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ORIGINAL SCIENTIFIC REPORT

Sentinel Lymph Node Biopsy in Early Breast Cancer: Magnetic Tracer as the Only Localizing Agent

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Abstract

Background The combined use of radioisotope and blue dye is the gold standard in sentinel lymph node (SLN) localization in early breast cancer. Superparamagnetic iron oxide (SPIO) has recently emerged as a non-inferior new tracer in sentinel lymph node mapping with fewer disadvantages. This study represents the first and the largest cohort of superparamagnetic iron oxide application in Asian population.

Methods Retrospective analysis of a prospectively maintained database was performed from August 2016 to December 2017. All patients with SLN localization by SPIO were included in this study.

Results A total of 328 breast cancer patients with 333 SLNB procedures were included in this study. Median age was 54 years (range 32–86). Median tumor size was 1.9 cm (range 0.1–12 cm).There were 138 breast-conserving surgeries and 195 mastectomies. All patients received injection of SPIO 1 day prior to operation. A total of 329 successful sentinel lymph node biopsy (SLNB) procedures were undertaken with 1514 sentinel lymph nodes (SLNs) identified. One hundred and fifty-three (10.1%) of the SLNs were positive for malignancy. There were 54 patients with macrometastases, 26 with micrometastases and 24 with isolated tumor cells. Sixty-seven patients underwent subsequent axillary dissection. Four patients failed sentinel lymph node identification with SPIO. The success rate of SPIO in sentinel lymph node localization was 98.8%.

Conclusion SPIO represents a feasible alternative in sentinel lymph node mapping with comparably high nodal detection rate.

Abbreviations

SLNB Sentinel lymph node biopsy
SLNs Sentinel lymph nodes
SPIO Superparamagnetic iron oxide

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Introduction

Sentinel lymph node biopsy (SLNB) has established its role as the standard of treatment for breast cancer patients with clinically node-negative disease. The overall survival and disease-free survival were shown to be statistically equivalent between SLNB and traditional axillary dissection groups. At the same time, it was associated with fewer disadvantages such as lymphoedema, reduced shoulder mobility and paresthesia [1]. Radioisotope and blue dye are

the most commonly used tracer agents in sentinel lymph node mapping, and its combined use was recognized as the gold standard with the highest identification rate of up to 96% and lowest false-negative rate of 5% [2–4].

However, both radioisotope and blue dye have several disadvantages. Technetium-99m sulfur colloid is the most widely used radioisotope, and its application requires the availability of nuclear medicine department and expertise. The handling and disposal of surgical specimen, contaminated swabs and drapes require compliance with local risk management protocol. This is strictly monitored, and annual on-site contamination test is required. On the other hand, blue dyes such as isosulfan blue or patent blue have been reported to cause allergic reactions, mostly urticaria. Life-threatening anaphylactic reaction is rare [5–7]. Local skin complications such as permanent skin tattoo have also been reported [5].

Superparamagnetic iron oxide tracer (Sienna®, Endomagnetics, Ltd., UK) has emerged recently as a new tracer for sentinel lymph node mapping. It is a dextran-coated nanoparticle (60 nm), which remains in SLNs from within minutes after injection in the breast to more than 30 days. The SLNs are then magnetically marked and can be detected by the handheld magnetometer (Sentimag®, Endomagnetics, Ltd., UK) as well as preoperative magnetic resonance imaging. These magnetically marked nodes are often stained brown or black, and with the help of magnetometer, an audible pitch variation can help in the accurate localization of the SLNs.

The use of SPIO in sentinel lymph node mapping has been studied in several non-inferiority trials in Europe [8–13], and their results were promising when compared to radioisotope and blue dye. In this study, we aim to evaluate this new magnetic technique as the only agent used for sentinel lymph node mapping.

Methods

Patient recruitment

We conducted a retrospective analysis from a prospectively maintained database. This retrospective study followed the principles of the Declaration of Helsinki, and informed consents were obtained from patients who were willing to participate. Between August 2016 and December 2017, all adult female patients with clinical and radiological node-negative breast cancers were invited to participate in this study. All recruited patients received triple assessment to establish the diagnoses of breast cancers. Pregnant or lactating patients, patients with known hypersensitivity to dextran compounds, patients with an iron-overload disease, and patients with pacemakers or other implantable devices on chest wall were excluded. All potential patients were identified by independent research nurses, and operation was carried out by one experienced breast surgeon (WTT) who had more than 10 years of experience in SLNB. All clinical data were stored in electronic medical system *ClinicSolution* 7.0.

Surgery

All recruited patients were admitted to hospital 1 day before operation as per usual practice. Subareolar injection of 2 ml of SPIO (SiennaXP®, 1 vial) was given by WTT the night prior to operation. The injection was made at the upper outer quadrant of the affected breast, followed by 5 min of massage. Radioisotope was also injected in a similar way at the subareolar region in the first 22 patients, and blue dye was omitted in all patients in this cohort. During the operation, WTT used the handheld magnetometer (Sentimag®) for sentinel lymph node localization. Metal retractors or instruments were removed from the surgical field while the magnetometer was used. All SLNs detected intraoperatively by handheld magnetometer or nodes that were stained black were excised for frozen section. SLNs were sliced and processed for histological examination, and immunohistochemistry was performed at the pathologist's discretion. Pathology of SLNs was reported as normal, or containing macrometastases (>2 mm), micrometastases (>0.2 mm, ≤2 mm) or isolated tumor cells (≤0.2 mm). WTT decided on the need of axillary dissection according to international guidelines. Detailed pathology report and disease staging were recorded into the database.

Statistical analysis

Patient and tumor characteristics were evaluated, and procedural success rate of SPIO in sentinel lymph node localization was calculated. All statistical analyses were performed with IBM SPSS, version 16, and statistical data were presented in percentages.

Results

From August 2016 to December 2017, 328 breast cancer patients (5 with bilateral breast cancers) were recruited. Majority of them received upfront operation, while one patient in this cohort had neoadjuvant chemotherapy. Altogether, 333 SLNB procedures were performed with SPIO. The first 22 patients received simultaneous injection of radioisotope. However, gamma probe was not in use except in two patients who had failed localization with SPIO. Patent blue dye injection was omitted in all patients.

Table 1 Patient and tumor characteristics (number of SLNB procedures = 333 in 328 patients)

	Study sample
Patient characteristics	
Age, years (median)	54 (32–85)
Body mass index, kg/m^2 (mean)	23.5 (±4.1)
Tumor characteristics	
Screening detected:	
Yes	143 (42.9%)
No	190 (57.1%)
Tumor side:	
Left (unilateral)	168 (51.2%)
Right (unilateral)	155 (47.3%)
Bilateral	5 (1.5%)
Tumor size, cm (median)	1.8 (0.1–12)
Multifocality of tumor	
Yes	22 (6.6%)
No	311 (93.4%)
Tumor location	
Upper outer quadrant	149 (44.7%)
Upper inner quadrant	59 (17.7%)
Lower inner quadrant	39 (11.7%)
Lower outer quadrant	73 (21.9%)
Central	13 (3.9%)
pT (pathological tumor staging)	
pTis	54 (16.2%)
pT1	190 (57.1%)
pT2	80 (24.0%)
pT3	9 (2.7%)
Tumor grade (one missing datum)	52 (15.6%)
1	112 (33.6%)
2	168 (50.5%)
3	
Ki-67 status (Fifty-four evaluation not performed as pTis)	
Low (≤14%)	63 (22.6%)
High (>14%)	216 (77.4%)
Estrogen receptor status (one missing datum)	
Positive	282 (84.9%)
Negative	50 (15.1%)
Progesterone receptor status (two missing data)	
Positive	238 (71.9%)
Negative	93 (28.1%)
HER2 status (two missing data)	
Positive	63 (19.0%)
Negative	236 (71.3%)
Equivocal (on FISH test)	32 (9.7%)

Patient and tumor characteristics are described in Table 1. Median age of this cohort was 54 years (32–86), and all patients were female. Median tumor size was 1.8 cm (0.1–12 cm). Fifty-four patients had in situ carcinoma, while others had invasive disease (267 invasive ductal carcinomas and 12 invasive lobular carcinomas).

Breast-conserving surgery was performed in 138 patients (41.4%), and mastectomy was done in 195 (58.6%). Thirty patients had history of ipsilateral breast lump excision unrelated to the current disease presentation. Ten patients received vacuum-assisted biopsy of breast lesions which confirmed the diagnosis of breast cancer. A total of 329 successful SLNB procedures were undertaken with 1514 SLNs identified. SPIO localization was successful in 137 patients receiving breast-conserving surgery (99.3%) and 192 patients with mastectomy (98.5%). A median of 4 SLNs was removed by SPIO in each patient. Four patients failed sentinel lymph node localization with SPIO, and two of them underwent axillary dissection. The third patient received successful SLN localization with radioisotope, which was negative for malignancy. The fourth patient had preoperative diagnosis of ductal carcinoma in situ, and therefore, axillary dissection was not performed. The overall successful rate was 98.8%.

Eighty patients (24.0%) had pathologically positive axilla with 153 positive SLNs identified. There were 26 patients with micrometastases and 54 with macrometastases. Sixty-seven patients (20.1%) underwent subsequent axillary dissection, including 52 patients with macrometastases and 13 with micrometastases. The remaining had initial negative frozen section, and axillary dissection was not performed. Two of the four patients with failed SPIO localization had metastatic axillary lymph nodes unidentified by SPIO, and they subsequently received completion axillary dissection.

There was no allergic reaction associated with SPIO injection during the study period.

Discussion

There is an increasing interest in the use of SLNB in the management of breast cancer since the late 1990s. It can predict axillary lymph node status with more than 95% accuracy [14–16], and it gradually replaces axillary dissection in clinically node-negative disease. In 2005, the American College of Clinical Oncology (ASCO) published a guideline regarding the appropriate use of SLN identification and sampling procedure in patients with early breast cancer and clinically negative axillary lymph nodes [17]. Krag et al. [18] published their large randomized controlled trial in 2010 and found equivalent overall survival, disease-free survival and regional control in the SLN group.

The conventional dual method of radioisotope and blue dye is recognized as the gold standard and is commonly practiced in our center. However, its application is also

associated with additional time, cost and coordination with operative lists [13]. The rate of allergic reactions with blue dye was reported to be from 1% to 3% [6, 19]. Rare local skin complications with blue dye have also been reported, such as infection [7]. The bluish skin stain typically lasted several months and may rarely cause permanent skin tattoos [12]. Therefore, the introduction of superparamagnetic iron oxide (SPIO) as a new tracer agent has shed some light on these problems. Karakatsanis et al. [12] found that SPIO would stay in SLN for at least up to 3 weeks and was present in tissue up to 515 days. Injections of SPIO can be achieved in a more flexible way in outpatient clinic, and this can facilitate operative list planning. Currently, there is no evidence of adverse reaction associated with interstitial injection of SPIO. Potential allergic reaction, injection site reaction or skin complications are possible. Some transient or long-term brownish skin discoloration may occur.

Several non-inferiority trials have been published in Europe comparing SPIO and radioisotope. The Sentimag Multicentre Trial [8] recruited 160 women in the UK and the Netherlands, and a total of 170 SLNB procedures were performed. The detection rate of SPIO was 94.4% and was comparable with the conventional method of radioisotope with or without blue dye. Thill et al. [9] conducted a multicenter and multinational non-randomized paired equivalence trial in Europe (The Central-European SentiMag study) and recruited 150 women with a total of 291 SLNs identified. SPIO achieved a higher nodal detection rate (97.3% vs. 91.8%) when compared to radioisotope. In particular, SPIO was associated with a higher malignancy detection rate. Similar studies performed in Spain [10, 13], France [11] and Norway [12] also showed a higher nodal detection rate of 92–97% with SPIO. The concordance rate of SPIO with the gold standard reached as high as 99% per patient and 97% per node.

To our understanding, our study represents the largest single cohort to use SPIO as the single tracer agent for SLN localization. In this cohort, SPIO was injected by the operating surgeon (WTT) the day prior to operation. Radioisotope was not injected except in 22 patients during the initial study period, and patent blue dye was omitted in all. This is different from what has been presented in the literature when SPIO was studied in non-inferiority trials. Patients received injection of at least two tracer agents, including SPIO, radioisotope with or without blue dye. In our hands, the success rate of SLN localization with SPIO reached 99%. This was compatible with the European evidence, and SPIO could achieve an equally well nodal detection rate as the gold standard. In this study, we aim to evaluate the feasibility of SPIO to replace the conventional method. Concordancy between SPIO and radioisotope in those 22 patients was not studied, as this has already been widely reported in the literature.

Four patients in our cohort failed SLN localization with SPIO. One of them has received neoadjuvant chemotherapy prior to SLNB. She had both SPIO and radioisotope injection, and SLN localization was successful only with radioisotope. Another patient with core biopsy showing ductal carcinoma in situ also received SPIO and radioisotope injection, but failed localization with both tracers. The final pathology showed no upstaging of disease, and axillary dissection was not necessary. The remaining two patients received mastectomy and SLNB for clinically T1 disease. Three SLNs were identified with SPIO for both patients, and paraffin section showed no malignancy. However, non-SLNs in the mastectomy specimen showed macrometastases and completion axillary dissection was performed for both patients. As radioisotope was not injected in these two patients, we could not conclude if these are non-SLNs or SLNs missed by SPIO. Nevertheless, these were uncommon and represented 0.6% in our cohort. To our understanding, there is currently no evidence to suggest a higher failure rate of SPIO in patients receiving neoadjuvant treatment. Further large-scale study may be necessary to evaluate the optimal tracer in this group of patients.

In the literature, the reported average number of SLNs removed ranged between 1.6 and 2.2 [8, 10, 11, 13]. SPIO was not inferior to radioisotope in the number of SLNs removed [8, 10, 11]. However, in the cohort published in the European Journal of Surgical Oncology, Rubio et al. [13] found significantly higher number of SLNs removed in SPIO when compared to radioisotope and the authors attributed this to the learning curve with this new tracer agent. Special plastic-made operating instruments such as Debakey forceps and retractors are needed to avoid interference of magnetometer, and repeated calibration of the machine is necessary to reset the magnetic baseline level. In our cohort, the median number of SLNs removed per patient was 4 for SPIO, which was also higher than that reported in the literature. As the duration of the study is short, we did not observe any significance difference in the number of SLNs removed in the initial and later half of the study period. However, there is yet no answer to the optimal number of SLNs that should be harvested in the literature. The NSABP B-32 trial indicated that removal of at least two lymph nodes was important to reduce the false-negative rate [20]. Bonneau et al. [21] correlated the number of SLNs harvested to the survival of patients in their large series of 144,517 patients in 2015, and the optimal number was identified to be three with better disease-specific survival. Further randomized controlled trial will be necessary to comment whether SPIO will result in overharvest of SLNs.

Interestingly, SPIO could stay in SLNs for up to 3 weeks according to observational study [12]. This

property allows not only a more flexible time for tracer injection by surgeon, but also a newer operative approach to patients with ductal carcinoma in situ. In our cohort, 54 patients in this cohort had ductal carcinoma in situ and 51 of them had negative SLN on paraffin section. Only three patients had isolated tumor cells identified in SLNs; hence, axillary dissection was not necessary. SPIO could allow a second-stage SLNB, even for those with mastectomy performed if final histopathology showed upstaging to invasive disease. The use of SPIO to avoid unnecessary SLNB in ductal carcinoma in situ is currently underway in our collaboration study.

To our understanding, there is no cost-effective analysis to compare between SPIO and conventional method of sentinel lymph node localization. Although the instrumental costs between SPIO and conventional method are comparable, the use of conventional method of radioisotope and blue dye is associated with extra manpower and costs. Expertise in nuclear medicine department and day admission for injection are required for radioisotope injection. Specially arranged specimen transportation for frozen section and paraffin section was necessary as per local risk management protocol. Annual on-site contamination test, monthly calibration of the pocket dosimeters and environmental contamination monitor and annual health checkup for surgeons all converged to extra costs. From our local data, the use of SPIO alone in SLN localization saves US $22,300 per year when compared to the conventional dual tracers. In our opinion, the use of SPIO as a single localizing agent in breast cancer will be an attractive idea.

One drawback of SPIO is persistent brownish skin discoloration at injection site [12, 13, 22]. The prolonged persistence of tracer agent at injection site can also result in artifact in MRI scan for up to 1.5 years. Due to limited study time frame, these clinical phenomena were not evaluated in the current study. Mammogram and ultrasonography of breasts remain the main imaging modalities for breast cancer surveillance. Therefore, the use of SPIO will not compromise the standard of care in breast cancer survivors. We are currently performing a randomized controlled trial in our center to address these issues.

This study represents the largest cohort on the use of SPIO in SLNB in Asian population. We recognize the intrinsic limitation of this study of being retrospective in nature which is subjected to selection bias. In addition, this study is a feasibility study on SPIO with no direct comparison between SPIO and conventional SLN identification methods. However, our study is based on the analysis of a reasonably sizable cohort with all procedures performed by a single experienced breast surgeon following strict, predefined study protocol. Nevertheless, further large-scale study will be necessary to evaluate and compare SPIO with conventional methods.

Conclusion

SPIO represents a feasible alternative in sentinel lymph node mapping with an equally high nodal detection rate, but simpler logistics and operative planning. It has the potential to become the standard of care in sentinel lymph node biopsy as a single tracer agent for breast cancer patients.

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