MOLECULAR IMAGING OF THE BONE: EMERGENCE OF F-18 FLUORIDE

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Mechanism of Bone Uptake of F-18 NaF

- Uptake proportional to local blood flow and osteoblastic activity
- Diffusion through capillaries into bone extracellular fluid
- Fluoride ion exchanges slowly with hydroxyl groups in hydroxyapatite crystal to form fluorapatite
- Preferential deposition at the surfaces of bone where remodelling and turnover is greatest.

F-18 NaF PET Bone Imaging

- F-18 NaF, first used (non coincidence PET) in the late 1960's/early 1970's with rectilinear scanners and high energy collimators.
- Resolution with rectilinear scanners not optimal and difficult to obtain F-18.
- F-18 now commercially available at a reasonable cost.
- High resolution PET-CT systems now available in most quality imaging centers.

1962 - 1973 Rise of the Sodium Fluoride Bone Scan

- Advances in instrumentation allows for "rapid" "efficient" imaging of the osseous system.
- Rectilinear scanners with two detector heads.
- Anger cameras with high energy collimation and shielding.
- Greater availability of Sodium Fluoride (rise of the cyclotrons).

Comparison of Fluorine-18 Bone Studies Obtained with Rectilinear Scanner and Scintillation Camera Equipped with High Energy Diverging-Hole Collimator

G. T. Krishnamurthy, M.B.B.S., M.S., Carol Walsh, M.D.
W. A. HUDSON, M.D., and W. W. SNALL, M.D.
Clinical Evaluation of Orally Administered Fluorine 18 for Bone Scanning
Alfred E. Jones, M.D.,, Nasser Ghued, M.D.,
George L. Danson M.S.P.H.,, and Fazil Nomin, Ph.D.
Radiology 167:131-131, April 1984

1971 - 1975
Fall of the Sodium Fluoride Bone Scan
Rise of the Tc-99m Phosphate compounds
- Clinical demonstration of Tc-99m phosphate applications in humans (Subramanian G, McAfee JG. 1971, Radiology 99, 192)
- Improved instrumentation allowed 30min whole body with high resolution
- Favorable dosimetry
- Cost effective

The clinical role of skeletal scanning
- [Images of skeletal scans]
Dose Consideration
MDT vs F-18 NaF

Radiation dose comparison

<table>
<thead>
<tr>
<th>Tc-99m MDP</th>
<th>Effective dose</th>
<th>Radiation dose (CT only)</th>
<th>Ratio of NaF/CT MDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaF-52 mCi</td>
<td>6.45 mrem</td>
<td>6.05 mrem</td>
<td>0.24</td>
</tr>
<tr>
<td>NaF-58 mCi</td>
<td>6.89 mrem</td>
<td>8.1 mrem</td>
<td>0.82</td>
</tr>
<tr>
<td>NaF-65 mCi</td>
<td>7.56 mrem</td>
<td>13.15 mrem</td>
<td>2.11</td>
</tr>
<tr>
<td>Tc-99m MDP</td>
<td>4.55 mrem</td>
<td>5.75 mrem</td>
<td>1</td>
</tr>
</tbody>
</table>

The above comparison does not include the dose from the CT component of the PET/CT study. This will vary based on how the CT is acquired as well as the type of equipment.

NaF or FDG to assess for bone mets

% of lesions

Type of metastasis
- Lung
- Breast
- Prostate
- Medulloblastoma
- Bronchial carcinoma

* Note: NaF/18F

Metastatic Disease
Improved sensitivity

Tc-99m MDP

F-18 NaF

Degenerative Disease
Improved sensitivity for all lesions
**Definition of Sensitivity**

- **True Positive (Tp)**
- **True Positive (Tp) + False Negative (Fn)**

Goal: Obtain high sensitivity without sacrificing specificity

**Definition of Specificity**

- **True Negative (Tn)**
- **True Negative (Tn) + False Positive (Fp)**

Goal: Obtain high specificity without sacrificing sensitivity (reduce Fp)

**Improved Specificity with PET-CT**

- CT gives anatomic localization of increased NaF when images are fused
- F-18 PET is highly sensitive in detecting metastatic as well as benign foci
- When CT is combined with NaF PET specificity for active PET foci is markedly improved

**The importance of PET-CT Fusion**

- Tc-99m-MDP and NaF PET are positive in many benign processes
- Fusion of CT and NaF images provide both anatomical and physiologic information which increases the accuracy of the combined PET-CT over CT or PET alone
- CT correlation and co-registration is essential for appropriate interpretation
Will NaF Bone Scans replace conventional Tc-99m-MDP?

- Improved resolution (superior for NaF compared to Tc-99m bone scans for detection of osteoblastic activity)
- Improved specificity due to CT component of PET/CT (PET-CT with high resolution CT now available)
- Eventually economics will prevail
  - Reimbursement issues
  - Equipment cost

Which tumors will benefit most from bone scans?
- Primarily, tumors which have significant osteoblastic activity
  - Prostate (mainly blastic)
  - Breast (mixed blastic and lytic)

| Most Common Tumors to Metastasize to Bone (% of bone met.
<table>
<thead>
<tr>
<th>Tumor</th>
<th>Appearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Blastic</td>
</tr>
<tr>
<td>Breast</td>
<td>Mixed</td>
</tr>
<tr>
<td>Lung</td>
<td>Profoundly Lytic</td>
</tr>
<tr>
<td>Renal Cell Ca</td>
<td>Profoundly Lytic</td>
</tr>
</tbody>
</table>

Optimum Use of Biomarkers for Detection of Osteoblastic Metastatic Disease

- Develop strategy for available biomarkers
  - Tc-99m-HMPAO (planar and SPECT)
  - NaF (PET/CT)
  - FDG (PET/CT)
- Consideration
  - Available instrumentation
  - Tumor type
  - Sensitivity, specificity, and accuracy
  - Economics

Guidelines for Performing Imaging Examinations

- Importance of establishing guidelines for bone scintigraphy
  - Reimbursement
  - Optimizing resources
  - Facilitate and speed decision-making in patient management

Guidelines for Performing Imaging Examinations

- Who formulates guidelines?
  - Professional societies (SNM, ACR, EANM...)
  - Government (CMS, state, counties...)
  - Other professional organizations (NCCN)
  - Payer/provider organizations (insurance companies, ACOs, others...)

PROSTATE CANCER
Prostate Cancer Imaging Strategy

- Osseous metastasis primarily blastic
- Highest sensitivity with NaF followed by Tc-99m-MDP
- PET-CT instrument of choice with NaF
  - Head to toe tomographic study in 20-30 mins
  - Tc-99m-MDP whole body planar plus SPECT of selected region when PET-CT or F-18 not available (SPECT-CT if available)
**Why NaF for Bone?**

- NaF PET may demonstrate numerous metastatic foci in asymptomatic patients with prostate cancer due to highly blastic process
- Head to toe scans are important since lower extremity lesions are weight bearing bones and subject to fracture
- Need high sensitivity study for early detection of bone metastasis as well as assessment of extent of disease

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**NaF vs FDG PET-CT**

- NaF PET-CT superior to FDG in cortical blastic metastatic disease (prostate, some breast and lung)
- FDG PET-CT superior to NaF in lytic and trabecular osseous metastatic disease
- In mixed tumors such as lung and breast, consider FDG-PET before NaF
- FDG best for staging (soft tissue information)
- FDG best for following response to therapy
- If FDG negative or equivocal do NaF PET-CT

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**NaF vs FDG Prostate CA**

65yo male with history of 8/10 Gleason Prostate CA.

The patient presents one year after initial treatment with elevated ALK, bone pain and elevated PSA.

Bone scan and FDG PET/CT ordered to restage the patient.
**FDG PET/CT vs Bone Scan in Aggressive Prostate cancer**

- Osseous lesions detected in 39 patients on bone scan and 32 on FDG PET/CT
- Many of the FDG PET/CT lesions became positive on bone scan in follow up
- FDG-PET scan positive in progressive and castrate resistant prostate cancer
- Number of lesions and SUV levels have prognostic value

Morales et al. Cancer Res 2010

**Prostate CA**

72yo male with history of prostate CA. Now with rising PSA

Restaging bone scan ordered

**MDP Bone Scan**

**F-18-PET**

**Breast Cancer Staging**

- Stage I: cancer has formed. Stage I is divided into stages IA and IB.
  - In stage IA, the tumor is 2 centimeters or smaller. Cancer has not spread outside the breast.
  - In stage IB, small clusters of breast cancer cells larger than 2 millimeters but not larger than 5 millimeters are found in the lymph nodes and either:
    - no tumor is found in the breast, or
    - the tumor is 2 centimeters or smaller.
**Breast Cancer Staging**

- **Stage IA**: The tumor is ≤2 cm and there are no lymph node metastases.
- **Stage IB**: The tumor is >2 cm but ≤5 cm and there are no lymph node metastases.
- **Stage IIA**: The tumor is >5 cm but ≤10 cm and there are no lymph node metastases.
- **Stage IIB**: The tumor is >10 cm but ≤20 cm and there are no lymph node metastases.
- **Stage IIIA**: The tumor is >20 cm and/or there are lymph node metastases.
- **Stage IIIB**: The tumor is any size and there are lung or bone metastases.
- **Stage IVA**: The tumor is any size and there is any distant metastasis.

**NCCN Guidelines Workup for Breast Cancer**

1. History and physical examination
2. Breast ultrasound
3. Semiquantitative breast ultrasound
4. Axillary ultrasound
5. Breast MRI
6. Additional studies may be ordered by the physician (e.g., PET/CT, bone scan, etc.)

**Prophylactic Chemotherapy**

- 

**FDG PET/CT**

- 

**NaF PET/CT**

- 

**Comparison of FDG with NaF**

- 

**Comparison NaF vs MDP**

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**Courtesty of Siemens**

**3/14/2014**
Case study

- 65yo female with a history of T3N2 breast cancer
- Elevated tumor markers and back pain
- FDG PET CT done for restaging
**Summary**

- Staging
  - Both NaF and FDG-PET may demonstrate osseous metastasis that may not be visualized with anatomical based imaging.
  - Predominantly osseous metastasis best seen with NaF while soft tissue or trabecular metastasis best seen with FDG.

**Breast Cancer Summary**

- NaF and FDG-PET/CT excellent for detection of osseous metastasis. Overall staging of subjects with breast cancer best with FDG PET/CT.
- When FDG-PET/CT demonstrates osseous metastasis, bone scan (NaF or MDP) may not be required. If the patient is symptomatic in regions not seen with FDG PET/CT.

**Summary**

- Response to therapy
  - FDG-PET allows early assessment of the effectiveness of systemic therapy.
  - Bone scan not a good indicator for early assessment of response to therapy due to healing process (may see flare response).

**Breast Cancer Summary**

- Subset of negative FDG PET/CT will be positive on F-18 (cortical blastic metastasis).
- FDG PET/CT better than NaF for monitoring therapeutic response.
LUNG CANCER
Both small cell and non small cell

Guidelines for NSCLC
National Cancer Comprehensive Network (NCCN)
Initial Evaluation
- Pathology review
- H&P (include performance status, weight loss)
- CT chest and upper abdomen, including adrenals
- CBC, platelets
- Chemistry profile
- Smoking cessation advice, counseling and pharmacotherapy

Guidelines for NSCLC
National Cancer Comprehensive Network (NCCN)
Pre-Treatment Evaluation
Stage IIA (T1–3, N2)
- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation
- PET/CT scan
- Brain MRI

Guidelines for NSCLC
National Cancer Comprehensive Network (NCCN)
Pre-Treatment Evaluation
Separate pulmonary nodule(s) (Stage IIB, IIIA)
- PFTs (if not previously done)
- Bronchoscopy
- Mediastinoscopy
- Brain MRI
- PET/CT scan

Guidelines for NSCLC
National Cancer Comprehensive Network (NCCN)
Pre-Treatment Evaluation
Stage IIB (peripheral T2a, N0)
Stage I (central T1b–T2a, N0)
Stage II (T1b–2ab, N1; T2b, N0)
Stage IIB (T3, N0)*
- PFTs (if not previously done)
- Bronchoscopy
- Mediastinoscopy and/or EBUS/EUS
- PET/CT scan
- Brain MRI (Stage III, Stage IIB [category 2B])

* T3, N0 related to size or satellites nodules.
* Testing is not listed in order of priority and is dependent upon clinical circumstances.
† Positive PET/CT scan findings need pathology or other radiologic confirmation.
Case Example

61yo male remote smoker
Presented with CP and abnormal CXR
Treated for pneumonia without resolution
CT documented right lower lobe mass
? Adenopathy
Scheduled for mediastinoscopy
Pre op PET for staging

Bone scans or FDG PET/CT


14 articles consisting of 34 studies

Future of F-18 Osseous Imaging

Continuous improvement in instrumentation
Extremely rapid whole body PET-CT (< 10min)
Extremely low dose PET-CT
Infection / inflammation imaging of the osseous system may give complimentary or superior information when used with / without MRI
PET-MRI
Reimbursement still a critical factor
### Summary

- NaF PET scans more sensitive than Tc-99-MDP planar and likely MDP SPECT (peer-reviewed articles lacking)
- NaF PET is more sensitive and specific than MDP SPECT-CT (literature lacking)
- NaF PET is more sensitive and specific than FDG-PET for bladder metastatic disease (prostate cancer)

### Summary

- NaF PET-CT highly recommended by NCCN for prostate and breast cancer
- NaF PET-CT excellent test when FDG-PET, CT and MRI are discordant with patient symptoms
- Economic considerations and evidence based medicine will eventually determine practice patterns, however, obstacles remain (esp for reimbursement)