NaF-PET
HDP-SPECT
FDG-PET
FCH-PET
Purpose of bone imaging

• 50% of cancer patients
• Prostate, breast, lung cancer

• Identify early bone involvement (staging)
• Determine the full extent of the skeletal disease
  – Risk of fracture
  – Risk of cord compression
• Treatment monitoring

Patients with bone metastasis only may survive for years
Hematogenous spread via venous system initiate as intramedullary lesions

90% in the distribution of the red active marrow: surrounding bone undergoes reactive changes

Osteoclastic / lytic
- rapid growth

Osteoblastic / sclerotic
- slower growth
- repair
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
Normal Bone Remodeling

Resorption
- **Osteoclasts** remove bone mineral and matrix, creating an erosion cavity (3-4 weeks)

Reversal
- Mononuclear cells prepare bone surface for new osteoblasts to begin building bone

Formation
- **Osteoblasts** synthesize a matrix to replace resorbed bone with new bone (3-4 months)

Resting
- A prolonged resting period follows until a new remodeling cycle begins

**Organic matrix (35%):**
- osteocytes, collagen, glycoprotein

**Inorganic matrix (65%):**
- osteoblasts, hydroxyapatite, Ca++, Mg++, K+, Na+, strontium, flourid, fosfor, clorid, disphosphonates
Methods

**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

**99mTcHDP SPECT**

**NaF PET:**
Osteoblast reaction to presence of tumor cells
Binding to calcium phosphate

**18F-FDG PET:**
deoxyglucose metabolism (upregulated in tumor and inflammatory cells)

**18F-/11C Choline PET:**
incorporated in phosphatidyl cholin (lectin)
in tumor cell membrane due to upregulation of choline kinase

**18F acetate/11C acetate PET:**
incorporated cytoplasmatic lipid synthesis
(phosphatidyl cholin and neutral lipids)
due to upregulation of fatty acid synthase
The pyrophosphate is a byproduct of cellular metabolism:

\[
\text{ATP} \rightarrow \text{AMP} + \text{pyrophosphate}
\]

Pyrophosphate

- a natural circulating inhibitor of mineralization in the blood and urine
- cannot enter the bones
  (alkaline phosphatase in the lining cells)
If a carbon is substituted for the oxygen a bisphosphonate is formed.

\[
\begin{align*}
\text{pyrophosphate} & \quad \text{disphosphonate} \\
\text{O} & \quad \text{O} \\
\text{P} & \quad \text{C} \\
\text{OH} & \quad \text{OH} \\
\end{align*}
\]

The bisphosphonates
• enter the bone
• attach very strongly to the bone mineral (calcium phosphate (hydroxyapatite))
Methylene diphosphonate (MDP)

Hydroxymethane Disphosphonate (HDP)
Intravenous administration
20%-60% cleared to the skeleton (Ca$^{++}$)
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
Imaging

- Imaging after 3-4 hours
- SPECT improves sensitivity to detect vertebral lesions 20-50% compared to planar imaging
Methods

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bone destruction (30-60% mineral bone loss)

CT:
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MRI:
involvement of bone marrow

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due to upregulation of fatty acid synthase
Stable fluoride is a natural trace element

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

- Intravenous administration
- Taken up by red blood cells (erythrocyte concentration is 50% of plasma concentration)
- Transport in red cells accounts for 30% of total flux in blood
- Single passage extraction of whole blood by bone is very rapid and close to 100%
- Renal clearance is dependent on urine flow rate, varying from 60-90% of GFR at high urine flow to 5% at low flow.
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
**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</td>
<td>Bladder</td>
<td>Bone surface</td>
</tr>
<tr>
<td>radiation</td>
<td></td>
<td></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</td>
<td>0.024</td>
<td>0.0057</td>
</tr>
</tbody>
</table>
Improved image quality, increased sensitivity, shorter examination time
Bone scan 99mTcHDP
24th April 2012

18F NaF PET (Gemini Dual)
31th May 2012

BS vs NaF
New gamma camera vs old PET-scanner
The decline in the use of $^{18}$F-NaF for skeletal scintigraphy did not reflect limitations of $^{18}$F-NaF as a tracer, but was the result of the difficulty in imaging 511-keV photons on a system optimized for the 140-keV photons of $^{99m}$Tc. The logistic challenges in the production and efficient delivery of a radioisotope with a physical half-life of 110 min.

Driven by the demand for $^{18}$F FDG technical and logistic limitations to the routine use of $^{18}$F-fluoride for bone imaging are no longer present. The increasing availability of PET systems renewed the interest in using $^{18}$F-NaF as a radiotracer for skeletal imaging.

Crime has dropped dramatically in several major cities, despite the recession.
Clinical use of 18F-NaF and BS in oncology

- Primary bone tumors
- Skeletal metastasis in patients with a range of primary tumors
  - Prostate
  - Breast
  - Lung
- Sclerotic and lytic lesions are visualised
Bone scan: Sclerotic vs lytic

Very sensitive to detect metastases with sclerotic changes (osteoblastic activity)

Less sensitive for predominately lytic bone lesions
Because of the increased resolution and tomographic capability of PET, it has been suggested that a fluoride bone scan is more sensitive than a bone scan to detect the minimal osteoblastic activity associated with lytic bone metastases.
18F NaF PET
Interpretation of NaF PET

**Difficult** to differentiate metastases from benign bone lesions. Cancer patients who are referred for a BS are usually **older**, and have a higher frequency of **degenerative and/or arthritic** bone disease. These benign bone processes can demonstrate the **same pattern** of fluoride uptake as metastases do, resulting in a higher chance of **false-positive** interpretation if evaluated by PET alone. **CT** is often helpfull.
Sclerotic, lytic & degenerative lesions

With courtesy of Marius
Green:
NaF positive sclerotic metastases
Yellow: NaF negative bone cyst
Blue: NaF positive spondylosis

Red: Ureter (physiologic excretion)
Interpretation of NaF PET
Interpretation of NaF PET
Interpretation of NaF PET
NaF-positive compression fracture
NaF-positive rib fracture
NaF-positive rib metastases
Conclusion

Improved sensitivity, specificity, and diagnostic accuracy of NaFPET or PET/CT over MDP/HDP bone scintigraphy have been consistently reported by numerous investigators in various cancers including prostate, breast, lung, and thyroid cancers.
Comparison of all studies with data on 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.
Methods

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

CT:
structural bone changes (non RECIST)

MRI:
involvement of bone marrow

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18F acetate/11C acetate PET:
incorporated cytoplasmatic lipid synthesis (phosphatidyl cholin and neutral lipids) due to upregulation of fatty acid synthase
FDG-PET and BS

The lesion was suspected by PET in January

The lesion was visible on CT in April

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.
Bone metastases

Diagnosis of bone metastases: a meta-analysis comparing $^{18}$FDG PET, CT, MRI and bone scintigraphy

Hui-Lin Yang · Tao Liu · Xi-Ming Wang · Yong Xu · Sheng-Ming Deng

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Abstract
Objective To perform a meta-analysis to compare $^{18}$FDG PET, CT, MRI and bone scintigraphy (BS) for the diagnosis of bone metastases.
Methods Databases including MEDLINE and EMBASE were searched for relevant original articles published from January 1995 to January 2010. Software was used to obtain pooled estimates of sensitivity, specificity and summary receiver operating characteristic curves (SROC).
Results 67 articles consisting of 145 studies fulfilled all inclusion criteria. On per-patient basis, the pooled sensitivity estimates for PET, CT, MRI and BS were 89.7%, 72.9%, 90.6% and 86.0% respectively. PET=MRI>BS>CT. (“=” indicates no significant difference, $P>0.05$; “>” indicated significantly higher, $P<0.05$). The pooled specificity estimates for PET, CT, MRI and BS were 96.8%, 94.8%, 95.4% and 81.4% respectively. PET=CT=MRI>BS. On per-lesion basis, the pooled sensitivity estimates for PET, CT, MRI and BS were 86.9%, 77.1%, 90.4% and 75.1% respectively. PET=MRI>BS>CT. The pooled specificity estimates for PET, CT, MRI and BS were 97.0%, 83.2%, 96.0% and 93.6% respectively. PET>MRI>BS>CT.
Conclusion PET and MRI were found to be comparable and both significantly more accurate than CT and BS for the diagnosis of bone metastases.

Keywords Bone metastases · PET · MRI · Bone scintigraphy · Meta-analysis

Introduction
Bone metastases are the commonest malignant bone lesion. Skeletal involvement occurs in 30%−70% of all cancer patients [1, 2]. Early detection of bone metastases has an
## Bone metastases

<table>
<thead>
<tr>
<th></th>
<th>FDG-PET</th>
<th>BS</th>
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</thead>
<tbody>
<tr>
<td><strong>Sensitivity %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>90</td>
<td>86</td>
</tr>
<tr>
<td>Lesion</td>
<td>87</td>
<td>75</td>
</tr>
<tr>
<td><strong>Specificity %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>97</td>
<td>81</td>
</tr>
<tr>
<td>Lesion</td>
<td>97</td>
<td>94</td>
</tr>
</tbody>
</table>

Reliable data on diagnostic accuracy in certain cancer types are of higher practical relevance.

Yang H et al. Diagnosis of bone metastases: a meta-analysis comparing 18F FDG PET, CT, MRI and bone scintigraphy Eur J Radiol 2011; 212604-17
Direct comparison between NaF-PET and FDG-PET has not been published.

Compared to BS NaF-PET is superior in lytic and blastic lesions.

FDG-PET is superior in lytic lesions and similar /inferior in sclerotic lesions.

FDG-PET has higher specificity than NaF-PET (degenerative lesions) even though both tracers are unspecific.
Methods

XR: bone destruction (30-60% mineral bone loss)
CT: structural bone changes (non RECIST)
MRI: involvement of bone marrow

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in tumor cell membrane due to upregulation of choline kinase

18F acetate/11C acetate PET:
incorporated cytoplasmatic lipid synthesis
(phosphatidyl cholin and neutral lipids)
due to upregulation of fatty acid synthase
• Bone scan is the most commonly used imaging modality to evaluate osseous metastases.

• Fluoride PET/CT is currently considered the most sensitive method to detect bone metastases in prostate cancer.

• 11C or 18F labeled acetate and choline have been reported to be superior (limited data)
Choline metabolism

\[ \text{HOCH}_2\text{CH}_2\text{N(CH}_3\text{)}_2 \]

\[ ^{11}\text{C}\text{Choline} \quad ^{11}\text{CH}_3 \]

Choline kinase phosphorylates the compounds resulting in the corresponding phosphorylcholin derivatives:

\[ \text{HOCH}_2\text{CH}_2\text{N(CH}_3\text{)}_2 \]

\[ ^{11}\text{C}\text{Choline} \quad ^{11}\text{CH}_3 \]

\[ \text{ATP} \quad \text{ADP} \]

\[ \text{Phosphatidylcholine} \]
Generalized bone metastases detected by FCH PET/CT (MIP-Image)
Prostate cancer: cholin & acetate

• Sensitivity, specificity
  NaF: 81%, 93%
  FCH 74% (ns), 99% (p=0.01)*

• Absence of tracer uptake in chronic degenerative lesions is a major advantage of FCH compared to NaF

Austrian study of 38 men compared 18F fluoride PET/CT scanning and 18F-FCH for the detection of bone metastases from prostate cancer
Prostate cancer: cholin & acetate

18F FCH negative and 18F fluoride PET–CT positive degenerative change in left pubis (white arrow).

Focal FCH uptake (grey arrow) in a malignant lesion in the prostate.

Concordant positive uptake (black arrow) in a malignant sclerotic lesion (left acetabulum) in 18F FCH and 18F fluoride PET–CT.
Prostate cancer: cholin & acetate

**FCH+**: Bone marrow metastases without bone reaction

**FCH-**: Heavily sclerotic lesions (antiandrogen treatment)

FCH positive malignant focus in the left pubis, turning FCH negative and sclerotic on subsequent scan (hormone therapy)
Metabolic and morphologic changes of bone metastases are dynamic processes, and combined imaging is best suited to capture the natural course of these changes to allow for management decisions and accurate assessment of treatment response.
Planar BS
SPECT
FDG-PET
NaF-PET
SPECT?
FCH-PET
FUTURE
PRESENT
PAST
Planar BS SPECT
Rūpintojėlis
Worrying Christ Statue