Moving a neodymium magnet promotes migration of magnetic tracer and increases the monitoring counts on the skin surface of sentinel lymph node in breast cancer

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Abstract
Background: We thought that moving a small neodymium magnet would promote migration of the magnetic tracer to the sentinel lymph node (SLN). Higher monitoring counts on the skin surface before incision help us detect SLNs easily and successfully. The aim of the present study was to verify enhancement of the monitoring count on the skin surface in SLN detection by the magnet movement in sentinel lymph node biopsy (SNB) using superparamagnetic iron oxide (SPIO) nanoparticles.

Methods: After induction of general anesthesia, superparamagnetic iron oxide nanoparticles were injected sub-dermally into the subareolar area or peritumorally. The neodymium magnet was moved over the skin from the injection site to the axilla to promote migration of the magnetic tracer without massage. A total of 62 patients were enrolled from February 2018 to November 2018; 13 cases were given 20 times magnet movement (Group A), 8 cases were given 1-min magnet movement (Group B), 26 cases were given a short (about 5 min) interval from injection to 1-min magnet movement (Group C), and 15 cases were given a long (about 25 min) interval before 1-min magnet movement by the magnetometer's head (Group D). In all cases, sentinel node biopsy was conducted using both the radioisotope (RI) and SPIO methods. The monitoring counts on the skin surface were measured by a handheld magnetometer and compared among the 4 groups. Changes in the monitoring count by interval and by magnet movement were evaluated. Results: The identification rates of the SPIO and RI methods were 100% and 95.2%, respectively. The mean monitoring counts of Group A, B, C, and D were 2.39 μT, 2.73 μT, 3.15 μT, and 3.92μT, respectively (p<0.0001; Kruskal-Wallis test). The monitoring counts were higher with longer magnet movement and with the insertion of an interval. Although there were no relationships between the monitoring count on the skin surface and clinicopathologic factors, magnet movement influenced strongly on the monitoring count on the skin surface. Conclusion: Moving a small neodymium magnet is effective for promoting migration of a magnetic tracer and increasing monitoring counts on the skin surface.

Introduction
Sentinel lymph node biopsy (SNB) has been established as the standard method for staging clinically node-negative breast cancer [1, 2], and SNB using superparamagnetic iron oxide (SPIO) nanoparticles
and a handheld magnetometer has been reported [3]. Although the radioisotope (RI) and dye-combined method had been thought to be the standard, SNB by SPIO has been performed because the RI method has the disadvantage of radiation exposure [4], regulations regarding radioisotope management [5], and pain of tracer injection [6, 7]. But SPIO method has drawbacks. It needs time to identify sentinel lymph nodes, and pigmentation of SPIO remains for a long period of time. We thought that moving a small neodymium magnet would promote migration of the magnetic tracer to the SLN. And magnet movement by a small neodymium magnet from the injection site to the axilla over the skin without massage after injection under general anesthesia was conducted in SNB by SPIO. Then we reported that it was useful to detect SLNs and the identification rate was extremely high with SPIO [8, 9].

The advantage of RI or SPIO method is that it assesses RI or SPIO uptake as monitoring counts on the skin surface quantitatively. Even in SNB by indocyanine green (ICG) method in gastric cancer, it was reported that fluorescence intensity in fluorescence nodes was evaluated using ICG intensity imaging software of the hyper eye medical system [10]. Higher monitoring counts on the skin surface before incision help us detect SLNs easily and successfully. In RI method, the measured value can be trusted even if the count is 1, but the reliability of monitoring counts on the skin surface is lowered when the response of magnetometer is weak, especially less than 1µT. To find the best procedure to obtain a higher count, the length of magnet movement was changed or an interval was inserted between injection and magnet movement. The aim of the present study was to verify enhancement of the monitoring count on the skin surface in SLN detection by the magnet movement.

Patients And Methods
The study was approved by the local ethics committees and was registered in University hospital Medical Information Network (UMIN) Clinical Registry (UMIN000029475). Written, informed consent was obtained from 69 patients from February 2018 to November 2018. SNB was conducted using both the RI and SPIO methods. Tc-99m phytate was injected the day preceding the surgery at a dose of 74 MBq, and a dose of 37 MBq was given if injected on the day of surgery. And it was injected intra-dermally or sub-dermally into the subareolar area or peritumorally. After induction of general
anesthesia, 0.5 ml of ferucarbotran (Resovist® Inj., FUJIFILM Toyama Chemical Co., Ltd., Tokyo, Japan) was injected sub-dermally into the subareolar area (total mastectomy case) or peritumorally (partial mastectomy case). The neodymium magnet (Neomag, KOKUYO Co., Ltd., Osaka, Japan) was moved over the skin 20 times from the injection site to the axilla to promote migration of the magnetic tracer without massage (Fig. 1). The dye method of SNB was not performed because of omission of massage after injection in this study. Before skin incision, the monitoring count on the skin surface was measured by a novel handheld magnetometer. The monitoring count was confirmed twice. The magnetometer developed by Tokyo University contains a small neodymium magnet in its tip (Fig. 1) [11, 12]. After skin incision, if the removed node had a measurable RI count or more than 1 µT by the magnetometer, it was considered an SLN.

To find the ideal procedure for achieving a 1.5 µT or higher count on the skin surface, the length of magnet movement was changed or an interval was inserted between the injection and magnet movement in this protocol. Several procedures were tried in 69 cases consecutively; 20 times magnet movement at first step, changing the length of magnet movement at the second step, insertion of interval at third step, and insertion of another interval and magnet movement by the magnetometer’s head at final step (Fig. 2). We proceeded to the next step after achieving higher counts than previous step. From these four steps, we chose four groups with the same procedure that consisted of more than 6 cases. Seven cases were excluded: 3 cases that were given 3-min magnet movement, 3 cases that had missing time records of at each check point, and 1 case in which a neodymium magnet instead of the magnetometer’s head was used. Then we enrolled 62 out of 69 cases. To compare the monitoring count by the length of the magnet movement or the interval from injection, 4 groups were analyzed: 13 cases that were given 20 times magnet movement (Group A); 8 cases that were given 1-min magnet movement (Group B); 26 cases that were given a short (about 5 min) interval from injection to 1-min magnet movement (Group C); and 15 cases that were given a long (about 25 min) interval before 1-min magnet movement by the magnetometer’s head (Group D). The short interval was the time for marking the resection area and so on preoperatively. The long interval was the time for preparation for surgery, such as operators’ hand washing and draping before skin incision. In
Groups A and B, only the monitoring count after magnet movement was evaluated. In the 41 cases in Groups C and D, the monitoring count and time from injection were evaluated at certain check points, such as after injection, after an interval, before magnet movement, and after magnet movement (Fig. 3). The monitoring counts on the skin surface after magnet movement were compared among the 4 groups. Changes in the monitoring count by interval and by magnet movement were evaluated. The Mann-Whitney test, Wilcoxon’s signed-rank test, Kruskal-Wallis test, and Friedman’s test were used as appropriate, with p < 0.05 considered significant.

Results
Table 1 shows the characteristics of the cases, and Table 2 shows the results of SNB. The identification rates of the SPIO and RI methods were 100% and 95.2%, respectively. It took an average of 79.9 minutes from the injection of ferucarbotran to the removal of the SLN. Because we performed SNB after making skin flap, the average time was slightly long. The lymph node retrieval rate was 3.0 nodes per patient overall, 2.0 nodes per patient with RI, and 2.9 nodes per patient with SPIO. There was no difference among four groups about the highest count of resected SLN by RI method (p = 0.2891). But mean values of the highest count of resected SLN by SPIO were different significantly (p < 0.0001). Of the 183 SLNs removed, 125 (68.3%) were identified by RI, and 182 (99.5%) were identified by SPIO. Of 19 SLNs that were histopathologically positive, 13 (68.4%) were identified by RI, and 19 (100%) were identified by SPIO. There were no cases with skin pigmentation after the operation, because the entire injected site could be resected during surgery.

Table 3 shows the results of the comparison among the 4 groups. The mean monitoring counts of Groups A, B, C, and D were 2.39 µT, 2.73 µT, 3.15 µT, and 3.92 µT, respectively (p < 0.0001; Kruskal-Wallis test). The monitoring counts were higher with longer magnet movement and with the insertion of an interval.

The relationship between time from injection and monitoring count in Groups C and D is shown as a scattergram in Fig. 4 and Fig. 5, respectively. Sequential lines mean each of the evaluated cases. Symbols show the mean values at check points, such as after injection, after an interval, before magnet movement, and after magnet movement. Although there were some cases in which the
monitoring counts were more than 1.5 μT after injection, the monitoring counts increased after magnet movement in all cases.

Sequences of the mean values at each check point in Groups C and D are shown in Fig. 6. The monitoring count gains per minute at each time point are also shown. At the same time points, there were no differences between Groups C and D. However, in the same group, monitoring count increases were significantly greater during magnet movement than after injection or during an interval. The monitoring counts increased gradually with time, but they increased more during magnet movement for a short period of time.

Although magnet movement influenced strongly on the monitoring count on the skin surface, there were no relationships between the monitoring count on the skin surface and clinicopathologic factors (Table 4).

Discussion
SNB has been established as the standard method for staging clinically node-negative breast cancer [1, 2]. The benefits of SNB by SPIO include the lack of radiation exposure, the fact that it can be performed at any hospital with or without a radioisotope department, and the fact that it can localize the sentinel lymph node (SLN) like the radioisotope (RI) method before skin incision [13]. In the SPIO method, the location of SLNs can also be indicated by the detector before skin incision [3, 14–18]. Thill reported that SNB using SentiMag® and Sienna+® (Endomagnetics, Inc., Austin, TX, USA) was useful in a multicenter study of the magnetic technique for detection of SLNs for breast cancer [15].

SNB was performed using ferucarbotran (Resovist® Inj., FUJIFILM Toyama Chemical Co., Ltd.) and a novel handheld magnetometer developed by Tokyo University in the present study. This method has drawbacks. It needs time to identify SLNs, and pigmentation of SPIO remains for a long period of time.

We then performed magnet movement using a small neodymium magnet to promote migration of the magnet tracer in the previous study [9]. That study involved 69 patients from March 2017 to January 2018. After induction of general anesthesia, 0.3 ml of ferucarbotran was injected into the subareolar area or peritumorally. The identification rate was 98.6% (68/69) with RI and 100% (69/69) with SPIO. Identification using the SPIO method with magnet movement was estimated to be better than 95%
(90% confidence interval: 95.75–100%). On the other hand, the identification rates of RI methods were slightly low (95.2%) in this study. But in the previous study, the identification rate was 98.6% (68/69: 90% confidence interval: 93.3%-99.9) with RI in our hospital. 95.2% was contained within confidence interval.

When using the RI method, it is easy to detect SLNs, because the RI probe can detect the radiation beam from SLNs. However, it is slightly difficult to detect SLNs by SPIO, because the magnetometer seeks a small tracer collection point. The purpose of the present protocol was to find the best procedure to obtain a higher count on the skin surface. Therefore, usefulness of magnet movement was evaluated from the perspective of the monitoring count on the skin surface in this study. After dose escalation of ferucarbotran from 0.3 ml (previous study) to 0.5 ml (Group A of this study) under 20 times magnet movement, the mean value of monitoring counts increased significantly from 1.37 μT to 2.39 μT (p < 0.0001, Mann-Whitney test), and the identification rate of SPIO was also 100%[9]. All patients had no pigmentation despite dose escalation. In the next step, the length of magnet movement was changed or an interval was inserted between injection and magnet movement to obtain a higher count on the skin surface. The monitoring counts increased with longer magnet movement and with insertion of an interval. The monitoring counts of resected SLNs were comparable to the monitoring counts on the skin surface. Then, higher monitoring counts on the skin surface helped detect SLNs easily and successfully. Ultimately, 1-min magnet movement by the magnetometer’s head about 30 min after tracer injection was the best procedure for obtaining a higher monitoring count. A small neodymium magnet was contained in the tip of the magnetometer developed by Tokyo University, and the magnetic force of this magnet was about five times as strong as the neodymium magnet Neomag. Several factors including obesity and age [19, 20] have been reported to affect the outcome of SNB, but there were no relationships between the SPIO method and these clinicopathologic factors in the present study. Moreover, of 19 SLNs that were histopathologically positive, 13 (68.4%) were identified by RI, and 19 (100%) were identified by SPIO. There was actually one case in which one sentinel lymph node that could not be identified by RI method but could be identified by SPIO method was positive for metastasis. Magnet movement by a small neodymium
magnet to promote migration of the magnetic tracer is a promising method of SNB by SPIO based on the identification rate, enhancing the monitoring count, and the precise and optimal detection of SLNs.

The principles of SNB are that injected small molecules pass through lymphatic vessels from the injected site and leach to the nodes by lymphatic flow. Thus, the outcome of SNB is affected by several factors, such as tracer infiltration into the lymphatic vessels, the flow of lymph, and lodging in the nodes. As for tracer infiltration into lymphatic vessels, a longer period of time from injection to detection [20, 21] and massage after injection [22] have been used. On the one hand, a small amount of tracer leached to the nodes; on the other hand, a large amount of tracer was left and spread in the surrounding breast tissue. Skin pigmentation would occur clinically if the tracer was colored [21]. The lymph flow was affected not only by patient factors including age and obesity, but also by tracer factors such as particle size [23]. Although particle size of ferucarbotran is small enough to flow smoothly, it was taken into neutrophils by phagocytosis and lodged in the lymph nodes. The magnetic movement by a neodymium magnet is useful and expected to localize SLNs smoothly and certainly in SNB by SPIO.

Conclusion
Magnet movement by a small neodymium magnet from the injection site to the axilla over the skin without massage after injection under general anesthesia was conducted in order to promote migration of the magnetic tracer in SNB by SPIO. Magnet movement was evaluated based on the monitoring count on the skin surface, and it was useful to promote migration of the magnetic tracer and to obtain higher monitoring counts on the skin surface. Magnet movement in SNB by SPIO can be performed easily and certainly during surgery without pigmentation.

Declarations
Ethics approval and consent to participate

The study was approved by the local ethics committees of Nippon Medical School Musashikosugi Hospital (reference number: 2015019) and was registered in University hospital Medical Information Network (UMIN) Clinical Registry (UMIN000029475). Written, informed consent was obtained from all
patients.

Consent for publication
Not applicable

Availability of data and materials
The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
MM collected and analyzed all patient data. EM collected patient data. TK, HT, SN, and MK advised to MM about this trial. AK and MS advised to MM about magnetometers. YO advised to MM about statistical analysis. All authors read and approved the final manuscript.

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Tables
Table 1 The characteristics of the cases

| Group               | A    | B    | C    | D    | Total |
|---------------------|------|------|------|------|-------|
| Cases               | 13   | 8    | 26   | 15   | 62    |
| Age (y) (mean)      | 51.1 | 61.9 | 56.8 | 58.6 | 56.7  |
| <=39                | 3    | 2    | 3    | 2    | 10    |
| 40-49               | 4    | 0    | 7    | 3    | 14    |
| 50-59               | 1    | 1    | 7    | 2    | 11    |
| 60-69               | 4    | 1    | 5    | 4    | 14    |
| >=70                | 1    | 4    | 4    | 4    | 13    |
| Body mass index (kg/m^2) (mean) | 22.2 | 25   | 22.3 | 23.5 | 22.9  |
| <25                 | 10   | 5    | 21   | 11   | 47    |
| >=25                | 3    | 3    | 5    | 4    | 15    |
| Tumor location      |      |      |      |      |       |
| Lateral/Central     | 9    | 8    | 19   | 9    | 45    |
| Medial              | 4    | 0    | 7    | 6    | 17    |
| T Classification    |      |      |      |      |       |
| Tis                 | 3    | 1    | 4    | 4    | 12    |
| T1                  | 9    | 6    | 19   | 8    | 42    |
| T2                  | 1    | 1    | 2    | 3    | 7     |
| T4                  | 0    | 0    | 1    | 0    | 1     |
| Assessment          |      |      |      |      |       |
| preoperative axillary lymph node | US/MRI/CT | 12   | 8    | 26   | 15    | 61    |
| Confirmed by FNA    | 1    | 0    | 0    | 0    | 1     |
| Surgery             |      |      |      |      |       |
| Partial mastectomy  | 9    | 6    | 16   | 8    | 39    |
| Mastectomy          | 4    | 2    | 10   | 7    | 23    |
| Histology           |      |      |      |      |       |
| DCIS                | 3    | 0    | 5    | 5    | 13    |
| IDC                 | 9    | 5    | 16   | 6    | 36    |
| Others              | 1    | 3    | 5    | 4    | 13    |
Table 2 The results of SNB

| Group | Total | A   | B   | C   | D   | Kruskal-Wallis p-Value |
|-------|-------|-----|-----|-----|-----|------------------------|
| Cases | 62    | 13  | 8   | 26  | 15  | 0.1048                 |
| Time from injection to removal of the SLN (mean) | 79.9 | 71.7 | 88.8 | 83.1 | 76.3 | 0.1048 |
| (range) | 45120 | 4595 | 70120 | 55110 | 50100 |                   |
| SLN detection by RI method | Success | 59 | 13 | 6 | 25 | 15 |
| Failure | 3 | 0 | 2 | 1 | 0 |                  |
| Lymph node retrieval rate (nodes) | Overall | 3 | 3 | 3.3 | 2.5 | 3.5 | 0.5524 |
| | RI method | 2 | 2.3 | 1.5 | 1.8 | 2.5 | 0.7357 |
| | SPIO method | 2.9 | 3 | 3.3 | 2.5 | 3.4 | 0.5524 |
| The highest count of resected SLN (RI) (mean) | 839.4 | 350.8 | 231.3 | 538.5 | 2108.7 | 0.2891 |
| (range) | 021500 | 701100 | 0800 | 04000 | 4021500 |                   |
| The highest count of resected SLN (SPIO) (mean) | 3.03 | 2.18 | 2.81 | 2.96 | 4.02 | <0.000 |
| (range) | 1.5110 | 1.535 | 2.045 | 2.040 | 2.5110 |                   |
| Metastasis of SLN | None | 50 | 12 | 6 | 18 | 14 |
| Micrometastasis | 2 | 0 | 0 | 2 | 0 |                      |
| Macrometastasis | 10 | 1 | 2 | 6 | 1 |                        |

Table 3 The results of the comparison among the 4 groups

| Group | Magnet movement Length | Timing | Cases | Monitoring count on the skin surface (μT) Mean* Range Mann-Whitney test p |
|-------|------------------------|--------|-------|-----------------------------------|--------|-------------|-------------------|----------|
| A     | 20 times               | After injection | 13   | 2.39 | 1.5~3.5 |                  | p = 0.06 |
| B     | 1 minute               | After injection | 8    | 2.73 | 2.5~3.0 |                  | p = 0.0130 |
| C     | After an interval (short) |               | 26   | 3.15 | 2.0~4.8 |                  | p = 0.00 |
| D     | After an interval (long) |               | 15   | 3.92 | 2.8~6.0 |                  |                   |

*p < 0.0001 (Kruskal-Wallis test)
| Factor                        | Cases | Monitoring count on the skin surface (μT) |
|------------------------------|-------|-----------------------------------------|
|                              |       | Mean  | Range | P value |
| Age (y)                      |       |       |       |         |
| ≤39                          | 10    | 3.36  | 2.060 | p=0.4423,*2 |
| 40-49                        | 14    | 3.33  | 2.545 |
| 50-59                        | 11    | 3.04  | 2.038 |
| 60-69                        | 14    | 2.79  | 1.540 |
| ≥70                          | 13    | 3.13  | 2.045 |
| Body mass index (kg/m²)      |       |       |       |         |
| <25                          | 47    | 3.15  | 2.060 | 0.8297,*1 |
| ≥25                          | 15    | 3.04  | 1.540 |
| Tumor location               |       |       |       |         |
| Lateral/Central              | 45    | 3.11  | 1.548 | 0.7268,*1 |
| Medial                       | 17    | 3.14  | 2.060 |
| T Classification             |       |       |       |         |
| Tis                          | 12    | 3.18  | 1.548 | 0.3634,*2 |
| T1                           | 42    | 3.06  | 2.060 |
| T2/T4                        | 8     | 3.35  | 2.540 |
| Surgery                      |       |       |       |         |
| Partial mastectomy           | 39    | 3.01  | 2.045 | 0.2466,*1 |
| Mastectomy                   | 23    | 3.3   | 1.560 |
| Histology                    |       |       |       |         |
| DCIS                         | 13    | 3.12  | 1.540 | 0.7149,*2 |
| IDC                          | 36    | 3.12  | 2.060 |
| Others                       | 13    | 3.12  | 2.545 |
| SLN detection by RI method   |       |       |       |         |
| Success                      | 59    | 3.13  | 1.560 | 0.7413,*1 |
| Failure                      | 3     | 2.93  | 2.533 |
| Metastasis of SLN            |       |       |       |         |
| None                         | 50    | 3.18  | 1.560 | 0.1867,*2 |
| Micrometastasis              | 2     | 2.4   | 2.325 |
| Macrometastasis              | 10    | 2.95  | 2.040 |

*1: Mann-Whitney test, *2: Kruskal-Wallis test
Magnet movement by a neodymium magnet a) After the magnet tracer is injected, we move the neodymium magnet (Neomag, KOKUYO Co., Ltd.) b) Over the skin from the injection site to the axilla repeatedly to promote migration of the magnetic tracer without massage. c) The handheld magnetometer developed by Tokyo University. It contains a small neodymium magnet in its tip. d) Evaluation of the monitoring count on the skin surface.
Figure 2

The consecutive steps and recruited cases during this study Seven cases were excluded: 3 cases that were given 3-min magnet movement, 3 cases that had missing time records of at each check point, and 1 case in which a different magnet was used. Then we enrolled 62 out of 69 cases.
Measuring monitoring count and timing of the magnet movement of 4 cohorts In Groups A and B, only the monitoring count after magnet movement was evaluated. In the 41 cases in Groups C and D, the monitoring count and time from injection were evaluated at specific check points, such as after injection, after an interval, and after magnet movement. Changes in the monitoring counts by interval and by magnet movement were evaluated.
Figure 4

Relationship between time from injection and monitoring count in Group C Sequential lines are the evaluated cases. Symbols are the mean values at check points, such as after injection, after an interval, and after magnet movement.
Figure 5

The mean values

- After injection
- After interval
- Before magnet movement
- After magnet movement

Relationship between time from injection and the monitoring count in Group D Sequential lines are the evaluated cases. Symbols are the mean values at check points such as after injection, after an interval, before magnet movement, and after magnet movement.
Sequences of the mean values at each check point and monitoring count gains per minute

The large arrow shows the timing of magnet movement in each group. Monitoring count gains are significantly higher during magnet movement than after injection or during an interval.