The accurate and reproducible detection of metastasis to lymph nodes has a substantial effect on the prognosis and treatment plans for patients with underlying malignant tumors. Contrast material–enhanced computed tomography (CT) and conventional magnetic resonance (MR) imaging are limited in the detection of metastatic disease in normal-sized lymph nodes. The sensitivity of current node size criteria in the detection of metastasis is very limited. To reduce the false-negative diagnosis rate, a smaller size criterion has to be applied at the expense of specificity. In reality, 5-10-mm-diameter lymph nodes without necrosis or extracapsular spread that are visible at CT or MR imaging
are in this indeterminate category and would meet such a criterion. Radiologists often describe the presence of lymph nodes without adequately addressing their origin or clinical importance. Thus, the current imaging-based diagnosis of nodal metastasis is inadequate.

Ferumoxtran 10 (Combidx; Advanced Magnetics, Cambridge, Mass) is a contrast agent consisting of ultrasmall superparamagnetic iron oxide particles that can enhance depiction of the normal function of the reticuloendothelial system at MR imaging. A lymph node with normal phagocytic function takes up a substantial amount of iron oxide particles and therefore markedly reduces the signal intensity (SI) following intravenous administration of iron oxide agents secondary to the magnetic susceptibility and T2 shortening effects of the iron oxide particles. Although tumoral uptake of ultrasmall iron oxide particles in intracranial tumors has been demonstrated for amionyx 1-3, a metastatic lymph node incorporates iron oxide particles much less than a normal lymph node and maintains a relatively high SI. These differences in SI between normal and metastatic nodes can be easily detected visually.

The earlier works of Weissleder et al (4-6) and Lee et al (7) greatly contributed to the development of ultrasmall superparamagnetic iron oxide agents. Several investigators (8-13) have reported the efficacy of iron oxide agents in the differentiation of metastatic and normal lymph nodes in animal models. Ferumoxtran 10 is also referred to as AMI 227, AMI Code 7227, BMS 180549, Combidx, Sinerem (in Europe), and dextran-coated ultrasmall superparamagnetic iron oxide agent.

The objectives of this study were to determine the safety and efficacy of ferumoxtran 10 for diagnosis of lymph node metastases from head and neck, chest, breast, abdominal, and pelvic carcinomas and to determine the clinical usefulness of this agent in the nodal staging of these cancers.

**MATERIALS AND METHODS**

**Study Design**

This was an open-label multicenter study involving 26 investigators from 22 institutions. Patients with primary malignancies who were suspected of having nodal metastases received ferumoxtran 10 (2.6 mg of iron per kilogram of body weight) intravenously and underwent MR imaging before and 24-36 hours after ferumoxtran 10 administration. Histopathologic correlation of metastases to lymph nodes (hereafter, lymph node metastases) was performed after surgery or percutaneous biopsy.

**Study Subjects**

Of the total of 152 patients who received ferumoxtran 10, five were excluded from the study: two who received less than 80% of the correct dose, one who did not undergo MR imaging, one who was imaged incorrectly, and one who did not meet the study recruitment criteria. The remaining 147 patients were evaluable. For blinded interpretation of the MR images, the images obtained in six healthy subjects from a previous doseranging study (14) were included for assessment of truly normal cases; thus, a total of 153 subjects were included in this study. The 147 evaluable patients included 29 patients with head and neck cancer, 32 with lung or mediastinal cancer, 23 with breast cancer, 26 with abdominal cancer, and 39 with pelvic cancer. Two patients had abdominal and pelvic cancers.

Patient inclusion criteria were age older than 18 years, a confirmed primary cancer, and the possibility of nodal metastases. At least one lymph node had to be visible on the precontrast MR images. Pregnant or lactating women and patients with lymphoma or small cell lung cancer were excluded. Patients who had undergone radiation treatment of the area of interest within the previous 6 months also were excluded. Our entire study was approved by the institutional review board at each participating institution, where all patients signed informed consent forms.

**Physical Characteristics and Administration of Ferumoxtran 10**

The physical characteristics of ferumoxtran 10 have been described in detail (8,12,15,16). Briefly, ferumoxtran 10 was provided in the form of a lyophilized powder consisting of ultrasmall superparamagnetic iron oxide particles covered with low-molecular-weight dextran. The iron oxide core is a form of nonstochiometric magnetite and is 4.3-6.0 nm in diameter; in a solution, the total particle diameter is 17-21 nm. Ferumoxtran 10 consists of biodegradable iron oxide particles that are metabolized in the same way as nonmagnetic iron dextran compounds; it enters the normal body iron pool in the metabolic pathway through transferin, ferritin, hemosiderin, and hebaglobin.

To administer ferumoxtran 10, we diluted the agent with 50 mL of saline and infused it through a 5-μm filter at a rate of 4 mL/min. A dose of 2.6 mg of iron per kilogram was chosen on the basis of results of a phase II dose-ranging study (14).

**MR Imaging**

MR imaging was performed in three patients with a 0.2-T MR imaging unit, in one patient with a 1.0-T unit, and in the remaining 143 patients with a 1.5-T unit. The basic MR imaging protocol included the acquisition of transverse T1-weighted spin-echo (580/11 [median repetition time msec/echo time msec], 256 × 192 matrix, one to two signals acquired) and transverse T2-weighted fast spin-echo (4,000/102, echo train length of eight to 16, 256 × 192 matrix, two signals acquired) images in 130 patients and the acquisition of conventional T2-weighted spin-echo images in 17 patients. Transverse T2*-weighted gradient-echo images (266/102, 20° flip angle, two signals acquired) were acquired in all 147 patients. The section thickness was 4 mm for imaging the head and neck and 5 mm for imaging the other body regions. The field of view was 18-20 cm for the head and neck and 34-42 cm for the other parts of the body.

**Interpretation of MR Images**

To reduce observer bias and minimize interobserver variability, teams of radiologists and oncologists who were not involved in patient enrollment interpreted the MR images. Four teams—each consisting of one radiologist and one oncologist, both blinded to the clinical histories and histopathologic results—were involved in image interpretation. Two teams interpreted the head and neck MR images independently, and the other two teams interpreted the MR images of the other body regions. The radiologist evaluated each lymph node visualized on the images for the presence or absence of metastatic disease. The oncologist assigned the nodal stage in each patient during the reading session by using the information provided by the radiologist.

MR images, without identifying markings, were displayed on a computer screen at Bio-Imaging Technologies, Newton, Pa. The readers interpreted the precontrast images twice: by using size criteria alone (ie, size-based diagnosis) and by using size criteria with other imaging features (ie, subjective reader diagnosis). Lymph node size was measured by using an elec-
tially evaluated the precontrast images. The team of blinded readers ini-
to evaluate the iron oxide-enhanced MR validated in large clinical studies.

features on the precontrast MR images
ence or absence of metastasis by using all
ologists were asked to determine the pres-
tronic caliper. A node larger than 10 mm
in short-axis diameter was considered metastatic according to the size criteria. For subjective reader diagnosis, the radi-
ologists were asked to determine the pres-
ence or absence of metastasis by using all
features on the precontrast MR images that they considered relevant. Although this reading protocol may simulate the
reading protocol may simulate the
size criteria protocol/ has not been
validated in large clinical studies.

Diagnostic guidelines (Fig 1) were used to evaluate the iron oxide-enhanced MR images. The team of blinded readers ini-
tially evaluated the precontrast images alone; then they evaluated the pre-
and postcontrast MR images together (ie, paired MR images). At least 2 weeks later, the blinded readers interpreted the post-
contrast MR images alone. To reduce re-
call bias, the order of case presentations in each MR image interpretation session was randomized.

Efficacy Evaluation

The diagnostic performance of feru-

and patient level. Node-level analysis in-
cluded the evaluation of all lymph nodes
seen by the blinded readers on both the pre-
and postcontrast MR images with which
there was histopathologic confirmation at
surgery or biopsy. Only those nodes for
which there was histopathologic correla-

Quantitative Analysis

SI was measured by calculating mean
region of interest SI values and SDs for
the lymph nodes, noise, and muscle seen
pre- and postcontrast MR images. These
calculations were performed by the
onsite investigators at each institution. A
region of interest was placed to cover a
whole node. Median percentage changes
in SI were calculated as follows: (postcon-
trast median value — precontrast median value)/(precontrast median value).

Safety Evaluation

Safety evaluation was performed in the
initial 152 patients who received feru-

Nodal Staging

The oncologists assigned the nodal stage
in each subject on the basis of the MR
image interpretations made by the radi-
ologists. No additional clinical informa-
tion, except primary tumor site, was pro-
vided to help determine nodal stage. The
oncologists determined the nodal stage
on the precontrast, paired, and postcon-
trast MR images by using the American
Joint Committee on Cancer staging sys-
tem. The MR results were correlated with
the final histopathologic nodal stages.

Statistical Analysis

For efficacy data evaluation, the McNe-
mar test was used to assess differences
between the pre- and postcontrast MR
images and between the precontrast and
paired MR images at node- and patient-
level analyses. Nodal staging data also
were analyzed by using the McNemar
test. The Wilcoxon signed rank test was
used to analyze the median values of
lymph node SI on the pre- and postcon-
trast MR images. For safety data evalua-
tion, the Wilcoxon signed rank test was
used to analyze changes in vital signs and
in laboratory findings. P < .05 was con-
sidered to indicate a significant differ-
ence in all statistical analyses.
RESULTS

Histopathologic Correlation

Of the 147 evaluable patients, 33 underwent biopsy and 101 underwent surgery. Thirteen patients underwent neither biopsy nor surgery because of their refusal, technical difficulty, an unstable clinical condition, or the discovery of a distant metastasis. The histopathologic nodal stages in the 134 patients who underwent biopsy or surgery were as follows: N0 in 59, N1 in 25, N2 in 30, and N3 in seven patients. The nodal stage in 13 patients was NX. Three hundred seventy-one lymph nodes were visible on pre- and postcontrast MR images and were correlated with the histopathologic findings by the onsite investigators. These lymph nodes included 108 metastatic nodes, 146 normal nodes, and 22 inflammatory nodes. Nineteen lymph nodes with indeterminate histopathologic findings and 76 lymph nodes that were visible on MR images were not removed. Thus, there was specific histopathologic correlation for 276 lymph nodes in the unblinded clinical phase of this study. Only those nodes that were seen by the blinded reader both before and after ferumoxtran 10 administration, and that could be accurately correlated with the histopathologic findings were included in the analysis.

Efficacy Evaluation

Overall diagnostic accuracy.—The sensitivity, specificity, and accuracy of the blinded MR imaging–based diagnoses made at node-level analysis by using (a) size criteria at precontrast MR imaging, (b) subjective reader assessment at precontrast MR imaging, (c) paired pre- and postcontrast MR imaging, and (d) postcontrast MR imaging only are shown in Table 1. The sensitivity achieved by using size criteria was low (54%), but specificity was high (82%). Subjective reader assessment resulted in increased sensitivity, to 91%, but decreased specificity, to 51%. These findings indicate that the blinded readers tended to diagnose more of the small nodes as metastatic. The overall accuracy of both precontrast MR imaging evaluations (ie, with size criteria and reader assessment) was approximately 70%. Postcontrast MR imaging led to improved sensitivity and specificity—both increased to 85%—and consequently to improved accuracy, to 85%. There was a significant difference in sensitivity between size criteria (at precontrast MR imaging) and postcontrast MR imaging (P < .001). Similarly, the specificity of subjective reader assessment (at precontrast MR imaging) significantly improved after ferumoxtran 10 administration (P < .006).

Node-level positive and negative predictive values.—The positive predictive values (PPVs) and negative predictive values (NPVs) of size criteria and subjective reader assessment at precontrast MR imaging, postcontrast MR imaging alone, and paired MR imaging are shown in Table 2. For size criteria at precontrast MR imaging, PPV was 74% and NPV was 65%. With postcontrast MR imaging, both PPV (84%) and NPV (84%) improved.

Receiver operating characteristic analysis in all body regions.—A receiver operating characteristic curve for size criteria was created by using a node size cutoff of every 5 mm (Fig 2a). These data showed high sensitivity and low specificity at 5-and 10-mm cutoffs and high specificity and low sensitivity at 15- and 20-mm cutoffs. The area under the receiver operating characteristic curve for size criteria was 0.762 (average of 0.756 for reader 1 and 0.769 for reader 2).

The receiver operating characteristic curve for postcontrast MR imaging created on the basis of the diagnostic guidelines in Figure 1 revealed improved diagnostic performance (Fig 2b) compared with that of size criteria alone. The area under the curve was 0.829 (average of 0.814 for reader 1 and 0.844 for reader 2).

Diagnostic accuracy of MR imaging of each anatomic region.—The efficacy of ferumoxtran 10–enhanced MR imaging of each anatomic region is illustrated in Figure 3. Results, particularly those obtained at precontrast MR imaging, varied among the anatomic regions. The overall accuracy of postcontrast MR imaging of the head and neck was 93% (average of 94% [47 of 50 nodes] and 92% [33 of 36 nodes] for readers 1 and 2, respectively), a significant improvement from the accuracy achieved at precontrast MR imaging: 69% (average of 76% [47 of 62 nodes] and 61% [28 of 46 nodes] for readers 1

---

**TABLE 1**

Sensitivity, Specificity, and Accuracy of MR Imaging in All Body Regions on a Node Level

<table>
<thead>
<tr>
<th>MR Evaluation</th>
<th>No. of Lymph Nodes</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size criteria</td>
<td>169</td>
<td>85 (66/78)</td>
<td>85 (77/91)</td>
<td>85 (143/169)</td>
</tr>
<tr>
<td>Subjective reader assessment</td>
<td>169</td>
<td>85 (66/78)</td>
<td>85 (77/91)</td>
<td>85 (143/169)</td>
</tr>
<tr>
<td>Precontrast imaging with reader assess.</td>
<td>169</td>
<td>85 (66/78)</td>
<td>85 (77/91)</td>
<td>85 (143/169)</td>
</tr>
<tr>
<td>Postcontrast imaging only</td>
<td>169</td>
<td>85 (66/78)</td>
<td>85 (77/91)</td>
<td>85 (143/169)</td>
</tr>
</tbody>
</table>

**Note.** — Numbers in parentheses are numbers (of nodes) on which percentages are based. According to precontrast MR imaging size criteria, nodes with a short-axis diameter of greater than 10 mm were considered metastatic. Blinded subjective reader diagnoses were based on all MR imaging features. Postcontrast MR imaging had higher sensitivity and accuracy than precontrast MR imaging with size criteria (P < .001) and higher specificity than precontrast MR imaging with subjective reader assessment (significance defined as P < .05 at one-sided McNemar test).

* Average of reader 1 and reader 2 values.
TABLE 2

<table>
<thead>
<tr>
<th>MR Evaluation</th>
<th>No. of Lymph Nodes</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast imaging with size criteria</td>
<td>173</td>
<td>72 (43/60)</td>
<td>68 (77/113)</td>
</tr>
<tr>
<td>Precontrast imaging with reader assessment</td>
<td>173</td>
<td>56 (74/132)</td>
<td>88 (36/41)</td>
</tr>
<tr>
<td>Paired imaging</td>
<td>173</td>
<td>75 (66/88)</td>
<td>84 (71/85)</td>
</tr>
<tr>
<td>Postcontrast imaging only</td>
<td>169</td>
<td>83 (66/80)</td>
<td>87 (77/89)</td>
</tr>
<tr>
<td>Reader 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast imaging with size criteria</td>
<td>158</td>
<td>76 (45/59)</td>
<td>62 (61/99)</td>
</tr>
<tr>
<td>Precontrast imaging with reader assessment</td>
<td>158</td>
<td>73 (73/100)</td>
<td>83 (48/58)</td>
</tr>
<tr>
<td>Paired imaging</td>
<td>157</td>
<td>80 (70/87)</td>
<td>80 (56/70)</td>
</tr>
<tr>
<td>Postcontrast imaging only</td>
<td>147</td>
<td>86 (67/78)</td>
<td>81 (56/69)</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses are numbers (of nodes) on which percentages are based. MR imaging and postcontrast MR imaging had higher PPV than precontrast MR imaging with either size criteria or subjective reader assessment. However, there was no substantial difference in NPV between pre- and postcontrast MR imaging.

* Average of reader 1 and reader 2 values.

---

**Figure 2.** (a) Receiver operating characteristic curves for size criteria at precontrast MR imaging. Area under the curve for size criteria is 0.763. Threshold 1: Lymph nodes larger than 20 mm in diameter are considered metastatic. Threshold 2: Lymph nodes larger than 15 mm in diameter are considered metastatic. Threshold 3: Lymph nodes larger than 10 mm in diameter are considered metastatic. Threshold 4: Lymph nodes larger than 5 mm in diameter are considered metastatic. (b) Receiver operating characteristic curves for postcontrast MR imaging—based diagnostic guidelines (see Fig 1). The area under the curve for postcontrast MR imaging was 0.829. Threshold 1: All lymph nodes assigned a guideline (#1–#7) in Figure 1 are considered nonmetastatic. Threshold 2: All lymph nodes assigned under category 1 or 2 are considered metastatic; those assigned under categories 3–7 are considered nonmetastatic. Threshold 3: All lymph nodes assigned under category 1 are considered metastatic, but nodes assigned under categories 2–7 are considered nonmetastatic. Threshold 4: All lymph nodes assigned under category 1–3 are considered metastatic; those assigned under categories 4–7 are considered nonmetastatic. Threshold 5: All lymph nodes assigned under categories 1–4 are considered metastatic; those assigned under categories 5–7 are considered nonmetastatic. Threshold 6: All lymph nodes assigned under categories 1–5 are considered metastatic; those assigned under category 6 or 7 are considered nonmetastatic. Threshold 7: All lymph nodes assigned under categories 1–6 are considered metastatic; those assigned under category 7 are considered nonmetastatic.

---

and 2, respectively) with size criteria and 80% (average of 82% [51 of 62 nodes] and 78% [36 of 46 nodes] for readers 1 and 2, respectively) with subjective reader assessment. The overall accuracy of postcontrast MR imaging was 83% (average of 85% [27 of 32 nodes] and 82% [28 of 34 nodes] for readers 1 and 2, respectively) in the abdomen and pelvis, 82% (average of 80% [45 of 56 nodes] and 85% [49 of 58 nodes] for readers 1 and 2, respectively) in the breast, and 73% (average of 77% [24 of 31 nodes] and 68% [13 of 19 nodes] for readers 1 and 2, respectively) in the chest and mediastinum (Fig 4).

The patterns of diagnostic accuracy for the breast and the head and neck region were similar: low sensitivity and high specificity with size criteria, high sensitivity and low specificity with subjective reader assessment, and improved sensitivity and specificity with postcontrast MR imaging. Conversely, the precontrast MR imaging results for the lung and mediastinum and the abdomen and pelvis indicated relatively high sensitivity and low specificity of size criteria (Fig 3).

Subjective reader assessment at precontrast MR imaging for the chest and abdomen-pelvis had high sensitivity but very limited specificity. Ferumoxtran 10–enhanced MR imaging, however, had fairly constant sensitivity and specificity (>80%) in the abdomen and pelvis with the same readers.

**Patient-level analysis.** The diagnostic accuracy of postcontrast MR imaging was also analyzed on a patient basis. Patient-level analysis involved the patients who had undergone surgery or biopsy. The histopathologic findings in all nodes that were removed were correlated with the characteristics of all nodes that were visible at MR imaging. The sensitivity, specificity, PPV, and NPV of MR imaging at...
Patient-level analysis are shown in Tables 3 and 4. The sensitivity of paired MR imaging (85%) was higher than that of size criteria (77%) (P < .05) (Table 3). The readers were able to correctly identify most patients who had at least one lymph node metastasis, regardless of whether they were evaluating pre- or postcontrast MR images. Therefore, there was no significant improvement in sensitivity with ferumoxtran 10 administration, as compared with the sensitivity of subjective reader assessment (at precontrast MR imaging).

In contrast, specificity was significantly higher when the readers evaluated the postcontrast MR images (75%) than when they used subjective assessment of the precontrast MR images (39%) (P < .001). The results were similar for all body regions combined and for individual body regions. Evaluation of the postcontrast MR images yielded the highest PPV. NPV was fairly consistent among the precontrast, paired, and postcontrast MR images; values ranged from 69% to 81%.

SI measurement.—The SI of the metastatic and nonmetastatic lymph nodes on precontrast T1-weighted spin-echo MR images increased after ferumoxtran 10 administration. The SI of lymph nodes on precontrast T2-weighted spin-echo and T2*-weighted MR images decreased after ferumoxtran 10 administration, as shown in Table 5. The metastatic nodes showed a greater increase in SI on the T1-weighted MR images than the nonmetastatic nodes (P < .001). The SI decreases in the nonmetastatic nodes on the T2- and T2*-weighted images were greater than those in the metastatic nodes; the most noticeable difference was measured on the T2*-weighted images (P < .001).
Effect of iron oxide enhancement on nodal staging.—The nodal stages assigned by the oncologists solely on the basis of the precontrast, paired, and postcontrast MR image findings are shown in Table 6. The correlations between histopathologic nodal stage and MR imaging–based nodal stage are shown in Table 7. There were significant differences in the nodal stages assigned by both blinded oncologists between pre- and postcontrast MR imaging and between precontrast and paired MR imaging. Nodal staging based on precontrast MR imaging findings was accurate in 23% and 33% of cases. Staging accuracy improved to 34% and 46% with paired MR imaging. Similarly, the accuracy of precontrast nodal staging improved from 24% and 34% to 45% and 49%, respectively, with contrast material enhancement (P < .05).

In this highly artificial setting, there were many patients for whom the teams of radiologists and oncologists were unsure of the nodal stage (NX) depicted on the precontrast MR images: The lymph nodes visible on the MR images had equivocal size and imaging characteristics. Of these patients with NX nodes at precontrast MR imaging, more than 50% received a more definitive and accurate diagnosis with ferumoxtran 10–enhanced MR imaging. It is perhaps more important that more than 70% of patients with suspicious node(s) at precontrast MR imaging received an accurate diagnosis of NO nodes at postcontrast or paired MR imaging.

Safety Data

Adverse events.—Overall, 43 (28%) of 152 patients had one or more adverse events during the study (Table 9). The most frequently reported adverse events were headache, back pain, vasodilatation, and urticaria, each of which occurred in 6% of patients. None of the adverse events was serious: Most were mild or moderate in severity and of short duration.

Twenty (13%) patients received treatment for adverse events: mostly acetaminophen for headache or other pain and diphenhydramine primarily for urticaria. The ferumoxtran 10 infusion was discontinued because of adverse events in four patients. Two of these four patients had back pain, one had chest pain, and one had infiltration at the injection site. In six patients, the infusion was temporarily suspended because of adverse events and then continued to completion without recurrence of the adverse events.

Physical examination.—Six of 152 patients had changes in physical examination results from the baseline findings at the time of MR imaging performed 24–36 hours after ferumoxtran 10 administration. For four of these six patients, the change in physical examination results included resolution of a restless foot in one patient, resolution of chest crackles in two patients, and stiff knees in one patient, was thought to be unrelated to ferumoxtran 10 infusion. Two of these patients had resolving urticaria, which was reported as an adverse event.

Vital signs.—There was no significant change in body temperature from the baseline temperature at any time in any patient. The mean values for systolic blood pressure, diastolic blood pressure, and respiratory rate decreased steadily from the baseline during the course of the study (P < .05, Wilcoxon signed rank test). The magnitude of these decreases was small: by 2–3 mm Hg for blood pressure and by 0.2–0.3 breaths per minute for respiratory rate. Heart rate decreased by about one beat per minute during the first 30 minutes after contrast material administration and returned to baseline by 24–36 hours.

Laboratory tests.—Overall, laboratory tests revealed no effect of ferumoxtran 10 on routine serum chemistry, hematologic, or urinalysis values. Because the principal ingredient and active component of ferumoxtran 10 is iron oxide, the iron metabolism data reflected the amount of iron distributed in the body at contrast agent administration, as expected. The amount of iron oxide administered is less than that in a unit of blood, and the changes in stored iron levels caused by contrast agent administration are not enough to
cause iron overload in a patient with normal iron levels.

As expected, the mean values for serum iron, total iron binding capacity, and percentage saturation increased significantly (P < .05) from baseline in the 24–36 hours following contrast agent administration. The mean serum ferritin level increased minimally and the mean serum transferrin level decreased minimally during this 24–36-hour period. All significant changes from baseline reflected the distribution of and metabolism induced by iron from ferumoxtran 10.

**DISCUSSION**

Results of this study, which to our knowledge involved the largest series of patients who received ferumoxtran 10 injection, showed that ferumoxtran 10 is safe and efficacious for the detection of nodal metastasis at MR imaging. Iron oxide–enhanced MR imaging had higher sensitivity and specificity for differentiating metastatic from normal nodes than both objective size criteria and subjective radiologist assessment (both at precontrast MR imaging). Ferumoxtran 10 performed best in the head and neck, yielding an overall accuracy of 93%.

Nodal staging improved significantly with iron oxide enhancement, with which a substantial number of patients in whom precontrast MR imaging findings indicated NX received an accurate diagnosis of N0 or N positive. Moreover, many of the patients with questionable nodal metastasis received an accurate diagnosis of N0 at postcontrast MR imaging; these cases reflected increased diagnostic confidence. In addition, there was a significant difference in SI between the metastatic and nonmetastatic lymph nodes on T2-, T2*- and T1-weighted MR images.

Several reports (17–23) have addressed the efficacy of ferumoxtran 10 for MR imaging of the head and neck, chest, abdomen, and pelvis. In a phase II trial of ferumoxtran 10, the diagnostic performance of MR imaging with this agent, which yielded a sensitivity of 95% and a specificity of 84% in the head and neck, was higher than that of conventional MR imaging (17). These results are close to those achieved in the present phase III clinical trial: sensitivity of 96% (average of 96% [25/26] and 96% [24/25] for readers 1 and 2, respectively) and specificity of 87% (average of 92% [22/24] and 82% [9/11] for readers 1 and 2, respectively) at postcontrast MR imaging of the head and neck. Results of a study (21) of head and neck cancer showed higher diagnostic performance at MR imaging performed with ferumoxtran 10 than at MR imaging.

### TABLE 3

<table>
<thead>
<tr>
<th>MR Evaluation</th>
<th>No. of Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast imaging with size criteria</td>
<td>112</td>
<td>79 (46/58)</td>
<td>59 (32/54)</td>
<td>70 (78/112)</td>
</tr>
<tr>
<td>Precontrast imaging with reader assessment</td>
<td>115</td>
<td>93 (34/58)</td>
<td>24 (13/54)</td>
<td>60 (67/112)</td>
</tr>
<tr>
<td>Paired imaging</td>
<td>101</td>
<td>84 (46/55)</td>
<td>65 (30/46)</td>
<td>75 (76/101)</td>
</tr>
<tr>
<td>Postcontrast imaging only</td>
<td>111</td>
<td>83 (48/58)</td>
<td>77 (41/53)</td>
<td>80 (89/111)</td>
</tr>
<tr>
<td>Reader 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast imaging with size criteria</td>
<td>122</td>
<td>75 (47/63)</td>
<td>61 (36/59)</td>
<td>68 (83/122)</td>
</tr>
<tr>
<td>Precontrast imaging with reader assessment</td>
<td>122</td>
<td>87 (55/63)</td>
<td>54 (32/59)</td>
<td>71 (87/122)</td>
</tr>
<tr>
<td>Paired imaging</td>
<td>119</td>
<td>86 (53/62)</td>
<td>67 (38/57)</td>
<td>76 (91/119)</td>
</tr>
<tr>
<td>Postcontrast imaging only</td>
<td>112</td>
<td>84 (51/61)</td>
<td>73 (37/51)</td>
<td>79 (88/112)</td>
</tr>
</tbody>
</table>

**Note.**—Numbers in parentheses are numbers (of patients) on which percentages are based. According to precontrast MR imaging size criteria, nodes with a short-axis diameter of greater than 10 mm were considered metastatic. Blinded subjective reader diagnoses were based on all MR imaging images.

<p>| Table 3: Sensitivity, Specificity, and Accuracy of MR Imaging in All Body Regions on a Patient Level |
|------------------------------------------------|------------------|-----------------|-----------------|--------------|</p>
<table>
<thead>
<tr>
<th>MR Evaluation</th>
<th>No. of Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast imaging with size criteria</td>
<td>112</td>
<td>79 (46/58)</td>
<td>59 (32/54)</td>
<td>70 (78/112)</td>
</tr>
<tr>
<td>Precontrast imaging with reader assessment</td>
<td>115</td>
<td>93 (34/58)</td>
<td>24 (13/54)</td>
<td>60 (67/112)</td>
</tr>
<tr>
<td>Paired imaging</td>
<td>101</td>
<td>84 (46/55)</td>
<td>65 (30/46)</td>
<td>75 (76/101)</td>
</tr>
<tr>
<td>Postcontrast imaging only</td>
<td>111</td>
<td>83 (48/58)</td>
<td>77 (41/53)</td>
<td>80 (89/111)</td>
</tr>
</tbody>
</table>

**Note.**—Numbers in parentheses are numbers (of patients) on which percentages are based. According to precontrast MR imaging size criteria, nodes with a short-axis diameter of greater than 10 mm were considered metastatic. Blinded subjective reader diagnoses were based on all MR imaging images.

**Table 4: PPV and NPV of MR Imaging in All Body Regions at Patient-Level Analysis**

<table>
<thead>
<tr>
<th>MR Evaluation</th>
<th>No. of Patients</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast imaging with size criteria</td>
<td>112</td>
<td>68 (46/68)</td>
<td>73 (32/44)</td>
</tr>
<tr>
<td>Precontrast imaging with reader assessment</td>
<td>112</td>
<td>57 (54/95)</td>
<td>76 (13/17)</td>
</tr>
<tr>
<td>Paired imaging</td>
<td>101</td>
<td>74 (46/62)</td>
<td>77 (30/39)</td>
</tr>
<tr>
<td>Postcontrast imaging only</td>
<td>111</td>
<td>80 (48/60)</td>
<td>80 (41/51)</td>
</tr>
<tr>
<td>Reader 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast imaging with size criteria</td>
<td>122</td>
<td>67 (47/70)</td>
<td>69 (36/52)</td>
</tr>
<tr>
<td>Precontrast imaging with reader assessment</td>
<td>122</td>
<td>67 (55/82)</td>
<td>80 (32/40)</td>
</tr>
<tr>
<td>Paired imaging</td>
<td>119</td>
<td>74 (53/72)</td>
<td>81 (38/47)</td>
</tr>
<tr>
<td>Postcontrast imaging only</td>
<td>112</td>
<td>78 (51/65)</td>
<td>79 (37/47)</td>
</tr>
</tbody>
</table>

**Note.**—Numbers in parentheses are numbers (of patients) on which percentages are based. Patient-level analysis revealed that PPV was improved approximately 10%–20% with iron oxide–enhanced MR imaging. There was no substantial difference in NPV.

* Average of reader 1 and reader 2 values.
TABLE 5
SI Measurements in Metastatic and Nonmetastatic Lymph Nodes

<table>
<thead>
<tr>
<th>MR Sequence</th>
<th>No. of Nodes</th>
<th>Precontrast MR</th>
<th>24–36-hour Postcontrast MR</th>
<th>Median SI</th>
<th>Median Change from Precontrast SI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-weighted SE</td>
<td>92</td>
<td>134</td>
<td>165</td>
<td>-18.4</td>
<td></td>
</tr>
<tr>
<td>T2-weighted SE</td>
<td>89</td>
<td>136</td>
<td>103</td>
<td>-23.0</td>
<td></td>
</tr>
<tr>
<td>T2* -weighted</td>
<td>89</td>
<td>78</td>
<td>70</td>
<td>-14.9</td>
<td></td>
</tr>
<tr>
<td>Nonmetastatic nodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-weighted SE</td>
<td>150</td>
<td>190</td>
<td>201</td>
<td>+2.3</td>
<td></td>
</tr>
<tr>
<td>T2-weighted SE</td>
<td>136</td>
<td>154</td>
<td>83</td>
<td>-48.2</td>
<td></td>
</tr>
<tr>
<td>T2* -weighted</td>
<td>123</td>
<td>74</td>
<td>41</td>
<td>-57.9</td>
<td></td>
</tr>
</tbody>
</table>

Note.—Statistically significant difference in SI changes between metastatic and nonmetastatic lymph nodes (P < .001, Wilcoxon signed rank test) was observed in all sequences. SE = spin echo.

TABLE 6
MR Imaging–Based Nodal Staging in Patients: Blinded Evaluation of Unmarked Images

<table>
<thead>
<tr>
<th>Nodal Stage*</th>
<th>Precontrast MR Images</th>
<th>Paired MR Images</th>
<th>Postcontrast MR Images</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reader 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>125</td>
<td>127</td>
<td>127</td>
</tr>
<tr>
<td>NX</td>
<td>55 (44)</td>
<td>36 (28)</td>
<td>29 (23)</td>
</tr>
<tr>
<td>N0</td>
<td>16 (13)</td>
<td>39 (31)</td>
<td>46 (36)</td>
</tr>
<tr>
<td>N1</td>
<td>21 (17)</td>
<td>22 (17)</td>
<td>19 (15)</td>
</tr>
<tr>
<td>N2</td>
<td>22 (18)</td>
<td>20 (16)</td>
<td>25 (20)</td>
</tr>
<tr>
<td>N3</td>
<td>6 (5)</td>
<td>5 (4)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reader 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total no. of patients</td>
<td>139</td>
<td>138</td>
<td>124</td>
</tr>
<tr>
<td>NX</td>
<td>8 (6)</td>
<td>7 (5)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>N0</td>
<td>18 (13)</td>
<td>49 (36)</td>
<td>50 (40)</td>
</tr>
<tr>
<td>N1</td>
<td>55 (40)</td>
<td>40 (29)</td>
<td>26 (21)</td>
</tr>
<tr>
<td>N2</td>
<td>48 (34)</td>
<td>35 (25)</td>
<td>34 (27)</td>
</tr>
<tr>
<td>N3</td>
<td>8 (6)</td>
<td>4 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (1)</td>
<td>3 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Note.—Data are numbers of patients. Numbers in parentheses are percentages. * Subcategories under N1, N2, and N3 were combined.

performed without it. A study (20) of abdominal and pelvic malignancies revealed ferumoxtran 10–enhanced MR imaging to have 93% sensitivity and 100% specificity. In a study (18) to investigate the efficacy of iron oxide contrast agents in patients with urologic and pelvic cancers, a sensitivity of 100% and a specificity of 80% were reported. A sensitivity of 88% and a specificity of 77% were achieved in a European phase III clinical trial of ferumoxtran 10 (30).

The nodal staging of cancer has a major influence on therapeutic decisions. When an imaging examination depicts a single suspicious metastatic node, biopsy, surgical resection, radiation therapy, chemotherapy, or a combination of all of these treatments is performed. The dilemma occurs when the lymph nodes seen at imaging or physical examination appear normal (24–26). Some patients with such findings, who are judged to have N0 disease, have metastatic nodes, and some of them do not. In the studies (27, 28) to reevaluate size criteria for head and neck cancer, 39% of patients with N0 disease at ultrasonography had metastatic nodes at surgery. When, if ever, is observing patients undergoing unnecessary treatment for possible metastatic disease? The false-negative rate was not negligible. We need to further investigate the false-negative cases and the potential reasons why ferumoxtran 10–enhanced MR imaging did not depict some metastatic lymph nodes. Some false-positive diagnoses of nodes are expected because granulomatous disease or infection can reduce the phagocytic activity of lymph nodes, mimicking metastatic nodes. Such false-positive nodes appear to be more of a problem in patients with chest or mediastinal disease. In two studies of the efficacy of ferumoxtran 10 at MR imaging of lung cancer, the specificities were different: 80% in one study (22) and 38% in the other (23).

In this study, we evaluated a subjective diagnostic method, reader assessment at precontrast MR imaging, and compared it with iron oxide–enhanced MR imaging. Reader assessment–based diagnoses might closely reflect how radiologists perform in their practices. As demonstrated in Tables 1 and 2, the radiologists performing these subjective interpretations tended to diagnose metastasis in nodes that were smaller than those that they diagnosed as metastatic by using size criteria. Because these blinded readers lowered their threshold for the diagnosis of metastatic nodes, specificity was sacrificed. Without a definitive diagnostic study, “overdiagnosing” may be a practical trade-off to avoid excluding treatment from some patients with cancer. Overdiagnosing metastatic nodes in some patients with cancer may cause less harm than missing metastatic nodes, but it results in large numbers of patients with N0 lesions undergoing unnecessary treatment for possible metastatic disease.

At both pre- and postcontrast MR imaging, node-level analysis yielded better results than patient-level analysis. The sensitivity of paired MR imaging was higher than that of precontrast MR imaging size criteria, and the specificity of postcontrast MR imaging was significantly improved (P < .001) compared with that of precontrast MR imaging–based reader assessment at patient-level analysis and thus led to fewer false-positive cases. However, the NPV of postcontrast MR imaging was not significantly improved compared with that of precontrast MR imaging. The European phase III trial (30) also revealed that the specificity and PPV for postcontrast MR imaging were higher than those for precontrast MR imaging; however, the sensitivity and NPV of precontrast MR imaging were high and did not improve following iron oxide–based contrast material adminis-
These results indicate that ferumoxtran 10 greatly reduced the number of false-negative cases but not the number of false-negative cases, in this phase III clinical trial. One potential source of false-negative cases was owing to the presence of a nodal mass conjoined with a primary tumor. This might have been a case in which the radiologist assigned a diagnosis of no nodal metastases but the pathologist observed residual nodal structures adjacent to the primary tumor and thus assigned a diagnosis of conglomerated metastatic nodes. This common problem is independent of the use of iron oxide particles and much less than that in organs and structures of the reticuloendothelial system, such as lymph nodes. As we expected, the SI measurements indicated substantial T1 and T2 relaxation mechanisms of ferumoxtran 10 in metastatic and normal nodes. As we expected, the T2 shortening effect was substantially more apparent in the normal nodes. The metastatic nodes had a greater increase in SI than the normal nodes on T1-weighted spin-echo MR images. It has been shown that ultrasmall superparamagnetic iron oxide particles are taken up by peripheral experimental gliomas in rodent models (2,3). Uptake of ferumoxtran 10 in human brain tumors has also been reported (1). Although the results of studies demonstrate iron oxide particle uptake in the cytoplasm of tumor cells, the degree of uptake is variable among brain tumors and much less than that in organs and structures of the reticuloendothelial system, such as lymph nodes. In our study, the increased SI in metastatic lymph nodes at T1-weighted MR imaging could have been due to either the uptake of iron oxide by tumor cells or a lack of relative T2 shortening effect in the metastatic nodes. The findings in this phase III clinical trial demonstrate how nodal staging can change with the use of ferumoxtran 10. Blinded clinical oncologists working together with blinded radiologists were asked to determine nodal stages on the basis of the radiologists’ reading of precontrast, postcontrast, and paired MR images. We found it interesting that the nodes diagnosed as NX at precontrast MR imaging were more definitively and accurately staged with iron oxide enhancement. These findings may have reflected the radiologists’ increased confidence in their assessments regarding the presence or absence of metastasis. More than 70% of patients who received a diagnosis of N0 positive (ie, having metastatic disease) with precontrast MR received a diagnosis of N0 (ie, no metastatic disease) with postcontrast MR, which was proved to be accurate at histopathologic correlation. This effect of ferumoxtran 10 on nodal

---

**TABLE 7**
Agreement between MR Imaging–based and Histopathologic Nodal Stages in Patients

<table>
<thead>
<tr>
<th>MR Imaging Group</th>
<th>Percentage of Patients with Nodal Stage Agreement*</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Precontrast MR Imaging</td>
<td>Paired MR Imaging</td>
</tr>
<tr>
<td>Reader 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast and paired imaging</td>
<td>23 (25/108)</td>
<td>34 (37/108)</td>
</tr>
<tr>
<td>Pre- and postcontrast imaging</td>
<td>24 (24/100)</td>
<td>…</td>
</tr>
<tr>
<td>Reader 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precontrast and paired imaging</td>
<td>33 (39/118)</td>
<td>46 (54/118)</td>
</tr>
<tr>
<td>Pre- and postcontrast imaging</td>
<td>34 (35/104)</td>
<td>…</td>
</tr>
</tbody>
</table>

* Percentages of patients for whom there was agreement between MR imaging–based nodal stage and histopathologic nodal stage. Numbers (of patients) used to calculate percentages are in parentheses.

† P values based on McNemar test results.

**TABLE 8**
Correlation of MR Imaging–based and Histopathologic Nodal Stages in Selected Patient Subgroups

<table>
<thead>
<tr>
<th>MR Imaging Nodal Stage</th>
<th>Reader 1</th>
<th>Reader 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Patients with MR-Histopathologic Stage Match*</td>
</tr>
<tr>
<td>NX at precontrast MR, but NOT N3 at paired MR</td>
<td>24</td>
<td>14 (58)</td>
</tr>
<tr>
<td>NX at precontrast MR, but N0–N3 at postcontrast MR</td>
<td>28</td>
<td>16 (57)</td>
</tr>
<tr>
<td>Not N0 at precontrast MR, but N0 at paired MR</td>
<td>20</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Not N0 at precontrast MR, but N0 at postcontrast MR</td>
<td>25</td>
<td>18 (72)</td>
</tr>
</tbody>
</table>

* Numbers of patients in whom the paired and/or postcontrast MR imaging–based nodal stage matched the histopathologic nodal stage (ie, that confirmed at surgery or biopsy). Note that 70%–80% of patients whose precontrast MR imaging nodal stage was not N0 received a correct diagnosis of nodal stage N0 with ferumoxtran 10–enhanced MR imaging. Numbers in parentheses are percentages.

---

786 - Radiology - September 2003

Anzal et al
contrast material is administered by means of drip infusion, which takes approximately 15–20 minutes to complete. The necessity of a nurse’s or physician’s presence at the time of infusion is also a subject for future discussion.

One of the limitations of the study design was the inclusion, for purposes of analysis, of patients who had undergone biopsy. Percutaneous biopsy occasionally involves sampling errors, which can cause analysis errors. Contrast-enhanced CT has been the imaging modality of choice for nodal metastasis detection in the majority of the body regions. Contrast-enhanced CT and iron oxide-enhanced MR imaging need to be compared to further evaluate what additional value this MR contrast agent has in the imaging work-up of patients with cancer.

Several minor adverse events (28%) were associated with ferumoxtran 10 administration in this study. This number was higher than those previously reported in the safety data from the phase I and II clinical trials of ferumoxtran 10 (15.31). Most adverse events began within 1 hour after contrast agent administration, were mild to moderate in severity, and resolved within 24 hours. The most frequent adverse events were headache, back pain, urticaria, and vasodilatation, which were treated with acetaminophen and/or diphenhydramine without substantial consequences. These adverse events are somewhat similar to those related to the use of ferumoxides (Feridex IV; Berlex Laboratories, Wayne, NJ), which consists of larger iron oxide particles. In the phase III trial of ferumoxides (32), back pain was the most frequent adverse reaction, occurring in 4% of the subjects. Lumbar pain has also been reported to be associated with the intravenous administration of a variety of colloids and emulsions. The exact physiologic mechanism is not well understood but is hypothesized to be occlusion of microvascular structures of the paraspinal muscles, renal artery spasm, or allergic reaction.

In conclusion, ferumoxtran 10 is a safe and effective MR imaging contrast agent for the detection of nodal metastasis. MR imaging enhanced with this iron oxide agent yielded higher sensitivity and specificity compared with objective size criteria and subjective radiologist assessment (both at precontrast MR imaging). Ferumoxtran 10 administration facilitated improved accuracy in the diagnosis of N0 disease. However, whether MR imaging enhanced with this agent can facilitate changes in treatment management and help improve the clinical outcome of patients with cancer by enabling better characterization of nodal status remains to be determined.

Acknowledgment: The authors acknowledge the participation of Thomas McCauley, MD, of Yale University, as a blinded reader in the described phase III clinical trial.

Authors: Yoshimi Anzai, MD, Catherine W. Piccoli, MD, Eric K. Outwater, MD, William Stanford, MD, David A. Bluemke, MD, PhD, Pamela Nurnberg, MD, Sanjay Saini, MD, Kenneth R. Maravilla, MD, David E. Feldman, MD, Udo P. Schmiedl, MD, James A. Brunberg, MD, Isaac R. Francis, MD, Steven E. Harms, MD, Peter M. Som, MD, Clare M. Tempany, MD, Robert D. Harris, MD, Judith K. Amorosa, MD, Arun N. Sukerker, MD, Robert J. Herfkens, MD, Patricia A. Hindgs, MD, Evan S. Siegelman, MD, Suresh K. Muhkerji, MD, Vijay M. Rao, MD, Patricia J. Mergo, MD, Pablo R. Ros, MD, MPHe, Peter L. Davis, MD, Joseph F. Mammone, MD, Jeffrey J. Brown, MD, Paula Jacobs, PhD, Marie R. Morris, MS, Laurie A. Loewer, MD, Kevin R. Fox, MD, Susan M. Campos, MD, Far Sean Leong, MD, Terese M. Weber, MD, David M. Yousef, MD.

Author affiliations: University of Washington School of Medicine, Seattle (T.A., K.R.M., U.P.S.); Thomas Jefferson University Hospital, Philadelphia, Pa (C.W.P., E.K.O., V.M.R.); University of Iowa Hospitals and Clinics, Iowa City (W.S.); Johns Hopkins Medical Institutes, Baltimore, Md (D.A.B., D.M.Y.); University of Texas Southwestern Medical Center, Dallas (P.N.); Massachusetts General Hospital, Boston (S.S.); Medical University of South Carolina, Charleston (D.E.F.); University of Michigan Medical Center, Ann Arbor (Y.A., J.A.B., I.R.F., S.K.M.); University of Arkansas for Medical Sciences, Little Rock (S.E.H.); Mount Sinai Hospital, New York (P.M.S.); Brigham and Women's Hospital, Boston, Mass (C.M.T., P.R.R.); Dartmouth-Hitchcock Medical Center, Lebanon, NH (R.D.H.); Robert Wood Johnson University Hospital, New Brunswick, NJ (J.K.A.); Illinois Masonic Medical Center, Chicago (A.N.S.); Stanford University Medical Center, Calif (R.I.H.); Emory University School of Medicine, Atlanta, Ga (P.A.H.); University of Pennsylvania Medical Center, Philadelphia (E.S.S., K.R.F.); University of North Carolina School of Medicine, Chapel Hill (S.K.M.); University of Florida College of Medicine, Gainesville (P.I.M., P.R.R.); University of Pittsburgh Medical Center, Pittsburgh (P.I., P.R.R.); Cooper University Medical Center, Camden, NJ (J.F.M.); Mallinckrodt Institute of Radiology, Washington University School of Medicine, St Louis, Mo (J.J.B.); Advanced Magnetics, Cambridge, Mass (P.J., M.R.M.); Bracco Diagnostics, Princeton, NJ (M.R.R.); Gillette Center for Women's Cancers, Dana-Farber Cancer Institute, Boston, Mass (S.M.C.); Lahey Clinic, Burlington, Mass (F.S.L.); and University of Alabama at Birmingham (T.M.W.).

Y.A., S.E.H., and E.S.S. have served as consultants to Advanced Magnetics in the past; P.R.R. is a consultant to Advanced Magnetics; P.I. is an employee of and minor stockholder in Advanced Magnetics; and M.R.M. was an employee of Advanced Magnetics at the time of this study.

Author contributions: Guarantors of integrity of entire study, Y.A., P.J., F.S.L.; study concepts, S.S.,...
References
viral-sized iron oxide particles ferromox-
ides and ferumoxtran 10 with a gadolin-
ium chelate in imaging intracranial tu-
2. Zimmer C, Weissleder R, Pros K, Bog-
danova A, Wright SC, Enoch WS. MR im-
diology 2000; 214:568-574.
efficiency lymphotrophic agent. Radiol-
mall superparamagnetic iron oxide: an intravascular contrast agent for assessing lymph nodes with MR imaging. Radiol-
ogy 1990; 175:494-498.
7. Lee AS, Weissleder R, Brady TJ, Witten-
8. Guimaraes R, Clement O, Bittoun J, Car-
non F, Faja G. MR lymphography with superparamagnetic iron nanoparticles in
rats: pathologic basis for contrast en-
9. Hamn B, Taupitz M, Huzs mann P, Wag-
ner S, Wolf KJ. MR lymphography with iron oxide particles: dose-response studies and pulse sequence optimization in rab-
bits. AJR Am J Roentgenol 1992; 158:183-
190.
Sj, Koutcher JA, Castellano RA. Characteriza-
tion of reactive versus tumor-bearing lymph
nodes with interstitial magnetic resonance
R, Weimann HJ. Investigation of mech-
lymphography using iron oxide nanopar-
ticles in rats: pharmacokinetics in the
lymphatic system after intravenous injec-
875-881.
MA. Ferumoxtran-10, a superparamag-
netic iron oxide as a magnetic resonance
enhancement agent for imaging lymph
15. Bengele HH, Palmacci S, Rogers J, Jung
CW, Genshaw J, Josephson L. Riodistrib-
ution of an ultrasmall superparamag-
netic iron oxide colloid, BMS 180549, by
different routes of administration. Mag-
tran-coated superparamagnetic iron oxide
for detection of lymph node metastases
in patients with head and neck can-
node metastases: safety and effectiveness of MR imaging with ultrasmall superpara-
magnetic iron oxide particles—initial clini-
ical experience. Radiology 1998; 207:
799-809.
19. Hanisghinhi MG, Saini S, Slater GJ, Schnall MD, Rifkin MD. MR imaging of pelvic lymph nodes in primary pelvic carci-
noma with ultrasmall superparamag-
netic iron oxide (Combidx): preliminary
observations. J Magn Reson Imaging 1997;
7:161-163.
20. Hanisghinhi MG, Saini S, Weissleder R,
et al. MR lymphangiography using ultra-
small superparamagnetic iron oxide in
patients with primary abdominal and pelvic malignancies: radiographic-pathol-
21. Hoffman HT, Quets J, Toshiaki T, et al. Func-
tional magnetic resonance imaging using iron oxide particles in characteriz-
ing head and neck adenopathy. Laryngo-
small superparamagnetic iron oxide in the evaluation of mediastinal lymph
nodes in patients with primary lung car-
cinoma. J Magn Reson Imaging 1999; 10:
468-473.
23. Pannu HK, Wang KP, Borman TL, Blumenke DA. MR imaging of mediastinal lymph nodes: evaluation using a super-
25. Hosal AS, Carrau RL, Johnson JT, Myers
EN. Selective neck dissection in the man-
agement of the clinically node-negative
26. Johnson JT. Selective neck dissection in
patients with squamous cell carcinoma of the upper respiratory and digestive tracts: a lack of adequate data. Arch Otolaryngol
27. van den Brekel MW, Castellinas JA, Snow
28. Dillon WP. Cervical nodal metastases: an-
other look at size criteria. AJNR Am J Neu-
29. Curtin HD, Ishwaran H, Mancuso AA, Dalley RW, Caudry DJ, McNeill BJ. Com-
parison of CT and MR imaging in staging of neck metastases. Radiology 1998; 207:
123-130.
31. Sharma R, Saini S, Ros PR, et al. Safety profile of ultrasmall superparamagnetic iron oxide ferumoxtran 10: phase II clini-
32. Ros PR, Freeny PC, Harms SE, et al. He-
patic MR imaging with ferumoxides: a multicenter clinical trial of the safety and