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Original article

The Central-European SentiMag study: Sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) vs. radioisotope

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ABSTRACT

Sentinel lymph node biopsy (SLNB) is the standard surgical procedure for the axilla in early node-negative breast cancer. To date, the "gold standard" to localize the sentinel lymph node (SLN) is the radiotracer ^{99m}Tc with or without blue dye. The aim of this study was to evaluate potential equivalency of the new SentiMag® technique in comparison to the "gold standard". Within this prospective, multicentric and multinational non-inferiority study including 150 patients ^{99m}Tc was compared with the magnetic technique, using superparamagnetic iron oxide particles (SPIOs, Sienna+®) for localization of SLNs. The results showed a detection rate per patient of 97.3% (146/150) for ^{99m}Tc vs. 98.0% (147/150) for Sienna+® with a similar average number of removed SLNs per patient and a higher per patient malignancy detection rate for the SPIO tracer. We obtained convincing results that magnetic SLNB can be performed easily, safely and equivalently well in comparison to the radiotracer method.

Introduction

Sentinel lymph node biopsy (SLNB) is widely accepted and has replaced primary axillary lymph node dissection as the staging procedure for early node-negative breast cancer. In 1994, Giuliano et al. [1] performed SLNB by injecting isosulphan blue dye around the tumour. In parallel, Krag et al. [2] and Veronesi et al. [3] introduced the use of a radioactive tracer, technetium-99m labelled nanocolloid (^{99m}Tc) and a hand-held gamma probe for SLN detection. To date, the "gold standard" to detect the sentinel lymph node (SLN) is the radiotracer alone, or in combination with blue dye [4,5].

However, there are drawbacks connected to the combination technique, such as radiation exposure of patients and healthcare personnel, strong legislative control, limitations in radiotracer availability, dependency on nuclear medicine units and allergic reactions to blue dye, which demonstrate a clinical need for new radiation-free but accurate methods for SLN localization.

In this study we used a handheld magnetometer (SentiMag®) to detect the magnetic response from iron oxide particles trapped in SLNs and a hand-held gamma probe to detect the ^{99m}Tc radiotracer in a parallel manner. As magnetic tracer we used Sienna+®, which is a superparamagnetic iron oxide (SPIO) compound, originally developed for contrast-enhanced magnetic resonance imaging. The aim of our study was to investigate the potential equivalency of the SentiMag® technique in comparison to the "gold standard" of SLNB.

Materials and methods

The SentiMag® technique

The SentiMag® technique is a non-radioactive detection system to magnetically mark and locate lymph nodes (LN) prior to their surgical removal and subsequent analysis. It consists of a hand-held magnetometer, the SentiMag®, and a magnetic tracer, Sienna+®, both CE-marked as medical devices class IIa. The tracer flows through the lymphatic system and becomes trapped in the SLNs. Sienna+® particle dimensions (60 nm) are similar to the radiotracer

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but more homogeneous. Its dark-brown colour acts as visual aid in intraoperative SLN identification.

Trial design and patient recruitment

We conducted a prospective, multicentre and multinational non-randomized paired equivalence study. From November 2012 until June 2013 we included 150 patients with histopathologically verified breast cancer. Patient and tumour characteristics are shown in Table 1. The study was approved by the local ethics committees and written informed consent was obtained from all patients. All patients planned to undergo SLNB with clinically and ultrasonographically node-negative invasive breast carcinoma or extended DCIS were eligible for participation in the study. Exclusion criteria included allergy to iron or dextran compounds, iron overload disease, pacemaker or ferrous metal-containing devices in the chest wall, pregnancy and lactation. Outside these exclusion criteria no further selection criteria were applied. The patient cohort therefore represents typical patients encountered in normal practice.

Axillary lymph node status was preoperatively examined by palpation and ultrasonography with or without lymph node fine needle aspiration cytology or true cut core biopsy. In most cases the primary tumour was located in the upper-outer quadrant (69/150, 46.0%) (see Table 1). We performed wide local excisions or quadrantectomy in 89.3%, oncoplastic techniques in 13.3% and modified radical mastectomy and nipple-sparing mastectomy with immediate reconstruction in 3.3% of the procedures.

Table 1
Patient and tumour characteristics of the 150 patients included. Results are given as mean values or frequencies in %.

Characteristic	Value
Age	57.6 y (range 29–85 y)
Height	164.7 cm (range 114–180 cm)
Weight	69.0 kg (range 46–120 kg)
Body mass index (BMI)	25.3 (range 17.1–46.9)
Menopausal status	
Premenopausal	52 (34.7%)
Perimenopausal	6 (4.0%)
Postmenopausal	92 (61.3%)
Carcinoma type	
Invasive carcinoma	131 (87.3%)
Ductal carcinoma *in situ*	19 (2.6%)
Tumour location	
Upper outer quadrant	69 (46.0%)
Upper inner quadrant	28 (18.7%)
Lower inner quadrant	14 (9.3%)
Lower outer quadrant	22 (14.7%)
Central	17 (11.3%)
Pathological tumour size	
pTis	19 (12.6%)
pT1a	6 (4%)
pT1b	23 (15.3%)
pT1c	65 (43.3%)
pT2	35 (23.3%)
pT3	2 (1.3%)
Pathological lymph node status	
pN0	108 (72%)
pNi+	7 (4.7%)
pN1mi	3 (2%)
pN1a	29 (19.3%)
pN2a	3 (2%)
Grading	
G1	25 (16.7%)
G2	90 (60%)
G3	35 (23.3%)
Hormone receptor status	
Estrogen receptor (ER)+	134 (89.3%)
Progesterone receptor (PR)+	125 (83.3%)
HER2 status	
HER2+	13 (8.7%)

Intraoperative proceedings

SLNs were initially marked with radioisotope following a 1- or 2-day protocol as usually performed in the participating centres (Fig. 1). The ^{99m}Tc nanocolloid in human albumin base (Nanocoll®) was injected periareolary or peritumorally and a lymphoscintigraphy was performed pre-operatively. After induction of general anaesthesia, 2 ml of Sienna+®, diluted to 5 ml with physiological saline, were injected into the subareolar interstitial tissue at least 20 min before SLNB, followed by 5 min massage to promote migration of the magnetic tracer. No additional injection of blue dye was performed. Before incision, count numbers of the skin, the injection site and the axillary area (hot spots) were measured both with the SentiMag® and gamma probe. Preparation and excision of LNs was conducted using both techniques in a strictly parallel manner, in order to simulate routine use of both techniques. To avoid any kind of interference with the magnetometer, polymer retractors and forceps were used while detecting the SLNs with the SentiMag® probe. All LNs marked with either tracer were excised. The diameter of the SentiMag® probe is slightly larger (6 mm) than that of the gamma probe, however larger incisions were not required and SLNB could be performed via the same incision the breast tumour was resected from, if desired. SLNs were removed following the definition that every LN marked with either radioisotope or SPIO tracer is a true SLN. A LN with less than 10% of the maximum SLN count number was defined as a non-SLN for both techniques. Therefore, SLNB was stopped when the residual activity in the axilla was less than 10%. SLNs and non-SLNs were submitted separately for histopathological examination. All SLNs were assessed intraoperatively by frozen section and postoperatively in formalin-fixed embedded sections using haematoxylin and eosin staining.

Study objectives and statistical analyses

The primary end point of the study was the proportion of successful SLNBs (detection rate per patient) with either the standard (radioisotope) or the magnetic (SPIO and hand-held magnetometer) technique. Assuming a 97% detection rate of the standard method [4], we defined a limit difference for equivalence of −5%. Therefore, the statistical threshold for detection rate has been prospectively set at 92% to accept non-inferiority of the magnetic method.

Secondary end points included the proportion of SLNs detected (nodal detection rate) as well as the proportion of pathologically positive results (malignancy rate) per patient and per node with either the standard or the magnetic technique. Moreover, the concordance and reverse concordance of successful detections (per patient and per node; overall and in terms of malignancy) were calculated. Concordance was defined as the number of simultaneously radioisotope- and SPIO-positive patients or nodes, divided by the number of patients or nodes marked by radioisotope. Reverse concordance was defined as the number of simultaneously radioisotope and SPIO positive patients or nodes, divided by the number of patients or nodes marked by the SPIO tracer. Only tumour positive patients or nodes were included in the malignancy concordance calculation. For all parameters a 95% Bayes confidence interval (CI) was calculated on the basis of binomial distribution. Detection rate was additionally tested in a right-sided binominal test with the alternative hypothesis that the proportion of successful SLNBs was greater than 0.92 for each tracer. A *p*-value of

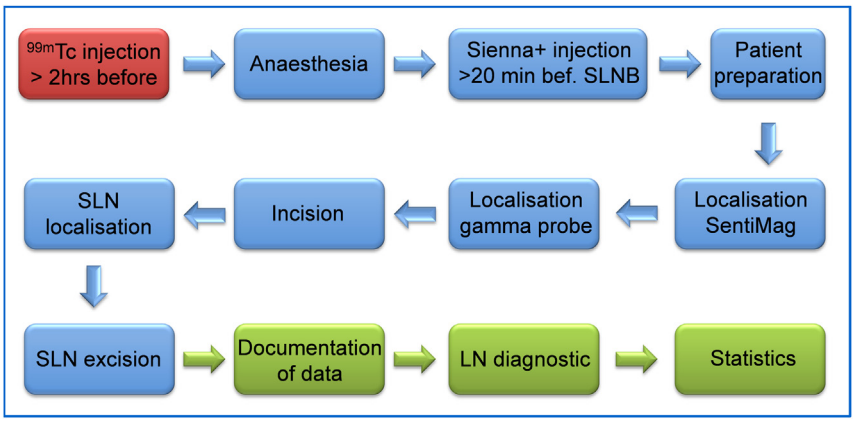

Fig. 1. Study workflow.

<0.05 indicated that the null hypothesis was rejected. All statistical calculations were performed using the R software, version 3.0.1 [6].

Results

Within this study we detected 291 SLNs in 150 patients using ^{99m}Tc and Sienna+®. Mean Sienna+® migration time was 26 ± 1 min, if the SLNB was performed first, or 66 ± 4 min, if breast surgery was performed before SLNB. Data analysis led to a detection rate per patient of 97.3% (146/150; CI 93.9–99.1%; $p = 0.0060$) for ^{99m}Tc vs. 98.0% (147/150; CI 94.8–99.4%; $p = 0.0017$) for Sienna+® (Fig. 2(A)). Per patient concordance rate was 99.3% (145/146; CI 96.8–99.9%) (Fig. 2(B)), whereas reverse per patient concordance rate was 98.6% (145/147; CI 95.7–99.7%). An average of 1.8 (^{99m}Tc, range: 1–9 nodes) and 1.9 (SPIO; range: 1–9 nodes) LNs were collected per patient. Nodal detection rate was 91.8% (267/291; CI 88.2–94.5%) for the radioisotope vs. 97.3% (283/291; CI 94.9–98.7%) for the SPIO tracer (Fig. 2(C)). Nodal concordance was calculated as 98.5% (263/267; CI 96.5–99.5%) and reverse nodal concordance as 92.9% (263/283; CI 89.5–95.5%).

For two patients, SLNB detection was unsuccessful with ^{99m}Tc but successful with Sienna+®. The patients were 48 and 44 years old, had a BMI of 21.1 and 25.3 and a tumour size of 40 mm and 29 mm, respectively. In both SLNs marked with Sienna+® macrometastases were found. Double SLN detection failure was found in a 75- and an 85-year old patient with a BMI of 31.9 and 25.4 and a tumour size of 48 mm and 15 mm, respectively. In the axillary lymph node dissection (ALND) of the first patient two macrometastases and in the second patient a histopathologically node negative axilla were found. Another 63 year old patient with a BMI of 28.9 and a tumour of 24 mm showed no Sienna+® and a low radioisotope signal for 2 histopathologically negative SLNs. Therefore, the malignancy detection rate per patient was 91.2% (31/34; CI 78.3–97.5%) for ^{99m}Tc vs. 97.1% (33/34; CI 87.1–99.7%) for the SPIO tracer (Fig. 2(E)) and 91.1% (^{99m}Tc; 41/45; CI 80.2–96.9%) vs. 95.6% (SPIO; 43/45; CI 86.5–99.1%) per node (Fig. 2(G)). The proportion of histopathologically positive results was 31/146 (^{99m}Tc: 21.2%; CI 15.2–28.4%) vs. 33/147 (SPIO: 22.4%; CI 16.3–29.7%) per patient and 41/267 (^{99m}Tc: 15.4%; CI 11.4–20.0%) vs. 43/283 (SPIO: 15.2%; CI 11.4–19.7%) per node. All histopathologically positive LNs detected with the conventional technique were also detected with the magnetic technique, resulting in a malignancy concordance rate of 100% per patient (31/31; CI 92.3–100%) (Fig. 2(F)) and 100% per node (41/41; CI 94.1–100%) (Fig. 2(H)). Reverse malignancy concordance was 93.9% per patient (31/33; CI 81.9–98.7%) and 95.3% per node (41/43, CI 85.9–99.0%). No complications in terms of allergic reactions, or irritations at the injection site were observed.

Discussion

Highly accurate methods and techniques are needed to identify SLNs correctly as well as to limit the number of false negative patients and the number of nodes in total. At present, the radiotracer/gamma probe technique is the most accurate stand-alone method for SLNB, which can be combined with blue dye [4]. Some inherent disadvantages of the conventional technique led us to evaluate if use of the SentiMag® technique could improve on existing methods. First, the radiotracer requires exposure of patient and healthcare personnel to radiation and is not available in every centre. Moreover, the parent isotope ^{99}Mo is made in just a few reactors worldwide, which has led to limited tracer availability in the past. Secondly, the strong signal after injection around the tumour, the so called “shine-through”, interferes with the detection of radiation from LNs and stray radiation in the axilla quite often disturbs the SLN detection as well. Thirdly, ^{99m}Tc has a 6 h half-life, which limits the timeframe of SLNB. Fourthly, detection rate for blue dye only is less than for the radiotracer alone [5], and intensive blue dye tattoos may be seen on the breast for several months. Fifthly, anaphylactic reactions related to blue dye can occur and may be life-threatening [7]. Furthermore, *in vitro* data indicates genotoxicity of blue dyes in the form of DNA strand breaks and increased levels of oxidative DNA lesions [8].

In contrast to that, the SentiMag® method offers advantages. The surgeon can inject the magnetic tracer by him or herself directly in the operation room, independent from complex time scheduling with the nuclear medicine department (usually, no marking on Sundays or on public holidays). Therefore, it allows a higher number of SLNBs per day. The preparation time of 20 min is much shorter than for the radioisotope (up to 29 h [9]) and there is no risk of unavailability for the tracer. Surgeons proceed with incision after obtaining a clear transcutaneous signal with the magnetometer, without preoperative imaging. Whether preoperative imaging is needed is a debatable question. Results from van der Ploeg et al. [10] and Straver et al. [4] question the usefulness of lymphoscintigraphy. Mathew et al. [11] performed re-exploration of the axilla after SLNB and found only 3% additional lymph nodes which were all histologically negative. Considering these data, it might not be disadvantageous for the SentiMag® technique that a lymphoscintigraphy is missing.

Concerning detection success, the primary efficiency endpoint of our study, we determined equivalency of the SentiMag®

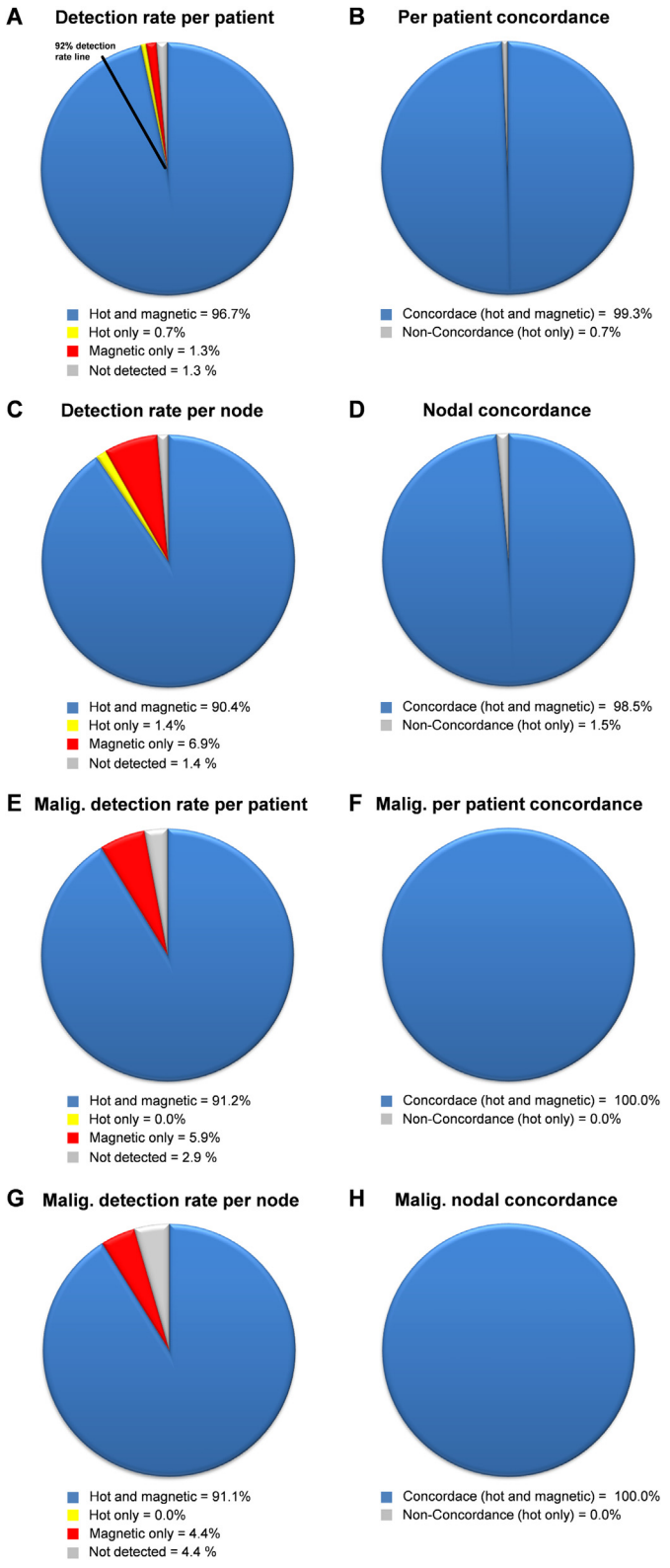

Fig. 2. Detection rates and concordance of Sienna+ and ^{99}Tc. A Detection rate per patient based on 150 patients. The statistical threshold for detection rate was prospectively set at 92% to accept non-inferiority of the magnetic method, which is marked by the black line in A. B Per patient concordance based on 146 patients successfully marked with radioisotope. C Detection rate per node based on 291 isolated SLNs. D Nodal concordance based on 267 hot nodes. E Malignancy detection rate per patient based on 34 patients positive for malignancy. F Malignancy per patient concordance based on 31 radioisotope positive and metastatic patients. G Malignancy detection rate per node based on 45 histopathologically positive nodes. H Malignancy nodal concordance based on 41 hot and malignant nodes.

technique with the gold standard, observing a per patient detection concordance of 99.3% (145/146). The statistical threshold for detection rate had been prospectively set at 92% to accept non-inferiority of the magnetic method, assuming a 97% detection rate of the standard method [4]. As data analysis resulted in a detection rate per patient of 97.3% (146/150) for ^{99m}Tc and 98.0% (147/150) for Sienna+®, these results established with a high degree of statistical probability that the SentiMag® technique performs equivalently well in comparison to the radiotracer method. Additional publications concerning the performance of the magnetic technique for SLNB are currently limited. In an initial pilot study SLN identification was successful in 100% when compared to blue dye and ^{99m}Tc [12]. Douek et al. presented their results of the SentiMAG Multicentre Trial recently and found a detection rate of 94.4% (151/160) for the magnetic technique that was slightly lower than our detection rate of 98.0% [13]. In agreement with our findings, Douek et al. detected slightly more SLNs with the magnetometer but without any significant difference (1.9 vs. 2.0 average per-patient-SLNs) to each technique and to the literature [10,13]. In contrast to our results, another working group used a different magnetometer and tracer (Ferucarbotran) and found a detection rate of only 77% [14]. Further performance evaluations, preferably assessing independent use of magnetic and radioactive tracers, would provide valuable information towards the efficacy of magnetic SLNB in routine use.

Interestingly, more pathologically positive SLNs were found with the SentiMag® technique compared to the radiotracer method, suggesting that magnetic SLNB performs equally well as the standard method in determining malignancy. The two patients where the SLN identification was successful with Sienna+® but not with the radioisotope were of younger age and had a low BMI, whereas the two patients with SLN detection failure for both techniques had an age >75 years and a higher BMI. The AMAROS trial showed a similar trend for a better detection rate for younger patients compared to older patients [4,15,16]. Following these observations, further comparative results could determine whether the SentiMag® technique might have a detection benefit for younger patients with a low BMI.

Another radiotracer-independent technique is the use of near-infrared (NIR) fluorescence imaging with indocyanine green (ICG). With this technique SLN detection rates of 99–100% are possible [17–22]. However, there are some limitations. First, the short time frame for SLNB of approximately 30 min as the NIR fluorescence signal in the SLN is only visible during that time [23]. Secondly, as tissue depth is limited to about 1 cm [9,18], a high BMI and thick subcutaneous fat tissue hampers detection. Therefore ICG might only be useful in patients with lower BMI. Thirdly, the imaging equipment to show the emission of light, such as the Fluorescence-Assisted Resection and Exploration (FLARE™) imaging system or the Photodynamic Eye (PDE) camera, are comparatively expensive and the application is more complicated [9,23]. Data concerning the use of a hybrid tracer, ICG- ^{99m}Tc-radiolabelled nanocolloid are promising, however it is a radioactive compound again [24].

In contrast to ICG, the SentiMag® technique provides a very comfortable timeframe. In the present study, the longest Sienna+® migration time before SLNB lasted 160 min. Despite the long time, SLN detection was successfully performed with the magnetometer. Regarding patients with a high BMI we found lower transcutaneous signals. Though, after skin incision a good signal was found in nearly every SLN. Compared to literature [10], we removed a similar number of SLNs (average of 1.9 SLNs) by using SentiMag®. However, with ICG the number of removed SLNs is higher (average of 3.4 SLNs) [22], which could lead to a possible higher morbidity. An explanation might be the mapping of several SLNs, as ICG can flow

to higher tier nodes with time passing [25]. In contrast, our results suggest that the SPIO tracer is well retained in the "true" SLNs, as in most cases the SLN with the highest count number was found to be the pathologically positive SLN (SPIO: 84.8%; 28/33 vs. ^{99}Tc: 88.0%; 27/31) for both markers if malignancy was present in the axilla of the patient. Moreover, all patients with malignant LN involvement would have been identified after sampling the two lymph nodes with the highest magnetic or radioisotope count even if more LNs were retrieved using either method, suggesting a low false negative rate if Sienna+® is to be introduced into clinical routine as standard method.

Conclusion

This prospective clinical study from four Central-European centers provided convincing results, that magnetic SLNB can be performed easily, safely and equivalently well in comparison to the standard radioactive method. Moreover, the SentiMag® technique can be rapidly implemented into daily routine and, thanks to its simple handling, preoperative preparation can be reduced to a minimum. If further and consistent results prove its efficacy, this technique has the potential to become standard of care.

Conflict of interest statement

M. Thill has received consultant and speaker honoraria from Sysmex Europe. The authors have no relevant affiliation or financial involvement with any organization or entity with financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from the disclosed.

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