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Evaluation of retroperitoneal and pelvic lymph node metastases with MRI and MR lymphangiography

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Abstract
Local, regional lymph node involvement is an essential prognostic factor and an important determinant of treatment choices for patients with retroperitoneal and pelvic cancer. Current cross-sectional imaging modalities, including computed tomography and magnetic resonance (MR) imaging, use the nonspecific criterion of size and are limited in their ability to differentiate benign from malignant lymph nodes. MR lymphography is a promising imaging modality in differentiating benign from metastatic lymph nodes and provides information on lymph node morphology and function. Ultrasmall superparamagnetic iron oxide (USPIO) particles with a long plasma circulation time are suitable as an MR contrast agent for intravenous MR lymphography. They are taken up by macrophages in normally functioning nodes and reduce the signal intensity of tissue in which they accumulate because of T2 and susceptibility effects of iron oxide. In metastatic nodes, macrophages are replaced by cancer cells, which lack reticuloendothelial activity and cannot take up USPIO. The main mechanisms that might explain a heterogeneous node appearance after USPIO injection are discussed. In published reports, USPIO has shown high degrees of sensitivity and specificity for characterizing lymph nodes in cancer patients. We review the development of USPIO compounds, their imaging characteristics, and our clinical experience.

Key words: Lymphatic system, magnetic resonance—Pelvic neoplasms, magnetic resonance—Retroperitoneal neoplasms, magnetic resonance—Lymphatic system, neoplasms—Magnetic resonance, contrast enhancement—Magnetic resonance, metastases.

Local, regional lymph node involvement is a key prognostic factor and an important determinant of treatment choices for patients with retroperitoneal and pelvic cancers. In particular, it is a highly contributive element in the selection of the most appropriate treatment modality, planning surgery or radiation therapy, and monitoring the response to therapy. With currently used cross-sectional imaging modalities, including computed tomography (CT) and magnetic resonance imaging (MRI), the detection of node metastases is largely based on the nonspecific criterion of size, and there are no definitive criteria for differentiating metastatic from benign nodes. Therefore, tissue-specific imaging technology is essential to improve the detection of node metastases. Ultrasmall superparamagnetic iron oxide (USPIO) is a novel contrast agent developed specifically for magnetic resonance (MR) lymphography [1–9]. Iron oxide particles are taken up by the macrophages in normal functioning nodes and provide information on lymph node morphology and function.

After physical examination, CT and MRI are currently the most frequently used methods for assessing lymph node status in cancer staging [10–14]. Ultrasonography (US) provides less contrast than CT and MRI and is more operator dependent. The only CT and MRI criterion that is generally accepted for the evaluation of node metastases is the size of the node, and it is assumed that large nodes are metastatic and small nodes are benign. However, false-negative findings for normal-sized metastatic nodes limit staging capabilities. Another limitation is that US, CT, and unenhanced MRI cannot distinguish metastatic nodes from nonmetastatic reactive nodes. Borderline-sized nodes remain indeterminate with these techniques. Other diagnostic criteria with CT and MRI include internal lymph node architecture and lymph node borders. A central zone of necrosis giving a heterogeneous appearance is rarely found in metastatic retroperitoneal and pelvic nodes and can be observed in infectious diseases, including tuberculosis. Extracapsular spread has a poor prognosis and is usually associated with bulky nodes. Surgical lymph node dissection allows accurate assessment but is invasive; published data on the accuracy

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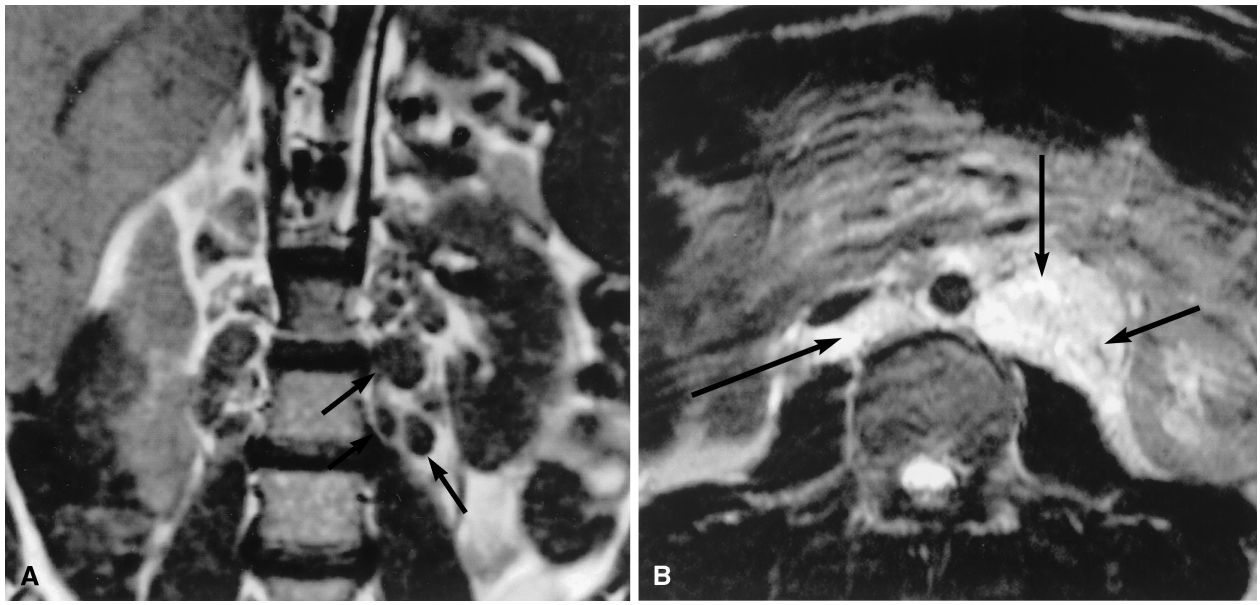

Fig. 1. A Numerous retroperitoneal lymph nodes (*arrows*) in a patient with tuberculosis, demonstrated by coronal T1-weighted SE (500/20) image. **B** Those retroperitoneal lymph nodes have a hyperintense and heterogeneous aspect on the T2-weighted FSE (8571/26) image.

of histologic analysis of intraoperative frozen sections of nodes conflict, and rates of false-negative results as high as 33% have been reported for pelvic node analyses [15]. The disadvantages of size discrimination with current cross-sectional imaging techniques and the associated morbidity and length of surgical procedures have prompted extensive research aimed at developing tissue-specific imaging methods, including USPIO-enhanced MR lymphography. USPIO as a contrast agent is still in the experimental stage. Our purpose is to review the detection of node metastases with CT and unenhanced MRI and the development of USPIO compounds, including their physicochemical structure, imaging characteristics, and initial clinical experience in patients with retroperitoneal and pelvic cancer.

Detection of nodal metastases with CT and unenhanced MRI

CT and MRI are two noninvasive imaging modalities currently used to detect nodal metastases. The diagnostic accuracy of MRI for nodal metastases is currently no better than that of CT because both methods use the same morphologic criterion, namely the size of the node, to distinguish between normal and metastatic lymph nodes [11–13, 16]. Signal intensities (SIs) of malignant nodes do not differ from those of benign nodes on T1- and T2-weighted images [17] (Fig. 1). T1 and T2 relaxation times of metastatic and normal nodes overlap considerably [17]. The reported sensitivity and specificity depend on technical parameters and diagnostic criteria. Optimization of the spatial resolution is essential to visualize normal-sized nodes, with a maximum diameter rarely exceeding 8 mm. Phased-array coils provide high-resolution MR images. The choice of the following parameters is crucial: field-of-view and section thickness for CT and MRI, matrix size, sequence, and number of excitations for MRI. CT and unenhanced MRI use a nonspecific size criterion to distinguish between normal and malignant lymph nodes, and the relative sensitivity and specificity can be adjusted by changing the threshold size. The cutoff for pelvic nodes varies in the literature, ranging from 0.6 to 1.5 cm [14], with the most generally accepted value being 0.8 cm. For retroperitoneal nodes, the threshold size varies from 1.0 to 1.5 cm [18]. Most normal nodes have an oval shape, whereas enlarged nodes appear round. This distinction is important, but not all reports have stated whether the maximal or the minimal diameter was used. In a series of 136 patients with uterine carcinoma, Kim et al. [13] found that the best criterion was the minimal axial diameter, with a cutoff of 10 mm for pelvic nodes. They reported 62.2% sensitivity and 97.9% specificity for unenhanced MRI. Reported accuracy rates differ, from 67% to 93% for CT [10, 19] and from 77% to 93% for MRI [13, 14, 20]. Based on a series of 134 consecutive patients with prostate or urinary bladder carcinoma, Jager et al. [14] reported an accuracy of 90% when they used a three-dimensional T1-weighted magnetization-prepared rapid gradient recalled echo (GRE) sequence, and they detected nodes with diameters as small as 3 mm. It is generally agreed that it is easier to distinguish lymph nodes from vessels with unenhanced MRI than with iodine-enhanced CT, especially in the pelvis.

Fine-needle aspiration biopsy (FNAB) is an invasive imaging modality. It is generally performed under CT guidance [10], but is also feasible under lymphangiographic [21], US [22], and MR [14] guidance. The reported sensitivities vary from 50% to 100%, depending on the size of the biopsy needle, the numbers of passages and biopsy sites, and the criteria used to select patients. FNAB is used to confirm metastatic involvement in enlarged and borderline lymph nodes. However, it is time consuming and expensive. The complication rate ranges from 0.05% to 2.5%. The current trend is to replace FNAB with laparoscopic or surgical lymph node dissection.

Physicochemical structure of USPIO compounds

Weissleder and his colleagues at Massachusetts General Hospital and Advanced Magnetics Inc. have played a key role in the development of USPIO contrast agents [1, 2, 9, 23, 24], including chemical, pharmaceutical, biological, and clinical aspects, and have contributed extensively to their preparations. Use of these agents for MR lymphography is still in the experimental stage. They are composed of iron oxide crystals coated with polymers to avoid uncontrolled aggregation of the magnetic crystals. USPIO salt solutions are prepared by coprecipitation of magnetite in the presence of a coating material. Electron microscopy shows that they contain an electron-dense crystal core consisting of multiple crystal aggregates covered with low-molecular-weight dextran. The preparation method determines the number of crystals per particle, the size of each individual iron oxide crystal, and the dispersion of the crystals within the carrier particle. Overall particle size depends on the core size and its surface coating. With AMI-227 (Sinerem, Laboratoire Guerbet, Aulnay-sous-Bois, France; Combidex, Advanced Magnetics, Cambridge, MA, USA), the mean particle size is 20 nm. These nanoparticles are composed of an iron oxide crystal core of 4.3–6.0 nm covered by low-molecular-weight dextran. Lowering the dextran:iron ratio increases the iron oxide core size and the r_2 and r_2:r_1 ratio. The T1 and T2 relaxivities are, respectively, 2.3×10^4 M/s and 5.3×10^4 M/s (20 MHz, 39°C) in 0.5% agar.

Administration and tolerability of USPIO compounds

Sinerem and Combidex are provided as lyophilized powders consisting of biodegradable USPIO particles, dextran, and dihydrated sodium citrate. They are reconstituted by mixing with 9.7 mL of 0.9% normal saline solution, yielding dark reddish-brown aqueous solutions, with an osmolality of 365 mOsm/kg. The doses used in clinical trials range between 1.7 and 2.6 mg of iron per kilogram of body weight, i.e., 0.085 and 0.13 mL/kg of reconstituted solution. The appropriate drug volume is then diluted in 100 mL of 0.9% saline and infused intravenously (IV) through a syringe with a 5-μm filter, with a recommended infusion time of 25–35 min.

Clinical tolerability is generally excellent [5–7, 23, 24]. However, side effects may include lumbar pain, rash, a transient decrease of blood pressure, and arrhythmia. As with other particulate agents, lumbar pain has been reported, at an overall frequency of 3–4%, but its precise cause is unclear [25]. It usually subsides spontaneously and allows resumption of contrast medium administration. USPIO particles do not significantly modify laboratory parameters, except for serum iron and ferritin levels [7]. The iron oxides are biodegraded in phagolysosomes within macrophages. The iron oxide core is incorporated first into the plasma iron pool and then into hemoglobin.

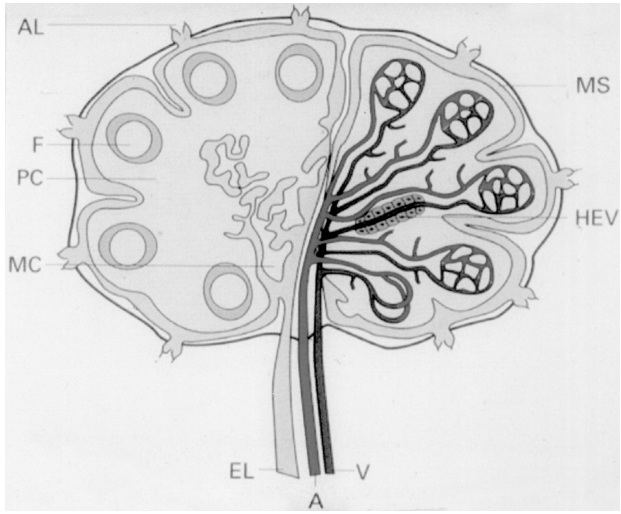

Fig. 2. Schematic drawing of a normal lymph node. The right half of the node shows the vascular supply and the left half shows the lymphatic supply. The node is surrounded by a fibrous capsule (solid line). A, nodal artery; AL, afferent lymphatic; EL, efferent lymphatic; F, lymphoid follicle with germinal center; HEV, high endothelial venules; MC, medullary cord; MS, marginal sinus; PC, paracortex; V, nodal vein.

Lymph node anatomy and physiology

Lymph nodes are solitary structures (Fig. 2) surrounded by thick fibrous capsules. Several afferent lymphatic vessels pass through the capsule and drain into marginal sinuses [26]. Lymph nodes contain a stromal trabecular network. The node parenchyma is divided into poorly defined cortical (paracortical and follicular) and medullary regions. The cortex is made up of lymphoid follicles, which consist of a germinal center containing B lymphocytes, reticulum cells, and histiocytes, and a peripheral

Table 1. Mean ± standard deviation percentages of the USPIO dose injected per gram of tissue according to the route of administration: comparative distribution 48 h later[a]

Tissue	Intravenous	Subcutaneous	Intra-arterial[a]
Liver	1.1 ± 0.2	0.3 ± 0.0	0.5 ± 0.4
Spleen	9.9 ± 1.2	0.7 ± 0.4	19.8 ± 6.1
Kidney	0.8 ± 0.1	0.6 ± 0.1	0.4 ± 0.1
Right popliteal nodes	8.3 ± 0.3	302 ± 246	32.9 ± 10
Left popliteal nodes	8.0 ± 0.2	0.32 ± 0.1	0.75 ± 0.4
Other nodes	47.9 ± 5.6	85.4 ± 76	141 ± 6.8

[a] Reprinted with permission from Weissleder et al. [8]
[b] Intra-arterial injection after histamine administration

area (paracortex) populated by T lymphocytes. The paracortex is densely cellular and extends from the capsule to the corticomedullary junction. Lymph drains from the afferent lymphatic vessels into the subcapsular (or marginal) sinuses. It then circulates through a complex cortical and medullary sinus network and exits through the efferent vessel. The lymph node hilus can be seen on the lower surface of the node through which the efferent lymphatic and the nodal artery and vein enter and exit, respectively. The nodal artery gives rise to a rich microvascular network. Metastatic foci mainly invade the subcapsular sinus and the medullary sinus regions. Nodal macrophages line the sinus system and are found mostly in the medullary cords.

Nodal uptake of USPIO after injection by different routes

Nodal particle uptake is highly dependent on the injection route. Weissleder et al. [8] and Bengele et al. [27] showed distinct percentages of uptake of the injected dose in rats as a function of the administration route (Table 1). Those results showed a symmetrical accumulation of USPIO in the right and left popliteal nodes after IV injection but highly asymmetrical accumulation after subcutaneous and intra-arterial injections, with very low incorporation by contralateral nodes. As expected, ipsilateral popliteal lymp node uptake was highest after subcutaneous injection because of the lymphatic drainage pattern, whereas only a minor percentage of USPIO reached the systemic circulation and, ultimately, the liver and spleen. Intra-arterial injection after histamine administration increased capillary permeability and thus resulted in more USPIO accumulation in ipsilateral nodes compared with IV injection.

Enhancement of normal nodes after IV administration of USPIO compounds

After IV infusion, USPIO particles are distributed to the lymph nodes via two distinct pathways, as first described by Weissleder et al [1]. The first is direct transcapillary passage through venules into the medullary sinuses within the lymph node, followed by phagocytosis. The second is nonselective endothelial transcytosis into the interstitial spaces throughout the body, followed by uptake of USPIO particles by draining lymphatic vessels and their transport to regional lymph nodes via afferent lymphatic channels. In normally functioning lymphatic tissue, USPIO particles are endocytosed by macrophages and cause a decrease of the SI by their magnetic susceptibility effect and T2-shortening effects. Clustering of USPIO particles inside macrophages results in a predominant susceptibility effect that reduces the nodal T2 by creating microscopic magnetic field gradients, with subsequent diffusion and irreversible loss of phase coherence [28]. In addition, the large magnetic moment of USPIO particles generates local field inhomogeneities, thereby promoting the dephasing of proton spins and accelerating transverse relaxation. Thus iron oxide nanoparticles have been used as negative contrast agents because their active uptake by normal lymph nodes results in a homogeneous decrease of SI on T2- and T2*-weighted images (Fig. 3).

The degree of nodal negative enhancement depends on dose and the pulse sequences used for MRI. In a study comparing four doses (1.1, 1.7, 2.6, and 3.4 mg Fe^{2+}/kg) in 24 healthy subjects, Hudgins et al. [24] found that the decrease of normal lymph node SI on postcontrast images was more pronounced with 2.6 than with 1.7 mg Fe^{2+}/kg. In their study on head and neck lymph nodes, Anzai et al. [6] found that AMI-227 at a dose of 1.7 mg Fe^{2+}/kg provided an 87% SI decrease on GRE images and a 75% SI decrease on T2-weighted spin echo (SE) images. In patients with urologic or pelvic cancers receiving AMI-227 at a dose of 1.7 mg Fe^{2+}/kg, we found a significant SI decrease on postcontrast T2- and T2*-weighted images in 16 of 21 (76%) benign nodes [7]. For five (24%) of the 21 normal nodes, the SI was unchanged on postcontrast T2- and T2*-weighted images relative to the SI on precontrast images [7]. This observation suggests that the 1.7 mg Fe^{2+}/kg dose of contrast agent was insufficient to induce the expected postcontrast SI decrease on T2- and T2*-weighted images. Thus, the dose of 2.6 mg Fe^{2+}/kg is now recommended. Because of their decreased SI, normal nodes are better visualized on postcontrast images, and enhanced MR lymphography usually detects more nodes than plain MRI.

In that study, we also found that the mean ± standard deviation of the SI ratio (post–AMI-227:pre–AMI-227) of benign nodes (0.28 ± 0.17) was significantly lower than that of metastatic nodes (0.97 ± 0.18) on the GRE T2*-weighted sequence. The SIs of the vast majority of malignant nodes were almost the same after USPIO administration on the T2*- and T2-weighted sequences used (Fig. 4). Choosing the most appropriate pulse sequences is essential for the success of MR lymphography. A constant homogeneous signal loss in normal nodes is

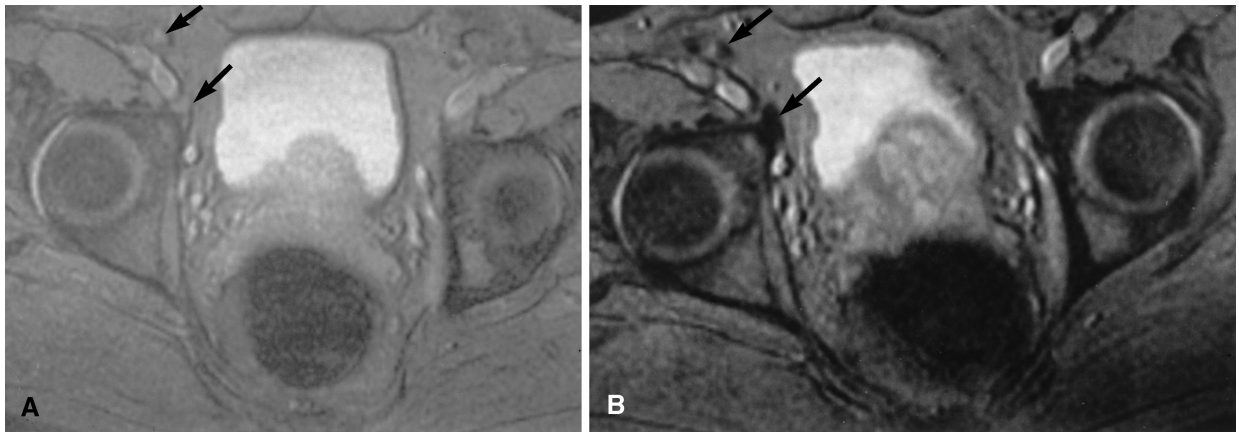

Fig. 3. A Benign external iliac nodes (*arrows*) in a patient with prostate carcinoma demonstrated on precontrast T2*-weighted GRE (500/18, 15° flip angle) image. **B** Postcontrast T2*-weighted GRE (500/18, 15° flip angle) image shows a homogeneous decrease of the SI within the nodes (*arrows*). Reprinted with permission from Bellin et al. [7].

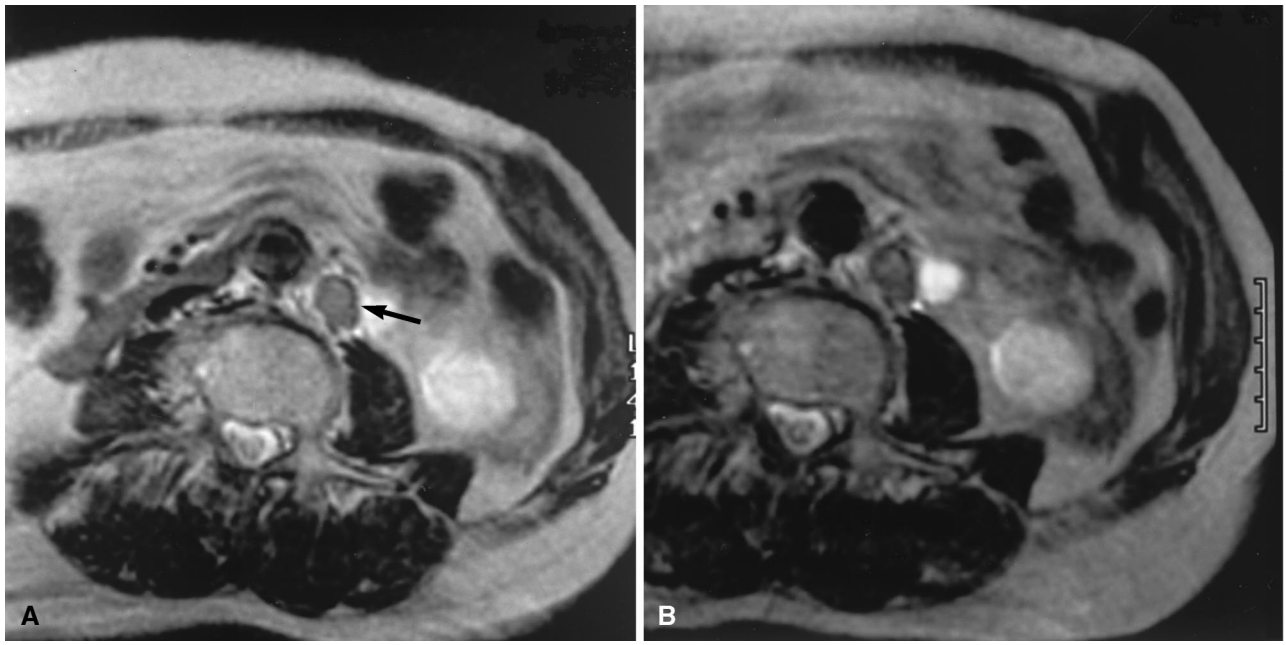

Fig. 4. Metastatic retroperitoneal nodes in a patient with transitional cell carcinoma. **A** Precontrast T2-weighted FSE (4000/119) image demonstrates a paraaortic node (*arrow*). **B** Postcontrast T2-weighted FSE (4000/119) image shows no significant modification of the SI of the node.

probably more evident on GRE T2*-weighted images than on SE T2-weighted images because GRE imaging is more sensitive to the magnetic susceptibility effects of USPIO uptake. However, the overall quality and spatial resolution of GRE images are poorer than those of T2-weighted fast spin echo (FSE) and SE images in most anatomic regions of the human body. Thus, heavily T2-weighted FSE imaging appears more suitable than GRE imaging for MR lymphography [7, 29]. Heavily T2-weighted FSE images also should be preferred to conventional SE images because they have a better inherent signal:noise ratio. In addition, Tanoura et al. [4] described a "blooming effect" on the GRE images of animals that had received high doses of USPIO ($>$2.6 mg Fe/kg). This blooming effect could reflect oversaturation and magnetic susceptibility effects and could lead to an overestimation of node size.

USPIO particles can increase SI (positive enhancement) on T1-weighted images in the following two situations: low local concentrations and nonclustering of USPIO particles. This enhancement has been reported in tumor tissue with leakage of USPIO particles (Fig. 5),

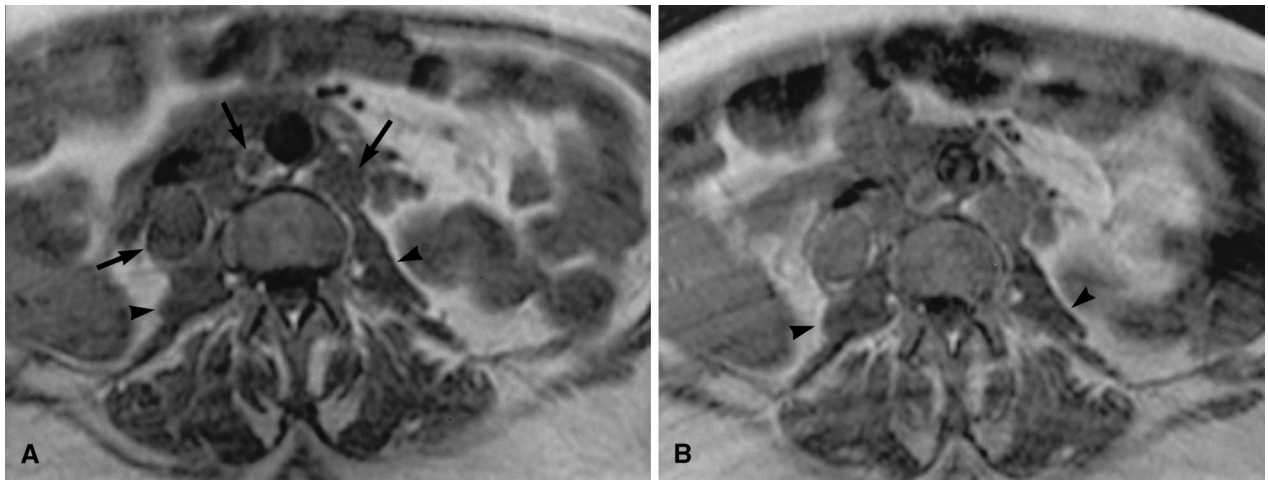

Fig. 5. Metastatic retroperitoneal nodes in a patient with transitional cell carcinoma. **A** Precontrast SE T1-weighted image (400/11) shows enlarged retroperitoneal nodes (*arrows*) with an SI comparable to that of the adjacent psoas muscles (*arrowheads*). **B** Postcontrast SE T1-weighted image (400/11) demonstrates postcontrast brightening of the nodes (positive T1 enhancement), which are hyperintense relative to the psoas muscles (*arrowheads*). Reprinted with permission from Bellin et al. [7].

probably resulting from increased capillary permeability and increased diffusion [3, 29, 30], but has not been observed in normal nodes.

After IV infusion, a small fraction of the injected dose accumulates in the spleen, liver, bone marrow, and kidney and may be responsible for a decrease of the SI of these organs on T2- and T2*-weighted images [7, 29].

The temporal window for imaging after IV infusion is wide, with the optimal time being 24 to 36 h after injection.

Detection of nodal metastases with USPIO-enhanced MRI

In the late 1980s, USPIO particles were developed to improve the detection of nodal metastases and enable differentiation of benign from metastatic nodes. Several experimental studies have shown that benign and metastatic lymph nodes have different enhancement patterns after IV injection of USPIO [1, 3, 4, 8]. Normal nodes actively incorporate the particles (Fig. 3), whereas metastatic nodes show no uptake (Fig. 4). It was initially assumed that the postcontrast signal of benign nodes on T2- and T2*-weighted images was decreased because of the magnetic susceptibility and T2 shortening effects of iron deposition, whereas metastatic nodes remained unchanged (Fig. 4). However, things became more complicated when Lee et al. [2] who used in vitro MRI at 9.4 T showed the heterogeneous uptake of USPIO particles inside normal nodes and that they were localized predominantly inside the peripheral sinusoidal macrophages. It has also been shown in animal experiments [3] and humans [31–34] that the normal tissue remaining in a metastatic node can take up particles, and thus that such a node can appear heterogeneous on postcontrast images. On T1-weighted images, postcontrast brightening in metastatic nodes has been demonstrated in animal experiments [3] and humans (Fig. 5) [7] and corresponds to altered capillary permeability in the tumor [30].

All published studies on humans have shown a trend toward improved diagnostic efficacy for differentiating benign from metastatic nodes with USPIO-enhanced MRI (Table 2). The first multicenter phase 2 clinical trial was published in 1994 by Anzai et al. [5]. Eleven patients with head and neck cancer were studied with MRI before and after administration of USPIO at a dose of 1.7 mg Fe^{2+}/kg. Forty of the 42 histologically proven metastatic nodes and 41 of 49 benign nodes were detected, yielding 95% sensitivity and 84% specificity. In addition, 13 of 14 normal-sized metastatic nodes were detected with enhanced MR lymphography. Concerning pelvic nodes, Harisinghani et al. reported their initial experience in six patients in 1997 [31], followed in 1999 by the results of phase 2 and 3 trials that enrolled 19 patients [9]. The results of both studies showed that the mean postcontrast SI on T2-weighted images for benign nodes was decreased, whereas the mean SI for malignant nodes was relatively unchanged. In the second study, the nodal SI was lower in 20 of 20 benign nodes and two malignant nodes. However, the decrease in the latter was heterogeneous as opposed to the homogeneous SI diminution in benign nodes.

The results of a phase 2 European trial, reported in 1998 [7], were based on 30 patients with urologic or pelvic cancer who received USPIO at a dose of 1.7 mg

Table 2. Summary of published clinical trials

Reference	*n* Patients	Region	USPIO dose (mg Fe/kg)	Tesla	%Sensitivity	%Specificity
5	11/12	ENT/head and neck	1.7	1.5	95	84
7	30	Pelvis, retroperitoneum	1.7	0.5–1.5	100	76
31	6	Pelvis	1.7	1.5	89	50
9	19	Pelvis + abdomen	1.7/2.6	1.5	ND	ND
34	35	Breast	2.6	1–1.5	64	94
33	50	Pelvis + abdomen	2.6	1.5	82	94

ND, not determined; USPIO, ultrasmall superparamagnetic iron oxide

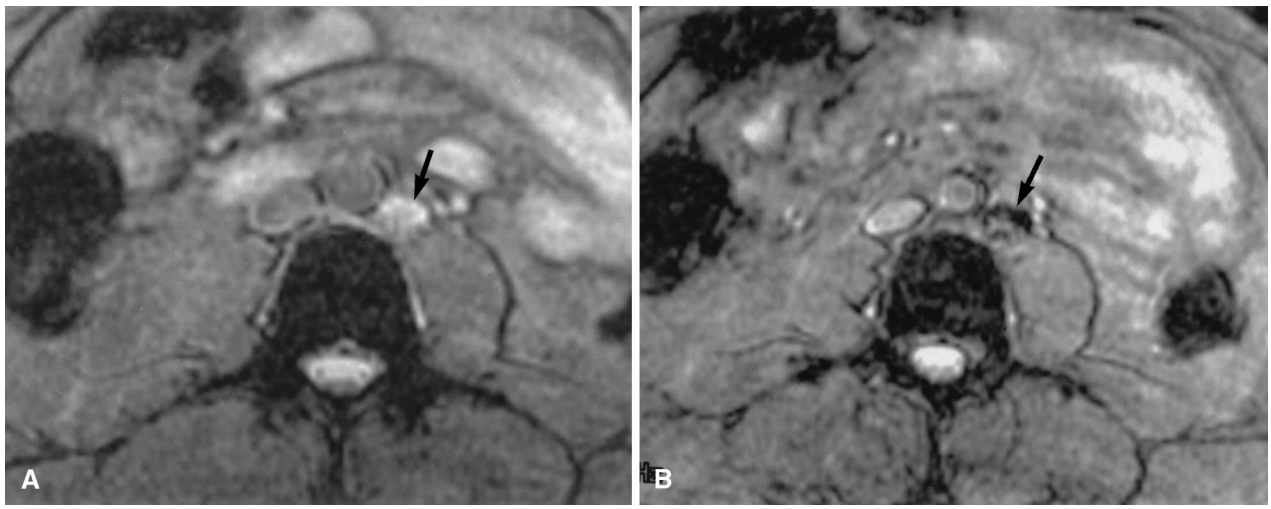

Fig. 6. Reactive node. **A** Precontrast GRE T2*-weighted image (300/15/15°) shows a moderately enlarged paraaortic node (*arrow*) with high SI. **B** Postcontrast GRE T2*-weighted image (300/15/15°) demonstrates partial enhancement at the anterior part of the node (*arrow*). Reprinted with permission from Bellin et al. [7].

Fe/kg. None of the metastatic nodes showed decreased SI, whereas nine of 27 (33%) metastatic nodes showed increased SI on postcontrast T1-weighted images that could be attributed to leakage of USPIO particles into tumor tissue. Of 21 benign nodes, 16 showed postcontrast SI decreases, indicating active USPIO uptake. The overall sensitivity was 100% and the specificity was 80%. The peak SI ratio distribution for metastatic nodes was significantly higher than that of benign nodes on GRE T2*-weighted images.

The results of European and American phase 3 trials were reported at the Congress of the Radiological Society of North America in 1999 [32–34]. Those results confirmed the potential of USPIO for differentiating metastatic from benign nodes in patients with pelvic cancer. Patients received USPIO at a dose of 2.6 mg Fe/kg and underwent surgery including lymphadenectomy within 10 days of the MR examination. Phased-array coils were used in all cases. For pelvic node evaluation, sensitivity and specificity of Sinerem-enhanced MRI versus plain MRI were, respectively, 82% and 94% versus 76% and 85% [33].

In those studies, false-negative results were attributed mainly to small foci of metastatic tissue in normal-sized nodes [32–35]. Therefore, optimization of the spatial resolution is crucial for the success of enhanced MRI [35]. False-positive results include benign reactive nodes with follicular hyperplasia (Fig. 6). Most reactive nodes are filled with lymphocytes but contain few macrophages and thus exhibit low phagocytic activity and low USPIO uptake [1, 7, 29]. Thus, USPIO incorporation into reactive nodes appears to depend on the abundance of macrophages. Localized nodal lipomatosis may account for the heterogeneous aspect of the node and generate a false-positive result. In initial studies, an insufficient dose of USPIO also may have been responsible for false-positive interpretations.

Future directions

Several issues remain to be addressed:

1. What is the spectrum of hyperplastic and inflammatory

lymph node aspects on postcontrast MR images? Does it correlate with histologic findings?
2. What is the threshold for detecting minimal disease in normal-sized nodes? Is quantification of nodal USPIO accumulation valuable in such cases?
3. Can USPIO compounds be used as novel therapeutic lymphotropic drug carriers?

In conclusion, USPIO-enhanced MRI appears to be a useful modality for characterizing lymph nodes in patients with primary abdominal or pelvic malignancies on the basis of enhancement patterns. Metastases in normal-sized nodes can be detected with high-resolution MRI, and the sensitivity and specificity of USPIO-enhanced MRI are better than those for precontrast MRI. However, additional studies are needed to determine the clinical indications of MR lymphography and its cost effectiveness.

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