DCE-MRI for prostate cancers – qualitative or quantitative assessments?

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2012 President, Cancer Imaging Society

ESUR Prostate Course 2013, Paris
63 yo physician, rising PSA (18ng/ml) – 1 neg TRUS Bx 
never wants to see a urologist again!

Why is DCE-MRI sometimes positive and other times negative? 
(Answer: depends on tumor histology)

Should DCE-MRI sequence also be used for index lesion localization? 
(Answer: depends on anatomic location)

How should DCE-MRI be communicated? 
(Answer: depends on the your referrer)

Template anteroseptal Bx  Gl 3+3; PZ Bx normal → Rx: HIFU
## MRI tools for prostate evaluations

<table>
<thead>
<tr>
<th>Tools</th>
<th>Biological property depicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1W &amp; T2W</td>
<td>Anatomy, tissue density, gland formation, fibrosis</td>
</tr>
<tr>
<td>Diffusion MRI (DWI, DW-MRI)</td>
<td>Extent of gland formation, cellular density, necrosis and perfusion. Correlates with volume &amp; grade.</td>
</tr>
<tr>
<td>Spectroscopy (MRSI)</td>
<td>Membrane turnover/energetics and replacement of normal glandular tissues. Correlates with volume &amp; grade.</td>
</tr>
<tr>
<td>Dynamic contrast enhanced (DCE-MRI)</td>
<td>Blood flow and vascular permeability</td>
</tr>
<tr>
<td>Targeted biopsy</td>
<td>MR guided and/or directed</td>
</tr>
</tbody>
</table>

### MRI Images

- T2W
- T1W+c sub
- Plasma volume
- b800
- ADC
- MRSI
- Creatinine
- Wash-in rate
- Leakage space
- Wash-out rate
- Choline
- Ch+Cr/Ci ratio
- MRSI
Dynamic contrast enhanced MRI (DCE-MRI)

- Where tissue enhancement is continuously monitored after bolus IV contrast medium over a short period of time
  - Low molecular weight contrast media (<1 kDa)
  - 2 distinct enhancement patterns observed (+ve or –ve)

\[ T_1W \]

**DCE-MRI**

Typical acquisition: images every 7-12s x 5-7 mins

\[ T_2^*W \]

**DSC-MRI**

Typical acquisition: every 1-2s x 1-2 mins
T2*W DSC-MRI

Injection
0.2 mmol/kg
Gd-DTPA

Fat
Tumour
Muscle

Signal Intensity

Time (seconds)

0 20 40 60 80 100 120

T2W MRI

ADC
Quantifying $T_2^*$W DCE-MRI

- relative Blood Volume (rBV)
- Mean Transit Time (MTT)
- relative Blood Flow (rBF)

$rBF = \frac{rBV}{MTT}$

Not today
Dynamic contrast enhancement (DCE-MRI)

Relative signal intensity vs. Time (minutes)

- PZ
- Fat
- Tumour
- BPH

T2W MRI

ADC
Analysis using subtraction images
Subtle extra-prostatic spread (T3a); blood only in seminal vesicles

Note Pagets disease of left hemipelvis
Options for evaluating time - signal enhancement on $T_1W$ DCE-MRI

- **Qualitative** - curve shape of signal enhancement data
- **Model-free indices** - describe one or more parts of enhancement curves
  - Wash-in, wash-out gradients, max amplitude, time to peak etc
  - Area under signal intensity or [Gd] curve (IAUGC)
- **Physiological indices** - from contrast medium concentration changes using pharmacokinetic modelling
  - DCE-MRI - extended Toft’s, St Lawrence & Lee, Shutter speed
Characterising curve shapes

Used in the clinic every day ++

Descriptive or by the use of classifiers

Kuhl et al. Radiology 1999; 211:101-110
Neubauer et al. Br J Radiology 2003; 76:3-12
Rising PSA after brachytherapy

T2W

T1W

Post C + FS

DCE-MRI

ROI

MRI
Rising PSA after brachytherapy

*DWI less effective with metal in place*
Multi-parametric MRI for post RRP recurrence detection

FDG-PET

DCE-MRI

Recurrence

Bladder wall

T2W

b900

ADC
Histology

**Signal intensity**

- Initial
- Fast
- Medium
- Slow
- Delayed
- Persistent
- Plateau
- Washout

**Time**


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3TP

Ca
PIN

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T2-W T2b

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Neubauer et al. Br J Radiology 2003; 76:3-12
Curve shapes helps improve prediction of ECE & overall staging accuracy in prostate cancer


<table>
<thead>
<tr>
<th>Predicting ECE</th>
<th>Predicting staging accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Correct</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Overall</td>
<td>87 (94/108)</td>
</tr>
<tr>
<td>Experienced readers</td>
<td>87 (49/56)</td>
</tr>
<tr>
<td>Less experienced readers</td>
<td>87 (45/52)</td>
</tr>
</tbody>
</table>

Options for evaluating time - signal enhancement on $T_1$W DCE-MRI

- **Qualitative** - curve shape of signal enhancement data
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Qualitative uptake characteristics

- Maximum enhancement %
- 90 %
- 10 %
- AUC (Area under Curve)
- Maximum Intensity
- Time Ratio (MITR)
- Initial Gradient
- Mean Gradient
- Onset Time
- Time (min)
- Relative Signal Intensity
- Injection
Area under SI or [Gd] curve (IAUGC)

IAUGC$_{60}$ before peak enhancement should reflect transfer constant (wash-in rate) and therefore be related to blood flow!
**IAUGC<sub>60</sub> correlations with wash-in rate (K<sub>trans</sub>) and rBF**

- **IAUGC (60 secs) against K<sub>trans</sub>**
  - $R^2 = 0.9332$

- **IAUGC(60 secs) versus K<sub>trans</sub>**
  - $R^2 = 0.8747$

These relationships are complex and do not apply to all lesions particularly when permeability is low & at the pixel level.


- **IAUGC (60 secs) against rBF**
  - $R^2 = 0.6549$

- **IAUGC(60 secs) versus rBF**
  - $R^2 = 0.4768$

16 patients with prostate cancer

19 patients with ovarian cancer
Options for evaluating time - signal enhancement on $T_1W$ DCE-MRI

- **Qualitative** - curve shape of signal enhancement data
- **Model-free indices** - describe one or more parts of enhancement curves
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Tofts’ modelling of T₁W DCE-MRI

- **Transfer constant** \( (K_{\text{trans}}; \ \text{wash-in rate; min}^{-1}) \) – contrast flow from blood to the interstitial space; represents both blood flow and permeability surface area
- **Extracellular leakage space** \( (v_e; \ %) \) – space between cells
- **Rate constant** \( (k_{\text{ep}}; \ \text{wash-out rate; min}^{-1}) \) – backflow of contrast from extravascular extracellular space into the intravascular compartment
- **Fractional blood volume** \( (v_p; \ %) \)
- **Initial area under Gd curve** \( (\text{IAUGC}_{60}; \ \text{mmol.s}) \) – amount of contrast reaching a tissue and being retained for 60 seconds
- **Enhancing pixels** \( (\%) \) – proportion of vascularised pixels
What does $K^{\text{trans}}$ actually mean?

- The parameter changes its meaning by anatomic location (brain vs non-brain; inside tumour vs outside)
- The parameter changes its meaning by therapy status
- Parameter value changes according to AIF used
- Quantitative metrics do not fit the data observed
Transfer constant ($k_{\text{trans}}$)*

- **Low permeability situations**
  (no contrast medium supply problem, vascular > interstitial concentration)
  
  transfer constant = permeability surface area product
  
  $\text{ml/g/min}$

- **High permeability situations**
  (most contrast medium leaves the vasculature, venous = interstitial concentration)
  
  transfer constant ~ blood plasma flow per unit tissue volume
  
  $\text{ml/g/min}$

*Tofts PS JMRI 1999; 10:232-233
Prostate cancer localisation with dynamic MRI and spectroscopy

Why does DCE-MRI not work in the transition zone?

Peripheral zone

MPKS = DCE-MRI score

Special case: transition zone cancers

- Transition zone (TZ) cancers - 25-30% of all cancers
- TZ cancers have lower Gleason scores, lower pathologic stages; up to 16% demonstrate progression if untreated
- Anterior TZ tumors are often missed by TRUS biopsy – delaying diagnosis
  - Prostatectomy series show Gl 4-5 components with extracapsular extension and positive resection margins in 9-10% of TZ cancers*

Detecting transition zone cancers (T2W-MRI)

- T2W criteria are reasonably good
  - Homogeneously low SI and/or irregular boundaries ("charcoal sign")
    with loss of internal structure, unsharp margins & invasion of TZ
    adenoma and its pseudo-capsule
  - Lenticular shape and/or interruption of the BPH pseudocapsule
  - Invasion of the anterior fibromuscular stroma (AFS) or the
    anterolateral capsule

- ROC analysis of endorectal T2W (1.5T): AUC of 0.73-0.84*

- Detection remains problematic particularly for smaller
  (<4cc), Gleason 6 disease within the TZ

- Problem with T2W detection: BPH which is histologically
  heterogeneous
  - Glandular, stromal, proliferative or mixed patterns

Images in 76-year-old man with TZ carcinoma with a Gleason score of 9 (5 + 4).
Images in 67-year-old man with glandular hyperplasia on the left side
DW- & DCE-MRI for detection of TZ cancers

- **DW-MRI**
  - Distinguishing glandular BPH and cancer is straightforward using high b-value DWI and ADC maps
  - Distinguishing stromal/proliferative BPH and cancer is partly problematic
    - Proliferative BPH: ↑SI on DWI (>b1000) and ↓ADC (like cancer)
    - Stromal BPH: often ↔ SI on (>b1000) and ↓ ADC

- **DCE-MRI**
  - Distinguishing glandular BPH and cancer is straightforward
  - Distinguishing stromal/proliferative BPH and cancer is problematic because proliferative BPH is hypervascular

Adding DCE-MRI to T2W decreases mpMRI performance in the transition zone

Would DCE-MRI be better for higher grade disease in the transition zone?

Delongchamps NB, et al. Multiparametric magnetic resonance imaging for the detection and localization of prostate cancer: combination of T2-weighted, dynamic contrast-enhanced and diffusion-weighted imaging. BJU Int. 2011 May;107(9):1411-8.
Adding DCE/DWI to T2W does not increase test performance in the transition zone regardless of Gleason score

1. Transition zone cancer cancer detection is best done using T2W and DW-MRI
2. The biology of the normal TZ hyperplasia and lower grade/vascularity of TZ tumors means that DCE can confuse MRI evaluations

Hoeks C M A et al. Radiology 2013;266:207-217
So when is quantitative DCE-MRI valuable?

- Therapy assessments when there are no changes in morphologic features
  - Early after starting therapy
  - When the whole organ become fibrotic due to therapy
  - When novel therapeutics with antiangiogenic properties are used
Multiparametric MR imaging in patients undergoing ultra-hypofractionated radiotherapy for localised prostate cancer

Radiotherapy 5 fractions (#) of 7.25Gy each given over 10 days

Changes in $\text{IAUGC}_{60}$ & $K_{\text{trans}}$ in the whole prostate ROI

K. Yip, et al. ESTRO 2012
Multiparametric MR imaging in patients undergoing ultra-hypofractionated radiotherapy for localised prostate cancer

5 patients with prostate cancer (3 no prior hormone therapy)
Radiotherapy 5 fractions (#) of 7.25Gy each given over 10 days

K. Yip, et al. ESTRO 2012
Response assessments in prostate cancer

Pre-treatment → 123 days → Post-treatment

PSA 6.0 ng/ml

PSA 1.2 ng/ml

Active surveillance – baseline (Dec 2008)

PSA 5.3ng/ml; TRUS - small foci of Gleason 3+3 plus prostatitis in PZ; TRUS missed anterior gland tumor (ADC 835 μm²/s)
On active surveillance

PZ:
T2W =3/5; DWI =2/5
DCE = 3/5; MRSI =1/5

Ant TZ
T2W =2/5; DWI =4/5
DCE =5/5; MRSI =1/5
Active surveillance – post antibiotics (Dec 2009)

PSA 5.9ng/ml; enlarging anterior gland tumor (ADC 835 → 583 μm²/s) with decreased enhancement in PZ.

Needs targeted biopsy the anterior TZ mass.
Validating PIRADS for lesion detection

Platinum Priority – Prostate Cancer
Editorial by Bertrand Tombal on pp. 997–998 of this issue

Validation of the European Society of Urogenital Radiology Scoring System for Prostate Cancer Diagnosis on Multiparametric Magnetic Resonance Imaging in a Cohort of Repeat Biopsy Patients

Daniel Portalez\textsuperscript{a,\dagger}, Pierre Mozer\textsuperscript{b,\dagger}, François Cornud\textsuperscript{c}, Raphaëlle Renard-Penna\textsuperscript{b}, Vincent Misrai\textsuperscript{a}, Matthieu Thoulouzan\textsuperscript{d}, Bernard Malavaud\textsuperscript{d,*}

\textsuperscript{a}Departments of Radiology, Clinique Pasteur, Toulouse, France; \textsuperscript{b}Department of Urology, Hôpital Pitié-Salpêtrière, Paris, France; \textsuperscript{c}Department of Radiology, Hôpital Cochin, Paris, France; \textsuperscript{d}Department of Urology, Hôpital de Rangueil, Toulouse, France
Validating PIRADS for lesion detection

- The score of each component correlates with the likelihood of “significant cancer” being present.

mpMRI test performance in low & intermediate risk patients undergoing template biopsy

- Test performance of T2W, DW-MRI & DCE for 3 readers
- 64 men; PSA 8.2 ng/ml (2.1-48); 51 with biopsy-proved cancer and 13 TRUS negative or no prior biopsy
- 54 men had cancer (3+3 = 19; 3+4 14; no men with ≥4+3)

<table>
<thead>
<tr>
<th>Cancer Definition</th>
<th>Sector Cancer Prevalence</th>
<th>ROC</th>
<th>Detection of cancer at quadrant level</th>
<th>Rule out cancer at quadrant level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Specificity %</td>
<td>PPV %</td>
</tr>
<tr>
<td>All cancers</td>
<td>49%</td>
<td>0.64-0.73</td>
<td>77-89</td>
<td>71-82</td>
</tr>
<tr>
<td>Gl=3+4</td>
<td>17%</td>
<td>0.71-0.80</td>
<td>68-78</td>
<td>35-41</td>
</tr>
</tbody>
</table>

Take home points

- Anatomic location (PZ/TZ) and pre-existing disease/biopsy artefacts determines diagnostic performance of DCE-MRI
- Using DCE-MRI in clinical practice should not be delayed/hindered by the complexities of the technique
  - The last 20 years of validation allows us to be confident that DCE-MRI (morphology, subtraction maps, curve shapes & semi-quantitative methods) work in the clinic
- Complex DCE analysis has roles in validation, drug development, and is needed for multiparametric assessments
- For clinical practice semi-quantitative analysis methods (morphologic and curve shapes should suffice for now!)