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ORIGINAL ARTICLE – BREAST ONCOLOGY

SentimagIC: A Non-inferiority Trial Comparing Superparamagnetic Iron Oxide Versus Technetium-99m and Blue Dye in the Detection of Axillary Sentinel Nodes in Patients with Early-Stage Breast Cancer

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ABSTRACT

Background. Sentinel lymph node biopsy (SLNB) is a highly accurate method for staging the axilla in early breast cancer. Superparamagnetic iron oxide mapping agents have been explored to overcome the disadvantages of the standard SLNB technique, which uses a radioisotope tracer with or without blue dye. One such agent, Sienna+, was shown to be non-inferior to the standard technique for SLNB in a number of studies. The SentimagIC trial was designed to establish the non-inferiority of a new formulation of this magnetic tracer, Magtrace (formerly SiennaXP).

Methods. Patients with clinically node-negative early-stage breast cancer were recruited from six centers in the US. Patients received radioisotope and isosulfan blue dye injections, followed by an intraoperative injection of magnetic tracer, prior to SLNB. The sentinel node identification rate was compared between the magnetic and standard techniques to evaluate non-inferiority and concordance.

Results. Data were collected for 146 procedures in 146 patients. The per patient detection rate was 99.3% (145/146) when using the magnetic tracer and 98.6% (144/146) when using the standard technique, while the nodal detection rate was 94.3% (348/369 nodes) when using the magnetic tracer and 93.5% (345/369) when using the standard technique (difference 0.8%, 95% binomial confidence interval lower bound − 2.1%). Of the 22 patients with positive sentinel lymph nodes (SLNs), 21 (95.4%) were detected by both the magnetic tracer and the standard technique. All malignant nodes detected by standard technique were also identified by the magnetic technique.

Conclusion. The magnetic technique is non-inferior to the standard technique of radioisotope and blue dye for axillary SLN detection in early-stage breast cancer. The magnetic technique is therefore a viable alternative.

Sentinel lymph node biopsy (SLNB) is now accepted as standard practice for staging the axilla in clinically node-negative, early-stage breast cancer patients. SLNB offers accurate staging with much lower morbidity than complete axillary node dissection, including lower levels of lymphedema, shoulder pain, and shoulder mobility problems.[1–4] Large randomized controlled trials have shown SLNB to be a robust technique, with detection rates of > 97% and low false negative rates.[3,5,6]

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Many surgeons currently utilize radioactive colloid as a mapping agent, either alone or in combination with blue dye.[7] Although the technique is highly accurate, there are disadvantages to these mapping agents. Use of radioactive colloid involves radiation exposure, requires a nuclear medicine department, and the short half-life of the isotope means that the injection must be administered on the day of or day before surgery, limiting scheduling flexibility. Continued shortages in the worldwide supply of technetium-99m (^{99m}Tc) have also been predicted.[8] Isosulfan blue dye carries a risk of anaphylaxis,[9] and methylene blue carries a risk of tissue necrosis and DNA damage.[10,11]

Superparamagnetic iron oxide (SPIO) particles have been shown to be suitable for lymph node mapping using a magnetic probe for nodal detection following local subcutaneous injection. Clinical studies and meta-analyses have compared the SPIO technique with the standard mapping technique in breast cancer.[12–20] and have shown non-inferiority to the standard technique of technetium-labeled colloid with or without blue dye.

Magtrace (Endomagnetics Limited, Cambridge, UK), is a blackish-brown suspension of carboxydextran-coated SPIO particles. The particle diameter is designed for lymphatic uptake and filtering out in the sentinel lymph nodes (SLNs) draining from the primary site.[21]

In previous studies, Sienna+ (Endomagnetics Limited), an SPIO tracer requiring dilution with saline prior to injection, was used. To reduce the injected volume of tracer for improved patient comfort, a new formulation of the tracer was developed—Magtrace (formerly known as SiennaXP)—containing the same SPIO particles, but not requiring dilution. These magnetic particles are detected using Sentimag, a handheld magnetic probe analogous to a handheld gamma probe.

This study was designed to establish the non-inferiority of Magtrace to the combination of radioisotope and blue dye for SLN detection, and to support a US regulatory clearance.

MATERIALS AND METHODS

Study Design and Patients

The Sentimag Intraoperative Comparison (SentimagIC) trial was a prospective, open-label, paired comparison study of Magtrace (test) and ^{99m}Tc sulfur colloid with isosulfan blue dye, for SLN detection in patients with early-stage breast cancer (NCT02336737).

The study included patients with a diagnosis of primary invasive breast cancer or ductal carcinoma in situ (DCIS) who were clinically node-negative and scheduled for SLNB. Patients were required to be 18 years of age or older, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and clinically node-negative axilla. Exclusion criteria included pregnancy or lactation; intolerance or hypersensitivity to isosulfan blue dye, iron, dextran compounds or Magtrace; previous axillary surgery, reduction mammoplasty or impaired lymphatic function (surgeon's judgment); previous radiation to the affected breast or axilla; a recent injection of ferumoxytol; iron overload disease; or implantable device in the chest wall, such as a pacemaker.

The study was conducted under an Investigational Device Exemption from the US FDA. Each site obtained Institutional Review Board approval, and written informed consent was received from each patient prior to enrollment.

Procedures

All patients underwent lymphatic mapping with magnetic tracer, radioisotope and blue dye injection. ^{99m}Tc sulfur colloid was injected in the breast preoperatively, either the day before or on the day of surgery, per the standard institutional protocols.

Intraoperatively, following induction of anesthesia, 2 ml of magnetic tracer were injected subcutaneously in the subareolar region at least 20 min before the SLNB was performed. Isosulfan blue dye was then injected per institutional protocol. A 5-min massage of the injection site was performed to promote migration of the magnetic mapping agent. Prior to incision, counts were recorded at the injection site and in the axilla using both the magnetic probe (Endomagnetics Limited) and the gamma probe.

Once the incision was made, SLNs were first identified using the Sentimag, either by the magnetic signal detected by the probe or via visual confirmation of the black/brown color of the tracer in the node. Non-metallic retractors were utilized in the axilla while the probe was in use. Magnetic counts were taken for each sentinel node prior to excision (in vivo) and again following removal of the node (ex vivo). A radioisotope count was also taken using the gamma probe both in vivo and ex vivo. All nodes identified by the Sentimag, the gamma probe, or by visual confirmation of blue dye or black staining were excised, and ex vivo counts were recorded for both detection systems. The SLNB was considered complete when the residual count in the axilla was $< 10\%$ of the highest ex vivo reading for both the radioisotope and magnetic tracer ('10% rule'[22]). In addition, nodes that, in the investigator's judgment, were highly clinically suspicious (i.e. hard or firm) were excised and considered as SLNs. All excised nodes underwent pathologic assessment. Only histologically confirmed nodes were included in the analysis. A postoperative follow-up visit was carried out between 6 and 22 days following the procedure.

Statistical Analysis

The statistical analysis was conducted according to a prespecified plan. The primary endpoint was the lymph node detection rate, defined as the number of lymph nodes identified by a specific method as a proportion of the total number of nodes detected.

The one-sided hypothesis of non-inferiority was tested using the method of Nam and Kwon,[23] assuming an expected rate for test and control of 95%, a non-inferiority margin (δ) of 5%, a discordance rate of 8%, and a one-sided test significance level (α) of 0.05.

A sample size of 265 nodes was sufficient to have 85% power to rule out (with a $< 5\%$ type I error rate) that the test nodal detection rate was non-inferior to the control detection rate, by no more than the non-inferiority margin of 5%.

RESULTS

Overall, 160 patients were enrolled between January and December 2015 at six participating sites. There were 146 evaluable patients; 13 withdrew prior to surgery and 1 was excluded from the analysis due to incomplete data (Fig. 1). Each site recruited at least 11 patients to the study. Patient and tumor characteristics are shown in Table 1.

The mean number of nodes excised per patient was 2.4 (standard deviation [SD] 1.19, median 2) for the magnetic tracer, 2.4 (SD 1.34, median 2) for the radioisotope with blue dye, and 2.3 (SD 1.38, median 2) for the radioisotope.

Primary Endpoint: Node Detection Rates

A total of 369 histologically confirmed SLNs were detected and excised. The node detection rate for the magnetic tracer was 94.3% (95% confidence interval [CI] 91.9–96.7%), and 93.5% (95% CI 91.0–96.0%) for the radioisotope plus blue dye (dual tracer). The magnetic tracer was shown to be non-inferior to the dual tracer within the prespecified margin of 5% with 85% power (difference in detection rate 0.8%; 95% binomial CI lower bound −2.1%; p value = 0.0065 for non-inferiority). Overall, 326 nodes were detected by both methods, giving

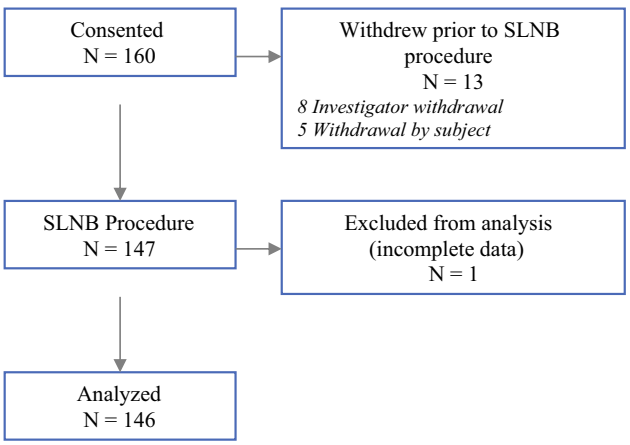

FIG. 1 Patient disposition in the study. *SLNB* sentinel lymph node biopsy

TABLE 1 Patient and tumor characteristics

Characteristic	Study patients
Age (years)	61.1 (12.3) [range 34.8–87.6]
Weight (pounds)	167.1 (38.5)
Height (inches)	63.7 (2.6)
BMI (kg/m^2)	29.0 (6.9) [range 17.5–51.7]
Tumor location	
UOQ	74/147 (50.3)
UIQ	28/147 (19)
LIQ	10/147 (6.8)
LOQ	26/147 (17.7)
Central/areolar	9/147 (6.1)
Pathologic T stage	
pTis	13/135 (9.6)
pT1a	19/135 (14.1)
pT1b	30/135 (22.2)
pT1c	33/135 (24.4)
pT2	33/135 (24.4)
pT3	7/135 (5.2)
Pathologic tumor size (mm)	
N	132
Mean (SD)	21.1 (18.4)
Median	16.0
Minimum, maximum	0.8, 107.0
ER status	
Positive	113/135 (83.7)
Negative	13/135 (9.6)
Not performed	9/135 (6.7)
PR status	
Positive	87/135 (64.4)
Negative	39/135 (28.9)
Not performed	9/135 (6.7)
HER2 status	
Positive	13/135 (9.6)
Negative	105/135 (77.8)
Not performed	17/135 (12.6)

Data are expressed as mean (SD) or *n/N* (%) unless otherwise specified

BMI body mass index, *SD* standard deviation, *UOQ* upper outer quadrant, *UIQ* upper inner quadrant, *LIQ* lower inner quadrant, *LOQ* lower outer quadrant, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2

a nodal detection concordance of 94.5% (326/345, 95% CI 92.1–96.9%).

Nineteen nodes (5.1%) were detected by the dual tracer but not by the magnetic tracer, and 22 nodes (6.0%) were detected by the magnetic tracer but not by the dual tracer. None of the discordant nodes were malignant. In every patient with a discordant node, at least one concordant node was also detected, except in one patient where a highly clinically suspicious node was found along with two discordant nodes. Overall, two nodes were not detected by the magnetic tracer or the dual tracer, but were highly clinically suspicious (Fig. 2, Table 2a).

The node detection rate for the radioisotope without blue dye was 91.6% (95% CI 88.8–94.4%). Nineteen nodes (5.1%) were detected by radioisotope but not by the magnetic tracer, and 29 nodes (7.9%) were detected by the magnetic tracer but not by radioisotope (Table 2b).

Patient Detection Rates

Patient endpoints were calculated as the number of patients in whom a given method detected at least one node, divided by the number of patients who underwent the SLNB procedure (Fig. 2, Table 2d–f).

Of the 146 patients with analyzable nodes, the dual tracer identified 144 (98.6%, 95% CI 96.7–100.0%), and the magnetic tracer identified 145 (99.3%, 95% CI 98.0–100.0%). At least one node was detected by both methods in 144 patients (98.6%). In one patient, two nodes were detected by the magnetic tracer but not by the dual tracer, and, in one patient, no nodes were identified by any tracer (Table 2d). The magnetic tracer detected nodes in all patients in which the dual tracer detected nodes, giving a concordance of 100.0% (144/144).

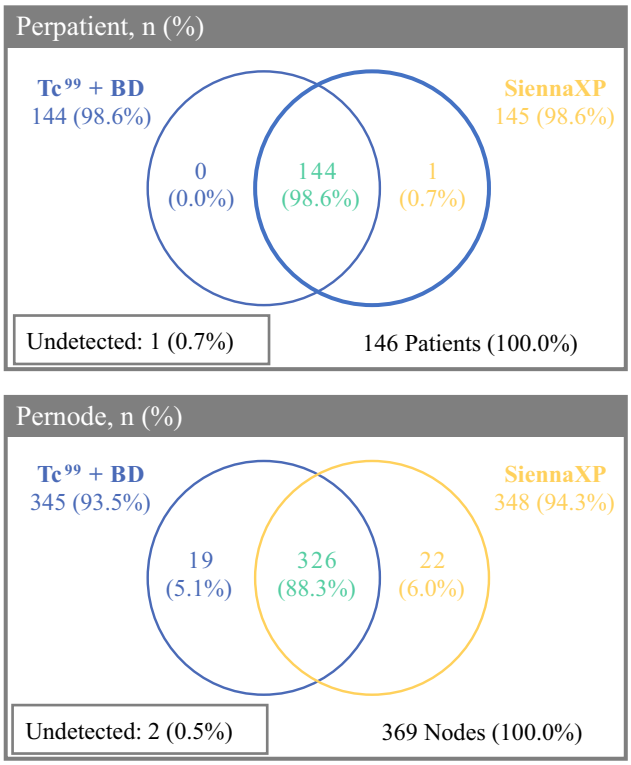

FIG. 2 Sentinel lymph node detection—per patient and node. *Tc*^{99} technetium-99m, *BD* blue dye

Detection Rates for Positive Nodes

A total of 25 positive SLNs were identified in 22 patients, of which 24 (96.0%, 95% CI 88.3–100.0%) nodes were identified by both the dual and magnetic tracers. In 21 of 22 (95.5%, 95% CI 86.8–100.0%) patients with positive nodes, a positive node was identified by both radioisotope and magnetic tracer. One positive node, the only positive node identified in that patient, was not identified by either tracer, but was identified as 'highly clinically suspicious' in the judgment of the surgeon intraoperatively.

Of the 24 malignant nodes identified by both the magnetic and dual tracers, 19 contained macrometastasis, and 5 contained micrometastasis. The 'highly clinically suspicious' node contained a macrometastasis.

In all patients with positive nodes identified by either the magnetic tracer or the dual tracer, all positive nodes were identified by *both* the magnetic and the dual tracer, resulting in a 100% concordance rate for positive SLNs.

Safety Results

An independent medical monitor reviewed and adjudicated adverse events (AEs) throughout the study.

A total of 69 AEs were reported in 56 (38.1%) patients, 9 of which were serious AEs (SAEs). The most common AEs were breast discoloration or hyperpigmentation, which occurred in 24 patients (16.3%) and ecchymosis or bruising, which occurred in 10 patients (6.8%) (Table 3).

No AEs were related to the Sentimag system, but 26 AEs in 25 patients were related to the magnetic tracer, none of which were serious. The most common magnetic tracer-related event reported was breast discoloration or hyperpigmentation, which occurred in 23 (15.6%) patients.

DISCUSSION

In this study, we show the Magtrace tracer to be non-inferior to radioisotope combined with blue dye for sentinel node detection in early-stage breast cancer in a combination of academic and community centers. The magnetic technique identified all patients in whom a malignant node

TABLE 2 Sentinel lymph node detection, per node and per patient, comparing the magnetic tracer with (a, d) radioisotope and blue dye; (b, e) radioisotope alone; and (c, f) blue dye alone

Per node detection rates [*n* (%)]			
	Magnetic tracer		Total
	Positive	Negative	
(a) Radioisotope and blue dye			
Positive	326 (88.3)	19 (5.1)	345 (93.5)
Negative	22 (6.0)	2[a] (0.5)	–
Total	348 (94.3)	–	369 (100.0)
(b) Radioisotope			
Positive	319 (86.4)	19 (5.1)	338 (91.6)
Negative	29 (7.9)	2[a] (0.5)	–
Total	348 (94.3)	–	369 (100.0)
(c) Blue dye			
Positive	175 (47.4)	5 (1.4)	180 (48.8)
Negative	173 (46.9)	16 (4.3)	–
Total	348 (94.3)	–	369 (100.0)
Per patient detection rates [*n* (%)]			
	Magnetic tracer		Total
	At least one node detected	No nodes detected	
(d) Radioisotope and blue dye			
At least one node detected	144 (98.6)	0 (0.0)	144 (98.6)
No nodes detected	1 (0.7)	1 (0.7)	–
Total	145 (99.3)	–	146[b] (100.0)
(e) Radioisotope			
At least one node detected	140 (95.9)	0 (0.0)	140 (95.9)
No nodes detected	5 (3.4)	1 (0.7)	–
Total	145 (99.3)	–	146[b] (100.0)
(f) Blue dye			
At least one node detected	117 (80.1)	0 (0.0)	117 (80.1)
No nodes detected	28 (19.2)	1 (0.7)	–
Total	145 (99.3)	–	146[b] (100.0)

Data are expressed as *n* (%)

[a]Two nodes were excised as highly clinically suspicious, with neither radioisotope nor magnetic signals

[b]One patient was excluded from the analysis due to missing data

was found when using the standard technique, and identified all the malignant nodes that the standard technique identified.

Several alternative lymphatic mapping agents have been explored to overcome the limitations of radioisotope and blue dye, including fluorescent dyes and SPIO tracers.[24] Fluorescent agents have been evaluated in trials, but their wider clinical use is limited because the small molecules travel rapidly through the lymphatics to higher echelon nodes. This requires the surgical team to coordinate the injection time to detect the first draining nodes. In addition, the attenuation of fluorescence by tissue limits the detection depth. Studies also report a higher than average number of nodes removed per patient.[25,26]

SPIO particles have historically been well-characterized and well-tolerated as magnetic resonance imaging (MRI) contrast agents.[27,28] In breast SLNB, using a previous formulation, i.e. Sienna+, investigators found the magnetic technique to be safe and non-inferior to standard mapping techniques. Three meta-analyses show strong agreement between Sienna+ and the standard technique in the detection of positive nodes.[18–20] SLNB with Sienna+ has also been studied in prostate cancer and melanoma.[29,30] This study of Magtrace, a formulation not requiring dilution, builds on the base of clinical data for Sienna+.

The most frequent AE related to the magnetic tracer was breast discoloration or hyperpigmentation. During the study, deeper injection helped reduce the incidence of

TABLE 3 Distribution of all adverse events

Adverse event type	Events [*N*]	Patients [*n* (%)]
Breast discoloration/hyperpigmentation	24[a]	24 (16.3)
Ecchymosis/bruising	10	10 (6.8)
Pain	5	5 (3.4)
Gastrointestinal disorder	3	3 (2.0)
Cellulitis	3	3 (2.0)
Skin ischemia	3	3 (2.0)
Cardiac disorder	3	3 (2.0)
Rash	2	2 (1.4)
Erythema	2	2 (1.4)
Other	14	14 (9.5)

[a]23/24 related to the magnetic tracer

discoloration, as reported elsewhere.[17] Long-term follow-up was not planned in this study, but a long-term study of patients seen up to 36 months following surgery reported that both the proportion of patients with skin discoloration and its intensity reduced over time.[31]

The magnetic tracer has been shown to generate a susceptibility artefact on precontrast MRI studies of the injection site. In one study, interpretation of the MRI scan was still possible in 70% of patients who received breast-conserving surgery. MRI of mastectomy patients was unaffected by artefacts.[32] In another report, at 1-year follow-up after SLNB and lumpectomy, while SPIO artefacts were present in the native MRI scan, a tumor was clearly visible on the post-contrast scan.[33]

Use of the magnetic tracer offers potential advantages over radioisotope. The radioisotope is usually injected by nuclear medicine staff, often in a different location from the operating room, requiring scheduling coordination between the two departments. In this study, 43.5% (64/147) of patients received their radioisotope injection in a different building, and, for 46 of these patients (31.3%), this was within driving distance from the surgery center. This inconvenience could be avoided by allowing intraoperative tracer administration by the breast surgeon.

Although the injection was performed intraoperatively in this study, the magnetic tracer has been reported to be readily detectable in lymph nodes up to 27 days post-injection,[34] and, in Europe, is indicated for injection up to 7 days before surgery. This offers hospitals greater scheduling flexibility to administer tracer preoperatively.

Injection of the agent prior to the surgery date has also been used to help reduce unnecessary SLNB when the preoperative diagnosis is DCIS.[35] In these cases, the tracer can be injected prior to surgery, allowing for later SLNB in the setting of a postoperative invasive cancer diagnosis. A similar approach could be applicable where SLNB is judged necessary in patients undergoing risk-reducing mastectomy in which there is high risk for occult malignancy, thus requiring postoperative nodal staging.[36]

As with all new technologies, a learning curve is expected, and surgeons reported that they felt comfortable after performing between three and five cases using the magnetic technique (personal communication).

CONCLUSIONS

This prospective multi-institutional study has shown the magnetic technique using the magnetic tracer with Sentimag to be non-inferior to the standard technique (^{99m}Tc and blue dye) for breast SLNB. The magnetic technique does not require the use of regulated radioactive material and avoids the risks of blue dye. It also has the potential to improve scheduling convenience for SLNB procedures, benefitting both surgical teams and patients.

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