Staging Advanced PCa and imaging response assessment

Jelle Barentsz
Geert Villiers and Anwar Padhani

Prostate MR Reference/Expert Center, Nijmegen, NL
Conflict of interest
I can be stubborn
NODES
N-Staging: When?
N-Staging: When?

EAU-Guidelines (2016)

N-staging in i.m.- and high-risk patients (>5%)
in general:

PSA >10 ng/mL
OR Gleason score >6
Or cT3 or higher
N-Staging: Where?
N-Staging: Where?

Obturator 30%
External Iliac 30%
Internal iliac 30%
Presacral 7%
Pararectal 4%
Common Iliac 1-2%

Variable spread: no single sentinel node
Pathways of spread
N-Staging: How?

EAU-Guidelines: gold standard = open or laparoscopic (extended) lymphadenectomy
1. No benefit in clinical outcome
1. No benefit in clinical outcome
2. More complications
1. No benefit in clinical outcome
2. More complications
3. But accurate assessment of cancer spread
N-Staging: How?

40% of $\Theta$ LN not detected with PLND

Heesakkers, Radiology 2008
Recent own data 16/26 \((62\%)\) ⊕ LN not removed

Pre-operative

Post-operative
Recent own data 16/26 (62%) ⊕ LN not removed

Pre-operative

Post-operative
Recent own data 16/26 (62%) ⊕ LN not removed

What is the relevance of very small ⊕ LN?
Size of metastatic nodes in PCa
Nano-Combidex-MRI
N-Staging: How: Imaging?
N-Staging: **How: Imaging?**

- CT
- MRI
- DWI
- Nano-MRI
- PET-CT
N-Staging: **How: Imaging?**

- **Sensitivity** for metastatic nodes: ~40%
  - CT: 42% (range 5%-94%)
  - MRI: 39% (range 6% - 83%)

**Specificity:** ~80%
- CT: 82% (range 80% - 83%)
- MRI: 82% (range 79% - 83%)
N-Staging: How: Imaging?

- Sensitivity for metastatic nodes: ~40%
  CT: 42% (range 5%-94%)
  MRI: 39% (range 6% -83%)
Problems current lymph node diagnosis

Metastatic LN

68% of ⊗ LM smaller than 5 mm\textsuperscript{1-3}

\textsuperscript{1}Thoeny, Radiology 2014; \textsuperscript{2}Birkenhauser, Eur Urol 2014; \textsuperscript{3}Fortuin, IJROB 2012
\textsuperscript{4}Hovels, Clin Radiol 2008; \textsuperscript{5}Heesakkers, Radiology 2008; \textsuperscript{6}Meijer, Radiology 2014
Problems current lymph node diagnosis

Metastatic LN

68% of $\Theta$ LM smaller than 5 mm$^{1-3}$

70% of $\Theta$ LM metastases are not detected by current imaging$^4$

$^1$Thoeny, Radiology 2014; $^2$Birkenhauser, Eur Urol 2014; $^3$Fortuin, IJROB 2012
Problems current lymph node diagnosis

Metastatic LN

68% of $\Theta$ LM smaller than 5 mm$^{1-3}$

70% of $\Theta$ LM metastases are not detected by current imaging$^4$

40% of $\Theta$ LM not detected with PLND$^5$

$^1$Thoeny, Radiology 2014; $^2$Birkenhauser, Eur Urol 2014; $^3$Fortuin, IJROB 2012
Problems current lymph node diagnosis

Metastatic LN

68% of ⊕ LM smaller than 5 mm$^{1-3}$

70% of ⊕ LM metastases are not detected by current imaging$^4$

40% of ⊕ LM not detected with PLND$^5$

50% of ⊕ LM outside COTG radiotherapy CTV$^6$

$^1$Thoeny, Radiology 2014; $^2$Birkenhauser, Eur Urol 2014; $^3$Fortuin, IJROB 2012
N-Staging: How?

- CT
- MRI
- DWI
- Nano-MRI
- PET-CT
Small lymph node

Decreased diffusion
  (High signal on b600)

Eiber, J Magn Reson Imaging 2011;33:1160
N-Staging: How?

Technique (3Tesla)

3D-T1 + 3D-T2 + DWI (b0, b500, b1000)

3 readers, correlation DWI - morphology

only normal-sized nodes (< 8 mm)

Results (per patient)

73% sensitivity, 86% specificity

missed nodes <5 mm (majority <3 mm)
N-Staging: How?

Technique (3Tesla)
3D-T1 + 3D-T2 + DWI (b0, b500, b1000)
3 readers, correlation DWI - morphology
only normal-sized nodes (< 8 mm)

Results (per patient)
73% sensitivity, 86% specificity
missed nodes <5 mm (majority <3 mm)
N-Staging: How?

- CT
- MRI
- DWI
- Nano-MRI
- PET-CT
Nano-MRI
ferumoxtran-10
Combidex/Sinerem
1.5 mm LN metastasis
1.5 mm LN metastasis
1.5 mm LN metastasis
**Sytematic Review: QUADAS-2**

### Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>True positives</th>
<th>False positives</th>
<th>False negatives</th>
<th>True negatives</th>
<th>Specificity [95% CI]</th>
<th>Sensitivity [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harisinghani 2003</td>
<td>33</td>
<td>2</td>
<td>0</td>
<td>45</td>
<td>1.00 [0.89, 1.00]</td>
<td>0.96 [0.85, 0.99]</td>
</tr>
<tr>
<td>Heesakkers 2008</td>
<td>50</td>
<td>23</td>
<td>11</td>
<td>291</td>
<td>0.82 [0.70, 0.91]</td>
<td>0.93 [0.89, 0.95]</td>
</tr>
<tr>
<td>Triantafyllou 2013</td>
<td>12</td>
<td>9</td>
<td>8</td>
<td>46</td>
<td>0.60 [0.36, 0.81]</td>
<td>0.84 [0.71, 0.92]</td>
</tr>
</tbody>
</table>

**Pooled Sensitivity** 88%

**Pooled specificity** 93%
Not (yet) available
It will soon be available
N-Staging: How?

- CT
- MRI
- DWI
- Nano-MRI
- PET-CT
$^{68}$Ga-PSMA PET-CT vs other tracers

$^{68}$GA-PSMA PET-CT
$^{68}\text{Ga}$ PSMA PET-CT

$^{68}\text{Ga(HBED-CC)-antibody}$

Prostate cancer

Kidneys

Salivatary Glands

Small bowel

$^{11}$C-Choline PET-CT vs nano-MRI 2005

Nodal Size

Fortuin Eur Urol 2013
$^{11}\text{C-Ch-PET-CT vs nano-MRI 2005 and} \ Nodal\ Size$
$^{11}$C-Ch- vs $^{68}$Ga-PSMA PET-CT and MRL

Nodal Size
$^{68}$Ga-PSMA PET-CT and nano-MRI 2017

Nodal Size
68Ga PSMA PET-CT

$^{68}$Ga PSMA PET-CT

LN Staging

12/30 high-risk patients; 53/608 LN metastases
$^{68}\text{Ga PSMA PET-CT}$

LN Staging

12/30 high-risk patients; 53/608 LN metastases

Sensitivity: 33%
Specificity: 100%
PPV: 100%
NPV: 53%

Buddaus, Eur Urol 2015
**68Ga PSMA PET-CT**

LN Staging

12/30 high-risk patients; 53/608 LN metastases

- Sensitivity: 33%
- Specificity: 100%
- PPV: 100%
- NPV: 53%

Median size detected LN: 13.6 mm
Median size undetected LN: 4.3 mm

Buddaus, Eur Urol 2015
$^{68}$Ga PSMA PET-CT
LN Staging

12/30 high-risk patients; 53/608 LN metastases

Smallest positive LN: 4.0 mm

Buddaus, Eur Urol 2015
WHOLE BODY MRI
# MET-RADS: WB-MRI sequences; by indications

<table>
<thead>
<tr>
<th>Sequence description</th>
<th>Core protocol</th>
<th>Extensions for comprehensive assessments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical use</td>
<td>Lesion detection &amp; characterization</td>
<td>Response assessment</td>
</tr>
<tr>
<td>1. Whole spine – sagittal, T1W, TSE</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Whole spine – sagittal, STIR (preferred) or fat suppressed T2W</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Whole body (vertex to mid thighs) – T1W, GRE Dixon technique. Fat image reconstructions are mandatory.</td>
<td>Axial or coronal</td>
<td>Axial and coronal</td>
</tr>
<tr>
<td>4. Whole body (skull base to mid-thighs) – axial, diffusion weighted, STIR fat suppression, contiguous slicing, multiple stations.</td>
<td>2 b-values</td>
<td>3 b-values</td>
</tr>
<tr>
<td>5. Whole body (vertex to mid thighs) – axial, T2W, TSE No fat suppression</td>
<td>Option</td>
<td>Yes</td>
</tr>
<tr>
<td>6. Regional assessments including small field of view images, brain studies and contrast enhancement</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Short MRI protocol in <30 mins (detection); Comprehensive MRI protocol in 45min (response)

- T1W-SE 2.14 min
- STIR-SE 3.20 min
- T1W-GRE 57 sec
- DWI b50-900: 17.01 mins
- b900 MIP
- b900 MPR
WB-MRI detects more malignant lesions/patient than bone scans

74 m CRPC on Enzalutamide. PSA 0.4 ng/ml
3 lesions on planar bone scan; 6 lesions on WB-MRI
74 m CRPC, PSA 0.4: residual active disease
Irregular/thick hyperintense rim on T2W-FS images, ↑cellularity on DWI: suspicious of active disease despite suppressed PSA
WB-MRI outperforms bone scans in detecting bone metastases & is as good as CT for lymph node evaluations.


- 100 men with high risk prostate cancer
- 5 independent reviewers (CT = 2; WB-MRI = 2; BS+X-ray = 1)
- Metastases prevalence (best value comparator): 68 patients
- MRI detected bone metastases in 7/8 of 55 BS negative patients

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>WB-MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>77-82</td>
<td>77-82</td>
</tr>
<tr>
<td>Specificity</td>
<td>95-96</td>
<td>96-98</td>
</tr>
<tr>
<td>PPV</td>
<td>92-95</td>
<td>94-97</td>
</tr>
<tr>
<td>NPV</td>
<td>84-87</td>
<td>84-87</td>
</tr>
</tbody>
</table>

Lymph node metastases (prevalence 44 patients)
- CT: 77-82, 95-96, 92-95, 84-87
- WB-MRI: 77-82, 96-98, 94-97, 84-87

Bone metastases (prevalence 51 patients)
- BS+X-ray: 86, 98, 98, 87
- WB-MRI: 98-100, 98-100, 98-100, 98-100

Fig. 2 – Whole-body magnetic resonance imaging (MRI) versus false-negative bone scintigraphy (BS) for bone metastasis detection in a 65-yr-old patient with newly diagnosed prostate cancer (prostate-specific antigen 18 ng/ml; Gleason score 7 [4 + 3]). (A) BS (anterior-posterior and posterior-anterior views) shows no significant lesion. (B) Coronal T1 and (C) diffusion-weighted MRI images of the whole body confirm bone metastases within L3 and the left iliac bone (arrows).
Biological processes involved in therapy induced changes in DWI

Solid cellular tumor

Microscopic cellular necrosis

Necrotic tissue

No Rx effect  Likely response  Highly likely response

95%  1500 µm²/s  95 centile of Ex1

27Feb12  23July12

Choline-PET/CT, MRI, and planar bone scan for bone metastasis detection in prostate cancer

Choline-PET/CT, MRI, and planar bone scan for bone metastasis detection in prostate cancer

$^{68}$Ga PSMA PET-CT and DWI WB-MRI
$^{68}$Ga PSMA PET-CT and DWI WB-MRI
$^{68}$Ga PSMA PET-CT and DWI WB-MRI
$^{68}$Ga PSMA PET-CT and DWI WB-MRI
$^{68}$Ga PSMA PET-CT and DWI WB-MRI

Your diagnosis?
Post-operative 68Ga PSMA PET-CT
pT2b N1 Mx, PSA NADIR 0.4, in 3 months 0.8

✓ 68Ga PSMA: Left positive node
✓ Rest normal
✓ Left ureter
✓ Right positive node
Current imaging tools: fit for purpose (detection & response)?

Platinum Priority – Review – Prostate Cancer

Rationale for Modernising Imaging in Advanced Prostate Cancer

Anwar R. Padhani, Frederic E. Lecouvet, Nina Tunariu, Dow-Mu Koh, Frederik De Keyzer, David J. Collins, Evis Sala, Stefano Fanti, H. Alberto Vargas, Giuseppe Petralia, Heinz Peter Schlemmer, Bertrand Tombal, Johann de Bono
mCRPC. Rx Enzalutamide. 2° resistance

<table>
<thead>
<tr>
<th>Screening</th>
<th>Week 13</th>
<th>Week 25</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA 45.5</td>
<td>PSA 0.6</td>
<td>PSA 0.3</td>
</tr>
</tbody>
</table>

Retroperitoneal nodes.
WB-MRI - no bone metastases
BS = no lesions

Retroperitoneal nodes improved.
WB-MRI = no lesions
BS = no lesions

Retroperitoneal nodes improved.
WB-MRI = 1 new bone metastasis
BS = no lesions
mCRPC. Rx Enzalutamide. Oligo-progression

Week 25; PSA 0.3 ng/ml
### Oligo-progression

- **Week 25**
  - PSA 0.3
  - Retroperitoneal nodes improved.
  - WB-MRI = 1 new bone metastasis
  - BS = no lesions

### Recorded date of progression

- **Week 37**
  - PSA 0.4
  - Retroperitoneal nodes worse.
  - WB-MRI = 5 bone lesions
  - BS = 2 lesions (outside flare period; needs confirmation)

### Poly-metastatic progression confirmed

- **Week 49**
  - PSA 1.5
  - Retroperitoneal nodes progressing. New lymphoedema.
  - WB-MRI = 7 bone lesions
  - BS = 7 lesions (1 on posterior projection)

---

The need to wait to confirm poly metastatic BS lesions (PCWG 2/3) before declaring progression results in (unacceptable) delays in starting the next therapy.

---

**Actual date of Oligo-progression**

<table>
<thead>
<tr>
<th>Week</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>0.3</td>
</tr>
</tbody>
</table>

**Recorded date of progression**

<table>
<thead>
<tr>
<th>Week</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>0.4</td>
</tr>
</tbody>
</table>

**Poly-metastatic progression confirmed**

<table>
<thead>
<tr>
<th>Week</th>
<th>PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>49</td>
<td>1.5</td>
</tr>
</tbody>
</table>
MET-RADS: standard for WB-MRI in metastatic cancer

Develop criteria to assess response of metastatic bone disease

METRADS: https://youtu.be/kDZjmERFFuk
Progression criteria on morphology

## Appendix table 3. MET-RADS-P regional response assessment categories 4-5

<table>
<thead>
<tr>
<th>Response Assessment Category (RAC)</th>
<th>Classification</th>
<th>Region</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Likely to be progressing</td>
<td>Local, nodal and visceral</td>
<td>• Changes depicting tumour progression that do not meet RECIST v1.1/PCWG criteria for progression (see below)</td>
</tr>
</tbody>
</table>
|                                   |                 | Bone   | • Evidence of worsening disease, but not enough to fulfil criteria for RAC 5.  
|                                   |                 |        | • Equivocal appearance of new lesion(s)  
|                                   |                 |        | • No change in size but increasing SI on high b-value images (with ADC values <1400 \( \mu m^2/s \)) consistent with possible disease progression*  
|                                   |                 |        | • Relapse disease: re-emergence of lesion(s) that previously disappeared or enlargement of lesion(s) lesions that had partially regressed/stabilized with prior treatments  
|                                   |                 |        | • Imaging depicted bone lesions that might be clinically significant (therefore excludes asymptomatic fractures in non-critical bones)  
|                                   |                 |        | • Soft tissue in spinal canal causing narrowing not associated with neurological findings and not requiring radiotherapy |
| 5                                 | Highly likely to be progressing | Local, nodal and visceral | • Changes depicting tumour progression that meet RECIST v1.1/PCWG criteria for unequivocal progression (see below) |
|                                   |                 | Bone   | • New critical fracture(s)/cord compression requiring radiotherapy/surgical intervention  
|                                   |                 |        | → only if confirmed as malignant by MRI signal characteristics  
|                                   |                 |        | • Unequivocal new focal/diffuse area(s) of metastatic infiltration in regions of prior normal marrow  
|                                   |                 |        | • Unequivocal increase in number/size of focal lesions  
|                                   |                 |        | • Evolution of focal lesions to diffuse neoplastic pattern  
|                                   |                 |        | • Appearance/increasing soft tissue associated with bone disease  
|                                   |                 |        | • New lesions/regions of high signal intensity on high b-value images with ADC value between 600-1000 \( \mu m^2/s \) |

*ADC cut-off values determined by measurements of untreated lesions [21,36,37] ; ** based on the reproducibility of ADC values of <20% [38,39].

Primary resistance to AR directed Rx

67 yo male with metastatic castrate resistant prostate cancer
Abiraterone and Zoladex
Progression on morphology & DWI/ADC maps
Primary resistance to AR directed Rx

67 yo male with metastatic castrate resistant prostate cancer
Abiraterone and Zoladex

29 April 16 - 30 August 16

[Imaging and Prostate Report]

Bladder + Rectal involvement

Response assessment categories (RAC): 1: Highly likely to be responding; 2: Likely to be responding; 3: No change; 4: Likely to be progressing; 5: Highly likely to be progressing. Single lesion 1 RAC only; ≥2 lesions/full disease use both RACs.
67 yo male with metastatic castrate resistant prostate cancer
Abiraterone and zoladex
Progression on morphology & DWI/ADC maps

Tumor vol: 155 mL
Tumor vol: 536 mL

Ex1
Ex2
95 cent of Ex1
1500 µm²/s

Syno.via Frontier MR Total Tumor Load software; Siemens Healthcare
Response criteria on morphologic MRI

### Appendix table 3. MET-RADS-P regional response assessment categories 1-3

<table>
<thead>
<tr>
<th>Response Assessment Category (RAC)</th>
<th>Classification</th>
<th>Region</th>
<th>Description</th>
</tr>
</thead>
</table>
| **1** Highly likely to be responding | Local, nodal and visceral | Bone | • Consistent with RECIST v1.1/PCWG criteria for unequivocal response (partial/complete). See below.  
• Return of normal marrow in areas previously infiltrated by focal/diffuse metastatic infiltration  
• Decrease in number/size of focal lesions  
• Evolution diffuse neoplastic pattern to focal lesions  
• Decreasing soft tissue associated with bone disease  
• Dense lesion sclerosis (edge to edge), sharply defined, very thin/disappearance of hyperintense rim on T2W-FS images  
• The emergence of intra/peri-tumoural fat within/around lesions (fat dot/halo signs)  
• Previously evident lesion shows increase in ADC from $\leq 1400 \, \mu m^2/s$ to $>1400 \, \mu m^2/s$ *  
• $\geq 40\%$ increase in ADC from baseline with corresponding decrease in high b-value SI; and morphological findings consistent with stable or responding disease ** |
| **2** Likely to be responding | Local, nodal and visceral | Bone | • Changes depicting tumour response that do not meet RECIST v1.1/PCWG criteria for partial or complete response (see below)  
• Evidence of improvement, but not enough to fulfil criteria for RAC 1. For example:  
• Previously evident lesions showing increases in ADC from $\leq 1000 \, \mu m^2/s$ to $<1400 \, \mu m^2/s$*  
• $>25\%$ but $<40\%$ increase in ADC from baseline with corresponding decrease in high b-value SI; and morphological findings consistent with stable or responding disease ** |
| **3** No change | All | | • No observable change |

*ADC cut-off values determined by measurements of untreated lesions [21,36,37]; ** based on the reproducibility of ADC values of $<20\%$ [38,39].

Metastatic Prostate Cancer (bone & nodes)
Pre & post 4x 4x docetaxel, goserelin & prednisolone

27Feb12

23July12

Retroperitoneal nodes and 2 sites of cord compression (PSA 93.8 ng/ml)

Looks worse on T1W. Can’t tell on T2W. Cord compression better. Excellent response on DWI. PSA 9.9 ng/ml.
Prostate Cancer

4x docetaxel, goserelin & prednisolone

27Feb12

23July12

27Feb12

23July12
mCNPC
4x docetaxel, goserelin & prednisolone

Biological processes involved in therapy induced changes in DWI

Solid cellular tumor

Microscopic cellular necrosis

Necrotic tissue

Take home messages

1. The Bone Scan has had its time
2. WB-MRI with DWI is emerging
3. METRADS is quite time consuming and a challenge for wide-spread use
4. New tracers (^{68}\text{Ga} \text{ PSMA}) \text{ PET-CT} are emerging, role in diagnosis and follow-up has to be established
FUTURE

1. For nodes nano (Combidex) MRI

2. For bone and local recurrence;
   \(^{68}\)Ga PSMA and/or WB-MRI (incl. DW)

METRADS: https://youtu.be/kDZjmERFF