PET Imaging in the Clinic: Predictive and intermediate endpoint biomarkers

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Conflict of Interest: Founder: Sofie Biosciences

PET/CT is the best modality for initial and subsequent management decisions in cancer

>2000 scanners installed in the US;
>2 Mil studies in 2012
Reasonable cost ($1-3 Mil)
Established business model
Cost-effectiveness shown for many cancers
Impact on Management documented (pioneering NOPR work)
Impact on outcome shown in some cancers (MUNICON, PLUS, etc)
6500 publications under PET/CT
17545 publications under FDG
18516 publications under PET cancer

PET/CT with 10-15% higher accuracy than PET or CT alone
One stop shop frequently requires intravenous contrast

CT is indispensable for the planning of all interventions (surgery, biopsy, radiation, etc.; RECIST still standard of care)

IV contrast-enhanced FDG PET/CT is superior to contrast-enhanced CT alone and to unenhanced FDG PET/CT

Use of IV contrast material increases lesion detectability (important in FDG negative lesions) iv) Cantwell et al. J Comput Assist Tomogr 2008; 34: 738-744 (metastatic liver lesions)

Multiphase contrast protocols are feasible

Oral contrast agents can aid in the evaluation of the GI tract

High attenuation values associated with high-density IV contrast cause attenuation-correction artifacts that are easily recognized

Multiphase contrast protocols

>85% of all PET/CT studies performed with iv contrast at UCLA
Multi-phase contrast in pancreas and liver

Aschoff et al; Eur J Nucl Med Mol Imaging 2012
The Strength of PET: Imaging the Hallmarks of Cancer; In other words, phenotyping

2000 PET probes and counting..
PET biomarker Definition

**Diagnostic/Phenotypic/Prognostic Biomarkers**
- Is the disease present?
- What is the phenotype?
- What is the prognosis?

**Predictive Biomarkers**
- Is the therapeutic target expressed?
- Will the drug work?
- 
  - $^{68}$Ga-DOTATATE; $^{18}$F-FES; $^{18}$F-FAC

**Interm. endpoint Biomarkers**
- Does the drug work?
  - $^{18}$F-FDG; $^{18}$F-AA; $^{18}$F-FLT

**PD/PK Biomarkers**
- How is the drug distributed?
- Is the target inhibited?

---

> 2000 PET probe have been synthesized, however 99.6% of clinical studies use one probe. Why is it so difficult?

- Poor rationale
- Limited needs assessments
- Validation
- Proof of clinical value

Reference book for PET pharmaceuticals 2004, Cydronics and Radiopharmaceuticals Center, Tokyo University

Ren lwata
What is the required evidence for “new” imaging probes?

<table>
<thead>
<tr>
<th>Category</th>
<th>Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feasibility</td>
<td>Easy to synthesize? Easy to distribute?</td>
</tr>
<tr>
<td>Assay</td>
<td>Does it measure what it is supposed to measure?</td>
</tr>
<tr>
<td>Accuracy</td>
<td>better than alternative; same, but at lower cost</td>
</tr>
<tr>
<td>Diagnostic value</td>
<td>How does test compare to other tests?</td>
</tr>
<tr>
<td>Therapeutic value</td>
<td>Does the test improve therapy?</td>
</tr>
<tr>
<td>Patient and societal value</td>
<td>Does the test improve patient outcome at reasonable cost (many outcome parameters should be considered)</td>
</tr>
</tbody>
</table>

Adapted from Jager et al; JNM 2001

Evidence Based Use of $^{18}$F-FDG PET/CT

- How is evidence for diagnostic tests generated?
- Biological evidence: Increased glycolysis is a hallmark of cancer and changes in FDG uptake are a sensitive marker of treatment response
- Cost of cancer imaging
How is evidence generated?

*Schueneman et al; APC club 2008:* “If a test fails to improve patient-important outcomes, there is no reason to use it, whatever its accuracy.”

| **Accuracy studies** | **Ungated RCT (¹⁸F-NaF trial)** |
| Test 1 vs. Test 2; gold standard biopsy, imaging follow up etc. | Comparison of 2 management strategies; one uses new test; the other one standard test |
| **Gated RCT** | Outcome: OS, quality of life, PFS |
| All pts undergo both tests; Randomization restricted to pts in whom test results would lead to different management decisions |

| **Decision modeling** | **Management decision studies** |
| Data based on literature | National Oncology PET Registry (NOPR) |
| Meta-analysis, expert opinions, etc. |
| Test performance rated by HTA groups, regulatory agencies, etc |

### Question Quality Assessment of Diagnostic Accuracy Studies (QUADAS) (14 questions)

<table>
<thead>
<tr>
<th>Question</th>
<th>Did patients receive the same reference standard regardless of the index test result?</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)?</td>
</tr>
<tr>
<td>7</td>
<td>Were index test results interpreted without knowledge of results of reference standard?</td>
</tr>
<tr>
<td>10</td>
<td>Were reference standard results interpreted without knowledge of results of index test?</td>
</tr>
<tr>
<td>11</td>
<td>Reference standard: Biopsy</td>
</tr>
</tbody>
</table>

**Question 6:** Did patients receive same reference standard regardless of the index test result?  
Sensitivity overestimated if biopsy only performed in positive scans

**Question 10:** Were index test results interpreted without knowledge of reference standard?  
Differentiation of SPNs is biased when PET reader knows results of histopathology
These questions may NOT make sense. (see Weber et al; JNM 2011;52 Suppl 2)

Were reference standard results interpreted without knowledge of results of index test? Histologic verification not possible unless a lesion has been identified by imaging.

Were reference standard results interpreted without knowledge of results of index test? Imaging used as follow up confirmation: Thus index test used as reference test.

Thus, it is impossible to design a study for detection of distant metastases by an imaging modality without violating 6/14 requirements made by QUADAS. Same true for all other imaging modalities.

Study Design to determine impact on outcome in pts with Glioblastoma

Pts with suspected recurrence by MRI

\[ \text{PET probe} \times \text{No PET (conventional imaging)} \]

\[ \text{x years} \]

\[ \pm \text{Management Changes} \]

Overall, PF Survival  Overall, PF Survival

Creating evidence for drug effectiveness is fairly straightforward.

This is not the case for diagnostic tests.

What if diagnostic tests are “better” than available therapeutics?

Herrmann et al; in progress
Evidence for FDG PET/CT imaging derived from Biology

Warburg effect: Cancer cells avidly take up and metabolize glucose to lactate even in the presence of oxygen

Nonproliferating cells
Proliferating cells
GLUCOSE

GLUTAMINE

Evidence for FDG PET/CT imaging derived from Biology

Vander Heiden; Cold Spring Harb Symp Quant Biol 2011

Deriving an “FDG uptake” metabolic gene expression signature

A Determine FDG uptake in cancer cell lines and primary human tumors
B Collect genome-wide RNA expression data
C Identify metabolic pathways (KEGG database) that are differentially enriched in FDG-high samples
D Discover relationship of FDG signature to other gene expression signatures (i.e., double negatives, housekeeping of human cancers, signaling signatures)
E DNA copy number alterations

Genome wide transcriptomal analysis


In vitro FDG uptake

N=18

Patient samples

N=1

Predictive of FDG uptake in breast cancer cell lines

©2011 by American Association for Cancer Research
52 patients with thymic epithelial tumors imaged with $^{18}$F-FDG

FDG-PET as a diagnostic/phenotypic biomarker in STS

FDG-PET as a diagnostic/phenotypic biomarker in STS
Reductions in tumor glucose use are an indicator of response to targeted therapy

Su et al; Clin Cancer Res 2006

Translation: Changes in tumor FDG uptake after Gefitinib treatment

Su et al; Clin Cancer Res 2006

Benz et al; J Nucl Med 2011
Reductions in tumor glucose use are an indicator of response to cytotoxic therapy

**Gene expression**

<table>
<thead>
<tr>
<th>Drug</th>
<th>0 hrs</th>
<th>24 hrs</th>
<th>48 hrs</th>
<th>72 hrs</th>
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<tbody>
<tr>
<td>etoposide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vincristine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-2 withdrawal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glut-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glut-3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MK-7</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>PFK-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18S rRNA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Protein expression**

<table>
<thead>
<tr>
<th>Drug</th>
<th>4 hrs</th>
<th>24 hrs</th>
<th>48 hrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>etoposide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>vincristine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-2 withdrawal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glut-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glut-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-actin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Glycolytic rate**

Relative glycolytic rate

- Capsules
- Etoposide
- Vincristine
- E, 3-Wt

**Translation:** Changes in tumor FDG uptake predict **histopathological response**

**Soft tissue sarcoma**

- Evilevitch/Benz; Clin Cancer Res 2008, 2009

**Breast CA**

- Schelling M et al. JCO 2000;18:1689-1695

- Rousseau C et al. JCO 2006;24:5366-5372
Early changes in Glucose metabolic activity predict long term survival

Herrmann et al; Clin Cancer Res 2012

Weber WA et al; JCD 2003

Impact on Management (NOPR)

The National Oncologic PET Registry (NOPR): Design and Analysis Plan

JNM 2007

ACR 2007

300 000 patients enrolled

JCO 2008

35-50% impact on management for staging/restaging/monitoring

Cancer 2009

Impact of Positron Emission Tomography/Computed Tomography and Positron Emission Tomography (PET) Alone on Expected Management of Patients With Cancer: Initial Results From the National Oncologic PET Registry

JNM 2008

JCO 2008

The Impact of Positron Emission Tomography (PET) on Expected Management During Cancer Treatment

Cancer 2009
Impact on Outcome?

- Mortality
- Morbidity
- Quality of life

**RCT** → Accuracy as surrogate marker → Effective Tx?

<table>
<thead>
<tr>
<th>Study</th>
<th>Journal</th>
<th>Procedure</th>
<th>Comparison</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruers 2009</td>
<td>JNM</td>
<td>Surgery for liver metastases</td>
<td>CT vs PET/CT</td>
<td>Red. # futile surgeries</td>
</tr>
<tr>
<td>Van Tinteren 2009</td>
<td>Lancet 2002</td>
<td>Presurgical staging NSCLC</td>
<td>PET vs convent. staging</td>
<td>Red. # futile surgeries</td>
</tr>
<tr>
<td>Fischer 2011</td>
<td>N Engl J 2011</td>
<td>Presurgical staging NSCLC</td>
<td>PET/CT vs. convent. staging</td>
<td>Red. # futile surgeries Mortality NS</td>
</tr>
</tbody>
</table>

Many ongoing trials...........

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Because of NOPR: PET Coverage in the USA

<table>
<thead>
<tr>
<th>Initial Treatment Strategy</th>
<th>Subsequent Treatment Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>Cover</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Cover</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>Cover</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Cover</td>
</tr>
<tr>
<td>NSCL</td>
<td>Cover</td>
</tr>
<tr>
<td>Ovary</td>
<td>Cover</td>
</tr>
<tr>
<td>Brain</td>
<td>Cover</td>
</tr>
<tr>
<td>Cervix</td>
<td>Cover</td>
</tr>
<tr>
<td>Small Cell Lung</td>
<td>Cover</td>
</tr>
<tr>
<td>STS</td>
<td>Cover</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Cover</td>
</tr>
<tr>
<td>Testes</td>
<td>Cover</td>
</tr>
<tr>
<td>Breast</td>
<td>Cover w/exception*</td>
</tr>
<tr>
<td>Melanoma</td>
<td>Cover w/exception*</td>
</tr>
<tr>
<td>Prostate</td>
<td>Non-Cover</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Cover</td>
</tr>
<tr>
<td>All Other Solid</td>
<td>Cover</td>
</tr>
<tr>
<td>Myeloma</td>
<td>Cover</td>
</tr>
<tr>
<td>All other not listed</td>
<td>Cover</td>
</tr>
</tbody>
</table>
How is imaging used and how expensive is it in cancer (Medicare)

CT anatomy  MRI: Anatomy +Function  PET/CT: +Molecular imaging

Imaging costs frequently named as one of the culprits for exploding costs
Adapted from Dinan et al; JAMA 2010; 1625-1631

<table>
<thead>
<tr>
<th>Indication</th>
<th>CT/MRI</th>
<th>CT/PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast CA</td>
<td>3.7</td>
<td>11</td>
</tr>
<tr>
<td>CRC</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>Lung CA</td>
<td>5.8</td>
<td>5.5</td>
</tr>
<tr>
<td>NHL</td>
<td>7.9</td>
<td>5.8</td>
</tr>
<tr>
<td>Prostate CA</td>
<td>4</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

What are the key cost drivers in cancer?

# PET scans during first 2 years after diagnosis

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>#PET/patient</th>
<th>Ann. increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast CA</td>
<td>0.2</td>
<td>53.6</td>
</tr>
<tr>
<td>Colorectal CA</td>
<td>0.3</td>
<td>41.6</td>
</tr>
<tr>
<td>Lung CA</td>
<td>1.0</td>
<td>35.9</td>
</tr>
<tr>
<td>NHL</td>
<td>1.1</td>
<td>38.7</td>
</tr>
<tr>
<td>Prostate CA</td>
<td>&lt;0.1</td>
<td>40.5</td>
</tr>
</tbody>
</table>

Adapted from Dinan et al; JAMA 2010

In-patient services, drugs, etc.
All Imaging: 4.6%
FDG-PET/CT: 1.0-1.5%

Yang, Czernin; JNM 2011
### Distribution of Cancers

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung cancer</td>
<td>29.9</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>24.5</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>12.4</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>11.7</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>8.1</td>
</tr>
<tr>
<td>Melanoma</td>
<td>2.7</td>
</tr>
<tr>
<td>GIST</td>
<td>1.0</td>
</tr>
<tr>
<td>Myeloma</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancer of unknown primary</td>
<td>1.0</td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>1.0</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>0.7</td>
</tr>
<tr>
<td>Other tumors</td>
<td>6.0</td>
</tr>
</tbody>
</table>

**Beyer et al; J Nucl Med 2011**

<table>
<thead>
<tr>
<th>Indication</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>5,516</td>
<td>19</td>
</tr>
<tr>
<td>Staging</td>
<td>6464</td>
<td>23</td>
</tr>
<tr>
<td>Restaging</td>
<td>5607</td>
<td>20</td>
</tr>
<tr>
<td>Suspected recurrence</td>
<td>5388</td>
<td>19</td>
</tr>
<tr>
<td>Monitoring</td>
<td>5,503</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>22,975</td>
<td></td>
</tr>
</tbody>
</table>

**NOPR data; Hillner et al; JCO 2008**

### How do we use FDG PET/CT across most cancers?

**Koolen et al; EJNMMI 2012**

**UCLA 2013**

**Initial treatment strategy**

**Diagnostic/Phenotypic/Prognostic Biomarker**

*Diagnosis, Staging*

**Subsequent treatment strategy**

**Intermediate endpoint Biomarker**

*Treatment Monitoring*
**Conclusion**

- FDG PET imaging has a strong and translatable underpinning in tumor biology
- Evidence based approaches never applied to MRI or CT (does this mean that these techniques are not useful?)
- Randomized trials difficult to conduct (no financial support, no stakeholders)
- Nevertheless, impact on management and outcome demonstrated

*The fundamental role of increased glucose metabolism is well established Do we really need to show the usefulness of PET for each cancer/each indication?*

---

**Can we image substrate utilization in cancer and what could we learn?**

**LAT1 expression and survival in lung CA**

+,-,+++: degree of staining for LAT1; n=60

*Nawashiro et al; Int J Cancer 2006*
Imaging AA Transport and Metabolism: Diagnostic and prognostic information

Why [18F]-FDOPA?

<table>
<thead>
<tr>
<th></th>
<th>18F-DOPA</th>
<th>MIBG</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>8/12 (66%)</td>
<td>4/12 (33%)</td>
<td>0.2</td>
</tr>
<tr>
<td>Soft tissue rec./metastases</td>
<td>38/45 (84%)</td>
<td>14/45 (31%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bone/bone marrow</td>
<td>95/99 (96%)</td>
<td>70/99 (71%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Imani et al; J Nucl Med 2009

Piccardo et al Eur J Nuc Med Mol Imaging 2011
**Management of primary brain tumors**

Symptoms: headaches, seizures, syncope, vomiting, changes in mental status

*Consider clinical trials at all stages, especially up front, adjuvant, and at relapse*

Multidisciplinary approach is necessary
- Neurosurgery
- Neuro- oncology
- Radiation therapy

Maximal resection when possible
- RTX + CTX
- Adjuvant CTX for anaplastic glioma and glioblastoma

**Progressive disease**
- Consider clinical trials
- Consider surgical resection at relapse
- Salvage chemotherapy using cytotoxics/cytostatics
- Consider Stereotactic Radiotherapy

(Median survival: 12 m; no treatment 7-9 m)

---

**Carcinoid**

A

**Med. thyroid CA**

B

111In-Octreotide  
Montavros; J Clin Endocr. Metab 2009

18F-FDOPA  
Verbeek; JNM 2012

**Presyn. AAAD activity**

FDOPA vs AADC expr.: p<0.0001  
Lu; JNM 2013

**Brain tumor imaging**

PET?
Strengths and limitations of MRI

- **ceT1**
- **FLAIR (edema)**
- **Spectroscopy**

MR Perfusion  FDOPA PET/MRI

1. Choline incr.
2. Aspart. decreased
3. Lipids increased

Adapted from Ricard et al; Lancet 2012

**18F-FDOPA imaging protocol (ca. 130 pts/year)**

- **Brain imaging**
  - 200 mg of Carbidopa 1 h prior to tracer injection
  - 
  - \[^{18}\text{F}\text{-FDOPA}: 5-10 \text{ mCi}\]
  - 10 min uptake period
  - 20 min scan

- **Whole body imaging**
  - 200 mg of Carbidopa 1 h prior to tracer injection
  - 
  - \[^{18}\text{F}\text{-FDOPA}: 5-10 \text{ mCi}\]
  - 45 min uptake period
  - 2-5 min/bed position
  - CT with/without iv and oral contrast

Taal et al; Cancer 2008
Diagnostic accuracy of $^{18}$F-FDOPA

<table>
<thead>
<tr>
<th>Ratio</th>
<th>% Sens</th>
<th>% Spec</th>
<th>% PPV</th>
<th>% NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>T/S &gt; 1.0</td>
<td>96</td>
<td>100</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>T/S &gt; 0.75</td>
<td>100</td>
<td>86</td>
<td>96</td>
<td>100</td>
</tr>
<tr>
<td>T/N &gt; 1.3</td>
<td>96</td>
<td>86</td>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>T/W &gt; 1.6</td>
<td>96</td>
<td>86</td>
<td>96</td>
<td>86</td>
</tr>
</tbody>
</table>

FDOPA detects LG and HG tumors

FDG positive in HG tumors

Chen et al; JNM 2006, Fueger et al; JNM 2010

Impact of $^{18}$F-DOPA PET on managing patients with brain tumors

<table>
<thead>
<tr>
<th>Tumor grade (n=58)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO I</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>WHO II</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>WHO III</td>
<td>15</td>
<td>26</td>
</tr>
<tr>
<td>WHO IV</td>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>12</td>
</tr>
</tbody>
</table>

Management changes in 24/58 patients

- W/W $\rightarrow$ Chemo 6/24 pts (25%)
- Chemo $\rightarrow$ W/W 4/24 pts (17%)
- Chemo $\rightarrow$ Surgery 2/24 pts (8%)
- R+C $\rightarrow$ C 2/24 pts (8%)
- W/W $\rightarrow$ R/C 2/24 pts (8%)

Prognostic implications

- N=20
- N=33

Walter et al; J Nucl Med 2012
[18F]-AA transport imaging (11C-MET, 18F-FET, 18F-FDOPA) for brain tumor imaging

<table>
<thead>
<tr>
<th>Feasibility</th>
<th>yes</th>
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<tbody>
<tr>
<td>Accuracy</td>
<td>yes</td>
</tr>
<tr>
<td>Diagnostic value</td>
<td>yes; pseudo-progression vs progression</td>
</tr>
<tr>
<td>Prognostic value</td>
<td>yes</td>
</tr>
<tr>
<td>Therapeutic value</td>
<td>Impact on Management: Yes</td>
</tr>
<tr>
<td></td>
<td>Does it result in better treatment?</td>
</tr>
<tr>
<td>Patient and societal value</td>
<td>Does it result in improved survival and/or quality of life, at acceptable cost/reduces costs at same outcome?</td>
</tr>
</tbody>
</table>

Prospective randomized trial under way for 18F-FDOPA

---

Study Design to determine impact on outcome in pts with cancer (UCLA, Kaiser Permanente, UC Irvine, University of Wuerzburg)

"positive MRI"

Randomization

<table>
<thead>
<tr>
<th>AA PET</th>
<th>No AA PET (conventional imaging)</th>
</tr>
</thead>
</table>

Intended Management

+/− Management Changes

Management change implemented?

OS, PFS

Herrmann et al; in progress

FDOPA, FET
Predictive Biomarkers: Is the therapeutic target expressed?

There are many PET probes for bone imaging:

<table>
<thead>
<tr>
<th>Probe</th>
<th>T/2 (min)</th>
<th>Target</th>
<th>Process</th>
<th>Applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{18}$F-NaF</td>
<td>110</td>
<td>Hydroxypatite</td>
<td>Bone formation</td>
<td>Osteoblastic</td>
</tr>
<tr>
<td>$^{18}$F-FDG</td>
<td>110</td>
<td>Glut1,3; hexokinase</td>
<td>Glycolysis</td>
<td>Osteolytic</td>
</tr>
<tr>
<td>$^{11}$C-Choline</td>
<td>20</td>
<td>Choline kinase</td>
<td>Lipid synthesis</td>
<td>Prostate</td>
</tr>
<tr>
<td>$^{18}$F-Choline</td>
<td>110</td>
<td>Choline kinase</td>
<td>Lipid synthesis</td>
<td>Prostate</td>
</tr>
<tr>
<td>$^{11}$C-Acetate</td>
<td>20</td>
<td>FAS</td>
<td>Lipid synthesis</td>
<td>Prostate</td>
</tr>
<tr>
<td>$^{11}$C-Meth</td>
<td>20</td>
<td>L-AAT</td>
<td>AA metabolism</td>
<td>Myeloma</td>
</tr>
<tr>
<td>$^{18}$F-DOPA</td>
<td>110</td>
<td>L-AAT</td>
<td>AA metabolism</td>
<td>NET</td>
</tr>
<tr>
<td>$^{68}$Ga-SSR</td>
<td>68</td>
<td>SSR 2,5</td>
<td>SSR expression</td>
<td>NET</td>
</tr>
<tr>
<td>$^{18}$F-Estradiol</td>
<td>110</td>
<td>ER</td>
<td>Receptors</td>
<td>Breast</td>
</tr>
<tr>
<td>$^{18}$F-FDHT</td>
<td>110</td>
<td>AR</td>
<td>Receptors</td>
<td>Prostate</td>
</tr>
<tr>
<td>$^{12}$Iodine</td>
<td>4.2 days</td>
<td>Na-l-symporter</td>
<td>Iodine metab.</td>
<td>Thyroid</td>
</tr>
<tr>
<td>$^{68}$Ga-PSMA</td>
<td>68</td>
<td>PSMA</td>
<td>Receptor exp</td>
<td>AI</td>
</tr>
<tr>
<td>$^{89}$Zr-mAB</td>
<td>78h</td>
<td>PSMA</td>
<td>Receptor exp</td>
<td>AI</td>
</tr>
<tr>
<td>$^{89}$Zr-mAB</td>
<td>78h</td>
<td>PSA</td>
<td>Receptor exp</td>
<td>AD</td>
</tr>
<tr>
<td>$^{18}$F-FACBC</td>
<td>110</td>
<td>LAT?</td>
<td>AA Transport</td>
<td>Recurrence</td>
</tr>
</tbody>
</table>
Does hormone receptor expression predict response to hormone treatment? Thus far no published evidence.

Numerous therapeutic approaches: Schematic representation of therapeutic targets of the AR pathway

Schematic representation of therapeutic targets of the AR pathway.

Current Opinion in Pharmacology Volume 8, Issue 4 2008 440 - 448
Yu Chen, Charles L. Sawyers, Howard I. Scher
Imaging targets in prostate cancer

**PSA (human kallikrein 3)**
- Serine protease
- Released into perivascular space; AR signaling dependent gene
- Specific for prostate CA

**PSMA (glycoprotein)**
- Cell migration
- Nutrient uptake
- Receptor function
- Not specific for PrCA

**PSCA (cell surface glycoprotein)**
- Overexpressed in localized prostate cancers; correlates with Gleason score, pathologic stage, AI.

---

**$^{89}$Zr-5A10**
- AB recognizes PSA prior to EC protein binding (Ulmert et al., 2012)

**$^{89}$Zr-7E11 (mAB)**
- Intracellular
- Treatment responses?
- Ruggiero A; JNM 2011

**EC:** $^{68}$Ga urea based peptidomimetic (HBED-CC)

---

**PD of MDV3100 (pure AR antagonist) measured with FDHT**

Baseline

4 weeks of MDV3100

Scher et al; Lancet 2010
Summary: Probes for diagnosing and phenotyping of bone metastases

**Diagnosis**
- \(^{99}\text{Tc}\) MDP
- \(^{18}\text{F}\)-NaF
- \(^{18}\text{F}\)-FDG, \(^{11}\text{C}/^{18}\text{F}\)-choline
- \(^{18}\text{F}\)-FACBC
- MRI
- CT
- PSA, PSMA, PSCA ligands

**Phenotyping**
- PSMA
- PSA
- PSCA
- \(^{18}\text{F}\)-FDG
- \(^{18}\text{F}\)-FACBC
- \(^{11}\text{C}/^{18}\text{F}\)-choline
- Hormone receptors

**Therapy**
- Hormonal Tx
- EBR
- Alpharadin
- Biphosphonates
- Small molecule inhibitors
- Chemotherapy

**Intermediate endpoint biomarkers**
- \(^{18}\text{F}\)-FDG
- \(^{11}\text{C}/^{18}\text{F}\)-choline
- IC PSMA?

**Initial treatment strategy**

**Subsequent strategy**

**Predictive PET biomarker for nucleoside analog prodrugs**

**Rationale**
- NA prodrugs require deoxycytidine kinase (dCK) for their activation (gemcitabine, clofarabine, decitabine, etc)
- dCK overexpressed to various degrees in many cancers
- Response rates are low
- Differential screening for pyrimidine NAs targeting dCK
- High binding affinity (low nm) in vitro

* Marechal et al; Cancer 2010
Who will respond?

Laing et al PNAS 2009

Probe Specificity and treatment response predictions

Sensitivity  Specificity  Response to gemcitabine

WT       KO      L1210, L1210K

Toy et al; Proc Natl Acad Sci 2010
Campbell et. al. J Nucl Med. 2010

Lee et al; J Nucl Med 2011
Clinical translation of predictive biomarkers

30 resectable patients imaged with $^{18}$F-FAC PET/CT

Excised tumor examined for dCK activity and expression

Correlation between dCK activity/expression and $^{18}$F-FAC uptake

What is the point? What does it mean for patients?

Translational Study 1
Resectable cancer

$^{18}$F-FAC PET

MRI

Surgery

Tumor fragment

Histology dCK Xenografts

Olive et al; Nature 2009

Translational Study 2
Non-resectable cancer

$^{18}$F-FAC PET

Gemcitabine

Clinical Course

Overall Survival Progression FS
Problems in study design

Sampling problems
- Small tissue fragments
Probe delivery
- Low tumor perfusion but high dCK activity
- High tumor perfusion but low dCK activity
Tumor stroma

\[ ^{18}\text{F}-\text{FAC} \text{ as Pharmacodynamic Marker of dCK inhibitors} \]

Dose: 50mg/kg

Captisol 4 h Oral
Di 39 oral
Di 39 intraperitoneal

At 50mg/kg the intraperitoneal administration is superior to oral administration

Radu group at UCLA
Summary: A rich portfolio of PET biomarkers

**Diagnostic/Phenotypic/Prognostic Biomarkers**

Is the disease present?

\(^{18}\text{F-FDG}; {^{18}\text{F-AA}, {^{18}\text{F-FLT} etc, choline, ect}}\)

**Predictive Biomarkers**

Is the therapeutic target expressed?

Will the drug work?

\(^{68}\text{Ga-DOTATATE}; {^{18}\text{F-FES, {^{18}\text{F-FAC}}}}\)

**Intermediate endpoint Biomarkers**

Does the drug work?

\(^{18}\text{F-FDG}; {^{18}\text{F-AA, {^{18}\text{F-FLT}}}}\)

---

A few words about MRI: Capabilities have dramatically expanded

These arguments have been made for PET/MRI

- No Radiation
- Molecular capabilities (Research)
- True simultaneous acquisition
- Better for selected indications
  - Brain
  - Prostate
  - Head/Neck
  - Pancreas
  - Liver

**But is there a good reason for marrying PET with MRI?**

Kauppinen/Peet; Cancer Biol Ther. 2011
Argument #1 for PET/MRI

CT carries a significant radiation risk

Radiation doses of as high as 25 mSv might increase cancer risk

Brenner DJ et al; Radiology 2011:
Greatly reduced relevance for patients with limited life expectancy

D. J. Shah et al; British Journal of Radiology 2012 “Risks of medical imaging at effective doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent”

“Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged”

Women of child bearing age
Pediatric population

Do magnetic fields have a mutagenic effect (Ames test)?


Increase in hypoxanthine-guanine phosphoribosyl transferase gene mutations

Increase in DNA strand breaks in rat brain cells

Increase in revertants in co-exposed Salmonella typhimurium TA 100

Increase in micronuclei in human lymphocytes (only in presence of the parallel static magnetic field)

Increase in the number of sister chromatid exchanges at 400 mT, but neither at 5 mT nor at 50 mT

Increase in hypoxanthine-guanine phosphoribosyl transferase gene mutations in co-exposed Chinese hamster ovary cells

Increase in hypoxanthine-guanine phosphoribosyl transferase gene mutations in p53 deficient human osteosarkoma cells

DNA repair mechanisms are powerful

Argument #2 for clinical PET/MRI: MRI is “better” than CT for some indications

In pancreatic cancer (Shrikhande et al; HPB 2012)
Choice between CT or MRI/MRCP is often determined by the availability of the modality and by the technical expertise; CT and MRI equally accurate

Liver metastases
Niekel et al; meta-analysis; Radiology 2010

<table>
<thead>
<tr>
<th>Modality*</th>
<th>Mean Sensitivity (%)</th>
<th>Mean Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT (n = 9)</td>
<td>91.6 (66.9, 92.8)</td>
<td>94.9 (92.0, 96.3)</td>
</tr>
<tr>
<td>MR imaging (n = 6)</td>
<td>81.2 (64.5, 69.6)</td>
<td>92.5 (89.0, 94.6)</td>
</tr>
<tr>
<td>FDG PET (n = 9)</td>
<td>94.1 (90.0, 95.9)</td>
<td>95.7 (92.7, 97.8)</td>
</tr>
<tr>
<td>FDG PET/CT (n = 5)</td>
<td>96.5 (84.2, 97.9)</td>
<td>97.2 (82.6, 98.3)</td>
</tr>
</tbody>
</table>

CT and MRI are underreporting vascular invasion in pancreatic cancer. MRA does not add information on vascular staging when compared with CT and MRI. (Zhang et al; Pancreatology 2012)

MRI and CT similarly accurate for characterizing cystic lesions (Lee et al; Clin. Radiology 2011; Visser et al; AJR 2007)

CT, MRI, PET and US with comparable performance in metastatic H/N cancer

Meta analysis : Liao et al; BMC Cancer 2012
Meta analysis: de Brondt et al; Eur J Radiol 2007

And even in prostate cancer LN staging......
CT Sens: 42%; MRI Sens: 39%
Meta-analysis: Hoevels et al; Clinical Radiology 2008

Same for recurrent nasopharyngeal CA
Meta-analysis: Liu et al; Radioth.and Oncology 2007

Using LN specific contrast MRI superior to CT; Mulicenter trial; Heesakkers et al; Lancet Oncology. 2008
Simultaneous measurements of molecular processes are important

18F FDG tumor uptake is reproducible
De Langen et al; JNM 2012

Study interval 1-4 days

Reproducibility of MRI Perfusion measurements (baseline vs 2-7 days later)
Ng et al; AJR 2010

The rate of reproducibility of DCE-MRI parameters is in the range of 10%–20%

Highly unlikely that gene expression, transcription and translation changes within minutes. Why then would we need integrated systems?

The business of PET/MRI; Trends in cancer imaging in the US (CMS data)

CT and MRI utilization 2006-2008

CT and MRI/pt within 2 y of diagnosis

Indication | CT/MRI |
--- | --- |
Breast CA | 3.7 |
CRC | 12 |
Lung CA | 5.5 |
NHL | 7.9 |
Prostate CA | 4 |

Adapted from Dinan et al; JAMA 2010; 1625-1631

Thus, CT is the dominating modality in cancer: Cost, operation, value
Almost all systems in academia or public health care

Courtesy of David Townsend

Interesting sales numbers Adapted from David Townsend

PET/CT 2002 – 2004: 360 Units shipped in US
A technical evolution and a clinical revolution

PET/MRI 2010 – 2012: 14 Units shipped in US
A technical revolution: But is there a real need?

<table>
<thead>
<tr>
<th></th>
<th>PET/CT (Mil $)</th>
<th>PET/MRI (Mil $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment</td>
<td>0.9 - 3</td>
<td>5+</td>
</tr>
<tr>
<td>Build out</td>
<td>1</td>
<td>2.5 (at UCLA)</td>
</tr>
<tr>
<td>Service contract/y</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Throughput</td>
<td>12-15 pts/d</td>
<td>6-8 pts/day</td>
</tr>
<tr>
<td>Reimbursement</td>
<td>$1250</td>
<td>$1250?</td>
</tr>
</tbody>
</table>

Great research tool: tumor perfusion; phenotyping of tumors using “molecular” MRI (predictive markers); improved diagnostic accuracy of PET/MRI over PET/CT?
But do I really need an integrated system to do this?
Summary: A rich portfolio of PET biomarkers

Diagnostic/Phenotypic/Prognostic Biomarkers
18F-FDG; AA, 18F-FLT; etc, choline, etc

Predictive Biomarkers
Is the therapeutic target expressed?
Will the drug work?
68Ga-DOTATATE; 18F-FES; 18F-FAC

Intermediate endpoint Biomarkers
Does the drug work?
18F-FDG, 18F-AA, 18F-FLT

A randomized trial to determine the value of 18F-NaF bone imaging in patients with prostate CA

If you design a good study you must be willing to accept the results..........!!!
The 3 most frequently used bone imaging probes

### Tumor Metabolism


### Bone Metabolism

#### Rapid renal clearance

<table>
<thead>
<tr>
<th>18F-NaF</th>
<th>ECF</th>
<th>Hydroxyapatite ↓ Hydroxyapatite</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>(100%)</td>
<td>Accumulation depends on area of exposed bone surface</td>
</tr>
<tr>
<td>30%</td>
<td>OH</td>
<td>2/3 Hydroxyapatite</td>
</tr>
</tbody>
</table>

#### Slow renal clearance

<table>
<thead>
<tr>
<th>99Tc-MDP</th>
<th>Chemisorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>[60%]</td>
<td>1/3 Calcium phosphate</td>
</tr>
</tbody>
</table>

**18F-NaF standard method for bone scintigraphy in 1960s (Blau 1962)**

**99Tc diphosphonates; Subramanian et al; Radiology 1971**

**Renewed interest due to PET and PET/CT and 99Mo/99Tc generator shortage**
### Incremental improvements

<table>
<thead>
<tr>
<th>amounts</th>
<th>SPECT</th>
<th>SPECT/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{99}$Tc MDP Planar</td>
<td>Good sensitivity</td>
<td>Limited specificity</td>
</tr>
<tr>
<td>$^{18}$F-NaF PET</td>
<td>Very high sensitivity</td>
<td>Limited specificity</td>
</tr>
</tbody>
</table>

### $^{18}$F-NaF PET/CT is superior to $^{18}$F-NaF PET and appears to be superior to $^{99}$Tc MDP

<table>
<thead>
<tr>
<th></th>
<th>$^{18}$F-NaF PET</th>
<th>$^{18}$F-NaF PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sens (%)</strong></td>
<td><strong>Spec (%)</strong></td>
<td><strong>Sens (%)</strong></td>
</tr>
<tr>
<td>All</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>Spine</td>
<td>50</td>
<td>86</td>
</tr>
<tr>
<td>Thoracic cage</td>
<td>76</td>
<td>40</td>
</tr>
<tr>
<td>Pelvic bones</td>
<td>83</td>
<td>67</td>
</tr>
<tr>
<td>Skull</td>
<td>80</td>
<td>30</td>
</tr>
<tr>
<td>Long bones</td>
<td>100</td>
<td>25</td>
</tr>
</tbody>
</table>

- **Patients**
  - PET: 88
  - PET/CT: 100*

- **$^{18}$F-NaF PET/CT is superior to $^{18}$F-NaF PET and appears to be superior to $^{99}$Tc MDP**

- **44 pts with Breast, Prostate, Lung, Colon, Ovary, Myeloma, Lymphoma, ...**

- **Even-Sapir et al; J Nucl Med 2004**

- **Enchondroma**

- **$p<0.05$**
**PET vs PET/CT: Reasons for false positives on 18F-NaF scans**

<table>
<thead>
<tr>
<th>Location</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral column</td>
<td>Degenerative disk disease, osteophytes, facet joint disease, Schmorl’s node, fracture</td>
</tr>
<tr>
<td>Thoracic cage</td>
<td>Radionecrosis, fracture, arthritic changes at the acromioclavicular and sternoclavicular joints, postop. changes</td>
</tr>
<tr>
<td>Pelvic bones</td>
<td>Avulsion injury, insufficiency fracture, Paget’s disease, arthritic changes, postoperative changes</td>
</tr>
<tr>
<td>Skull and facial bones</td>
<td>Sinusitis, mastoiditis, osteoma</td>
</tr>
<tr>
<td>Long bones</td>
<td>Enchondroma, subchondral cyst, trochanteric bursitis, tendinitis, stress fracture</td>
</tr>
</tbody>
</table>

Sub-chondral bone cyst in prostate CA

Einat Even-Sapir et al; J Nucl Med 2004

---

**Where are we going? Strategy for 18F-NaF Approval**

**CMS NCD February 26, 2010**

18F-NaF-PET should be covered only under an approved coverage with evidence development (CED) study

At that time no qualifying clinical study that would enable this coverage

Now there is, once again NOPR!

<table>
<thead>
<tr>
<th></th>
<th>18F-FDG NOPR</th>
<th>18F-NaF NOPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PET scans registered</td>
<td>157,453</td>
<td>8,475</td>
</tr>
<tr>
<td>PET scans consented/eligible</td>
<td>116,953</td>
<td>6,417</td>
</tr>
<tr>
<td># facilities (minimum 1 scan)</td>
<td>1,693</td>
<td>633</td>
</tr>
</tbody>
</table>

But, NOPR alone no longer sufficient..

NOPR data Courtesy Barry Siegel 2012
**18F-NaF PET/CT versus 99mTc-MDP for Detecting Bone Metastases: A Randomized International Multi-center Trial (19 sites in US, Switzerland, Australia, Austria)**

Currently 530 pts enrolled

Randomization (Image Metrix)

\[
\begin{align*}
\text{Pre-scan questionnaire} \\
\text{On-site visual analysis (score); clinical report}
\end{align*}
\]

\[
\begin{align*}
\text{Post-scan questionnaire} \\
\text{6 m follow up (questionnaires; source data)} \\
\text{Reference standard (other imaging modalities, tumor markers)} \\
\text{Independent Truth Panel to determine presence of absence of bone metastases} \\
\text{Independent expert panel to re-read and score scans}
\end{align*}
\]

**Surprising Preliminary Results**

<table>
<thead>
<tr>
<th>Bone Mets</th>
<th>18F-NaF PET/CT</th>
<th>99mTc-MDP</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos</td>
<td>18/155 (11.6%)</td>
<td>23/167 (13.8%)</td>
<td>41/322 (12.7%)</td>
</tr>
<tr>
<td>Neg</td>
<td>137/155 (88.4%)</td>
<td>144/167 (86.2%)</td>
<td>281/322 (87.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>155</td>
<td>167</td>
<td>322</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>18F-NaF PET/CT</th>
<th>99mTc-MDP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.8687</td>
<td>0.9272</td>
</tr>
<tr>
<td>2</td>
<td>0.9267</td>
<td>0.9450</td>
</tr>
<tr>
<td>3</td>
<td>0.9645</td>
<td>0.9566</td>
</tr>
</tbody>
</table>

\[18F-NaF\] does not appear to be superior.....
**18F-FDG can be used for monitoring of breast CA bone metastases**

_Du et al.; J Clin Oncol 2007;3440-3447_

**Osteolytic met responding**

<table>
<thead>
<tr>
<th>CT</th>
<th>PET</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="L3" alt="CT Image" /></td>
<td><img src="3m" alt="PET Image" /></td>
<td>![PET/CT Image](more sclerotic)</td>
</tr>
<tr>
<td><img src="7m" alt="CT Image" /></td>
<td><img src="PET" alt="PET Image" /></td>
<td><img src="PET/CT" alt="PET/CT Image" /></td>
</tr>
<tr>
<td><img src="24m" alt="CT Image" /></td>
<td><img src="PET" alt="PET Image" /></td>
<td><img src="PET/CT" alt="PET/CT Image" /></td>
</tr>
</tbody>
</table>

**Osteoblastic met non-responding**

<table>
<thead>
<tr>
<th>CT</th>
<th>PET</th>
<th>PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="L5" alt="CT Image" /></td>
<td><img src="3m" alt="PET Image" /></td>
<td><img src="larger" alt="PET/CT Image" /></td>
</tr>
<tr>
<td><img src="PET" alt="CT Image" /></td>
<td><img src="PET" alt="PET Image" /></td>
<td><img src="PET/CT" alt="PET/CT Image" /></td>
</tr>
<tr>
<td><img src="PET" alt="CT Image" /></td>
<td><img src="PET" alt="PET Image" /></td>
<td><img src="PET/CT" alt="PET/CT Image" /></td>
</tr>
</tbody>
</table>

**Change in morphology and 18F-FDG uptake following treatment**

- **Initially Osteolytic (77)**
  - Treatment
  - 81% FDG - and Sclerotic
  - 19% FDG + Osteolytic
  - All negative at late fu

- **Osteoblastic (41)**
  - Treatment
  - 52% FDG - Sclerotic
  - 48% FDG + Size ↑
  - All negative at late fu

- **Mixed (11)**
  - Treatment
  - 45% FDG - Sclerotic
  - 55% FDG + het.
  - All negative at late fu

**Cumulative Survival (%)**

- Breast CA: n=25

**FDG PET provides**
- Phenotypic information
- Prognostic information (see prostate CA)
- Response assessments

_Morris et al; Clin Cancer Research 2005 (anti-microtubule CTX)_{38}
Probes, Metabolism, Images


But what do we learn?

Choline PET  Choline PET

NaF PET

Beheshti et al; Seminars in Nuclear Medicine 2009

Potential applications of Choline analogs in Prostate cancer

Beheshti et al; Radiology 2010

Detection of recurrence (18F-choline)

<table>
<thead>
<tr>
<th>Literature data</th>
<th>N</th>
<th>PSA range* or mean</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cimitan et al.</td>
<td>100</td>
<td>1</td>
<td>Higher Sens when PSA (&gt;2–5 ng/ml)</td>
</tr>
<tr>
<td>Husarik et al.</td>
<td>68</td>
<td>0.36–100†</td>
<td>Lower Sens when PSA (&lt;2–5 ng/ml)</td>
</tr>
<tr>
<td>Beheshti et al.</td>
<td>21</td>
<td>56 ± 64*</td>
<td>Heavily sclerotic bone metastases may be 18F-FCH-neg</td>
</tr>
<tr>
<td>Panebianco et al.</td>
<td>84</td>
<td>2</td>
<td>18F-NaF/CT-negative bone marrow mets may be 18F-FCH pos.</td>
</tr>
<tr>
<td>Casamassima et al.</td>
<td>71</td>
<td>0.2–2†</td>
<td>18F-FCH more spec. than 18F-fluoride</td>
</tr>
</tbody>
</table>

Bauman et al; Prostate Cancer and Prostatic Diseases 2012

Most likely more aggressive phenotype (higher PSA levels, higher PSA velocity); probably useful for identifying site of recurrence

Initial Diagnosis
Gleason score 7; PSA: 7.8 ng/ml

Treatment Monitoring

Before and after 3 m of taxol

The utility of PET is expanding and the emphasis is shifting: Lets focus on phenotyping and predictive biomarkers

1990s: \(^{18}\text{F-FDG}\) and others as diagnostic/prognostic biomarkers (more work to be done; see \(^{18}\text{F-NaF}\))

2000s: \(^{18}\text{F-FDG}\) and others as intermediate endpoint biomarkers (more work to be done; standardization; reimbursement)

2010s: Predictive biomarkers (\(^{18}\text{F-FES,^{18}\text{F-DHTS, etc}}\))
- PET in drug development (PK and PD)
- Theranostics

Advanced PET/CT: Understand biology of disease
Use imaging probes to determine whether the therapeutic target is present and whether the target is inhibited by the drug (PD)

Future of PET/CT

- **Diverse portfolio of PET probes for research and clinic**
  - Diagnostic
  - Phenotypic
  - Prognostic
  - Predictive
  - Intermediate endpoint
- Drug development (PK and PD markers)
- Theranostics (precise organ dosimetry can be studied)

Together with CT: Most powerful current diagnostic tool in oncology
Role of PET/MRI to be determined (no doubt about research applications)

Challenges

- Standardization
- 2000 PET probes (do they make sense?)
- Close cross disciplinary collaborations (Biologists, radio-chem, chemistry, mol. imaging, radiologists, oncologists, material scientists, etc.)
- High regulatory bar (management, outcome, costs, reimbursement)