Updates in Imaging of Advanced Prostate Cancer

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Nothing to disclose
Outline

• MRI, PET/CT → what is the difference?

• Which PET tracers?

• Basis for uptake in Prostate Cancer (PCa)?

• Potential clinical uses
  – Beyond cancer detection and staging
  – Focus on non-invasive assessment of tumor biology
Prostate MRI: the beginning

• Initial focus on zonal anatomy

MR Imaging of the Prostate Gland: Normal Anatomy

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Prostate MRI in 2015: The role of MRI has evolved!

• Zonal Anatomy is still immensely important
Prostate MRI in 2015: The role of MRI has evolved!

• Prostate MRI ≠ staging only

• It’s about providing meaningful information relevant to patient management in specific clinical contexts

• Move away from the “one size fits all” approach to prostate MRI and towards a “wearing the right hat for the right outfit” approach
Clinically Low-risk Prostate Cancer

The critical question: does the MR fit with the biopsy result?

**Patient 1:**
Gleason 6, PSA 5, cT2a

Axial T2WI

Coronal T2WI

Repeat bx:
Gleason 6, 1 core +, 5% tumor

**Patient 2:**
Gleason 6, PSA 5, cT2a

Axial T2WI

Coronal T2WI

Repeat bx:
Gleason 4+3, 4 cores + 50-70% tumor

Vargas,...,Hricak. Journal of Urology 2012
Clinically Low-risk Prostate Cancer

What is the problem with random prostate biopsies?

Gleason 4+4=8
Gross ECE
Prostate Cancer Clinical States

- Clinically Localized Disease
- Rising PSA
- Clinical Metastases: Non-Castrate
- Rising PSA: Castrate
- Clinical Metastases: Castrate

Scher HI et al. Urology 2000
Prostate Cancer Clinical States

- Clinically Localized Disease
- Rising PSA
- Clinical Metastases: Non-Castrate
- Clinical Metastases: Castrate
- Rising PSA: Castrate

Scher HI et al. Urology 2000

MRI
Prostate Cancer Clinical States

Clinically Localized Disease → Rising PSA

Clinical Metastases: Non-Castrate → Rising PSA: Castrate
Clinical Metastases: Castrate

Scher HI et al. Urology 2000
PET Radiotracers

<table>
<thead>
<tr>
<th>Isotope</th>
<th>Pharmaceutical compound</th>
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<tbody>
<tr>
<td>F18</td>
<td>Fluorodeoxyglucose (FDG)</td>
</tr>
<tr>
<td>C11</td>
<td>Choline</td>
</tr>
<tr>
<td>N13</td>
<td>Aminoacids</td>
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<tr>
<td>O15</td>
<td>Sodium Fluoride</td>
</tr>
<tr>
<td>Zr89</td>
<td>Receptors: FDHT, PSMA, Bombesin</td>
</tr>
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<td>Ga68</td>
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PET has revolutionized cancer imaging!

Fluorodeoxyglucose

$^{18}\text{F-FDG}$

GLUT

$^{18}\text{F-FDG}$

$^{18}\text{F-FDG-6P}$

HK

$^{18}\text{F-FDG}$

G6-Pi

Cancer cell
FDG and Prostate Cancer

• For the initial diagnosis and staging of prostate cancer, FDG PET is considered limited.

• Patterns of GLUT expression in PCa is variable →
  – Affected by dedifferentiation, aggressiveness, androgen sensitivity, hypoxia.
  – Overlap in tracer uptake in normal and abnormal prostate tissue (including inflammation!)
PET tracers used in Prostate Cancer

- Cell Metabolism
- Bone Matrix
- Receptors and Membrane Proteins
PET tracers used in Prostate Cancer

Cell Metabolism

- Glucose: $^{18}$F-FDG
- Choline: $^{11}$C-choline, $^{18}$F-choline
- Acetate: $^{11}$C-acetate, $^{18}$F-acetate
- Amino Acids: $^{18}$F-FACBC
Choline

- Precursor for phospholipid synthesis
  - Major components of the cellular membrane
- Enters the cell through choline transporters
- Can be labeled with $^{11}$C or $^{18}$F
- FDA approval → evaluation of recurrence
Choline

• Pooled sensitivity and specificity of 86% and 93% for detecting PCa
• Performance correlated to PSA levels
• Recent study compared Choline PET and MRI:
  – Choline better for lymph nodes
  – MRI better for prostate bed
  – Both good for bone metastases

Giovacchini et al. J Urol. 2010
Kitajima K et al. J Nuc Med. 2014
PET tracers used in Prostate Cancer

Cell Metabolism

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  - $^{18}$F-choline
- Acetate
  - $^{11}$C-acetate
  - $^{18}$F-acetate
- Amino Acids
  - $^{18}$F-FACBC
Acetate

• Major sources of acetate consumption:
  – Krebs cycle
  – Production of phospholipids in cellular membranes

• Upregulation of fatty acid synthetase ➔ basis of PCa uptake
Acetate PET

• Uptake appears unaffected by androgens (in contrast to FDG and choline)

• Study comparing $^{11}$C-Acetate PET and MRI
  – Sensitivity/specificity (tumors >5 mm):
    • 62%/80% for PET/CT and 82%/95% for MRI
  – >9 mm, comparable accuracy for PET and MRI

Emonds KM et al. EJNMMI research. 2013
Mohsen B et al. BJU Int 2013
Mena E et al. JNM. 2012
PET tracers used in Prostate Cancer

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Aminoacids (AA): Leucine

- Basis for uptake in Pca: \( \uparrow \) AA transport + \( \uparrow \) protein synthesis
- \(^{18}\text{F-FACBC}\) tumor uptake comparable to FDG; but bladder excretion \( \downarrow \) 20-fold; \( \uparrow \) cancer/inflammation uptake ratios
- SUVmax \( \uparrow \) tumor than in normal prostate
- Sensitivity/specificity for tumor detection slightly \( \uparrow \) for MRI (73/79\%) than FACBC (67/66\%)
- Recurrence: Sensitivity/specificity 90/40\% for prostatic fossa vs 55/97\% in distant disease (n=93)

Oka S et al. JNM 2007
Turkbey B et al. Radiology. 2014
PET tracers used in Prostate Cancer

Bone Matrix

$^{18}$F-NaF
Sodium Fluoride (NaF)

- Developed in 1962; FDA approved 1972
- Uptake mechanism similar to “bone scan”
  - ↑blood clearance, ↑ bone/background ratio, ↓ interval from administration to imaging
- Similar pitfalls to bone scan
  - accumulates in bone matrix; not cancer cells → no uptake in non-bone metastases
  - Uptake in degenerative bone disease
  - Flare phenomenon
Gleason 8. PSA 22. Metastases? Anything outside of the pelvis?
Anything outside the pelvis?
PET tracers used in Prostate Cancer

Receptors and Membrane Proteins

Androgen Receptor (AR)
- $^{18}$F-FDHT

Gastrin Releasing Peptide Receptor (GRP-R)
- $^{18}$F, $^{68}$Ga, $^{64}$Cu, $^{177}$Lu
- Bombesin analogues

Prostate Specific Membrane Antigen (PSMA)
- Antibodies
  - $^{111}$In, $^{64}$Cu, $^{89}$Zr, $^{90}$Y, $^{177}$Lu
  - 7E11, J591
- Antibody Fragments “Minibodies”
  - 89Zr-Df-IAB2M
- Small molecules
  - $^{18}$F-DCFBC
Androgen Receptor (AR) gene activation is a hallmark of castration-resistant prostate cancer.
The Androgen Receptor (AR)

• AR → ligand-dependent transcription activator involved in cellular proliferation and differentiation

• Almost all PCa patients initially respond to androgen deprivation, but eventually progress to a castration-resistant clinical state → bypassing or sensitizing the AR pathway

• Novel therapies targeting the AR have shown ↑ survival → recent FDA/EU approval
- 38 patients with castration resistant prostate cancer and discrete bone lesions

- All underwent CT, FDG PET and FDHT PET

- CT features (including Hounsfield Units), SUVmax from FDG and FDHT PET
1. Bone metastases demonstrate variable appearance on CT

- Densely sclerotic
- Groundglass
- Mixed
- Lytic
2. CT density is inversely associated with FDG and FDHT PET uptake

Reader 1: $r = -0.30; P < .001$
Reader 2: $r = -0.31; P < .001$

Reader 1: $r = -0.27; P = .001$
Reader 2: $r = -0.37; P < .001$
3. Preliminary associations with clinical outcomes

- # lesions on CT, FDG and FDHT PET associated with overall survival (p<0.05)

- ↑ SUVmax on FDHT, shorter overall survival (P=0.02)

- No association between SUVmax on FDG PET and survival (P = 0.38-0.65)
FDHT for documenting pharmacologic targeting

- FDHT PET pre- and 4 weeks post enzalutamide
- Uptake suppression: drug hits the pharmacologic target (AR)

Scher HI. The Lancet 2010
FDHT for measuring dose related targeting efficacy

- FDHT PET pre- and 4 weeks post ARN-509
- Uptake suppression: dose dependent

Rathkopf D E et al. JCO 2013
Rathkopf D E et al. JCO 2013
Movember GAP 2 Imaging Project: FDHT

- Multi-institutional study, Co-PIs
  - MSKCC (lead site): Vargas, Morris
  - Royal Marsden London: Chua
  - VUMC Amsterdam: Hoekstra
  - Austin Health Australia: Scott

- Total funding: $2.8 million
FDHT PET for guiding AR-targeted therapy

- **Is there a target present?**
  - No: Alternative drug
  - Yes: Is there a response to the drug?
    - No: Alternative therapy
    - Yes: Continue therapy
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Small molecules
- $^{18}$F-DCFBC
Gastrin Releasing Peptide Receptor

• “Bombesin-like peptide family”
• Pca $\rightarrow$ GRP-R overexpression at the mRNA and protein levels (low to non-detectable in benign prostate)
• Can be labeled with $^{68}$Ga $\rightarrow$ generator produced
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Prostate Specific Membrane Antigen (PSMA)

• Transmembrane protein normally expressed in prostate epithelium, bowel, renal tubular cells and salivary glands

• PSMA expression imaged with labeled:
  – Monoclonal antibodies (Mab)
    • 7E11: labeled with $^{111}$In (SPECT); $^{89}$Zr (PET)
    • J591
  – Antibody fragments: “Minibodies”
  – Small molecules
7E11: What happened to capromab pendetide- ProstaScint®?

- FDA approved in 1996; labeled with $^{111}$In
- 7E11 binds to the intracellular domain of PSMA → only accessible if there is membrane disruption (e.g. dead or dying cells)
- The number of available targets for binding of the tracer is limited → low sensitivity for detecting viable tumor sites
- In contrast to PET, SPECT remains only semiquantitative in the clinical setting
Humanized monoclonal antibody J591

• Targets the extracellular domain of PSMA → accessible even if no membrane disruption

• The number of available targets for binding of the tracer better that 7E11 → higher sensitivity for detecting viable tumor sites

• Labeled with $^{64}$Cu, $^{89}$Zr or $^{90}$Y and $^{177}$Lu for therapy

• Other mAb: 3/A12, 3/E7, 3/F11 and 3C6
Castration resistant PCA. ↑ PSA. Recurrence?

CT

FDG

$^{89}$Zr-J591

Memorial Sloan Kettering Cancer Center
Use of WB-MRI is increasing: beyond simple detection

Blackledge et al. Plos One 2014
Summary

- PET is being increasingly used for the assessment of prostate cancer
- FDA approved tracers: FDG, Choline, NaF
- Tracers to watch:
  - Androgen receptor imaging (FDHT)
  - PSMA imaging
  - Bombesin
- Whole-body MRI may also have a role
- More research needed to determine which probe(s) should be used for each clinical scenario