Whole body Diffusion Weighted MRI (WB-DWI) in the assessment and treatment response of multiple myeloma (MM).

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Learning objectives

• To review with case examples (>100 WB-DWI patients with plasma cell dyscrasias) the bone marrow assessment of patients with myeloma (MM) or plasmacytoma.

• To correlate appearances on signal intensity (SI) and apparent diffusion coefficient (ADC) maps in relation to the degree of bone marrow infiltration.

• To illustrate that it is possible to quantify whole body tumour burden and demonstrate bone marrow changes in the therapy assessment setting.

Background

• Multiple myeloma (MM) is a heterogeneous group of plasma cell neoplasms that primarily involve bone marrow but sometimes may occur in the soft tissue. The disease varies in its presentation and its course.

• Currently, the assessment of tumour burden and therapeutic response in MM occurs in a multi-modal approach with the combination of x-ray skeletal surveys, symptom assessments, bone marrow biopsies and serum markers (monoclonal paraproteins and free light chains).

• Skeletal bone survey insensitivity, sampling errors and oligosecretory disease are potential problems in such assessments. Changes in the level of the serum paraprotein and/or urinary light chain excretion form the basis of assessing the response to therapy and monitoring the progress of the disease but these are not always accurate.

• In non-secretory myeloma it is difficult to monitor disease accurately. Serial bone marrow examinations are helpful but is invasive and the patchy nature of marrow involvement in myeloma makes it difficult to accurately interpret small changes in the percentage of plasma cells present.

• The introduction of novel therapeutic agents, such as bortezemib and lenalidomide, has resulted in substantial improvements in survival. However, novel therapies are expensive and may cause significant adverse effects. Accurate evaluation of response to treatment is critical to the effective management of MM patients.

• An accurate, reproducible, non-invasive technique to assess tumour burden and response is required clinically and for drug development.

• A review of the literature shows inverse correlations between ADC and histological cell density in a variety of soft tissue tumors (Koh, Padhani. Magn Reson Imaging Clin N Am. 2011). Paradoxically, Hillengass et al. Br J Haematol. (2011) recently showed a positive correlation between ADC and bone marrow cellularity (p<0.001) in MM. This finding suggests a complex,

- Whole body diffusion weighted imaging (WB-DWI) appears to be a promising method for evaluating MM before and after therapy (Horger M, et al. AJR 2011). The advantages of WB-DWI are that it involves no ionizing radiation, no injections of isotopes or contrast medium are needed, is quick to perform & read and provides quantitative assessments.

### Imaging findings OR Procedure details

- **Figure 1:** A whole-body MRI with WB-DWI takes approximately 45-50 mins. The protocol applied in our institute are T1W and T2W with fat-sat or STIR sequences for the whole spine. For the body; axial T1W and STIR, DWI (b50 and b900). Diffusion-weighted images are acquired in 4 imaging stations (5mm thick, 50 slices/station) using surface coils with free-breathing.

- **Figure 2:** The varied appearances of MM. Diffuse (mild to intense) homogenous and inhomogenous patterns as well as focal/multifocal lesions can be seen.

- Top left panel: 76 year old female with relapsed MM and normal immunoglobulins. Previous radiotherapy to the lumbar spine.

- Top right panel: 53 year old male with a new diagnosis. There is a diffuse pattern and extra-osseous disease in the left paravertebral region.

- Bottom left panel: 62 year old male with relapsed MM pre-treatment.

- Bottom right panel: same patient as botton left panel 6 weeks post bortezomib treatment, a proteasome inhibitor. Disease progression with increasing BM infiltration and extraosseous disease.

- **Figure 3:** 66 year old with C1 plasmacytoma and low level infiltration of the bone marrow. This spine looks normal on T1W and T2W images but on WB-DWI the bone marrow is hyperplastic. It is important to realise that normal elderly patients generally have a hypocellular patterns and any hypercellularity should be considered with suspicion for representing smouldering myeloma. The bottom right panel shows the C1 vertebral body plasmacytoma on the ADC map.

- **Figure 4.** The same patient as in figure 3 post-treatment. Note the reduction in signal intensity within the bone marrow in the botton left panel in keeping
with a response to treatment. The mean ADC within the C1 vertebral body has increased to >2000 µm²/sec suggesting successful cell-kill.

- **Figure 5:** **Non-linear correlation between cell density and ADC.** There is a non-linear relationship between bone marrow cell density and ADC values related to the relative amount of cells, fat and water. Low water content and high proportion of fat within yellow bone marrow leads to low signal intensity and ADC values. Gradual displacement of fat and increasing water and cells increases signal intensity and ADC values. When all the fat has been replaced, increasing cell density within the confines of a fixed marrow space finally leads to decreases in ADC values. See figures 6 & 7 for an illustrative case.

- **Figure 6:** The correlation between cell density and ADC can be seen in this patient with progressive MM. Progression despite therapy with increasing signal intensity on b900 images can be seen. There is extensive bone marrow involvement in the pre-therapy scan done in April 2010 with some response seen after post chemotherapy (Bortezomib + Prednisolone x 4 cycles) in a subsequent scan done on August 2010. Further 2 subsequent scans done in June and September 2011 show further progression of disease as evidenced by diffuse involvement of bone marrow. Note the development of kyphosis, extra-osseous disease related to the ribs and the development of pelvic fractures fractures (arrows).

- **Figure 7:** Same patient as Figure 6. ADC values initially increase with tumour progression with the displacement of the normal bone marrow. A decrease in ADC occurs with further disease progression.

- **Figure 8:** **Changes in water diffusivity with successful therapy.** The image demonstrates a 'shift' in the ADC histogram to the 'right' following treatment. The median ADC value is higher post-treatment when a volume of interest is analyzed over the entire pelvic bone marrow. When myeloma is treated successfully, then tumour cell death results in initial increased water diffusivity manifested as higher ADC values (Horger M et al. AJR 2011 Jun;196(6):W790-5). We can see that the magnitude of ADC increases are much greater than the smaller increases in ADC change seen in disease progression in figures 6&7.

- **Figure 9:** **Differential response to therapy shown by histogram analysis.** Fusion images from STIR MR imaging and ADC map of right rib region of interest show no change in ADC (pretherapy, 874 µm²/sec; posttherapy, 834µm²/sec) (top row) but increases in ADC of spinal (pretherapy, 887µm²/sec; posttherapy, 1215µm²/sec) and left ninth rib lesions (pretherapy, 986 µm²/sec; posttherapy, 1433 µm²/sec) (middle row).
• Figure 9 continued: Bottom right: Histograms before (blue) and after (orange) therapy were obtained by using whole-body tumor regions of interest defined on pretherapy images applied to posttherapy volume after image registration. Pretherapy bimodal histogram changes to trimodal histogram (mean pretherapy [PRIOR] ADC, 1010 µm$^2$/sec +/-573; ADC, 1366µm$^2$/sec +/- 562).

• Figure 10: **Role for WB-DWI in plasmacytoma.** WB-DWI is useful for defining the anatomic extent of tumours and for therapy planning (eg. radiotherapy). It has a role in confirming the diagnosis of solitary plasmacytoma. The figure, demonstrates a large plasmacytoma involving the right scapula. The anatomic extent is better defined on MRI than CT; the bone marrow of the proximal humerus is not involved on the MRI but the CT could be interpreted as being involved by disease.

**Images for this section:**

![Whole body MRI protocol (45-50 mins)](image)

- **Whole spine –T1W & T2W+FS**
  - For metastasis detection
- **Axial T1W and STIR using TIM CT option**
  - Moving table (with breath holding)
  - Dixon technique (T1-ip, T1-op, water and fat images)
- **Diffusion sequences**
  - DW-MRI @ b50 & b900
  - 4 stations – whole body
  - DWI ~6.45 mins / station
  - Free breathing. Surface coils. No IV contrast medium

**Fig. 1:** Whole Body MRI - Protocol
Fig. 2: The varied appearances of MM.
Fig. 3: Diagnosed C1 vertebral body plasmacytoma and background 'smouldering' MM.
**Fig. 4:** Post-treatment of C1 plasmacytoma and of background bone marrow disease.
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

**Fig. 5:** Correlation between cell density and ADC
Progressive multiple myeloma

<table>
<thead>
<tr>
<th>Pre-therapy</th>
<th>Bortezomib+Pred x4 cycles</th>
<th>Follow-up Clinical progression</th>
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<tr>
<td>06-Apr-2010</td>
<td>20-Aug-2010</td>
<td>20-Jun-2011</td>
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<td>22-Sept-2011</td>
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Develops sacral & left pubic bone fractures
Extra-osseous soft tissue disease

Fig. 6: Progression of disease in multiple myeloma
Fig. 7: Progressive multiple myeloma
Fig. 8: Changes in the ADC histogram pre- and post-treatment with a biological agent.
Fig. 9: Relapsed multiple myeloma: Post chemotherapy
Fig. 10: Solitary Plasmacytoma. Diffusion MRI versus CT.
Conclusion

1. WB-DWI enables non-invasive and quantitative assessments of the bony marrow in MM patients and overcomes the limitations of conventional imaging in detection and therapy assessment settings.
2. WB-DWI is useful for monitoring therapy when conventional markers (M-Protein or serum free light chain assay) of response are inadequate (such as in hyposecretory disease).
3. MRI is useful in tumour definition and therapy planning (for example, radiotherapy and vertebroplasty).
4. WB-DWI has a role in confirming the diagnosis of a solitary plasmacytoma.
5. In our practice WB-DWI has largely replaced skeletal bone surveys for response assessments and in those with significant extramedullary disease.

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