PSMA: A “PET” Detective for Prostate Cancer

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Background

- CT/MRI and bone scan are not recommended for prostate cancer staging until PSA level has reached 10 or 20 ng/mL because of low accuracy and sensitivity (Wollin et al, BJU Int. 2015).
- CT, MRI, FDG- or choline-based PET/CT are not sensitive for the detection of lymph nodes metastases smaller than 8-10 mm in short axis (Hovel et al. Clin Radiol 2008).
- 68Ga-PSMA-11 PET/CT has increased accuracy and high specificity for bone, lymph nodes and visceral organ metastasis.
- It is recommended to stage recurrent prostate cancer especially for low PSA values between 0.2-10 ng/mL (Fendler et al. Eur J Nucl Med Mol Imaging 2017)
- 68Ga-PSMA-11 PET/CT not yet FDA approved.

DISCLOSURE: NONE
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Limitations of CT, MRI, and non-PSMA PET for staging prostate cancer

**CT/MRI**
- Evaluate lymph node based on size and morphology.
- However, almost 80% of metastatic lymph nodes in prostate cancer are smaller than 8 mm size threshold (Maurer et al, *Nat rev Urol* 2016).
- MRI: limited field of view
  - CT: sensitivity 42%, specificity 82%
  - MR: sensitivity 39%, specificity 82%

**Non-PSMA PET**
- 11C-choline, 18F-choline, 18F-fluorocholine, 11C-acetate
  - Moderate pooled sensitivity 39.2% (range 33-45%)
  - High specificity ≥ 95%
- Poor sensitivity → current guideline does not recommend non-PSMA PET for lymph node staging
FDA Approved PET for Recurrent Prostate Cancer

18F-Fluciclovine (Axumin) PET and 11C-Acetate PET

- 11C-Acetate PET was approved by FDA in September 2012.
- 18F-Fuciclovine (Axumin) PET was approved by FDA in May 2017.
- Both are approved for patients with suspected biochemical recurrence (BCR).
- 11C-Acetate PET/CT: poor pooled sensitivity for lymph node metastases (Meta-analysis, Evangelista et al, *Eur Urol* 2013.)
- 18F-Fluciclovine PET/CT is superior to 11C-Acetate PET/CT in detecting local recurrence and distant metastases (lymph node and bone) (Nanni et al, *Clin Nucl Med* 2015).
- A retrospective study of 10 patients with BCR underwent 18F-Fluciclovine PET/CT and 68Ga-PSMA-11 PET/CT (Calais et al, *J Nucl Med* 2017): 68Ga-PSMA-11 PET/CT may be better.
  - 5/10 patients (50%) were negative on 18F-Fluciclovine PET/CT had positive 68Ga-PSMA-11 PET/CT.
  - 68Ga-PSMA-11 PET/CT detected additional lymph node metastasis.
Negative 11C-Acetate PET vs. Positive 68Ga-PSMA-11 PET

70 year-old male status radical prostatectomy in 2002 with biochemical recurrence treated with salvage radiation and systemic hormone therapy in 2008. Now PSA 6.5 ng/mL in 2016. A 2 mm para-aortic lymph node with intense PSMA uptake was morphologically normal on CT and negative on 11C-Acetate PET/CT only 5 months ago.
PSMA (prostate specific membrane antigen)

- PSMA: type II transmembrane protein.
- Similar to transferrin receptor
- PSMA→ truncated→ PSM’ inside cytoplasm.
- Dysplastic and/or neoplastic transformation→ transfers PSMA from apical membrane to the luminal surface of the ducts.
- Expressed in adenocarcinoma prostate cancer
- Androgen-independent prostate cancer→ leads to further PSMA expression
- PSMA:PSM’ ratio increases as prostate tumor cells increase in Gleason grade.
- Gallium-68 (68Ga) labeling most common for diagnostic imaging.
- 68Ga-PSMA-11 excretion: majority kidney, some hepatobiliary.
Normal Distribution of 68Ga-PSMA-11 PET

- Salivary glands/parotid glands/lacrimal gland
- Liver, spleen
- Small intestine, colon
- Kidneys, ureters, bladder

Coronal 3D reconstruction PET image demonstrating normal physiologic distribution of Ga68-PSMA.
Pitfalls, False Negatives and False Positives

- 10% prostate cancer does not express PSMA
  - Sensitivity and specificity of PSMA detection: both 86% per-patient analysis.
- Other cells express PSMA
  - For example: astrocytes, jejenum brush border cells
- Liver metastases
  - High background uptake. Liver metastases lose PSMA expression.
- False positive: neovasculature of non-prostate cancer
  - Colon cancer, esophageal cancer, thyroid cancer, lung cancer, renal cell cancer, brain tumors
- False positive
  - Stellate ganglion, Paget’s bone disease, ribs
False Positive: Paget’s bone disease

Coronal CT (A), Ga68-PSMA PET/CT fusion (B), and bone scan (C). 64 year-old male with recurrent prostate cancer and Paget’s bone disease. Diffuse mild PSMA activity is seen in the right hemipelvis correlating to Paget’s bone disease, which was also diffusely active on bone scan (yellow arrows).
False Positive: Lung adenocarcinoma

Axial PET (A), Ga68-PSMA-11 PET/CT axial fused (B), and axial CT chest (C). 68 year-old male with recurrent prostate cancer and lung nodule. PSA 7.9 ng/mL. Restaging PSMA-11 PET demonstrated focal PSMA-11 uptake of a 11 mm right upper lobe nodule (yellow arrows). Percutaneous core biopsy of the right upper lobe nodule yielded primary lung adenocarcinoma.
False Negative: perirectal lymph node recurrence

Axial PET (A), 68Ga-PSMA-11 PET/CT axial fused (B), and axial CT pelvis (C). 65 year-old male with recurrent prostate cancer. PSA 0.43 ng/mL. PSMA-11 PET/CT demonstrated a round right mesorectal 6-7 mm lymph node without significant PSMA-11 uptake (SUVmax 0.9). CT guided lymph node biopsy yielded metastatic adenocarcinoma from prostate origin (PSA+, PSMA+, p53+).
Current Literature Review
Retrospective Data - Baseline Detection


- 130 patients with intermediate risk to high risk prostate cancer who underwent radical prostatectomy and pelvic lymph node dissection.
- Lymph node staging before treatment: sensitivity 65.9%. Specificity 98.8%.
- False negative
  - PSMA-negative primary tumors
  - Micrometastases in single lymph node


- Systemic review and meta-analysis
- 16 articles involving 1309 patients overall. 2 studies included outcomes of PSMA-PET performed for primary staging.
- 40% (95% CI 19-64%) of scans were positive for primary staging.
- Growing but limited evidence supporting use of PSMA-PET for primary staging.
Current Literature Review
Retrospective Data – Biochemical Recurrence (BCR)

- 248 patients with BCR after radical prostatectomy. 222 (89.5%) patients with positive 68Ga-PSMA PET
- Median PSA 1.99 ng/mL (0.2-59.4)

Results
- Detection rate correlates with PSA level: 96.8% for PSA ≥ 2; 57.9% for PSA 0.2 to <0.5.
- Detection rate correlates with PSA velocity: 81.8% for <1 ng/mL/yr; 100% for ≥ 5ng/mL/yr
- No significant correlation with PSA doubling time
- Higher Gleason (≥ 8) → better detection rate
- 81 patients (32.7%) PET finding only (CT missed)
- 61 patients (24.6%) PET found additional findings
- No significant correlation between putative sensitivity and androgen deprivation therapy
Current Literature Review
Retrospective Data - Biochemical Recurrence (BCR)

- 319 patients with BCR. 82.8% with positive 68Ga-PSMA scan results.

Results
- Positively correlated with PSA level
- Positively correlated with the administration of androgen deprivation therapy (ADT)
  - Patients with ADT at time of scan → more frequently positive PET
  - Patients with more advanced disease on ADT
- No correlation with Gleason score
- Lesion-based
  - Sensitivity 76.6%, Specificity 100%, NPV 91.4%, PPV 100%.
- Patient-based sensitivity 88.1%

- Post-hoc analysis, 4 institutions, 270 patients with BCR after prostatectomy without prior radiotherapy at PSA<1 ng/mL.
- Radiation Therapy Oncology Group (RTOG) consensus clinical target volumes (CTV) that included both the prostate bed and pelvic lymph nodes were contoured on CT.
- 68Ga-PSMA-11 PET/CT images were analyzed by a nuclear medicine physician.
- PSMA-positive lesions not covered by planning volumes on consensus CTV → major potential impact on treatment planning.

**Results**

- 52/270 (19%): at least one PSMA-positive lesion not covered by the consensus CTV.
- 33/270 (12%): extra-pelvic PSMA-positive lesions.
- 19/270 (7%): PSMA-positive lesions within the pelvis but not covered by consensus CTV.
- Two most common PSMA-positive locations outside the consensus CTV: bone (23/52, 44%) and perirectal lymph nodes (16/52, 31%).

**Conclusion**: Post-hoc analysis of 68Ga-PSMA-11 PET/CT implies a major impact on SRT planning in 52/270 patients (19%) with BCR (PSA < 1.0 ng/mL). Justifies a randomized imaging trial of SRT with or without 68Ga-PSMA-11 PET/CT investigating its clinical benefit.
Current Guidelines

Localization in recurrence:
• Strong retrospective data
• $^{68}$Ga-PSMA recommended: especially patients with low PSA 0.2-10 ng/mL
• Can guide salvage therapy

Primary staging:
• Several retrospective studies
• For high risk disease: Gleason > 7; PSA > 20 ng/mL; T2c-3a.
• $^{68}$Ga-PSMA MAY replace CT/MRI/Bone scan for lymph nodes and bone metastasis.
• Local tumor localization: multiparametric prostate MRI cannot be replaced
Axial CT with contrast (A), 68Ga-PSMA-11 PET (only), and fused 68Ga-PSMA-11 PET/CT (C) at the level of prostatectomy bed.

75 year-old male status post prostatectomy in 2004, now with PSA 0.3 ng/mL, BCR. Subcentimeter soft tissue along right surgical margin demonstrated significant PSMA-11 uptake. Patient was then treated with additional radiation.
Biochemical Recurrence Restaging

Axial CT (A) and 68Ga-PSMA-11 PET/CT fused (B) at the level of clavicles. Axial CT (C) and 68Ga-PSMA-11 PET/CT fused (D) at the inferior aorta. Coronal 68Ga-PSMA-11 PET 3D (E). 56 year-old male with recurrent prostate cancer. 68GA-PSMA-11 PET demonstrated PSMA positive subcentimeter lymph nodes in the left supraclavicular and infrarenal bilateral paraaortic regions, highly suspicious for metastatic disease.
Oligometastatic Recurrence

Sagittal 68Ga-PSMA-11 PET 3D (A), Axial CT at various lymph node stations in the pelvis (B-D). 65 year-old male with recurrent prostate cancer status post prostatectomy in 2014. PSA 0.28 ng/mL. There are four metastatic lymph nodes demonstrated significant PSMA-11 uptake: left external iliac (5 mm, B), left pelvic sidewall (10 mm, C), right posterior pelvic (3 mm, D), and right mesorectum (4 mm, E).
Primary Staging

Axial 68Ga-PSMA-11 PET/CT fused (A, B, C), Sagittal PET only (D), and Sagittal PET/CT fused (E).

72 year-old male newly diagnosed PCa with two positive foci on biopsy. Primary 68Ga-PSMA-11 staging scan demonstrated two intense PSMA-11 uptake foci in the right posterior peripheral apex and right anterior peripheral base (blue arrows, A, B, D, and E). A small 2 mm right external iliac lymph node with mild to moderate PSMA-11 uptake is concerning for early metastasis (yellow arrow, C).
Primary Staging

Axial T2 (A), DCE (B), ADC (C), and DWI (D) MRI prostate. Axial Ga68-PSMA-11 PET/CT fused (E) and PET only (F). Coronal 3D PET (G). 68 year-old male with newly diagnosed prostate cancer. PSA 8.6 ng/mL. MRI prostate and Ga68-PSMA-11 PET/CT two weeks apart. Focal intense PSMA-11 uptake is seen in right posterior peripheral apical gland corresponding to MRI prostate finding for suspicious lesion.
Current Guidelines

Staging before and during PSMA-directed radiotherapy:
• Imaging before PSMA-directed therapy (radioligand therapy) is crucial.

Targeted biopsy after previously negative biopsy:
• Consider for high suspicion even with negative biopsy. May be valuable
• 68Ga-PSMA PET combined with mpMRI for biopsy guidance.

Monitoring of systemic treatment in metastatic patients:
• Potential application
• Is 68Ga-PSMA PET/CT better than bone scan or CT? NO DATA YET.
Restaging after Therapy

3D Coronal 68Ga-PSMA-11 PET (A & B).
59 year-old male with metastatic prostate cancer (bone and soft tissue) underwent 3 rounds of 177Lu-PSMA in Germany. Pre-and post-therapy 68Ga-PSMA-11 PET/CT (3 months apart) demonstrated significant overall improvement in soft tissue and bone mets (despite a few new bone mets).
PSMA PET MRI

• MRI has superior soft tissue resolution compared to CT
• PSMA PET/MRI can better localize primary disease in the prostate.
• Some retrospective data suggests that 68Ga-PSMA-11 PET/CT is more useful for lymph node metastases and local staging in high-risk prostate cancer (Tulsyan et al. *Nucl Med Commun*. 2017).
• Registration/metrics agreement between MRI and PET and halo artifacts around bladder and kidneys have been some challenging issues that will need to be addressed with additional research (Domachevsky et al. *Clinical Radiology* 2017).
• Fusion MRI/PET guided biopsy can be helpful for patients with high clinical suspicion but with negative biopsy (MRI guided or TRUS guided).
Lutetium-177 PSMA for Systemic Therapy: Theranostics

• Lutetium-177 (177Lu) desirable physical properties
  • Shorter range of beta-emitter → better irradiation of small tumors
  • Emits low-energy gamma rays at 208 and 113 keV: great ex vivo imaging
  • Relatively long physical half-life (6.73 days)
  • Allow for the delivery of high activities of 177Lu PSMA to prostate cancer cells.

• Easily administered targeted therapy, intravenously injected, renally excreted, overall safe.

• Effective for tumor cells that express a high density of the PSMA receptor (pre-treatment PSMA imaging is crucial).

• Limited number of published trials and retrospective studies, but with good results showing significant treatment response and well tolerated low-grade toxicities.

• Needs prospective analysis of efficacy in randomized trials to evaluate survival benefit.

Lutetium-177 PSMA for Systemic Therapy: Theranostics

- First-in-human 68Ga-PSMA (Imaging & Therapy) I&T
  - High contrast detection of bone lesions, lymph node, and liver metastases
- 2 patients: treated with 177Lu-PSMA
  - effective, safe with no detectable side effects

- 31 patients hormone- and/or chemo-refractory with progression
- 68Ga-PSMA PET/CT image first
- Then treat with with 177Lu-DKEZ-617 PSMA (Lu-PSMA) quarterly
- Results based on biochemical response criteria:
  - Complete response 2/31
  - Partial response 20/31
  - Stable disease 3/31
  - Progress disease 6/31
- Safe and well tolerated. 2 patients with mild hemoglobin toxicity.
Conclusion

• Current recommendation for Gallium 68-PSMA-11 PET, but not FDA approved.
  • Staging for recurrent prostate cancer
  • Especially low PSA level: 0.2-10 ng/mL

• More research needed is needed, especially prospective data.

• PSMA PET MRI and Lu177 PSMA will further change our understanding of diagnosis and therapy for prostate cancer.