SPECT/CT and PET/CT of Bone disease

Helle Westergren Hendel
MD PhD, assistant professor
Department of Nuclear Medicine
PET & Cyclotron
Member of PhD Coordinator Committee
Faculty of Health
Institute of Clinical Medicine
Herlev Hospital
University of Copenhagen, Denmark
Methods for evaluation of the skeleton

**XR:**
bone destruction (30-60% mineral bone loss)

**CT:**
structural bone changes (non RECIST),
lytic:50-75% destroyed trabecular bone

**WB-MRI, DW-MRI:**
involvement of bone marrow, functional

**DXA:** bone mineral density

**US:** blood flow, soft tissue

**SPECT**
99mTc HDP/MDP (BS)
White blood cell scintigraphy (WBC)
Bone marrow scintigraphy

**PET:**
NaF
FDG
Choline/acetate etc
Radiopharmaceuticals

**Bone remodelling**
- NaF
- Biphosphonates

**Infection/inflammation**
- FDG
- WBC
- Ga-citrate
- Nannocolloids
- IgG/albumin

**Specific tumor markers**
123I, 123I mIBG,
111In SST, 64 Cu DOTA
Clinical application of PET/SPECT

- Bone pain
  - Metastatic tumour
  - Benign bone tumour
  - Trauma
  - Avascular necrosis
  - Infection
  - Osteomalacia, Paget’s disease
- Malignancy
  - Initial staging and recurrence
  - Discordant scan/X-ray findings
  - Assessment of extent of disease
  - Assessment of response to therapy
  - Hypertrophic pulmonary osteoathropathy
  - Primary bone tumours
- Benigne bone disease
  - Othopedic disorders
  - Sports/exercise related injuries
  - Metabolic bone disease – Paget’s disease, hyperparathyroidism
  - Infection
  - Benign bone tumors
  - Degenerative disease
- Miscellaneous
  - Vascular abnormalities
  - Abnormalities of the renal and urinary tract
  - Soft tissue accumulation of dihphsphonate

Methods

Bone Scan (BS):
Pharmacokinetics of biphosphonates

Intravenous administration
20%-60% cleared to mineral phase of the skeleton (hydroxyapatite and amorphous calcium phosphate)

Remainder excreted through the kidneys

Plasma protein binding is often a significant factor
- 30% immediately after injection
- 50% by 4 hours
- 70% by 24 hours

Renal clearance is comparable with GFR and independent of urine flow rate

Uptake is affected by:
- Blood flow
- Extraction efficiency
- Vitamin D
- Parathyroid hormone
- Corticosteroids
- Intraosseoustissure pressure
- Capillary permability
- Acid-base balance
- Sympathetic tone
Standard:
Delayed imaging: 4+ hrs
Regional or WB SPECT

3 phase imaging
Arterial phase: blood flow
Blood pool phase: increased vascular permeability and flow
Delayed imaging (3-4 hours): osteoblastic activity

SPECT improves sensitivity to detect vertebral lesions
20-50% compared to planar imaging
Clinical application of PET/SPECT

• Bone pain
  – Metastatic tumour
  – Benign bone tumour
  – Trauma
  – Avascular necrosis
  – Infection
  – Osteomalacia Paget’s disease

• Malignancy
  – Initial staging and recurrence
  – Discordant scan/X-ray findings
  – Assessment of extent of disease
  – Assessment of response to therapy
  – Hypertrophic pulmonary osteoarthropathy
  – Primary bone tumours

• Benigne bone disease
  – Orthopedic disorders
  – Sports/exercise related injuries
  – Metabolic bone disease – Paget’s disease, hyperparathyroidism
  – Infection
  – Benign bone tumors
  – Degenerative disease

• Miscellaneous
  – Vascular abnormalities
  – Abnormalities of the renal and urinary tract
  – Soft tissue accumulation of dihphsphonate
Bone pain
  – Trauma
  – Avascular necrosis
  – Infection

Benigne bone disease
  – Orthopedic disorders
  – Sports/exercise related injuries
  – Metabolic bone disease – Paget’s disease, hyperparathyroidism
  – Infection
  – Degenerative disease
Clinical application of PET/SPECT

Bone pain
  - Trauma
  - Avascular necrosis
  - Infection

Benigne bone disease
  - Orthopedic disorders
  - Sports/exercise related injuries
  - Metabolic bone disease – Paget’s disease,
    hyperparathyroidism
  - Infection
  - Degenerative disease
65 y female with pain in left hemipelvis

4 month ago moped accident

Fractures with minimal displacement
Fracture of femoral neck

Garden I fracture: Incomplete and minimally displaced (impacted)
Bone pain
- Trauma
- Avascular necrosis
- Infection

Benigne bone disease
- Orthopedic disorders
- Sports/exercise related injuries
- Metabolic bone disease – Paget’s disease, hyperparathyroidism
- Infection
- Degenerative disease
Healing may be affected by disruption of the arterial blood supply to the fracture site and the femoral head. There are many other causes for osteonecrosis (irradiation, hypercortisolism, renal transplant, alcoholism etc). Other vulnerable sites: humeral head, body of the thalus-scaphoid bone.
A childhood hip disorder initiated by a disruption of blood flow to the femoral head. Avascular necrosis or osteonecrosis occur due to the lack of blood flow, the bone dies. The bone stops growing. Over time, healing occurs by new blood vessels infiltrating the dead bone and removing the necrotic bone which leads to a loss of bone mass and a weakening of the femoral head.

4 y old with Calvé-Legg-Perthes
On the right side
Clinical application of PET/SPECT

Bone pain
- Trauma
- Avascular necrosis
- Infection (WBC, bone marrow, FDG)

Benigne bone disease
- Orthopedic disorders
- Sports/exercise related injuries
- Metabolic bone disease – Paget’s disease, hyperparathyroidism
- Infection
- Degenerative disease
Infection/inflammation

FDG
Accumulation in neutrophils, macrophages and activated leucocytes in relation to their metabolic rate and the number of glucose transporters.

Autologous WBC
Specific migration to the site of inflammation

Ga-citrate, nannocolloids, IgG/albumin
Increased blood flow
Enhanced vascular permeability
Osteomyelitis

- Infection and inflammation of the bone or bone marrow.
- Classified on the basis of
  - causative organism
  - the route
  - duration
  - anatomic location
  - acute/chronic
**Bone scan**

Very sensitive (>80%),
specificity (planar) is low (50%)
Specificity (SPECT/CT) is high (>80%)

A positive BS should lead to further investigation of the affected region.
**WBC scan**
Because of physiologic uptake into bone marrow, sensitivity and specificity may be impaired

Combined with Nannocolloid for bone marrow
Sensitivity and specificity > 90%

Combined with BS
Sensitivity and specificity > 90%
**WBC imaging:**

Low sensitivities (app 50%)

Due to inability of leucocytes to migrate to the encapsulated infection

A **photopenic lesion** is not specific for infection and, together with the physiologic uptake of WBC into the bone marrow, hamper accurate detection of spinal infection
Spondylitis and spondylodiscitis

**FDG PET**
- Sensitivity > 95%
- Specificity > 85%

*Surgery < 6 mo:*
- Specificity = 75%

*Osteosyntetic material present:*
- Specificity = 65%
Case 14

[Images of medical scans and measurements, including a measurement of 35 cm]
Septic/aseptic loosening?

Extremely important because the treatment is very different.

Combined WBC and marrow imaging has an accuracy of 90% and is the method of choice.

There is little role for FDG.
Loosening

Post operative high uptake:

12 months

24 months
Infection? WBC

WBC scan

BS
**Adults, hematopoietic marrow:** the skull, vertebrae, ribs, sternum, pelvis and proximal portions of the humerus and femur.

Fatty marrow in other bones may contain islands of hematopoietic tissue.

Variations are frequent.

Acquired alterations: surgery, trauma, **infection** and other destructive processes.
Combined $^{111}$In-white blood cell (WBC)/$^{99m}$Tc-diphosphonate bone and/or $^{111}$In-WBC/$^{99m}$Tc-sulfur colloid marrow scans are preferred in difficult cases of osteomyelitis at sites with existing bone alteration and/or adjacent soft-tissue infection.
Femoral osteotomy due to Calvé-Legg-Perthes.

Now young adult.
Removal of osteosynthesis material due to pain.

No pain relief.

Infection?
Infection? WBC and marrow
Infection? WBC scan
WBC SPECT/CT: diabetic foot amputation. Soft tissue infection extending into bone.
69 y male severe kyfoscoliosis; osteotomies and fixation of vertebral spine to pelvis and sacrum in order to stabilise the vertebral spine

Initially good effect, however colapse after some months.

Severe pain, reduced pulmonary function and abdominal pain.

Hospitalised due to infection

Where?
Bone pain
- Trauma
- Avascular necrosis
- Infection (WBC, bone marrow)

Benigne bone disease
- Othopedic disorders
- **Sports/exercise related injuries**
- Metabolic bone disease – Paget’s disease, hyperparathyroidism
- Infection
- Degenerative disease
There is one suffering from Osgood Slatter at each football team.
• Calcaneus – jumping
• Tibia/fibula – running
• Patella – hurdles
• Pelvis – gymnastics, football
• Ribs – swimming, rowing, weight lifting
• Vertebra – weight lifting
Sports/exercise related injuries
Medial tibial stress syndrome (MTSS), exertional shin pain, medial traction periostitis
Sports/exercise related injuries
Clinical application of PET/SPECT

Bone pain
- Trauma
- Avascular necrosis
- Infection (WBC, bone marrow)

Benigne bone disease
- Orthopedic disorders
- Sports/exercise related injuries
- Metabolic bone disease – Paget’s disease, hyperparathyroidism
- Infection
- Non infectious inflammatory disease
Reumatoid arthritis

Gouty Arthritis
Non infectious inflammatory disease

22 y female
With painful joints

52 y female with pain in right shoulder
The role of nuclear medicine imaging in the assessment or RA is currently unclear.

Paradigmatic changes have been taken place in the treatment of RA in the last 2 decades requiring highly sensitive imaging modalities that will also allow to repeated imaging.

SPECT and FDG-PET may play a role in the early diagnosis of RA, patient exposure to radiation however hinders their use in repeated assessments.

US and MRI are likely to play the most important role.
Clinical application of PET/SPECT

**Bone pain**
- Trauma
- Avascular necrosis
- Infection (WBC, bone marrow)

**Benign bone disease**
- Orthopedic disorders
- Sports/exercise related injuries
- Metabolic bone disease – Paget disease, hyperparathyroidism, renal osteodystrophy
- Infection
- Degenerative disease
Paget disease (of the bone)

Excessive breakdown and formation of bone, followed by disorganized bone remodelling.

The bone weaken, resulting in, misshapen bones, fractures, and arthritis in the joints near the affected bones. May have bone pain, headache, back pain, or a nerve-related symptoms

**Often localized to only a few bones in the body.**
The pelvis, femur, and lower lumbar vertebrae are the most commonly affected bones.

Elevated levels of serum alkaline phosphatase may occur.
Paget disease
**Metabolic bone disease**

**Renal osteodystrophy**  
(chronic kidney disease-mineral and bone disorder, CKD-MBD)

**Osteomalacia**  
(vitamin D-deficiency)

**Hyperparathyroidism**

Disorders caused by abnormalities of minerals (calcium, phosphorus, magnesium) or vitamin D leading to dramatic clinical disorders that are commonly reversible once the underlying defect has been treated.
Metabolic bone disease

- Prominence of calvaria and mandible
- Increased tracer uptake in axial skeleton
- Reduced renal activity, faint or absent kidney images
- “Tie sternum” beading of the costochondral junction
- Increased tracer uptake in long bones
- Increased tracer uptake in periarticular areas
• Bone pain
  – Metastatic tumour
  – Benign bone tumour
  – Trauma
  – Avascular necrosis
  – Infection
  – Osteomalacia Paget’s disease

• Malignancy
  – Initial staging and recurrence
  – Discordant scan/X-ray findings
  – Assessment of extent of disease
  – Assessment of response to therapy
    – Hypertrophic pulmonary osteoarthropathy
  – Primary bone tumours

• Benign bone disease
  – Orthopedic disorders
  – Sports/exercise related injuries
  – Metabolic bone disease – Paget’s disease, hyperparathyroidism
  – Infection
  – Benign bone tumors
  – Degenerative disease

• Miscellaneous
  – Vascular abnormalities
  – Abnormalities of the renal and urinary tract
  – Soft tissue accumulation of dihydrosphosphate

A medical condition combining clubbing and periostitis of the small hand joints, especially the distal interphalangeal joints. Distal expansion of the long bones as well as painful, swollen joints and synovial villous proliferation are often seen.

May occur alone (primary), or secondary to diseases like non-small cell lung carcinoma, tuberculosis, emphysema, HD, cystic fibrosis, liver cirrhosis, IBD, Etc.

BS shows symmetric periostitis; the tram line sign.
Clinical application of PET/SPECT

Bone pain
- Metastatic tumour
- Trauma
- Avascular necrosis
- Infection (WBC, bone marrow)

Malignancy
- Initial staging and recurrence

Benigne bone disease
- Orthopedic disorders
- Sports/excercise related injuries
- Metabolic bone disease
- Paget’s disease,
  hyperparathyroidism
- Infection
- Degenerative disease

Miscellaneous
- Vascular abnormalities
Osteogen sarcoma - examples
FDG avidity in sarcomas

Pooled sensitivity and specificity: 0.91 and 0.85
Malignant lymphoma
Clinical application of PET/SPECT

Bone pain
  - Metastatic tumour
  - Trauma
  - Avascular necrosis
  - Infection (WBC, bone marrow)

Malignancy
  - Initial staging and recurrence

Benigne bone disease
  - Othopedic disorders
  - Sports/exercise related injuries
  - Metabolic bone disease
  - Paget’s disease
  - hyperparathyroidism
  - Infection
  - Degenerative disease

Miscellaneous
  - Vascular abnormalities
Purpose of bone imaging in metastatic disease

Identify *early* bone involvement and extent of disease

**Functional imaging**
- BS/SPECT
- NaF PET/CT
- FDG PET/CT

Determine the risk of fracture and cord compression

**Morphologic imaging**
- CT and MRI

Patients with bone metastasis only may survive for years
Bone SPECT/CT

Sclerotic bone metastases from prostate cancer
NaF PET: Spinal cord compression

NaF PET/IdCT

MRI

Th10
FDG PET: cord compression
**NaF PET: Indications**

**Osseous metastases**

Insufficient information exists to recommend the following indications in all patients (may be appropriate in certain individuals)

<table>
<thead>
<tr>
<th>Back pain/unexplained bone pain</th>
<th>Avascular necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child abuse</td>
<td>Osteonecrosis of the mandible</td>
</tr>
<tr>
<td>Abnormal radiographic/laboratory findings</td>
<td>Metabolic bone disease</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>Paget’s disease</td>
</tr>
<tr>
<td>Trauma</td>
<td>Bone graft viability</td>
</tr>
<tr>
<td>Inflammatory/degenerative arthritis</td>
<td>Prosthetic joints</td>
</tr>
<tr>
<td></td>
<td>Reflex sympathetic dystrophy</td>
</tr>
<tr>
<td></td>
<td>Monitoring response to therapy</td>
</tr>
</tbody>
</table>
NaF PET: Indications (benigne)

Insufficient information

Child abuse  Osteomyelitis  Stress fracture  Paget  Increased PTH
NaF PET/CT
Stable fluoride is a natural trace element

> 99% of whole-body fluoride is present in the skeleton as fluoroapatite

18F is a diagnostic molecular imaging agent used for identification of new bone formation
Pharmacokinetics of NaF

Intravenous administration

Taken up by red blood cells; erythrocyte concentration 50% of plasma concentration

Negligible protein binding

Single passage extraction of whole blood by bone is close to 100%; less than 10% in the blood after 1 h

Clearance (tubular reabsorption): dependent on urine flow rate

60-90% of GFR at high flow
5% at low urine flow

63-y-old man with prostate cancer. Visibility of lesions increases with time. Acquisition time: 12, 30, 57, and 119 min p.i of 121MBq 18F-NaF

Average time–activity curves for blood pool and normal bone in patients with prostate cancer
Uptake reflects blood flow and bone remodeling:

18F is substituted for hydroxyl groups in hydroxyapatite, and covalently binds to the surface of new bone.

Uptake is higher in new bone (osteoid) due to higher availability of binding sites.

Processes that result in minimal osteoblastic activity, or primarily osteolytic activity, may not be detected.
Uptake is higher in new bone (osteoid) due to higher availability of binding sites.

Processes that result in minimal osteoblastic activity, or primarily osteolytic activity, may not be detected.

NaF PET may be more sensitive than BS to detect the minimal osteoblastic activity associated with lytic bone metastases.

Kawaguchi M et al. 18F-fluoride uptake in bone metastasis: morphologic and metabolic analysis on integrated PET/CT.
Lytic or sclerotic

Lytic (osteoclastic)
- All cancer types
- Bladder, kidney, thyroid, multiple myeloma

Sclerotic (osteoblastic)
- Prostate, breast
- Occasionally: lung, stomach, pancreas, cervix
- Infrequently: CRC

Mixed

Skeletal involvement is seen in 20-70% of all cancer patients
Lytic (osteoclastic) metastases

Lytic metastases from leiomyosarcoma

A lytic metastasis is hypodense (dark)
Lytic (osteoclastic) metastases

Lytic metastases from RCC
Deposition of NaF

Greater deposition in the axial skeleton than in the appendicular skeleton and in the bones around joints than in the shafts of long bones. Changes over time
Deposition of NaF

Image acquisition

Normal bone

Metastasis

10 min 30 min 90 min

SUVmax

Deposition of NaF

Graph

Max

Metastasis

Metastasis

Normal bone

10 min 30 min 90 min
*Ugeholdt H Sammenligning af tiden pr bed-position ved 18F-NaF PET-knogleundersøgelser. Bachelorprojekt, bioanalytikeruddannelsen København, professionshøjskolen Metropol, København 2011

Acquisition times

N = 32

30 s/bed 60 s/bed 90 s/bed 120 s/bed
Deposition of NaF
18F NaF is injected intravenously (direct or catheter).

**Adult activity:**
185-370 MBq. Higher activity may be used in obesity

**Pediatric activity:**
Weight-based (2.22 MBq/kg; min 18.5 MBq - max 185 MBq)

Patients should be well hydrated to promote rapid excretion (decrease radiation dose and improve image quality)

No fast, all medications can be taken

No recommendation about interruption of breastfeeding, But limited contact with baby
Image quality and sensitivity of PET is 2-3 orders of magnitude compared to planar/SPECT.

The gamma camera (collimator system) acquire ~0.01% of emitted photons.

The PET scanner (coincidence detection) acquire ~1% of emitted photons.

Fluoride PET has higher spatial resolution than bone scan.

The favorable kinetic characteristics of sodium fluoride provide better bone–soft tissue contrast ratio than that of HDP imaging.
## Effective radiation dose

### Table 1
Comparison between PET and conventional bone scintigraphy.

<table>
<thead>
<tr>
<th></th>
<th>Skeletal PET</th>
<th>Conventional bone scintigraphy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiopharmaceutical</td>
<td>F-18 sodium fluoride</td>
<td>Tc-99m MDP</td>
</tr>
<tr>
<td>Physical half life</td>
<td>110 min</td>
<td>6 h</td>
</tr>
<tr>
<td>Emissions</td>
<td>511 keV photons from positron annihilation</td>
<td>140 keV photons</td>
</tr>
<tr>
<td>Spatial resolution</td>
<td>3–6 mm</td>
<td>4–15 mm</td>
</tr>
<tr>
<td>Binding to serum protein</td>
<td>Minimal</td>
<td>30% initially, 70% at 24 h</td>
</tr>
<tr>
<td>Clearance</td>
<td>Rapid</td>
<td>Relatively slow</td>
</tr>
<tr>
<td>Total uptake by bone</td>
<td>~50%</td>
<td>~30%</td>
</tr>
<tr>
<td>Organ receiving highest radiation</td>
<td>Bladder</td>
<td>Bone surface</td>
</tr>
<tr>
<td>Time to imaging after injection</td>
<td>30–60 min</td>
<td>3–6 h</td>
</tr>
<tr>
<td>Effective radiation dose (mSv/MBq)</td>
<td><strong>200 x 0.0024 = 4.8</strong></td>
<td><strong>740 x 0.0057 = 4.2</strong></td>
</tr>
</tbody>
</table>
Comparison with BS

BS planar                      multi FOV SPECT         NaF PET
posterior                   anterior

Even-Sapir E  JNM 2006
Similar to bone scan:

Kidneys, ureters, bladder normally seen
Symmetric uniform uptake in adults
Increased uptake in metaphyses in children/adolescents

Visualization of diffuse/focal increased bone uptake
Local hyperemia may cause soft tissue uptake

Osteolytic processes may not be detected
Degree of uptake does not differentiate between benign and malignant lesion
The pattern of uptake may be helpful
CT correlation is often helpful
**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**

Even-Sapir E et al JNM 2004;45:272-8

<table>
<thead>
<tr>
<th>18F NaF</th>
<th>Lesion-to-Lesion</th>
<th>Patient-to-patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>72</td>
<td>88</td>
</tr>
<tr>
<td>PET/CT</td>
<td>85</td>
<td>100</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PET</td>
<td>72</td>
<td>56</td>
</tr>
<tr>
<td>PET/CT</td>
<td>97</td>
<td>100</td>
</tr>
</tbody>
</table>

NaF PET/CT > NaF PET > MDP/HDP SPECT > MDP/HDP planar
Comparison of BS/SPECT with 18F-Fluoride PET or PET/CT:
11 studies, 425 patients.
350 analyzed on a patient basis, 225 on a lesion basis
Sensitivity and specificity of NaF PET/CT

- On a patient basis: 96.2% and 98.5%
- On a lesion basis: 96.9% and 98.0%
- The diagnostic accuracy of PET or PET/CT was significantly higher than that of the planar and SPECT bone scintigraphy.
In osteolytic metastases, FDG uptake is higher compared to sclerotic lesions because of the presence of a larger amount of tumor cells with high glycolytic rate.

Sclerotic metastases contain smaller amounts of viable tumor cells and exhibit therefore less FDG uptake.
Comparison of NaF and FDG


Research Article

Prospective Evaluation of $^{99m}$Tc MDP Scintigraphy, $^{18}$F NaF PET/CT, and $^{18}$F FDG PET/CT for Detection of Skeletal Metastases

Andrei Iagaru $^{1}$, Erik Mittra $^{1}$, David W. Dick $^{2}$ and Sanjiv Sam Gambhir $^{1,2,3,4}$

(1) Department of Radiology, Division of Nuclear Medicine, Stanford University Medical Center, 300 Pasteur Dr, Room H-2200, Stanford, CA 94305, USA
(2) Department of Radiology, Molecular Imaging Program at Stanford (MIPS), Stanford, CA, USA
(3) Department of Bioengineering, Stanford, CA, USA
(4) Department of Materials Science & Engineering, Stanford, CA, USA
Comparison of NaF and FDG

Methods
• Prospective study
• N = 52 patients
• Gold standard
  – histological 46%
  – clinical follow-up
  – other imaging studies

Results patient basis:
• 24/52 NaF
  – Sens/spec = 95.8/92.9
  – NPV/PPV = 92.0/96.3
• 16/52 FDG
  – Sens/spec = 66.7/96.4
  – NPV/PPV = 77.1/94.0
  – 28/52 FDG extraskeletal metastases

Superior image quality and evaluation of skeletal disease extent with NaF over FDG. FDG detects extraskeletal disease that can change disease management.

*Sarcoma = 19, Prostate cancer = 18, Breast cancer = 6, Colon cancer = 2, Bladder cancer = 1, Lung cancer = 1, Malignant paraganglioma = 1, Lymphoma = 1, GIST=1, RCC=1, Salivary gland cancer = 1
The role of $^{18}$F-fluoride PET-CT in the detection of bone metastases in patients with breast, lung and prostate carcinoma: a comparison with FDG PET/CT and $^{99m}$Tc-MDP bone scan

Nishikant Avinash Damle, Chandrasekhar Bal, G. P. Bandopadhyaya, Lalit Kumar, Praveen Kumar, Arun Malhotra, Sneh Lata
## Methods

Prospective

N = 115

- breast 72
- prostate 49
- NSCLC 30

**Gold standard:**

MRI

CT

Histology when feasible

## Results

Whole group:

- Sensitivity = 100%
- NPV = 100%

## Conclusion:

To rule out bone metastases in cases where there is a high index of suspicion NaF is the most reliable investigation.
Several researchers concluded that 99mTc MDP SPECT is superior to 18F FDG PET in detecting bone metastases in breast cancer and that the sensitivity for osteoblastic lesions is limited with 18F FDG PET/CT.

Surveillance of metastatic spread to the skeleton in breast cancer patients based on FDG PET alone is not possible.

(Igaru et al 2012, Damle et al 2013)
Prostate cancer

(N=49, metastases confirmed in 32)

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F-FDG PET/CT</td>
<td>71.9 % (CI = 53–85.6 %)</td>
<td>100 % (CI = 77.1–100 %)</td>
<td>100 % (CI = 82.2–100 %)</td>
<td>65.4 % (CI = 44.4–82.1 %)</td>
<td>81.6 % (CI = 70.7–92.5 %)</td>
</tr>
<tr>
<td>$^{18}$F-fluoride PET/CT</td>
<td>100 % (CI = 86.7–100 %)</td>
<td>70.6 % (CI = 44–88.6 %)</td>
<td>86.5 % (CI = 70.4–94.9 %)</td>
<td>100 % (CI = 69.9–100 %)</td>
<td>89.8 % (CI = 80.3–97.7 %)</td>
</tr>
<tr>
<td>$^{99m}$Tc-MDP bone scan</td>
<td>96.9 % (CI = 82–99.8 %)</td>
<td>41.2 % (CI = 19.4–66.5 %)</td>
<td>75.6 % (CI = 59.4–87.1 %)</td>
<td>87.5 % (CI = 46.7–99.3 %)</td>
<td>77.5 % (CI = 65.8–89.2 %)</td>
</tr>
</tbody>
</table>

Table 5 Total number of lesions

<table>
<thead>
<tr>
<th>Test</th>
<th>$^{18}$F-FDG PET/CT</th>
<th>$^{18}$F-fluoride PET/CT</th>
<th>$^{99m}$Tc-MDP bone scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of positive patients</td>
<td>15/30</td>
<td>23/30</td>
<td>24/30</td>
</tr>
<tr>
<td>Total number of lesions</td>
<td>124</td>
<td>188</td>
<td>102</td>
</tr>
<tr>
<td>Sclerotic</td>
<td>90</td>
<td>163</td>
<td>83</td>
</tr>
<tr>
<td>Lytic</td>
<td>17</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Mixed</td>
<td>17</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Total number of true positives</td>
<td>15/30</td>
<td>19/30</td>
<td>19/30</td>
</tr>
<tr>
<td>Total number of lesions in true positives</td>
<td>124</td>
<td>177</td>
<td>89</td>
</tr>
<tr>
<td>Sclerotic</td>
<td>90</td>
<td>153</td>
<td>70</td>
</tr>
<tr>
<td>Lytic</td>
<td>17</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>Mixed</td>
<td>17</td>
<td>12</td>
<td>11</td>
</tr>
</tbody>
</table>
The Detection of Bone Metastases in Patients with High-Risk Prostate Cancer: \( ^{99m} \text{Tc-MDP} \) Planar Bone Scintigraphy, Single- and Multi-Field-of-View SPECT, \(^{18} \text{F-Fluoride} \) PET, and \(^{18} \text{F-Fluoride} \) PET/CT

Einat Even-Sapir, MD, PhD \(^1 \) \(^2 \), Ur Metser, MD \(^1 \) \(^2 \), Eyal Mishani, PhD \(^3 \), Gennady Lievshitz, MD \(^1 \), Hedva Lerman, MD \(^1 \) and Ilan Leibovitch, MD \(^2 \) \(^4 \)

Methods: Prospective study

- \( N = 44 \) BS + NaF PET/CT
- 24 patients + multi-FOV SPECT
- 20 patients + single FOV SPECT

JNM 2006
Prostate cancer

TABLE 2
Assessment of Skeletal Metastatic Spread by Planar $^{99m}$Tc-MDP BS, Planar and SPECT BS, $^{18}$F-Fluoride PET, and $^{18}$F-Fluoride PET/CT: Patient-Based Analysis in 44 Patients with High-Risk Prostate Cancer

<table>
<thead>
<tr>
<th>Modality</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planar BS</td>
<td>57 (35)</td>
<td>57 (95)</td>
<td>59 (89)</td>
<td>55 (44)</td>
</tr>
<tr>
<td>Planar + SPECT†</td>
<td>78 (39)</td>
<td>67 (86)</td>
<td>72 (75)</td>
<td>74 (31)</td>
</tr>
<tr>
<td>$^{18}$F-Fluoride PET</td>
<td>100 (48)</td>
<td>62 (95)</td>
<td>74 (92)</td>
<td>100 (63)</td>
</tr>
<tr>
<td>$^{18}$F-Fluoride PET/CT</td>
<td>100 (87)</td>
<td>100 (100)</td>
<td>100 (100)</td>
<td>100 (87)</td>
</tr>
</tbody>
</table>

*Analysis considering equivocal reading as positive for malignancy. In parentheses, analysis considering equivocal results as negative for malignancy.

$^{99m}$Tc-MDP BS including planar and a single-FOV SPECT in 20 patients and planar and multi-FOV SPECT in 24 patients.

M = malignant; E = equivocal; B/N = benign or normal.

Equivocal and malignant interpretation were categorized as suggestive for malignancy.
Detection of bone metastases in patients with lung cancer: $^{99m}$Tc-MDP planar bone scintigraphy, $^{18}$F-fluoride PET or $^{18}$F-FDG PET/CT

Stefan Krüger, Andreas K. Buck, Felix M. Mottaghy, Ellen Hasenkamp, Sandra Pauls, Christian Schumann, Thomas Wibmer, Tobias Merk, Vinzenz Hombach, Sven N. Reske
Lung cancer

NSCLC is not curable in patients with bone / distant metastases.

N = 30 Bone mets confirmed: 19 patients
25 by other imaging modalities/5 by histopathology

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹⁸F-FDG PET/CT</td>
<td>78.9 %</td>
<td>100 %</td>
<td>100 %</td>
<td>73.3 %</td>
<td>86.7 %</td>
</tr>
<tr>
<td>(CI = 53.9–93 %)</td>
<td>(CI = 67.9–100 %)</td>
<td>(CI = 74.7–100 %)</td>
<td>(CI = 44.8–91.1 %)</td>
<td>(CI = 76.9–96.4 %)</td>
<td></td>
</tr>
<tr>
<td>¹⁸F-fluoride PET/CT</td>
<td>100 %</td>
<td>63.6 %</td>
<td>83.6 %</td>
<td>100 %</td>
<td>86.7 %</td>
</tr>
<tr>
<td>(CI = 79.1–100 %)</td>
<td>(CI = 31.6–81.6 %)</td>
<td>(CI = 60.5–94.3 %)</td>
<td>(CI = 56.1–100 %)</td>
<td>(CI = 76.9–93.4 %)</td>
<td></td>
</tr>
<tr>
<td>⁹⁹ᵐTc-MDP bone scan</td>
<td>100 %</td>
<td>54 %</td>
<td>79.2 %</td>
<td>100 %</td>
<td>83.3 %</td>
</tr>
<tr>
<td>(CI = 79.1–100 %)</td>
<td>(CI = 24.6–81.9 %)</td>
<td>(CI = 57.3–92.1 %)</td>
<td>(CI = 51.7–100 %)</td>
<td>(CI = 72.8–93.8 %)</td>
<td></td>
</tr>
</tbody>
</table>
Combined $^{18}$F-Fluoride and $^{18}$F-FDG PET/CT Scanning for Evaluation of Malignancy: Results of an International Multicenter Trial

Andrei Iagaru$^1$, Erik Mittra$^1$, Camila Mosci$^1$, David W. Dick$^1$, Mike Sathekge$^2$, Vineet Prakash$^3$, Victor Iyer$^3$, Paula Lapa$^4$, Jorge Isidoro$^4$, Joao M. de Lima$^4$, and Sanjiv Sam Gambhir$^5$

$^1$Stanford University Medical Center, Stanford, California; $^2$Pretoria University Hospital, Pretoria, South Africa; $^3$Aalborg University Hospital, Aalborg, Denmark; $^4$Serviço de Medicina Nuclear, Hospitais da Universidade de Coimbra, Coimbra, Portugal; and $^5$Departments of Radiology, Bioengineering, Materials Science, and Engineering, Molecular Imaging Program at Stanford (MIPS), Stanford University School of Medicine, Stanford, California

N = 62 patients
Design: prospective, FDG PET/CT and combined FDG/NaF PET/CT.
NaF FDG cocktail approach

62 patients
- 15 non malignant
- 47 malignant

16 comb. > FDG
29 comb. = FDG
2 soft tissue

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Gender</th>
<th>Cancer type</th>
<th>Imaging indication</th>
<th>Lesions detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>47</td>
<td>F</td>
<td>Breast</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>48</td>
<td>F</td>
<td>Breast</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>Breast</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>59</td>
<td>F</td>
<td>Breast</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>47</td>
<td>F</td>
<td>Breast</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>63</td>
<td>F</td>
<td>Breast</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>59</td>
<td>F</td>
<td>Breast</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>43</td>
<td>F</td>
<td>Breast</td>
<td>Initial treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>57</td>
<td>F</td>
<td>Breast</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>27</td>
<td>F</td>
<td>Lung</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>74</td>
<td>M</td>
<td>Prostate</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>Prostate</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>32</td>
<td>M</td>
<td>Rectal</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>32</td>
<td>M</td>
<td>Rectal</td>
<td>Subsequent treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>50</td>
<td>M</td>
<td>Unknown primary</td>
<td>Initial treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>Unknown primary</td>
<td>Initial treatment strategy</td>
<td>Combined &gt; 18F-FDG alone</td>
</tr>
<tr>
<td>59</td>
<td>F</td>
<td>Breast</td>
<td>Subsequent treatment strategy</td>
<td>18F-FDG alone &gt; Combined</td>
</tr>
<tr>
<td>70</td>
<td>M</td>
<td>Prostate</td>
<td>Subsequent treatment strategy</td>
<td>18F-FDG alone &gt; Combined</td>
</tr>
</tbody>
</table>
“Combined 18F NaF/18F FDG PET/CT shows promising results when compared with separate 18F NaF PET/CT and 18F FDG PET/CT for evaluation of cancer patients”

Ignaru et al 2012
Prospective comparison of combined $^{18}$F-FDG and $^{18}$F-NaF PET/CT vs. $^{18}$F-FDG PET/CT imaging for detection of malignancy

Frank I. Lin · Jyotsna E. Rao · Erik S. Mittra · Kavitha Nallapareddy · Alka Chengapa · David W. Dick · Saniiv Sam Gambhir · Andrei Iagaru
115 patients
  41 prostate
  39 breast
  22 sarcoma
  13 others*

Procedure
NaF PET/CT
FDG PET/CT
combined NaF+FDG PET/CT (simultaneous injections)

Three scans performed sequentially within 4 weeks of each other

*lung, bladder, CRC, cervix, kidney, NHL, larynx, paraganglioma
**NaF FDG cocktail approach**

**NaF PET/CT:**
67/115 osseous metastases

**FDG PET/CT:**
38/115 osseous metastases
48 extraosseous lesions on FDG

**Combined NaF+FDG PET/CT**
19 osseous metastases more extensive on combined scan than on FDG
29 osseous metastases seen on NaF and combined but not on FDG
NaF FDG cocktail approach

• Combined NaF and FDG PET scans increases sensitivity in detection of osseous lesions compared with FDG PET/CT alone
  Simultaneous injection or subsequent injection on same day with similar results

• Limitations
  No histologic confirmation for all detected lesions
  Additional lesions detected on the combined scans may not all represent metastases

Lin et al 2012
Methods for evaluation of the skeleton

**XR:**
bone destruction (30-60% mineral bone loss)

**CT:**
structural bone changes (non RECIST),
lytic:50-75% destroyed trabecular bone

**WB-MRI, DW-MRI:**
involvement of bone marrow

**SPECT**
99mTc HDP/MDP (BS)
White blood cell scintigraphy (WBC)
Bone marrow scintigraphy
123I, 123I mIBG, 111In somatostatin
Others…

**PET:**
NaF
FDG
Choline/acetate
Others….DOTA etc
Treasure your Bones!