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Diffusion-weighted imaging for non-invasive and quantitative monitoring of bone marrow infiltration in patients with monoclonal plasma cell disease: A comparative study with histology

Jens Hillengass, Tobias Bäuerle, Reiner Bartl, Mindaugas Andrusis, Fabienne Mcclanahan, Frederik Laun, Christian M Zechmann, Rajiv Shah, Barbara Wagner-Gund, Dirk Simon, et al.

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Diffusion-weighted imaging for non-invasive and quantitative monitoring of bone marrow infiltration in patients with monoclonal plasma cell disease: A comparative study with histology

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3 **Diffusion-weighted imaging for non-invasive and quantitative monitoring of bone**
4 **marrow infiltration in patients with monoclonal plasma cell disease: A comparative**
5 **study with histology**
6

7 **SHORT TITLE:** Quantitative DWI in monoclonal plasma cell disease
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SUMMARY

Bone marrow plasma cell infiltration is a crucial parameter of disease activity in monoclonal plasma cell disorders. Until now, the only way to quantify such infiltration was bone marrow biopsy or aspiration. Diffusion-weighted imaging (DWI) is an MRI-technique which may mirror tissue cellularity by measuring random movements of water molecules. To investigate if DWI is capable of assessing bone marrow cellularity in monoclonal plasma cell disease, we investigated 56 patients with multiple myeloma or monoclonal gammopathy of undetermined significance, and 30 healthy controls with DWI of the pelvis and/ or the lumbar spine. In 25 of 30 patients, who underwent biopsy, bone marrow trephine and DWI could be compared. Of the patients with symptomatic disease 15 could be evaluated after systemic treatment. We found a positive correlation between the DWI-parameter apparent diffusion coefficient (ADC) and bone marrow cellularity as well as micro-vessel density ($p < 0.001$ respectively). A significant difference of ADC was seen between patients and controls ($p < 0.01$) and before and after systemic therapy ($p < 0.001$). We conclude that DWI allows monitoring bone marrow infiltration in a non-invasive, quantitative way, suggesting that after further investigations on larger patient groups this might become a useful tool in clinical work-up to assess tumour burden.

KEYWORDS

Diffusion-weighted imaging, monoclonal gammopathy of undetermined significance, multiple myeloma, cellularity, microcirculation

INTRODUCTION

Multiple Myeloma (MM) is a malignant lymphoproliferative B-cell disease characterized by the accumulation of monoclonal plasma cells in the bone marrow. The malignant plasma cells are located predominantly in spine and pelvis (Collins 2004). Approximately 80% of patients with MM develop skeletal complications including bone pain, osteolytic lesions, pathologic fractures, and hypocalcaemia. In contrast to symptomatic MM, monoclonal

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2
3 gammopathy of undetermined significance (MGUS) and smouldering multiple myeloma
4 (sMM) are asymptomatic precursors, defined by the absence of end organ damage (EOD)
5 related to MM. EOD is defined as hypocalcaemia, anaemia, renal failure, or lytic bone lesions
6 attributable to the plasma-cell disorder. In MGUS, per definition monoclonal protein is below
7 30 g/l and concentration of monoclonal plasma cells in bone marrow is lower than 10% (Kyle
8 2003).

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16 Magnetic resonance imaging (MRI) has been shown to be of great diagnostic and prognostic
17 value in monoclonal plasma cell disease and has been included as a diagnostic tool in the
18 consensus guidelines of the international myeloma working group for diagnostics of MGUS
19 as well as MM (Dimopoulos, *et al* 2009). With this technique, focal and diffuse infiltration of
20 malignant plasma cells in bone marrow can be detected Stäbler (Baur, *et al* 2002, Lecouvet,
21 *et al* 1998, Stabler, *et al* 1996). Focal lesions in MRI can be counted and measured. It has
22 been demonstrated that the number of these lesions is of prognostic significance in
23 symptomatic as well as asymptomatic plasma cell disease (Hillengass, *et al* 2010, Walker, *et*
24 *al* 2007). However, the degree of diffuse infiltration can only be assessed by approximation -
25 mostly by comparison of signal intensity of bone marrow to the inter-vertebral disc. **First**
26 **attempts to measure microcirculation and bone marrow infiltration in monoclonal plasma cell**
27 **diseases were undertaken using dynamic contrast enhanced MRI. It could be demonstrated**
28 **that amplitude A was higher in regions with increased vessel density (Nosas-Garcia, *et al***
29 **2005) and that it is an adverse prognostic factor for disease progression in patients with**
30 **progressive multiple myeloma (Hillengass, *et al* 2007). Furthermore, recent publications**
31 **show a benefit of dynamic contrast-enhanced MRI in assessment of treatment response (Lin,**
32 ***et al* 2010). Diffusion-weighted imaging (DWI) is an MRI technique based on the detection of**
33 **the random movement of water molecules which are in constant Brownian motion (Le Bihan,**
34 ***et al* 1988). In biologic tissues, this diffusion is restricted by interactions with cell membranes**
35 **and macromolecules. The degree of restriction is correlated to micro-structural factors such**
36 **as the tissue cellularity and the integrity of cell membranes (Gauvain, *et al* 2001, Guo, *et al***
37 **2002, Koh and Collins 2007, Lang, *et al* 1998, Sugahara, *et al* 1999). For quantitative**
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3 evaluation, the so called apparent diffusion coefficient (ADC) can be calculated. It has been
4
5 shown previously that ADC correlates inversely with tissue cellularity for example in primary
6
7 brain tumours (Chenevert, *et al* 2006).
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9
10 This study was conducted under the hypothesis that the ADC in bone marrow would be
11
12 correlated negatively with the degree of myeloma infiltration, assuming that this might reflect
13
14 an increase in cellularity. To evaluate this, we obtained DWI measurements and biopsies
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16 from the corresponding site in patients in different stages of monoclonal plasma cell disease.
17
18 Furthermore, we compared the DWI findings of the lumbar spine of patients with those of 30
19
20 healthy controls to learn whether there would be differences throughout the axial bone
21
22 marrow.
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24

25 26 27 **MATERIALS AND METHODS**

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29 This study was approved by the institutional ethics committee. All patients and controls were
30
31 examined only after written informed consent had been obtained. Bone marrow biopsies
32
33 were required for clinical reasons before initiation of systemic treatment.
34
35

36 37 38 *CHARACTERISTICS OF PATIENTS AND CONTROLS*

39
40 Among the 56 patients included, 40 suffered from symptomatic MM (26 untreated, 14 in
41
42 remission after systemic therapy). Of the remaining 16 patients, 12 had sMM, 1 had a single
43
44 plasmacytoma with signs of additional systemic disease activity ("indolent myeloma"), 1 had
45
46 a solitary plasmacytoma outside the examined area and 2 had MGUS. Among the 40
47
48 symptomatic patients, 14 had previously been treated systemically but none of those who
49
50 underwent bone marrow biopsy. Characteristics of patients and healthy controls are listed in
51
52 Table I. Bone marrow biopsy was evaluable in 25 patients.
53

54
55 Among 26 patients with symptomatic MM examined before onset of treatment, 15 could be
56
57 re-evaluated with DWI a second time, i.e. after therapy. All patients received high dose
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59 chemotherapy with autologous stem cell transplantation after induction with one of three
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different regimens (VAD = vincristine, doxorubicin, Dexamethason, n = 1; TAD = thalidomide,

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3 doxorubicin, Dexamethason, n = 11; PAD = bortezomib, doxorubicin, Dexamethason, n = 3)
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5 followed by a mobilization chemotherapy with CAD (Cyclophosphamid, doxorubicin,
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7 Dexamethason). All patients except one were enrolled in the multi centre trial of the German
8
9 speaking multiple myeloma group (GMMG-HD3/HD4), but the inclusion into the study
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11 presented here did not depend on enrolment into the GMMG-HD3/HD4 trial.
12
13

14 15 16 *MRI PROTOCOL*

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18 MR imaging was performed on a 1.5 -Tesla system (Symphony; Siemens medical solutions,
19
20 Erlangen, Germany). Sagittal T1-weighted spin-echo (SE) (TR/TE = 450/12 ms) and short
21
22 inversion time inversion recovery (STIR) (TR/TE/IR 3600/60/150 ms) sequences with 4-mm
23
24 section thickness, 256 or 242 x 512 matrix, 250 x 500 mm field of view were performed in all
25
26 patients.
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29 Diffusion weighted imaging was performed using an axial half-Fourier acquired single-shot
30
31 turbo spin echo (HASTE) sequence with the following parameters: 3 slices, 30 averages,
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33 three b-values (0, 400 and 700 s/mm² in phase, slice and read direction separately), FOV
34
35 480 mm, matrix 128 x 128, slice thickness 6 mm, TR/TE 1000/111 ms, FA 150°, BW 260
36
37 Hz/pixel phase encoding direction A-P, turbo factor 64, total imaging time 11 minutes.
38

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40 The lumbar spine in sagittal orientation and the pelvis in transversal orientation were
41
42 investigated in a single passage. In 18 patients a T1-weighted image of the pelvis was
43
44 repeated after bone marrow biopsy to locate the entry of the biopsy needle (Fig 1).
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47 48 49 *DWI DATA EVALUATION*

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51 DWI-data were post-processed using in-house developed software based on MeVisLab
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53 (Fraunhofer MEVIS, Bremen, Germany). The ADC was calculated using
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$$55 \quad ADC = \frac{1}{b} \ln \left(\frac{S_0}{S} \right)$$

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3 using 2 b-values (0 and 400 as well as 0 and 750 s/mm², referred to as ADC₄₀₀ and ADC₇₅₀
4
5 respectively). S₀ corresponds to the signal measured at b = 0 s/mm² and S to the signal
6
7 measured at b > 0 s/mm².
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10 11 *ACQUISITION OF BONE MARROW BIOPSY AND SMEAR*

12
13 After DWI of the lumbar spine and the pelvis, biopsies were performed with an 8G Yamshidi
14
15 needle (T-Lok Bone Marrow Biopsy Needle, Angiotech, Medical device technologies Inc.,
16
17 Gainesville FL, USA) and were fixed with a solution of methanol (100%)/formol (4%) 2:1. The
18
19 biopsies were dehydrated and embedded in methyl methacrylate without decalcification, and
20
21 semi thin sections were cut at 3 µm. Then, they were stained by using Gallamin-blue-Giemsa
22
23 as described previously (Islam and Frisch 1985). In addition, blood vessels were stained
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25 using anti-CD34 monoclonal antibodies (Dako Deutschland GmbH, Hamburg, Germany) and
26
27 plasma cells using anti-CD138 antibodies (Biermann, Bad Nauheim, Germany). The
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29 antibodies were visualized by alkaline phosphatase anti-alkaline phosphatase (APAAP)
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31 standard technique (Dako Deutschland GmbH, Hamburg, Germany).
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38 *HISTOLOGICAL ASSESSMENT*

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40 All preparations were performed by a single histopathologist (R.B.) experienced in the
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42 diagnosis of MM. For analysis of histological and cytological findings a semi-quantitative
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44 classification was applied as shown in table II adapted and modified from a system proposed
45
46 by Riccardi et al. (Riccardi, *et al* 1990). To assess the vascular density the bone marrow
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48 biopsies stained for CD34 were digitalized using an Aperio slide scanner (Aperio, Vista, CA,
49
50 USA) and the micro vessel number was calculated per 50000 µm² using the micro vessel
51
52 density algorithm (Aperio, Vista, CA, USA). Software based assessment of micro vessel
53
54 density was performed and controlled by another experienced pathologist (M.A.) also blinded
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56 to the stage of disease of the patients.
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PARAMETERS OF CYTOLOGICAL SMEAR

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3 The parameters "cellularity" and "plasma cell infiltration" in the cytological smear were
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5 retrieved from the electronic patient data base of the hematologic department. In our
6
7 institution bone marrow smears were routinely evaluated by a minimum of two experienced
8
9 cytologists in consensus.
10

11 12 13 *STATISTICAL ANALYSIS*

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15 To compare the histological parameters "fibres" and "haematopoiesis" with ADC of DWI an
16
17 exact Wilcoxon rank sum test was performed. To analyze the ordered values of histological
18
19 parameters and of the cytological parameter "cellularity" the Jonckheere-Terpstra test
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21 (Hollander 1973) for increasing trend was performed. The p-values were subsequently
22
23 adjusted by Holm's method to control the family-wise error rate at 0.05 (Holm 1979).
24
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26
27 Correlation between ADC and continuous parameter "plasma cell infiltration" of cytological
28
29 smear was assessed with Spearman's rho including 95% confidence intervals (95%-ci).
30

31
32 To compare ADC between each patient group and healthy controls Wilcoxon rank sum test
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34 was performed. ADC before and after systemic therapy was analyzed by exact Wilcoxon
35
36 signed-rank test.
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39 All Wilcoxon rank sum tests and Wilcoxon signed-rank tests were two-sided at significance
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41 level of 5%. Statistical analyzes were carried out using the software package R, version 2.9.2
42
43 (R-Development-Core-Team 2009) together with the R packages "coin", version 1.0-6, and
44
45 "clinfun", version 0.8.7 for the Jonckheere-Terpstra test.
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50 51 **RESULTS**

52 53 *CORRELATION OF ADC OF THE PELVIS WITH HISTOLOGICAL FINDINGS*

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55 After adjustment of p-values for multiple testing, the degree of plasma cell infiltration and
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57 vascular density correlated positively with ADC₄₀₀ and ADC₇₅₀ with a p-value of < 0.001 for all
58
59 comparisons. No correlation with the degree of fibres, fat r physiologic haematopoiesis was
60
found.

CORRELATION OF ADC OF THE PELVIS WITH PARAMETERS OF CYTOLOGICAL SMEAR

Because the quantification of different cells is easier in cytological smear, the correlation of ADC₄₀₀ and ADC₇₅₀ with cytology-based cellularity and plasma cell concentration in bone marrow was analyzed.

Bone marrow cellularity over all and percentage of plasma cell infiltration in cytological smear were positively correlated with ADC₄₀₀ and ADC₇₅₀, respectively. P-values and Spearman's correlation coefficients are shown in table III.

COMPARISON OF HEALTHY CONTROLS AND PATIENTS IN DIFFERENT STAGES OF DISEASE

Median ADC₄₀₀ / ADC₇₅₀ was $4.0 \times 10^{-4} / 2.7 \times 10^{-4} \text{ mm}^2/\text{s}$ in healthy controls compared to $5.3 \times 10^{-4} / 4.0 \times 10^{-4} \text{ mm}^2/\text{s}$ in symptomatic MM, yielding a statistically significant difference between these two groups ($p = 0.003$ and 0.002 for ADC₄₀₀ and ADC₇₅₀, respectively). No differences were found between patients with either plasmacytoma, MGUS, sMM or symptomatic MM after treatment and healthy controls, respectively (Fig 2).

CHANGES OF ADC AFTER SYSTEMIC TREATMENT:

Out of 15 patients with MM examined before and after systemic treatment 12 had achieved at least a near complete remission. Two patients were in partial remission and one in stable disease. Median ADC₄₀₀ and median ADC₇₅₀ decreased significantly from $6.5 \times 10^{-4} / 4.4 \times 10^{-4} \text{ mm}^2/\text{s}$ before to $3.2 \times 10^{-4} / 2.2 \times 10^{-4} \text{ mm}^2/\text{s}$ after therapy ($p < 0.001$ respectively) (Fig 3 and table IV).

DISCUSSION

The assessment of tumour cell mass in MM was the main aim of the Durie/ Salmon staging system which has been in use over decades and for a long time has been guideline for

1
2
3 treatment decision (Durie and Salmon 1975). As in most other malignant diseases the extent
4
5 of tumour cell burden is important in MM as well. This is true both for initial diagnostic as well
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7 as for assessment of residual disease after effective therapy. Furthermore, both the degree
8
9 of plasma cell concentration in bone marrow and changes in bone marrow microenvironment
10
11 have been demonstrated to be of great importance in the pathophysiology of monoclonal
12
13 plasma cell diseases (Klein, *et al* 2003, Pagnucco, *et al* 2004). Most studies on this subject
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15 have been based on the evaluation of histological findings of bone marrow trephine as gold
16
17 standard. However, biopsies entail several disadvantages: First of all, fixation techniques
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19 have to be applied to conserve the sample. Second, the biopsy site may not be
20
21 representative, and a biopsy in another location might yield different results. Notably, multiple
22
23 myeloma may involve the bone marrow in either a diffuse or a patchy fashion. Furthermore,
24
25 bone marrow biopsy is an invasive examination with risk for local infections and bleeding
26
27 which is moderately tolerated by patients especially if it is performed repeatedly. All things
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29 considered, the development of non-invasive techniques of assessment of bone marrow
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31 microenvironment is of utmost importance.
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36 MRI has been shown to be the most sensitive imaging technique to detect plasma cell
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38 infiltration in bone marrow of patients with MM (Lecouvet, *et al* 1999, Ludwig, *et al* 1987,
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40 Mahnken, *et al* 2002). This technique has the important advantage that it does not expose
41
42 the patient to irradiation as for example computed tomography or positron emission
43
44 tomography. In MRI focal lesions caused by malignant infiltration are present in 30 - 50% of
45
46 MM-patients and can be counted and measured to a certain extent, however with necessity
47
48 of time and effort (Bauerle, *et al* 2009, Baur, *et al* 2002, Ghanem, *et al* 2006, Kusumoto, *et al*
49
50 1997, Lecouvet, *et al* 1998, Moulopoulos, *et al* 2010, Stabler, *et al* 1996). The prognostic
51
52 significance of the number and presence of those lesions has been shown recently
53
54 (Hillengass, *et al* 2010, Walker, *et al* 2007). Diffuse infiltration, which can be detected in
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56 nearly the same proportion of patients, has also been demonstrated to be of prognostic as
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58 well as pathophysiologic significance (Hillengass, *et al* 2010, Moulopoulos, *et al* 2010,
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60 Moulopoulos, *et al* 2005), but it is hard to assess and impossible to quantify.

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3 DWI has been used for several years for tumour characterization and therapy monitoring with
4
5 the rationale that the ADC would reflect cellularity. This applicability of DWI has first been
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7 demonstrated in primary brain tumours (Chenevert, *et al* 2006) but recent publications also
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9 have focused on cancer in other organs (Koh and Collins 2007). Our own results suggest,
10
11 however, that cellularity is unlikely to be the only factor influencing the DWI signal.

12
13 First, the ADC was positively correlated with the degree of plasma cell infiltration in both
14
15 histology and bone marrow smears. Had cellular density been the dominant factor the
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17 correlation should have been inverse. Indeed, recent reports on pancreatic cancer and liver
18
19 fibrosis have indicated a strong influence of perfusion effects on the measured ADC (Lemke,
20
21 *et al* 2009, Luciani, *et al* 2008). This relates to the intra-voxel incoherent motion (IVIM)
22
23 theory, first proposed by Le Bihan in 1988 (Le Bihan, *et al* 1988). This theory describes a
24
25 strong signal decay at low b-values ($b < 300 \text{ s/mm}^2$) caused by perfusion effects. The DWI-
26
27 sequence used in this study, does not allow for the extraction of these perfusion components
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29 since we did not measure a whole set of different b-values, especially including low ones.
30
31 Most probably, the measured ADC is influenced by a combination of perfusion and tissue
32
33 microstructure. Increased vascularity would lead to an increase in ADC, whereas increased
34
35 cellularity would lead to a decrease in ADC.

36
37 Since the vascular density increases with bone marrow infiltration as shown in this study as
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39 well as previously (Sezer, *et al* 2001), we infer that the here reported positive correlation
40
41 between ADC and cellularity and vascular density can be attributed to a dominant effect of
42
43 perfusion on the ADC. This should be further investigated using IVIM-DWI. We also believe
44
45 that this effect may have occurred in other studies producing similar results, because several
46
47 studies have shown the same trend as our analysis (Chan, *et al* 2002, Nonomura, *et al* 2001,
48
49 Pui, *et al* 2005).

50
51 Further developments are under way to differentiate the diffusion and the perfusion part of
52
53 the ADC. If this goal is achieved DWI can be used to estimate initial tumour mass, to monitor
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55 effects of therapy and to display tissue characteristics - both perfusion and cellularity - in
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57 bone marrow non-invasively and without the need of contrast agents in patients with MM.
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3 The comparison of healthy individuals with patients in different stages of plasma cell disease
4 revealed a significant difference between patients with symptomatic MM and controls. ADC
5 values increased from healthy controls and MGUS or plasmacytoma patients over sMM to
6 symptomatic patients. In patients examined after response to systemic chemotherapy ADC
7 decreased nearly to the level of normal controls (Fig 2). Especially in patients with hypo- or
8 asecretory MM DWI might, **after further advancements**, provide a possibility to measure
9 disease activity without the need of frequent bone marrow biopsies. Furthermore, vertebral
10 bodies or other regions with high infiltration, in danger of pathologic fracture can be identified
11 in advance.
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16 In conclusion, DWI **comprises the possibility to** allow for the monitoring of bone marrow
17 infiltration in a non-invasive, quantitative way and further developments **and investigations in**
18 **larger patient groups** will have to show if it should be incorporated into the diagnostic
19 repertoire in patients with monoclonal plasma cell disease.
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Jens Hillengass, Tobias Bäuerle, Reiner Bartl, Mindaugas Andrulis, Fabienne McClanahan, Christian Zechmann, Rajiv Shah, Barbara Wagner-Gund, performed the research. Jens Hillengass, Stefan Delorme, Tobias Bäuerle and Bram Stieltjes designed the research study. Frederik Laun, Dirk Simon, Heinz-Peter Schlemmer, Stefan Delorme and Bram Stieltjes contributed essential tools. Kai Neben, Anthony Ho and Hartmut Goldschmidt contributed patients for the study. Jens Hillengass, Christiane Heiss, Stefan Delorme and Bram Stieltjes analysed the data. Jens Hillengass and Bram Stieltjes wrote the paper.

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3 **FIGURE 1:** (A and B) T1-weighted MR image (orientation: axial) of the pelvis of a patient with
4 multiple myeloma after biopsy. The arrow marks the puncture channel. (C) Diffusion-
5 weighted axial image of the pelvis of the same region before biopsy with a manually drawn
6 region of interest (white line). (D) Histological section of a bone marrow trephine of the pelvis
7 with diffuse high grade infiltration by plasma cells stained for CD138.
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11 **FIGURE 2:** Median ADC ($10^{-4}\text{mm}^2/\text{s}$) of controls, patients with MGUS (MGUS), smoldering
12 myeloma (sMM), multiple myeloma before (MM) and in remission after systemic treatment
13 (MM post) at b-values of 400 and 750 s/mm^2 respectively.
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16 **FIGURE 3:** Median ADC ($10^{-4}\text{mm}^2/\text{s}$) of patients with symptomatic MM before and after
17 systemic treatment
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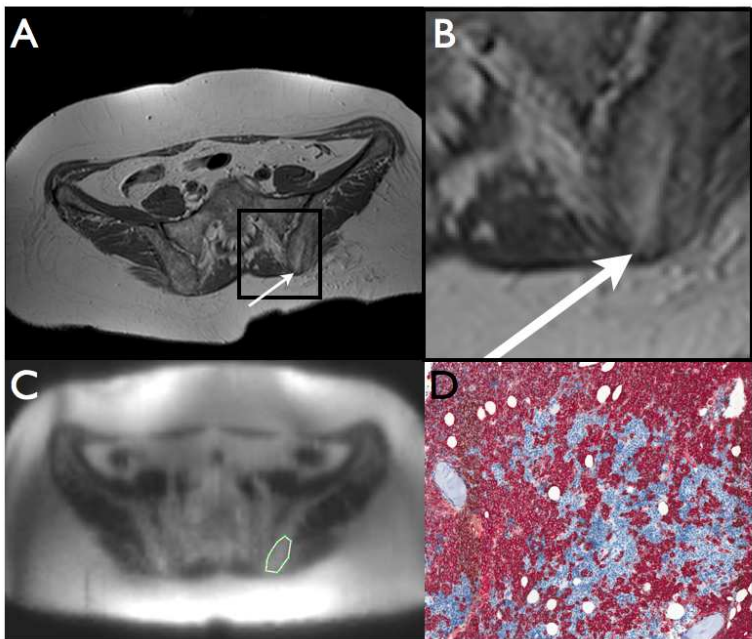


Figure 1
361x270mm (72 x 72 DPI)

Review

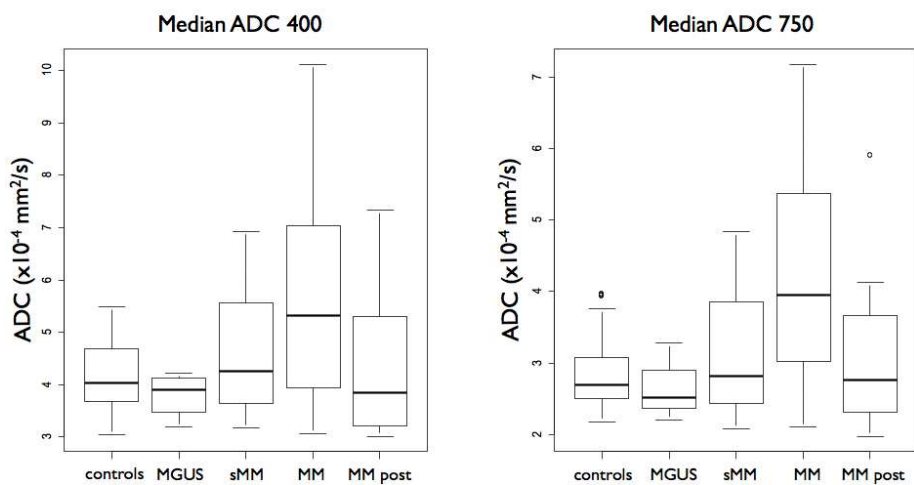


Figure 2
361x270mm (72 x 72 DPI)

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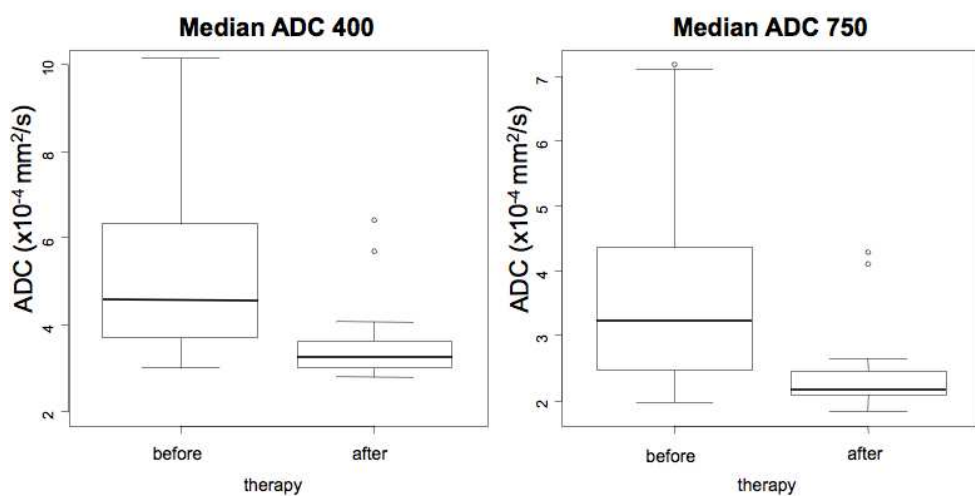


Figure 3
282x211mm (72 x 72 DPI)

review

Table I: Characteristics of patients and healthy controls**Patients**

median age [range] (years)	57 [35 – 75]
female sex (n, %)	22 (39%)
MGUS (n)	2
with bone marrow biopsy	0
solitary plasmacytoma (both in thoracic spine)	2
with bone marrow biopsy	1
smoldering myeloma	12
with bone marrow biopsy	9
untreated symptomatic multiple myeloma	26
with bone marrow biopsy	20
follow-up after systemic treatment	15
pre-treated symptomatic multiple myeloma	14
with bone marrow biopsy	0

Controls

median age [range] (years)	56 [29 – 74]
female sex (n, %)	14 (47%)

Peer Review

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Table II: Histological and cytological classification

Histology	
Degree of plasma cell infiltration	0 no (< 5 %) 1 low 2 mild 3 moderate 4 severe
Fibers	0 no 1 reticular 2 dense
Physiological haematopoiesis	0 normal 1 reduced 2 absent
Fatty tissue	0 normal 1 reduced 2 atrophic
Vascular density	0 low 1 moderate 2 high
Cytology	
Percentage of plasma cells	0-100%
Bone marrow cellularity*	1 reduced 2 normal 3 increased

*Cellular fraction compared to fatty vacuoles

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Table III: Correlation of the parameters of cytological smear and ADC of the pelvis

	plasma cell concentration	cellularity
ADC 400	CC 0.3196 [0.06997, 0.5692] p = 0.0354	p = 0.0419
ADC 750	CC 0.3705 [0.11, 0.631] p = 0.0151	p = 0.0364

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60**Table IV: median ADC of the pelvis and degree of bone marrow infiltration**

	median ADC ₄₀₀ in pelvis [$\times 10^{-4}$ mm ² /s]	median ADC ₇₅₀ in pelvis [$\times 10^{-4}$ mm ² /s]	bone marrow infiltration [%]
MGUS	3.9 [3.2, 4.2]	2.5 [2.2, 3.3]	5.0 [3.0, 8.0]
sMM	4.3 [3.2, 6.9]	2.8 [2.1, 4.8]	12.5 [5.0, 82.0]
MM	5.3 [3.1, 10.1]	4.0 [2.1, 7.2]	44.0 [5.0, 95.0]
MM post treatment	3.9 [3.0, 7.3]	2.8 [2.0, 5.9]	5.0 [2.0, 25.0]

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