18F-Choline: Prostate Cancer

18F-choline PET/CT: an increasing role in cancer evaluation
Epidemiology

- Approximately 15.3 percent of men will be diagnosed with prostate cancer at some point during their lifetime, based on 2008-2010 SEER data.
- In 2011, there were an estimated 2,707,821 men living with prostate cancer in the United States.

<table>
<thead>
<tr>
<th>Estimation</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated New Cases</td>
<td>233,000</td>
</tr>
<tr>
<td>% of All New Cases</td>
<td>14.0%</td>
</tr>
<tr>
<td>Estimated Deaths</td>
<td>29,480</td>
</tr>
<tr>
<td>% of All Deaths</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

SEER Stat Fact Sheets: Prostate Cancer
Risk factors

• Diet
  – Tomatoes, vegetables, soy, red meet,
  – fish (protect!)
• Pharmaceutical agents
• Occupational and environmental exposures
• Family history
• Genetic factors
Prostatic specific antigen

- The availability of PSA with a growing and aging population has resulted in a dramatic increase in the incidence of prostate cancer (PCa).
- Sensitivity of PSA test is roughly 67.5-80% and specificity is 60-70%
- A PSA concentration >4 ng/mL, is followed by a complete
Diagnosis

- Detection or primary cancer
  - PSA (free, total, F/T ratio and trend)
  - Digital rectal examination
  - Biopsy (12-14-24 core-biopsy)

- Staging of Pca
  - TNM staging system
  - Histologic Grading: the Gleason Score
  - Imaging (MRI/BS/c.e.CT, PET)
Treatment choice - risk category-based (1)

Very low* and low*
- ≥20 yrs → Active surveillance
- 10-20 yrs → Observation
- <10 yrs → RT or brachytherapy
- RP

Intermediate*
- 10-20 yrs → RP+PLND
- <10 yrs → RT+ADT±brachytherapy
- Observation

* Based on expected patient survival
Treatment choice - risk category-based (2)

- High
  - RT+ADT or
  - RT+brachytherapy±ADT or
  - RP+PLND

- Very high
  - RT+ADT or
  - RT+brachytherapy±ADT or
  - RP+PLND or
  - ADT

- Metastatic
  - ADT or RT+ADT
Choline metabolism in Cancer

- Aboagye et al (1999; 59: 80-84) identified **malignant transformation rather than just cell proliferation** as the cause of abnormal choline metabolism in cancers (especially in breast and prostate cancer)

- Phosphocholine is both a precursor and a breakdown product of phosphatidylcholine, which together with other phospholipids and neutral lipids, **forms the characteristic bilayer structure of cellular membranes and regulates membrane integrity**

- Four different types of choline-transporting transmembrane systems have been **implicated in cancer**:
  - high-affinity choline transporters (CHTs),
  - choline transporter-like proteins (CTLs),
  - organic cation transporters (OCTs)
  - organic cation/carnitine transporters (OCTNs)
# Choline metabolism in Cancer

<table>
<thead>
<tr>
<th>Cancer site*</th>
<th>PCho</th>
<th>GPC</th>
<th>tCho</th>
<th>Enzyme expression</th>
<th>Enzyme activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Cancer</td>
<td>Normal</td>
<td>Cancer</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>0.48±0.08</td>
<td>0.91±0.20</td>
<td>0.86±0.11</td>
<td>0.68±0.17</td>
<td>0.64±0.10 and 1.79±0.24</td>
</tr>
<tr>
<td>Breast (?)</td>
<td>0.03±0.03</td>
<td>0.79±0.55</td>
<td>0.04±0.04</td>
<td>0.28±0.20</td>
<td>0.07±0.07</td>
</tr>
<tr>
<td>Liver</td>
<td>0.17±0.11</td>
<td>1.36±0.50</td>
<td>2.46±0.37</td>
<td>0.59±0.15</td>
<td>ND</td>
</tr>
<tr>
<td>Prostate</td>
<td>0.02±0.07</td>
<td>0.39±0.40</td>
<td>0.29±0.26</td>
<td>0.57±0.87</td>
<td>0.31±0.33</td>
</tr>
</tbody>
</table>

CCT, CTP:phosphocholine cytidylyltransferase; CHKα, choline kinase-α; CHT1, choline transporter 1; CT, choline transport; CTL, choline transporter-like; GPC, glycerophosphocholine; OCT, organic cation transporter; PCho, phosphocholine; PC-PLC, phosphatidylcholine-specific phospholipase C; PLD, phospholipase D1; tCho, total-choline-containing compounds.
The elevation of tCho expression is a specific biomarker of prostate cancer and correlates with Gleason score and aggressiveness.
Choline and PET

18F-Choline*

**PROS:**
- The longer half-life of 18F (110 min) allows transportation of 18F-choline to centers without a cyclotron;

**CONS:**
- An early urinary appearance in the urinary tract due to an incomplete tubular reabsorption, that can be a drawback when considering local recurrence.

11C-Choline

**PROS:**
- A major advantage of this radiotracer is its rapid blood clearance (5 min) and its rapid uptake within prostate tissue (3–5 min).
- It has a negligible urinary elimination, which, in selected cases, proves to be an advantage.

**CONS:**
- The 20 min half-life of 11C restricts the use of 11C-Choline to centers with an onsite cyclotron.

*18F-Fluoromethylcholine (FCH), 18F-fluoroethylcoline (FEC) and fluoromethyl-methylethyl-2-hydroxyethylammonium choline (FMMCH)
18F-fluoromethylcholine (FCH)

18F-fluoroethylcholine (FEC)
Biodistribution of 18F-choline PET

Thanks to Annibale Versari, Reggio Emilia, ITALY
Both the 18F-labelled choline derivatives can be successfully used for detecting prostate cancer recurrence. The two tracers showed comparable physiological distribution and uptake.

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Tilki et al**</td>
<td>Restaging, 56</td>
<td>68.4%</td>
<td>73.3%</td>
<td>70.2%</td>
<td>Pelosi et al*</td>
<td>Restaging, 56</td>
<td>82.7%</td>
<td>96.2%</td>
<td>89.2%</td>
</tr>
<tr>
<td>Wurshmidt et al</td>
<td>Restaging, 26</td>
<td>92%</td>
<td>-</td>
<td>-</td>
<td>McCarty et al**</td>
<td>Restaging, 26</td>
<td>96%</td>
<td>96%</td>
<td>96%</td>
</tr>
<tr>
<td>Steuber et al*</td>
<td>Staging, 20</td>
<td>0%</td>
<td>100%</td>
<td>-</td>
<td>Poulsen et al*</td>
<td>Staging, 25</td>
<td>100%</td>
<td>95%</td>
<td>96%</td>
</tr>
</tbody>
</table>

*patient-based analysis; **lesion-based analysis
European Farmacopea
only
Metil-18F-Choline
FCH
Protocol acquisition

- Patient preparation:
  - No preparation
  - A specific diet, eliminating some foods
  - A fasting of at least 6 hours

- Image protocol:
  - Dynamic image from 1 to 8 min
  - A very early WBS (8 minutes)
  - Middle early WBS (30 minutes)
  - A conventional WBS (60 minutes)
  - A late WBS after 120 minutes
18F-Choline PET or PET/CT in PCa

• Initial staging
• Restaging
  – Progressive increase in PSA value
• Radiotherapy planning
  – After RP and before a salvage RT
  – After elective RT
• Evaluation of response to therapy
  – Hormone therapy, Chemotherapy
T-Staging

111 patients with an untreated PCa
- A significant correlation between sections with highest Choline uptake and sextants with maximal tumoral infiltration at histological analysis ($r=0.68; p=0.0001$)
- No correlation between SUVmax and PSA value or Gleason Score was found ($P=0.10$ and 0.28)

Oyama et al. found that 18F-FDG PET may be useful in the subset of patients with suspected poorly differentiated primary tumors (Gleason sum score above 7) and higher serum PSA values.

Beheshti et al., Radiology 2010; 254: 925-33
About T-stage

~ MRI (± an endorectal coil) is superior in terms of sensitivity and specificity for initial local assessment of PCa compared to radiolabelled choline PET/CT.

~ MRI is superior to Choline PET for the detection of some features of the disease (extracapsular disease, invasion of the seminal vesicles) that would impact the management of the PCa.

~ Routine **Choline-PET is not indicated** for pre-treatment local T staging.
### N-Staging

**Nomograms** are graphical statistical tools that use different variables to correlate the potential risk (based on PSA value, Gleason Score, Clinical Staging)

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N of pts</th>
<th>Sensitivity % (IC 95%)</th>
<th>Specificity %, (IC 95%)</th>
<th>PPV % (IC 95%)</th>
<th>NPV % (IC 95%)</th>
<th>Accuracy % (IC 95%)</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hacker et al, 2006</td>
<td>20</td>
<td>80 (55-100)</td>
<td>33 (4-63)</td>
<td>47 (16-78)</td>
<td>45 (23-67)</td>
<td>1 8 2 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Husarik et al, 2008</td>
<td>43</td>
<td>20 (15-55)</td>
<td>100</td>
<td>90 (81-100)</td>
<td>91 (82-99)</td>
<td>1 38 0 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beheshti et al, 2010</td>
<td>130*</td>
<td>45 (30-60)</td>
<td>96 (91-100)</td>
<td>82 (70-94)</td>
<td>79 (71-88)</td>
<td>18 86 4 22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poulsen et al, 2010</td>
<td>25</td>
<td>100</td>
<td>95 (87-100)</td>
<td>75 (26-100)</td>
<td>100</td>
<td>3 21 1 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poulsen et al, 2012</td>
<td>210**</td>
<td>73.2 (58.1-84.3)</td>
<td>87.6 (81.8-91.7)</td>
<td>58.8 (45.2-71.3)</td>
<td>93.1 (88-96.1)</td>
<td>-</td>
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</tr>
</tbody>
</table>

*intermediate-high risk pts; **the mean diameter of the TN-LN metastases was significantly larger than that of the FN-LN (10.3 mm vs. 4.6 mm, p < 0.001).
High risk and very high risk prostate cancer and the role of choline PET/CT at initial staging

Laura Evangelista, Fabio Zattoni, Andrea Guttilla, Anna Rita Cervino, Michele Gregianin, Marta Burei, Filiberto Zattoni, Giorgio Saladini

25 PCa patients:
- 11 (44%) had a positive PET/CT finding in prostate gland,
- 7 (28%) in prostate and loco-regional lymph nodes,
- 3 (12%) in prostate, lymph nodes and bone
- 4 (16%) cases only in prostate and bone.
- The SUVmax of lymph nodes ranged between 1.51-15.89 and the value was correlated with the size of lesions (r=0.93; p<0.01).

<table>
<thead>
<tr>
<th>Procedure</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100</td>
</tr>
<tr>
<td>Specificity</td>
<td>75</td>
</tr>
<tr>
<td>PPV</td>
<td>60</td>
</tr>
<tr>
<td>NPV</td>
<td>100</td>
</tr>
<tr>
<td>Accuracy</td>
<td>82</td>
</tr>
</tbody>
</table>

Per patient analysis in 11 pts undergoing surgical treatment

10.4 mm
8.3 mm
6.7 mm
### 18F-choline vs. 11C-Choline and N-stage

<table>
<thead>
<tr>
<th></th>
<th>18F-Choline (n. study: 4)</th>
<th></th>
<th>11C-Choline (n. study: 6)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pooled value (CI 95%)</td>
<td>Chi-square/I-square</td>
<td>Pooled value (CI 95%)</td>
<td>Chi-square/I-square</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.40 (0.27-0.53)</td>
<td>11.35/73.6%</td>
<td>0.58 (0.45-0.70)</td>
<td>16.37/69.5%</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.96 (0.91-0.98)</td>
<td>6.63/54.7%</td>
<td>0.94 (0.90-0.97)</td>
<td>4.77/0%</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>6.44 (1.64-25.30)</td>
<td>1.05/56.9%</td>
<td>8.99 (4.43-18.27)</td>
<td>5.52/9.4%</td>
</tr>
<tr>
<td>Negative likelihood ratio</td>
<td>0.74 (0.45-1.21)</td>
<td>12.19/75.4%</td>
<td>0.39 (0.16-0.92)</td>
<td>33.31/85%</td>
</tr>
<tr>
<td>Diagnostic odds ratio</td>
<td>10.64 (1.32-85.91)</td>
<td>3/65%</td>
<td>29.19 (10.44-81.57)</td>
<td>5.70/12.3%</td>
</tr>
</tbody>
</table>

Evangelista et al, Eur Urol 2013
About N-stage

- Choline-PET/CT seems to have better performances than conventional imaging in LN staging.
- Choline-PET/CT accuracy is still not sufficient because of the limited spatial resolution of the technique.
  - NPV of the technique in identifying microscopic disease and/or small pathological nodes remains suboptimal, limiting its usefulness in the definition of prophylactic volumes.
M-Staging

The majority of studies involving patients at initial staging of disease, demonstrated the advantages of 18F-Choline PET for bone metastases.

~~~ In the early phase of the bone metastatic process (bone marrow infiltration), Choline-PET is more sensitive (Beheshti et al, 2010)

~~~ In the last phase of the bone metastatic process, in the presence of sclerotic lesions, Choline-PET seems more specific, with no uptake in non-viable lesions (De Bari et al, 2014)
Medullary bone lesions
18F-Choline vs. 18F-Fluoride

Langsteger et al, QJNMMI 2011

<table>
<thead>
<tr>
<th>Per patient overall</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCH</td>
<td>20/22=91%</td>
<td>16/18=89%</td>
<td>36/40=90%</td>
</tr>
<tr>
<td>F-Na</td>
<td>20/22=91%</td>
<td>15/18=83%</td>
<td>35/40=88%</td>
</tr>
</tbody>
</table>

FCH and F-Na PET/CT scans indicated metastatic disease in 56% of patients with high-risk prostate cancer without conclusive evidence of metastases on a previous 99m Tc-MDP bone scan.

*high risk patients
Imaging Bone Scan

BONE SCAN

ANT POST

18F-CHOLINE PET/CT

18F-NA PET

COREGISTRATE PET and CT
About M-staging

- **Choline-PET/CT** is an optimal imaging modality for the assessment of viable PCa burden in the skeleton.
- Choline-PET could be recommended for all patients with suspected metastasis and/or with high risk PCa as it could potentially **change the therapeutic approach**.

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>N of pts</th>
<th>Change in management</th>
<th>Why</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beheshti et al, 2010</td>
<td>130*</td>
<td>19 (15%)</td>
<td>Distant LN and bone mets</td>
</tr>
<tr>
<td>Beheshti et al, 2010</td>
<td>83**</td>
<td>17 (20%)</td>
<td>Distant LN and bone mets</td>
</tr>
<tr>
<td>Beheshti et al, 2008</td>
<td>38</td>
<td>2 (5%)</td>
<td>Osteomedullary lesions</td>
</tr>
<tr>
<td>Langsteger et al,</td>
<td>49</td>
<td>6 (12%)</td>
<td>Distant LN and bone mets</td>
</tr>
<tr>
<td>Evangelista et al, EANM 2013</td>
<td>25***</td>
<td>9 (36%)</td>
<td>Distant LN and bone mets</td>
</tr>
</tbody>
</table>

*intermediate and high risk patients; **high risk patients, ***high and very high risk of patients

....in staging!
............. advantages at initial staging

Prostate gland

Lymph node

Bone
Restaging or Biochemical progression disease

- Patients with a rising PSA after a primary local treatment (radiotherapy, surgery, brachytherapy) can be considered as:
  - “oligometastatic” or “oligo-recurrent”;
  - “extensive metastatic” or with systemic disease
## Diagnostic performance in restaging setting

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N of pts</th>
<th>Standard of reference</th>
<th>Sens. % (IC 95%)</th>
<th>Spec. %, (IC 95%)</th>
<th>PPV % (IC 95%)</th>
<th>NPV % (IC 95%)</th>
<th>Acc. % (IC 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Husarik et al, 2008</td>
<td>68</td>
<td>Histological examination</td>
<td>90 (83-97.7)</td>
<td>100</td>
<td>100</td>
<td>45.5 (18-89)</td>
<td>91.1 (84-98)</td>
</tr>
<tr>
<td>Pelosi et al, 2008</td>
<td>56</td>
<td>Biopsy/imaging/FUP</td>
<td>82.7 (69-97)</td>
<td>96.2 (89-100)</td>
<td>96 (89-100)</td>
<td>83.8 (70-98)</td>
<td>89.2 (81-97)</td>
</tr>
<tr>
<td>Henninger et al, 2013</td>
<td>35</td>
<td>Biopsy/histology/imaging/FUP</td>
<td>64.3 (47-82)</td>
<td>57.1 (21-94)</td>
<td>85.7 (73-99)</td>
<td>28.6 (5-62)</td>
<td>62.9 (47-79)</td>
</tr>
<tr>
<td>Schillaci et al, 2012</td>
<td>49</td>
<td>Biopsy/histology/imaging/FUP</td>
<td>91.7 (83-100)</td>
<td>100</td>
<td>100</td>
<td>81.3 (60-100)</td>
<td>93.9 (87-100)</td>
</tr>
<tr>
<td>Marzola et al, 2013</td>
<td>233</td>
<td>Biopsy/histology/imaging/FUP</td>
<td>100</td>
<td>97 (94-100)</td>
<td>98 (95-100)</td>
<td>100</td>
<td>99 (97-100)</td>
</tr>
</tbody>
</table>

### a) Prostatic fossae recurrence

### b) Lymph node recurrence

### c) Skeletal recurrence
## Restaging in Prostatic fossae recurrence

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N of pts</th>
<th>Site of disease</th>
<th>Standard of reference</th>
<th>Sens. % (IC 95%)</th>
<th>Spec. %, (IC 95%)</th>
<th>PPV % (IC 95%)</th>
<th>NPV % (IC 95%)</th>
<th>Acc. % (IC 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vees et al, 2007</td>
<td>11*</td>
<td>Local recurrence</td>
<td>Histological examination</td>
<td>43 (6-71)</td>
<td>50 (10-99)</td>
<td>60 (23-96)</td>
<td>33 (12-79)</td>
<td>45 (16-74)</td>
</tr>
<tr>
<td>Panebianco et al, 2010</td>
<td>84**</td>
<td>Local recurrence</td>
<td>TRUS biopsy and PSA values</td>
<td>83 (74-91)</td>
<td>63 (29-96)</td>
<td>95 (91-100)</td>
<td>28 (3-59)</td>
<td>81 (73-89)</td>
</tr>
</tbody>
</table>

*Pts at very low PSA values (<1 ng/mL); ** PSA ranged between 0.8-2.5 ng/mL

<table>
<thead>
<tr>
<th>Imaging modality</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI</td>
<td>93%</td>
<td>88%</td>
<td>99%</td>
<td>58%</td>
<td>93%</td>
</tr>
<tr>
<td>(if PSA as gold standard)</td>
<td>92%</td>
<td>75%</td>
<td>96%</td>
<td>60%</td>
<td>89%</td>
</tr>
<tr>
<td>(if TRUS as gold standard)</td>
<td>94%</td>
<td>100%</td>
<td>100%</td>
<td>57%</td>
<td>94%</td>
</tr>
<tr>
<td>PET/CT</td>
<td>83%</td>
<td>43%</td>
<td>95%</td>
<td>28%</td>
<td>81%</td>
</tr>
<tr>
<td>(if PSA as gold standard)</td>
<td>62%</td>
<td>50%</td>
<td>88%</td>
<td>18%</td>
<td>60%</td>
</tr>
<tr>
<td>(if TRUS as gold standard)</td>
<td>92%</td>
<td>33%</td>
<td>98%</td>
<td>43%</td>
<td>91%</td>
</tr>
</tbody>
</table>
Restaging LN recurrence

<table>
<thead>
<tr>
<th>Author, year</th>
<th>N of pts</th>
<th>Standard of reference</th>
<th>Sens. % (IC 95%)</th>
<th>Spec. % (IC 95%)</th>
<th>PPV % (IC 95%)</th>
<th>NPV % (IC 95%)</th>
<th>Acc. % (IC 95%)</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Husarik et al, 2008</td>
<td>23</td>
<td>Histological examination</td>
<td>100 (59-97)</td>
<td>70</td>
<td>78.2 (61-95)</td>
<td>-</td>
<td>78 (61-95)</td>
<td>18</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

- Pelvic/retroperitoneal salvage lymph node dissection
- Limited accuracy in case of micrometastatic
Visceral Metastases

October, 2012

February, 2013

PSA: 46 ng/mL

PSA: 78 ng/mL
Trigger PSA...

<table>
<thead>
<tr>
<th>Detection rate</th>
<th>PSA&lt;1ng/mL</th>
<th>PSA&lt;2ng/mL</th>
<th>PSA&lt;5ng/mL</th>
<th>PSA&gt;5ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20%</td>
<td>71.4%</td>
<td>44%</td>
<td>73%</td>
</tr>
<tr>
<td></td>
<td>36%</td>
<td>43%</td>
<td>62%</td>
<td>86.7%</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>55.6%</td>
<td>80%</td>
<td>87%</td>
</tr>
<tr>
<td></td>
<td>29%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

18F-Choline PET detection rate %

- **PET-positive**
  - a "fast" PSA kinetic
  - mean PSAdt=6 months
  - mean PSAvel=9.3 ng/mL/yr

- **PET-negative**
  - a "slow" PSA kinetic
  - mean PSAdt=15.4 months
  - mean PSAvel=0.9 ng/mL/yr

(Marzola et al, CNM 2013)
A population of 1000 pts with recurrent Pca undergoing 18F-Choline PET in two Italian centers and 1 Slovene center

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>IC95%</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>1.038</td>
<td>1.020-1.056</td>
</tr>
<tr>
<td><strong>GS=7</strong></td>
<td>0.288</td>
<td>0.205-0.404</td>
</tr>
<tr>
<td><strong>GS&gt;7</strong></td>
<td>0.446</td>
<td>0.323-0.616</td>
</tr>
<tr>
<td>Surgery yes vs. no</td>
<td>0.686</td>
<td>0.563-0.834</td>
</tr>
<tr>
<td>RT yes vs. no</td>
<td>1.408</td>
<td>1.173-1.689</td>
</tr>
<tr>
<td>HT yes vs. no</td>
<td>1.980</td>
<td>1.606-2.441</td>
</tr>
<tr>
<td>Ongoing HT yes vs. no</td>
<td>1.424</td>
<td>1.178-1.721</td>
</tr>
<tr>
<td>Chemotherapy yes vs. no</td>
<td>1.385</td>
<td>1.149-1.668</td>
</tr>
<tr>
<td>1&gt;PSA&lt;2</td>
<td>0.184</td>
<td>0.112-0.300</td>
</tr>
<tr>
<td>PSA≥2</td>
<td>0.470</td>
<td>0.282-0.785</td>
</tr>
</tbody>
</table>
### 18F-choline vs. 11C-Choline and restaging

<table>
<thead>
<tr>
<th></th>
<th>All Pooled value (%95 CI)</th>
<th>11C-choline* (n. study: 12)</th>
<th>18F-choline* (n. study: 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sensitivity</strong></td>
<td>85.6% (82.9-88.1)</td>
<td>81.8% (77.9-85.2)</td>
<td>91.8% (88.0-94.7)</td>
</tr>
<tr>
<td><strong>Specificity</strong></td>
<td>92.6% (90.1-94.6)</td>
<td>91.4% (88.3-93.9)</td>
<td>95.6% (91.2-98.2)</td>
</tr>
<tr>
<td><strong>Positive likelihood ratio</strong></td>
<td>8.53 (3.62-20.09)</td>
<td>7.19 (2.59-19.99)</td>
<td>11.75 (1.86-74.39)</td>
</tr>
<tr>
<td><strong>Negative likelihood ratio</strong></td>
<td>0.17 (0.11-0.28)</td>
<td>0.20 (0.13-0.29)</td>
<td>0.11 (0.03-0.46)</td>
</tr>
<tr>
<td><strong>Diagnostic odds ratio</strong></td>
<td>62.123 (24.78-155.72)</td>
<td>53.77 (29.02-99.62)</td>
<td>132.55 (7.59-2315.5)</td>
</tr>
</tbody>
</table>

*all site of disease

Evangelista et al, CNM 2013
Main critical issues

• Histological confirmation of Choline-PET/CT findings is rarely available, also because
  – anastomotic biopsy presents a low positive detection rate, especially for PSA levels <1 ng/mL;
  – salvage pelvic lymph node dissection is not routinely performed in patients with a biochemical cancer relapse and evidence of nodal disease;
  – biopsy at the bone level is not commonly performed.

• In the majority of investigations, clinical follow-up and conventional instrumental examinations are used to confirm Choline-PET findings, making these studies primarily observational.
About restaging

- The **overall detection rate** of 18F-Fluorocholine-PET was significantly increased when the trigger PSA increases, but higher PSA levels are often a sign of metastatic spread, which is a contraindication for potentially curable local treatments.

- **PSAdt and PSAvel**, should be taken into account to stratify patients with a biochemical failure to be referred to a Choline PET/CT.

- **MRI was more helpful**, particularly when there is a **low likelihood of distant metastases**

- **Micro-metastatic lymph node lesions can be missed** by 18F-Choline PET (pay attention to guide salvage RT!!!)
ADT and 18F-choline findings

- Choline-PET/CTs are more frequently positive (higher positive detection rate) in hormone-resistant patients than in hormone-sensitive patients.
- In patients who develop a biochemical failure during ADT, hormone therapy itself does not significantly affect the uptake of Choline in sites of disease recurrence.

- DeGrado et al. (DeGrado et al, Cancer Res 2001;61:110–7) confirmed the inhibitory effect of ADT on the uptake of radiolabelled Choline.
Doubts about PET and ADT

- In vitro and in vivo studies provide quite strong evidence that the uptake of radiolabelled Choline is significantly reduced by ADT in patients with hormone-sensitive PCa. In these patients, **ADT should probably be started after the pre-treatment PET/CT**, even though this indication for the Choline-PET/CT remains debated.

- **No indications about the correct timing between the withdrawal of ADT and the execution of the PET/CT** could be obtained from the available literature.

- There is **insufficient evidence to support the withdrawal of ADT** before Choline-PET/CT in patients with hormone-resistant PCa.
Radiation treatment

- “Theragnostic imaging” in radiotherapy is the properly coined term to describe the introduction of molecular images to draw and more selectively treat each voxel of tumor volume with dose painting based on biological and functional characterization.
  - Biological Target Volume (BTV)
  - Gross Tumour Volume (GTV)
Radiation treatment planning

• In this setting, integrated PET/CT are showing several interesting applications in defining the BTV.
• Despite the potential interest of Choline-PET/CT, the contouring methods based on it are still are not considered totally reliable, due to uncertainties to establish fixed absolute and relative thresholds of primary and recurrent PCa to identify the BTV.
• Semiautomatic segmentation techniques, using thresholds adapted case per case, have been performed to simplify RT planning in the prostate and are under investigation.
Radiation treatment planning

- In a large clinical experience on 66 PCa patients undergoing a 18F-Fluorocholine PET/CT for treatment planning: a matching between the lobe(s) with a positive biopsy and the GTV defined on PET was confirmed in 97% of cases.

- Treatment planning with dose escalation to intraprostatic lesion by 18F-Fluorocholine-PET/CT does not impact the toxicity profile (by the administration of a specific questionnaire)

Pinkawa et al, Strahlenther Onkol 2010; 186: 600-6 Pinkawa et al, Radiation Oncol 2012; 7:4
Re-irradiation

- 18F-Fluorocholine-PET/CT-based GTV in local recurrent PCa after initial irradiation, in 17 pts.
  - manual delineation (GTV\text{man}) by radiation oncologist and nuclear medicine physicians,
  - a fixed threshold of 40% and 50% of the maximum signal intensity (GTV\text{40\%} and GTV\text{50\%}),
  - signal-to-background ratio-based adaptive thresholding (GTV\text{SBR}),
  - a region growing (GTV\text{RG}) algorithm.

Validated semi-automated segmentation techniques for 18F-Choline PET-guided GTV delineation allow to lower inter-observer variability compared to manual techniques

FEC-PET/CT could be helpful in dose escalation in PCa allowing boost doses > 60 Gy to metastatic lymph nodal regions if PET/CT planned image-guided IMRT, is used.

(Würschmidt et al. Radiation Oncology 2011, 6:44)
**RT planning and 18F-choline PET**

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Promising data are emerging from several retrospective series, but other prospective studies are needed to implement the benefit of radiotherapy with a PTV based on Choline-PET imaging in primary and loco-regionally relapsing PCa.</td>
<td>• Low negative predictive value, because it can miss microscopically affected nodes and the intraprostatic microscopic disease.</td>
</tr>
</tbody>
</table>
Response to Enzulamide

- Enzulamide is a new generation hormone therapy, able to produce a survival improvement in CRPC pts pre-treated with docetaxel.

- Preliminary data showed a good concordance between the Choline-PET response and biochemical response in either responding or progressing pts, while most of the pts with stable metabolic parameters showed a good PSA reduction.

<table>
<thead>
<tr>
<th>Metabolic response</th>
<th>PSA response</th>
<th>Agreement PSA- FCH PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP (≥30%)</td>
<td>&lt; 50% 9</td>
<td>PR: 9/10= 90%</td>
</tr>
<tr>
<td></td>
<td>Stable 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progression 1</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>&lt; 50% 8</td>
<td>SD: 1/10= 10%</td>
</tr>
<tr>
<td></td>
<td>Stable 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progression 1</td>
<td></td>
</tr>
<tr>
<td>PD (≤30%)</td>
<td>&lt; 50% 1</td>
<td>PD: 6/8= 75%</td>
</tr>
<tr>
<td></td>
<td>Stable 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progression 6</td>
<td></td>
</tr>
</tbody>
</table>

Maines F, J Clin Oncol 32, 2014 (suppl 4; abstr 76)
Response to Abiraterone

Design
29 metastatic CRPC pts progressing after docetaxel chemotherapy received Abiraterone acetate (1,000 mg daily with prednisone 5 mg twice daily in continuous 28-day cycles).

Results
PSA decline and CTCs levels correlated in 55%
In 41% of pts with a 50% or more decline in PSA both a CTCs response and a FCH PET/CT response was observed.

Conclusions
Monitoring pts with CRPC who receive Abiraterone using both CTCs and metabolic imaging indicate discrepancy in 45% with response assessment using PSA.

Le Moulec S et al, J Clin Oncol 30, 2012 (suppl 5; abstr 63)
A 67-year old man with PCa treated by RP+LNPD (pT3bN1; GS: 9; positive margins). Serial monthly PSA (0.56 ng/mL->2.37 ng/mL->3.03 ng/mL) therefore HT (Enantone)

October, 2012

PSA 3.03 ng/mL

June, 2013

PSA 0.001 ng/mL
Baseline

SUVmax: 17.98
SUVavg: 6.22

Post-chemotherapy

SUVmax: 6.98
SUVavg: 4.25
Take home message

- **Initial staging**
- **Restaging**
  - Progressive increase in PSA value
- **Radiotherapy planning**
  - After RP and before a salvage RT
  - After elective RT
- **Evaluation of response to therapy**
  - Hormone therapy, Chemotherapy