PROSTATE CANCER: LATEST IN IMAGING TESTS AND STAGING CLASSIFICATION

Jin Wei Kwek  MBBS, FRCR(UK), FAMS
Senior Consultant,  Div of Oncologic Imaging,
Dy Director, Div of Cancer Education
Adj Asst Prof, Duke-NUS Medical School
SCOPE

• Diagnosis of prostate cancer, staging classification and risk assessment

• Imaging tests and applications.
Diagnosis of Prostate Cancer

Trans-Rectal US guided Biopsy

- High specificity but Low sensitivity (FN up to 30%)
- May miss aggressive cancer and detect insignificant cancer
- Missed Cancers: Apex, Lateral and Anterior cancers
- Potential role for imaging in detecting clinically significant tumour and guiding biopsy

Patel AR et al Urol 2004
TNM Staging Classification

- **Majority new diagnosed cT1c – non palpable**
- **T2** Tumour confined within the prostate:
  - T2a Tumour involves one half of one lobe or less
  - T2b Tumour involves more than half of one lobe, but not both lobes
  - T2c Tumour involves both lobes
- **T3** Tumour extends through the prostatic capsule:
  - T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
  - T3b Seminal vesicle(s) invasion
- **T4** Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
TNM Staging Classification

N-Regional Lymph Nodes (Below common iliac bifurcation)
- NX Regional lymph nodes cannot be assessed
- N0  No regional lymph node metastasis
- N1  Regional lymph node metastasis

M-Distant Metastasis
- M1a Non-regional lymph node(s)
- M1b Bone(s)
- M1c Other site(s)
## TABLE 1. Summary of Changes Between the Seventh and Eighth Editions

<table>
<thead>
<tr>
<th>CHANGE</th>
<th>DETAILS OF CHANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition of primary tumor (T)</td>
<td>Pathologically organ-confined disease is considered pT2 and no longer subclassified by extent of involvement or laterality.</td>
</tr>
<tr>
<td>Histologic grade (G)</td>
<td>The Gleason score (seventh edition criteria) and the grade group (eighth edition criteria) should both be reported.</td>
</tr>
<tr>
<td>AJCC prognostic stage groups</td>
<td>Stage III includes select, organ-confined disease based on prostate-specific antigen and Gleason/grade group status.</td>
</tr>
<tr>
<td>Statistical prediction models</td>
<td>Those statistical prediction models that satisfy all necessary criteria are included in the staging manual.</td>
</tr>
</tbody>
</table>

Abbreviation: AJCC indicates American Joint Committee on Cancer.

Ref: CA Cancer J Clin 2017;67:245-253
AJCC 8th Ed: Radiological Considerations

1) T Stage: MRI most useful for demarcation of extent of primary tumour and extraprostatic extension.

2) Nodal Involvement: Both CT and MRI understages nodal involvement.

3) Bony Metastasis: T99m standard for osteoblastic bony metastasis.

4) Visceral Metastasis: CT and MRI useful for visceral metastasis but this is rare for initial staging.
Prostate Cancer Risk Classification

Based on PSA findings, Clinical/DRE results and histopathological findings at TRUS biopsy:

- **Low-risk**: PSA <10 ng/mL, and biopsy Gleason score ≤6, *Gleason Grade Group 1* or clinical stage T1–T2a

- **Intermediate-risk**: PSA 10–20 ng/mL, Gleason score 7 (3+4=7/GGG 2 or GS 4+3+7/GGG 3) or clinical stage T2b-T2c.

- **High-risk Localised**: PSA >20 ng/mL, Gleason score 8–10, or clinical stage T2c.

- **High-risk Locally Advanced**: Any PSA, any GS cT3-4, or cN+

  *ESMO Practice Guidelines, Parker C et al Ann Oncol 2015, NCCN v2/2017*
Low Risk Prostate Cancer

- Options: radical surgery, radiation therapy or active surveillance.
- 15.6% have higher grade cancer on final histology
- Presence of higher % of positive cores, length of core involvement, PSA density are associated with risk of understaging.
  - Parker C et al Ann Oncol 2015
- **Very Low risk**: PSA<10 ng/mL, GS ≤6/Gleason Group 1, and Clin stageT1c, < 3 cores positive, each core <50% +ve, PSA density <0.15 ng/mL/g
  - (ESMO Practice Guidelines 2015, NCCN guidelines v2 2017)
- Potential for MR imaging to confirm absence of clin significant disease, stratify patients for active surveillance, plan nerve and continence sparing surgery, and focal therapy
Prostate Cancer Risk Assessment

**Intermediate-risk patients:** Being staged for curative intent.
- Risk of extra-prostatic spread rises significantly.
- DRE understages cancer.
- Role of MRI in detecting extra-capsular disease by means of a “staging protocol” [2b, A].

**High-risk patients:** Risk of metastasis
- Bone scintigraphy and CT scan or whole-body MRI or choline PET to detect skeletal or nodal metastases [III, B]

*EAU Guidelines 2015*

*ESMO Practice Guidelines 2015*
Imaging Tests and Applications

**Imaging Tests:**
- MpMRI
- Bone scan and CT scan
- WB-MRI
- Choline PET-CT
- Ga68 PSMA PET-CT

**Applications:**
- Detection of clinically significant tumour foci
- Loco-regional Staging
- Systemic Staging and Follow-up
- Biochemical Recurrence
MRI Prostate

High resolution T2 W MRI

- Detection of tumour focus in conventional T2 Anatomical Imaging limited by presence of BPH, haemorrhage and prostatitis/fibrosis.

High resolution T2 W MRI
Multiparametric MRI

- Additional functional parameters increases confidence in tumour detection and local staging.

<table>
<thead>
<tr>
<th>Tools</th>
<th>Biological Property Depicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>DW-MRI</td>
<td>Extent of gland formation and cellular density</td>
</tr>
<tr>
<td>DCE-MRI</td>
<td>Angiogenesis, vascular permeability</td>
</tr>
<tr>
<td>$^1$H-MRSI</td>
<td>Cell membrane turnover and replacement of normal glandular tissue</td>
</tr>
</tbody>
</table>
Diffusion Weighted MRI

Essential component of mp - MRI:

• Short acquisition time and high contrast resolution.
• Increase sensitivity and specificity of tumour detection.  
  
  *Woodfield CA AJR 2010*

• Adds confidence to detection of extra-capsular spread for inexperienced readers.

T2 W  
B=1000
Prostate cancer - high signal intensity on DWI at high b-values and low signal intensity/value on ADC maps

ADC values allow quantitative assessment
Diffusion Weighted MRI

- DWI measures the Brownian motion of water molecules
- Reduced diffusion of water in cancer – increased cellularity of malignant lesions, with reduced intra- and extracellular space
- Lower ADC value correlates with Higher Gleason score.


Tamada et al JMRI 2008, Woodfield CA AJR 2010
Prostate cancer shows early intense enhancement and washout.
DCE-MRI: High temporal resolution (<10 s) with axial T1W 3D gradient echo sequences at 3mm thickness at an injection rate of 3 mL/s.
Combined with T2WI and DWI to improve tumour localisation and local staging.
MR $^1$H Spectroscopy Imaging

- 3D Chemical shift imaging
- Highly specific “fingerprints of chemical compounds in MR spectrum”.
- Generally abandoned ACRIN 6659: AUC of 0.60 for MRI vs 0.58 for MRI + MRSI

Weinreb et al Radiol 2009;251:122

MRI Prostate Cancer

Normal:
Prominent citrate peak 2.6 ppm

Prominent choline/creatine peak 3.2 + 3.0 ppm

MRI in Prostate Cancer Detection

- MpMRI has excellent sensitivity for detection of tumour foci 5mm of Gleason score 7 of more:
- For GS7, PCa detection rate is 82-88% for 5-20mm and 97% for more than 20mm foci.
- For GS>7, PCa detection rate is 93% for 5-20 mm and 100% for more than 20 mm foci.

Hoeks CM Eur Urol 2012
MpMRI in Prostate Cancer Detection

- MpMRI may also detect anterior tumours as well as tumours at apex missed by systematic biopsy.
  - Hoeks CM Radiol 2013, Lemaitre L Eur Radiol 2009

- Before repeat biopsy for benign biopsy results, MpMRI recommended with view to MR guided or MRI-TRUS fusion biopsy [III,B]
  - ESMO Practice Guidelines 2015
MpMRI in Prostate Cancer Detection

- MpMRI detects more aggressive PCa foci of GS7 and above.  
  *Turkbey B et al J Urol Nov 2011*

- Potential as a pre-biopsy triage test to increase detection of significant PCa foci with a few trials published.  

MRI is not recommended routinely prior to initial prostate biopsy, but emerging data suggest that, in men undergoing initial biopsy, targeting using MRI/ultrasound fusion may increase the detection of clinically significant, higher-risk (Gleason grade ≥ 4+3) disease while lowering the detection of lower-risk (Gleason sum 6 or lower-volume Gleason grade 3+4) disease. All men with indications for biopsy should receive the standard 12-core TRUS-guided biopsy regardless of MRI results.

Follow-up for benign biopsy results – consider multiparametric MRI and/or refined prostate biopsy techniques image guidance using MRI/ultrasound fusion, transperineal, or saturation prostate biopsies.

*NCCN guidelines Version 1.2016*
MpMRI in Prostate Cancer Detection

- Inter-reader variability is a concern for MpMRI.
- PIRADS (2012) proposed to standardize interpretation but 2 recent papers suggested PIRADS did not improve inter-reader variability.  
  Rosenkrantz Radiol 2013, Vache T Radiol 2014
- PIRADS v2 introduced at RSNA 2014
  - “simple system” with 39 prostate sectors,
  - Score PZ on DWI,
  - Score TZ on T2W,
  - DCE of secondary importance.
  - Score of 1-5 but really “Yes”, “Maybe”, “No”
MpMRI in T staging

- MpMRI currently most useful imaging test for local staging [2b, A]

  EAU Guidelines 2015

- Extraprostatic extension into periprostatic adipose tissue, neurovascular bundle and bladder neck - Stage T3a

![T2 W](image1.png)  
Right NVB invasion

![T2 W](image2.png)  
Right ECE – focal bulge
MpMRI in T staging

- Seminal vesicle invasion (SVI) corresponds to stage 3b

Normal Seminal Vesicles

Seminal Vesicles Invasion
Systemic Staging - Nodal Staging

- **CT and MRI** indirectly assess nodal invasion by measurement of nodal short axis diameter.
- Sensitivity is <40% with 10mm threshold.
- Recommended in NCCN v2 2017 Guidelines for:
  - T3, T4
  - T1, T2 with normogram predicting >10% risk of nodal metastases (but level of evidence is low).
- **Choline PET-CT** sensitivity for intermediate risk patients is 8.2% in region based and 18.9% in patient based analysis.  
  
  *Joniau S Eur Urol 2013.*

- **MRI with ultra-small particles of iron oxide (USPIOs)** improves detection of microscopic nodal metastases but is limited by lack of availability.
  
  *Hovel AM Eur Radiol 2004*
Systemic Staging - Bone Metastases

- **Tc99M Bone Scan** – Wide spread availability and low cost

- **NCCN guidelines v2 2017**:
  - T1 and PSA >=20
  - T2 and PSA >= 10
  - T3 or T4
  - GS 8 or more
  - **symptomatic patients**, independent of PSA level, Gleason score or clinical stage. *Abuzallouf S, J Urol 2004*

- Low sensitivity and requires radiography or MRI for detection of pathological fractures and complications.
Systemic Staging - Bone Metastases

- MRI more sensitive and specific than bone scan and targeted radiography in detection of bone metastases. (Sen/Spec of 98-100%)
- Also detects pathological fractures and complications like cord compression.

MRI detects more bony metastases and pathological fracture of T8.
Systemic Staging - Bone Metastases

- More sensitive and specific than combined bone scan, targeted radiography and abdominopelvic CT.
  
  *Pasaglou V, Prostate 2014*

- Meta-analysis – MRI better than choline PET-CT and bone scan for detection of bone metastases.
  
  *Shen G, Skeletal Radiol 2014*
Wb-MRI for Nodal and Bone Metastases

- ESUR guidelines recommended a bone and nodal MR algorithm for systemic staging of prostate cancer.  
  *Barentsz JO, Eur Radiol 2012*

- A combined prostate MR and whole body MR protocol including DWI is technically robust for both loco regional staging and evaluation of nodal and bony metastases.

- Advantages include:
  - **Single study for local and systemic staging**, thus improving patient’s convenience.
  - **WB-MR** is well tolerated and all patients in this study completed examination without complications.

*Abstract presented at AOCR 2014*
Combined MR Prostate and wb-MRI

- 66 years old male with prostate cancer GS4+4 (PSA=90 ng/ml)
- T2 hypointense focus in the right peripheral zone with restricted diffusion and focal bulge.
- Combined T2w and DWI sequences increases confidence in detection of tumor focus in the right peripheral zone as well as right extra-capsular extension.
- The ADC value of the focus was 0.503 X 10^{-3} mm^2 which confirms the presence of tumor focus compared to normal left peripheral lobe ADC value of 1.237 x 10^{-3} mm^2.
Combined MR Prostate and wb-MRI

- Enlarged left external iliac lymph node (arrow)
- DWI showed higher CNR as compared to all other sequences which facilitates lesion detection.
Combined MR Prostate and wb-MRI

- 68 years old male with metastatic prostate cancer (PSA=8.6 ng/ml, Gleason score 5+5)
- Bony metastasis (arrow) involving the right pubic bone which is better visible on coronal T1w as compared to coronal T2w TIRM sequences.
Combined MR Prostate and wb-MRI

- Bony metastasis (arrow) involving the right pubic bone which is better visible on axial T1w as compared to axial DWI sequences.

- Incidental note is made of a bursa in front of the right hip joint medial to the ilio psoas muscle.
Biochemical Recurrence

- In patients with BCR after RT considered for local salvage therapy, prostate MpMRI may be used to localise abnormal areas and guide biopsy (3, C).  
  *EUA guidelines 2015*
- Local recurrence after RP: imaging needed only if histological proof is mandatory before salvage Rx or localization change treatment planning.
- 70 year old male, post radical prostatectomy, PSA 20.9 ng/ml

---

**T2w**  
**DWI b=800**  
**ADC**
Biochemical Recurrence after RP

- Choline based (F18 or C11) PET - low sensitivity and specificity for BCR when PSA is low
- Not recommended if PSA < 1ng/ml (3, A)
  
  *EUA guidelines 2015*

- Prostatic –specific membrane antigen (PSMA) – transmembrane protein overexpressed in PCa cells.

- **G68 PSMA PET** – emerging tech for detection of cancer spread in late stage PCa and biochemical recurrence (BCR).

- Early studies show significantly higher detection of BCR at low PSA levels.

Normal Ga68-PSMA PET
Biochemical Recurrence after RP: Ga-68-PSMA ligand PET

- Recent meta-analysis of 16 articles, 1309 patients
  Perera M et al Eur Urol. 2016 Jun 27

- Overall 40% positive in primary staging and 76% positive in Biochemical Recurrence

- Detection of recurrence in low PSA levels.

<table>
<thead>
<tr>
<th>PSA levels (ng/ml)</th>
<th>Detection rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2</td>
<td>95%</td>
</tr>
<tr>
<td>1 - 2</td>
<td>76%</td>
</tr>
<tr>
<td>0.2 - 1</td>
<td>58%</td>
</tr>
<tr>
<td>0 – 0.2</td>
<td>42%</td>
</tr>
</tbody>
</table>

- Shorter PSA doubling time increased PSMA PET positivity (64% vs 92% using PSAdt 6 mo) with per-patient analysis:
  - Sensitivity 80%
  - Specificity 97%
68 Ga-PSMA PET-CT

- **Primary Staging in high risk disease**
  - Possible improved sensitivity for nodal and bony metastasis still under investigation.
  - Cannot replace MRI for local tumour staging
  - **False positive** in benign lesions (thyroid adenoma, Paget’s disease, schwannoma, TB, adrenal adenoma, splenic sarcoidosis, coeliac ganglion uptake mimic adenopathy) as well as solid tumours (eg colon, breast, RCC, HCC) and neo vasculature.
  - **False negatives** (advanced metastatic castration resistance prostate cancer mets can lose PSMA expression)

  *Wolfgang P F, Eur J Nuc Med 2017; Rauscher I, Cancer Imaging 2017*
Ga-68-PSMA HBED PET/CT in Recurrent Disease after Radical Prostatectomy

6 months post radical prostatectomy & pelvic lymphadenectomy. Gleason 4+4, margin positive. PSA 12.4 ng/dl, PSA doubling time 2 months

Histology: recurrence Gleason 4+4

(Slide courtesy of Dr Winnie Lam, Nuc Med SGH)
Ga-68-PSMA HEBD PET in Recurrent Disease after Radical Prostatectomy

- Radical prostatectomy 10 years ago. Gleason 3+4, pT3b.
- PSA started rising 1 year later, started ADT.
- Castrate resistant prostate cancer (CRPC) 2 years later. PSA went up to 5.

(Slide courtesy of Dr Winnie Lam, Nuc Med, SGH)
Ga-68-PSMA HEBD PET in Recurrent Disease after Radical Prostatectomy

- 67 year old post radical prostatectomy
- PSA rising from 0.6 to 1
Ga-68-PSMA HEBD PET in Recurrent Disease after Radical Prostatectomy

- 67 year old post radical prostatectomy
- PSA rising from 0.6 to 1
Conclusion

• MpMRI has excellent sensitivity for GS 7 and higher tumours and targeted biopsy based on MR abnormalities recommended for negative TRUS systematic biopsy.
• Localised prostate cancer classified into low, intermediate and high risk groups for prognosis and management.
• MpMRI useful for local staging, particularly in intermediate and high risk groups.
• MpMRI can detect higher grade cancers and has potential to exclude significant cancer in stratification of patients considering active surveillance, and in planning nerve and continence sparing surgery.
Conclusion

- CT and bone scan used in systemic staging of high risk groups and follow-up monitoring of metastatic disease.
- Wb-MRI is more sensitive than bone scan and CT scan for detecting bony metastases.
- MRI prostate with wb-MRI can be utilised for combined local and systemic staging when available.
- Ga-68 PSMA PET is a promising modality for systemic staging and detection of recurrence after radical prostatectomy.
QUESTIONS?

Thank you for your attention!