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Original

Comparison of Clinical Feasibility of Magnetic Sentinel Lymph Node Biopsy with Resovist and the Radioisotope Method for Breast Cancer

Keiko Yanagihara[1], Tamami Yamakawa[1], Sena Kato[1], Miki Tamura[1] and Koji Nagata[2]

[1]Department of Breast Surgery and Oncology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan
[2]Department of Pathology, Nippon Medical School Tama Nagayama Hospital, Tokyo, Japan

Background: Sentinel lymph node biopsy (SLNB) is the standard procedure for axillary staging in early breast cancer. Although the radioisotope (RI) method is highly accurate, it requires nuclear medicine facilities and exposes patients to radiation. Superparamagnetic iron oxide (SPIO) tracers were shown to be noninferior to RI in trials outside Japan but are not approved in Japan. Resovist (ferucarbotran), an MRI contrast agent containing SPIO, may be an alternative. This study compared the feasibility and diagnostic performance of Resovist-based magnetic SLNB with the RI method.

Methods: This paired study analyzed 27 breast cancer cases treated with both RI-based and Resovist-based magnetic SLNB. Resovist 0.8 mL was injected subcutaneously above the tumor or into the periareolar region, and the site was gently massaged. The injection-site skin and subcutaneous tissue were excised to prevent pigmentation. Identification rates were assessed at the patient and node levels, and subgroup analysis of patients stratified by body mass index (BMI <25 vs. ≥25) was performed. McNemar's and Fisher's exact tests were used.

Results: SLN identification was 100% (27/27 patients) for RI and 88.9% (24/27) for the magnetic method. Among 49 nodes, the results were RI+/Mag+ for 34, RI+/Mag− for 6, and RI−/Mag+ for 9, yielding detection rates of 81.6% (RI) and 87.8% (magnetic). No allergic reactions, pigmentation, or injection site complications occurred. BMI had no significant effect ($p > 0.05$).

Conclusions: Resovist-based magnetic SLNB was feasible and safe, and had detection rates comparable to those of RI. Optimization of injection conditions may further improve accuracy.

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Keywords: breast cancer, sentinel lymph node biopsy, superparamagnetic iron oxide, magnetic tracer, radioisotope

Introduction

Sentinel lymph node biopsy (SLNB) yields accurate information with minimal morbidity, such as lymphedema and shoulder dysfunction[1,2], and has thus replaced axillary lymph node dissection as the standard procedure for axillary staging in clinically node-negative breast cancer.

The conventional radioisotope (RI) method, which uses technetium-99m-labeled colloid, achieves high identification and low false-negative rates[3]. However, it requires specialized facilities, adherence to radiation regulations, and coordination with nuclear medicine departments, posing logistic barriers to smaller institutions[4,5]. To overcome these limitations, non-radioactive alternatives have been developed. Among them, tracers containing superparamagnetic iron oxide (SPIO) nanoparticles—detectable with a magnetic probe—have been validated internation-

Correspondence to Keiko Yanagihara, keikof@nms.ac.jp
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ally[6–9]. The Nordic SentiMAG and SentiDose trials demonstrated that SPIO-based magnetic SLNB is noninferior to RI methods: detection rates for both exceeded 95% and false-negative rates were comparable[7,8]. Magnetic tracers such as Sienna+ and Magtrace are not approved in Japan. However, Resovist (ferucarbotran), an MRI contrast agent approved in Japan, contains SPIO particles of comparable size and magnetization[10]. Resovist might therefore be an alternative magnetic tracer for SLNB. Preclinical studies have confirmed its lymphatic migration and safety profile[11,12].

The present study compared the feasibility and diagnostic performance of Resovist as a magnetic tracer with the RI method in breast cancer surgery. In addition, we explored whether body mass index (BMI) affects magnetic SLN detection, as prior studies have suggested variable identification rates in obese patients[13].

Materials and Methods

Study Design and Population

This single-center paired study analyzed data from 27 breasts of patients with clinically node-negative invasive breast carcinoma undergoing SLNB between July and September 2025. Exclusion criteria were prior axillary surgery, past metal allergy, and contraindications to SPIO injection. All patients provided written informed consent, and the study was approved by the ethics committee of the affiliated hospital (approval No. F-2024-147).

Procedures

For the RI method, technetium-99m-labeled colloid was injected subcutaneously into the areola on the day before surgery. For the magnetic method, Resovist 0.8 mL was injected above the tumor or into the periareolar region immediately before surgery, after which the injection site was gently massaged to promote lymphatic migration. The injection-site skin and subcutaneous tissue were excised to avoid postoperative pigmentation. Sentinel nodes were detected intraoperatively with a gamma probe (for RI) and a handheld magnetic probe (TAKUMI).

A node was defined as sentinel if RI or magnetic counts were greater than zero. Intraoperative selection followed the "10% rule" for RI detection, meaning that any node with counts ≥10% of the hottest node was also excised[14]. All nodes were examined histologically using hematoxylin-eosin staining and immunohistochemistry when necessary.

Table 1 Patient characteristics (n = 27)

Variable	*n* (%) or median [range]
Age, years	56 [32–84]
Body weight, kg	56.7 [36.8–97.0]
Height, cm	156 [137–167]
BMI, kg/m^2	23.2 [14.4–38.6]
Tumor size, mm	16 [0–37.9]
Breast-conserving surgery	6 (22.2%)
Mastectomy	21 (77.8%)
Estrogen receptor positive	23 (85.2%)
Progesterone receptor positive	17 (63.0%)
HER2 overexpression (IHC3+ or FISH+)	2 (7.4%)
Ki-67, %	23 [1–99]
Neoadjuvant chemotherapy	2 (7.4%)
Node metastasis	1 (3.7%)

Statistical Analysis

McNemar's test was used for paired comparisons between RI and magnetic methods. Fisher's exact test was used for subgroup analysis of patients stratified by BMI (<25 vs. ≥25). Statistical analyses were performed using R version 4.3, with significance set at $p<0.05$.

Results

Patient Characteristics

Patient demographics and tumor characteristics are summarized in **Table 1**. A total of 27 cases from 26 patients were analyzed. One patient with bilateral breast cancer was included and evaluated as two cases. The median age was 56 years (range, 32–84 years), median body weight was 56.7 kg (range, 36.8–97.0 kg), median height was 156 cm (range, 137–167 cm), and median BMI was 23.2 kg/m^2 (range, 14.4–38.6 kg/m^2). The median tumor size was 16 mm (range, 0–37.9 mm). Nineteen tumors (70.4%) measured ≤20 mm, and 8 (29.6%) were 21–50 mm in size. Breast-conserving surgery was performed in 6 cases (22.2%), and 21 (77.8%) underwent mastectomy.

Regarding immunohistochemical characteristics, estrogen receptor (ER) was positive in 23 cases (85.2%) and negative in 4 (14.8%). Progesterone receptor (PgR) was positive in 17 (63.0%) and negative in 10 (37.0%). HER2 overexpression (IHC 3+ or FISH-amplified) was detected in 2 cases (7.4%). The median Ki-67 labeling index was 23% (range, 1–99%). Two patients (7.4%) received neoadjuvant chemotherapy before surgery. One patient (3.7%) had a metastatic sentinel node measuring 5 mm, whereas 26 patients (96.3%) were node-negative.

Table 2 Node-level cross-tabulation between the RI and magnetic methods (49 nodes)

	RI + *n* (%)	RI − *n* (%)	Total *n* (%)
Magnetic +	34 (69.4%)	9 (18.4%)	43 (87.8%)
Magnetic −	6 (12.2%)	0 (0.0%)	6 (12.2%)
Total	40 (81.6%)	9 (18.4%)	49 (100%)

The table shows the concordance between RI and magnetic SLN detection at the node level. Concordant positivity (RI +/Mag +) accounted for 69.4% of all nodes, while 18.4% were detected only by the magnetic method (RI −/Mag +). The overall node-level detection rates were 81.6% for RI and 87.8% for magnetic SLNB.

Identification Performance

The median interval from Resovist injection to sentinel lymph node (SLN) excision was 61 minutes (range, 37–99 minutes). No procedure-related allergic reactions, pigmentation, or injection site complications were observed.

At the patient (case) level, the identification rate was 100% (27/27) for the RI method and 88.9% (24/27) for the magnetic method. Three patients (11.1%) had no SLN detected by the magnetic probe despite successful RI identification. The node-level concordance and relative proportions of RI-positive and magnetic-positive nodes are summarized in **Table 2**. A total of 49 SLNs were evaluated. The distribution was as follows: RI+/Magnetic+ in 34 nodes, RI+/Magnetic− in 6, and RI−/Magnetic+ in 9. The overall node-level detection rates were 81.6% (40/49) for the RI method and 87.8% (43/49) for the magnetic method. McNemar's test revealed no significant difference between the two techniques ($p = 0.48$).

Although the magnetic technique identified slightly more nodes, these additional detections (RI−/Magnetic+) were considered to represent possible tracer overflow rather than true additional sentinel nodes. Pathological assessment confirmed that all metastatic nodes were in the RI+/Magnetic+ category, thus confirming the diagnostic adequacy of both techniques.

BMI Subgroup Analysis

To assess the potential effect of body habitus, patients were stratified by BMI (<25 kg/m^2 vs. ≥25 kg/m^2). In the lower BMI group ($n = 22$), SLN was identified in 100% (22/22) of cases with the RI method and in 90.9% (20/22) of cases with the magnetic method. In the higher BMI group ($n = 5$), both methods achieved 100% identification with RI but only 60.0% (3/5) with the magnetic method (**Table 3**). However, Fisher's exact test showed no significant difference between BMI subgroups for either detection technique ($p > 0.05$).

Table 3 Patient-level identification rate by BMI subgroup

BMI group (kg/m^2)	No. of cases	RI identification	Magnetic identification
<25	22	100% (22/22)	90.9% (20/22)
≥25	5	100% (5/5)	60.0% (3/5)
Total	27	100% (27/27)	88.9% (24/27)

Safety Outcomes

No patient experienced allergic reactions, local inflammation, or skin pigmentation. The routine excision of injection-site skin and subcutaneous tissue effectively prevented visible iron staining, which has been reported in previous SPIO studies. No postoperative complications such as hematoma, infection, or wound dehiscence were observed. Overall, both methods were well tolerated and technically feasible, and had comparable identification rates and no adverse events.

Discussion

This paired clinical study demonstrated that magnetic SLNB using Resovist achieved comparable identification to the conventional RI method. Although the magnetic technique had a slightly lower patient-level detection rate (88.9%), the node-level rate (87.8%) exceeded that of RI (81.6%). These results confirm the technical feasibility and clinical safety of Resovist as a tracer for magnetic SLNB.

Our findings are consistent with international multicenter studies using SPIO-based tracers, including the Nordic SentiMAG, SentiDose, and SentimagIC trials, which reported noninferiority of magnetic tracers compared with RI and blue dye combinations[6–8,15]. SPIO-based SLNB is also associated with logistical advantages—injection timing is flexible, radioactive isotopes are unnecessary, and overall costs are lower[16,17].

In addition, the SPIO tracer Sienna+ has been evaluated in multiple trials and meta-analyses. Teshome et al.[18] reported noninferiority of Sienna+ compared with standard RI-guided techniques in early breast cancer: identification rates at the patient level (97.1% vs. 97.5%) and node level (92.7% vs. 93.2%) were comparable, and there was no increase in false negatives. Likewise, Piñero-Madrona et al.[19] confirmed equivalent detection and safety profiles between SPIO (Sienna+) and conventional RI/blue dye combinations (95.7% vs. 97.1%). Douek et al.[20] compared SPIO (SentiMAG/Magtrace) with RI. The

detection rates were 95.0% for the standard method and 94.4% for the magnetic method, demonstrating noninferiority.

Importantly, none of these multicenter studies found differences between RI- and SPIO-guided SLNB in long-term oncologic outcomes such as recurrence-free or overall survival. This suggests that magnetic methods provide equivalent staging accuracy and prognostic relevance. However, further studies with extended follow-up are warranted in order to confirm survival equivalence in magnetic SLNB using Resovist and other SPIO tracers.

Intraoperative SLN identification in this study adhered to the 10% rule, a conventional standard endorsed by the American Society of Breast Surgeons[14]. According to Bai et al.[21], this criterion captures 98.3% of positive sentinel nodes, with only 1.7% of metastases detected below the 10% threshold. Although Hersi et al.[22] later argued that strict application might increase unnecessary node removal, the 10% rule remains widely accepted as a balance between sensitivity and procedural efficiency. In magnetic SLNB, an analogous threshold has not yet been standardized, and applying the RI-based principle provides a pragmatic reference for clinical evaluation. The slightly higher number of nodes detected magnetically in our study (43 vs. 40) likely reflects tracer over-diffusion beyond the sentinel basin rather than superior sensitivity.

An additional technical refinement in our study was the excision of injection-site skin and subcutaneous tissue, which successfully prevented postoperative pigmentation. SPIO-induced staining is a known aesthetic issue that persists for several months[23]. None of our patients developed pigmentation or inflammatory changes, confirming the effectiveness of this approach.

Previous studies reported inconsistent correlations between BMI and SLN detectability using SPIO tracers. Taruno et al.[6,16] observed slightly lower magnetic detection rates in obese patients, although differences were not significant. In our cohort, the SLN identification rate was 100% (n=27) at the patient level and 96% (52/54) at the node level, with no significant difference between patients with a BMI <25 and those with a BMI ≥25 (100% vs. 100%). Similarly, our data showed only a nonsignificant trend toward reduced identification in patients with higher BMI, suggesting that excessive subcutaneous fat might attenuate magnetic signal strength but without any clinical impact on overall detection feasibility. The number of patients with a high BMI was small, suggesting that further investigation is necessary.

This study's strengths include its prospective paired design, simultaneous dual-tracer comparison, and the use of a readily available agent. Limitations include the small sample size, absence of long-term false-negative analysis, and its single-center scope. Future research should focus on optimizing injection timing and tracer dose, defining magnetic count thresholds analogous to the 10% rule, and evaluating reproducibility across centers.

In conclusion, magnetic SLNB using Resovist demonstrated feasibility and safety comparable to RI-guided SLNB. With further protocol optimization, this radiation-free method could become a practical and accessible alternative for sentinel node identification in hospitals lacking nuclear medicine facilities.

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