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ORIGINAL ARTICLE

Magnetic resonance lymphography of sentinel lymph nodes in patients with breast cancer using superparamagnetic iron oxide: a feasibility study

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Abstract

Background The sentinel lymph node (SLN) biopsy technique using superparamagnetic iron oxide (SPIO) as a tracer instead of radioisotopes has been described. To further advance this technique, we evaluated preoperative SPIO-MR sentinel lymphography to facilitate the accurate identification of the lymphatic pathways and primary SLN.

Methods A prospective study was performed in ten patients with breast cancer and clinically negative axillary lymph nodes. None of the patients received preoperative chemotherapy. After 1.6 ml of SPIO (ferucarbotran) was injected in the subareolar breast tissue, sentinel axillary lymph nodes were detected by MRI in T2*-weighted gradient echo images and resected using the serial SPIO-SLN biopsy procedure with a handheld magnetometer.

Results In one patient, gadolinium-enhanced MR imaging was performed at the same time as SPIO-MR lymphography, and this patient was excluded from further analysis. In all patients (9/9) SLNs were detected by SPIO-MR sentinel lymphography and successfully identified at surgery. The number of SLNs detected by lymphography (mean 2.7) significantly correlated with SLNs identified at surgery (mean 2.2). One patient had nodal metastases. In one patient, skin color changed to brown at the injection site and resolved spontaneously. There were no severe reactions to the procedure or complications in any patient.

Conclusions This is the first study to evaluate SPIO both as a contrast material in MR sentinel lymphography and as a tracer in SLN biopsy using an integrated method. The acquired three-dimensional imaging demonstrated excellent image quality and usefulness to identify SLN in conjunction with SLN biopsy.

Keywords Breast cancer · Sentinel lymph node biopsy · Superparamagnetic iron oxide · MR lymphography

Introduction

Sentinel lymph node (SLN) biopsy is the standard of care for many patients with breast cancer and is commonly performed using a radioisotope [1, 2]. However, throughout the world, many hospitals lack the facilities for using radioisotopes.

Sentinel lymph node biopsy is an invasive technique and associated with radiation exposure by the use of a radioactive tracer not only for patients but also the surgeon, pathologist, and other medical staff. The supply line of radioisotopes is unreliable in many parts of the world. In 2009 the National Research Universal (NRU) reactor in Canada was taken offline for immediate repairs; the NRU supplies about 50 % of the world's molybdenum-99 supply, used to make 99m (Tc 99m). In 2010, the disruption of

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air travel by the volcanic eruption in Iceland adversely affected the delivery of molybdenum-99, as well.

Superparamagnetic iron oxide (SPIO, ferucarbotran) has been approved for intravenous use in contrast-enhanced magnetic resonance imaging (MRI) of the liver. In humans, this agent is incorporated into the reticuloendothelial system. Interstitial administration of SPIO is taken up as iron oxide in lymph nodes [3, 4]. We developed a new SLN biopsy technique using a SPIO tracer-guide procedure and a handheld magnetometer instead of radioisotopes [5]. SPIO and patent blue dye were injected in the subareolar breast tissue during the operation. The rate of detection of SLN was 90 % by the combination method with a sensitivity of 86 % and accuracy of 96 %. This study showed that SPIO injected into breast tissue rapidly migrates to SLNs [5].

On the basis of the previous study, we developed a novel method, MR lymphography using SPIO. Sentinel lymph nodes have been successfully identified using SPIO-MR lymphography. This is the first prospective study to validate consecutive sentinel lymphography and biopsy using SPIO, which involves no radiation exposure to patients or medical staff.

Materials and methods

Patients

This study was approved by the Institutional Review Board of the Oyama Municipal Hospital. Ten patients were enrolled after obtaining written informed consent. In the first patient, gadolinium-enhanced MR imaging was performed at the same time as SPIO-MR sentinel lymphography, and this patient was excluded from further analysis. The study included nine patients, eight (88.9 %) with invasive ductal carcinoma and one (11.1 %) with invasive lobular carcinoma, admitted to Oyama Municipal Hospital, Tochigi, Japan from October 2009 to April 2010. All nine patients (mean age 60.8 ± 11.7 years) consented to participate in this prospective study and were scheduled for breast surgery. All patients had histologically confirmed primary breast carcinoma and clinically negative axillary lymph node metastases prior to operation. None of the patients received preoperative chemotherapy.

Position in MRI and the MRI marking technique

MR imaging was performed with a 1.5-T imaging system (EXCELART vantage; Toshiba Medical Systems Corporation, Tochigi, Japan) in the supine position with their arms elevated, similar to the position used during surgery. Breath Care® (Kobayashi Pharmaceutical Co. Ltd., Osaka, Japan) pills have been reported to be effective as an MRI marker [6], and were placed along the lateral edge of the pectoralis major muscle (Fig. 1).

The SPIO agent Risovist® (FUJIFILM RI Farm Co., Ltd., Tokyo, Japan) contains 540 mg ferucarbotran per milliliter (27.9 mg iron/ml), consisting of hydrophilic carboxydextran-covered SPIO particles. Iron oxide nanoparticles have been used as "negative contrast agents", i.e., their active uptake by normal lymph nodes results in a homogeneous decrease in signal intensity on T2-star (T2*)-weighted images [3, 4, 7]. A 1.6-ml dose of Risovist® (ferucarbotran) was injected in the subareolar breast tissue. Following a few minutes of massage to promote migration of the iron tracer through the lymphatic vessels, imaging of the axillary region was performed 20 min after injection of SPIO. Enhanced lymph nodes at 20 min on MR lymphography were defined as the "sentinel" lymph node.

After localization, a T2*-weighted 3D gradient echo (GRE) sequence was obtained using a surface coil in a transverse plane before and after injection of SPIO; this sequence demonstrated the accumulation of iron in the breast tissue using the following parameters: (repetition time, 32 ms; echo time, 9 ms; matrix, 256 × 256; flip angle, 18°; section thickness, 3.0 mm; overlap, 1.5 mm; signal averaging, 1; imaging time, approximately 5 min).

Three-dimensional image reconstruction

DICOM data sets were transferred to a workstation (M900 Quadra, Ziosoft) and transverse axillary images generated. Coronal images were reformatted from transverse images. Three-dimensional MR images were reconstructed by focusing on the relationship between the pectoralis major muscle, the latissimus dorsi muscle, the axillary vein and

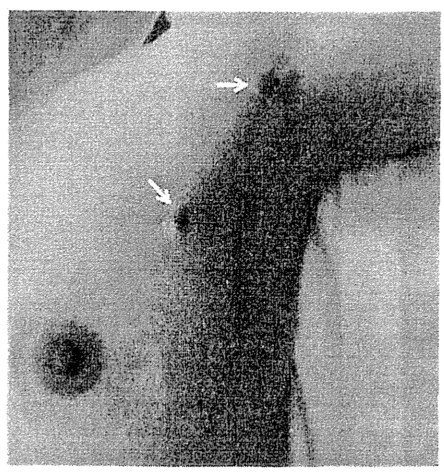

Fig. 1 Pre-MRI lymphography marking. Two points along the lateral edge of the pectoralis major are marked with pills, the first point is the insertion at the humerus, the second is the junction of the lateral edge of the pectoralis and mammary line (*arrows*)

SLNs based on the post-contrast MR images with volume-rendering techniques by an experienced radio-technologist (Y.S.). On axial source images of MR sentinel lymphography and post-processed three-dimensional images, all axillary lymph nodes were identified and their number, size, and anatomical level recorded. The evaluation of axillary lymph nodes was performed by a board-certified radiologist (S.K.) and a surgeon (M.S.), with extensive experience in breast MR imaging and surgery, and the final diagnosis established by consensus.

By using three-dimensional images as an anatomical guide, we drew an outline of the SLNs with pill-markers to be used as reference points in the operating room.

To measure correlation between the number of lymph nodes delineated by MR sentinel lymphography and harvested SLNs at biopsy, Spearman's correlation coefficient (ρ) was calculated using the "Statistical Compute Form File ystat2000.xls file (IGAKUTOSYOSYUPPANSYA, Tokyo, Japan)".

Comparison to gadolinium-enhanced MR images and enhanced CT

In our institution, enhanced CT (Brilliance 64-slice CT by Philips, 1.25 mm-thick, 120 kV, 200–300 Auto-mA) using iopamidol (Omnipaue® 100 ml at a rate of 1 ml/s) is done routinely to survey for metastases in axillary lymph nodes as well as distant metastases. Gadolinium-enhanced MR (Magnevist® 20 ml, 2 ml/s, axial early subtraction 3D fast spoiled GRE 7.7/1.8 with a 30° flip angle) images are used to evaluate the local staging of breast cancer including multifocal lesion, extension of tumor, and axillary lymph node metastasis [8].

Image classification of SLN enhanced pattern

Visual analysis of SPIO-MR imaging was previously reported in various organs [4, 7, 9–11]. Lymph nodes were classified into two patterns based on imaging: lymph nodes showing an overall low signal intensity on T2* images and lymph nodes having a partial and obscure low signal intensity on T2* images. On their pathological examination, overall enhanced lymph nodes were diagnosed as non-metastatic, whereas partial and obscure enhanced lymph nodes were diagnosed as metastatic. According to their criteria, SLNs delineated in SPIO-MR lymphography were classified into two patterns and pathologically examined after harvesting to evaluate the presence of metastases.

Surgery

Sentinel node biopsy using SPIO was performed as described previously [5]. In brief, after the induction of general anesthesia, a subareolar injection of 1.6 ml Risovist® (ferucarbotran) and 1 % patent blue dye was performed 5 min before surgery, and then the injection site massaged gently to promote migration using the same technique as MR lymphography. SLNs were detected transdermally by a prototype magnetometer (Kyoushin, Tochigi, Japan). Lymph nodes located just under the marking site determined by MR lymphography were counted by the magnetometer and defined as sentinel nodes, and removed first. Axillary dissection was then performed after SLN biopsy.

Results

Node-to-node correlation between MR imaging and surgical findings

In all patients (9/9), SLNs were successfully localized by MR lymphography. "Hot spots" were identified over the skin using the magnetometer probe at the SLN locations identified on the MR images. No patients with negative SLNs had metastases in other lymph nodes. To date, the only problem caused by the injection of ferucarbotran has been a brown change in skin color that lasts about 2 months and then resolves spontaneously. There have been no allergic or other acute reactions observed.

A node-to-node-based comparison between SPIO-MR imaging and operative findings was undertaken to assess the relationship between the localization by MR lymphography and SLN biopsy. SPIO-MR sentinel lymphography detected a total of 24 lymph nodes as SLNs (average 2.7) in the nine enrolled patients. The mean size of sentinel nodes on MR lymphography was 11 (range 7–20) mm. At surgery, 20 lymph nodes were harvested as SLNs (average 2.2). Pathological analysis revealed that one of the nine patients had axillary lymph node metastases. In this patient, both of the two SLNs harvested at surgery were diagnosed as positive on frozen section. A correlation coefficient of $\rho = 0.81$ (Spearman's rank, significant) was found between the number of SLNs seen with MR lymphography and the number of harvested SLNs detected by the magnetometer at surgery. Details of the study are shown in Table 1.

Comparison to gadolinium-enhanced MR images and enhanced CT

Sentinel lymph nodes could not be delineated on pre-injection MR imaging by a T2*-weighted gradient echo sequence (Fig. 2a). Twenty minutes after injection of SPIO into the subareolar breast tissue, SLNs were enhanced on SPIO-MR lymphography. Lymph nodes without SPIO enhancement were not seen and considered as non-sentinel (Fig. 2b). On

Table 1 Correlation of number between SLNs on SPIO-MR lymphography and SLNs harvested on SLNB

No.	Age (years)	Side	BMI (kg/m^2)	Pathology	Tumor size (mm)	SLNs on SPIO-MR lymphography (*n*)	SLNs harvested on SLNB (*n*)	Metastatic SLNs (*n*)	Metastatic LNs (*n*)
1	60	L	23.7	IDC	23	2	1	0	0
2	46	L	21.9	IDC	28	1	2	0	0
3	66	L	18.6	ILC	7	4	4	0	0
4	70	L	28.8	IDC	15	3	2	0	0
5	45	R	24.6	IDC	10	4	3	0	0
6	74	L	23.0	IDC	14	2	2	0	0
7	64	L	30.2	IDC	15	3	3	0	0
8	74	L	20.9	IDC	10	2	1	0	0
9	48	L	20.8	IDC	27	3	2	2	12

Correlation between the number of SLNs delineated of MR lymphography and those detected by the magnetometer was significant ($\rho = 0.81$)
IDC invasive ductal carcinoma, *ILC* invasive lobular carcinoma

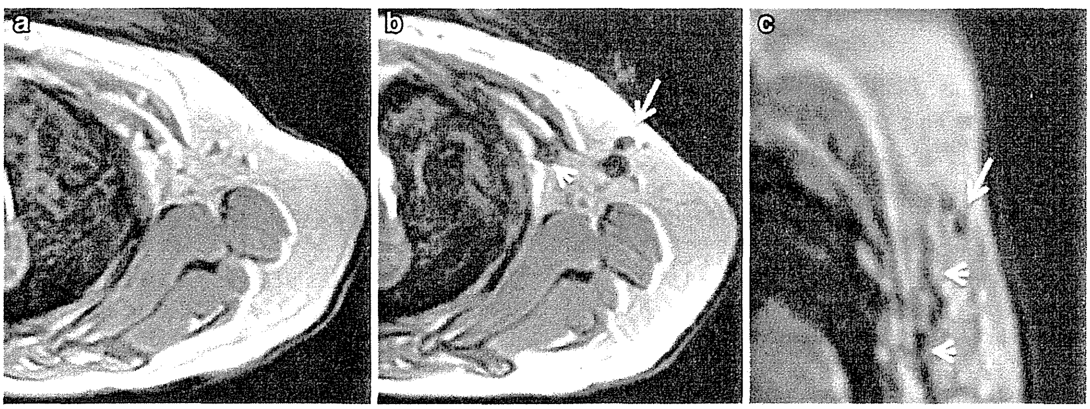

Fig. 2 SPIO-MR lymphography in a T2*-weighted gradient echo (T2*-GRE) sequence. During the pre-injection phase in T2*-GRE, SLNs could not be delineated by MR imaging (**a**). Twenty minutes after injection of SPIO into the subareolar breast tissue, MR sentinel lymphography demonstrates two SPIO enhanced SLNs, one lateral to the pectoralis major classified as a lower axillary node (*arrow*), and one was beneath the pectoralis minor classified as a midaxillary node (*short arrow*). Non-SLNs could not be demonstrated because they lack SPIO enhancement (**b**). Reconstructed coronal image shows lymphatic pathway (*short arrow*) drained into the SLN (*arrow*) (**c**)

the reconstructed coronal view, the lymphatic pathway was recognized to drain into the enhanced SLN. (Fig. 2c).

Intravenous enhanced CT did not identify SLNs among axillary lymph nodes. While gadolinium-enhanced MR images clearly delineated multifocal lesions and a few axillary lymph nodes, these lymph nodes could not be distinguished from non-SLN or SLN, too. SPIO-MR lymphography accurately localized primary SLNs by visualizing the direct connection between these lymph nodes and the draining lymphatic vessels from the SPIO injection site (Fig. 3). Information derived from MR sentinel lymphography assisted in the performance of the SLN biopsy.

Three-dimensional MR SLN lymphography

From axial image data (Fig. 4a), three-dimensional MR lymphography images were reconstructed. The relationship between marking pills, SLNs, and anatomical structures were simulated including the details of draining lymphatic vessels (Fig. 4b, c). The delineated lymphatic vessels could be observed through the transparent skin surface using a see-through mode (Fig. 4b). These images were used to simulate the skin incision during an SLN biopsy (Fig. 4c) and rotated allowing any angle of view on the display. The simulated images of MR lymphography matched the operative findings of surrounding structures, the pectoralis major/minor muscles, latissimus dorsi muscle, serratus anterior muscle, lateral thoracic artery/vein, and fine lymphatic vessels. (Fig. 4d).

SLNs with metastases on MRI lymphography

The present MR lymphography demonstrated strong suspicion of metastatic nodes having a partial and obscure low signal intensity on T2* images (Fig. 5a, b), in which SLNs macrometastases were revealed on pathological examination. A node was considered non-metastatic if it showed a homogenous low signal intensity (Figs. 2b, 3, 4a) and metastatic if the entire lymph node or a focal area did not show low signal intensity (Fig. 5a, b) on MR imaging. To confirm the migration of SPIO to the metastatic lymph nodes, SLNs were examined histologically with Berlin blue stain (iron stain), which showed that blue-stained ferucarbotran had moved along the lymphatic sinus around the metastatic lesion (Fig. 5c).

The sensitivity, specificity, and accuracy of MR imaging for the diagnosis of sentinel node metastases were all 100.0 %. However as a pilot study, only a limited number of patients have been investigated.

Fig. 3 Complex drainage lymphatic pathways and SLNs in SPIO-MR sentinel lymphography. SPIO-MR sentinel lymphography clearly visualized the direct connection between the injection site of SPIO (*arrow*) and a series of afferent lymphatic vessels drained into two SLNs with SPIO enhancement (*short arrow*), located lateral to the pectoralis major muscle. Two SLNs were enhanced and confirmed as having no metastases on pathological examination after surgery

Discussion

Although SLN biopsy is the standard of care for many patients with breast cancer, further development to increase sensitivity and decrease invasiveness will benefit patients. Lymphoscintigraphy cannot demonstrate accurate anatomy of SLNs, because of limitations in spatial resolution and the lack of detailed anatomy of the surrounding structures [12]. In contrast to radio-colloid scintigraphy, we introduced a new three-dimensional image reconstruction technique, SPIO-MR lymphography, as a simulation tool for SLN biopsy. On three-dimensional MR lymphography, images of the pectoralis major, latissimus dorsi, axillary vein, lateral thoracic artery/vein, and SLNs were generated and rotated freely to simulate the skin incision and locate SLNs at various anatomic levels.

The localization of SLNs using MR imaging in the prone position differs from that in the operative (supine) position. Therefore, some authors have reported and emphasized the importance of preoperative MR imaging in the supine position [13]. In the present study, the supine position with elevation of the arms and an MR marking technique using commercially available tablets were adopted for precise preoperative simulation [6].

With imaging techniques available today including intravenous enhanced MRI or CT, axillary SLNs cannot be distinguished from non-SLNs on the basis of the size or

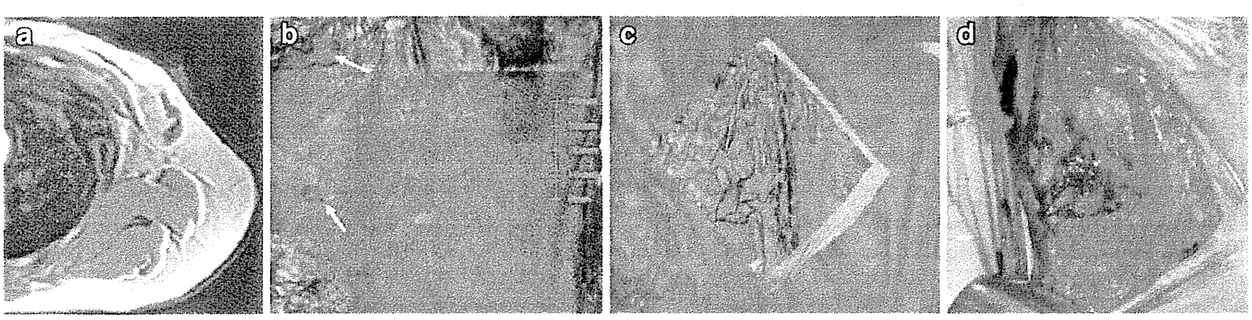

Fig. 4 SLN biopsy without metastases. A transverse T2*-weighted image of the axilla shows a lymph node with overall low signal intensity (**a**). Using the see-through mode of three-dimensional lymphography, SLNs are located using the reference of the marking pills (*arrows*) (**b**). Through the window of a simulated skin incision, the relationship between the vessels accompanying the lateral pectoral nerve, lateral thoracic artery/vein, and SLN were simulated in detail (**c**). Using SLN biopsy after three-dimension lymphography, the blue-stained SLN and surrounding fine vessels were comparable to those shown on MR-SLN lymphography (**d**)

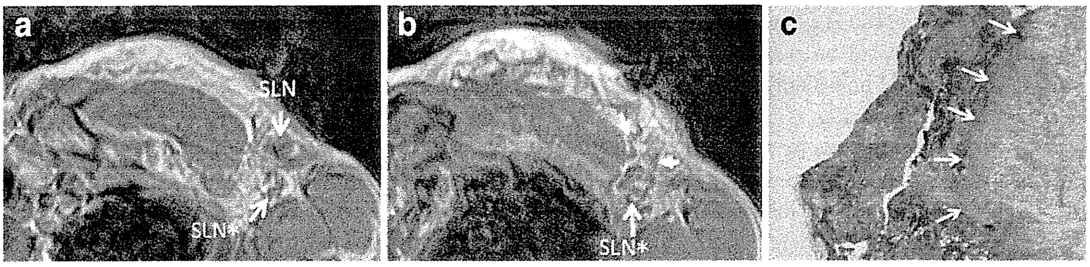

Fig. 5 SNL biopsy with metastatic lesions. A transverse T2*-weighted image of the axilla shows two obscure SLNs (**a**) and two lymphatic vessels (*short arrows* in **b**) and an obscure SLN with partial signal intensity decrease (**a**, **b**). These lymph nodes are more heterogeneously enhanced than non-metastatic SLNs. Pathologic examination confirmed the presence of metastatic lesions (*arrows* in **c**) in the LN corresponding to the SLN* in **a**, **b**. Histologic images show iron accumulation stained by Berlin blue stain, which is specific to iron (Berlin blue stain, ×4) (**c**)

shape of a lesion. Preoperative assessment of sentinel lymph nodes is limited. Lymphography including MRI or CT with direct injection of contrast material into the breast tissue has been reported [4, 12, 14, 15]. In serial SLN biopsies following MR or CT imaging, radioisotope or blue dye was used as the tracer. Using that approach, it is possible that resected SLNs identified using radioisotope/dye may be different from SLNs demonstrated on CT/MRI lymphography. This is the first study to demonstrate the use SPIO as both contrast material and tracer.

Ishiyama et a. [14] performed a dynamic MR lymphography scan using an undiluted solution of SPIO. MR lymphography showed the SLN at 10–20 min and another lymph node designated as "non sentinel" at 90 min. They concluded that the best imaging was obtained at 10–20 min. We performed post-contrast MR imaging based on these results.

The benefit of SPIO is that it is commonly used as a contrast material, and the tracer shows a significant correlation between the number of SLNs detected by SPIO MR lymphography and those harvested at SPIO SLN biopsy. While SPIO-MR sentinel lymphography detected a total of 24 nodes as SLNs, a total of 20 lymph nodes were harvested as SLNs. This difference may indicate that the sensitivity of the SPIO magnetometer is less than that of MR lymphography for the identification of SLNs. Further improvement of the magnetometer is underway in consultation with a physicist and further studies are needed. SLN biopsy using radioisotopes may image many SLNs that should be harvested owing to the nature and size of the radioactive tracer [16]. Only one or two SLNs are enough in SPIO biopsy, because SPIO-MR lymphography accurately identifies the SLNs by visualizing lymph flow. Precise orientation in the axilla is essential and reduces the false negative rate during SLN biopsy.

The behavior of injected material is largely a function of particle size and interstitial pressure. The largest particles (>200 nm) will stay at the injection site and the smallest (<5 nm) will rapidly disperse into the bloodstream. Particles between 5 and 10 nm will rapidly enter the lymphatics, but visualize numerous nodes. The optimal particle size to allow migration to relatively few regional nodes is probably 10–200 nm [2, 16]. Ferucarbotran particles consist of low molecular weight carboxydextran-coated iron oxide (3–5 nm) predominantly of the gamma-Fe_2O_3 form with a diameter ranging from 57 to 59 nm [17], which is considered a suitable particle size for sentinel lymphography and biopsy.

During lymphography with the direct injection of SPIO, lymph nodes infiltrated by malignant cells are indistinct and show a drop in the signal intensity on T2*-GRE images (Fig. 5a, b). Pathologically, iron stain shows that the uptake of SPIO by macrophages was interfered with by tumor cells (Fig. 5c). Previous MR imaging with interstitial SPIO injection for the detection of metastases in SLNs localized by CT lymphography was reported to demonstrate a sensitivity, specificity, and accuracy of detection at 84.0, 90.9, and 89.2 %, respectively. [4]. In the present study only a small number of patients were included; however, SPIO-MR lymphography may validate the detection of nodal metastases.

CT imaging is reported to be the most frequently used method for assessing lymph node status in cancer staging. MRI also has been reported for this purpose but generally has lower spatial resolution [7, 18], whereas ultrasonography is likely to be affected by physician bias. Much thinner section thickness or higher field strength such as a 3-T MR system may improve the accuracy of detecting metastases in axillary lymph nodes. Chest CT gives a radiation exposure at least 7 mSv each time [19]. MR lymphography could be a more acceptable modality because of its lack of radiation exposure, even if MR might be inferior to CT in resolution power.

The T2*-GRE technique on MR imaging has been shown to be useful in assessing organ-specific iron load in patients with thalassemia [20] and the detection of tiny hemosiderin deposits due to previous bleeding from a cerebral aneurysm [21]. Ultra-small superparamagnetic iron oxide (USPIO) is another type of superparamagnetic nanoparticle and consists of an iron oxide crystalline core of 4.3–6.0 nm, smaller than SPIO, which has been introduced as a contrast agent for intravenous MR lymphography on T2*-gradient echo images [22]. We chose a gradient-echo T2*-gradient echo sequence rather than a spin-echo T2 sequence because of greater sensitivity to iron deposition using SPIO [21].

In the first patient, gadolinium-enhanced MR imaging was performed at the same time as SPIO-MR sentinel lymphography, after gadolinium administration. The lengthy presence of gadolinium in SLNs showed a radiologically relevant interaction with SPIO enhancement and thus interfered with the interpretation of MR images. After that, gadolinium-enhanced MR imaging was performed separately from SPIO-MR sentinel lymphography, which is not convenient for the patient. When discussing the utility of this technique, the practical benefits exceed the level of inconvenience.

In this study, ferucarbotran, a clinically approved intravenous contrast material, was injected in the subareolar breast tissue. While use of this agent is not specifically approved for imaging breast lesions, this off-label use was approved by the institutional review board and all patients provided informed consent. There have been no allergic or other acute severe reactions to this agent. One of ten patients had a minor skin color change, which resolved spontaneously within 2 months. After observing this minor adverse effect, we injected the material into naturally brown circumareolar tissue to avoid this minor adverse effect. From April 2008 to March 2010, SLN biopsy using the same technique of direct SPIO injection was performed in 30 patients [5] including the one patient with a skin color change reported in this study. No other side effects were recognized. Some patients have also since undergone MRI for medical examinations with no side effects.

Motomura et al. [4] reported no local or systemic adverse events in their MR lymph node imaging with interstitial diluted SPIO (100–500 fold) injections in 102 patients with breast cancer. However, they performed post-contrast MR imaging at 24–36 h after contrast administration. Further study is necessary to confirm the optimal timing and concentration of SPIO to improve the accuracy of this technique and to evaluate metastatic lesions including micrometastases.

To our knowledge, this is the first prospective study of serial sentinel lymphography and SLN biopsy using SPIO without radiation exposure. The SPIO-MR sentinel lymphography technique offers an accurate means of performing SLN biopsy in patients with breast cancer.

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