In-Phase and Out-of-Phase MR Imaging of Bone Marrow: Prediction of Neoplasia Based on the Detection of Coexistent Fat and Water

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OBJECTIVE. The purpose of this study was to determine if gradient-echo MR imaging with TEs selected with fat and water in phase and out of phase can help predict the likelihood of neoplastic or nonneoplastic lesions in bone marrow.

SUBJECTS AND METHODS. Thirty consecutive patients with 31 suspected bone marrow lesions underwent MR imaging, including two spoiled gradient-echo sequences identical in all parameters except TE, which was chosen such that fat and water were either in phase or out of phase. Relative ratios of the abnormal bone marrow signal intensity and a control site on the in-phase and out-of-phase images were measured. The images were also assessed independently by two reviewers who were unaware of the patients’ identities and clinical histories. Reviewers assessed decreased marrow signal intensity relative to control sites on the out-of-phase and in-phase images. Pathologic confirmation was obtained in 16 patients (17 lesions); the remainder of patients had either established diagnoses or determination of benignity based on stability of findings at 1 year. Relative ratios were compared with the Student’s t-test and receiver operating characteristic (ROC) curve analysis, and the reviewers’ scores were evaluated with ROC curve analysis.

RESULTS. The relative signal-intensity ratios were 1.03 ± 0.13 for the neoplastic group and 0.62 ± 0.13 for the nonneoplastic group (p < .0001). ROC curve analysis of the signal-intensity ratios showed a z-score of .99. A ratio cutoff value of 0.8 resulted in a 95% sensitivity and a 95% specificity for detection of neoplasm. Both reviewers achieved 100% sensitivity and 94–100% specificity for detection of neoplasms.

CONCLUSION. In-phase and out-of-phase gradient-echo MR imaging of bone marrow signal-intensity abnormalities can help predict the likelihood of neoplastic or nonneoplastic lesions.

Bone marrow consists of fat and cellular marrow elements supported by a structural matrix including trabecular bone. Cellular bone marrow elements are known to regress in a predictable fashion from appendicular locations with age [1–6], although remnant or regenerative red marrow is common, especially in the proximal metaphysis of the humerus and femur and in the pelvis and spine [7–11]. Difficulty in MR image interpretation occasionally arises when patients with localized skeletal complaints have marrow signal intensity inconsistent with fat on their images. Differentiation among traumatic, neoplastic, and inflammatory processes is often not possible with MR imaging, and assessment of marrow after chemotherapy or radiation therapy is limited [12–16]. Most neoplasms completely replace bone, fat, and hematopoietic elements in bone marrow, whereas most nonneoplastic abnormalities found in bone marrow, such as trauma, hyperplastic red marrow, and ischemia, typically do not completely replace the fat within marrow (Rosenberg AE, personal communication). Thus, detection of fat within marrow would be expected to make neoplasm a less likely cause of MR signal-intensity abnormalities in the marrow. In-phase and out-of-phase MR imaging allows detection of fat in lesions and thus may be predictive of whether a signal-intensity abnormality seen in the marrow is likely caused by neoplastic or nonneoplastic lesions. The purpose of this study was to determine whether gradient-echo MR imaging, with TEs selected so that fat and water were in phase and out of phase, could help predict the likelihood of neoplastic or nonneoplastic causes of signal-intensity abnormality in bone marrow.

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Subjects and Methods

**Background**

Spins of lipid and water differ in their rotational frequency by 3.5 parts per million when exposed to an external magnetic field. Because of this frequency difference, signal generated during MR imaging from tissue containing both lipid and water will have a TE-dependent variation in signal resulting not only from transverse relaxation and susceptibility (T2*) effects but also from phase interference of lipid and water spins. Because gradient-echo sequences do not refocus signal with a 180° refocusing pulse, the different resonance frequencies of water and lipid protons cause the signal contribution of these two populations to cycle in and out of phase with respect to each other as TE increases [17, 18]. At 1.5 T, this cycling occurs at intervals of 2.1 msec, being in phase at a TE of 4.2 msec and out of phase at TEs of 2.1 and 6.3 msec.

When a short TE is used, the contribution to signal intensity from T2* effects should be small. On an in-phase image, signal intensity is formed by the sum of signals from the lipid and water spins; on an out-of-phase image, signal intensity results from the difference in signal from the lipid and water spins. Thus, voxels that contain both water and fat will decrease in signal intensity on out-of-phase images, whereas voxels containing water but no fat will have little or no change in signal intensity on out-of-phase images.

**Subjects**

We studied 30 consecutive patients who were referred for MR imaging because of localized skeletal complaints or suspected osseous lesions based on plain film or CT imaging. One patient had two anatomic regions studied. Clinical information and indications for MR imaging are provided in Tables 1 and 2. Thirteen of these patients had a history of malignancy and plain film, bone scan, or CT findings that prompted additional evaluation with MR imaging. Seventeen patients had symptoms or signs referable to the skeletal site under study. The study group consisted of 14 male and 16 female patients, with a mean age of 50 years (range, 1–87 years). The study was approved by our institution's Review Board for Human Studies.

**Methods**

All patients were studied with one of two 1.5-T MR imaging units (Signa 4.8 or 5.3; General Electric Medical Systems, Milwaukee, WI). Various standard imaging sequences were routinely used, including T1-weighted spin-echo (400–600/14–20 [TR range/TE range]), T2-weighted spin-echo (2000–2800/14–20, 80), and fast multplanar inversion recovery (4000–6000/60–100; inversion time, 100–140 msec; echo train length, eight) sequences. Imaging before and after IV administration of contrast material with

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**TABLE I**

<table>
<thead>
<tr>
<th>Lesion No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>History</th>
<th>RSIR</th>
<th>Pathology (follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>71</td>
<td>Right thigh pain, permeated lytic in mid femur on radiographs</td>
<td>1.38</td>
<td>Poorly differentiated adenocarcinoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>50</td>
<td>Breast cancer with sternal mass and positive bone scan; mass arising from sternum on MR imaging</td>
<td>1.26</td>
<td>Documented osseous metastatic disease at other locations; presumed additional focus of metastatic disease</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>63</td>
<td>Known refractory anemia in blast crisis; prominent diffuse signal-intensity changes on T1 and T2 sequences on MR imaging</td>
<td>1.17</td>
<td>Previously documented leukemia transformation in pelvis by bone marrow aspiration</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>10</td>
<td>Knee pain; mixed lytic and sclerotic lesion in distal femur on radiographs</td>
<td>1.14</td>
<td>Osteosarcoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Female</td>
<td>61</td>
<td>Breast cancer; pain and lytic lesion in right femur on radiographs</td>
<td>1.05</td>
<td>Metastatic adenocarcinoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>64</td>
<td>Sacral mass; remote history of renal cell carcinoma</td>
<td>1.04</td>
<td>Metastatic renal cell carcinoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>4</td>
<td>Pathologic fracture of proximal femur</td>
<td>1.04</td>
<td>Fibrous dysplasia&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Female</td>
<td>29</td>
<td>Incidental lytic lesion of metacarpal detected while evaluating for scaphoid fracture</td>
<td>1.01</td>
<td>Giant cell tumor&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>Male</td>
<td>66</td>
<td>Metastatic prostatic cancer; new abnormal bone scan focus in right ischium; focal signal-intensity abnormality in right ischium on MR imaging</td>
<td>1.00</td>
<td>Presumed metastasis; known additional osseous metastases</td>
</tr>
<tr>
<td>10</td>
<td>Female</td>
<td>72</td>
<td>Hypercalcemia and foot drop, with CT showing iliac mass extending into sciatic notch</td>
<td>1.00</td>
<td>Poorly differentiated adenocarcinoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>64</td>
<td>Lytic lesion of proximal tibia epiphysis on radiographs and CT</td>
<td>0.97</td>
<td>Osteosarcoma metastasis&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>68</td>
<td>Polycthemia vera; lytic lesion in humerus on radiographs</td>
<td>0.96</td>
<td>Focal leukemia mass&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>16</td>
<td>Mixed lytic and sclerotic lesion in proximal tibia on radiographs</td>
<td>0.95</td>
<td>Osteosarcoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>14</td>
<td>Male</td>
<td>50</td>
<td>Left hip pain; lytic lesion in acetabulum on radiographs</td>
<td>0.93</td>
<td>Poorly differentiated metastatic adenocarcinoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>15</td>
<td>Female</td>
<td>87</td>
<td>Multiple myeloma; new lesion in right femur on radiographs; focal signal-intensity abnormality in right femur on MR imaging</td>
<td>0.92</td>
<td>Myeloma documented by bone marrow aspiration; presumed additional focus of myeloma</td>
</tr>
<tr>
<td>16</td>
<td>Male</td>
<td>64</td>
<td>Knee pain; mixed lytic and sclerotic lesion of distal femoral metaphysis on radiographs</td>
<td>0.91</td>
<td>Osteosarcoma&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>17</td>
<td>Male</td>
<td>24</td>
<td>Leukemia, status postchemotherapy; new hip pain</td>
<td>0.88</td>
<td>Residual leukemic foc&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note. — RSIR = relative signal-intensity ratio.  
<sup>a</sup>Lesions that were confirmed pathologically.  
<sup>b</sup>Separate lesions in the same patient.
fat-suppressed T1-weighted spin-echo sequences was performed in four patients. Two excitations were acquired for all sequences except the T2-weighted spin-echo sequence, for which one excitation was acquired. Field of view, matrix size, slice thickness, and inter-slice gap were tailored to the specific site under study. Choice of coils was also dependent on the specific anatomic site under study.

In addition to the routine sequences, all enrolled patients underwent imaging with two fast multiplanar spoiled gradient-echo sequences. Imaging and localizing parameters for a given patient were tailored to the specific site under study and were identical on the two sequences, except for TE, which was selected to image lipid and water spins in phase (4.2 msec) or out of phase (2.4-2.9 msec or 6.3 msec). Ideally, the TE on the out-of-phase images would be 2.1 msec (with fat and water spins directly opposed); however, TE ranged between 2.4 and 2.9 msec in 18 patients because of inherent gradient limitations imposed by the selection of the other imaging parameters. Also, because of gradient limitations, an out-of-phase TE of 2.4-2.9 msec could not be selected in 12 patients, and thus an out-of-phase TE of 6.3 msec was chosen for these patients. Although a TE as short as possible should be chosen to minimize signal-intensity differences due to T2 effects, these effects would likely be small with the short TEs used in the study. TR ranged from 100 to 170 msec. Other imaging parameters included a flip angle of 75°, one excitation, a 256 × 192 matrix, and a 32-kHz bandwidth.

Circular regions of interest as large as possible to include only the abnormal marrow signal intensity under study were selected, identical in location on the in-phase and out-of-phase images, and the signal-intensity values were recorded. In addition to the foci of abnormal bone marrow signal intensity, signal intensity in normal-appearing hematopoietic bone marrow (if present) and a skeletal muscle, bladder cavity, or saline-phantom control site were recorded. Control sites were chosen as homogenous tissues containing little or no mixed water and fat, which would not experience loss of signal on the out-of-phase images due to opposed lipid and water spins. Signal-intensity ratios were expressed for the in-phase images and the out-of-phase images as signal-intensity ratio = normal or abnormal bone marrow signal-intensity / control signal intensity (muscle, urine [in bladder], or saline phantom).

Relative signal-intensity ratios were then expressed for comparison of the out-of-phase ratios with the in-phase ratios as relative signal-intensity ratio = signal-intensity ratio (out-of-phase image) / signal-intensity ratio (in-phase image).

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**TABLE 2**

<table>
<thead>
<tr>
<th>Lesion No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>History</th>
<th>RSIR</th>
<th>Pathology (follow-up)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>Female</td>
<td>46</td>
<td>Bone marrow transplant for breast cancer with recent fall and new area of increased activity in right acetabulum on bone scan</td>
<td>0.81</td>
<td>Mature trilinear hematopoiesis*</td>
</tr>
<tr>
<td>19</td>
<td>Female</td>
<td>87</td>
<td>Status after fall with hip pain and MR imaging showing focal signal-intensity abnormality in left acetabulum</td>
<td>0.79</td>
<td>Acetabular fracture lines shown on subsequent CT</td>
</tr>
<tr>
<td>20</td>
<td>Female</td>
<td>48</td>
<td>Leg pain; stress fracture suggested clinically; focal area of abnormal signal intensity in mid tibia on MR imaging</td>
<td>0.73</td>
<td>Pain and MR imaging findings resolved at follow-up assessment</td>
</tr>
<tr>
<td>21</td>
<td>Female</td>
<td>56</td>
<td>Status after stroke with striking asymmetric humeral osteopenia on radiographs and proximal metaphysis signal intensity suggesting prominent cellular marrow on MR imaging</td>
<td>0.72</td>
<td>Presumed osteoporosis of paralysis; stable at follow-up imaging</td>
</tr>
<tr>
<td>22</td>
<td>Male</td>
<td>41</td>
<td>Sickle cell anemia and leg pain, possible avascular necrosis on radiographs of tibia</td>
<td>0.71</td>
<td>Diffusely diminished tibia signal intensity on MR imaging consistent with marrow infarction; stable at follow-up imaging</td>
</tr>
<tr>
<td>23</td>
<td>Male</td>
<td>40</td>
<td>Knee pain</td>
<td>0.69</td>
<td>Avascular necrosis on MR imaging, stable at follow-up imaging</td>
</tr>
<tr>
<td>24</td>
<td>Female</td>
<td>53</td>
<td>Painful hip, history of avascular necrosis in knee; MR imaging showed asymmetric acetabular signal intensity on symptomatic side</td>
<td>0.59</td>
<td>Pain and MR imaging findings resolved at follow-up assessment</td>
</tr>
<tr>
<td>25</td>
<td>Female</td>
<td>40</td>
<td>Evaluation for hip pain and uterine leiomyomas; very prominent diffuse hematopoietic marrow pattern shown on MR images</td>
<td>0.58</td>
<td>Stable at follow-up imaging</td>
</tr>
<tr>
<td>26</td>
<td>Male</td>
<td>72</td>
<td>Multiple focal lytic lesions of spine on radiographs and CT</td>
<td>0.58</td>
<td>Hematopoietic marrow*</td>
</tr>
<tr>
<td>27</td>
<td>Female</td>
<td>1</td>
<td>Knee swelling, possible JRA, with MR imaging showing abnormal signal intensity in distal femur and large joint effusion</td>
<td>0.57</td>
<td>Aspiration of joint fluid revealed no evidence of infection; subsequent clinical diagnosis of JRA with bone marrow edema</td>
</tr>
<tr>
<td>28</td>
<td>Female</td>
<td>52</td>
<td>Fell on coccyx, abnormal coccyx signal intensity on MR imaging</td>
<td>0.52</td>
<td>Coccyx fracture diagnosed clinically; symptoms and MR imaging findings resolved at follow-up assessment</td>
</tr>
<tr>
<td>29</td>
<td>Male</td>
<td>61</td>
<td>Status after radiation therapy for prostatic cancer with pain and lysis in os pubis on radiographs and signal-intensity abnormality on MR imaging</td>
<td>0.52</td>
<td>No tumor or infection; pathologic findings consistent with previously irradiated bone*</td>
</tr>
<tr>
<td>30</td>
<td>Female</td>
<td>40</td>
<td>Breast cancer; possible metastatic disease to femurs on radiographs</td>
<td>0.48</td>
<td>Stable at follow-up MR imaging; MR imaging findings considered to represent prominent hematopoietic marrow</td>
</tr>
<tr>
<td>31</td>
<td>Female</td>
<td>73</td>
<td>Rectal cancer, asymmetric increased density in right ilium on radiographs, and focal abnormal signal intensity in right ilium on all sequences on MR imaging</td>
<td>0.36</td>
<td>Normal hematopoietic marrow; stable at follow-up MR imaging*</td>
</tr>
</tbody>
</table>

Note: *RSIR = relative signal-intensity ratio, JRA = juvenile rheumatoid arthritis.

*Lesions that were confirmed pathologically.

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signal-intensity ratio (in-phase image), to determine if a change occurred in the signal intensity of the lesion with out-of-phase imaging. A decrease in signal intensity was considered indicative of both lipid and water protons within the lesion.

The out-of-phase and in-phase images for each patient were then reviewed independently by two radiologists, who were experienced in musculoskeletal MR imaging and were unaware of patient identity and clinical information, to visually determine if the signal intensity of the lesion relative to the control site decreased on the out-of-phase images compared with the in-phase images. Each radiologist graded each patient’s images on a five-point scale of confidence for identification of decreased signal intensity in the lesion as follows: grade 1, definitely no decrease in signal intensity in the lesion relative to the control site on out-of-phase images; grade 2, probably no decrease in signal intensity in the lesion relative to the control site on out-of-phase images; grade 3, indeterminate; grade 4, probably a decrease in signal intensity in the lesion relative to the control site on out-of-phase images; grade 5, definitely a decrease in signal intensity in the lesion relative to the control site on out-of-phase images. The two radiologists then reviewed the images together and gave each patient a consensus grade.

Sixteen patients (17 lesions) underwent biopsy or definitive surgery subsequent to MR imaging, and their lesions were categorized as neoplastic or nonneoplastic. Of the remaining 14 patients’ lesions, four were designated neoplastic (one myeloma, one refractory anemia in blast crisis, one metastatic breast cancer, and one metastatic prostate cancer) on the basis of multiple additional osteous lesions of proven pathology; one was designated as nonneoplastic on the basis of a later established clinical diagnosis of juvenile rheumatoid arthritis.

Six were designated nonneoplastic on the basis of resolution of symptoms and imaging findings after at least 1 year, one was designated nonneoplastic on the basis of a subsequent CT diagnosis of acetabular fracture, and two were diagnosed as nonneoplastic on the basis of MR imaging findings diagnostic of avascular necrosis of bone and stability of findings at 1 year.

**Statistical Analysis**

Means and SDs were calculated for the relative signal-intensity ratios of the neoplastic and nonneoplastic groups and for the normal-appearing marrow group. The mean values of the relative signal-intensity ratios were compared with the Student’s t test using commercially available spreadsheet software (Excel 4.0; Microsoft, Redmond, WA). Significance was defined at p less than .05. Receiver oper-

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**Fig. 1.**—Binormal model generated from relative signal-intensity ratios shows two populations. Nonneoplastic population (solid line) has mean relative signal-intensity ratio of 0.62. Neoplastic population (dotted line) has mean relative signal-intensity ratio of 1.03. Modeled probability distributions of relative signal-intensity ratios are plotted for each group.

**Fig. 2.**—Receiver operating characteristic (ROC) curve of relative signal-intensity ratios for predicting bone lesions as neoplastic versus nonneoplastic. Area under ROC curve, z, is .99.

**Fig. 3.**—Tradeoff between sensitivity (dotted line) and specificity (solid line) as function of relative signal-intensity ratio used as cutoff value between nonneoplastic and neoplastic groups. Value of 0.81 results in sensitivity and specificity values of 95%. As cutoff value is lowered, sensitivity increases but specificity decreases.

**Fig. 4.**—40-year-old woman undergoing pelvic MR imaging to evaluate uterine leiomyomas and hip pain who was found to have prominent diminished signal intensity throughout bone marrow consistent with hematopoietic red marrow. **A.** Coronal in-phase spoiled gradient-echo MR image (140/2.2 [TR/TE]; flip angle, 75°) of pelvis shows diffuse intermediate to low signal intensity throughout marrow of pelvis and proximal femurs with signal intensity similar to that of muscle and remnant high signal intensity attributed to fat in right femoral greater trochanter. **B.** Coronal out-of-phase spoiled gradient-echo MR image (140/2.9; flip angle, 75°) of pelvis shows pronounced decrease in marrow signal intensity with signal intensity lower than that of muscle and in same distribution as findings on in-phase images in A. Note that areas of fatty marrow in right greater trochanter (arrow) and left femoral head do not decrease in signal intensity, compared with in-phase image, because of minimal water content.
In-Phase and Out-of-Phase MR Imaging of Bone Marrow

**Fig. 5.**—63-year-old man with refractory anemia in blast transformation. 
**A.** Coronal in-phase spoiled gradient-echo MR image (140/2.4; flip angle, 75°) of pelvis shows diffuse low signal intensity throughout visualized marrow. Note that marrow has signal intensity that is lower than that of muscle and slightly higher than that of urine in bladder. 
**B.** Coronal out-of-phase spoiled gradient-echo MR image (140/2.4; flip angle, 75°) of pelvis shows signal intensity in marrow to be similar to that of muscle and higher than that of urine in bladder.

**Results**

Seventeen neoplastic lesions (including one tumorlike lesion of bone [fibrous dysplasia] and 14 nonneoplastic lesions) were studied. The relative signal-intensity ratios for the neoplastic and nonneoplastic lesions are given in Tables 1 and 2. The mean relative signal-intensity ratio for lesions in the neoplastic group was 1.03 ± 0.13 (mean ± SD) with a range of 0.88–1.38. The mean relative-signal intensity ratio for lesions in the nonneoplastic group was 0.62 ± 0.13 (range, 0.36–0.81). Hematopoietic marrow with a healthy MR appearance separate from the lesions being assessed was evaluated in 16 patients (normal marrow group); the mean relative signal intensity ratio for this group was 0.63 ± 0.21 (range, 0.16–0.82). The mean relative signal-intensity ratios for both the neoplastic group and the normal marrow group were significantly lower than for the neoplastic group (p < .0001 and p < .0001, respectively). No significant difference existed between the mean relative signal-intensity ratios for the nonneoplastic and normal marrow groups (p = .71).

On the basis of the relative signal-intensity ratios for lesions in the neoplastic and nonneoplastic groups, a binormal model was plotted (Fig. 1). This binormal model resulted in an ROC curve with a z-score of .99 (Fig. 2). The z-score is indicative of the accuracy of a test in a patient group with equal populations with and without disease [21]. For a 95% sensitivity for detection of neoplasm, the relative signal-intensity ratio cutoff was 0.81 with a resultant specificity of 95% (Fig. 3). For a 99% sensitivity, the relative signal-intensity ratio cutoff was 0.72 with a resultant specificity of 82% (Fig. 3).

Visual interpretation of the in-phase images showed the signal intensity of both neoplastic and nonneoplastic lesions to be similar to the signal intensity of control sites (Figs. 4–9). On the out-of-phase images, the signal intensity of neoplastic lesions was similar to that of control sites (Figs. 4, 6, 8, and 9). The visual interpretations resulted in classification of most lesions into the extreme categories of the five-point scale (36 of 64 interpretations were classified as grade 1 or 5 and only four of 64 were classified as grade 3). This distribution of data implied excellent decision performance, preventing generation of ROC curves for the visual interpretations. Using grades 1–3 as indicative of neoplasm, both readers and the consensus readings had 100% sensitivity and 94–100% specificity for detection of neoplasm (Table 3).

**Discussion**

Although quantitative methods of estimating marrow water and fat fractions are accurate and well established [22–30], such methods are not available on most MR imaging systems. However, nonquantitative assessment for the presence of fat and water components is widely available using gradient-echo techniques with selection of TE such that fat and water signals are in phase or out of phase. In-phase and out-of-phase gradient-echo MR imaging has been well established for the assessment of fat and water components in adenal adenoma [31–33]. For bone marrow applications, the potential use of assessing marrow lesions with in-phase and out-of-phase MR imaging was first shown in 1985 [34] and has been reported to be useful in monitoring the distribution of hematopoietic marrow as a function of age and erythrocyte demand in vivo [11]; this technique has also been applied to the assessment of specific diffuse bone marrow abnormality such as polycythemia vera, myelofibrosis, and multiple myeloma [35, 36]. However, to our knowledge, no one has previously reported the potential usefulness of the technique in discriminating between neoplastic and nonneoplastic lesions, which would be helpful in assessing those cases in which abnormal marrow signal intensity is detected but the cause of the abnormal signal intensity is unknown.

Our results showed that in-phase and out-of-phase spoiled gradient-echo MR imaging was helpful in predicting the likelihood of neoplastic or nonneoplastic signal abnormality in bone marrow. Visual assessment and expression of relative signal-intensity ratios were found to be of similar accuracy. Using binormal models that fitted curves to the neoplastic and nonneoplastic groups of relative signal-intensity ratios, we generated ROC curves that revealed 95% sensitivity and specificity for detection of neoplasm at a relative signal-intensity ratio cutoff value of 0.81. However, in our limited group of patients, no overlap occurred in relative signal-intensity ratios, because no neoplastic lesion had a value greater than 0.81, and no neoplastic lesion had a value less than 0.88. Thus, for our...
Fig. 6.—41-year-old man with sickle cell anemia undergoing MR imaging of legs to assess for bone infarct. 
A. Coronal in-phase spoiled gradient-echo MR image (100/4.2 [TR/TE; flip angle, 30°]) of legs shows diffuse heterogeneous marrow pattern. 
B. Coronal out-of-phase spoiled gradient-echo MR image (100/6.3; flip angle, 30°) of legs shows marrow signal intensity to be markedly diminished relative to that of muscle.

Fig. 7.—61-year-old woman with breast cancer undergoing MR imaging because of new right thigh pain. 
A. Coronal in-phase spoiled gradient-echo MR image (150/4.2 [TR/TE; flip angle, 30°]) of right thigh shows diffuse heterogeneous signal intensity throughout right femur with area of focal endosteal thinning in mid diaphysis (arrow). 
B. Coronal out-of-phase spoiled gradient-echo MR image (150/6.3; flip angle, 30°) of right thigh shows marrow signal intensity to be diffusely diminished relative to that of muscle except at site of focal endosteal thinning (arrow). Biopsy revealed metastatic adenocarcinoma.

Patient group, a cutoff value between 0.81 and 0.88 would result in 100% sensitivity and specificity for detection of neoplasm. The purpose and results of our study should not suggest that in-phase and out-of-phase gradient-echo MR imaging has application in discriminating among the many neoplastic or nonneoplastic causes of abnormal signal intensity in bone marrow. Rather, we suggest that the technique is useful in identifying the presence of fat coexistent with water in marrow lesions [34], thus predicting the likelihood of neoplasm in patients with marrow signal-intensity abnormalities. This likelihood is possible because most neoplastic lesions of
Fig. 8.—87-year-old woman who had fallen underwent radiography that revealed no abnormalities and MR imaging that showed focal rounded area of signal-intensity abnormality in anterior wall of left acetabulum.
A, Axial in-phase spoiled gradient-echo MR image (162/4.2 [TR/TE]; flip angle, 75°) of left hip shows focal area of diminished signal intensity in anterior wall of left acetabulum (arrow) similar to that of muscle.
B, Axial out-of-phase spoiled gradient-echo MR image (162/2.7; flip angle, 75°) of left hip shows signal intensity in anterior wall (arrow) that is lower in intensity relative to that of muscle (arrowhead). Findings were attributed to nonneoplastic cause, and fracture was favored diagnosis.
C, Axial CT image of left acetabulum, obtained after MR imaging study, shows fracture of anterior wall of left acetabulum (arrow) and fracture of left sacrum (not shown).

Fig. 9.—73-year-old woman with newly diagnosed rectal cancer who underwent bone scan (not shown) that revealed isolated area of asymmetrically increased activity in right posterior ilium suspected to be metastatic lesion.
A, Axial CT image of pelvis shows asymmetric heterogeneous increased attenuation in right posterior ilium (arrows).
B, Axial T1-weighted spin-echo image (500/11 [TR/TE]) shows asymmetrically diminished signal intensity throughout right posterior ilium (arrows) compared with contralateral side.
C, Axial in-phase spoiled gradient-echo MR image (160/4.2; flip angle, 75°) of pelvis shows signal intensity in right posterior ilium (arrows) to be lower than that of contralateral posterior ilium and signal intensity similar to that of muscle.
D, Axial out-of-phase T1-weighted spoiled gradient-echo MR image (160/2.5; flip angle, 75°) of pelvis shows signal intensity in right posterior ilium (arrows) to be markedly diminished compared with that of muscle. Biopsy revealed normal cellular marrow.
Bone marrow exist as solid masses with advancing fronts that completely destroy and replace all lipid and hematopoietic elements, whereas most nonneoplastic lesions (with the exception of tumorlike lesions of bone such as bone cysts and fibrous dysplasia) do not exist as solid masses but rather as infiltrative hemorrhagic or inflammatory elements that come in with, rather than replace, fat (Rosenberg AE. personal communication). Signal that decreases in intensity on out-of-phase compared with in-phase images indicates that fat and water are present in an area of marrow signal-intensity abnormality [17, 18, 31, 34], making neoplasm less likely. On the other hand, signal intensity that does not decrease on out-of-phase images indicates that fat and water are not coexistent, making neoplasm more likely. Marrow dominated by fat also will not decrease in signal intensity on out-of-phase images; however, the presence of fatty marrow is readily recognized by its high signal intensity on conventional T1-weighted images (Fig. 4). In our study, tissues with significant signal contributions from both lipid and water (such as the cases of edema within avascular necrosis and fractures and normal and hyperplastic hematopoietic marrow) had cancellation of signal on the out-of-phase images, resulting in decreased signal intensity compared with the in-phase images. On the other hand, tissue dominated by water spins (such as the cases of metastases and primary bone tumors, histologically found to completely replace fat within the marrow space) showed little or no decrease in relative marrow signal intensity on the out-of-phase images compared with the in-phase images. The out-of-phase images of the 4-year-old boy with fibrous dysplasia (a nonneoplastic but tumorlike bone lesion) maintained high signal intensity compared with in-phase images, by virtue of the lesion's complete replacement of marrow fat. Other tumorlike nonneoplastic lesions of bone, such as unicameral bone cysts, would also be expected to maintain high signal intensity on out-of-phase images compared with in-phase images.

Assessing marrow lesions with gradient-echo in-phase and out-of-phase MR imaging has several advantages. A major advantage is that the technique can be performed rapidly. Imaging with in-phase and out-of-phase gradient-echo sequences adds at most 4–5 min to total imaging time. In addition, the technique is widely available; in-phase and out-of-phase gradient-echo MR imaging is standard on most systems. Finally, because both quantitative and visual interpretation appear equally accurate for assessment of focal marrow abnormalities, either can be used, thus allowing for rapid interpretation from visual assessment. The high accuracy of both visual assessment and expressed relative signal-intensity ratios for bone marrow analysis is similar to results found for adrenal lesions [31]. The potential clinical use of this technique for avoiding unnecessary biopsy was shown in four of our patients in the nonneoplastic group listed in Table 2 (Figs. 8 and 9). Three of the patients had findings at radiography, CT, or MR imaging that led to biopsy of the lesions. The fourth patient had an initial clinical diagnosis of an acetabular neoplastic lesion until subsequent CT in preparation for biopsy showed a fracture. All four of the lesions showed marked decrease in signal intensity on the out-of-phase images (Figs. 8B and 9D). With our current experience, we would now choose to follow up rather than biopsy these lesions.

Several limitations to our study exist. The first was that several patients did not have direct pathologic correlation. However, these subjects either had pathologically documented disease in other skeletal locations or had diagnosis determined with follow-up of at least 1 year. Inclusion of this group of patients was thought to be important to determine the use of the technique in a broad spectrum of marrow processes. Exclusion of this group might have biased our results because most patients who underwent biopsy were proven to have neoplastic lesions. We also knew that we may have included some cases in which normal or hyperplastic hematopoietic marrow was present. Again, this inclusion was permitted to assess the range of expected findings with the technique. Another limitation of our study was that several patients required the use of a TE of 6.3 msec on the out-of-phase images because of technical considerations. Ideally, an out-of-phase image with the shortest possible TE—namely, 2.1 msec—would be preferred to avoid confounding signal loss due to T2* effects. However, the contribution to signal loss due to these effects was thought to be small because of the short time interval between a TE of 4.2 and 6.3 msec. The third limitation of our study was that only 30 patients were examined. We consider this patient population small because a large variety of lesions can affect bone marrow. Therefore, our results should be considered preliminary and in need of further evaluation. One group of lesions absent from our study was osteomyelitis, which we would expect to exhibit a range of relative signal-intensity ratios, depending on the degree of infiltration of marrow by inflammatory cellular elements and on whether abscess formation occurred. It is noteworthy that one of our subjects, who had been treated for leukemia and found histologically to have substantially improved but residual disease, had the lowest relative signal-intensity ratio of the neoplastic group. This finding suggests that experience with a larger patient population may result in more overlap of relative signal-intensity ratios among patients with specific forms of neoplastic and nonneoplastic marrow abnormalities. Results of other studies that evaluated patients with myeloproliferative syndromes [35] and multiple myeloma [36] suggest that these infiltrative disorders can contain neoplastic elements admixed with fat and can show decreased signal intensity on out-of-phase imaging in at least some patients. Future studies involving large patient groups may be helpful to determine the usefulness of this technique for specific marrow disorders. In conclusion, this study found that in-phase and out-of-phase gradient-echo MR imaging could help predict the likelihood of neoplastic or nonneoplastic lesions in bone marrow.

References
In-Phase and Out-of-Phase MR Imaging of Bone Marrow

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