Imaging Bone Metastases to Measure Response and Direct Therapy

Emphasis on PET Imaging

David A. Mankoff, MD, PhD
Division of Nuclear Medicine
Seattle Cancer Care Alliance
University of Washington

work supported by NIH Grants CA72064, CA124573, CA42045, AR059138, S10 RR17229
Bone Metastasis Imaging

- Review of normal bone physiology
  - Bone function and composition
  - Different imaging methods applied to bone
- Bone Metastases
  - Pathophysiology
  - PET applications to breast cancer
  - PET applications to prostate cancer
Bone Physiology

How Differing Imaging Methods Depict Different Facets Bone Physiology
Normal Bone Physiology

Bone Formation: Osteoblasts

- Corticosteroids
- Parathyroid hormone, prostaglandins, cytokines

Bone Resorption: Osteoclasts

- Parathyroid hormone, 1,25-dihydroxyvitamin D₃, T₄
- Corticosteroids, prostaglandin E₂

Roodman, NEJM 350:16, 2004
Normal Bone Architecture

Roodman, NEJM 350:16, 2004
Imaging Different Facets of Bone Structure and Physiology

- Bone Mineralization: Bone Scan, Fluoride PET
- Radiographic Density: X-Ray, CT
- Bone Mineral Density: DEXA
- Composition and Vascularity: MRI

Vascularity

Osteoblasts

Osteoclasts

New bone
Radiotracer Bone Imaging

- Images incorporation of components of mineralized bone
- Regional image of new bone formation
- Functional, not structural

- Ca$^{++}$
- F$^{-}$
- $^{99m}$Tc-MDP
- Phosphate
Imaging Bone Deposition: Bone Scan vs. Fluoride PET

**$^{18}\text{F}^-$**
- Inherently tomographic (PET)
- Quantitative

**$^{99m}\text{Tc}^-$ MDP**
- Planar or tomographic (SPECT)
- Quantitative analysis limited

Coronal | Sagittal | Anterior | Posterior
Fluoride PET Can Measure Kinetics
Measure Rate of Delivery (Flow) and Bone Formation

Dynamic Uptake Curves

Compartmental Model

$^{18}$F-Fluoride PET Kinetic Analysis

Metastases Flux, $Ki$ vs. Transport, $K1$

$Ki$ vs. $K1$ may reveal **osteoblastic** & **osteolytic** phenotypes

(Doot, SNM, 2008)
PET Imaging: FDG Uptake and Retention

Blood Cells

Glucose ↔ Glucose ↔ Glucose-6P → Glycolysis

FDG ↔ FDG ↔ FDG-6P ×

Glucose

Fluorodeoxyglucose (FDG)

F*
FDG and Fluoride PET: Normal Findings

FDG PET

- Normal bone not seen
- Relatively insensitive to mechanical pathology (fx, DJD)

Fluoride PET

- Normal bone visualized
- Sensitive to mechanical pathology

(arrows = sacral stress findings from recent childbirth)
GCSF Rx Alters FDG Distribution in Normal Bone Marrow

(Doot, J Nucl Med, 2007)
Bone Pathophysiology

Bone Metastases
Bone Metastases: Why So Common?

• “Soil and seed” hypothesis
  • Many tumor cells “like” bone - the seed
    • Tumors alter bone physiology to meet needs
    • Make factors that interact with bone - e.g, PTHrp
    • May be genetically pre-disposed to bony site
  • Bone is a good environment for tumors
    • Rich vasculature
    • Bone elicits tumor growth factor in response to factors from tumor cells
Bone Architecture: Metastasis

Normal Bone

Lytic Metastasis

Blastic Metastasis

Roodman, NEJM 350:16, 2004
Mechanisms of Bone Metastasis: Lytic

Kakonen, Cancer 97 (Suppl 3): 834, 2003
Mechanism of Bone Metastasis: Blastic

Mohammad, Clinical Orthopaedics and Related Research 415S, 2003
Bone Metastases: Lytic or Blastic?

- Primarily lytic
  - Most common physiology
  - Lung, myeloma, thyroid, renal
  - “Purely” lytic: myeloma, thyroid
- Primarily blastic
  - Prostate cancer
- Mixed
  - Breast cancer
  - Approximately 80% lytic, 20% blastic
Bone Metastases: Imaging Modalities

Detecting Bone Metastases: Bone Scan

- Images increased bone formation due to tumor
  - Blastic mets: excess bone formation
  - Lytic mets: blastic reaction to bone lysis
- “Purely lytic” mets not well seen - myeloma, thyroid
Detecting Bone Metastases: Bone Scan versus Fluoride PET

(Shirrmeister, J Ncl Med 42:1800, 2001)

• Fluoride PET and MDP SPECT more sensitive than planar bone scan
• But affected management in < 10% of cases
FDG PET to Detect Bony Metastatic Disease: Caution!

- Cook et al., J Clin Oncol 16: 3375, 1998
- 23 patients with confirmed bone metastases
- FDG PET “spot” imaging
- Compared to [Tc-99m] MDP scintigraphy
- Results (number of lesions seen):
  - Sclerotic lesions: MDP > FDG PET
  - Lytic lesions: FDG PET > MDP
- Conclusions: FDG PET and MDP scintigraphy are complementary
FDG versus Fluoride PET
Lytic versus Sclerotic Metastases

FDG

Lytic

Sclerotic

Mixed

Fluoride
PET/CT for Breast Cancer Metastases
May Detect Both Lytic and Sclerotic Mets,
…but more Studies Needed

Mixed lytic/sclerotic disease depicted by FDG PET/CT
Imaging Bone Metastases by PET

Breast Cancer: Monitoring Response
Bone Metastasis Response Evaluation by Standard Imaging is Complex!

FDG PET to Monitor Breast Cancer Bone Metastasis Response

- **Bone scan and MRI:**
  - Great for detecting bone metastases
  - Not good for monitoring therapy
- **Hypothesis:**
  Quantitative FDG PET provides a direct measure of bone metastases activity and can monitor response of breast cancer bone metastases.
Bone Metastasis Monitoring by Bone Scan: Response?

Pre-Rx

Post-Rx
Bone Scan “Flare” With Treatment Response Leads to Transient Worsening of Bone Scan

(Schneider, J Nucl Med 35: 1748, 1994)
Bone Lesions Become More Sclerotic After Treatment
Lytic Lesions Not Seen Previously Can Become Visible

Pre-Rx

Post-Rx

(Wade, AJR 186: 1783, 2006)
FDG PET Measures Breast Cancer Bone Metastasis Response
Change in FDG SUV Correlates with Response and Change in Tumor Markers

\[ \tau = 0.40 \ (p < 0.001) \]

(Stafford, Acad Radiol, 2002)

\[ \tau = 0.45 \ (p < 0.002) \]

vs CA 27.29
FDG Uptake Predicts Outcome of Bone-Dominant Breast Cancer
(Specht, Br Ca Res Treat, 2007)

Time to Progression

% Decline in FDG SUV

> 41%  p = 0.0054
< 41%

Time to Skeletal-Related Event

Initial SUV

> 5.1  p = 0.028
< 5.1

FDG Uptake Predicts Outcome of Bone-Dominant Breast Cancer
(Specht, Br Ca Res Treat, 2007)
FDG PET/CT to Measure Bone Metastasis Response
(Du, J Clin Oncol 25: 3340, 2007)

- Look for both structural and metabolic changes
- Both predicted TTP
FDG PET/CT to Measure Bone Metastasis Response
Tateishi, Radiology 247: 189, 2008

- Monitor both structural and metabolic changes
- Both predicted TTP
Combination of FDG and Fluoride PET To Monitor Bone Metastasis Response

(Gralow, SABCS, 2005)

Lytic Metastases

FDG

Pre- Post-

F-

Pre- Post-

Blastic Metastases

Response seen best by FDG

Progression seen best by F-
Imaging Bone Metastases by PET

Prostate Cancer
FDG in Prostate Cancer
Poor Visualization of Blastic Metastases
Prostate Cancer Bone Metastases
Visualization via Aberrant Lipid Synthesis

$^{18}$F-fluorcholine (FCH)

FDG PET  FCH PET

(courtesy Edward Coleman, Duke University)

$^{11}$C-acetate

FDG PET  Acetate PET

(courtesy Evan Yu, UW/SCCA)
Prostate Cancer Bone Metastasis Response
Serial Assay of Lipid Synthesis Using Acetate PET


Pre-Treatment
PSA 432

Post-Treatment
PSA < 1

Bone Scan

11C-Acetate PET
Prostate Metastasis Response by Serial Fluoride PET with Kinetic Analysis
Measure Effects of Targeted Therapy

Compartmental Model

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Bone tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unbound bone pool</td>
</tr>
<tr>
<td>[F]</td>
<td>k₂</td>
</tr>
</tbody>
</table>

Effect on Blood Flow & Vasculature
Effect on Bone Formation

(Yu, ACRIN and DOD Concept)
PET Imaging of Bone: Summary

- Bone imaging matched to physiology of normal bone and bone metastases

- Bone metastases
  - Detection
    - Fluoride, bone scan good for blastic mets
    - FDG PET good for lytic mets
    - Choline, acetate for blastic mets, especially prostate?
  - Response
    - Standard imaging problematic
    - FDG PET very promising for all but purely blastic lesions
    - Fluoride PET may be helpful for blastic lesions and bony response to treatment - breast and prostate
    - Choline, acetate for prostate cancer?
- PET/CT helpful for both applications