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Effects of iron oxide particles on MRI and mammography in breast cancer patients after a sentinel lymph node biopsy with paramagnetic tracers

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ABSTRACT

Objective: The aim of this study is to evaluate the effect of iron oxide particle deposition on follow-up mammograms and MRI examinations of patients who underwent sentinel lymph node detection with iron oxide particles.

Materials and methods: Two hundred and eighteen patients who had sentinel lymph node biopsy (SLNB) with iron oxide particles were evaluated. Follow-up MRI and mammography were available in 36 and 69 cases respectively. MRI examinations were evaluated for ferromagnetic artifacts that were graded as follows: 0 = No artifact, 1 = Focal area, 2 = Segmental and 3 = Regional signal void artifact. Mammography artifacts were evaluated for the presence of dense particles. Pearson's chi-square test was used for statistical analyses and $P < 0.05$ was accepted as significant.

Results: MRI artifact grading was as follows: Grade 0: 11 (30.6%), Grade 1: 14 (38.9%), Grade 2: 3 (8.3%), and Grade 3: 8 (22.2%). The grade of artifacts differed across surgery types ($P = 0.019$). Grade 3 artifacts were higher in breast conserving cases whereas Grade 0 was more frequent in subcutaneous mastectomy cases. Three out of 69 (4.4%) cases who had follow-up mammography had artifacts due to iron oxide particle accumulation which presented as Grade 3 MRI artifact in all.

Conclusion: Accumulation of iron oxide particles after SLNB with paramagnetic tracers causes artifacts on follow-up MRI examinations in half of the cases but it is significantly low in mammograms. These artifacts may be confusing in the evaluation of the images. Radiologists must be aware of these tracers and their artifacts whereas patients should be questioned for the type of SLNB before a follow-up examination.

1. Introduction

The standard method for the evaluation of the axilla for breast cancer surgery is sentinel lymph node biopsy. Although conventional detection of the sentinel lymph node is the injection of blue dye, radioisotope tracers are accepted as the gold standard. However, there are some drawbacks for radioisotope tracers such as strong regulations, the need for a nuclear medicine unit, limitations in availability and supply, radiation exposure for patients and health professionals.[1–3] Research of new methods as an alternative to radioisotope tracer method like superparamagnetic iron oxide nanoparticles (SPIO), indocyanine green fluorescence (fICG), indigocarmine blue dye, tattooing with black carbon, intraoperative ultrasound (IOUS), and contrast-enhanced ultrasound (CEUS) with microbubbles is still ongoing.[4]

Sentinel lymph node detection with iron oxide particles (Sentimag® technique) is a new technique that uses small magnetic particles (Sienna+ ®) as a tracer and the size of the particles is 60 nm.[1–3,5,6] The same principle with the radioisotope injection is used for the injection of the particles and a handheld magnetometer (Sentimag®) device is utilized for tracing the magnetic particles in detecting the sentinel node. The magnetic tracer is more homogenous compared to the radiotracer and its unique dark brown color can also be visualized during the detection of the sentinel node. This new technique showed promising results with a detection rate of as high as 97.3% which is in line with the radiotracer method studies.[1–3,5,6] The method is safer compared to radioisotope tracers as it avoids radiation exposure related issues and can be administered in the operation room, on the same day of the operation.

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However, deposition of the iron oxide particles in the breast tissue may cause artifacts in the follow-up breast examinations such as MRI and mammography.[7–9] These studies showed impaired MRI images in approximately 40% of the patients.[8,9]

The aim of this study is to evaluate the effect of iron oxide particle deposition on follow-up mammograms and MRI examinations of patients who underwent sentinel lymph node detection with iron oxide particles.

2. Material and method

Institutional review board approval was obtained. Every patient was informed, and consent was taken. We have evaluated 218 consecutive patients who had sentinel lymph node detection with iron oxide particles between January 2016 and July 2019. The inclusion criteria were having a follow-up mammogram and/or follow-up MRI examination. Patients who did not attend to follow-up imaging were excluded. Mammogram and MRI cases were evaluated in different cohorts as there were mammography follow-up cases without MRI examinations. All patient information and patient images were retrieved from the electronic RIS and PACS systems. The type of surgery such as segmental mastectomy, skin sparing mastectomy and modified mastectomy was obtained from the patients' RIS data and compared with the radiologic images.

A follow-up mammography examination was performed in 69 of 91 cases (median age 51, range 32–85) who had a segmental mastectomy (lumpectomy or quadranectomy). The remaining 127 patients had a skin-sparing or modified mastectomy. Mammograms of these remaining patients were not evaluated as only the images of the contralateral breast were acquired. The average time for mammography examinations was 11 months (range 8–14 months).

A follow-up MRI was performed in 36 patients (median age 49, range 37–68). Twenty-five of these patients underwent a segmental mastectomy and also had mammograms. Two of the remaining 11 cases were mastectomy patients and had only mammograms of the contralateral breast. Nine patients had bilateral skin-sparing mastectomy and had mammograms along with their MRI examinations. The median time between surgery and MRI examination was 19 months (range: 3–38 months).

2.1. Sentinel lymph node detection

The injection of the magnetic particles (Sienna+ ®) was made according to the literature.[1] A periareolar interstitial injection of the 2 ml of the tracer which was diluted to 5 ml with saline was made 20 min before the operation. The injection site was massaged for 5-min for better distribution. A detailed technical definition can be found in the literature.[1]

2.2. Mammography

All mammography images were taken with digital mammograms (Amulet Innovality, Fuji, Japan, and Pristina, GEHC, Milwaukee, USA). Each patient had 2D CC and 3D MLO tomosynthesis with a synthetic 2D view of each breast. The mammograms that were taken in the 6th month after the termination of radiotherapy were evaluated.

2.3. MRI

MRI examination was done with 1.5 T magnet (Symphony, TIM upgrade and Aera, Siemens Healthcare, Erlangen, Germany), with 7 channel breast coil (Sense coil, Innova, Germany) or with 16 channel phased-array breast coil (Siemens Healthcare, Erlangen, Germany).

MRI study included an axial turbo spin-echo T2-weighted sequence with TR/TE 6510/70 ms, field of view (FOV) 34 cm, acquisition matrix 384 × 384, slice thickness 3 mm. Dynamic contrast enhanced MRI (DCE-MRI) studies were acquired by Flash 3D FATSAT volumetric sequences with TR/TE 5.16/2.38 ms, FOV 340 mm, acquisition matrix 384 × 288, slice thickness 1 mm with a temporal resolution of 62 s in the first center, and 3D volumetric interpolated Non-FATSAT sequences with TR/TE 5.01/1.77 ms, FOV 300 cm, acquisition matrix 512 × 460, slice thickness 1 mm with a temporal resolution of 82 s in the second. Subtracted contrast-enhanced dynamic images were used as standard. After DCE-MRI sequences, one sagittal CE T1 weighted Flash 3D acquisition was performed with TR/TE 12.2/6.07 ms, FOV 240 mm, 256 × 192 matrix, 1 mm thickness, for both breasts.

Contrast agent, either 0.1 mmol/kg Gadobutrol (Gadovist®, Bayer Schering Pharma, Berlin, Germany) or 0.1 mmol/kg gadoterate meglumine (Dotarem®, Guerbet, Villepinte, France), was administered.

2.4. Evaluation

The susceptibility artifact in MRI images due to iron-oxide particles was evaluated by two radiologists, each with more than 20 years of experience in breast imaging. The evaluation was made together, and the decision was made in consensus. The susceptibility artifact was classified with a 4-scale evaluation as follows: 0 = No artifact, 1 = Focal area of signal void artifact (less than 5 mm), 2 = Segmental area of signal

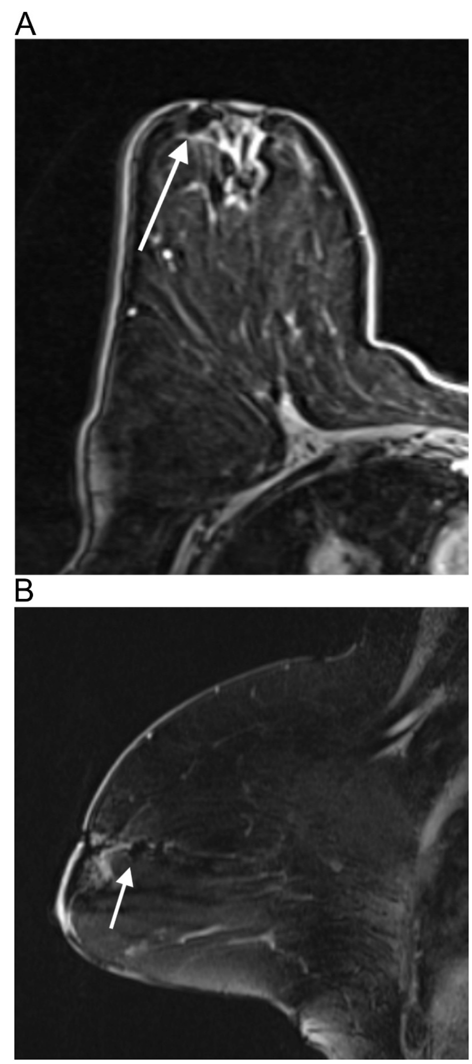

Fig. 1. (A) 68-year-old woman with a segmental mastectomy on the right breast. Axial T1W postcontrast image shows a small subcutaneous focal artifact (Grade 1) on 12:00 o'clock (white arrow). (B) Note the artifact (white arrow) on the sagittal T1 weighted image with late contrast of the same patient.

void artifact, 3 = Regional signal void artifact (Figs. 1–3). The artifacts were evaluated on T2W, T1W noncontrast, and T1 weighted dynamic contrast enhanced images. The artifacts were compared with the mammography images in order to differentiate from an artifact caused by a possible surgical clip and those that were caused by surgical clips were excluded.

The artifacts in the mammograms were evaluated for the presence of dense particles by the same radiologists and a decision was taken in consensus.

The grades of artifacts were compared with the surgery types and with the time between surgery and the examination. Pearson's chi-square test was used for statistical analyses and $p < 0.05$ was accepted as significant.

3. Results

3.1. MRI findings

Thirty-six patients were evaluated for MRI images. The number of cases according to artifact grading was as follows: Grade 0: 11 (30.6%),

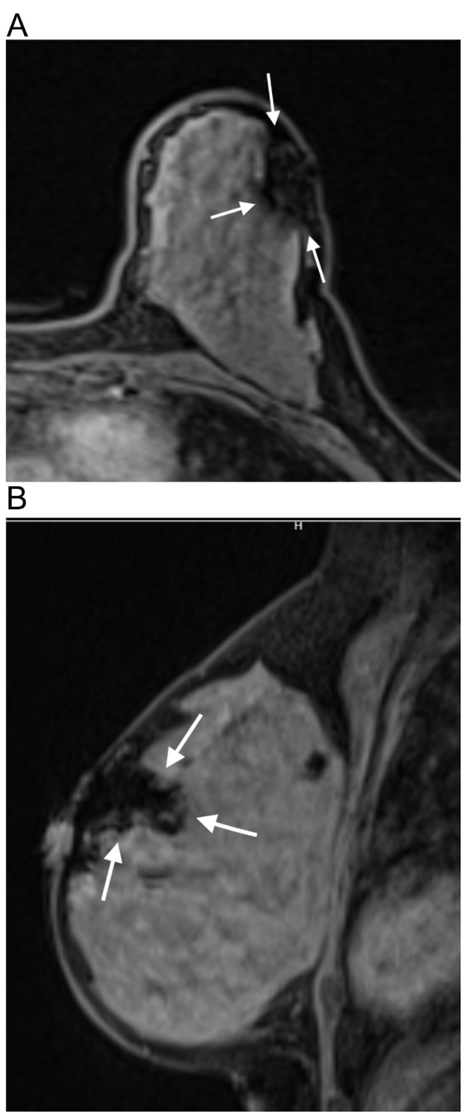

Fig. 2. (A) 40-year-old woman with a segmental mastectomy on the left breast. Axial T1W postcontrast image shows a subcutaneous segmental artifact (Grade 2) on the upper outer quadrant (arrows). (B) Note the artifact (arrows) on the sagittal T1 weighted image with late contrast of the same patient.

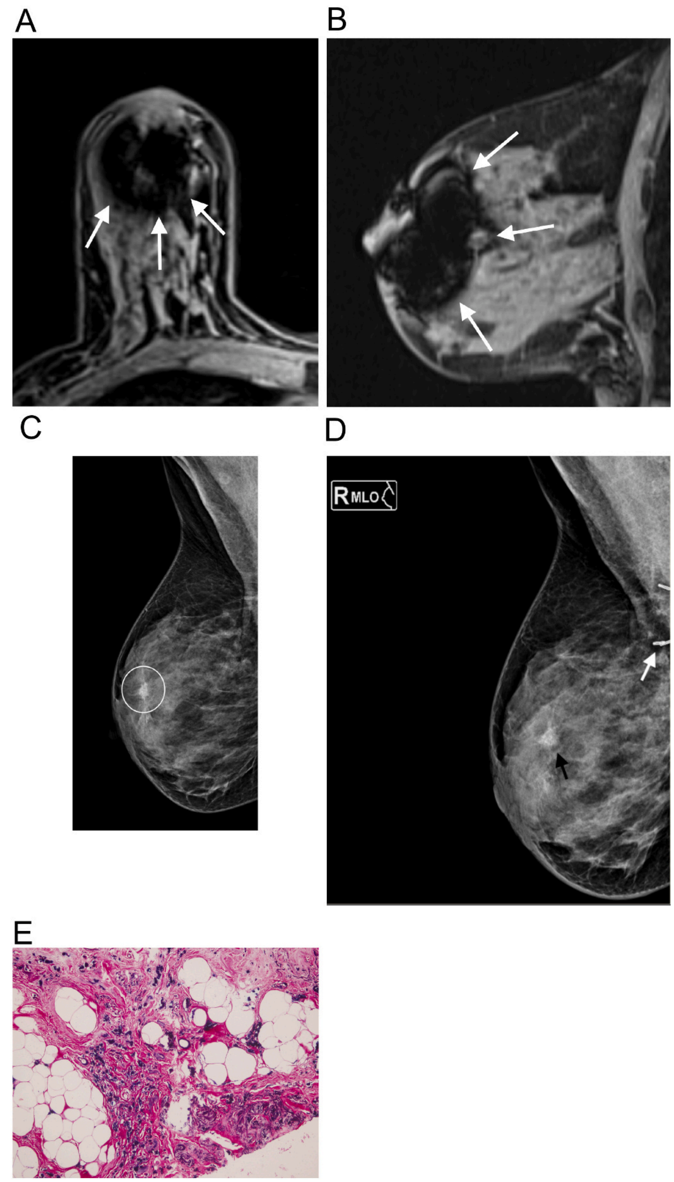

Fig. 3. 42-year-old woman with a segmental mastectomy of the right breast. (A) MRI examination 24 months after surgery shows a grade 3 artifact on T1 weighted axial contrast enhanced image (black arrows). (B) Sagittal late T1 weighted contrast enhanced image shows the artifact exaggerated compared to axial images (black arrows). (C) MLO mammogram same time with the MRI examination shows the accumulation of the iron oxide particles as a dense irregular lesion with ill-defined margins (black circle). (D) MLO view showing the operation site (white arrow) and the artifact (black arrow) on the same view. (E) Cut biopsy specimen stained with Prussian blue showing iron particles in the breast tissue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Grade 1: 14 (38.9%), Grade 2: 3 (8.3%), and Grade 3: 8 (22.2%).

The distribution of artifacts according to the types of surgery is given in Table 1. There was a statistical difference between segmental mastectomy (breast conserving surgery) and subcutaneous mastectomy (P = 0.019) regarding the grade of the artifacts. Accumulation of the iron oxide particles in the breast tissue caused serious artifacts (grade 2 or 3) on T1W and DCE-MRI T1W images which obscured the affected tissue in 30.6% of the patients (Figs. 3, 4). The artifacts were more likely to occur in patients who had a segmental mastectomy but less frequent in those who had a subcutaneous mastectomy (P = 0.019). Interestingly, we have observed grade 1 artifacts in 4 (44.4%) of the cases who had a

Table 1
Distribution of grades of MRI artifacts according to surgery types.

	Surgery types			
Grades of MRI artifacts	Segmental mastectomy	Subcutaneous mastectomy	Mastectomy	Sum
0	4	5	2	11
1	10	4		14
2	3			3
3	8			8
Sum	25	9	2	36

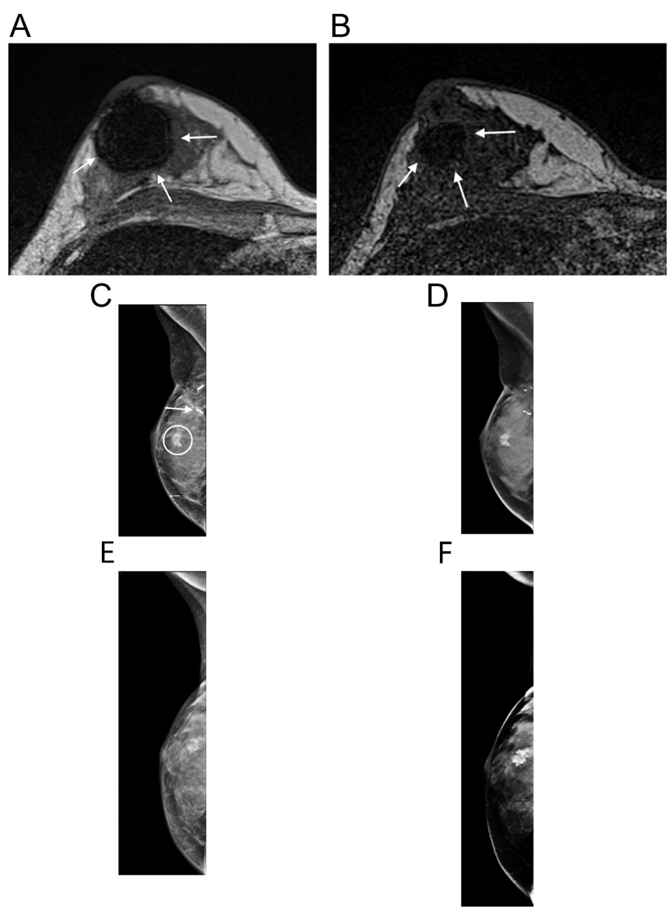

Fig. 4. 36-year-old woman with a segmental mastectomy of the right breast. (A) MRI examination 14 months after surgery shows a large grade 3 artifact (arrows) on NON FATSAT T1 weighted axial contrast enhanced image. (B) MRI examination 38 months after surgery shows a grade 3 artifact (arrows) on NON FATSAT T1 weighted axial contrast enhanced image. The artifact is gradually smaller when compared to the first MRI examination (panel B). (C) MLO mammogram 14 months after surgery shows the accumulation of the iron oxide particles as a dense irregular lesion with ill-defined margins (white circle). Note the operation site marked by surgical clips is far from the artifact (arrow). (D) MLO tomosynthesis slice of panel C shows the lesion mimicking malignant features. (E) MLO mammogram 38 months after surgery shows identical features with panel C. (F) MLO tomosynthesis of panel E shows the lesion features.

subcutaneous mastectomy (Fig. 5). On the other hand, 48.8% of the cases who had a segmental mastectomy showed grade 2 or grade 3 artifacts which masked a larger region (Figs. 2–4).

The mean time span between the operation and MRI examination was 20 months. There was no correlation between the grade of artifact and the time of MRI examination after surgery ($P=0.36$). Three of our patients had their second follow-up MRI on the 36th, 38th, and 41st months after the operation respectively; the first two patients had grade 3 and the third patient had grade 2 artifacts that have not changed their grades compared to the prior MRI examinations. However, one of these cases who still had grade 3 artifact on the second MRI examination (38th month) showed a relatively smaller artifact compared to the first MRI examination that was taken on the 14th month after the surgery. On the contrary, the size of the artifact hasn't changed on the mammograms by time (Fig. 4). The average time for the first MRI examination of patients with grade 3 artifacts after the surgery was 20.6 months.

3.2. *Mammography findings*

Three out of 69 (4.4%) cases who had follow-up mammography had artifacts due to iron oxide particle accumulation and all presented grade 3 artifacts on MRI. In other words, these cases consisted of 37.5% (three out of eight patients) of the cases with grade 3 artifacts on MRI images. The accumulated particles caused dense irregular and ill-defined lesions, mimicking malignant features on mammograms (Figs. 3, 4). One of these patients underwent 3D tomosynthesis guided vacuum biopsy. The histopathology of the specimen revealed iron deposition in the breast stroma and associating small amounts in the histiocytic cytoplasm that was demonstrated with the Prussian blue staining method (Fig. 3E). The tomosynthesis images of the artifact were not different than the 2D images in the differential diagnosis. These artifacts were mass like lesions with irregular borders and indistinct margins with high density (Fig. 4).

4. Discussion

This study showed that iron oxide particle deposition after an SLNB caused artifacts both on MRI and mammography images on follow-up examinations. However, the artifacts were less frequently seen on mammograms compared to MRI. The accumulation of these particles formed an irregular shape with indistinct margins which was mimicking a dense irregular mass on mammograms that did not resemble the typical appearance of accumulated microparticles. We believe that the cognizance of such artifacts on follow-up mammograms of breast cancer patients is important for breast radiologists as the use of these particles for SLNB is increasing. However, this finding was detected in only three patients' mammograms although a higher rate of artifacts was depicted on MRI. In fact, a higher rate of mammography artifacts would be expected consistent with the frequent susceptibility artifacts on MRI. Nonetheless, tiny metal particle deposition can lead to susceptibility artifacts even if they are not evident on mammograms.[10] This may explain the absence of artifacts on mammograms despite the prominent susceptibility artifacts on MRI due to the heavy accumulation of iron oxide particles in some of our cases.

Severe MRI artifacts that may obscure a possible recurring focus were present in almost half of our patients who had a segmental mastectomy. A similar study with 24 cases used a different grading system and the authors reported a 12% rate of severe artifacts whereas interpretation of images was impossible, in their cases with segmental mastectomy.[9] However, they have reported a higher rate of impaired images with different grades of artifacts in line with our findings (40% vs 48.8%).

Patients who had a skin-sparing mastectomy with implants frequently showed grade 1 artifact. Although these artifacts were very small, they had the potential to mask a millimetric local subcutaneous recurrence (Fig. 5). Notwithstanding that the breast tissue is removed by subcutaneous mastectomy, the remaining thin line of subcutaneous fat tissue may harbor a possible recurrence.

Ferromagnetic particles cause inhomogeneity in the magnetic field that results in metallic artifacts which is also referred to as susceptibility artifacts. These artifacts are seen as signal intensity void, distortion of the image in the proximity of these objects, and more severe in gradient echo images which are mostly used in DCE-MRI of the breast.[10,11] They may also cause the failure of fat saturation depending on its magnitude.

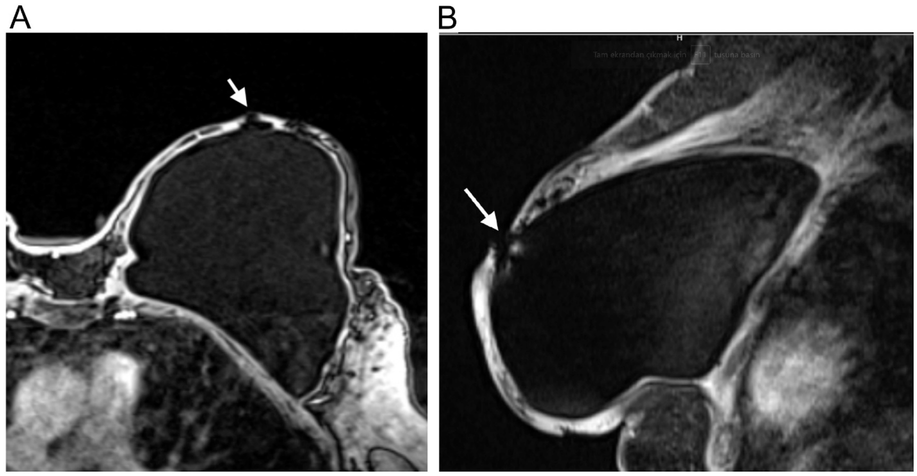

Fig. 5. (A) 37-year-old woman with bilateral subcutaneous mastectomy with implant placement. Axial T1W postcontrast image shows a small subcutaneous retro areolar focal artifact (Grade 1) on 12:00 o'clock (white arrow). (B) Note the artifact (white arrow) on the sagittal T1 weighted image with late contrast of the same patient.

The severity of the artifact and distortion may preclude the detection of a possible recurrence.[12] Signal void artifact can be minimized with SE sequences and fast SE sequences with a short echo time. On the other hand, a distortion artifact can be overcome by increasing the slice selection pulse bandwidth and readout bandwidth with a trade-off for an increased specific absorption rate (SAR).[10–13] The sequences used in our MRI protocol were 3D gradient echo sequences in both magnets. There is one case report in the literature that reported the benefit of maximization of both slice selection and readout bandwidths in gradient echo T1W sequences, on the third follow-up (18th month) MRI examination of a patient who had sentinel lymph node biopsy with iron oxide particles.[14] The authors reported that they observed fewer distortion artifacts on this 3rd follow-up MRI compared to prior MRI examinations without a bandwidth adjustment. However, they explain the decrease of the metal artifact by a possible effect of the long-time span between this third MRI examination and the operation rather than the adjustments made in the bandwidths of the gradient echo sequences.[14] In our cohort; three of our patients did not show any diminution of the artifacts despite an average follow-up time of 20.6 months which we believe is long enough to expect a reduction in the susceptibility artifacts if time was a variable for the decrease. The radiologists should be aware of this procedure and the patients must be questioned for the technique of SLNB before the examination. Thereby, switching to the acquisition protocols which are less susceptible to iron oxide can be an alternative. However, further studies are needed to show the diagnostic accuracy of these possible alternative techniques.

There are some limitations of this study. First, the readers were not blinded but were aware of the procedure during the evaluation of MRI and mammography images. However, we do not believe that it is a reason for bias as the artifacts were not subtle. Furthermore, susceptibility artifact is well known by the radiologists and easy to recognize. Second, due to the retrospective nature of the study, we were not able to try different MRI protocols that might help to reduce these susceptibility artifacts. It is crucial to introduce less susceptible, alternative MRI protocols for patients who had SLNB with iron oxide particles.

In conclusion, iron oxide particle injection for SLNB is a new procedure and not well known by breast radiologists. Severe susceptibility artifacts, which are a potential risk for masking recurrences, are frequently detected in patients who had SLNB with iron oxide particles during segmental mastectomy. Although mammography images are less affected, the accumulation of these particles can cause confusion in the evaluation of mammograms as they can mimic malignant lesions. Patients, particularly those who had a segmental mastectomy, should be questioned for the type of sentinel lymph node biopsy before the follow-up examination.

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