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ORIGINAL ARTICLE – BREAST ONCOLOGY

Use of a Magnetic Tracer for Sentinel Lymph Node Detection in Early-Stage Breast Cancer Patients: A Meta-analysis

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ABSTRACT

Background. Sentinel lymph node (SLN) dissection involves lymphatic mapping and selective removal of clinically negative lymph nodes at highest risk for harboring metastases. Lymphatic mapping is most often performed using radioisotope with or without blue dye (standard tracers). Sienna+®, a superparamagnetic iron oxide that can be detected using the Sentimag® magnetometer, is an alternative mapping agent to identify SLNs that has been investigated in five clinical trials. This meta-analysis was performed to determine if Sienna+® is non-inferior for SLN detection when compared to standard tracers.

Methods. Five clinical trials comparing Sienna+® to a standard technique were identified, and data from these studies were used to determine the agreement by Kappa statistic between Sienna+® and standard tracers in identifying SLNs and malignant SLNs. The trials included 1683 SLNs identified in 804 patients. Data from the studies were imbalanced, therefore additional agreement indices were utilized to compare techniques. The estimated difference between the techniques was analyzed and a margin of $\leq$5 % was used to determine non-inferiority.

Results. Agreement between the Sienna+® and standard tracers was strong for SLN detection by patient [prevalence-adjusted bias-adjusted kappa (PABAK) 0.94, 95 % confidence interval (CI) 0.89–0.98], moderate to substantial for SLN detection by node (PABAK 0.68, 95 % CI 0.54–0.82), and strong for the detection of malignant SLNs by patient (PABAK 0.89, 95 % CI 0.84–0.95). Sienna+® demonstrated non-inferiority compared with standard tracers.

Conclusions. The Sienna+® mapping agent is non-inferior to the standard method for SLN detection in patients with clinically node-negative breast cancer.

Sentinel lymph node (SLN) dissection is routinely used to evaluate the disease status of the axilla in breast cancer patients presenting with clinically node-negative disease. Landmark trials have demonstrated the feasibility and accuracy of this procedure with high SLN identification rates and low false-negative rates.[1–3] Importantly, this minimally invasive approach is associated with less morbidity than axillary lymph node dissection, with lower rates of arm dysfunction, paresthesia, and lymphedema.[4–8]

Since the introduction of SLN dissection in breast cancer management in the 1990s, several techniques for lymphatic mapping to identify SLN(s) have been described. The blue-dye technique was first described by Giuliano et al. and included peritumoral injection of isosulfan blue dye at the primary tumor site with visualization of blue lymphatics and lymph nodes within the axilla.[9] Investigators from the US and Europe independently described utilization of technetium sulfur colloid injected within the breast and detected intraoperatively using a handheld gamma probe.[10,11] The optimal technique has been debated in the literature, with studies suggesting improved accuracy in SLN detection with the use of radioisotope alone or in combination with blue dye, and other studies suggesting sufficient mapping with blue dye alone.[12–15] The disadvantages of these traditional mapping agents include regulation of the radioisotope, radiation exposure, anaphylaxis to the blue dye, and staining of the tissues at the primary tumor site.

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In an attempt to overcome these limitations and potentially streamline the process of SLN identification, alternative lymphatic mapping agents are under investigation.[16,17] One such agent is Sienna+®, a magnetic agent that is comprised of a super paramagnetic iron oxide combined with a carboxydextran coating and mixed in injectable saline. It is injected into the breast where it is taken up by the lymphatics, and travels to the lymph nodes where it is detected using a handheld magnetometer, Sentimag® (Endomagnetics Inc, Cambridge, UK). This approach allows for identification of the SLNs using the magnetometer, as well as visualization via a color change where the nodes are stained brown or black.

Five European trials have evaluated Sienna+® compared to the standard technique utilizing radioisotope with or without blue dye.[18–22] Data from these trials were used to complete this meta-analysis. The primary objective was to determine if the Sienna+® magnetic tracer is non-inferior to the standard technique utilizing radioisotope with or without blue dye in detecting SLNs in early-stage, clinically node-negative breast cancer.

METHODS

Five clinical trials were identified that compared Sienna+® for SLN detection with a standard technique utilizing radioisotope with or without blue dye in breast cancer patients with clinically node-negative disease. Each trial described a similar procedure whereby Sienna+® was injected in a subareolar location followed by gentle massage of the breast to facilitate uptake into the breast lymphatics. Following this, the Sentimag® probe was used to detect the signal in the axilla to identify the SLN(s). In all five trials, radioisotope was used for SLN identification. In two studies, the addition of blue dye was left to the surgeon's discretion.[18,21] SLNs were defined as lymph nodes which demonstrated a signal with the magnetometer and/or gamma probe until the background signal in the axilla was less than 10 % of the highest ex vivo node count or with a demonstrated color change (either brown/black from Sienna+ and/or blue). Three of the five studies also defined suspicious palpable nodes as SLNs.[18,20,21] The SLN detection rate by each technique was reported and compared. In each of the studies, SLN detection was further categorized as the SLN detection rate per patient, SLN detection rate per node, and SLN malignancy detection rate per patient.

The primary objective of this meta-analysis was to determine if Sienna+® is non-inferior to current standard tracers utilized for SLN detection in clinically node-negative early-stage breast cancer. To assess this, the within-study difference in SLN detection rate and the variance of the difference between Sienna+® and standard tracers was calculated. The inverse variance weighted average of the difference across studies was computed using a random effects model, with the assumption that the SLN detection rates for the two methods are independent. The amount of heterogeneity, defined as the variation of study outcomes, among the studies was estimated by the restricted maximum-likelihood estimator. Cochran's Q-test was used to test for heterogeneity.[23] Sienna+® was determined to be non-inferior if the non-inferiority margin was ≤ 5 %.

A secondary objective of this meta-analysis was to assess the agreement between Sienna+® and the current standard tracers for SLN detection. The test results across studies was noted to be highly imbalanced, with a high prevalence of 'positive' testing results, i.e. in the majority of cases SLNs were identified by both methodologies. To account for this highly imbalanced data across studies, in addition to the commonly used agreement measure (the Kappa statistic), other agreement indices were used to assess the level of agreement between the magnetic technique and the standard. These agreement indices included: (i) proportion of overall agreement (both techniques identifying an SLN or both not identifying an SLN); (ii) percentage of positive agreement (both techniques identifying an SLN); (iii) percentage of negative agreement (both techniques not identifying an SLN); (iv) prevalence index; (v) bias index; and (vi) prevalence-adjusted bias-adjusted kappa (PABAK). Of these, the PABAK is the most informative value to describe the agreement between the two approaches as it adjusts for imbalances secondary to differing prevalence (defined as the frequency of the result studied, i.e. both methods identifying an SLN, neither identifying an SLN, the standard technique only identifying an SLN, or the magnetic technique only identifying an SLN) and bias among the studies. We first computed the estimate of these indices and their corresponding standard error for each study. The formulas for computing these agreement indices for each study are included in the electronic supplementary table. The average of these agreement indices across studies was computed, weighted by inverse variance using a random effect model. All analyses were performed in R with the 'metafor' package.[24]

RESULTS

A total of 804 patients were enrolled in the five trials and underwent SLN dissection for early-stage breast cancer with detection of at least one SLN. Cumulatively, 1683 SLNs were identified. A histologically positive SLN was identified in 222 patients. Table 1 details SLN detection by technique reported in each of the trials per patient, per

TABLE 1 Sentinel lymph node identification reported in the individual trials comparing the use of Sienna+® with a standard technique (technetium with or without blue dye) per patient, per node, and per sentinel lymph node-positive patient

	Douek et al.[18] (%)	Thill et al.[19] (%)	Rubio et al.[20] (%)	Pinero-Madrona et al.[21] (%)	Ghilli et al.[22] (%)	Total (%)
Per patient						
SLNs identified by						
n	160	150	120	181	193	804
Both techniques	146 (91)	145 (97)	111 (93)	177 (98)	187 (97)	766 (95)
Magnetic technique only	5 (3)	2 (1)	5 (4)	0	2 (1)	14 (2)
Standard technique only	6 (4)	1 (1)	2 (2)	1 (< 1)	4 (2)	14 (2)
Neither technique	3 (2)	2 (1)	2 (2)	3 (2)	0	10 (1)
Per node						
SLNs identified by						
n	404	291	287	321	380	1683
Both techniques	268 (66)	263 (90)	207 (72)	260 (81)	344 (91)	1342 (80)
Magnetic technique only	55 (14)	20 (7)	57 (20)	32 (10)	20 (5)	184 (11)
Standard technique only	29 (7)	4 (1)	23 (8)	17 (5)	16 (4)	89 (5)
Neither technique	52 (13)	4 (1)	NR	12 (4)	0	68 (4)
Per SLN-positive patient						
SLNs identified by						
n	35	34	36	60	57	222
Both techniques	33 (94)	31 (91)	32 (89)	52 (87)	54 (95)	202 (91)
Magnetic technique only	0	2 (6)	2 (6)	3 (5)	1 (2)	8 (4)
Standard technique only	1 (3)	0	1 (3)	1 (2)	2 (3)	5 (2)
Neither technique	1 (3)	1 (3)	1 (3)	4 (7)	0	7 (3)

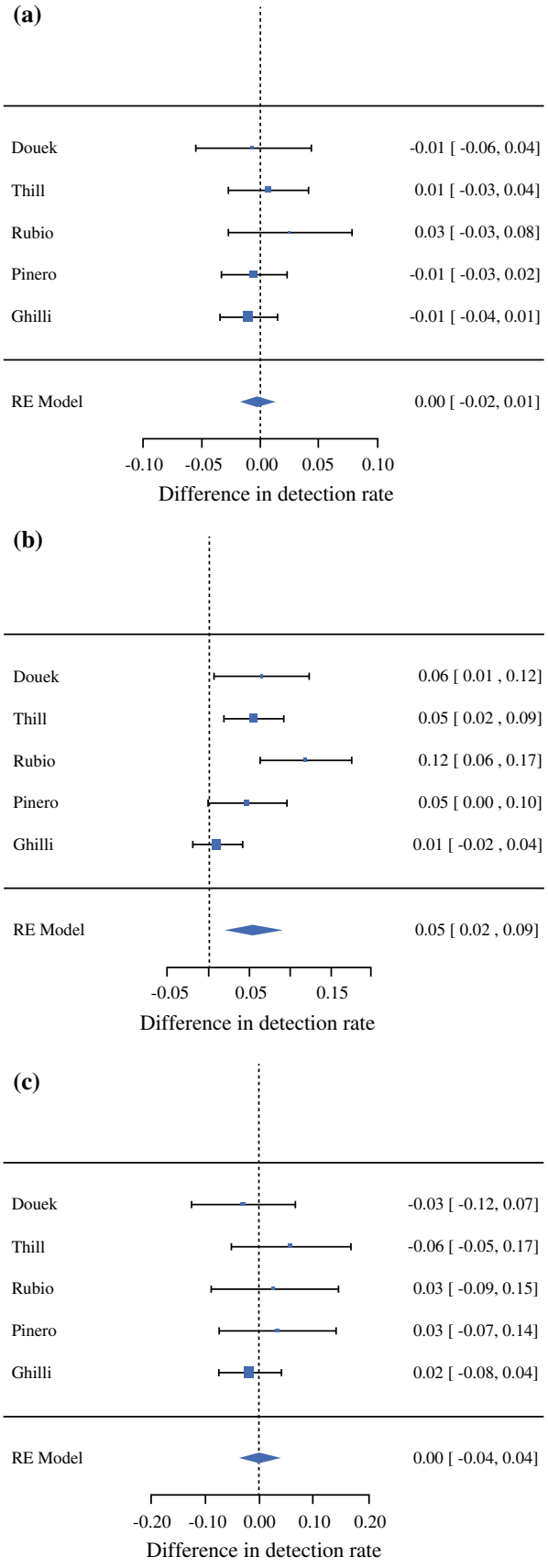
SLN sentinel lymph node, *NR* not reported

node, and per SLN positive patient. The discordance rates between the two methods were low for SLN detection per patient (3.5 %), per node (16.2 %), and malignant SLN per patient (5.8 %). The magnetic technique was favored when SLN detection was defined per node or per patient with a positive SLN. In ten patients, an SLN was not identified by either method. Of the cases with failed detection, seven patients were reported to have at least one malignant node. These data were not explicitly reported in the study from Rubio et al.[20] Figure 1 shows the differences in SLN detection rate between Sienna+® and the standard technique per patient, per node, and malignant SLN detection rate per patient.

A summary of the meta-analysis of the agreement indices for SLN detection per patient (Table 2) demonstrates strong overall agreement between the methods of SLN identification, with a PABAK of 0.94 [95 % confidence interval (CI) 0.89–0.98]. Significant heterogeneity was noted among studies for the proportion of overall agreement, proportion of positive agreement, and PABAK. The difference in the SLN identification rate per patient between the two methods was estimated to be −0.3 % (95 % CI −1.7 to 1.2). The detection rate per node for Sienna+® was therefore non-inferior to the standard tracer(s) technique, with a non-inferiority margin of 5 %.

A summary of the meta-analysis of the agreement indices for SLN detection per node is shown in Table 3. The overall agreement between the methods was moderate to substantial, with a PABAK of 0.68 (95 % CI 0.54–0.82). Significant heterogeneity was noted among studies for most agreement indices. The difference in detection rate per node between Sienna+® and the standard tracer technique was estimated to be 5.5 % (95 % CI 2–8.9 %), favoring Sienna+®.

A summary of the meta-analysis of the agreement indices for malignant SLN detection per patient is shown in Table 4. The overall agreement between the two methods was strong, with a PABAK of 0.89 (95 % CI 0.84–0.95). The difference in detection rate per patient between the Sienna+® and standard tracer(s) techniques was estimated to be 0.2 % (95 % CI −3.7 to 4.2). The malignancy detection rate per patient for Sienna+® was therefore non-inferior to the standard tracer(s) technique, with a non-inferiority margin of 5 %.



◀ **FIG. 1** Difference in detection rate utilizing Sienna+® versus a standard technique employing technetium with or without blue dye. **a** SLN detection rate per patient; **b** SLN detection rate per node and **c** per patient with a malignant SLN. *SLN* sentinel lymph node

DISCUSSION

Radioisotope and blue dye are well-established agents used for lymphatic mapping and SLN detection. Despite their proven utility, there are disadvantages to their use leading to interest in evaluating alternative mapping agents. In order for such agents to have clinical utility, they must be shown to be non-inferior to radioisotope with or without blue dye for performing SLN dissection. This meta-analysis confirmed that Sienna+®, a magnetic mapping agent, is non-inferior with respect to SLN identification per patient, as well as per SLN. Importantly, non-inferiority was also shown with respect to the ability to accurately identify patients with malignant SLN(s).

Interestingly, among the five trials used for this meta-analysis, in cases when there was discordance in SLN detection, there were a greater number of nodes identified using Sienna+® compared with using a standard methodology of radioisotope with or without blue dye. This is significant because the number of SLNs identified has implications for the accuracy of the procedure. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 study showed that the false-negative rate of SLN dissection is 17.7 % if one SLN is identified compared with 10 and 6.9 % if two or three SLNs are found, respectively.[25] However, it is also known that the majority of patients with a positive SLN will have that positive node identified within the first four nodes harvested, suggesting that there is minimal utility in identifying five or more SLNs.[26] Although there were differences in the individual trials with respect to the number of SLNs identified by one technique versus the other, as well as the rate of identifying histologically positive nodes using one technique versus the other, the absolute numbers are small in each trial. It should be emphasized that the overall analysis showed no statistically significant differences between Sienna+® and the standard agents with respect to the identification of SLN(s) or malignant SLN(s).

In addition to being able to identify SLN(s), in order for alternative agents such as Sienna+® to be considered for routine clinical use, the agent must also be safe. Allergic reactions associated with lymphatic mapping have been described, primarily related to the use of blue dye, and, although uncommon, are a potentially life-threatening complication.[27] Our group previously reported that 1.1 % of patients experience a severe anaphylactic reaction to isosulfan blue dye with decreased severity of the reaction

TABLE 2 Summary of the meta-analysis of the agreement indices for sentinel lymph node detection per patient

Agreement indices	Estimate	95 % CI	*p* Value of test of heterogeneity
Difference in detection rate between the two methods	−0.3 %	−0.17 to 1.2 %	0.78
Proportion of overall agreement	96.9 %	94.6 to 99.1 %	0.003
Proportion of positive agreement	98.4 %	97.2 to 99.6 %	0.004
Proportion of negative agreement	40.7 %	10.1 to 71.4 %	NA[a]
Cohen's kappa	0.491	0.206 to 0.776	0.077
PABAK	0.937	0.893 to 0.982	0.003

CI confidence interval, *NA* not applicable, *PABAK* prevalence-adjusted bias-adjusted kappa

[a] Cannot be estimated due to zero value for negative agreement in the Ghilli et al. study[22]

TABLE 3 Summary of the meta-analysis of the agreement indices for sentinel lymph node detection per node

Agreement indices	Estimate	95 % CI	*p* value of test of heterogeneity
Difference in detection rate between the two methods	5.5 %	2 to 8.9 %	0.0145
Proportion of overall agreement	83.8 %	76.8 to 90.9 %	0
Proportion of positive agreement	90.6 %	86.1 to 95.1 %	0
Proportion of negative agreement	22.2 %	0.8 to 43.5 %	NA[a]
Cohen's kappa	0.158	−0.053 to 0.37	<0.001
PABAK	0.667	0.536 to 0.818	0

CI confidence interval, *NA* not applicable, *PABAK* prevalence-adjusted bias-adjusted kappa

[a] Cannot be estimated due to zero value for negative agreement in the Ghilli et al. study[22] and not reported in the Rubio et al. study [20]

TABLE 4 Summary of the meta-analysis of the agreement indices for malignant sentinel lymph node detection per patient

Agreement indices	Estimate	95 % CI	*p* value of test of heterogeneity
Difference in detection rate between the two methods	2.0 %	−3.7 to 4.2 %	0.67
Proportion of overall agreement	94.7 %	91.8 to 97.6 %	0.85
Proportion of positive agreement	97.2 %	95.6 to 98.8 %	0.84
Proportion of negative agreement	39.4 %	7.4 to 71.3 %	NA[a]
Cohen's kappa	0.543	0.287 to 0.799	0.80
PABAK	0.894	0.835 to 0.953	0.85

CI confidence interval, *NA* not applicable, *PABAK* prevalence-adjusted bias-adjusted kappa

[a] Cannot be estimated due to zero value for negative agreement in the Ghilli et al. study[22]

with routine prophylaxis to include administration of famotidine, diphenhydramine, and a glucocorticoid.[28,29] Anaphylaxis was reported in 0.1 % of patients in the American College of Surgeons Oncology Group (ACOSOG) Z0010 trial after SLN surgery in cases with isosulfan blue dye.[30] Use of methylene blue dye as a mapping agent has also been described and is less commonly associated with allergic reactions but may result in skin necrosis.[31] Although these adverse effects are seen in a small percentage of patients, given the number of SLN procedures performed globally, this potentially places a substantial number of patients at risk. Among the studies included in this meta-analysis, there were no significant adverse events associated with the use of the Sienna+®. Douek et al. described one patient with transient hypotension after dye injection, although it is unclear if this was related to Sienna+® or blue dye.[18] Postoperative skin discoloration secondary to the Sienna+® was also described by both Rubio et al. and Ghilli et al., affecting 19.4 and 47.3 % of patients, respectively.[20,22] Ghilli et al. reported that after mean follow-up of 5.9 months, this skin staining resolved in 21.1 %, improved in 70.4 %, remained stable in 7.1 %,

and worsened in 1.4 % of patients affected. The authors suggest that this side effect was reduced with deeper injection of the Sienna+®.[22] Additionally, it has been noted that Sienna+® may complicate subsequent magnetic resonance imaging (MRI) examinations. In a small study of ten MRI scans performed in six patients, void artifacts were noted at the subareolar injection site in all scans. All artifacts were greater than 5 mm in greatest dimension, suggesting that they could potentially obscure important clinical findings. In at least one patient, this artifact was present 25 months after injection. Additional studies regarding the impact of Sienna+on MRI scans is required as this may be an important consideration in high-risk patients in whom follow-up MRI is clinically indicated.[32]

It should be noted that patients with hypersensitivity to iron or dextran compounds and those with pacemakers or metal implants were excluded from the trials and would not be candidates for using Sienna+® for SLN mapping. Related to this, it is important to note that when using Sienna+®, the surgeon must employ non-metal instruments as there is interference between metal and the Sentimag® probe. This may present a challenge in obese patients who may require additional instruments to facilitate dissection in the deep axilla. Another potential advantage of Sienna+® over a standard method utilizing technetium is the avoidance of radiation exposure. Such exposure may be a concern for patients and providers. In addition, there are regulatory considerations related to the radioisotope often necessitating reliance on nuclear medicine for radioisotope maintenance and even administration. Sienna+® is not subject to these regulatory constraints and is injected intraoperatively by the surgeon, thereby eliminating reliance on nuclear medicine. The intraoperative injection may also enhance patient satisfaction as the injection is administered after the induction of anesthesia.

Although this analysis includes a small number of trials, each describes a similar intraoperative technique and paired comparison study design. All studies enrolled clinically node-negative patients with either invasive breast cancer or ductal carcinoma in situ, and allowed patients to undergo lumpectomy or total mastectomy. By pooling the trial data, this meta-analysis provides increased statistical power to support the finding of non-inferiority, and suggests generalizability of the technique to a wider population. Limitations of this analysis include the variable use of blue dye, which was not standardized across studies. In addition, clinicopathologic features were not consistently reported across the studies and thus were not included for comparison in this analysis. Overall, the data were highly imbalanced, such that in the majority of cases an SLN was identified by either method. This is expected given the high SLN identification rate, and was appropriately adjusted for in the statistical analysis when comparing the techniques.

CONCLUSIONS

This meta-analysis of five trials investigating Sienna+® as an alternative mapping agent for SLN dissection in a total of 804 women has confirmed that Sienna+® is not inferior to radioisotope with or without blue dye, the standard methodology currently employed globally by most surgeons for SLN detection. Sienna+® may therefore be a valuable alternative to radioisotope and blue dye, and is already approved for use in Europe. An ongoing multicenter trial in the US will provide additional information regarding the accuracy of this technique for consideration by the US FDA.[17]

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