Monitoring bony metastases response with diffusion MRI

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Objectives

- To illustrate the potential of whole body DWI in the therapy response assessment of bone metastases
- To illustrate that there are 4 patterns of response when signal intensity and ADC values are evaluated
- To provide advice on how to use WB-DWI in conjunction with anatomic MRI to successfully gauge bone marrow therapy response

- Padhani AR & Gogbashian A. Bony metastases - assessing response to therapy with whole body diffusion MRI. Cancer Imaging 2011; - in press
Monitoring bone therapy response

- Symptoms assessments (analgesic requirements) and development of skeletal related events are markers of therapeutic efficacy in clinical trials.
- Serum markers are not useful for therapy response for the majority of tumors that metastasize to bone:
  - Serum PSA: not reliable in late stage hormone-refractory prostate disease; flare phenomenon in responding patients*
  - CA15-3: moderate sensitivity for metastatic disease (60-65%); flare reaction in responding breast cancer patients**
- Serum/urinary markers of osteoblastic and osteoclastic activity monitor bone response NOT tumor response.
- Circulating tumor cells (CTCs) are emerging as strong response biomarkers for breast, colorectal and prostate cancers.

*Scher HI et al. JCO 2008; 26:1148-59
**Duffy MJ. Clin Chem 2006; 52:345-51
Evaluating bony disease by MRI: combining sequences into whole body examinations

- **T1-weighted spin-echo, T2-weighted (FS) & STIR**
  - Cellular and water content
- **T2*-weighted GRE (IP/OP)**
  - Fat:water ratio and susceptibility induced by trabecular bone
- **Dynamic contrast enhanced MRI**
  - Vascularisation
- **Ultrashort TE (UTE)**
  - Trabecular bone structure
- **DW-MRI**
  - Perfusion, cell density, fat and water content

* Schmidt GP, et al. Whole-body MRI for the staging and follow-up of patients with metastasis. Eur J Radiol 2009; 70: 393–400
Whole body DWI for metastasis detection

- Widespread availability
- Better than CT scans and bone scans for lytic bony disease
- Also provides information about soft tissue disease
- Advantages
  - No ionizing radiation
  - No injections of isotopes or contrast medium
  - Quick to perform & read
  - Quantitative
- At a glance assessments
  - Improves whole body MRI performance

WB-DWI sub-protocol
(STIR for FS – total 25mins)

<table>
<thead>
<tr>
<th>Coils</th>
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<tr>
<td>TE (ms)</td>
<td>min ( 67)</td>
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<td>TI (ms)</td>
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<td>Half scan factor</td>
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<tr>
<td>b-values</td>
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<td>NE</td>
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<td>Scan time/station (mins)</td>
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</tr>
</tbody>
</table>

Scouts; T1W/STIR Whole body
4 stations; 50 slices, 5mm; b50, b900
Normal bone marrow pattern

- Normal adult BM distribution established by 25 yo
  - Yellow bone marrow: 10-20% water, fat cells (↓SI)
  - Red bone marrow: 40-60% water & more cells (↑SI)
- Variable red BM atrophy and trabecular bone loss after 40 yo (>♀)
  → Increase in yellow bone marrow
Non-linear (paradoxical) relationship between ADC & bone marrow cellularity

- **Yellow (fatty) marrow** → low SI & ADC
  - Low water content & cellularity
  - Fat acts as a barrier to water diffusion repelling water
  - Low perfusion

- **Red bone marrow** → higher SI & ADC
  - More cells and water
  - Less big fat cells & more small cells
  - Higher perfusion

- **Tumor & BM hyperplasia** → highest SI but variable ADC
  - Highest water content & cellularity within restricted bone marrow space
  - Highest perfusion
Assessing WB-DWI response to Rx

- Changes in tumor burden/volume
- Changes in signal intensity on high b-value images
  - Reflects changes in water diffusivity and water content
- Changes in ADC values
  - Objective evaluations of water diffusivity
  - Amenable to numerical analysis
  - Heterogeneity assessments are made possible
    - Histogram & pixel map analyses (parametric response maps)
Multiple Myeloma

cyclophosphamide, dexamethasone, thalidomide (CDT) and bortezomib

Biological processes involved in therapy induced changes in DWI

Solid cellular tumor

Microscopic cellular necrosis

Necrotic tissue

WB-DWI

Metastatic bone disease: not responding to therapy

- New areas of focal abnormal signal intensity
- Increasing extent (becoming confluent) and intensity of lesions
- For BM disease ADC values can ↓, ↔ or ↓ (heterogeneous; but remains below thresholds)!
Signal intensity changes in non-response

47 yo F – metastatic breast cancer 1st Taxanes/APD then Letrozole
Increases in tumour volume & ADC values with progression

- 51 yo F metastatic breast cancer
- Bone and liver disease
- Pre and post Taxanes/ APD/ Herceptin
- Bone tumor volume 29.3 → 179.2 cm$^3$
- ADC 780 → 930 μm$^2$/s
DW-MRI and cellularity in bone marrow

Disease progression can cause modest increases, stable or slight decreases in ADC

Yellow marrow 10% H₂O
Red marrow 40-60% H₂O
Hyperplastic/moderate tumour infiltration 60-80% H₂O
Dense malignant infiltration >80% H₂O

Signal intensity on high b-value images
BM hyperplasia: increased SI but stable ADC

40 F – post-partum, left mastectomy and axillary nodal dissection

Rx adjuvant chemotherapy with G-CSF support

30-July 2010

ADC 920 ± 266 → 920 ± 211 μm²/s
Myeloma progression

↑ SI & ↓ ADC

11-Jan-10

1-April-10

62M Multiple Myeloma – Rx Bortezomib

11th Jan

1st April

b800

ADC

900 µm²/s

725 µm²/s
Variable changes in ADC in non-responders (stable + progression)

- 26 patients with metastatic prostate cancer
- Chemotherapy
- 100 lesions
  - 33 in responders
  - 59 in progressors
  - 8 stable
- Limits of reproducibility of normal BM ± 86 µm²/s

WB-DWI

Bony disease responding to therapy

- Decrease in volume of focal abnormal signal intensity
- Signal intensity changes generally decrease but occasionally unchanged/increase if there is a strong inflammatory response
- ADC values: marked increases
Breast cancer (triple negative)
Rx GemCarbo + APD (bisphosphonate)

<table>
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<tr>
<th>29-July-2010</th>
<th>01-Oct-2010</th>
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<tbody>
<tr>
<td>T1W</td>
<td>T1W</td>
</tr>
<tr>
<td>T2W+FS</td>
<td>T2W+FS</td>
</tr>
<tr>
<td>WB-DWI b900</td>
<td>WB-DWI b900</td>
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</tbody>
</table>

Decreases in DW-MRI is due to a combination of changes in tissue water content and cellularity
Breast cancer (triple negative)  
Rx GemCarbo + APD (bisphosphonate)

- 37F – perimenopausal
- Triple negative, metastatic breast cancer
- Rx – GemCarbo plus APD
- Diffuse increase in ADC values
- ADC 883 → 1905 μm²/s
- Cut-off values: 650 & 1500 μm²/s
Decreasing cellularity

ADC

Signal intensity on high b-value images

Effective Rx

Non-effective Rx

Yellow marrow 10% H₂O
Red marrow 40-60% H₂O
Hyperplastic/moderate tumour infiltration 60-80% H₂O
Dense malignant infiltration >80% H₂O

Decreasing cellularity

Effective Rx

Non-effective Rx
Breast cancer
Rx Capecitabine (3 cycles) + APD

<table>
<thead>
<tr>
<th>21-Jan-2011</th>
<th>04-April-2011</th>
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<tbody>
<tr>
<td>T1W</td>
<td>T1W</td>
</tr>
<tr>
<td>T2W+FS</td>
<td>T2W+FS</td>
</tr>
<tr>
<td>b900</td>
<td>b900</td>
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T1W and T2W+FS images for 21-Jan-2011 and 04-April-2011, with b900 sequences also included.
Breast cancer Rx capcitabine + APD

- 41F – postmenopausal
- Metastatic breast cancer - asymptomatic (before and during Rx)
- Rx – cepcitabine (3 cycles) plus APD
- Signal intensity is unchanged but marked increase in ADC values
- ADC → mean 900 to 1500 μm²/s
- Cut-off values: 650 & 1500 μm²/s
Increasing ADC correlates with: Decreasing cellularity, Effective Rx, and Hyperplastic/moderate tumour infiltration (60-80% H\textsubscript{2}O).

Decreasing ADC correlates with: Necrosis (T2-shine through), Non-effective Rx, and Dense malignant infiltration (>80% H\textsubscript{2}O).

Signal intensity on high b-value images:

- Yellow marrow: 10% H\textsubscript{2}O
- Red marrow: 40-60% H\textsubscript{2}O
- Hyperplastic/moderate tumour infiltration: 60-80% H\textsubscript{2}O
- Dense malignant infiltration: >80% H\textsubscript{2}O

Necrosis (T2-shine through)
Progression with bisphosphonates → response with docetaxel + bisphosphonates

Response with GemCarbo+bisphosphonates → relapse after stopping Rx
**Proposed response criteria of BM lesions EARLY after starting cytotoxic Rx**

<table>
<thead>
<tr>
<th>SI on high b-value images</th>
<th>ADC in relation cut-off</th>
<th>Biological inference and response assessment</th>
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</thead>
<tbody>
<tr>
<td>↑</td>
<td>Most pixels &lt;cut-off</td>
<td>Persistent hypercellularity → no evidence of response</td>
</tr>
<tr>
<td>↑</td>
<td>Most pixels &gt;cut-off</td>
<td>Necrosis, T2-shine through → evidence of response</td>
</tr>
<tr>
<td>↓</td>
<td>Most pixels &gt;cut-off</td>
<td>Hypocellularity → evidence of response</td>
</tr>
<tr>
<td>↓</td>
<td>Most pixels &lt;cut-off</td>
<td>Possible sclerotic or fibrotic reaction → indeterminate for response</td>
</tr>
</tbody>
</table>

ADC change needs to be judged in relation to cut-off values defined from untreated patients examined using the same imaging protocol. This is likely to be tumor type dependent. Criteria may not apply to non-cytotoxic therapies. The timeline for the applicability of these criteria are undefined.

Padhani AR & Gogbashian A. Bony metastases - assessing response to therapy with whole body diffusion MRI. Cancer Imaging 2011; - in press.
Some outstanding R&D questions

- It is not clear what proportion of tumor cells have to be killed for ADC changes to become detectable by DW-MRI
  - Does the mechanism of cell death affect DW-MRI appearances?

- What is the reproducibility of WB-DWI ADC estimates (that is, how much of measured change can be considered “real”)?
  - What factors affect the measurement reproducibility?

  → Essential information for the development of WB-DWI as a pharmacodynamic biomarker for use in drug trials

- How much change in ADC results in patient benefit (improvements in symptoms and survival) for the variety of available therapies?

  → Essential information for the development of WB-DWI as a tool for personalized medicine

Take home points

- **WB-DWI** is a SI based tool for **bone marrow lesion detection and therapy response**
  - Lytic bone deposits are better seen than sclerotic lesions
- **Non-linear (paradoxical) relationship** between ADC & bone marrow signal intensity
  - Disease progression causes heterogeneous changes in ADC
  - Response assessments → larger ADC increases
- **WB-DWI should always be interpreted with conventional imaging findings**
- **WB-DWI has not yet been proven to impact meaningful health outcomes in patients with metastatic bone disease**

Padhani AR & Gogbashian A. Bony metastases - assessing response to therapy with whole body diffusion MRI. Cancer Imaging 2011; - in press