

Prognostic significance of magnetic resonance imaging of bone marrow in previously untreated patients with multiple myeloma

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Background: Magnetic resonance imaging (MRI) has been a useful technique for the assessment of patients with multiple myeloma (MM). We evaluated the prognostic significance of different MRI patterns in symptomatic patients with MM.

Patients and methods: A total of 142 symptomatic MM patients underwent MRI before treatment. MRI patterns of involvement were correlated with known prognostic variables, including the International Staging System (ISS), response to treatment and survival.

Results: Focal marrow lesions were identified in 50% of patients, diffuse marrow replacement in 28%, a variegated pattern in 14% and normal pattern in 8%. When patients with the diffuse pattern were compared with patients with the other MRI patterns, they had features of more advanced disease such as higher ISS, anemia, hypercalcemia, elevated lactate dehydrogenase and extensive marrow plasmacytosis. Response rate was similar among patients with different MRI patterns. Median survival was 24 months for patients with the diffuse pattern, 51 months for those with the focal pattern, 52 months for those with the variegated pattern and 56 months for patients with the normal pattern ($P = 0.001$). The presence or absence of a diffuse MRI pattern separated patients with ISS stages I and II into two subgroups with significantly different survival times of 28 months and 61 months, respectively ($P = 0.01$). Furthermore, a diffuse MRI pattern predicted inferior outcome regardless of whether or not patients had received high-dose therapy with autologous stem cell transplantation.

Conclusion: Diffuse marrow replacement on MRI adds to the evaluation of patients with multiple myeloma and their management.

Key words: MRI, multiple myeloma, prognosis

Introduction

Multiple myeloma is a malignant disorder of plasma cells that affects the bone marrow. It is usually associated with the presence of a monoclonal immunoglobulin in the serum and/or urine and with the presence of lytic bone lesions. Conventional radiographs of the skeleton are routinely obtained during the work-up of patients with suspected myeloma. Abnormal skeletal radiographs are detected in >80% of patients. The presence and number of punched-out lytic bone lesions formed the basis of the clinical staging system introduced in 1975 by Durie and Salmon [1]. The presence of multiple lytic lesions places the patients in stage III. As many as 70% of patients with multiple myeloma are classified as having stage III disease, but this group is heterogeneous with survival ranging from a few months to

several years. According to the Durie and Salmon staging system, absence of bone lesions on plain radiographs is associated with a lower stage and improved survival. However, the prognostic value of radiographic findings may be controversial, and in some series patients with skeletal surveys that appeared normal actually had a worse prognosis than patients with minimal lytic changes [2]. In recent years a number of readily available and easily reproducible laboratory variables have emerged as important prognostic factors for patients with multiple myeloma. In an attempt to circumvent the shortcomings of the Durie and Salmon staging system, the International Myeloma Working Group recently proposed an International Staging System (ISS) for multiple myeloma which is based on serum albumin and β_2 -microglobulin [3].

Magnetic resonance imaging (MRI) is a non-invasive technique which can sample a large volume of bone marrow. This modality depicts bone marrow abnormalities in multiple myeloma with greater sensitivity than conventional radiographs and CT [4]. In our current study we evaluated the correlation of

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different MRI patterns with the ISS and with the outcome of patients with previously untreated symptomatic multiple myeloma.

Patients and methods

Between January 1990 and December 2001, 142 patients with previously untreated multiple myeloma who had an indication for treatment underwent MRI studies of the thoracic and lumbar spine. This examination was performed before initiation of antimyeloma therapy. Patient status was updated in December 2004, so that the minimum follow-up for all patients was 3 years.

These patients were classified according to the recently proposed International Staging System (ISS) for multiple myeloma: stage I, serum β_2 -microglobulin <3.5 mg/l and serum albumin ≥ 3.5 g/dl; stage II, neither stage I nor III; stage III, serum β_2 -microglobulin ≥ 5.5 mg/l. All patients received primary treatment with high-dose dexamethasone-containing regimens such as vincristine and doxorubicin administered as a 4 day continuous infusion with dexamethasone pulses (VAD), melphalan–dexamethasone, VAD bolus or VAD with liposomal doxorubicin and the hyper-CVAD regimen [5–7]. High-dose therapy (HDT) with autologous stem cell transplantation was administered to 61 patients. These patients received HDT during various phases of their disease, and 90% were aged <65 years at the time of administration. The conditioning regimen consisted of high-dose melphalan 200 mg/m^2 i.v. in 80% of patients, while the remaining patients received high-dose melphalan with total body irradiation or a combination of thiotepa, busulfan and cyclophosphamide as previously described [8–10].

MRI patterns were defined as described previously [4, 11]. Briefly, four patterns were identified. A normal pattern required no evidence of abnormal signal. The focal pattern consisted of localized areas of abnormal marrow. On T_1 -weighted images, focal lesions are darker than yellow marrow and slightly darker than or isointense with red marrow. On T_2 -weighted images they are brighter than both red and yellow marrow, and on enhanced T_1 -weighted images they enhance to various degrees depending on the vascularity of the underlying pathologic process. In the diffuse MRI pattern of abnormal marrow, the normal bone marrow is completely replaced by the abnormal process. The intervertebral disks appear brighter than or are isointense with the diseased marrow. On T_1 -weighted images, there is a diffuse decrease in the signal intensity of the marrow. On T_2 -weighted images a variable increase in the signal intensity of the abnormal marrow is observed. After the administration of intravenous contrast, the abnormal marrow enhances. The intervertebral disks appear darker than the enhanced spine. The variegated pattern consists of innumerable small foci of disease on a background of intact marrow. The small lesions of the variegated pattern are dark on T_1 -weighted images and bright on T_2 -weighted images, and they enhance after the administration of intravenous contrast.

Response to treatment was assessed according to the EBMT criteria [12]. Survival was calculated from the start of treatment to death from any cause or the last follow-up visit, whichever occurred first.

Results

Patients and disease features are shown in Table 1. Several patients had features of advanced disease such as severe anemia, hypercalcemia, renal impairment and elevated serum lactate dehydrogenase (LDH). Patients were evenly distributed to the three ISS stages (Table 1). Half of the patients had a focal MRI pattern, whereas a normal MRI pattern was detected in $<10\%$ of patients. After the administration of primary treatment, 56% of patients achieved an objective response (i.e. complete

Table 1. Patients and disease features

	Percentage
Male	58
Age ≥ 65 years	30
Myeloma type	
IgG	53
IgA	25
Other	22
Hemoglobin <8.5 g/dl	20
Calcium ≥ 11.5 mg/dl	21
Creatinine >2 mg/dl	19
LDH ≥ 250 IU/l	15
BMBC $\geq 40\%$	48
ISS	
I	38
II	30
III	32
MRI pattern	
Normal	8
Focal	50
Variegated	14
Diffuse	28

and partial response). Overall median survival was 38 months (95% confidence interval 24–52 months). At the time of final analysis 75% of our patients had died.

Table 2 shows correlations of MRI patterns with patients and disease features and with response to treatment and survival. The incidences of patient gender, age, myeloma type and renal impairment were similar among the four MRI patterns. However, patients with the diffuse MRI pattern presented more often with anemia, hypercalcemia, elevated serum LDH and more extensive bone marrow plasmacytosis than patients with the other MRI patterns. Furthermore, half of the patients with diffuse MRI were assigned to ISS III (Table 2). Objective response after treatment was not influenced by MRI patterns. However, MRI pattern had a profound impact on patient survival. The median survival exceeded 4 years in patients with normal, focal or variegated MRI but was only 2 years in patients with diffuse marrow replacement (Figure 1).

In view of the inferior outcome of patients with diffuse MRI we subsequently evaluated the possible impact of MRI pattern in patients who presented with low or intermediate stage (ISS I + II) or with high stage (ISS III). Table 3 shows that the presence or absence of diffuse MRI pattern separated the patients with ISS I + II into two subgroups with significantly different outcomes. The prognostic value of diffuse MRI (19 patients) was less prominent among the 40 patients with ISS III, but the patient number was smaller. Table 3 also shows that a diffuse MRI predicted an inferior outcome in patients regardless of whether or not they received HDT.

Table 2. Correlation of MRI pattern with patients and disease features

	Normal (%)	Focal (%)	Variegated (%)	Diffuse (%)	<i>P</i> value
Patients	8	50	14	28	
Males	42	59	65	56	0.6
Age ≥65 years	8	37	25	28	0.2
Myeloma type					
IgG	75	51	40	59	
IgA	25	21	45	21	0.1
Other	0	28	15	20	
Hemoglobin <8.5 g/dl	8	16	15	36	0.04
Calcium ≥11.5 mg/dl	8	13	25	39	0.01
Creatinine >2 mg/dl	17	14	30	23	0.4
LDH ≥250 IU/l	10	9	10	31	0.02
BMPC ≥40%	33	34	45	80	<0.001
ISS					
I	64	52	28	16	
II	18	26	50	34	0.002
III	18	22	22	50	
Objective response	58	52	65	45	0.5
Median survival	56	51	52	24	0.001

BMPC, bone marrow plasmacytosis.

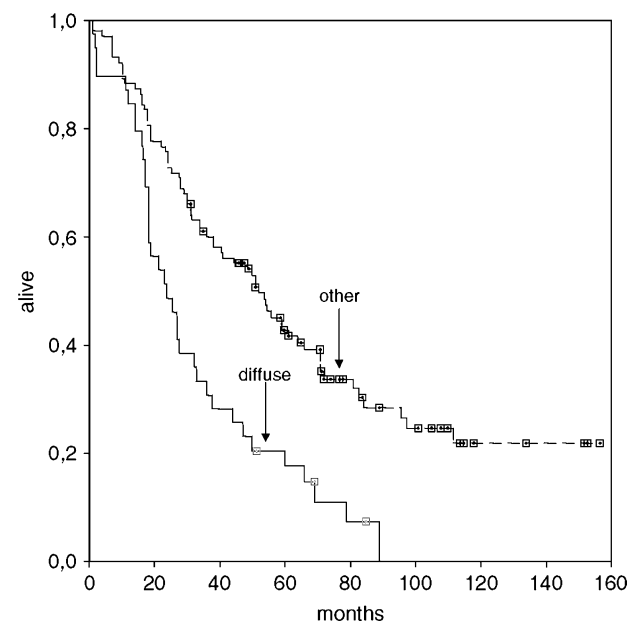


Figure 1. Survival of patients according to the presence or absence of diffuse MRI pattern.

Discussion

MRI has been widely available for the evaluation of myeloma for >15 years. During this time several specific advantages have emerged. MRI should be part of the staging procedures in patients with solitary bone plasmacytoma to improve assessment of the extent of the local tumor for definition of radiation

Table 3. Survival correlations of diffuse MRI and other MRI patterns according to ISS and to administration of high-dose therapy (HDT)

	Median survival (months)		<i>P</i> value
	Diffuse MRI	Other MRI	
ISS			
I + II	28	61	0.01
III	18	30	0.6
HDT			
Yes	36	55	0.05
No	18	48	0.0002

fields and to rule out occult lesions elsewhere [13]. This modality can accurately detect spinal and/or nerve root compression and can assess soft tissue extension. The findings of a large focal lesion in the spine with or without cord impingement may need attention to local management. It may also help differentiate between osteoporotic and malignant vertebral compression fractures. Presence of an abnormal MRI pattern occurs in 30–50% of patients with early stage asymptomatic myeloma and indicates an increased likelihood of progression within the next 2 years [14–16]. In patients with active myeloma, serial MRI monitoring can be useful to assess response to treatment [17]. However, it is less clear whether different abnormal patterns of marrow involvement confer a different prognosis in patients with symptomatic myeloma requiring treatment.

An MRI protocol for the study of bone marrow consists of T_1 -weighted images, short τ inversion recovery or fast spin echo T_2 -weighted images with fat saturation and contrast-enhanced T_1 -weighted images. MRI is a qualitative measure, i.e. the degree of marrow infiltration by bone marrow biopsy and the degree of hyperintensity on STIR sequence may be difficult to correlate. T_1 -weighted MR images are most sensitive in depicting abnormal bone marrow. In patients with focal bone marrow patterns, MRI may reveal lesions as small as 5 mm but it may not show microscopic disease. In patients with the diffuse MRI pattern the change in signal intensity depends on the percentage of neoplastic cells in the bone marrow, i.e. bone marrow plasmacytosis below 10% may be associated with a false-negative MRI study.

We evaluated a large number of patients with previously untreated symptomatic multiple myeloma who had undergone MRI of the spine before initiation of antimyeloma therapy in order to assess the prognostic significance of this imaging modality. Furthermore, with a minimum follow-up of 3 years we are able to provide mature survival data for our patients. Over 90% of our patients had an abnormal MRI examination and the focal pattern was the most common pattern. Approximately a quarter of our patients had a diffuse pattern of marrow replacement which was associated with features of more advanced disease such as severe anemia, extensive bone marrow plasmacytosis, hypercalcemia and elevated serum LDH. These findings expand our preliminary observation and the findings of other series [11, 18–20]. Moreover, a diffuse MRI pattern was more frequently associated with ISS III disease than the other MRI patterns. Half of patients with the diffuse pattern were stage III

whereas half of patients with the focal pattern were stage I. The diffuse pattern was also associated with a significantly inferior survival when compared with the other abnormal MRI patterns or a normal MRI study. We believe that this is a consequence of the more advanced disease associated with this MRI pattern. Similar findings have also been reported by others [18, 19]. However, Lecouvet et al. [20] did not observe inferior survival of their patients with the diffuse pattern when compared with those with a focal pattern despite the fact that the former patients had features of more advanced disease. This discrepancy might have been due to the small number of patients included in their series. More recently, Baur et al. [21] performed MRI studies of 77 patients with multiple myeloma and observed that patients with the normal or variegated pattern had a significantly better survival than patients with the diffuse or focal pattern.

Our analysis indicated that the presence of a diffuse MRI pattern could separate patients with ISS I or II into two subgroups with different survival times. Thus the median survival of 28 months for patients with ISS I or II and a diffuse MRI was similar to the median survival of 24 months for patients with ISS III. The presence or absence of a diffuse MRI pattern was less significant in patients with ISS III, and this was more likely to be due to the small number of patients. Based on our data, we believe that an MRI study may be of particular value in patients with low- or intermediate-stage multiple myeloma (ISS I or II). There is limited information regarding the prognostic significance of different MRI patterns in patients treated with high-dose therapy and autologous stem cell transplantation. Lecouvet et al. [22] evaluated 25 patients and observed that individual MRI parameters did not correlate with response duration and survival. Our data indicated that the negative impact of a diffuse MRI pattern was present in both patients who received conventional chemotherapy only and patients who received high-dose therapy. Further studies on the role of MRI in patients undergoing high-dose therapy are needed. Recent evidence suggests that the diffuse MRI pattern is associated with increased neovascularization of the bone marrow [23]. This observation may also explain the impaired prognosis of patients with the diffuse MRI pattern.

Recent studies have used oligonucleotide microarray profiling and biochemical and immunohistochemical analyses to identify molecular determinants of bone lesions in patients with multiple myeloma. It was found that overexpression of the *dickkopf1* gene and overproduction of its corresponding protein DKK1 was associated with the presence of focal lesions on MRI studies [24]. Similar analyses may identify differences in the activation of genes in patients with diffuse MRI compared with other MRI patterns. We conclude that MRI pattern of involvement has prognostic significance in patients with multiple myeloma who require treatment; diffuse marrow involvement by MRI adds to the evaluation of patients with multiple myeloma and their management.

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