

Prognostic Significance of Focal Lesions in Whole-Body Magnetic Resonance Imaging in Patients With Asymptomatic Multiple Myeloma

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ABSTRACT

Purpose

With whole-body magnetic resonance imaging (wb-MRI), almost the whole bone marrow compartment can be examined in patients with monoclonal plasma cell disease. Focal lesions (FLs) detected by spinal MRI have been of prognostic significance in symptomatic multiple myeloma (sMM). In this study, we investigated the prognostic significance of FLs in wb-MRI in patients with asymptomatic multiple myeloma (aMM).

Patients and Methods

Wb-MRI was performed in 149 patients with aMM. The prognostic significance of the presence and absence, as well as the number, of FLs for progression into sMM was analyzed.

Results

FLs were present in 28% of patients. The presence per se of FLs and a number of greater than one FL were the strongest adverse prognostic factors for progression into sMM ($P < .001$) in multivariate analysis. A diffuse infiltration pattern in MRI, a monoclonal protein of 40 g/L or greater, and a plasma cell infiltration in bone marrow of 20% or greater were other adverse prognostic factors for progression-free survival in univariate analysis.

Conclusion

We recommend use of wb-MRI for risk stratification of patients with asymptomatic multiple myeloma.

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INTRODUCTION

Asymptomatic multiple myeloma (aMM) is a disorder that originates from monoclonal plasma cells. It is defined by a serum concentration of a monoclonal protein greater than 30 g/L and/or 10% or greater clonal plasma cells in bone marrow.¹ Patients with aMM do not need the systemic treatment that patients with symptomatic multiple myeloma (sMM) would require.² The annual progression rate into sMM is 10% per year for the first 5 years; the cumulative probability of progression is 73% at 15 years, but there is great interindividual variability.³ Therefore, the identification of predictors of progression into sMM is of great importance.

Until now, the most widely accepted clinical risk factors for aMM for progression into sMM have been concentration and type of serum M protein, amount of Bence Jones Protein excretion in urine, pattern and percentage of bone marrow plasma cells, and reduction of uninvolved immunoglobulins (Igs).³⁻⁵

Among imaging methods, magnetic resonance imaging (MRI) has the highest sensitivity for detecting bone marrow involvement in multiple myeloma. Spinal MRI is recommended for clinical work-up of patients with monoclonal gammopathy of undetermined significance, solitary plasmacytoma, and aMM.⁶ In sMM, greater than seven focal lesions (FLs) detected by axial MRI (ie, spine and sacral bone) has been of adverse prognostic significance.⁷ With fast sequences and a rolling table device available, MRI can be performed as a whole-body protocol (wb-MRI).⁸ This is important, because not examining the appendicular skeleton will miss approximately 50% of FLs,⁹ of which those will also be occult to plain film radiographs that have not yet caused destruction of mineralized bone. We hypothesized that the presence of FLs as well as the number would be of prognostic significance for progression-free survival in patients with aMM in a similar fashion as they have already been shown to be in sMM.⁷

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PATIENTS AND METHODS

Patients

From November 2003 to April 2008, a total of 149 individuals with aMM (73 women and 76 men) were examined with wb-MRI. The median age was 58 years (range, 25 to 81 years). Staging followed the classification proposed by the International Myeloma Working Group, but this classification did not include MRI findings.¹ In 16 patients, a localized plasma cell tumor plus evidence of systemic disease according to other factors, such as elevated monoclonal protein or percentage of plasma cells in bone marrow, were present. None of the patients had signs of bone disease besides one with osteolysis caused by the plasma cell tumor, and none of the patients were treated systemically until sMM occurred later. The only therapy was local irradiation with a dose of 25 to 50 Gy in 14 patients and a tumor extirpation in two patients. Like the other patients in this study, those patients would not have had an indication for a systemic treatment after definitive local therapy, such as irradiation and/or surgery; hence, we decided to include them into this analysis. Patients with true solitary plasmacytoma were excluded from this analysis, because other survival rates and prognostic factors for this entity have been described in the literature.

The median time of follow-up for the whole patient group was 23.7 months, and information about patients was last updated in January 2009. Retrospective evaluation of wb-MRI data of patients with MM in our clinic had been approved by the institutional ethics review board.

MRI Protocol

Wb-MRI was performed with two 1.5-Tesla, whole-body systems (Magnetom Avanto, Siemens Medical Solutions, Erlangen, Germany) with phased-array, body-matrix surface coils (Siemens Medical Solutions, Erlangen, Germany) that had the following parameters: T1-weighted turbo-spin echo sequence (TR = 627 milliseconds [ms]; TE = 11 ms) of the head (voxel size, $1.25 \times 1.25 \times 5 \text{ mm}^3$; scan time, 2 minutes 4 seconds), thorax and abdomen (voxel size, $1.25 \times 1.25 \times 5 \text{ mm}^3$; scan time, 2 minutes 4 seconds), pelvis ($1.25 \times 1.25 \times 5 \text{ mm}^3$; scan time, 2 minutes 4 seconds), and leg (voxel size, $1.25 \times 1.25 \times 5 \text{ mm}^3$; scan time, 2 minutes 4 seconds), all in coronal orientation; T2-weighted short- τ inversion recovery (STIR) sequence (TR = 3,340 ms; TE = 109 ms; TI = 160 ms) of the head (voxel size, $1.25 \times 1.25 \times 5 \text{ mm}^3$; scan time, 1 minute 20 seconds), thorax and abdomen (voxel size, $1.25 \times 1.25 \times 5 \text{ mm}^3$; scan time, 1 minute 20 seconds), and pelvis (voxel size, $1.25 \times 1.25 \times 5 \text{ mm}^3$; scan time, 1 minute 20 seconds), all in coronal orientation; T1-weighted turbo spin echo sequence (TR = 400 ms; TE = 11 ms) of the spine in sagittal orientation (voxel size, $1.836 \times 1.836 \times 3.5 \text{ mm}^3$; scan time, 1 minute 16 seconds); T2-weighted FLASH 2D sequence (TR = 402 ms; TE = 12 ms) of the spine in sagittal orientation (voxel size, $0.84 \times 0.84 \times 5 \text{ mm}^3$; scan time, 1 minute 38 seconds). The patients were positioned with arms along their bodies, and the series covered the region between the skull vertex and the midcalf. Depending on the body height of the patient, the distal calves and the feet were not included.

Image Analysis

All MRI scans were read by two experienced radiologists (K.F., M.A.W.) in consensus who were blinded to the diagnosis of the patients and who counted the number of FLs in the axial skeleton (ie, spine and sacral bone), the extra-axial skeleton (ie, all other parts of the skeleton), and in soft tissue separately. Furthermore, diffuse bone marrow infiltration in the axial skeleton was recorded according to the criteria proposed by Staebler and Baur.^{10,11} FLs presented with decreased signal intensity in T1-weighted images and with increased signal intensity in T2-weighted images. Diffuse infiltration was characterized as homogeneous signal decrease in T1- and increase in T2-weighted images compared with the signal intensity of the vertebral disk. Lesions in typical locations for degenerative changes were not counted.

Evaluation of Progression-Free Survival

Follow-up took place every 3 to 6 months and included clinical history and examination as well as serum and urine markers. A radiologic skeletal survey (RSS) was obtained for occurrence of symptoms or an increase in monoclonal protein levels; the average interval between x-ray studies was 2

years. The start of systemic therapy was defined as the date of event for the analysis of progression-free survival.

Statistical Analysis

The search for an optimal cutoff point in number of FLs with respect to progression-free survival into symptomatic disease was performed by using maximally selected rank statistics.¹²⁻¹⁴

Univariate Analysis

The significance of the number of focal FLs in wb-MRI greater than the cutoff point, the presence of a diffuse infiltration pattern in MRI, and the presence of established adverse prognostic markers for aMM for the progression into sMM was analyzed. Time to progression into sMM was estimated by using the Kaplan-Meier method. Group comparisons were made by using a log-rank test. The prognostic value of a number of FLs greater than the cutoff point for the probability of progression was analyzed in a Cox proportional hazard regression model.

Multivariate Analysis

Risk factors analyzed in multivariate analysis were M protein concentration of $\geq 40 \text{ g/L}$; presence of an IgA monoclonal protein; reduction of uninvolved Igs; presence of urinary Bence Jones Protein and a plasma cell infiltration in bone marrow of $\geq 20\%$.³⁻⁵ MRI-derived risk factors were the number of FLs greater than the cutoff point and the presence or absence of diffuse bone marrow involvement. Multivariate analysis was performed with a Cox proportional hazards regression model.

Backward variable selection was performed for the multivariate model with a significance level for staying in the model of 0.2 to select the most important risk factors for progression-free survival into symptomatic disease.¹⁵ Correlation analysis between the different risk factors was done by using the Kendall τ test.

RESULTS

Optimal Cutoff Point for the Number of FLs

Search for an optimal cutoff point of the number of FLs revealed that patients with greater than one FL had significantly shorter progression-free survival than those without or with only one FL ($P < .001$). The Kaplan-Meier plot for progression into symptomatic disease is shown in Figure 1.

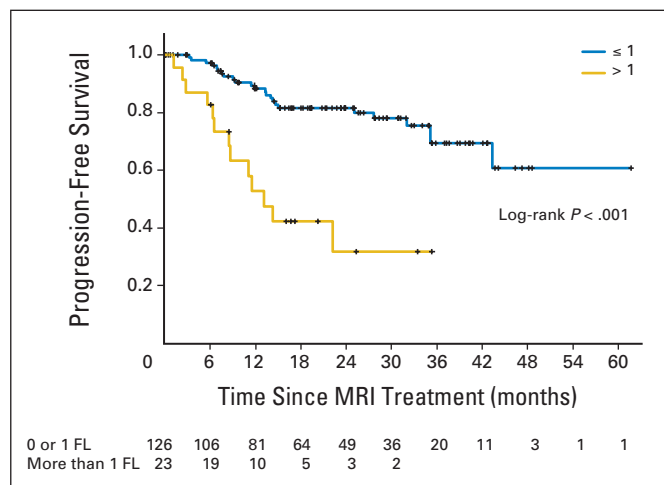


Fig 1. Kaplan-Meier plots for progression into symptomatic myeloma of patients who had no or one focal lesion (FL) compared with patients who had greater than one FL. The median time to progression was not reached (last event at 43 months) for the patient group with no or one FL and 13 months for the patient group with greater than one FL, respectively. MRI, magnetic resonance imaging.

Table 1. Comparison of the Number of FLs and Bone Marrow Patterns in wb-MRI

Patterns by No. of Focal Lesions	Bone Marrow Pattern	
	Normal	Diffuse
No FL	69	38
One FL		
Axial	6	3
Extra-axial	4	6
Greater than one FL		
Axial	2	1
Extra-axial	5	4
Axial + extra-axial	3	8

Abbreviations: FL, focal lesion; wb, whole body; MRI, magnetic resonance imaging.

Incidence of FLs

In the whole patient group, FLs were detected in 42 (28%) of 149 patients (number of FL range, one to > 20). The number of patients with FLs in the axial skeleton only was 12 (8%); in the extra-axial skeleton only, 19 (13%); and in both locations, 11 (7%). In the group with merely extra-axial lesions, 10 of 19 patients had just one FL. In the study sample, individuals who had FLs in the extra-axial skeleton only were more frequent than those in whom FLs were only located in the axial skeleton (19 v 12 patients). Of 23 patients with greater than one focal lesion, nine patients had extra-axial lesions only, which would have been missed by axial MRI alone.

In 16 patients with initial plasma cell tumor, nine had merely one of these lesions in wb-MRI, and seven showed additional FLs. In this group, seven patients developed signs of disease progression with need for systemic treatment. From those patients, one had only a single lesion, and the others had two or more FLs.

FLs and Diffuse Infiltration Pattern

The groups of patients with different numbers of FLs and with or without diffuse infiltration pattern in bone marrow are listed in Table 1. In 60 patients (40%), a diffuse bone marrow infiltration was detected in MRI whether or not FLs were present. Of 107 patients without any FLs, 38 patients (36%) presented with a diffuse bone marrow infiltration on MRI.

Notably, nine of the 19 patients (6% of the whole patient group) who had only extra-axial FLs had entirely normal spines and pelvises (ie, no visible diffuse bone marrow involvement). Of these nine patients, four had only one FL. Thus, had MRI been limited to the spine

Table 2. Results of the Univariate Analysis for Progression-Free Survival

Univariate	Hazard Ratio	P
MRI-FL greater than cut-off point of one FL	4.05	< .001
Diffuse bone marrow infiltration in MRI	3.14	< .001
M-protein concentration \geq 40 g/L	5.71	.005
Presence of IgA	0.61	.26
Reduction of uninvolved Ig	0.66	.35
Presence of urinary Bence Jones Protein	1.34	.38
Plasma cell infiltration in bone marrow \geq 20%	2.14	.03

Abbreviations: MRI, magnetic resonance imaging; FL, focal lesion; Ig, immunoglobulin.

and pelvis only, the skeletal involvement by MM would have been completely missed.

Disease Progression

Comparison of the 16 patients with additional solitary plasma cell tumor—of which 14 also had corresponding osteolysis—with the 133 patients without any plasma cell tumor revealed no significant differences in progression-free survival. Therefore, these patients were included in the analysis.

Univariate Analysis

The univariate analysis revealed that the presence of FLs as well as greater than one FL, diffuse bone marrow infiltration in MRI, a monoclonal protein of greater than 40 g/L and a plasma cell infiltration in bone marrow of greater than 20% were adverse prognostic factors for progression into symptomatic disease. Results for all analyzed parameters are shown in Table 2.

Multivariate Analysis

Multivariate analysis of the MRI and non-MRI parameters revealed that the presence and the number of FLs as well as a diffuse bone marrow infiltration in MRI remained the only significant adverse prognostic factors for progression into symptomatic disease in our cohort when analysis was adjusted for the other prognostic parameters mentioned in the Patients and Methods section. Results of this analysis are listed in Table 3 for all risk factors (upper part) and for the most significant risk factors determined by backward selection (lower part). Clinical characteristics of the 23 patients with greater than one FL who developed necessity of systemic treatment are listed in Table 4.

Correlations of Prognostic Parameters

Analysis of the relationship of the MRI parameters and the prognostic factors listed in Table 1 revealed no significant correlations. Comparison of serum levels of β 2 microglobulin or albumin, which are standard prognostic factors for sMM, in patient groups with or without FLs did not reveal a significant difference ($P = .6$ and $P = .06$, respectively).

DISCUSSION

This study demonstrates, for the first time to our knowledge, the prognostic significance of FLs detected by wb-MRI in patients with

Table 3. Results of the Multivariate Analysis of All Variables and of Selected Variables for Progression-Free Survival

Variable by Multivariate Analysis Type	Hazard Ratio	P
Full model		
MRI-FL above cutoff point of one FL	3.01	.002
Diffuse bone marrow infiltration in MRI	2.37	.03
M protein concentration \geq 40 g/L	1.87	.44
Presence of IgA	0.84	.71
Reduction of uninvolved Ig	1.03	.95
Presence of urinary Bence Jones protein	0.94	.87
Plasma cell infiltration in bone marrow \geq 20%	1.30	.53
Final model after backward selection		
MRI-FL cutoff point	3.25	< .001
Diffuse bone marrow infiltration in MRI	2.64	.006

Abbreviations: MRI, magnetic resonance imaging; FL, focal lesion; Ig, immunoglobulin.

Table 4. Initial Clinical and Demographic Characteristics of the 23 Patients With FLs of 37 Patients Developing Necessity of Systemic Treatment

Characteristic	Patients	
	No.	%
Non-MRI prognostic factor		
M protein > 40 g/L	2*	9
IgA	5*	22
Reduction of uninvolved Ig	18*	78
Presence urinary Bence Jones Protein	13*	57
Plasma cell infiltration in bone marrow	12*	52
No. of non-MRI risk factors per patient		
0	2	9
1	5	22
2	6	26
3	7	30
4	3	13
5	0	0
Patient characteristic		
Type of immunoglobulin		
IgG	16*	70
IgA	5*	22
Bence Jones	2*	9
Age > 50 years	19*	83
Female sex	14*	61

Abbreviations: FL, focal lesion; MRI, magnetic resonance imaging; Ig, immunoglobulin.
*Multiple mention is possible, as one patient can have more than one risk factor and more than one characteristic, respectively.

aMM for progression into symptomatic disease for the first time. We found that the detection of more than one FL had the highest adverse prognostic significance in our cohort.

First investigations with MRI in MM were published in 1987 by Ludwig et al¹⁶ in *Lancet*. Later studies with this technique in monoclonal plasma cell disease revealed focal, diffuse, or variegated growth patterns in bone marrow.^{10,17,18} Although most of those studies compared normal versus abnormal bone marrow patterns, the investigation by Mouloupoulos et al¹⁸ was the only one to find that a diffuse infiltration is a bad prognostic sign. In this study, a diffuse bone marrow infiltration was associated with a shorter progression-free survival. However, this kind of pattern is assessed subjectively as either present or absent,¹¹ and the signal intensity of normal vertebral disks was the reference. Any attempt at grading diffuse infiltration (eg, mild, moderate, or severe) is, in our view, inadequate. Furthermore, the aspect of bone marrow in MRI is influenced by several other factors, like age or bone marrow activation, because of other causes like an infectious disease.^{19,20} Despite these concerns, we found that the presence of a diffuse bone marrow infiltration in MRI was, indeed, relevant for prognosis. Additional developments, like diffusion-weighted imaging or other techniques, may contribute to a better quantification of diffusely distributed plasma cells in bone marrow.

It was impressively demonstrated by Walker et al⁷ in 611 patients with sMM treated on the Arkansas Total Therapy 2 protocol that the presence of seven or more FLs is an independent adverse prognostic factor. These results raised the question if a nodular manifestation of MM in MRI is accompanied by a worse prognosis compared with diffusely infiltrated or normal bone marrow. In our study, sample a cutoff point of more than one FL in wb-MRI was the best discriminator between high and low risk for progression into sMM.

In all recent studies investigating the prognostic significance of MRI in plasma cell disorders, the vertebral column only, including partly the sacral bone or pelvis as region where most MM lesions can be expected, was scanned. Although this technique is easy to perform within relatively short examination times, it misses a significant number of FLs.⁹ In our cohort, extra-axial FLs would have been missed in 30 (20%) of 149 patients if only an axial MRI had been performed. In the 42 patients with proven FLs, 45% actually had exclusively extra-axial lesions. In 1997, first results on the use of wb-MRI were published.⁸ Modern MRI scanners with affordable technical extensions (ie, body matrix coil and moving table device) allowed scanning of the whole body within reasonable time (ie, 30 to 45 minutes) and with sufficient diagnostic resolution. The feasibility of this technique in patients with sMM recently has been demonstrated.^{21,22}

Especially for aMM, the degree of plasma cell infiltration detected by unilateral bone marrow histology or aspirate has been of prognostic significance.^{3,23} However, MM often involves the skeleton in a patchy, rather than homogeneous, fashion. Therefore, bone marrow histology is potentially subject to sampling errors, if the histology is intended to estimate the severity of the disease and the true burden of malignant plasma cells.

In our study, 40% of patients had a diffuse infiltration and also had only a few FLs. Therefore, it was expected that the bone marrow samples would be representative and that the bone marrow diagnostic also would be significant with regard to the prognosis.

The multivariate analysis, including the MRI parameters, revealed, however, that monoclonal protein and plasma cell infiltration were not independent (ie, not significant) when analysis was adjusted for the other parameters. Correlation analysis of the MRI parameters with the established prognostic factors revealed no significant relationship. However, the *P* value for the correlation of M protein and FL was .05 and, therefore, nearly missed the significance level. Because of this relationship, the loss of significance of M protein may be caused by a statistical effect.

End organ damage currently is the most important factor for the classification and the decision to treat systemically in monoclonal plasma cell disease. Therefore, serum calcium, renal damage, anemia, and bone destruction (ie, osteoporosis or focal lytic bone lesions) are the most important parameters (ie, CRAB criteria¹). Because the bone involvement often leads to fractures, pain, and immobilization with all their sequelae, it can be considered the major clinical manifestation with respect to quality of life as well as survival.²⁴

For the detection of myeloma bone disease, RSS is in general still considered the gold standard imaging method in sMM according to the recent consensus panel of the International Myeloma Workshop. This technique displays osteolyses if a reduction of greater than 30% to 50% of mineralized bone has occurred.²⁵ The obvious limitations of RSS and biopsy led to attempts to better assess the true extent of MM, particularly by using modern cross-section imaging methods. Among these MRI, computed tomography (CT), and positron emission tomography (PET)/PET-CT have contributed to the assessment not only of lytic bone lesions but also of bone marrow involvement without bone destruction, and even of extramedullary disease.²⁶⁻²⁸ We used MRI in this study, because it has been proven that MRI findings correlate highly significant with plasma cell infiltration in bone marrow.²⁹ Furthermore, comparison of the different techniques demonstrated that MRI is superior to plain x-ray films, CT, and PET.^{21,22,30} CT has a higher resolution than wb-MRI and may be better suitable to

detect small lytic lesions in mineralized bone, but MRI has the highest sensitivity for bone marrow involvement in MM,^{22,26} even if the mineralized bone is still intact. Furthermore, the occurrences of a significant lytic bone lesion that escapes detection by MRI will be rare.

It is unclear how to handle those patients in whom FLs in MRI are detected but no other criteria supporting the initiation of systemic therapy are found. In our study population, several patients had FLs but did not develop any sign of end organ damage within a median observation period of 23.7 months. Dinter et al³¹ examined the impact of wb-MRI findings on the decision process of the responsible physician.³¹ However, the cohort was relatively small, and no prospective comparison of treatment initiation versus a watch-and-wait strategy was made. Obviously, there is a need for prospective studies to investigate additional characteristics to support the initiation of systemic antineoplastic therapy in this group of patients.

In conclusion, the presence of FLs detected in wb-MRI, as well as their number, are highly significant adverse prognostic factors for patients with aMM. We recommend performing wb-MRI for risk stratification in this group of patients. However, it needs to be examined prospectively whether patients in whom MRI shows lesions will benefit from a treatment that they would not receive if only standard imaging protocols were used.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

In our cohort of 149 patients during the follow-up time, 37 patients developed symptoms that led to an initiation of systemic treatment. In detail, 33 patients were treated because of occurrence of CRAB symptoms (renal insufficiency, n = 4; anemia, n = 4; bone disease in conventional radiography, n = 25). The other patients were treated because of clinical symptoms, as pain caused by extra-osseous tumor parts (n = 2), development of systemic AL-amyloidosis (n = 1), and increasing immunoglobulin in serum greater than 50 g/L (n = 1) to prevent complications.