Objective

- Existing MR tumor biomarkers in routine practice
- Emerging MR tumor biomarkers at various stages of development
Imaging biomarker roadmap

Technical (assay) validation
Imaging biomarker evaluated in vitro, in animals, and in humans

Biological and clinical validation
Imaging biomarker is a reliable measure used to test hypotheses in clinical cancer research

Cost effectiveness
Imaging biomarker routinely used in the management of patients with cancer within the healthcare system

O’Connor et al, Nat Rev Clin Oncol 2017
MRI tumor biomarkers in clinical use (crossed translational gap 2)

### Biomarker Table

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Characteristic</th>
<th>MRI sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established biomarkers in clinical practice</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staging</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNM stage</td>
<td>Tumor morphology, presence of nodes, and metastases</td>
<td>T2-weighted, T1-weighted imaging ± diffusion weighted, postcontrast-enhanced imaging</td>
</tr>
<tr>
<td>Response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECIST (Response Evaluation Criteria In Solid Tumors)</td>
<td>Change in tumor size</td>
<td>T2-weighted imaging</td>
</tr>
</tbody>
</table>

Anatomic or morphology based MRI biomarkers

- Primary tumor volume changed from 130 to 40 cc from pre-treatment to week 6 of RT
- Adaptive replanning at week 3 or 4?

Modified table, Dregley I et al, JMRI 2018
Anatomic or morphology based MRI biomarkers

**Good Responder**

Pre-induction | Pre RT | Early RT | Mid RT | Post RT
---|---|---|---|---

**Poor Responder**

Pre-induction | Pre RT | Early RT | Mid RT | Post RT
Validated tumor biomarkers in clinical cancer research (have crossed the first translational gap)

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Characteristic</th>
<th>MRI sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validated biomarkers in clinical cancer research</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apparent diffusion coefficient (ADC)</td>
<td>Cellularity</td>
<td>Diffusion-weighted imaging, at least 2 b-values</td>
</tr>
<tr>
<td>Initial area under the gadolinium curve (iAUGC)</td>
<td>Perfusion</td>
<td>Dynamic T1-weighted imaging following intravenous injection of gadolinium-based contrast agent</td>
</tr>
<tr>
<td>Transfer constant ($K_{trans}$)</td>
<td>Permeability</td>
<td></td>
</tr>
</tbody>
</table>
Diffusion Weighted MRI (DW-MRI)

Koh and Collins, AJR 2007
DW-MRI

Pre-treatment TX-0 MRI
Week-1 TX-1 MRI
Week-2 TX-2 MRI
Week-3 TX-3 MRI

T2 fatsat      DWI      ADC

Intra-TX Week 3

Paudyal R et al, JMRI 2016
Challenges

Robust DWI in large trial setting – technical challenges

DWI QIBA profile - Claim statements for the tumor ROI in brain, breast, liver
Head and neck & prostate

Based on the current literature, %RC values for tumor apparent diffusion coefficient (ADC) region of interest (ROI) measurements derived from monoexponential modeling of DWI data in three different organs are as follows: brain = 11%,\textsuperscript{30-32} liver = 26%,\textsuperscript{33-36} and prostate = 47%.\textsuperscript{37-40} This assumes the wCV for tumors in the brain is 3.97%, 9.38% for the liver, and 16.97% for the prostate. The claim states -

Malyarenko D et al, JMRI 2013
Shukla-Dave et al, JMRI 2019
Boss MA, et al, ISMRM 2014
Dynamic contrast enhanced MRI (DCE-MRI)

FIGURE 9: Representative MR images from a recurrent hepatocellular carcinoma patient (57 years old, male) acquired on a 3T MRI scanner. DCE MRI image showing (a) enhancing tumor and (b) contrast enhancement time course. (c) The gadolinium concentration time course and extended Tofts model fit and (d) composite ADC map generated from DWI with $b = 0, 600 \text{s/mm}^2$ from the same patient. (Images contributed by Sachin Jambawalikar, Columbia University Medical Center.)

Shukla-Dave et al, JMRI 2019
The $v_p$ deceased from 36.7 preoperatively to 1.85 at 1 hour post-RT (a 95% decrease) $K_{\text{trans}}$ decreased from 14 preoperatively to 1 hour post-RT (a 71.4% decrease)
DCE-MRI: Semiquantitative parameters

Time to half peak (tthp) | Mean (min)
---|---
Pre-tx | 0.175
After 8 Gy 1st fraction | 0.142
After 40 Gy 5th fraction | 0.175
Four weeks Post-tx | 0.103

IAUCtthp | Mean (min)
---|---
Pre-tx | 0.38
After 8 Gy 1st fraction | 0.275
After 40 Gy 5th fraction | 0.358
Four weeks Post-tx | 0.16
Challenges

Robust DCE-MRI in large trial setting – technical challenges

DCE QIBA profile - Claim statements for the tumor ROI in brain, breast, liver, Head and neck & prostate

curves for the aorta and tumor in the liver. The currently available test–retest DCE data have illustrated that the %RC for $K_{\text{trans}}$ in a tumor ROI is 21.3% for brain and 55.7% for prostate.\textsuperscript{41,42} The statistical approach used to derive this performance claim information for DCE profile is similar to the one applied in the QIBA/DWI profile.

QIBA DCE T1 phantom

Shukla-Dave et al, JMRI 2019
Biomarkers undergoing validation in research studies

**TABLE 4. Emerging Biomarkers Undergoing Validation in Research Studies**

<table>
<thead>
<tr>
<th>Emerging biomarkers</th>
<th>Measure/biological correlate</th>
<th>MRI sequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>( f, D^* )</td>
<td>Pseudoperfusion</td>
<td>Multiple low b-value diffusion weighted imaging (intravoxel incoherent motion, IVIM)</td>
</tr>
<tr>
<td>Kurtosis (( K_{app} ))</td>
<td>Microstructural complexity</td>
<td>Diffusion kurtosis imaging (DKI)</td>
</tr>
<tr>
<td>R2* R1 ΔR2* ΔR1</td>
<td>Relaxation rate Oxygenation</td>
<td>Blood oxygenation level dependent imaging (BOLD) Tissue oxygenation level dependent imaging (TOLD) ± oxygen/carbogen challenge</td>
</tr>
<tr>
<td>Elasticity Viscosity</td>
<td>Tissue mechanics and viscoelastic parameters</td>
<td>Elastography: motion sensitive sequence to encode shear wave propagation</td>
</tr>
<tr>
<td>Specific metabolites, eg, Choline</td>
<td>Metabolite concentration</td>
<td>Spectroscopy</td>
</tr>
<tr>
<td>T1 T2</td>
<td>Relaxation time Microenvironment</td>
<td>Multiecho relaxometry imaging</td>
</tr>
</tbody>
</table>

CEST, T1rho

Modified table, Dregley I et al, JMRI 2018
Spectroscopy
Metabolic mapping and prostate cancer grading: high grade cancer: Gleason 8

↑tCho, ↓citrate identify cancer in the prostate gland.

for quantification, use \([t\text{Cho} + \text{Cr}]/\text{Cit}\)

Zakian, et. al., Radiology 2005;234(3):804-14
Emerging: Chemical Exchange Saturation Transfer or CEST

Patient 1

Patient 2

**Tumour volume decreased**
- at 1 MONTH
- (compared to PRE-TREATMENT)

**Tumour volume increased**
- at 1 MONTH
- (compared to PRE-TREATMENT)

Desmond KL et al, MRM 2017
Emerging: 3D T1rho Relaxometry

Villanueva-Meyer et al, European Journal of Radiology 2017
Conclusion

- Many existing and emergent tumor biomarkers but only few are in clinical use

- Reproducibility and repeatability of these markers is essential before they can move to final stages of biomarker development

- Quantitative imaging networks including QIBA are actively pursuing these efforts and continue to develop and add technical and clinical profiles for existing and emerging biomarkers
Questions