft, tibia, and fibula. Normal bone accumulation was not evaluated in the 10 subjects who had bone metastases, Paget's disease or rheumatoid arthritis.

Image Protocol: PET image acquisition and reconstruction information is presented; images were created with and without attenuation correction. Methods for defining ROIs are presented. The count ratios of normal bone and abnormal skeletal lesions to gluteus muscle were calculated as bone-to-muscle ratios; the count ratios of abnormal skeletal lesions to normal bones were calculated as bone-to-bone ratios. The paired t-test was used to determine the significant difference between SUVs for bones of the extremities and bones in the trunk.

Images with and without attenuation correction were interpreted by three physicians experienced with PET scan evaluation, with four weeks of separation between readings. Each image was given a score depending on the likelihood of abnormality (1=definitely normal, 5=definitely abnormal). One region of each image was designated to review; other regions were not reviewed, even if they appeared abnormal. Designated regions evaluated by multiple physicians included 10 regions with tumor, six regions with necrosis, five regions with fracture, four regions with rheumatoid arthritis, two regions with spondylosis, one region with osteoarthritis, one region with Paget's disease, one region with suspected hemangioma on MRI, and three regions without disease.

Primary Endpoints: Specificity and sensitivity of ^{18}F-fluoride PET performed with and without attenuation correction.

Results: For all normal bones except the femoral head and lumbar vertebrae, PET images without attenuation correction showed significantly higher mean bone-to-muscle ratios than those with attenuation correction ($p<0.05$). For abnormal bones, bone-to-muscle ratios and bone-to-bone ratios without attenuation correction were significantly higher than those with attenuation correction ($p<0.005$). Sarcomas demonstrated the highest uptake, followed by necroses. Sensitivity of images with and without attenuation correction was 83.3% and 85.6%, respectively. Specificities with and without attenuation correction were 88.9%. Attenuation correction does not appear to be necessary for accurate evaluation of ^{18}F-fluoride PET images.

Safety Issues: No safety issues were mentioned in the study.

3. Summary of Published Safety and Effectiveness Data

There is an approved NDA for sodium fluoride F 18 injection, indicated for PET as a bone imaging agent to define areas of altered osteogenic activity (NDA 17-42). The FDA's prior approval of this agent for this indication serves to demonstrate existence of adequate safety and effectiveness information for this product at the indicated dose [0.5−2 mCi (18.5−74 MBq), maximum 4 mCi (148 MBq)] administered as an intravenous injection.

Although approved for use in 1972, the use of ^{18}F-fluoride waned in the 1970s due to the ready availability of ^{99m}Tc-labeled diphosphonates. The interest in ^{18}F-fluoride as a bone imaging agent increased in the 1990s with increased availability and improved technology of PET scanners, which offer higher spatial resolution and sensitivity than conventional gamma cameras used in planar BS and SPECT. Several articles discussing experience with the clinical use of ^{18}F-fluoride have been published since that time, and are reviewed in this summary. The majority of these studies used doses of ^{18}F-fluoride higher than the approved dose, with doses ranging from 0.5 to 20 mCi.

Diagnostic imaging has played a major role in the evaluation of patients with bone metastases, and this application is the focus of the majority of the recent published literature on use of ^{18}F-fluoride PET. For detection of bone metastases in cancer patients, doses typically ranged from 8 to 12 mCi. In this dose range, excellent image quality with higher spatial resolution than convention BS is obtained [1, 14]. There is evidence that ^{18}F-fluoride PET is more sensitive and selective than conventional BS for diagnosis and detection of bone metastases [8–12, 45]. Use of low-dose CT in conjunction with ^{18}F-fluoride PET improves sensitivity and specificity, and improves the ability to distinguish benign from malignant lesions [12]. Because of these advantages, and advancements in cost-effectiveness, it has been suggested that ^{18}F-fluoride PET will replace conventional bone scan for detection of bone metastases within several years [10, 11]. Studies presented in this review showed sensitive and specific detection of bone metastases with administration of ^{18}F-fluoride PET at doses ranging from 7−20 mCi (261−740 MBq). Several of these studies included subjects with multiple types of cancer; studies in cohorts specific to lung, breast and prostate cancer patients are also presented. No safety issues were mentioned in any of these publications nor were any safety reports identified in a search of FDA’s Adverse Event Reporting System (AERS) database.

Two studies evaluating use of ^{18}F-fluoride PET to diagnose the cause of back pain in adolescents have been published. Lim *et al.* [40] studied 94 young patients between four and 26 years of age, with a mean age of 15 years and median age of 16 years. Patients were dosed intravenously with 0.06 mCi ^{18}F-NaF/kg-bw (maximum 4 mCi). Ovadia *et al*. [41] used ^{18}F-fluoride PET-CT to diagnose the cause of back pain in 15 adolescents ranging in age from nine to 19 years of age (mean 14 years) who were dosed with 5−10 mCi (185−370 MBq) ^{18}F-fluoride. Two case studies involving administration of ^{18}F-fluoride to juveniles have been reported: a 15-year-old female

(dose not specified) and a four-month-old male (0.5 mCi); no safety issues were mentioned in either of these reports. However, radiation exposure in the pediatric population should be avoided if at all possible because of the sensitivity of children to radiation.

Other publications on the use of ^{18}F-fluoride PET include evaluation of osteoporosis (2.43−8 mCi; 90−296 MBq), condylar hyperplasia (4 mCi; 150 MBq), bone graft healing (0.1 mCi/kg-bw; 3.7 MBq/kg-bw), back pain (12−15 mCi, 444−555 MBq), other skeletal disorders (5−10 mCi, 185−370 MBq), and the pharmacokinetics of bone influx (5−10 mCi, 185−370 MBq). Normal volunteers were included in some of these evaluations. Laverick *et al.* [19] found that the radiation burden of ^{18}F-fluoride PET was comparable to that of ^{99m}Tc-MDP, and better than that of SPECT. No safety issues were identified.

In summary, evidence from published studies in cancer patients indicates that ^{18}F-fluoride PET is superior to ^{99m}Tc-MDP planar scintigraphy or SPECT in detecting primary bone cancer and skeleton metastases from a wide range of cancers, including cancer of the breast, lung, and prostate. ^{18}F-Fluoride PET detected more lesions and demonstrated higher contrast between malignant and normal bone. Unlike ^{99m}Tc-MDP scan, which has a low detection rate for lesions in the spine and pelvis, the detection efficiency of ^{18}F-fluoride PET is independent on anatomic localization of lesions. The very high resolution and target-to-background contrast of ^{18}F-fluoride PET can potentially reduce its specificity; however, correlating PET with CT findings substantially help differentiate malignant from benign lesions. ^{18}F-fluoride PET is also effective in other applications involving altered osteogenic activity, such as detecting skeletal injury, diagnosing causes of back pain, diagnosing osteoporosis, and monitoring effectiveness of bone regeneration therapy. Although the dose of ^{18}F-fluoride approved 37 years ago in the United States for detecting areas of altered osteogenic activity is 0.5 −2 mCi, the doses used in the studies presented in this summary were as high as 20 mCi, with no safety issues identified. In addition, the recommended dose of IASOflu®, a sodium fluoride F18 injection product that recently received marketing approval in France, is 4 MBq/kg-bw, or 280 MBq (7.6 mCi) for a 70 kg adult. High degrees of sensitivity and specificity have been achieved at these higher doses, and no safety issues have been identified.

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Table 1. Review of Published Literature on Use of ^{18}F-Fluoride PET to Define Areas of Altered Osteogenic Activity

Author/Year	Cohort	No. of Subjects	Dose of ^{18}F-fluoride	Efficacy Comments	Safety Comments	Reference
Well-Controlled Studies of Bone Metastases						
Beheshti, 2008	Prostate cancer patients	38	10–15 mCi (370–550 MBq)	^{18}F-fluoride PET-CT was more sensitive, ^{18}F-FCH PET-CT was more specific, for detection of metastatic bone disease.	None	[6]
Petren-Mallmin, 1998	Breast cancer patients	5	5.4–10.8 mCi (185–370 MBq)	Focally increased ^{18}F-fluoride uptake was seen in both osteolytic and osteoblastic bone lesions as defined by CT; lesions less than 3 mm on CT were not detected by ^{18}F-fluoride PET.	None	[7]
Schirrmeister, 1999	Breast cancer patients	34	10 mCi (370 MBq)	^{18}F-fluoride PET was more sensitive than ^{99m}Tc-MDP BS for detection of metastatic bone lesions.	None	[8]
Hetzel, 2003	Lung cancer patients	103	7–20 mCi (261–740 MBq)	^{18}F-fluoride PET was more sensitive and more specific than ^{99m}Tc-MDP BS and SPECT for detection of malignant bone lesions; the costs of ^{18}F-fluoride PET and SPECT were higher than for ^{99m}Tc-MDP BS.	None	[9]
Schirrmeister, 2001	Lung cancer patients	53	10–15 mCi (370–555 MBq)	^{18}F-fluoride PET and SPECT were more sensitive than ^{99m}Tc-MDP BS for detection of metastatic bone lesions.	None	[10]
Schirrmeister, 2001	Thyroid cancer patients	35	10–15 mCi (370–555 MBq)	The sensitivity of ^{99m}Tc-MDP BS combined with WBI was higher than for BS alone, and comparable to ^{18}F-fluoride PET and MRI.	None	[11]
Even-Sapir, 2004	Oncology patients	44	8–12 mCi (296–444 MBq)	^{18}F-fluoride PET-CT is both sensitive and specific for detection of sclerotic and lytic malignant lesions; offers advantages over ^{18}F-fluoride PET and ^{99m}Tc-MDP BS.	None	[12]

Table 1. Review of Published Literature on Use of ^{18}F -Fluoride PET to Define Areas of Altered Osteogenic Activity *(continued)*

Author/Year	Cohort	No. of Subjects	Dose of ^{18}F-fluoride	Efficacy Comments	Safety Comments	Reference
Hoegerle, 1998	Oncology patients	60	2.7±0.3 mCi (100±10 MBq)	^{18}F-fluoride PET combined with ^{18}F-FDG PET was more sensitive and specific than ^{18}F-fluoride PET alone, and correlated well with findings from other imaging modalities.	None	[13]
Hoh, 1993	Patients with skeletal disorders and normal volunteers	38 (19/19)	5−10 mCi (185−370 MBq)	No unexpected sites of ^{18}F-fluoride uptake were seen in normal volunteers; ^{18}F-fluoride PET had improved contrast and localization of benign and malignant bone lesions compared with planar imaging methods.	None	[14]
Schirrmeister, 1999	Oncology patients	44	10 mCi (370 MBq)	^{18}F-fluoride PET was more sensitive than ^{99m}Tc-MDP BS for detection of bone lesions, and was independent of anatomical location.	None	[45]
Other Oncology Studies						
Bhargava, 2008	Case report	1	9.8 mCi (363 MBq)	^{18}F-fluoride PET was used to locate a lytic lesion in the heel of a 59-year-old male with metastatic renal cancer.	None	[15]
Langsteger, 2006	Patients with malignant tumors or diseases	100+	Not specified	In patients diagnosed by both ^{18}F-fluoride and ^{18}F-FDG PET-CT (n=20), lesions not detected by ^{18}F-fluoride were mostly small osteolytic metastases or located in the bone marrow; lesions not detected by ^{18}F-FDG PET-CT were mostly tumors known to have less FDG avidity (*e.g.,* medullary thyroid cancer, renal cell carcinoma).	None	[1]

Table 1. Review of Published Literature on Use of ^{18}F -Fluoride PET to Define Areas of Altered Osteogenic Activity *(continued)*

Author/Year	Cohort	No. of Subjects	Dose of ^{18}F-fluoride	Efficacy Comments	Safety Comments	Reference
Tse, 1994	Case report	1	Not specified	^{18}F-fluoride PET was used to diagnose the nature of pulmonary nodules in a 42-year-old female with fibrous dysplasia, metastatic osteogenic sarcoma, and a breast mass.	None	[16]
Wade, 2006	Case report	1	Not specified	Osseous flare response in a 27-year-old woman with infiltrating ductal carcinoma was compared using ^{18}F-fluoride PET, ^{18}F-FDG PET -CT, ^{99m}Tc-MDP BS, and MRI	None	[17]
Well-controlled Studies in Benign Bone Disease						
Gamie, 2008	Patients with back pain	67	12−15 mCi (444−555 MBq)	^{18}F-fluoride PET was used to identify the cause of back pain in 84% of patients who could not be diagnosed by standard x-ray, CT and/or MRI.	None	[18]
Laverick, 2008	Patients with suspected condylar hyperplasia	5	4 mCi (150 MBq)	Uptake of ^{18}F-fluoride correlated with the site of suspected disease identified by clinical examination and plain radiographs; the mandibular condyle that showed increased ^{18}F-fluoride correlated with histological diagnosis in all patients.	The radiation burden using ^{18}F-fluoride is comparable to that of ^{99m}Tc-MDP BS and better than that of SPECT	[19]
Sterner, 2007	Patients with painful TKA	14	9.4 mCi (350 MBq)	^{18}F-fluoride PET was superior to x-ray, showing excellent spatial resolution and differentiation of aseptic loosening from simple synovitis.	None	[20]

Table 1. Review of Published Literature on Use of ^{18}F -Fluoride PET to Define Areas of Altered Osteogenic Activity *(continued)*

Author/Year	Cohort	No. of Subjects	Dose of ^{18}F-fluoride	Efficacy Comments	Safety Comments	Reference
Well-controlled Studies of Bone Metabolism and Repair						
Berding, 1995	Patients with pedicle grafts for mandibular reconstruction	9	10 mCi (370 MBq)	Increased blood flow and osteoblastic activity in healing grafts was apparent in ^{18}F-fluoride images; there was a lack of influx in areas of potential necrosis.	None	[21]
Brenner, 2004	Bone graft patients	34	0.1 mCi /kg-bw; (3.7 MBq/kg-bw)	^{18}F-fluoride PET is useful for assessment of fluoride metabolism and normal healing in bone grafts of the limbs.	None	[22]
Cook, 2002	Patients with Paget's disease	7	4.9 mCi (180 MBq)	A correlation between BSALP and K_{bone} supports the use of K_{bone} as a marker of regional bone formation. Results of influx and flow determination were consistent with the known pathophysiology of Paget's disease.	None	[24]
Forrest, 2006	Patients with osteoarthritis and hip resurfacing	10	6.8 mCi (250 MBq)	SUVs were higher in resurfaced hips than in nonresurfaced hips; the difference was only significant in the lateral aspect of the femoral head.	None	[25]
Frost, 2003	Postmenopausal osteoporotic women	18	2.43 mCi (90 MBq)	^{18}F-fluoride PET was useful as a non-invasive method for monitoring changes in bone metabolism during treatment with risedronate	None	[26]
Frost, 2004	Postmenopausal women	72	2.43 mCi (90 MBq)	Differences in bone metabolism kinetics between osteoporotic, osteopenic and normal subjects were evident in ^{18}F-fluoride PET scans.	None	[27]

Table 1. Review of Published Literature on Use of ^{18}F -Fluoride PET to Define Areas of Altered Osteogenic Activity *(continued)*

Author/Year	Cohort	No. of Subjects	Dose of ^{18}F-fluoride	Efficacy Comments	Safety Comments	Reference
Installe, 2005	Patients with Paget's disease	14	10.75±1.1 mCi (397±41 MBq)	Uptake of ^{18}F was higher in pagetic than normal bone; ^{18}F-fluoride PET could be used to track changes in bone metabolic with bisphosphonate therapy.	None	[28]
Messa, 1993	Patients with end-stage renal disease	22	10 mCi (370 MBq)	Low-turnover and high-turnover lesions of osteodystrophy could be distinguished using ^{18}F-fluoride PET.	None	[29]
Piert, 1999	Patients who had hip revision arthroplasty	16	4.8–10 mCi (160–370 MBq)	^{18}F-fluoride PET showed early host bone formation in allogenic bone grafts; allogenic bone graft metabolism decreased over time.	None	[30]
Schiepers, 1998	Subjects with hip trauma and suspected osteonecrosis	5	8.1–10 mCi (300–370 MBq)	The ratio of BBF and influx rate measured using ^{18}F-fluoride PET was predictive of treatment outcome (conservative therapy *vs*. surgery).	None	[31]
Sorensen, 2003	Patients who had undergone THA and impaction bone allografting	5	4.8–10.3 mCi (180–380 MBq)	Angiogenesis and new bone formation visualized using ^{18}F-fluoride PET occurred early after impaction of morselized bone allografts around the femoral component in revision THA.	None	[32]
Studies of Bone Pharmacokinetics:						
Blake, 2002	Healthy postmenopausal women	69	0.03 mCi (1 MBq)	Women who were and were not taking HRT could be differentiated using the pharmacokinetic parameter, K_{bone}.	None	[33]

Table 1. Review of Published Literature on Use of ^{18}F -Fluoride PET to Define Areas of Altered Osteogenic Activity *(continued)*

Author/Year	Cohort	No. of Subjects	Dose of ^{18}F-fluoride	Efficacy Comments	Safety Comments	Reference
Brenner, 2004	Bone graft patients	33	6.8–10 mCi (250–370 MBq)	Good correlation was obtained between K_{PAT} and K_{NLR}, K_{PAT} and SUV, and K_{NLR} and K_{SUV}; SUV has limited usefulness in areas of low metabolic activity.	None	[23]
Cook, 1999	Normal postmenopausal women	10	4.86 mCi (180 mBq)	Pharmacokinetic investigation; the non-invasive scaled population input function (IFp) and corrected image-derived input function from the aorta (IFi) correlated well with an arterial input function (IFa) directly measured from a radial artery line.	None	[34]
Frost, 2007	Postmenopausal women	43	2.4 or 4.9 mCi (90 or 180 MBq)	Regional bone turnover at the lumbar spine measured using ^{18}F-fluoride PET and global skeletal bone turnover measured by BSALP and urinary deoxypyridinoline have a similar relationship to changes in BMD.	None	[35]
Hawkins, 1992	Healthy male volunteers, breast cancer patient	12 (11 healthy, 1 breast cancer)	5–10 mCi (185–370 MBq)	Steady-state ratio of ^{18}F-fluoride ion is higher in plasma than in blood, and skeletal kinetics are consistent with three-compartment model.	None	[36]
Hirata, 2005	Patients with osteoporosis, spondylosis deformans, and normal volunteers	12 (5/5/3)	5–8 mCi (185–296 MBq)	A one-point blood sampling method for calculating input function in ^{18}F-fluoride PET was identified.	None	[37]

Table 1. Review of Published Literature on Use of ^{18}F -Fluoride PET to Define Areas of Altered Osteogenic Activity *(continued)*

Author/Year	Cohort	No. of Subjects	Dose of ^{18}F-fluoride	Efficacy Comments	Safety Comments	Reference
Park-Holohan, 2001	Postmenopausal women	70	0.03 mCi (1 MBq)	Pharmacokinetic investigation. Urine flow rates >5 ml/min are necessary to ensure a constant renal clearance of ^{18}F; 30% of circulating ^{18}F-fluoride is transported in red cells; bone kinetic data for ^{18}F are more accurately reported as whole-blood clearance rather than plasma clearance.	None	[38]
Schiepers, 1997	Subjects with skeletal disorders	9	8.1−10 mCi (300−370 MBq)	Fluoride kinetics measured using ^{18}F-fluoride PET were consistent with pathophysiology of the studied metabolic disorders	None	[39]
Studies in the Pediatric Population:						

Table 1. Review of Published Literature on Use of ^{18}F -Fluoride PET to Define Areas of Altered Osteogenic Activity *(continued)*

Author/Year	Cohort	No. of Subjects	Dose of ^{18}F-fluoride	Efficacy Comments	Safety Comments	Reference
Lim, 2007	Young patients with back pain (age range 4−26 years)	94	0.06 mCi /kg-bw; max. 4 mCi (2.1 MBq/kg-bw; max. 148 MBq)	^{18}F-fluoride PET was able to locate cause of back pain in 55% of subjects who could not be diagnosed by other methodologies.	Effective dose is similar for ^{18}F-NaF and ^{99m}Tc-MDP (3.5 mGy *vs*. 2.8 mGy); bone surface dose is higher for ^{99m}Tc-MDP (33.4 mGy *vs*. 6.0 mGy for); bladder wall dose is slightly higher for ^{18}F-NaF (32.4 mGy *vs*. 24.4 mGy).	[40]
Ovadia, 2007	Young patients with back pain (age range 9−19 years)	15	5−10 mCi (185−370 MBq)	Use of ^{18}F-fluoride PET-CT lead to diagnosis of cause of back pain in 10 of 15 subjects; in the remaining subjects with no findings on ^{18}F-fluoride PET-CT, pain resolved spontaneously.	No issues; suggest using conventional procedures first due to cost and radiation exposure.	[41]
Brunkhorst, 2002	Case study	1	Not provided	^{18}F-fluoride PET and ^{18}F-FDG PET were used to evaluate extent of metastatic disease in a 15-year-old osteosarcoma patient.	None	[42]

Table 1. Review of Published Literature on Use of ^{18}F -Fluoride PET to Define Areas of Altered Osteogenic Activity *(continued)*

Author/Year	Cohort	No. of Subjects	Dose of ^{18}F-fluoride	Efficacy Comments	Safety Comments	Reference
Drubach, 2008	Case report	1	0.5 mCi (18 MBq)	^{18}F-fluoride PET was used to locate skeletal injuries in a four-month-old male.	None	[43]
Studies Evaluating Alternative PET Technique Variables						
Tayama, 2007	Various	32	5 mCi (185 MBq)	^{18}F-fluoride PET without attenuation correction showed higher mean bone-to-muscle ratios than those with attenuation correction; attenuation correction is not necessary for accurate visual interpretation of ^{18}F-fluoride PET images.	None	[44]