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# $T_1$-weighted MR-lymphography after intramammary administration of Gadomer-17 in pigs

## *$T_1$-gewichtete MR-Lymphographie nach intramammärer Injektion von Gadomer-17 in Mausschweine*



**Zusammenfassung**

**Ziel:** Untersuchung der Kontrastmittelanreicherung lokoregionärer Lymphknoten und Lymphbahnen nach intramammärer Injektion von Gadomer-17. **Material und Methoden:** Die $T_1$-gewichtete MR-Lymphographie wurde bei 8 Hausschweinen nach intramammärer Injektion von 5 – 10 µmol/kg Körpergewicht (KG) Gadomer-17 in einem 1,5 Tesla MR-Gerät durchgeführt. Dabei wurden $T_1$-gewichtete 3D Gradientenechosequenzen 10 – 120 Minuten nach Kontrastmittelapplikation in koronarer und sagittaler Schnittführung akquiriert. Die Kontrastmittelanreicherung des die Milchleiste drainierenden lymphatischen Systems wurde qualitativ durch zwei Radiologen im Consensus mittels einer Dreipunkteskala bewertet. **Ergebnisse:** Die $T_1$-gewichtete MR-Lymphographie nach intramammärer Injektion von Gadomer-17 ließ sich bei allen Versuchstieren erfolgreich durchführen. Eine Dosis von 5 µmol/kg KG war für die lymphographische Darstellung der Milchleiste und der abführenden Lymphwege am besten geeignet. Die Kontrastmittelanreicherung des lokoregionären Lymphsystems der Mamma wurde bei 5 Versuchstieren mit gut und bei drei Versuchstieren mit sehr gut bewertet. **Schlussfolgerung:** Die intramammäre Injektion von Gadomer-17 ermöglicht eine qualitativ gute MR-Lymphographie des lokoregionären lymphatischen Systems der Mamma. Eine Nutzung dieser neuen MR-Technik zur Bestimmung des Wächterlymphknotens bei Patienten mit Brustkrebs ist vorstellbar.

**Schlüsselwörter**
Magnetresonanztomographie · Kontrastmittel · MR Lymphographie · Wächterlymphknoten · Mamma

**Abstract**

**Purpose:** To evaluate the enhancement of regional lymph nodes and lymphatic vessels after intramammary injection of Gadomer-17. **Materials and Methods:** $T_1$-weighted MR-lymphography was performed in 8 domestic pigs after intramammary injection of 5 – 10 µmol/kg bodyweight (bw) Gadomer-17 on a 1.5 T-MR scanner. $T_1$-weighted 3D gradient-echo images were acquired 10 to 120 minutes after contrast material injection in coronal and sagittal planes. The contrast enhancement of the draining lymphatic system was qualitatively assessed by two radiologists applying a three grade scale. **Results:** $T_1$-Weighted MR-lymphography after intramammary injection of Gadomer-17 was feasible in each pig. A dose of 5 µmol/kg body weight Gadomer-17 was best suited for MR-lymphography of the mammary line and the draining lymphatic system. Enhancement of regional lymph nodes and lymphatic vessels was classified as good in 5, and excellent in three cases. **Conclusions:** Intramammary injection of Gadomer-17 allows for good quality $T_1$-weighted MR-lymphography of mammary gland draining regional lymph nodes and lymphatic vessels. This new technique might offer potential for the evaluation of the sentinel lymph node in patients with breast cancer.

**Key words**
Magnetic resonance imaging · Contrast agents · MR-lymphography · Sentinel lymph node · Breast

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## Introduction

Recent developments of interstitial $T_1$-weighted MR-lymphography with dedicated contrast agents offer great potential for various applications [1–3]. The macrocyclic $T_1$-type contrast agent Gadomer-17 showed good results for the performance of interstitial MR-lymphography within the extremities, the abdomen and for the visualization of the thoracic duct [4]. Of major clinical concern are lymphatic mapping techniques in patients with breast cancer, which so far have not been studied by MR lymphography. The aim of our experimental study was to evaluate the feasibility of MR-lymphography of the breast draining lymphatic system after intramammary administration of Gadomer-17.

## Materials and Methods

### Contrast agent

Gadomer-17 is a synthetic dendritic gadolinium complex, chelating 24 gadolinium (Gd) ions, with a molecular weight of 17 kd [5]. The $T_1$-relaxivity, determined spectroscopically (Minispec PC-20, Bruker Instruments, Karlsruhe) in water at 0.47 T and 40° is 17.3 l/(mmol(s) [5]. Blood and plasmakinetics of Gadomer-17 were investigated by the manufacturer with use of a two-compartment distribution model in different species [5]. The blood/plasma half-lives in rats are two minutes for the (initial) a-phase and 37 minutes for the (second) b-phase. The LD-50 in mice was found to be ≥ 30 mmol/kg. In our study, Gadomer-17 solutions with 250 mmol Gd/l were used.

### Animal experiments

All animal studies were approved by the institutional review board for animal research. A total of 8 female domestic pigs, weighing 37.8–44.9 kg were included in the study. The animals were first sedated with use of intramuscular administration of 0.2 ml/kg azaperone (Stresnil, Jansen-Cilag, Neuss, Germany), 0.05 ml/kg atropine sulfate 1% (Atropine; Braun, Melsungen) and 0.1 ml/kg ketamine (Ketamin 10%, Sanofia-Ceva, Düsseldorf, Germany) and then anesthetized with intravenous injection of 3–4 ml pentobarbital sodium (Narcoren; Rhone Merieux, Laupheim, Germany) as needed. After endotracheal intubation, all animals received assisted mechanical ventilation throughout the experiments.

The two most proximally located mammary glands of the milk line on either side were chosen for contrast material injection. MR-lymphography was performed before and after intramammary injection of 10 µmol/kg bw (1.6–1.7 ml) Gadomer-17 per breast in two pigs and 5 µmol/kg (0.75–0.9 ml) Gadomer-17 per breast in 6 pigs. MR-lymphograms of the mammary line and of the cervical-thoracic region were performed to cover the lymph drainage route from the mammary glands to the superficial cervical lymph nodes. This drainage route is typical for the mammary glands of pigs [6].

### MR imaging

All MR examinations were performed with the pigs in supine position on a 1.5 Tesla superconducting magnet (Gyroscan ACS-NT, Philips, Best, The Netherlands), equipped with high-performance gradients. The MR protocol started with the acquisition of a $T_1$-weighted gradient-echo localizer sequence composed of three slice stacks oriented in coronal, sagittal and axial planes.

Postcontrast MR lymphograms were obtained 10–120 minutes following contrast material administration within time intervals of 10–15 minutes. Imaging of the mammary glands of the milk line was performed with use of a ring-shaped surface coil. Coronal $T_1$-weighted 3D gradient-echo sequences were acquired with a repetition time of 9.6 msec, an echo time of 4.7 msec and a flip angle of 30°. 50 slices were acquired with a slice thickness of 2.4 mm, a 1.2 mm-overlap, a field-of-view of 200 mm with a rectangular field-of-view of 70% and a matrix size of 212 · 256. The scan time was 35.6 sec during which the mechanical ventilation was suspended to achieve breathhold conditions. Maximum intensity projections were calculated from the original 3D data sets in coronal planes.

MR-lymphograms of the lower neck/upper thorax were acquired in breathhold technique with $T_1$-weighted 3D gradient-sequences in coronal and sagittal planes with a repetition time of 8.8–9.5 msec, an echo time of 4.3–4.7 msec and a flip angle of 40°. 70 slices were acquired with a slice thickness of 2.4 mm, a 1.2 mm-overlap, a field-of-view of 400–440 mm with a rectangular field-of-view of 75% and a matrix size of 327 · 512. The scan time was 1.14–1.21 minutes. Maximum intensity projections were calculated from the original 3D data sets in coronal and sagittal planes.

### Image analysis

The contrast enhancement of the superficial cervical lymph nodes and lymphatic vessels were qualitatively evaluated by two experienced radiologists in consensus. A three grade-scale [1,4] was used for the assessment of the draining lymphatic system, classifying the enhancement as 1) poor, if only a few lymph nodes and no lymphatic vessels were visible, 2) good, if several lymph nodes and a few lymphatic vessels were delineated or 3) excellent, if several lymph nodes and lymphatic vessels showed excellent enhancement. Furthermore, the peak enhancement of the lymphatic system, which was characterized by the highest amount of enhancing lymph nodes and lymphatic vessels delineable on a single MR-lymphogram, was evaluated in dependence on the time after contrast material injection.

## Results

MR-lymphography of the mammary glands and of the draining regional lymph nodes and lymphatic vessels after intramammary injection of Gadomer-17 was feasible in each pig. In two pigs, a dose of 10 µmol/kg Gadomer-17 per breast caused severe susceptibility artifacts within the mammary gland (Fig. **1**), although the enhancement of the draining lymphatic system was classified as good. In 6 pigs, which received an intrammamary injection of 5 µmol/kg Gadomer-17 per breast, susceptibility artifacts within the mammary glands were markedly reduced. Afferent and efferent lymphatic vessels between the mammary glands of the milk line (Fig. **2**) and lymphatic vessels draining to the superficial cervical lymph nodes (Fig. **3,4**) were visualized. The enhancement of regional lymphatic vessels and lymph nodes was classified as good or excellent in three cases, respectively. Peak enhancement of regional lymph nodes and lympha-

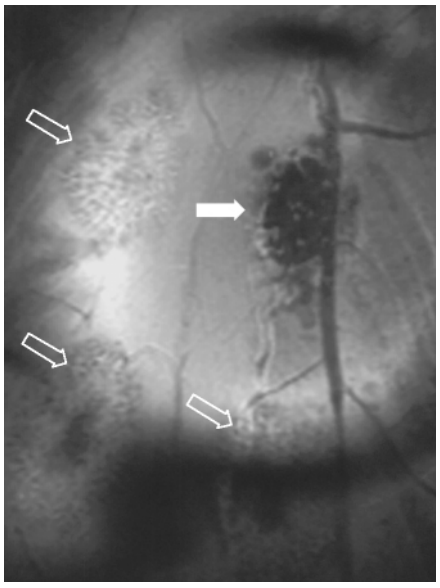

**Abb. 1** MIP image of $T_1$-weighted 3D gradient-echo sequence (TR/TE 9.6 msec/4.7 msec, flip angle 30°, surface coil) of the milk line in the coronal plane. The mammary glands of the milk line (open arrows) are visualized. The left upper mammary gland (arrow) shows signal void due to susceptibility artifacts after intramammary injection of 10 μmol/kg bw Gadomer-17.

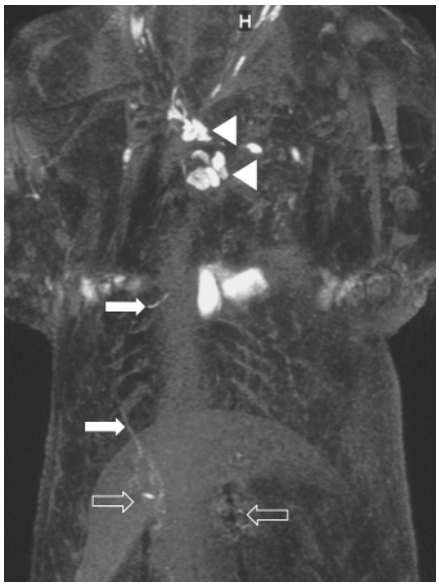


**Abb. 3** Coronal MIP image of $T_1$-weighted 3D gradient-echo sequence (TR/TE 8.8 msec/4.3 msec, flip angle 40°, body coil) of upper abdomen and thorax. The draining lymphatic vessels (bold arrows) can be followed from the mammary glands (open arrows) to superficial cervical lymph nodes (arrow heads).

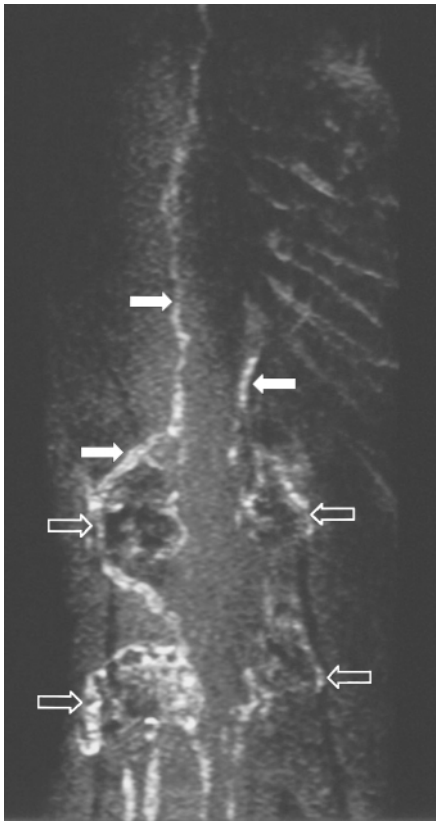

**Abb. 2** Coronal MIP image of $T_1$-weighted 3D gradient-echo sequence (TR/TE 9.1 msec/4.4 msec, flip angle 40°, body coil) of the milk line after intramammary injection of 5 μmol/kg Gadomer-17. Draining lymphatic vessels (straight arrows) are depicted between the mammary glands (open arrows) and can be followed cranially were they lead to superficial cervical lymph nodes (Figs. **3, 4**).

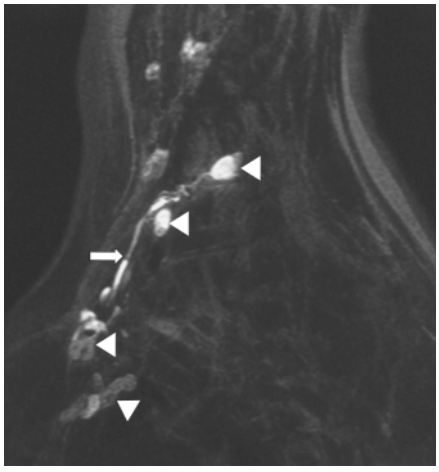

**Abb. 4** Sagittal MIP image of $T_1$-weighted 3D gradient-echo sequence (TR/TE 8.8 msec/4.3 msec, flip angle 40°, body coil) of the upper thorax and lower neck. Superficial cervical lymph nodes (arrow heads) as well as lymphatic vessels (arrow) are demonstrated.

tic vessels was noticed on the MR-lymphograms obtained 20 to 30 minutes after contrast material injection.

## Discussion

The status of axillary lymph nodes represents the most important prognostic factor for patients suffering from breast cancer. Axillary lymphadenectomy is still recommended as the standard staging technique. Postsurgical complications of axillary dissection include lymph-edema, sensor-motor disturbances, pain and limitations of shoulder motions and may occur in up to 30% of patients [7]. Because mammographic screening programs increase the rate of early detected breast cancer, axillary nodal metastases are found in only 20–30% of cases. Thus, many patients do not benefit from prophylactic axillary dissection [8].

As an alternative to axillary lymphadenectomy, sentinel lymph node dissection has been developed in recent years. The sentinel lymph node, which is the first lymph node encountered by lymphatic vessels draining a tumor, reflects the tumor status of the entire lymphatic drainage basin [9]. Identification of one or more sentinel lymph nodes may be performed by probe directed lymphatic mapping techniques after administration of technetium 99m ($^{99m}$TC) labeled radioactive tracers, vital blue dye mapping techniques, or combination of both [10–13]. The success rates for sentinel lymph node dissection reported varies between 86% and 99% [12,14–15].

However, lymphoscintigraphy lacks spatial resolution and results in radiation exposure not only for the patient but also for the surgeon. Moreover, not every breast tumor is palpable and some may only be visible on MR images. Thus, the development of MR-lymphography for use in breast cancer patients is attractive. Recent studies demonstrated that subcutaneous injection of

the $T_1$-type contrast agent Gadomer-17 into the extremities is highly efficient for the visualization of regional lymph nodes and lymphatic vessels [4]. Because breast lymphoscintigraphy is performed with peritumoral or intratumoral injections especially in deep parenchymal lesions, we focused on the evaluation of intramammary injection of Gadomer-17 in our study.

One major advantage of Gadomer-17 is the small injection volume needed to produce a sufficient lymphographic effect [4]. In our study only 0.75 – 0.9 ml of contrast agent solution were used per breast yielding a good contrast enhancement of the draining lymphatic basin. To avoid major susceptibility artifacts within the breast, the primarily injected dose of 10 µmol/kg was reduced by 50 %. This small dose was efficient to cover the large distance from the milk line (upper abdomen) to the superficial cervical lymph nodes, which typically drain the mammary glands in pigs.

With regard to sentinel lymph node identification, dynamic MR-lymphograms within 30 minutes allow us to follow the lymph flow to the draining lymph nodes, as already performed with lymphoscintigraphy. If one or more sentinel lymph nodes are identified by MR-lymphography, it is possible to perform an MR-guided percutaneous biopsy of the node or preoperative marking using coils [16].

In summary, intramammary injection of Gadomer-17 allows for good quality MR-lymphograms of the lymphatic drainage basin of the mammary glands in pigs. Identification of the sentinel lymph node in breast cancer patients appears to be possible with this new technique, but further studies are warranted.





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