Magnetic Resonance Imaging in Multiple Myeloma: Diagnostic and Clinical Implications

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ABSTRACT

Purpose
Magnetic resonance imaging (MRI) permits the detection of diffuse and focal bone marrow infiltration in the absence of osteopenia or focal osteolysis on standard metastatic bone surveys (MBSs).

Patients and Methods
Both baseline MBS and MRI were available in 611 of 668 myeloma patients who were treated uniformly with a tandem autologous transplantation–based protocol and were evaluated to determine their respective merits for disease staging, response assessment, and outcome prediction.

Results
MRI detected focal lesions (FLs) in 74% and MBS in 56% of imaged anatomic sites; 52% of 267 patients with normal MBS results and 20% of 160 with normal MRI results had FL on MRI and MBS, respectively. MRI- but not MBS-defined FL independently affected survival. Cytogenetic abnormalities (CAs) and more than seven FLs on MRI (MRI-FLs) distinguished three risk groups: 5-year survival was 76% in the absence of both more than seven MRI-FLs and CA (n = 276), 61% in the presence of one MRI-FL (n = 262), and 37% in the presence of both unfavorable parameters (n = 67). MRI-FL correlated with low albumin and elevated levels of C-reactive protein, lactate dehydrogenase, and creatinine, but did not correlate with age, beta-2-microglobulin, and CA.

Resolution of MRI-FL, occurring in 60% of cases and not seen with MBS-defined FL, conferred superior survival.

Conclusion
MRI is a more powerful tool for detection of FLs than is MBS. MRI-FL number had independent prognostic implications; additionally, MRI-FL resolution identified a subgroup with superior survival. We therefore recommend that, in addition to MBS, MRI be used routinely for staging, prognosis, and response assessment in myeloma.


INTRODUCTION

Multiple myeloma (MM) is a B-cell malignancy of antibody-secreting plasma cells expanding in the bone marrow.1 Symptoms develop as a result of anemia, immunosuppression, renal failure, hypercalcemia, and bone destruction with painful pathologic fractures. Eventually, up to 80% of patients suffer vertebral compression fractures or pathologic fractures of long bones.2 These occur either as a result of diffuse osteoporosis or, more commonly, at the site of osteolytic lesions, as a consequence of both activation of osteoclasts and inactivation of osteoblasts mediated by the interaction of myeloma cells with the bone marrow microenvironment.3

Abnormalities detectable on metastatic bone survey (MBS) examination develop relatively late in this bone-destructive process, particularly in the spine, when 50% to 75% focal decalcification has ensued.4 Magnetic resonance imaging (MRI) is now well established as a useful tool for the diagnosis of truly solitary plasmacytoma of bone5 and for staging and response assessment of non-secretory MM.6 The presence of some focal lesions (FLs) on MRI (MRI-FLs) in smoldering MM defines a subgroup with a higher propensity for progression to symptomatic MM.7 A role of MRI in the staging and management of symptomatic MM has also been demonstrated retrospectively in a relatively small group of patients.8 We now report on the results of a prospective
systematic evaluation of both MRI and MBS before and after treatment with Total Therapy 2 (TT2).9

**PATIENTS AND METHODS**

**Patients and Treatments**

Between October 1998 and February 2004, 668 newly diagnosed patients (ages 75 years or younger, no more than one cycle of prior therapy) with progressive or symptomatic MM were enrolled in the TT2 trial. Details of patient characteristics and treatment and clinical outcome have recently been reported.9 All participants had provided written informed consent in keeping with institutional and National Cancer Institute (National Institutes of Health, Bethesda, MD) guidelines. The protocol had been approved by the institutional review board and the US Food and Drug Administration, and was monitored by a data safety and monitoring board, as required by the National Cancer Institute for phase III trials.

**Laboratory Evaluation**

MM work-up included serum and urine protein electrophoresis; quantitation of serum immunoglobulin levels, 24-hour urinary protein excretion, serum beta-2-microglobulin (B2M) and C-reactive protein (CRP) levels; and bone marrow aspirates and biopsies for morphologic interpretation. These tests, along with MM markers, were performed at baseline before protocol therapy, before each of the subsequent three phases of treatment and then every 6 to 12 months until relapse.

**Definitions of Response and Relapse by Myeloma Protein and Bone Marrow Criteria**

Complete remission (CR) required the absence of monoclonal immunoglobulin on immunofixation analysis of serum and urine, normal bone marrow aspirate, and biopsy microscopic examinations similar to criteria introduced by Blade et al.10 Relapse from CR was diagnosed on the reappearance of a monoclonal protein in serum or urine. New or larger FLs on MBS or MRI, hypercalcemia, bone marrow monoclonal plasmacytosis, or the development of extramedullary lesions all constituted additional criteria of relapse from CR or partial remission (PR) and of disease progression in case PR had not been achieved.

**Imaging**

Baseline MRI and MBS examinations were evaluated in a prospective manner. Because of time and cost constraints, MRI examinations were limited to the axial bone marrow as the predominant site of active hematopoiesis in the adult, whereas MBS included long bones. MRI studies were performed with a series of sequences to permit identification of focal or diffuse bone marrow involvement, including spin echo (T1 and T2 weighted [-wt]), gradient-echo (T2-wt), short TI inversion recovery (STIR), and gadolinium-enhanced spin echo sequences (with and without fat suppression).11 MBS examinations were performed with digital radiographs (two views of chest; views of ribs, lateral skull, and vertebral column; and anteroposterior views of pelvis, shoulders, and extremities, including hands and feet). Data collected included regional location, number, and size (maximum axial dimension in centimeters to the nearest millimeter) of focal intramedullary lesions compatible with MM (excluding lesions characteristic of hemangiomas and degenerative disease); regional location and number of compression fractures of vertebral bodies; and the overall marrow signal characteristics on the various imaging sequences (hyper-, iso-, or hypointense signal in relationship to paraspinal musculature on T1-wt or to normal intervertebral disc signal on STIR, and whether the signal appearance was homogeneous or heterogeneous).

MRI-FLs with an axial diameter of at least 0.5 cm were reliably identified (assuming the absence of masking or other interference). Large MRI-FLs can be obscured if the marrow background signal is similar to the MRI-FL signal because of diffuse marrow infiltration with tumor or other conditions of high water content in the marrow space as a consequence of growth-factor stimulation or bone marrow recovery after chemotherapy. Thus, although exceptions exist, a 0.5-cm axial diameter is near the lower range of confident detection of FLs by both MRI and MBS, particularly in terms of reproducibility. We, therefore, did not consider focal appearances on MRI or MBS to be FL that were smaller than 0.5 cm in one axial dimension because of an unacceptably high false-positive rate.

Two completely separate groups of radiologists were involved in reading MRI (R.W., R.V.H., E.E., E.J.A.) and MBS examinations (three individuals including R.W.).

**MRI Response and Relapse Criteria**

Response to treatment on MRI implied normalization of the diffuse marrow signal and decrease in size and/or number of intramedullary MRI-FLs and sites of extramedullary tumor. MRI-defined CR (MRI-CR) implied the achievement of a hypointense homogeneous background signal on STIR imaging and resolution of FLs. Progression or relapse on MRI was diagnosed when there was an increase in size and/or number of MRI-FLs, or development of extramedullary disease and/or development of abnormal diffuse marrow signal (adjusted for age in the absence of iatrogenic marrow stimulation).12

**Statistical Analysis**

The Kaplan–Meier method13 was used to estimate overall survival, with group comparisons made using the log-rank test.14 Overall survival was defined from the date of registration until death from any cause; survivors were censored at the time of last contact. Univariate and multivariate analyses of prognostic factors were carried out using Cox regression.15 Standard prognostic factors of overall survival were dichotomized using cut points. The cut points for albumin and B2M were based on the ones reported as part of the International Staging System16; the cut points for the remaining variables were based on optimal outcome prediction (biologic cut points).17 The cumulative incidence of CR was estimated using the method outlined in Gooley et al18 and was compared using the log-rank test. A χ² test was used to compare the number of MRI-FLs in relation to baseline parameters.

**RESULTS**

**Patient Characteristics and Outcome by Study Arm**

Data are as of October 2006. Baseline laboratory characteristics of the 611 patients with both baseline MRI and MBS examinations were similar to those of the entire population of 668 patients enrolled onto TT2.9 The median follow-up of 405 surviving patients was 55 months (range, 2 to 99 months); 305 patients had suffered an event (relapse or death), and 206 had died. In the absence of a difference in overall survival between thalidomide and control groups, the two study arms were combined for the purpose of this analysis.

**Comparison of MRI and MBS Results**

Figures 1 and 2 depict serial MRI and MBS examinations for two representative patients. Many more FLs were detected with MRI than with MBS. Whereas MRI-FL size typically decreased or resolved, FL size on MBS remained unchanged even in patients achieving clinical CR (CCR). Relapse was accompanied by reappearance of MRI-FLs in originally involved sites often associated with new locations.

At baseline, MBS examination identified osteolytic FLs in long bones (outside the sites examined by MRI) in 99 (16%) of the 611 patients, representing 8% of all MBS-detected FLs. In a comparison of all areas imaged by both techniques, at least one FL was detected in 451 patients (74%) on MRI and in 344 patients (56%) on MBS; 128 (21%) had no FL by either technique, whereas 312 (51%) showed FL on both MBS and MRI; of 267 patients without FL on MBS, 139 (52%) had FL on MRI; and among 160 without FL on MRI, 32 (20%) had FL on MBS examination. Computed tomography (CT)—guided fine needle aspiration (FNA) of MRI-FLs, performed in 125 patients, demonstrated focal osteolysis at the site of MRI-FL in 121 (97%).
The mean FL number among those with FLs was 13.4 with MRI and 7.8 with MBS; the mean FL number for all 611 patients was 9.9 with MRI and 4.4 with MBS (Table 1). Significantly higher proportions of patients had FL on MRI than on MBS in spine (78% v 16%; \( P < .001 \)); pelvis (64% v 28%; \( P < .001 \)) and sternum (24% v 3%; \( P < .001 \)); similar percentages were noted with both techniques in skull and shoulders, and lower fractions were seen on MRI than on MBS in ribs (10% v 43%; \( P < .001 \)) and long bones (ie, humeri and femora; 37% v 48%; \( P = .006 \)). These findings also applied to patients with higher FL number (MRI-FL > 7, MBS-FL > 5, representing biologic cutoff values).

**Prognostic Implications of Imaging Studies in the Context of Baseline Laboratory Variables With CCR and MRI-CR As Time-Dependent Covariates**

Of 17 baseline variables examined, survival was adversely affected by the presence of cytogenetic abnormalities (CAs), elevated serum levels of B2M and lactate dehydrogenase (LDH) and
advanced age (Table 2). Of the imaging parameters, higher FL number on both MRI and MBS and heterogeneity of the diffuse marrow signal on MRI STIR images (indicating micronodular disease) were prognostically harmful. MRI-FL size and diffuse background hyperintensity on STIR images were not prognostically significant. Both CCR and MRI-CR favored superior survival. On multivariate analysis, MRI- but not MBS-defined FL number was an independent adverse baseline feature for overall survival independent of baseline CA and B2M elevation and time-dependent CCR.

Kaplan-Meier plots of survival revealed inferior outcome among patients with more than seven MRI-FLs, whereas those without and with up to seven FLs had similar survival (Fig 3). When the presence of CA was considered in addition to MRI-FL, three subgroups could be distinguished: 5-year survival estimates were 76% in the absence of CA and seven or fewer FLs (n = 276), approximately 61% in the presence of one of these adverse features (n = 262), and 37% among patients with higher MRI-FL number and CA (n = 67; P < .001).

Fig 2. Baseline short T1 inversion recovery magnetic resonance image (MRI) coronal views of pelvis show no focal lesions (FL). Over time, the patient develops a left sacral lesion and a lesion of the left lesser trochanter (A, arrows). X-rays of (B, top panel) the pelvis and (B, bottom panel) the proximal left femur at comparable time frames fail to demonstrate the FL seen on MRI.
A higher number of MRI-FLs (> 7) and MBS-FLs (> 5) was significantly associated with higher serum levels of LDH, CRP, and creatinine, as well as, in the case of MRI-FL, hypoalbuminemia (Table 3). Levels of B2M, bone marrow plasmacytosis, and hemoglobin, as well as CA, age, sex, race, and immunoglobulin isotype were not correlated with FL number.

### Table 1. Baseline Anatomic Distribution of FLs on MRI and MBS

<table>
<thead>
<tr>
<th>Technique</th>
<th>Skull</th>
<th>Cervical</th>
<th>Thoracic</th>
<th>Lumbar</th>
<th>Pelvis</th>
<th>Ribs</th>
<th>Sternum</th>
<th>Scapulae</th>
<th>Clavicles</th>
<th>Humeri</th>
<th>Femora</th>
<th>Total</th>
</tr>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>64</td>
</tr>
<tr>
<td>Total No. of studies</td>
<td>1,223</td>
<td>434</td>
<td>1,473</td>
<td>710</td>
<td>976</td>
<td>91</td>
<td>313</td>
<td>169</td>
<td>116</td>
<td>203</td>
<td>250</td>
<td>6,056</td>
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<tr>
<td>No. of patients with &gt; 0 FL</td>
<td>176</td>
<td>162</td>
<td>308</td>
<td>258</td>
<td>288</td>
<td>43</td>
<td>107</td>
<td>67</td>
<td>87</td>
<td>134</td>
<td>451</td>
<td>1,091</td>
</tr>
<tr>
<td>% of patients with &gt; 0 FL</td>
<td>39</td>
<td>35.9</td>
<td>68.3</td>
<td>57.2</td>
<td>63.9</td>
<td>9.5</td>
<td>23.7</td>
<td>14.9</td>
<td>12.0</td>
<td>19.3</td>
<td>29.7</td>
<td>1,091</td>
</tr>
<tr>
<td>Mean No. of FL</td>
<td>6.95</td>
<td>2.68</td>
<td>4.78</td>
<td>2.75</td>
<td>3.39</td>
<td>2.11</td>
<td>2.93</td>
<td>2.52</td>
<td>2.15</td>
<td>2.33</td>
<td>1.87</td>
<td>13.43</td>
</tr>
<tr>
<td>Patients with MRI-FL (n = 451)</td>
<td>6.95</td>
<td>2.68</td>
<td>4.78</td>
<td>2.75</td>
<td>3.39</td>
<td>2.11</td>
<td>2.93</td>
<td>2.52</td>
<td>2.15</td>
<td>2.33</td>
<td>1.87</td>
<td>13.43</td>
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<tr>
<td>All patients (N = 611)</td>
<td>2.00</td>
<td>0.71</td>
<td>2.41</td>
<td>1.16</td>
<td>1.60</td>
<td>0.15</td>
<td>0.28</td>
<td>0.19</td>
<td>0.33</td>
<td>0.41</td>
<td>0.41</td>
<td>9.91</td>
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<td>MBS</td>
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<td>64</td>
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<td>Total No. of studies</td>
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<td>35</td>
<td>22</td>
<td>41</td>
<td>282</td>
<td>398</td>
<td>9</td>
<td>50</td>
<td>111</td>
<td>128</td>
<td>344</td>
<td>2,683</td>
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<tr>
<td>No. of patients with &gt; 0 FL</td>
<td>160</td>
<td>18</td>
<td>13</td>
<td>31</td>
<td>96</td>
<td>148</td>
<td>9</td>
<td>46</td>
<td>50</td>
<td>111</td>
<td>128</td>
<td>344</td>
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<tr>
<td>% of patients with &gt; 0 FL</td>
<td>46.5</td>
<td>5.2</td>
<td>3.8</td>
<td>9.0</td>
<td>27.9</td>
<td>43.0</td>
<td>2.6</td>
<td>13.4</td>
<td>14.5</td>
<td>32.0</td>
<td>36.9</td>
<td>344</td>
</tr>
<tr>
<td>Mean No. of FL</td>
<td>6.28</td>
<td>1.94</td>
<td>1.69</td>
<td>1.32</td>
<td>2.94</td>
<td>2.67</td>
<td>1.00</td>
<td>2.09</td>
<td>2.32</td>
<td>2.76</td>
<td>2.72</td>
<td>7.80</td>
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<tr>
<td>Patients with MBS-FL (n = 344)</td>
<td>6.28</td>
<td>1.94</td>
<td>1.69</td>
<td>1.32</td>
<td>2.94</td>
<td>2.67</td>
<td>1.00</td>
<td>2.09</td>
<td>2.32</td>
<td>2.76</td>
<td>2.72</td>
<td>7.80</td>
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<tr>
<td>All patients (N = 611)</td>
<td>1.64</td>
<td>0.06</td>
<td>0.04</td>
<td>0.07</td>
<td>0.46</td>
<td>0.65</td>
<td>0.01</td>
<td>0.16</td>
<td>0.19</td>
<td>0.50</td>
<td>0.57</td>
<td>4.39</td>
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</table>

Abbreviations: FL, focal lesion; MRI, magnetic resonance imaging; MBS, metastatic bone survey.

### Special Entities: History of Preceding Monoclonal Gamopathy of Undetermined Significance, Nonsecretory Myeloma, or Macrofocal Disease

Among 39 patients with a documented prior history of monoclonal gamopathy of uncertain significance (MGUS) or a preceding smoldering disease course, FLs were absent in 13 patients (44%) compared with 147 (26%) of 572 patients without such prior history (P = .02).

### Table 2. Survival Implications of Baseline Standard and Imaging Parameters With CCR and MRI-CR As Time-Dependent Covariates

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. Affected</th>
<th>Total No.</th>
<th>%</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>### Univariate</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Abnormal cytogenetics</td>
<td>141</td>
<td>454</td>
<td>31</td>
<td>2.75</td>
<td>1.99 to 3.78</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>&gt; 7 MRI-FLs</td>
<td>219</td>
<td>457</td>
<td>48</td>
<td>1.83</td>
<td>1.32 to 2.54</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>B2M &gt; 6.5 mg/dL</td>
<td>90</td>
<td>457</td>
<td>20</td>
<td>1.65</td>
<td>1.14 to 2.37</td>
<td>.007</td>
</tr>
<tr>
<td>Age ≥ 65 years</td>
<td>82</td>
<td>457</td>
<td>18</td>
<td>1.63</td>
<td>1.11 to 2.38</td>
<td>.012</td>
</tr>
<tr>
<td>B2M ≥ 3.5 mg/dL</td>
<td>172</td>
<td>457</td>
<td>38</td>
<td>1.60</td>
<td>1.16 to 2.20</td>
<td>.004</td>
</tr>
<tr>
<td>MRI heterogeneous</td>
<td>114</td>
<td>457</td>
<td>25</td>
<td>1.52</td>
<td>1.08 to 2.14</td>
<td>.015</td>
</tr>
<tr>
<td>&gt; 5 MBS-FLs</td>
<td>129</td>
<td>434</td>
<td>30</td>
<td>1.52</td>
<td>1.08 to 2.14</td>
<td>.017</td>
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<td>LDH &gt; ULN</td>
<td>134</td>
<td>456</td>
<td>29</td>
<td>1.45</td>
<td>1.04 to 2.04</td>
<td>.029</td>
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<tr>
<td>CCR</td>
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<td>0.39 to 0.77</td>
<td>&lt; .001</td>
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<tr>
<td>MRI-CR</td>
<td>0.57</td>
<td>0.40 to 0.81</td>
<td>.002</td>
<td></td>
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<tr>
<td>### Multivariate</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Abnormal cytogenetics</td>
<td>130</td>
<td>430</td>
<td>30</td>
<td>2.45</td>
<td>1.75 to 3.43</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>&gt; 7 MRI-FLs</td>
<td>211</td>
<td>430</td>
<td>49</td>
<td>1.89</td>
<td>1.30 to 2.75</td>
<td>&lt; .001</td>
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<tr>
<td>B2M ≥ 3.5 mg/dL</td>
<td>157</td>
<td>430</td>
<td>37</td>
<td>1.62</td>
<td>1.15 to 2.27</td>
<td>.005</td>
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<tr>
<td>&gt; 5 MBS-FLs</td>
<td>127</td>
<td>430</td>
<td>30</td>
<td>1.11</td>
<td>0.77 to 1.61</td>
<td>.573</td>
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<tr>
<td>CCR</td>
<td>0.54</td>
<td>0.38 to 0.78</td>
<td>&lt; .001</td>
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<tr>
<td>MRI-CR</td>
<td>0.71</td>
<td>0.49 to 1.04</td>
<td>.078</td>
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</table>

NOTE. P value from Wald $\chi^2$ test in Cox regression. Multivariate results were not statistically significant at .05 level. All univariate P values are reported regardless of significance. The multivariate model uses stepwise selection with an entry level of .1; the variable remains if it meets the .05 level. A multivariate P value > .05 indicates that the variable was forced into the model, with significant variables chosen using stepwise selection. Variables included MRI-FL > 7, x-ray > 5, serum calcium, sex, maximum MRI-FL size, hyperintense (background on STIR weighted images), random assignment to thalidomide, age ≥ 65 years, albumin < 3.5 g/dL, heterogeneous (background on STIR weighted images), creatinine ≥ 2.0 mg/dL, B2M ≥ 3.5, B2M > 5.5, CRP ≥ 8 mg/L, Hb < 10, LDH > ULN, and any cytogenetic abnormalities.

Abbreviations: CCR, clinical complete response; CR, complete remission; HR, hazard ratio; MRI, magnetic resonance imaging; FL, focal lesion; B2M, beta-2-microglobulin; MBS, metastatic bone survey; CRP, C-reactive protein; Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal; STIR, short TI inversion recovery.
MRI-FLs, present in 27 of 30 patients with nonsecretory MM, provided a valuable tool for assessing response, traditionally relying only on serial bone marrow examinations. Thus, bone marrow–defined CR occurred in 22 (81%) of these 27 patients, and MRI-CR was documented in 41% of patients at 36 months.

Of 57 patients with MRI-FL, random bone marrow examination from the posterior iliac crest revealed less than 10% monoclonal plasma cells; 43 (75%) fulfilled diagnostic criteria of MM due to M-protein levels and/or osteolytic lesions, whereas the remaining 14 patients would have been considered as having MGUS. CT-FNA and biopsy of MRI-FLs showed unequivocal involvement with MM. In these 14 patients, MRI-FL number averaged 14 FLs (range, two to 40 FLs).

**MRI-CR and CCR**

Time-dependent cumulative proportions of patients achieving MRI-CR revealed significant gradations when considering baseline MRI-FL features: the 76 patients without FL had the steepest onset and highest level of MR-CR, followed by the group of 185 with up to seven FLs; the slowest onset and lowest MRI-CR frequency was in the group of 196 patients with more than seven MRI-FLs (Fig 4A). The time to CCR was similar for the three MRI-FL subgroups (data not shown) and mirrored the time to MRI-CR only for patients with seven or fewer MRI-FLs. Among the patients achieving MRI-CR, significant proportions remained without CCR at 48 months, indicating the persistence of M-protein producing tumor clones in the absence of imaging abnormalities (Fig 4B). According to a landmark analysis of 319 patients surviving at least 36 months, MRI-CR status conferred superior survival (Fig A1A, online only). Further examination in the context of MRI-FL baseline status revealed that MRI-CR status was

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>MRI-FL</th>
<th>MBS-FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP &gt; 8.0 mg/L</td>
<td>32</td>
<td>34</td>
</tr>
<tr>
<td>Albumin &lt; 3.5 g/dL</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>LDH &gt; ULN</td>
<td>23</td>
<td>24</td>
</tr>
<tr>
<td>Creatinine ≥ 2.0 mg/dL</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviations: MRI, magnetic resonance imaging; MBS, metastatic bone survey; FL, focal lesion; CRP, C-reactive protein; LDH, lactate dehydrogenase; ULN, upper limit of normal.
especially beneficial among the 124 patients with more than seven MRI-FLs (Fig A1B, online only).

**MRI Patterns of Relapse**

Serial MRI examinations were available in 76 patients with MRI-FL at baseline who had relapsed from CCR. At the time of relapse from CCR, MRI-FLs were absent in 22 (29%) and present in 54 patients (71%), including 20 (26%) with new MRI-FLs outside of the areas of initial involvement, 21 (28%) with MRI-FLs that were larger than the original lesions, and 11 (15%) with both an increase in original size and new MRI-FLs; in two patients, MRI-FL remained unchanged from baseline to CCR to relapse.

**DISCUSSION**

This study represents the first comprehensive report on baseline and follow-up MRI and MBS examinations in a large group of uniformly treated patients with MM. The average number of FLs was higher on MRI than on MBS, and higher proportions of patients had FLs detected by MRI than by MBS in spine, pelvis, and sternum, with the converse pertaining to rib cage, humeri, and femora (Table 1). FLs were identified in more than one half of patients (n = 125) lacking MBS-defined FL; of those, 121 (97%) had osteolytic FLs on CT examination of the involved sites, indicating that MRI-FLs were indeed related to myeloma activity, which was further confirmed by FNA in these cases, not otherwise meeting stringent criteria for the diagnosis of multiple myeloma. The converse, detection of FLs on MBS without corresponding MRI abnormalities, was seen in 20% of patients in anatomic regions imaged by both MRI and MBS. This discrepancy may result from poor MRI resolution in the rib cage because of respiratory motion and incomplete MRI visualization of ribs, humeri, and femora.

MRI-FLs correlated with serum levels of CRP, albumin, LDH, and creatinine (Table 3). Hypoalbuminemia and CRP elevation are both mediated by interleukin-6,19 a major survival factor in MM,20 but recently also shown to be indirectly involved in long myeloma-related bone disease.21 LDH elevation has been recognized as a feature of high-risk MM, associated frequently with extramedullary disease manifestations and the presence of CAs,22 which, in this analysis, was not related to a high number of MRI-FLs. Thus, CA may develop when MM with preexisting FL transforms to aggressive disease or may be present de novo in a highly proliferative tumor, causing clinical symptoms before FLs develop.

Presence of more than seven MRI-FLs was an independent adverse feature for survival (as well as event-free survival, not shown; Table 2). Other independent harmful baseline features included the presence of CAs and elevated serum levels of LDH and B2M. The adverse implications of CAs are now well established.23 Indeed, the combined information of CAs and MRI-FLs distinguished three risk groups with none, one, or both adverse features present.

Serial MRI studies, available in nearly 90% of patients through consolidation and maintenance phases, permitted assessment of resolution of FL over time and detection of recurrence, typically in identical anatomic sites. When examined in the context of the time to CCR, MRI- CR occurred with a significant delay of 41 to 58 months in patients presenting with more than seven FLs compared with the remainder without or with fewer FL (Fig 4A). The comparison of MRI-CR and CCR per subgroup (0 FL, ≤ 7 FL, > 7 FL; Fig 4B) revealed approximately 30% of cases of MRI-CR without CCR. This discordance may reflect higher M-protein–producing capacity per myeloma cell in diffusely compared with focally growing MM clones, as suggested by the lower frequency of FL in MGUS-evolved MM24; conversely, these FLs may be composed of less mature plasma cells. Comparison of gene expression profiles of purified plasma cells obtained from FL and random bone marrow samples revealed differentially expressed genes, one of which was DKK1 (manuscript in preparation), a gene previously reported to be hyperepressed in cases with both MRI-FLs and x-ray focal osteolytic lesions.25 Although our results confirm and extend previous studies, the intimate relationship between DKK1 expression and plasma cell growth patterns (ie, focal v interstitial) is not completely clear. FL-type MM cells may remain dormant, and very likely represent the origin of eventual disease relapse in a substantial proportion of patients, which not infrequently occurring without concomitant M-protein rise (hypo- or nonsecretory MM relapses). Thus, MRI-CR favored prolonged survival (Fig 1), especially among patients with a higher number of FLs (Fig 2). The lack of MBS-FL resolution has long been appreciated and can be attributed to osteoblast inactivation or lack of maturation from a mesenchymal precursor cell compartment as a result of Wnt signaling inhibition via MM cell–generated DKK1.3,25

Collectively, our data justify the routine application of MRI in addition to MBS examination in MM (1) as the appropriate imaging tool that permits detection of eventually devastating FL before osteolytic disease is recognized on MBS; (2) as an independent staging tool with prognostic implications (one that should replace MBS-FL used in the Durie-Salmon staging system)26 after accounting for the presence of cytogenetic abnormalities, LDH, and B2M; (3) as a means of documenting a superior state of CR conferring survival advantage, especially evident in patients with a high number of FLs at baseline; (4) as a tool for detecting and staging nonsecretory and macrofocal myeloma, with the latter often having minimal or no myelomatous involvement on random bone marrow examination; and (5) as a method of detecting nonsecretory or macrofocal relapse that is becoming a more common problem in advanced stages of intensely treated patients. We recommend follow-up MRI examinations of FLs every 6 months to document radiologic response until disappearance of FLs, and then annually until relapse.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

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REFERENCES


Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).