$^{18}$F NaF PET/CT in the Evaluation of Skeletal Malignancy

Andrei Iagaru, MD

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Introduction

- $^{18}$F NaF PET/CT in Primary Bone Cancers
- $^{18}$F NaF PET/CT in Bone Metastases
- Future Directions
$^{99m}Tc$ MDP
DJD

Single metastasis

Multiple metastases
- $^{18}$F NaF has desirable characteristics (rapid blood clearance and bone uptake) for high quality functional imaging of the skeleton.

- $^{18}$F NaF PET/CT is able to detect osseous lesions with improved results when compared to $^{99m}$Tc MDP planar and SPECT bone scintigraphy.

- $^{18}$F NaF PET/CT allows for shorter imaging time, thus improving patients’ convenience and benefiting the overall workflow of the imaging facility.
Introduction

18F NaF PET/CT in Primary Bone Cancers

18F NaF PET/CT in Bone Metastases

Future Directions
The utility of $^{18}$F NaF PET and PET/CT in the management of osteosarcoma has been evaluated in preliminary reports, usually with small number of participants included.

Quantitative $^{18}$F NaF PET/CT may also be useful for monitoring therapy response, including the response to neoadjuvant chemotherapy before surgical resection.

$^{18}$F NaF PET/CT may allow the detection of viable, non-necrotic, and, thus, chemotherapy-resistant parts of the tumor, possibly predicting prognosis.
22 year-old man with Ewing’s sarcoma
60 year-old man with Ewing’s sarcoma
41 year-old man with osteosarcoma
60 year-old woman with multiple myeloma


- $^{18}$F NaF images are useful in mapping patterns of bone metabolism, as well as identifying extraosseous site of bone formation or calcification.

- A patient with polyostotic fibrous dysplasia, metastatic osteogenic sarcoma, and a breast mass presented with pulmonary nodules.

- $^{18}$F NaF PET imaging was useful in confirming the nature of the pulmonary nodules.
- Introduction
- $^{18}$F NaF PET/CT in Primary Bone Cancers
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- Future Directions
Qualitative assessment of conventional bone scintigraphy with $^{99m}$Tc MDP is an insensitive method for monitoring the treatment response of bone metastases.

$^{18}$F-fluoride positron emission tomography (PET) might serve as a suitable alternative biomarker of the treatment response.

Semi-quantitative $^{18}$F-fluoride PET is more accurate than the qualitative comparison of scans and correlates with the PSA response and ALP activity.
Qualitative response assessment. MIP images at 0 and 12 weeks in two subjects, subject A and subject B, showing no significant qualitative change.
Mean SUVmax, PSA and ALP changes. Mean SUVmax, PSA and ALP changes at 6 and 12 weeks as a percentage of baseline levels in the five subjects (A to E).
Prospective Evaluation of the Clinical Value of Planar Bone Scans, SPECT, and $^{18}$F-Labeled NaF PET in Newly Diagnosed Lung Cancer

*The Journal of Nuclear Medicine* • Vol. 42 • No. 12 • December 2001

Holger Schirrmeister, Gerhard Glatting, Jürgen Hetzel, Karin Nüssle, Coskun Arslanemir, Andreas K. Buck, Kerstin Dziuk, Andreas Gabelmann, Sven N. Reske, and Martin Hetzel

The Detection of Bone Metastases in Patients with High-Risk Prostate Cancer: $^{99m}$Tc-MDP Planar Bone Scintigraphy, Single- and Multi-Field-of-View SPECT, $^{18}$F-Fluoride PET, and $^{18}$F-Fluoride PET/CT

*The Journal of Nuclear Medicine* • Vol. 47 • No. 2 • February 2006

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$^{2,4}$
Ø 52 patients with proven malignancy, referred for evaluation of skeletal metastases

Ø 37 men and 15 women, 19 - 84 year-old (average: 55.6 ± 15.9)

Ø 19 sarcoma, 18 prostate cancer, 6 breast cancer, 2 colon cancer, 1 bladder cancer, 1 lung cancer, 1 malignant paraganglioma, 1 lymphoma, 1 gastrointestinal stromal tumor, 1 renal cancer and 1 salivary gland cancer

Ø $^{99m}$Tc MDP bone scintigraphy, $^{18}$F NaF PET/CT and $^{18}$F FDG PET/CT were subsequently performed within 1 month
61 year-old woman with metastatic breast cancer

\( ^{99m} \text{Tc MDP} \quad ^{18} \text{F FDG} \quad ^{18} \text{F NaF} \)
61 year-old woman with metastatic breast cancer
73-year-old man with metastatic prostate cancer
73-year-old man with metastatic prostate cancer

\[ ^{18} \text{F FDG PET/CT} \quad ^{18} \text{F NaF PET/CT} \]
<table>
<thead>
<tr>
<th></th>
<th>$^{99m}$Tc MDP bone scan</th>
<th>$^{18}$F NaF PET/CT</th>
<th>$^{18}$F FDG PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal lesions</td>
<td>22/52</td>
<td>24/52</td>
<td>16/52</td>
</tr>
<tr>
<td>Other lesions</td>
<td>N/A</td>
<td>N/A</td>
<td>28/52</td>
</tr>
</tbody>
</table>

- The image quality and evaluation of extent of disease was superior by $^{18}$F NaF PET/CT over $^{99m}$Tc MDP scintigraphy in all 22 patients with skeletal lesions on both scans and over $^{18}$F FDG PET/CT in 11/16 patients with skeletal metastases on $^{18}$F FDG PET/CT.

- In 2 patients (one with sarcoma and another with prostate cancer), the $^{18}$F NaF PET/CT showed skeletal metastases not seen on either of the other 2 scans.

- Extra-skeletal metastases were identified by $^{18}$F FDG PET/CT in 28/52 participants.
Diagnostic effectiveness:

<table>
<thead>
<tr>
<th></th>
<th>Bone scan</th>
<th>NaF PET/CT</th>
<th>FDG PET/CT</th>
<th>FDG PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>87.5</td>
<td>95.8</td>
<td>66.7</td>
<td>92.9</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>75.7–93.0</td>
<td>85.2–99.2</td>
<td>54.7–70.1</td>
<td>83.1–97.2</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>92.9</td>
<td>92.9</td>
<td>96.4</td>
<td>92.9</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>82.7–97.6</td>
<td>83.8–95.7</td>
<td>86.2–99.4</td>
<td>91.7</td>
</tr>
<tr>
<td><strong>PPV</strong></td>
<td>91.3</td>
<td>92.0</td>
<td>94.1</td>
<td>80.3–96.7</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>79.0–97.1</td>
<td>81.8–95.2</td>
<td>77.3–98.9</td>
<td>83.1–97.2</td>
</tr>
<tr>
<td><strong>NPV</strong></td>
<td>89.7</td>
<td>96.3</td>
<td>77.1</td>
<td>91.7</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>79.9–94.2</td>
<td>86.9–99.3</td>
<td>69.0–79.5</td>
<td>80.3–96.7</td>
</tr>
<tr>
<td><strong>Accuracy</strong></td>
<td>90.4</td>
<td>94.2</td>
<td>82.7</td>
<td>92.3</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>79.5–95.5</td>
<td>84.4–97.3</td>
<td>71.7–85.8</td>
<td>81.8–97.0</td>
</tr>
</tbody>
</table>

*CI confidence interval, PPV positive predictive value, NPV negative predictive value*
10 participants (5 men, 5 women, 47-81 year-old) diagnosed with cancer and known osseous metastases

The diagnoses included breast cancer (5 participants), prostate cancer (3 participants), salivary gland cancer (1 participant) and renal cancer (1 participant)

$^{18}$F NaF PET/CT, $^{18}$F FDG PET/CT and WBMRI were performed within 1 month for each participant
The image quality and evaluation of extent of disease was superior by $^{18}$F NaF PET/CT compared to $^{99m}$Tc-MDP scintigraphy in all patients with skeletal lesions and compared to $^{18}$F FDG PET/CT in 3 of the patients with skeletal metastases.

$^{18}$F NaF PET/CT showed osseous metastases where $^{18}$F FDG PET/CT was negative in another 3 participants.

Extra-skeletal metastases were identified by $^{18}$F FDG PET/CT in 6 participants.

WBMRI with the combination of IDEAL, STIR and DWI pulse sequences showed fewer lesions than $^{18}$F NaF PET/CT in 5 patients, same number of lesions in 2 patients and more lesions in 1 patient.

When compared to $^{18}$F FDG, WBMRI showed fewer lesions in 3 patients and the same amount of lesions in 6 patients.
73 year-old man with prostate cancer
65 year-old man with prostate cancer
67 year-old man with urothelial cancer
65 year-old man with RCC
58 year-old man with prostate cancer
72 year-old woman with breast cancer
Introduction

18F NaF PET/CT in Primary Bone Cancers

18F NaF PET/CT in Bone Metastases

Future Directions
Combined $^{18}$F-Fluoride and $^{18}$F-FDG PET/CT Scanning for Evaluation of Malignancy: Results of an International Multicenter Trial


Andrei Iagaru¹, Erik Mitra¹, Camila Mosci¹, David W. Dick¹, Mike Sathekge², Vineet Prakash³, Victor Iyer³, Paula Lapa⁴, Jorge Isidoro⁴, Joao M. de Lima⁴, and Sanjiv Sam Gambhir⁵

- 115 patients with proven malignancy who had separate $^{18}$F NaF PET/CT, $^{18}$F FDG PET/CT and a combined $^{18}$F NaF/$^{18}$F FDG PET/CT scans for evaluation of malignancy (total of 3 scans each)
- 63 men and 52 women, 19-84 year-old (average: 58.5 ± 14.3)
- Tumor type: prostate cancer (41 participants), breast cancer (39 participants), sarcoma (22 participants), and other cancers (13 participants)
- The interval between the first and third scan ranged 3-28 days (average: 6.7±4.9 days)
- A direct comparison for each detected lesion was performed among the 3 scans
74 year-old man with metastatic prostate cancer.
45 year-old woman with metastatic breast cancer
38 year-old woman with metastatic breast cancer
18F NaF & 18F FDG PET/CT

68-year-old man with metastatic colon cancer
75-year-old man with metastatic prostate cancer
Primary: breast (Denmark)
<table>
<thead>
<tr>
<th>Skeletal lesions</th>
<th>$^{18}$F FDG PET/CT</th>
<th>$^{18}$F NaF PET/CT</th>
<th>$^{18}$F NaF &amp; $^{18}$F FDG PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>38/115</td>
<td>67/115</td>
<td>67*/115</td>
<td></td>
</tr>
</tbody>
</table>

- $^{18}$F NaF PET/CT and $^{18}$F FDG PET/CT scans identified malignant lesions in 82/115 enrolled patients (71.3%)
- 19 participants: $^{18}$F NaF > $^{18}$F FDG (osseous metastases)
- 29 patients: $^{18}$F NaF positive, $^{18}$F FDG negative (osseous metastases)
- 18 participants: $^{18}$F NaF = $^{18}$F FDG (osseous metastases)
- 1 patient: $^{18}$F FDG positive, $^{18}$FNaFG negative (osseous metastases)
- 48 participants had no osseous metastases identified on the $^{18}$F NaF PET/CT or the $^{18}$F FDG PET/CT scans

*2 skull lesions missed
$
\begin{array}{|c|c|c|c|}
\hline
\text{Other lesions} & 18^F \text{FDG PET/CT} & 18^F \text{NaF PET/CT} & 18^F \text{NaF} \& 18^F \text{FDG PET/CT} \\
\hline
\text{48/115} & \text{N/A} & \text{48*/115} \\
\hline
\end{array}
$

- $18^F$ FDG PET/CT detected lesions outside the skeleton in 48/115 participants (42.2%)
- The most common extra skeletal sites of metastases were lymph nodes (28/115 patients), lungs (14/115 patients) and the liver (8/115 patients)
- The combined $18^F$ NaF/$18^F$ FDG PET/CT scans missed three $18^F$ FDG-avid lung nodules in 2 patients and two $18^F$ NaF-avid skull lesions in another 2 patients. These 4 patients had other sites of metastatic disease in addition to the ones not clearly identified on the combined PET/CT.

**Subcentimeter lung nodules missed**
## Diagnostic effectiveness:

<table>
<thead>
<tr>
<th></th>
<th>CT only</th>
<th>PET/CT</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FDG</td>
<td>NaF</td>
<td>NaF/FDG</td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>51.9</td>
<td>51.9</td>
<td>92.6</td>
<td>96.3</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>31.9-71.3</td>
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<td>75.7-99.1</td>
<td>81.0-99.9</td>
<td></td>
</tr>
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<td>96.9</td>
<td>90.6</td>
<td>84.4</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>56.6-88.5</td>
<td>83.8-99.9</td>
<td>75.0-98.0</td>
<td>67.2-94.7</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>63.6</td>
<td>93.3</td>
<td>89.3</td>
<td>83.9</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>40.7-82.8</td>
<td>68.1-99.8</td>
<td>71.8-97.7</td>
<td>66.3-94.5</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
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<td>70.5</td>
<td>93.5</td>
<td>96.4</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>47.5-79.8</td>
<td>54.8-83.2</td>
<td>78.6-99.2</td>
<td>81.7-99.9</td>
<td></td>
</tr>
</tbody>
</table>
There are approximately 2 million $^{99m}$Tc MDP bone scans performed for detection of cancer annually in the US and approximately 1 million $^{18}$F FDG PET/CT scans performed in the same population. This can potentially amount to a total of approximately $130$ million saved annually in reimbursement.

<table>
<thead>
<tr>
<th></th>
<th>$^{99m}$Tc MDP bone scan</th>
<th>$^{18}$F FDG PET/CT</th>
<th>$^{18}$F NaF/$^{18}$F FDG PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical fee:</td>
<td>$275$</td>
<td>$1,421$</td>
<td>$1,421$</td>
</tr>
<tr>
<td>Professional fee:</td>
<td>$48$</td>
<td>$140$</td>
<td>$140$ ($280$)</td>
</tr>
<tr>
<td>$^{99m}$Tc MDP:</td>
<td>$100$</td>
<td>$250$</td>
<td>$250$</td>
</tr>
<tr>
<td>Total:</td>
<td>$423$</td>
<td>$1811$</td>
<td>$1,961$ ($2,101$)</td>
</tr>
</tbody>
</table>

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$^{99m}$Tc MDP: $100$

$^{18}$F FDG: $250$

$^{18}$F NaF: $150$

Total: $2,234$

Total: $1,961$ ($2,101$)
# Radiation Dosimetry

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Radiation Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>¹⁹⁹⁰Tc MDP bone scan</td>
<td>420 mRem</td>
</tr>
<tr>
<td>¹⁸F FDG PET/CT</td>
<td>1650 mRem*</td>
</tr>
<tr>
<td>¹⁸F NaF &amp; ¹⁸F FDG PET/CT</td>
<td>1650 mRem**</td>
</tr>
<tr>
<td></td>
<td>500 mRem**</td>
</tr>
<tr>
<td></td>
<td>1000 mRem**</td>
</tr>
</tbody>
</table>

* 110 mRem/mCi from ¹⁸F FDG and 1000 mRem from the low-dose CT

** 110 mRem/mCi from ¹⁸F FDG, 100 mRem/mCi from ¹⁸F NaF and 1000 mRem from the low-dose CT
The uptake mechanism of $^{18}$F NaF resembles that of $^{99m}$Tc-MDP, with better pharmacokinetic characteristics including faster blood clearance and 2-fold higher uptake in bone.

Uptake of $^{18}$F NaF reflects blood flow and bone remodeling.

The use of novel hybrid PET/CT systems has significantly improved the specificity of $^{18}$F NaF imaging, because the CT component of the study allows morphologic characterization of the functional lesion and more accurate differentiation between benign lesions and metastases.
Concerning bone scintigraphy with $^{18}$F NaF, the following statement is correct:

a) $^{18}$F NaF is less protein bound in the blood, therefore allowing shorter time from injection to imaging when compared to $^{99m}$Tc MDP

b) $^{18}$F NaF is the only FDA-approved radiopharmaceutical for skeletal imaging

c) $^{18}$F NaF PET/CT imaging requires special patient preparation

d) $^{18}$F NaF is most useful for evaluation of lytic skeletal lesions
Published results suggest the most appropriate use of $^{18}$F NaF PET/CT is in the following clinical scenarios:

a) To differentiate between benign and malignant bone lesions
b) To evaluate for skeletal metastases when results of other imaging studies are equivocal
c) To evaluate for pulmonary metastases
d) To measure tumor hypoxia