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# Value of whole body MRI and dynamic contrast enhanced MRI in the diagnosis, follow-up and evaluation of disease activity and extent in multiple myeloma

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ABSTRACT

*Purpose:* To evaluate the significance of dynamic contrast enhanced MRI (DCE-MRI) and whole body MRI (WB-MRI) in the diagnosis, prognosis and assessment of therapy for patients with monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma (MM).
*Materials and methods:* The retrospective study includes 219 patients providing 463 WB-MRI and DCE-MRI investigations for the subgroups MGUS ($n = 70$), MM active disease ($n = 126$; this includes 70 patients with new diagnosis of MM, according to the International Staging System (ISS): 41.4% ISS stage I, 20.0% ISS stage II, 7.1% ISS stage III, 31.4% insufficient for staging; and 56 patients with '(re-)active disease': 16.07% relapse, 32.14% progressive disease and 51.79% stable disease) and MM remission ($n = 23$; 60.87% complete remission, 17.39% very good partial remission and 21.74% partial remission). Investigations of patients with hereditary multiple exostoses ($n = 5$), neurofibromatosis ($n = 7$) and healthy persons ($n = 9$) were added as control subjects ($n = 21$). WB-MRI evaluation was done by evaluating thirteen skeletal regions, providing a 'skeletal score'. DCE-MRI images of the spine, were analyzed with regions-of-interest and time-intensity-curves (TIC).
*Results:* All TIC parameters can significantly differentiate between the predefined subgroups ($p < 0.001$). One hundred days after autologous stem cell transplantation a 75% decrease of the slope wash-in value ($p < 0.001$) can be seen. A cubic regression trend between 'skeletal score' and slope wash-in (adj.$R^2 = 0.412$) could demonstrate a significant increase bone marrow perfusion if MM affects more than 10 skeletal regions ($p < 0.001$), associated with a poorer prognosis ($p < 0.001$).
*Conclusion:* DCE-MRI evaluation of the spine is useful for diagnosis of MM, follow-up after stem cell transplantation and evaluation of disease activity. A combined evaluation with WB-MRI and DCE-MRI provides additional micro-vascular information on the morphologic lesions and could help categorize patients with MM in two different groups to offer useful therapeutic and prognostic advise.


## 1. Introduction

Multiple myeloma (MM) is a hematological malignancy characterized by proliferation of monoclonal plasma cells in the bone marrow. This disease evolves from an asymptomatic stage, monoclonal gammopathy of undetermined significance (MGUS), and progresses over smoldering myeloma (sMM) to symptomatic disease (MM). The gold standard diagnostic test for MM is a bone marrow biopsy to define the amount of atypical plasma cells and forms the basis of the diagnostic classification system of the International Myeloma Working Group (IMWG) [1,2].

Imaging patients with MM is very important for the assessment of the extent and severity of disease at presentation, identification of complications and assessment of therapy response. Historically skeletal surveys have been used as the gold standard for radiological screening of osteolytic punched-out-lesions at diagnosis. Over recent years whole body magnetic resonance imaging (WB-MRI) has become the diagnostic modality of choice to localize tumoral

*Abbreviations:* ASCT, autologous stem cell transplantation; a.U., arbitrary units; A, artery; CR, complete response; DCE-MRI, dynamic contrast enhanced MRI; IMWG, International Myeloma Working Group; ISS, international staging system; MPNST, malignant peripheral nerve sheath tumor; MRI, magnetic resonance imaging; MVD, micro vascular density; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; M, muscle; NF, neurofibromatosis; PR, partial response; PET, positron-emission tomography; PD, progressive disease; ROC, receiver operating characteristics; ROI, region of interest; SI, signal intensity; sMM, smouldering multiple myeloma; SD, stable disease; T, time; TIC, time-intensity curve; TVA, total vascular area; V, vertebra; VGPR, very good partial response; WI, wash-in; WO, wash-out; WB-MRI, whole body-MRI.

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invasion in bone marrow and to assess the extent of disease [3,4]. MRI now contributes; together with the findings on conventional radiographs, PET scanning and laboratory tests; to the Durie-Samon Plus staging system, predictive for overall survival [3,5,6]. Besides morphological evaluation of the spine, functional imaging with dynamic contrast enhanced MRI (DCE-MRI) is now frequently used to better evaluate disease activity [7]. DCE-MRI provides information on tissue vascularization and perfusion, capillary permeability and volume of the interstitial space by analysis of the migration of contrast medium from the vascular into the interstitial space [8].

The aim of this retrospective study was to assess the extent of bone marrow invasion with WB-MRI, and to evaluate the activity of disease by measuring vascularization and perfusion of the spinal bone marrow with DCE-MRI, in patients with MGUS and MM, and to determine the value of these techniques in diagnosis, prognosis and assessment of therapy response. To investigate therapy response, a subgroup analysis was done on patients receiving an autologous stem cell transplantation (ASCT).

## 2. Materials and methods

### 2.1. Patients

This observational retrospective study was conducted in our University Hospital and approved by the institutional ethics committee. Informed consent was obtained from all patients and controls. The study population consists of 219 patients with a total of 463 WB-MRI and DCE-MRI investigations between April 2005 and November 2011. The patients were classified according to the IMWG diagnostic criteria based on laboratory, clinical and histopathological results. The study population was divided into the following subgroups ($n$ = number of patients/number of studies; mean age; % male): MGUS ($n$ = 70/78; 62 years; 50% male), MM active disease ($n$ = 126/257; 61 years; 63% male) and MM remission ($n$ = 23/128; mean age 62 years; 61% male) and controls ($n$ = 21/26; mean age 49 years; 52% male). The subgroup 'MM active disease' includes 70 patients with a new diagnosis, with corresponding stages according to the International Staging System (ISS) [9]: 41.4% ISS stage I, 20.0% ISS stage II, 7.1% ISS stage III, 31.4% insufficient for staging; and 56 patients with (re-)active disease: 16.07% relapse, 32.14% progressive disease (PD) and 51.79% stable disease (SD), according to the IMWG response criteria [10]. MM remission includes patients with a good response after receiving therapy with 60.87% complete response (CR), 17.39% very good partial response (VGPR) and 21.74% partial response (PR), also according to the IMWG response criteria [10]. Follow-up data could be obtained from 21 patients who received SCT, all patients are currently in CR after SCT. Investigations of patients with hereditary multiple exostoses ($n$ = 5) and neurofibromatosis ($n$ = 7), investigated to exclude malignancy, and healthy persons ($n$ = 9) were added as controls subjects. Patients with NF and HME are frequently referred for WB-MRI and DCE-MRI to our institution to exclude malignant peripheral nerve sheath tumor (MPNST) and chondrosarcoma respectively.

### 2.2. Laboratory investigations

Results from the imaging studies were correlated to different variables obtained from laboratory analysis. The most important biological parameters derived from peripheral blood analyses were $\beta_2$-microglobulin (mg/L) and albumin (g/L), according to the ISS with $\beta_2$-microglobulin as one of the best prognostic variables for MM and simple reliable marker for staging [9,11,12]. The percentage plasma cells resulting from bone marrow analysis is still the gold standard for the diagnosis of MM and has therefore been used as the comparative diagnostic variable in this research article.

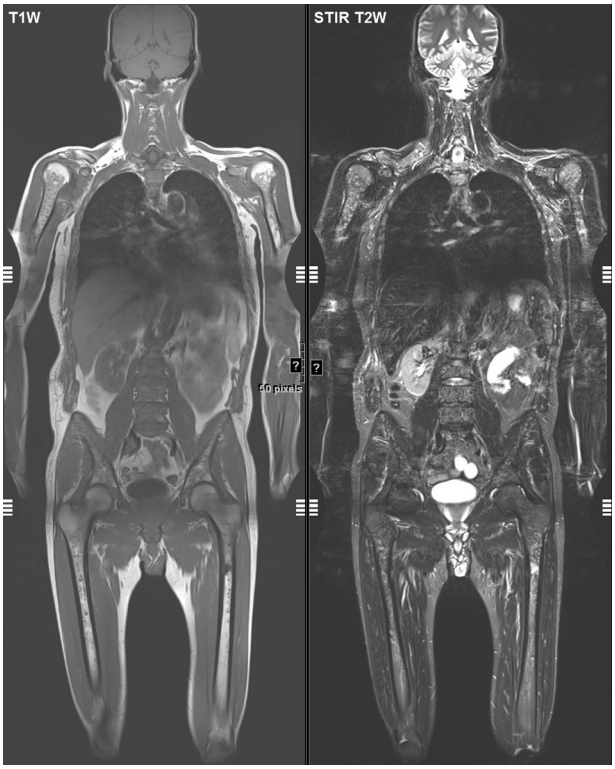


**Fig. 1.** Coronal T1 and STIR-T2 WB-MR images displaying full bone marrow infiltration in the humeri, femora, pelvis and lower lumbar spine. Lesions with low or intermediate signal intensity are seen in T1-weighted images and lesions with high signal intensities are seen in fat saturated T2-weighted images.

### 2.3. Imaging protocol

Imaging was performed on a 1.5 Tesla MRI-scanner (Magnetom Avanto, Siemens Healthcare, Erlangen, Germany). Morphological WB-MR imaging was performed using multiple

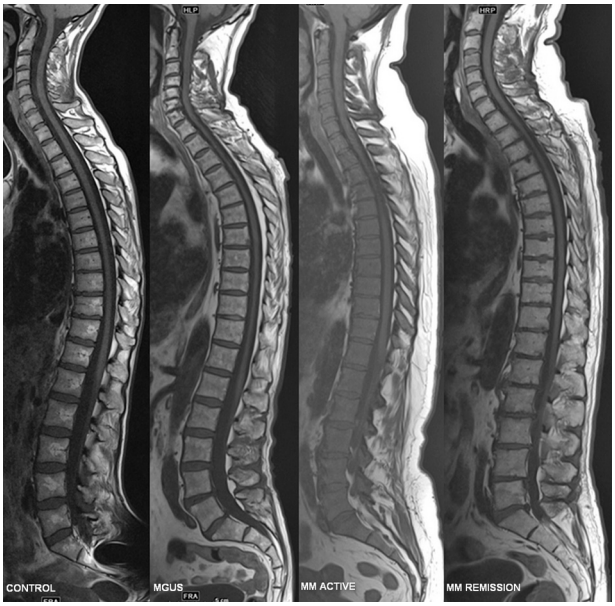


**Fig. 2.** Sagittal T1 weighted WB-MR images, from left to right: control subject with a normal spine, patient with MGUS and no spinal involvement, patient with active MM and a 'full' infiltration pattern and last a patient in remission with fatty appearance of bone marrow.