Imaging in the PSA-only Recurrent Setting

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Disclosures

• NONE
Incidence of Biochemical Recurrence after surgery or radiation for clinically localized prostate cancer

• Occurs within 10 years in 20-40% of patients after RP (0.2 ng/ml x2), 30-50% after RT (nadir +2.0 ng/ml, Phoenix)

• Median time to BCR is typically 2 to 3 years, but can occur up to 20 years after primary therapy

Clinical Dilemmas in Men with BCR

• Cannot tell where recurrent disease is located
• Absolute PSA levels tend to correlate with disease burden and risk for metastasis
• Shorter PSADT associated with higher risk of metastasis
• Time to BCR is prognostic in most, but not all, studies

Darwin OM et al. *Front Oncol.* 2012;2:1-6
Diagnostic Evaluation of Patients with BCR

- No guidelines on frequency of evaluation of men with BCR

Factors affecting BCR imaging use after RP.
  - Risk group before surgery,
  - Gleason score,
  - Stage,
  - Serum PSA,
  - PSADT after recurrence

- Cross sectional imaging and conventional Tc-99m bone scans are rarely positive in asymptomatic men with PSA <10 ng/mL
- Imaging should be performed more frequently when PSADT ≤10 months
- Options: TRUSP bed + biopsy; mMRI; WB MRI

NCCN© website
<table>
<thead>
<tr>
<th>Tracer</th>
<th>Half-life (min)</th>
<th>Cyclotron</th>
<th>Mechanism of action</th>
<th>Excretion</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>FDA Status</th>
<th>Panel Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-11 choline</td>
<td>20</td>
<td>Onsite</td>
<td>Cell membrane synthesis</td>
<td>Hepatic</td>
<td>32–93</td>
<td>40–93</td>
<td>✓ Cleared</td>
<td>May be used for detection of biochemically recurrent small-volume disease in soft tissues</td>
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<tr>
<td>F-18 fluorocholine</td>
<td>110</td>
<td>Regional</td>
<td>Amino acid transport</td>
<td>Renal</td>
<td>37–50</td>
<td>40–100</td>
<td>✓ Cleared</td>
<td>May be used for detection of biochemically recurrent small-volume disease in soft tissues</td>
</tr>
<tr>
<td>F-18 NaF</td>
<td>110</td>
<td>Regional</td>
<td>Adsorption within bone matrix</td>
<td>Hepatic</td>
<td>87–100</td>
<td>62–89</td>
<td>✓ Cleared</td>
<td>May be used after bone scan for further evaluation of equivocal findings</td>
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<tr>
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<td>Onsite</td>
<td>Lipid synthesis</td>
<td>Lung</td>
<td>59–69</td>
<td>83–98</td>
<td>✗ Not cleared</td>
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<tr>
<td>Ga-68 PSMA</td>
<td>68</td>
<td>Generator (no cyclotron)</td>
<td>PSMA analog</td>
<td>Renal</td>
<td>76–88</td>
<td>88–100</td>
<td>✗ Not cleared</td>
<td>May be used in clinical trial or registry</td>
</tr>
</tbody>
</table>

* Interpret with caution; few studies used biopsy/surgery as gold standard; see Nuclear imaging, above, for references.
Meta-analysis: $^{11}$C-Choline-PET/CT for Prostate Cancer Biochemical Recurrence

- 18 studies (2,126 patients)  
  - Pooled detection rate 62%

- 12 studies (1270 patients with adequate data to assess sensitivity and specificity  
  - Pooled sensitivity (Sens) 89%  
  - Pooled specificity (Spec) 89%

- Local recurrence: Sensitivity 61%, Specificity 97%

- Nodal/distant metastasis: 36% detection rate

- Bone Metastasis: 25% detection rate


\[ ^{11}\text{C}-\text{Choline-PET/CT Sensitivity by PSA Level} \]

- Overall sensitivity specificity 85%/93%
  - Pooled analysis of 358 patients post-RP with BCR (≥ 2 consecutive PSA measurements greater than 0.2ng/mL)
- Detection Rate by PSA level:
  - PSA 0.2 to 1 ng/mL : 19%
  - PSA 1 to 3 ng/mL : 46%
  - PSA >3 ng/mL : 82%

Choline C11 PI 2015.
**18F- Fluciclovine**

- *anti*-1-amino-3[18F]flurocyclobutane-1-carboxylic acid

- L-leucine analog accumulates in prostate cancer cells
  - Relatively little renal excretion
  - Not metabolized like 11C-methionine

- Uptake related to functional activity of amino acid transporters, which are upregulated in prostate cancer cells
- Axumin
- Initial US approval in 2016
- Indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood PSA levels following prior treatment
Multicenter Study of FACBC-PET/CT in Biochemically Recurrent Prostate Cancer

• 596 patients with BCR after RP and/or RT

• PSA median range: 2.0 (0.05-82.0)

• Endpoints
  • Detection rate stratified by baseline PSA
  • Diagnostic performance vs pathology reference standard (N=143)

Fluciclovine in Biochemically recurrent Prostate Cancer
Prospective Study of $^{18}$F-Fluciclovine vs $^{11}$C-CholinePET/CT in BCR PC

- Both imaging studies performed ≤ 1 week (N-89)
  - Median PSA 3.35 ng/mL (range, 0.20-20.72 ng/mL)

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>$^{11}$C-Choline, %</th>
<th>$^{18}$F-Fluciclovine, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>32</td>
<td>37</td>
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<tr>
<td>Specificity</td>
<td>40</td>
<td>67</td>
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<tr>
<td>PPV by disease site</td>
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<tr>
<td>Overall (n-89)</td>
<td>90</td>
<td>97</td>
</tr>
<tr>
<td>Local</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>82</td>
<td>91</td>
</tr>
<tr>
<td>Bone</td>
<td>83</td>
<td>100</td>
</tr>
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Nanni C et al. EJNM 2016; 43:1601
## FACBC-PET vs. $^{11}$C-Choline-PET

### Table 11  Positive predictive value of the two tracers for different relapse series

<table>
<thead>
<tr>
<th>Site</th>
<th>Positive predictive value (%)</th>
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<tbody>
<tr>
<td></td>
<td>$^{11}$C-Choline</td>
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The LOCATE study

• $^{18}$F-Fluciclovine detected lesions in 57% of patients
  - PSA :0-0.5ng/mL : 31%
  - >0.5 - 1.0ng/mL : 50%
  - >1.0 - 2.0ng/mL : 66%
• Management plans were revised in 126/213 patients (59%, 95% CI 52-66)
• 78% were “major” changes involving a change in treatment modality
• 70% were informed by positive $^{18}$F-Fluciclovine PET/CT findings

Figure 1. A, in 68-year-old male after radical prostatectomy with PSA rising to 0.4 ng/ml fluciclovine (18F) transverse PET/CT detected recurrence (arrow) in left prostate bed. B, in 67-year-old male after radical prostatectomy with sipuleucel-T and bicalutamide, PSA rising to 0.91 ng/ml and negative bone scan sagittal fluciclovine (18F) PET/CT detected 3 to 4 mm presacral node (arrow). C, in 64-year-old male after radical prostatectomy with PSA rising rapidly to 3.7 ng/ml 2 weeks before scanning transverse fluciclovine (18F) PET/CT (bone window) detected solitary bone metastasis (arrow) in right proximal femur.
MGH Experience with 125Fluciclovine PET

- PSA $\leq 0.3$ ng/ml   No detection
- 0.3-0.5 ng/mL detection ~ 25%
- 0.5-1.0 ng/mL detection 45%, (30% equivocal)
- 1-2 ng/mL 76% detection rate
- 2-5 ng/mL 94% detection rate
- >5 ng/mL 100% detection rate

Caveat: multireader QA project of imaging attributes and not absolute truths

Personal Communication: Edwin Palmer, MD/ MGH Nuclear Medicine
Figure 3

5-year bFFS (0.2 ng/mL <= Median PSA <= 0.6)
5-year bFFS (0.6 < Median PSA <= 1.0)
5-year bFFS (1.0 < Median PSA <= 2.0)

Expected 5-year bFFS with PSA 0.4 ng/mL
Expected 5-year bFFS with PSA 0.8 ng/mL
Expected 5-year bFFS with PSA 1.5 ng/mL
Grade 3 GH/GU Toxicity
Expected Rate of Late Grade 3 GH/GU Toxicity

Probability of Disease Control or Toxicity (%)
Salvage Radiotherapy Dose
Prostate Specific Membrane Antigen (PSMA)

• PSMA is normally expressed by cells in the CNS, normal prostate, proximal renal tubules and salivary gland

• High expression in prostate cancer cells (with further increases when tumors become castration resistant)

• New small molecule ligands target the extracellular domain of PSMA (Prostascint, targets the intracellular domain)

• F-18 and Ga-68 agents under investigation

Positron emission tomography/computed tomography PET/CT with $^{68}$GA-PSMA11 is more accurate than $^{18}$F-Fluciclovine PET/CT at detecting recurrent prostate cancer in men.

- 50 consecutive patients with biochemical recurrence and PSA levels of $\geq 0.2$ and $\leq 2.0$ ng/mL

- All patients underwent PSMA and Fluciclovine PET/CT scans median time interval six days

- Each scan interpreted by three independent blinded expert readers not involved in study and data acquisition
• detection rate significantly lower with Fluciclovine than PSMA

• -PET/CT per patient 26% versus 56% P = .003

• -Pelvic-nodes 8% versus 30% P = 0.003

• -Any extra pelvic lesions 0% to 16% P = 0.008

• In addition, reader agreement for PSMA PET/CT images were significantly higher ( Fluciclovine PET/CT .67 versus 0.2, P = 0.015 )
Conclusion

• PSMA should be standard of care

• the authors felt the main explanation for these results is much higher tumor to PET signal ratio PSMA than with Fluciclovine
Standard of Care Versus Metastases-directed Therapy for PET-detected Nodal Oligocurrent Prostate Cancer Following Multimodality Treatment: A Multi-Institutional Case-control study

T. Steuber, C. Jilg et al. European Association of Urology. 2018;2405-4569
Staging $^{68}$Ga-PSMA PET/CT. Gleason 4 + 5. PSA 19 ng/mL. Intense $^{68}$Ga-PSMA avid primary disease in prostate with $^{68}$Ga-PSMA avid superficial left inguinal node metastasis.
Primary prostate cancer. PIRADS 4/5 left lobe of prostate on multiparametric MRI. Fused to $^{68}$Ga-PSMA PET/CT images for MRI in-bore guided targeted biopsy.
PET scans for Biochemical Recurrence

• Detection rate dependent on PSA level (lack of histologic correlation)

• Flucyclovine seems to be more sensitive than Choline

• PSMA-based scans may be most accurate

• PET scans can change treatment decisions

• Unknown whether such treatment changes make a difference in ultimate outcomes compared to SOC