

# Gadofluorine M

1

. 2 . . . . 3 . 2 . 2 . 2 . 2 . 2

: MR Gadofluorine M

: 31 10 , 16

, 5 .

VX2

. 1.5 T MR T1, T2

SPGR Gadofluorine M (5  $\mu$ mol/mL 4 mL) 가

SPGR 15, 30, 60, 90 . MR

, 3

가 가 가

: 26 MR 2

24 9 46

, 15 71 ( 28 )

117 5 mm 102

24 MR 5 mm 101 (99.1%)

, 3

97.6% (82/84), 98.2% (215/219), 95.3% (82/86), 99.1% (215/217) ( $p <$

0.05).

: Gadofluorine M MR

.

(positron emission tomography,

PET) 20% 90%

(2, 5, 8, 9).

(CT), (MR)

가 가

, 가 (8), 가

(10).

(sentinel lymph node biopsy)

(4, 11, 12),

1

2

3

(0420080 - 1)

2006 1 7

2006 5 29

가

MR

가

T2

: Gadofluorine M

ultrasmall superparamagnetic iron oxide(USPIO)  
(13 - 18) T1 gadolinium chelate  
(19 - 27). Gadolinium chelate

, T1 , T1

, T2 USPIO  
(21, 23, 25).  
1 - 2  
(21, 23 - 25,

27).

MR ,  
(20,

26), MR  
가  
Gadofluorine (paramagnetic) T1  
Gadofluorine M (Schering, Berlin, Germany) (27)  
MR ,

( )  
2.0 - 2.5 kg (New Zealand

white rabbit) 31  
31 10  
, 16 , 5  
10  
5 1 cc  
1 2 ( 1 3 ) , 5  
1cc  
, 1 - 2 MR (28).  
VX2 21

1 cc , 3 - 5 MR (21, 27, 28).

MR .

MR  
Ketamine hydrochloride (Ketalar; Yuhan Yanghang, Seoul,  
Korea) xylazine hydrochloride (Rompun; Bayer Korea,  
Seoul, Korea) 1:1 1 mL/kg

1.5 T MR (Signa, GE Medical Systems, Milwaukee,  
WI, U.S.A.) (spin echo)

T1 (TR/TE: 400/12 msec), fast spin  
echo T2 (TR/TE: 3500/84 msec)  
Gadofluorine M fast spoiled gradient -  
recalled (SPGR) (TR/TE/flip angle: 19.7/1.8 msec/30 °)  
16 × 16 cm

, 2 mm  
, 5 µmol/mL Gadofluorine M 4  
mL (5 µmol/kg) 가  
1 15 , 30 , 60 , 90 SPGR  
가

MR  
가 31 MR  
가 , T1,  
T2 Gadofluorine M SPGR

SNR) (signal to noise ratio,  
3 - 10 mm ( 4 mm) (region  
of interest, ROI) ROI  
( $SNR = SI_{LN} / SI_{NOISE}$ ),

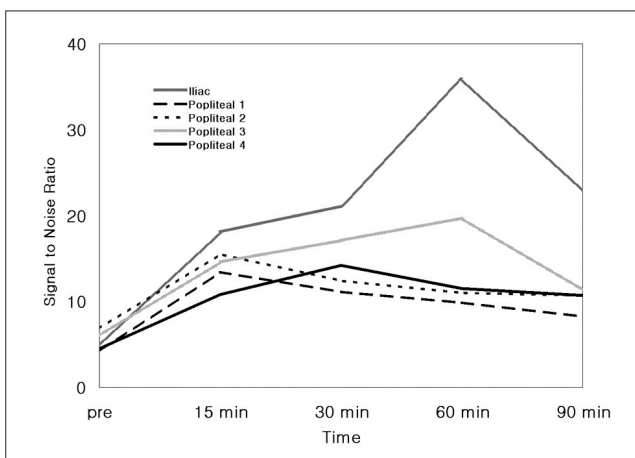
ROI  
Gadofluorine M T1, T2  
SPGR 3

, 가  
, 가  
가  
(27).  
1.5 cm 가 1 cm

MR  
thiopental sodium (Pentothal; Choong Wae  
Pharmacy, Seoul, Korea)

10%  
0.5 mm  
hematoxylin - eosin . 1 가

5% SNR  
 , 5 - 25%, 25 - 50%, 50 - 75%, 75 - 95%, 95%  
 MR  
 MR 1:1 , MR  
 가  
 ,  
 , MR 가  
 .  
 Gadofluorine M MR  
 , ,  
 95%  
 ,  
 kappa  
 SAS version 8.01 (SAS Institute Inc.,  
 Cary, NC, U.S.A.)  $p$  0.05  
 SNR  
 MR 31 1  
 1  
 5 MR 4  
 1  
 . 5 가



**Fig. 1.** Sequential change of SNR in five lymph nodes (four popliteal, one iliac) of normal control on pre- and post-injection MR. The popliteal and iliac lymph nodes show maximum enhancement of 220 - 330% at 15 - 60 minutes and 740% at 60 minutes.

15-60 ( 30  
 ) 2.2-3.3 ( 3.0 ) SNR 가  
 60 7.4 SNR  
 (Fig. 1).

MR  
 2 24  
 MR 가 가  
 9 46  
 15 71  
 117 5 mm  
 102 34 ,  
 83 5 mm 가 15 (12.8%),  
 5 - 10 mm가 52 (44.4%), 10 - 15 mm가 22 (18.8%), 15  
 mm 28 (23.9%) . 15  
 7 38 가 , 8  
 33 28 가 . 28  
 5 - 10 mm가 5 (17.9%),  
 10 - 15 mm가 6 (21.4%), 15 mm 17 (60.7%) ,  
 4 (14.3%), 24  
 (85.7%) (Table 1).  
 5% 가 1 , 5 - 25% 1 , 25 - 50% 1 , 50 -  
 75% 5 , 75 - 95% 12 , 95 % 8 .

MR  
 24 T1, T2  
 Gadofluorine M MR 101  
 33 , 68 . 5 - 10 mm  
 51 , 10 - 15 mm 22 , 15 mm 28  
 5 mm 102 7 mm

**Table 1.** Pathologically-Proven Lymph Nodes of the 24 Rabbits in the Study

	Hyperplastic LN	Metastatic LN	Total
Diameter < 5 mm	15	0	15
Diameter 5 - 10 mm	47	5	52
Diameter 10 - 15 mm	16	6	22
Diameter > 15 mm	11	17	28
Total	89	28	117

**Table 2.** MR Lymphography-Detected Lymph Nodes of the 24 Rabbits in the Study

	Hyperplastic LN	Metastatic LN	Total
Diameter 5 - 10 mm	46	5	51
Diameter 10 - 15 mm	16	6	22
Diameter > 15 mm	11	17	28
Total	73	28	101

:

Gadofluorine M

(Table 2). MR 5 mm

MR

97.6% (82/84), 98.2% (215/219), 95.3% (82/86), 99.1% (215/217)

1

96.4% (27/28), 98.6%

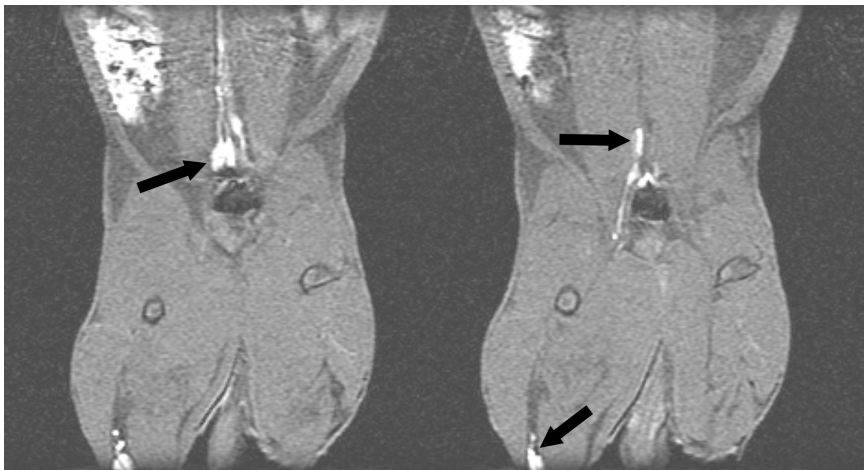
(72/73), 96.4% (27/28), 98.6% (72/73), 2

96.4% (27/28), 97.3% (71/73), 93.1% (27/29), 98.6%

(71/72), 3 100.0% (28/28), 98.6% (72/73),

96.6% (28/29), 100% (72/72) (Table 3, 4) (Fig. 2, 3).

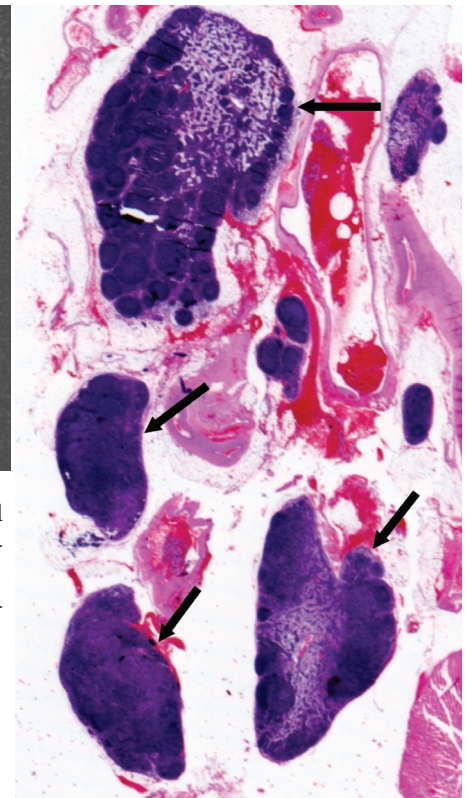
5 - 10 mm, 10 - 15 mm, 15 mm



A

**Fig. 2. A.** Fat suppressed two continuous SPGR images, 15 minutes after interstitial injection of Gadofluorine M in hyperplasia-induced model. Images show enhancement of popliteal and iliac lymph node groups (arrows) as well as lymphatic vessels.

**B.** Photomicrography reveals multiple hyperplastic lymph nodes (arrows) (hematoxylin and eosin,  $\times 1$ ).



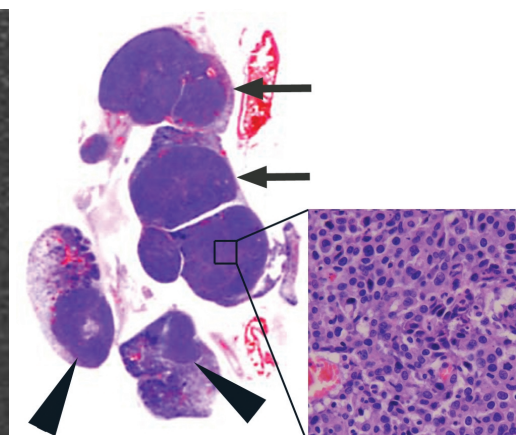
B



A

**Fig. 3. A.** Fat suppressed two continuous SPGR images, 30 minutes after interstitial injection of Gadofluorine M in metastasis-induced model. Images show non-enhancing (arrows) and partially enhancing lymph nodes (arrowheads).

**B.** Photomicrographs revealed multiple lymph nodes with complete (arrows) and partial (arrowheads) replacement by tumor (hematoxylin and eosin,  $\times 1$  and  $\times 200$ ).



B

가 , 가가 가 ,  
5 - 10 mm  
가 가  $p = 0.05$   
(Table 3, 4).  
kappa 3  
5 - 10 mm, 10 - 15 mm, 15 mm  
kappa  $> 0.8$  ( $p < 0.001$ ),  
kappa = 0.78 ( $p < 0.001$ )

1 cm 가  
3  
82.1% (23/28), 55.4% (46/83), 46.0% (23/50), 90.2%  
(46/51) , 1.5 cm 가  
60.7% (17/28), 86.7% (72/83), 60.7% (17/  
28), 86.7% (72/83)

Gadofluorine M macrocyclic gadolinium  
1,530 g/mol perfluorotyl chain  
가 (micelles) (27).  
Gadofluorine M

MR

1 - 2

(25).

Misselwitz (27) VX2  
Gadofluorine M (0.025 - 0.05 mmol/kg)  
12 10 Gadofluorine M MR

**Table 4.** Sensitivity, Specificity, Positive and Negative Predictive Values of MR Lymphography for Popliteal and Iliac Lymph Nodes

Reader	Variables	Location of LNs	
		Popliteal LNs ( $n = 33$ )	Iliac LNs ( $n = 68$ )
1	SN (%)	100.0 (4/4)	95.8 (23/24)
	SP (%)	96.6 (28/29)	100.0 (44/44)
	PPV (%)	75.0 (4/5)	100.0 (23/23)
	NPV (%)	100.0 (28/28)	97.8 (44/45)
2	SN (%)	100.0 (4/4)	95.8 (23/24)
	SP (%)	93.1 (27/29)	100.0 (44/44)
	PPV (%)	66.7 (4/6)	100.0 (23/23)
	NPV (%)	100.0 (27/27)	97.8 (44/45)
3	SN (%)	100.0 (4/4)	100.0 (24/24)
	SP (%)	96.6 (28/29)	100.0 (44/44)
	PPV (%)	75.0 (4/5)	100.0 (24/24)
	NPV (%)	100.0 (28/28)	100.0 (44/44)
Mean	SN (%)	100.0 (12/12)	97.2 (70/72)
	SP (%)	95.4 (83/87)	100.0 (132/132)
	PPV (%)	75.0 (12/16)	100.0 (70/70)
	NPV (%)	100.0 (83/83)	98.5 (132/134)

Abbreviations: SN, sensitivity; SP, specificity;  
PPV, positive predictive value; NPV, negative predictive value

**Table 3.** Sensitivity, Specificity, Positive and Negative Predictive Values of MR Lymphography for Lymph Nodes with Variable Size

Reader	Variables	Size of LNs			
		5 - 10 mm ( $n = 51$ )	10 - 15 mm ( $n = 22$ )	$> 15$ mm ( $n = 28$ )	All size ( $n = 101$ )
1	SN (%)	100.0 (5/5)	100.0 (6/6)	94.1 (16/17)	96.4 (27/28)
	SP (%)	100.0 (46/46)	100.0 (16/16)	90.1 (10/11)	98.6 (72/73)
	PPV (%)	100.0 (5/5)	100.0 (6/6)	94.1 (16/17)	96.4 (27/28)
	NPV (%)	100.0 (46/46)	100.0 (16/16)	90.1 (10/11)	98.6 (72/73)
2	SN (%)	100.0 (5/5)	100.0 (6/6)	94.1 (16/17)	96.4 (27/28)
	SP (%)	97.8 (45/46)	100.0 (16/16)	90.1 (10/11)	97.3 (71/73)
	PPV (%)	83.3 (5/6)	100.0 (6/6)	94.1 (16/17)	93.1 (27/29)
	NPV (%)	100.0 (45/45)	100.0 (16/16)	90.1 (10/11)	98.6 (71/72)
3	SN (%)	100.0 (5/5)	100.0 (6/6)	100.0 (17/17)	100.0 (28/28)
	SP (%)	100.0 (46/46)	100.0 (16/16)	90.1 (10/11)	98.6 (72/73)
	PPV (%)	100.0 (5/5)	100.0 (6/6)	94.4 (17/18)	96.6 (28/29)
	NPV (%)	100.0 (46/46)	100.0 (16/16)	100.0 (10/10)	100.0 (72/72)
Mean	SN (%)	100.0 (15/15)	100.0 (18/18)	96.1 (49/51)	97.6 (82/84)
	SP (%)	99.3 (137/138)	100.0 (48/48)	90.1 (30/33)	98.2 (215/219)
	PPV (%)	93.8 (15/16)	100.0 (18/18)	94.2 (49/52)	95.3 (82/86)
	NPV (%)	100.0 (137/137)	100.0 (48/48)	93.8 (30/32)	99.1 (215/217)

Abbreviations: SN, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value

: Gadofluorine M

USPIO 10 mg/kg  
(18)

T1

Gadofluorine M

MR Gadofluorine M 5 mm  
102 101 (99.1%)

97.6% (82/84), 98.2% (215/219)

MR  
50 - 90% (3, 5, 8)

5% 가 1.5 cm  
1 , 가 가

가 MR , MR

가

가 (imaging sequence) , MR

5 mm

, MR 99.1%

hematoxylin - eosin

Gadofluorine M MR  
가 ,

Gadofluorine M MR

1. Steinkamp HJ, Cornehl M, Hosten N, Pegios W, Vogl T, Felix R. Cervical lymphadenopathy: ratio of long-to-short axis diameter as a predictor of malignancy. *Br J Radiol* 1995;68:266-270
2. Clement O, Luciani A. Imaging the lymphatic system: possibilities and clinical applications. *Eur Radiol* 2004;14:1498-1507
3. van den Brekel MW. Lymph node metastases: CT and MRI. *Eur J Radiol* 2000;33:230-238
4. Lernevall A. Imaging of axillary lymph nodes. *Acta Oncol* 2000;39:277-281
5. Williams AD, Cousins C, Scoutter WP, Mubashar M, Peters AM, Dina R, et al. Detection of pelvic lymph node metastases in gynecologic malignancy: a comparison of CT, MR imaging, and positron emission tomography. *AJR Am J Roentgenol* 2001;177:343-348

6. Steinkamp HJ, Wissgott C, Rademaker J, Felix R. Current status of power Doppler and color Doppler sonography in the differential diagnosis of lymph node lesions. *Eur Radiol* 2002;12:1785-1793
7. Kim JH, Beets GL, Kim MJ, Kessels AG, Beet-Tan RG. High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? *Eur J Radiol* 2004;52:78-83
8. Torabi M, Aquino SL, Harisinghani MG. Current concepts in lymph node imaging. *J Nucl Med* 2004;45:1509-1518
9. Buscombe JR, Holloway B, Roche N, Bombardieri E. Position of nuclear medicine modalities in the diagnostic work-up of breast cancer. *Q J Nucl Med Mol Imaging* 2004;48:109-118
10. Goo JM, Im JG, Do KH, Yeo JS, Seo JB, Kim HY, et al. Pulmonary tuberculoma evaluated by means of FDG PET: findings in 10 cases. *Radiology* 2000;216:117-21
11. Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, et al. The sentinel node in breast cancer: a multicenter validation study. *N Engl J Med* 1998;339:941-946
12. Krynyckyi BR, Kim CK, Goyenechea MR, Chan PT, Zhang ZY, Machac J. Clinical breast lymphoscintigraphy: optimal techniques for performing studies, image atlas, and analysis of images. *Radiographics* 2004;24:121-145
13. Weissleder R, Elizondo G, Wittenberg J, Lee AS, Josephson L, Brady TJ. Ultrasmall superparamagnetic iron oxide: an intravenous contrast agent for assessing lymph nodes with MR imaging. *Radiology* 1990;175:494-498
14. Michel SC, Keller TM, Frohlich JM, Fink D, Caduff R, Seifert B, et al. Preoperative breast cancer staging: MR imaging of the axilla with ultrasmall superparamagnetic iron oxide enhancement. *Radiology* 2002;225:527-536
15. Mack MG, Balzer JO, Straub R, Eichler K, Vogl TJ. Superparamagnetic iron oxide-enhanced MR imaging of head and neck lymph nodes. *Radiology* 2002; 222:239-244
16. Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, van de Kaa CH, et al. Noninvasive detection of clinically occult lymph node metastases in prostate cancer. *N Engl J Med* 2003;348:2491-2499
17. Taupitz M, Wagner S, Hamm B, Binder A, Pfefferer D. Interstitial MR lymphography with iron oxide particles: results in tumor-free and VX2 tumor-bearing rabbits. *AJR Am J Roentgenol* 1993;161:193-200
18. Wunderbaldinger P, Josephson L, Bremer C, Moore A, Weissleder R. Detection of lymph node metastases by contrast-enhanced MRI in an experimental model. *Magn Reson Med* 2002;47:292-297
19. Torchia MG, Misselwitz B. Combined MR lymphangiography and MR imaging-guided needle localization of sentinel lymph nodes using Gadomer 17. *AJR Am J Roentgenol* 2002;179:1561-1565
20. Suga K, Yuan Y, Ogasawara N, Okada M, Matsunaga N. Localization of breast sentinel lymph nodes by MR lymphography with a conventional gadolinium contrast agent. Preliminary observations in dogs and humans. *Acta Radiol* 2003;44:35-42
21. Misselwitz B, Platzek J, Raduchel B, Oellinger JJ, Weinmann HJ. Gadofluorine 8: initial experience with a new contrast medium for interstitial MR lymphography. *MAGMA* 1999;8:190-195
22. Ruehm SG, Corot C, Debatin JF. Interstitial MR lymphography with a conventional extracellular gadolinium-based agent: assessment in rabbits. *Radiology* 2001;218:664-669
23. Staatz G, Nolte-Ernsting CC, Adam GB, Grosskortenhaus S, Misselwitz B, Buckner A, et al. Interstitial T1-weighted MR lymphography: lipophilic perfluorinated gadolinium chelates in pigs.



- Radiology* 2001;220:129-134
24. Herborn CU, Lauenstein TC, Vogt FM, Lauffer RB, Debatin JF, Ruehm SG. Interstitial MR lymphography with MS-325: characterization of normal and tumor-invaded lymph nodes in a rabbit model. *AJR Am J Roentgenol* 2002;179:1567-1572
  25. Misselwitz B, Schmitt-Willich H, Michaelis M, Oellinger JJ. Interstitial magnetic resonance lymphography using a polymeric T1 contrast agent: initial experience with Gadomer-17. *Invest Radiol* 2002;37:146-151
  26. Ruehm SG, Schroeder T, Debatin JF. Interstitial MR lymphography with gadoterate meglumine: initial experience in humans. *Radiology* 2001;220:816-821
  27. Misselwitz B, Platzek J, Weinmann HJ. Early MR lymphography with gadofluorine M in rabbits. *Radiology* 2004;231:682-688
  28. Moon WK, Chang KH, Weinmann HJ, Koh YH, Im JG, Yeon KM, et al. Dynamic contrast-enhanced MR imaging of bacterial abscess and VX2 carcinoma in rabbits: comparison of gadopentetate dimeglumine and a macromolecular contrast agent. *AJR Am J Roentgenol* 2000;174:1385-1389

## Differentiation of Hyperplastic from Metastatic Lymph Nodes Using a Lymph Node Specific MR Contrast Agent Gadofluorine M<sup>1</sup>

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**Purpose:** We wanted to evaluate the value of a lymph node specific MR contrast agent, Gadofluorine M, for the differentiation of hyperplastic and metastatic lymph nodes.

**Materials and Methods:** This study included thirty-one rabbits. In ten rabbits, an injection of egg yolk or feces of rat into the calf muscles induced hyperplasia of the lymph node. In sixteen rabbits, metastasis of the lymph node was induced by implantation of VX2 tumor. Five rabbits were normal control models. We acquired the T1-, T2-weighted and SPGR coronal imaging before enhancement with 1.5 T MR. After injection of Gadofluorine M (5  $\mu$ mol/mL, total amount: 4 mL) interstitially into the interdigital skin fold of the hind limb, we acquired the SPGR coronal imaging at 15, 30, 60 and 90 minutes. We calculated the signal-to-noise ratios on the sequential images, and we recorded the number, size and location of the popliteal and iliac lymph nodes. Three readers assessed the state of the lymph nodes according to the pattern of enhancement: they were deemed hyperplastic nodes when totally enhanced and as metastatic nodes when there was no or partial enhancement. We also compared the imaging patterns with the histopathological results.

**Results:** Among the 26 hyperplasia- or metastasis-induced rabbits, two rabbits were excluded because of failure to be enhanced. Histopathologic evaluation of the 24 rabbits detected one hundred seventeen lymph nodes: forty-six lymph nodes in nine hyperplasia-induced rabbits and seventy-one (metastasis in twenty-eight) lymph nodes in fifteen metastasis-induced rabbits. Out of one hundred two lymph nodes that were larger than 5 mm in size, MR enabled us to detect one hundred one lymph nodes (99.1%). The means of sensitivity, specificity, and the positive and negative predictive values for the diagnosis of lymph node metastasis by three readers were 97.6% (82/84), 98.2% (215/219), 95.3% (82/86), and 99.1% (215/217), respectively ( $p < 0.05$ ).

**Conclusion:** Interstitial MR lymphography using Gadofluorine M showed excellent results in differentiating hyperplastic from metastatic lymph nodes.

**Index words :** Magnetic resonance (MR), contrast media  
Lymphatic system, MR