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ORIGINAL ARTICLE – BREAST ONCOLOGY

Sentinel Node Biopsy Using a Magnetic Tracer Versus Standard Technique: The SentiMAG Multicentre Trial

Michael Douek, MD[1,2], Joost Klaase, MD[3], Ian Monypenny, MD[4], Ashutosh Kothari, MS[2], Katalin Zechmeister, MD[5], Douglas Brown, MD[6], Lynda Wyld, PhD[7], Philip Drew, MD[8], Hans Garmo, PhD[1], Olorunsola Agbaje, PhD[1], Quentin Pankhurst, PhD[9], Bauke Anninga, MSc[1,10], Maarten Grootendorst, MSc[1,10], Bennie ten Haken, PhD[10], Margaret A. Hall-Craggs, MD[11], Arnie Purushotham, MD[1,2], Sarah Pinder, MD[1,2] and On behalf of the SentiMAG Trialists Group

[1]Division of Cancer Studies, Department of Research Oncology, King's College London, London, UK; [2]Guy's & St. Thomas' Hospitals NHS Foundation Trust, London, UK; [3]Medisch Spectrum Twente, Enschede, The Netherlands; [4]University Hospital of Wales at Llandough, Cardiff, UK; [5]Norwich and Norfolk University Hospitals, Norwich, UK; [6]Ninewells Hospital and Medical School, Dundee, UK; [7]University of Sheffield, Sheffield, UK; [8]Royal Cornwall Hospitals NHS Trust, Truro, Cornwall, UK; [9]University College London, London, UK; [10]University of Twente, Enschede, The Netherlands; [11]University College Hospital, London, UK

ABSTRACT

Background. The SentiMAG Multicentre Trial evaluated a new magnetic technique for sentinel lymph node biopsy (SLNB) against the standard (radioisotope and blue dye or radioisotope alone). The magnetic technique does not use radiation and provides both a color change (brown dye) and a handheld probe for node localization. The primary end point of this trial was defined as the proportion of sentinel nodes detected with each technique (identification rate).

Methods. A total of 160 women with breast cancer scheduled for SLNB, who were clinically and radiologically node negative, were recruited from seven centers in the United Kingdom and The Netherlands. SLNB was undertaken after administration of both the magnetic and standard tracers (radioisotope with or without blue dye).

Results. A total of 170 SLNB procedures were undertaken on 161 patients, and 1 patient was excluded, leaving 160 patients for further analysis. The identification rate was 95.0 % (152 of 160) with the standard technique and 94.4 % (151 of 160) with the magnetic technique (0.6 % difference; 95 % upper confidence limit 4.4 %; 6.9 % discordance). Of the 22 % (35 of 160) of patients with lymph node involvement, 16 % (25 of 160) had at least 1 macrometastasis, and 6 % (10 of 160) had at least a micrometastasis. Another 2.5 % (4 of 160) had isolated tumor cells. Of 404 lymph nodes removed, 297 (74 %) were true sentinel nodes. The lymph node retrieval rate was 2.5 nodes per patient overall, 1.9 nodes per patient with the standard technique, and 2.0 nodes per patient with the magnetic technique.

Conclusions. The magnetic technique is a feasible technique for SLNB, with an identification rate that is not inferior to the standard technique.

Sentinel lymph node biopsy (SLNB) is now the standard technique used in breast cancer patients with a clinically and radiologically negative axilla. SLNB for breast cancer was introduced in the 1990s and significantly reduces the morbidity associated with axillary node dissection, including lymphedema, seroma, numbness, wound infection, reduced shoulder mobility, and chronic pain.[1,2] The gold

This study was conducted on behalf of the SentiMAG Trialists Group (Study Collaborators).
The members of the SentiMAG Trialists Group (Study Collaborators) are listed in the Appendix.
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Protocol version: 6.0, October 8, 2012.
Trial Registrations: ISRCTN: 35827879 (http://www.controlled-trials.com/ISRCTN35827879/); The Netherlands: NTR3283 (http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3283).
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M. Douek, MD
e-mail: michael.douek@kcl.ac.uk

standard for SLNB is the *combined technique*, using both blue dye and radioisotope injection.[3,4] In the AMAROS trial with 1,953 patients, the identification rate with the combined technique was 97 %.[5] In the ALMANAC trial, the identification rate with the combined technique was 96.0 %, and with radioisotope or blue dye alone, it was 85.6 %.[6]

However, the combined technique has significant drawbacks. The use of radioisotope exposes patients and healthcare workers to radiation, is heavily controlled by legislation (both on the specific training for operators and on the subsequent disposal of surgical waste), and provides poor preoperative spatial resolution on lymphoscintigraphy. As a result of the latter, some centers have stopped undertaking routine preoperative lymphoscintigraphy. Intraoperative blue dye injection can obscure the surgical field and frequently leaves a skin residue (tattoo stain), which can take months to fade and is occasionally permanent. There is also up to a 0.4 % risk of anaphylaxis, as a result of which some centers in the United Kingdom have stopped using blue dye. There is thus a clinical need to develop new techniques for detecting sentinel nodes without these drawbacks.[7,8]

We developed a noninvasive method for identifying the sentinel node by using a superparamagnetic iron oxide (SPIO) contrast agent (Endorem, Guerbet, France), injected subcutaneously into the breast rather than intravenously. We demonstrated proof of principle to identify sentinel nodes by using a handheld prototype magnetometer.[9,10] When injected intravenously, SPIOs have been used as contrast agents for magnetic resonance imaging (MRI), and their characteristics are well recognised.[11,12] When injected subcutaneously, SPIO moves into sentinel nodes within minutes, and iron deposition is seen predominantly within sinuses and in macrophages. In the event of metastatic involvement of the node, SPIOs are seen to deposit within uninvolved areas of the node only.[13] The nodes can be visualized on MRI and at operation and are often colored brown or black (Fig. 1).[14]

This research work led on to the development of 2 CE marked devices: an injectable magnetic tracer (Sienna+®, Endomagnetics Ltd., UK) and a handheld magnetometer (SentiMag®, Endomagnetics Ltd., UK). Sienna+, a blackish-brown sterile aqueous suspension of superparamagnetic carboxydextran-coated iron oxide particles, is a magnetic tracer that is intended for use with the SentiMag device. The carboxydextran coating prevents agglomeration while maintaining biocompatibility. The particle diameter, including the organic coating, is 60 nm (Z-averaged diameter; <0.25 polydispersity), ideally suited for SLNB. This diameter enables the SLNs to selectively filter out the particles and is similar to the particle size of standard radioisotope tracers (60 nm).

The SentiMAG Multicentre Trial evaluated a new magnetic technique for SLNB against the standard (radioisotope with or without blue dye). The magnetic technique

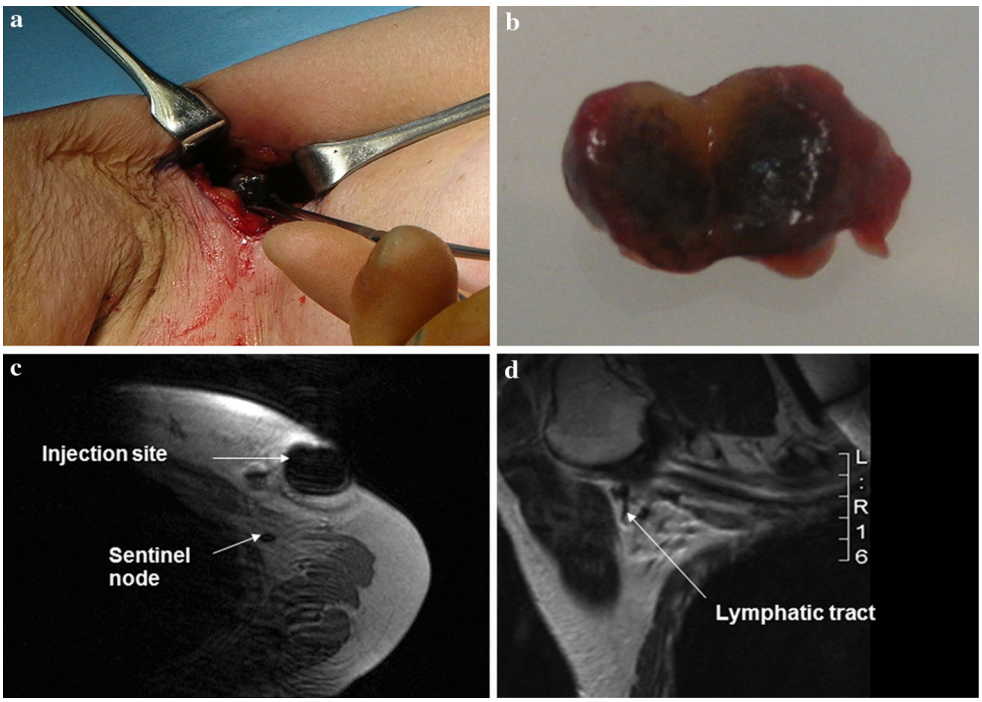

FIG. 1 Sentinel node biopsy with a subcutaneous injection of SPIO (Endorem, Guerbet, France) into the breast: **a** Sentinel node identified in right axilla. **b** Sentinel lymph node with black SPIO deposition. **c** MRI showing the injection site and a sentinel node. **d** Two sentinel lymph nodes and a lymphatic tract, seen on axillary MRI

provides both a color change (brown or black) and a handheld probe for node localization. The trial compared the identification rate of sentinel nodes with the new magnetic technique against that of the standard technique.

METHODS

Trial Design

The SentiMAG Multicentre Trial, an international phase II paired equivalence trial, was opened for recruitment at six centers in the United Kingdom and one in The Netherlands. The participating centers were selected as centers experienced with SLNB from both teaching and district general hospitals with relatively high-volume practice (>300 cases of newly diagnosed breast cancer per annum). The principal investigators attended an initial meeting which included methodologic training and a trial of the devices. After Ethics Committee approval in the United Kingdom, the trial was started before separate Ethics Committee approval was obtained in The Netherlands. At the start of the trial, a site visit was undertaken to train the local team. The magnetic technique was standardized by the chief investigator and surgeons were trained to follow the same technique.

Data collection was undertaken by using Autonomy Teleform (Autonomy Plc., Cambridge, UK) with either electronic clinical record forms or eForms. Electronic data were then processed in a Structured Query Language (SQL) database. All clinical record forms were validated by research nurses against source data, the local site file and also the database. The chief investigator, principal investigators, and members of the Trial Management Committee were blinded to all data until accrual of 160 patients. An independent Data Monitoring Committee received confidential unblinded reports, including data on complications, after 50 patients, after 100 patients, and on accrual of 160 patients.

Patient Recruitment

Between February 29, 2012, and October 3, 2012, patients with breast cancer (including ductal carcinoma in-situ) scheduled for SLNB and who were clinically and radiologically node negative (preoperative ultrasound results were normal or indeterminate/abnormal and had benign fine-needle aspiration or core biopsy) were recruited. Patients with male breast cancer and pregnant women were suitable as long as they were scheduled to undergo SLNB with radioisotope. All patients had to be available for follow-up for at least 12 months. We excluded patients with known intolerance or hypersensitivity to iron or dextran compounds, magnetic tracers, or SPIOs; with known hypersensitivity to blue dye (only in centers where blue dye was standard practice for SLNB); who could not or did not receive radioisotope; with an iron-overload disease; and with pacemakers or other implantable devices on the chest wall. Potential patients were identified by the investigators, the direct medical team and research nurses after screening of the patients' medical records or case presentation at the multidisciplinary team meetings. An invitation letter was sent to eligible patients together with the patient information sheet. Patients who were willing to participate in the trial provided informed written consent on the day of elective surgery or at a prior hospital visit. Details of all patients approached about the trial were recorded on the patient screening log and kept in the Investigator Site Files.

Surgery

All centers were experienced with SLNB and the standard technique used at the individual centers was used during this trial. SLNB was undertaken successfully by using the handheld magnetometer after training with the chief investigator (M.D.). For sentinel node localization patients received standard radioisotope injection preoperatively. Of seven centers, five used the combined technique, one used radioisotope alone, and another used selective blue dye on some patients. The timing and mode of administration of radioisotope (and blue dye, when used; Patent Blue V, Guerbet, France) was documented in the clinical record forms. The magnetic technique was standardized at all sites. A 5-ml periareolar subcutaneous injection (into the retroareolar subcutaneous space) was administered, consisting of 2 ml of magnetic tracer (Sienna+) diluted with 3 ml of normal saline. This was injected intraoperatively (after induction of anesthesia) followed by a 5-min massage. The magnetic tracer was administered before blue dye when this was used. Blue dye was administered (in centers using the combined technique) according to local protocols. During surgery the surgeon used the handheld magnetometer for skin localization of the sentinel lymph node and then the gamma probe to confirm the position. After incision, the surgeon used the handheld magnetometer for sentinel node localization (Fig. 2). The gamma probe was used only after magnetometer-detected nodes were identified and removed and for *ex vivo* counts. Similarly, blue tracts were not followed until after the handheld magnetometer was used to locate and excise sentinel nodes. All sentinel nodes detected intraoperatively by using the handheld magnetometer or gamma probe or nodes that were blue or black, were excised. All metal retractors were removed from the surgical field while the magnetometer was used. Surgeons

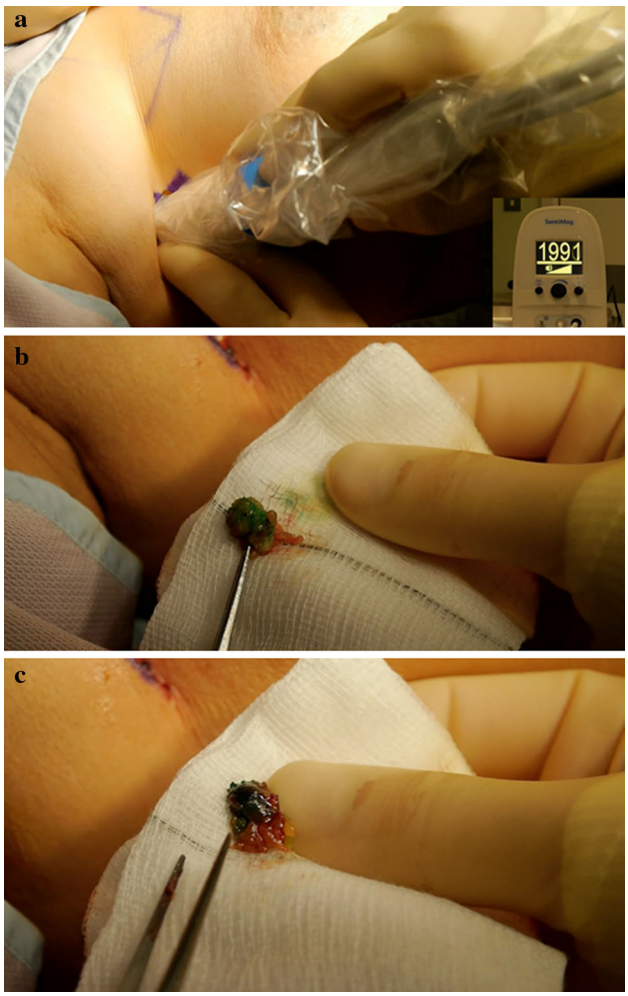

FIG. 2 Sentinel node biopsy undertaken with the combined technique and with magnetic tracer (Sienna+, Endomagnetics Ltd., UK). The third sentinel node had a very high magnetometer count (8595 units) and no gamma count (0). On histology, this was the only node with a metastasis (micrometastasis; 1 of 3 nodes). **a** The magnetometer identified a node with a high count in the right axilla. **b** The node is *blue*; **c** the same node is also *black* on the other side

used fixed sutures, plastic retractors, or both for retraction. After readings were taken, any metal retractors were reinserted into the wound. Excision of nodes with the handheld magnetometer was undertaken by using the same cutoff used for the gamma probe. Any node with a count of 10 % or more of the node with the highest count (with the handheld magnetometer and then gamma probe) was excised. Beyond four sentinel nodes, surgeons noted the background count (with both devices) and excised additional nodes only at their discretion. Any palpable nodes were also removed. Any adverse events, complications, or reactions were noted during surgery and postoperatively. Patients were followed up at a postoperative visit and also at 3 months.

Histopathology

All sentinel nodes were sent for evaluation according to local protocols. All protocols were reviewed by the lead pathologist (S.P.). All nodes measuring 5 mm or less in maximum dimension were sliced and processed (usually in 2 or 3 portions or 2 halves). Nodes greater than 5 mm in maximum diameter were sliced thinly at 2-mm intervals and were all processed for histologic examination. Immunohistochemical assessment of sentinel lymph nodes was not undertaken routinely, even if of lobular subtype. However, if suspicion of metastatic tumor cells was high, then immunohistochemistry for epithelial markers was undertaken at the pathologist's discretion.

Nodes were reported as normal or containing macrometastases (>2 mm), micrometastases (>0.2, ≤2 mm), and isolated tumor cells (≤0.2 mm). The last were regarded as node negative. In addition, the size of the largest metastatic deposit was recorded.[15]

Primary End Points

The primary end point of this trial was defined as the proportion of sentinel nodes detected with each technique (identification rate). A successful procedure for each technique was defined as the detection of at least one sentinel node. For the standard technique, a successful procedure was defined as the detection of at least one node that was either radioactive or blue (when blue dye was used). We also evaluated the mean number of nodes excised overall, with the standard and with the magnetic techniques.

Statistical Analysis

The trial was designed to investigate the SLNB identification rates between the standard and the magnetic techniques. With 160 patients, a 97 % proportion detected by standard SLNB, and a proportion discordance of 0.052. For non-inferiority the upper 95.0 % confidence limit was expected to not exceed 5 % with 80 % power. The Newcombe–Wilson score method was used to construct the upper confidence limit.[16]

RESULTS

Patient Characteristics

A total of 170 SLNBs were performed on 161 patients. One patient was excluded because of inadequate intraoperative documentation, leaving 160 patients for further analysis. In the 9 patients with bilateral disease, the SLNB

TABLE 1 Patient and tumor characteristics

Variable	*n*	(%)
Mammographic screen-detected		
Yes	76	(47.5)
No	84	(52.5)
Age		
27–50	51	(31.9)
51–69	85	(53.1)
70+	24	(15.0)
Type of surgery		
Mastectomy	48	(30.0)
Breast-conserving surgery	92	(57.5)
SLNB as a stand-alone procedure	20	(12.5)
Nodal status by largest metastasis		
Normal	121	(75.6)
Micrometastasis	10	(6.2)
Macrometastasis	25	(15.6)
Isolated tumor cells	4	(2.5)
Lymphovascular invasion		
Present	36	(22.5)
Not present	120	(75.0)
Not known	4	(2.5)
Invasive/noninvasive		
Invasive	146	(91.3)
Grade		
1	25	(17.1)
2	82	(56.2)
3	36	(24.7)
Not assessable	1	(0.7)
Tumor size		
T1	82	(56.2)
T2	52	(35.6)
T3	7	(4.8)
Not assessable	5	(3.4)
Estrogen receptor status		
Positive	129	(88.4)
Negative	16	(11.0)
Not performed	1	(0.7)
HER2 status		
Positive	15	(10.3)
Negative	128	(87.7)
Not assessed	3	(2.1)
Tumor type		
Invasive, ductal/no special type	99	(67.8)
Invasive, pure special type	30	(20.5)
Invasive, mixed type	10	(6.8)
Invasive, other malignant type	6	(4.1)
Invasive, type not reported	1	(0.7)
Noninvasive only	14	(8.8)
In-situ type		
Ductal carcinoma in-situ (DCIS)	14	(100)

performed on the more significant tumor (higher Nottingham Prognostic Index) was used for calculating identification rate, and so 160 SLNB procedures on 160 patients were evaluated. The patient and pathologic characteristics are shown in Table 1.

Sentinel Lymph Node Biopsy

The magnetic technique was found to be easy to use by the surgeons, although identification of axillary hot spots required more skill. Plastic retractors were used by some, but not all surgeons. The sentinel node identification rate was 95.0 % (152 of 160) with the standard technique and 94.4 % (151 of 160) with the magnetic technique (Table 2). The identification rate with gamma probe alone was 90.6 % (145 of 160). The discordance rate between the standard and the magnetic techniques was 6.9 %. Of 9 SLNB procedures that were not successful with the magnetic technique, 2 were found to have lymph node involvement (macrometastasis) and 1 of these was detected with the standard technique (1 blue; both not hot on gamma probe).

A total of 132 patients (83 %) received blue dye and all patients received magnetic dye. Three dye-related reactions were observed. Of these, 2 were related to blue dye (blue rash without systemic reaction); 1 was indeterminate but related to dye injection (transient drop in blood pressure during surgery and rash in a patient with dark skin).

Histopathology

Of 22 % (35 of 160) of patients with lymph node involvement, 16 % (25 of 160) had at least 1 macrometastasis, and 6 % (10 of 160) had at least 1 micrometastasis as the largest metastatic deposit. Another 2.5 % (4 of 160) had individual tumor cells. Of 25 patients with at least 1 macrometastasis, 23 of 25 were identified with the magnetic technique and 24 of 25 with the standard technique. All patients in whom the largest metastatic deposit was a micrometastasis were correctly identified with both magnetic and standard techniques (10 of 10). Of 404 lymph nodes removed, 297 (74 %) were "true" sentinel nodes (as detected by the standard technique), and 268 (66.7 %) were

TABLE 2 Identification (detection) rates by method of detection with 95 % upper confidence limit for difference in identification rates between the standard and magnetic techniques

Gamma probe with or without blue dye	Magnetic technique		Total
	Failed detection	Successful detection	
Failed detection, *n* (%)	3 (1.9)	5 (3.1)	8 (5.0)
Successful detection, *n* (%)	6 (3.8)	146 (91.3)	152 (95.0)
Total, *n* (%)	9 (5.6)	151 (94.4)	160 (100.0)
Difference, %	0.6	95 % upper confidence limit	4.4
Discordance, %	6.9		

also identified by the magnetic technique. Of 107 nodes not identified by the standard technique, 55 nodes (51.4 %) were identified by the magnetic technique and 24 of these nodes were identified in 11 patients in whom the standard technique failed, leaving 31 women with 1 node removed from each. A total of 52 nodes (12.9 %) were removed by palpation alone, and 29 nodes (7.2 %) were identified by the standard technique and not by the magnetic technique. The lymph node retrieval rate was 2.52 nodes per patient overall, 1.86 nodes per patient with the standard technique, and 2.02 nodes per patient with the magnetic technique (Table 3).

DISCUSSION

In this trial we have shown that the magnetic technique described is feasible for SLNB in a multicenter setting. It was not inferior to the standard technique (0.6 % difference; 95 % upper confidence limit of 4.4 %; 6.9 % discordance), with a 95 % confidence limit below the 5 % limit set out in the trial design to define non-inferiority. The discordance rate of 6.9 % is slightly higher than expected. The effect on the upper confidence limit for the difference in identification rates by an increased discordance rate is that it increases the upper confidence limit. We still observed non-inferiority despite this. The average number of nodes removed with either method was also no different (1.9 vs. 2.0 per patient). However, the magnetic technique does not always identify the same nodes as the standard technique, which may be a limitation because this results in false-negative staging. This could also result from competition between the dyes for the same nodes and thus, a randomized controlled trial is needed to confirm non-inferiority.

The recognized drawbacks of radioisotope use, including exposure to radiation, heavy control by legislation, and poor preoperative spatial resolution on lymphoscintigraphy, have prompted an interest in different tracers. Indocyanine green (ICG) assists in identification of the nodes and has been used alone with an identification rate of 73.8–99 % or in combination with blue dye or

TABLE 3 Numbers of nodes removed in the trial cohort ($n = 160$) and mean per patient, by mode of detection (a); in Table 3b, the number of nodes removed from patients with a successful SLNB with the magnetic technique ($n = 146$) is shown, as is whether they were detected by the standard technique

(a)

Gamma probe with or without blue dye		Magnetic technique		
		Failed detection	Successful detection	Total
Failed detection	*n*	52	55	107
	Mean	0.32	0.34	0.67
Successful detection	*n*	29	268	297
	Mean	0.18	1.68	1.86
Total	*n*	81	323	404
	Mean	0.51	2.02	2.52

(b)

Gamma probe with or without blue dye		Magnetic technique		
		Failed detection	Successful detection	Total
Failed detection	*n*	42	49	91
	Mean	0.29	0.34	0.62
Successful detection	*n*	20	267	287
	Mean	0.2	1.83	1.97
Total	*n*	62	316	378
	Mean	0.42	2.16	2.59

radioisotope.[17–22] Although Sugie et al.[20] achieved an identification rate of 99 % (98 of 99) with ICG, the average number of nodes removed per patient was 3.4 (range, 1–8), higher than with the magnetic technique. This suggests that in view of its very small size, ICG may also be transported to higher-echelon nodes, causing higher node counts if used in isolation. An intraoperative near-infrared fluorescence imaging system has been developed to detect sentinel lymph nodes colored by ICG. However, it is unlikely that near-infrared fluorescence cameras will be available soon because of high complexity and cost.[23,24] The magnetic technique has significant advantages in that it can replace the need for blue dye and can be visualized on MRI. The magnetic tracer is not currently licensed as a contrast agent, and the SentiMAG Trial is also evaluating the utility of preoperative axillary MRI for localization and characterization of sentinel nodes. It is chemically similar to SPIOs, which act as "negative" imaging contrast agents on MRI because they alter the local magnetic field gradients. SPIOs can identify sentinel node metastasis on MRI.[14] This may provide a noninvasive method of imaging the complete lymphatic drainage pathway from the tumor (replacing lymphoscintigraphy), thus determining the involvement and location of sentinel nodes. Sentinel nodes are found to be negative in the vast majority of patients and the rate of positive nodes was 23 % in this trial. SLNB is certainly less invasive, but it is not noninvasive. More accurate imaging of the axilla by using MRI, may also facilitate targeted removal of sentinel nodes under local anesthetic as a day-case procedure or even as a diagnostic interventional procedure.

Magnetic tracers and a handheld magnetometer might just be what surgical researchers have been looking for as a tool that could be used to act on what is seen on MRI. There are numerous other potential clinical applications of magnetic tracers in cancer surgery.[11,12] These may require specific modifications of the magnetometer, as well as the evaluation of other magnetic tracers.

CONCLUSIONS

This multicenter trial is the first to demonstrate the feasibility of this magnetic technique for SLNB. When compared with the standard technique for SLNB, the magnetic technique is not inferior. This trial is practice-changing, for those surgeons who are using blue dye alone for SLNB. The data also confirm that it is now safe to proceed with a randomized controlled trial to validate the magnetic technique on its own, to evaluate the independent magnetic identification rate and procedure-related morbidity.

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Disclosure None.

APPENDIX

SentiMAG Trialists Group (Study Collaborators)

Mr Michael Douek, CI, Chair of TMG (King's College London). Prof Arnie Purushotham, Co-Chair TMG (King's College London); arniepurushotham@gmail.com. Mr Muneer Ahmed, TMG (King's College London); muneer.ahmed@kcl.ac.uk. Mr Bauke Anninga, CTC, TMG (King's College London); bauke.anninga@kcl.ac.uk. Mr Douglas Brown, PI, TMG (Ninewell's Hospital and Medical School, Dundee, UK); douglasbrown@nhs.net. Dr Fernanda Castro, CTM, TMG (Guy's & St Thomas' Hospitals, London); fernanda.castro@gstt.nhs.uk. Professor Philip Drew, PI, TMG (Royal Cornwall Hospitals NHS Trust, Truro, Cornwall, UK); philip.drew@rcht.cornwall.nhs.uk. Mr Joost Klaase, PI, TMG (Medisch Spectrum Twente, Enschede, The Netherlands); j.klaase@mst.nl. Dr Hans Garmo STAT, TMG (King's College London); hans.garmo@kcl.ac.uk. Mr Maarten Grootendorst, CTC, TMG (King's College London); maarten.grootendorst@kcl.ac.uk. Dr Bennie ten Haken, TMG (MIRA-NeuroImaging, University of Twente, Enschede, The Netherlands); b.tenhaken@utwente.nl. Mr Ashutosh Kothari, TMG (Guy's & St Thomas' Hospitals); ashutosh.kothari@gstt.nhs.uk. Professor Margaret Hall-Craggs, TMG (University College Hospital, London); margaret.hall-craggs@uclh.nhs.uk. Janet MacSweeney, TMG (King's College London); janet.mac_sweeney@kcl.ac.uk. Mrs April Matthews BSc(Hon), PA, TMG (ICPV - Independent Cancer Patients' Voice, London); april.a.matthews@gmail.com. Mr Ian James Monypenny, PI, TMG (University Hospital of Wales at Llandough, Cardiff, UK); ian.monypenny@wales.nhs.uk. Dr Agbaje Olorunsola, STAT, TMG

(King's College London); olorunsola.agbaje@kcl.ac.uk. Professor Quentin Pankhurst, TMG (University College London); q.pankhurst@ucl.ac.uk. Ms Vernie Ramalingam, CTM, TMG (Guy's & St Thomas' Hospitals, London); vernie.ramalingam@gstt.nhs.uk. Mr Simon Pilgrim, TMG (Norwich and Norfolk University Hospitals, Norwich, UK); sipilgrim@hotmail.com. Professor Sarah Pinder, TMG (King's College London); sarah.pinder@kcl.ac.uk. Joost Pouw, MSc, TMG (MIRA-NeuroImaging, University of Twente, Enschede, The Netherlands); j.j.pouw@utwente.nl. Ms Lynda Wyld, PI, TMG (University of Sheffield, Sheffield, UK); l.wyld@sheffield.ac.uk. Miss Katalin Zechmeister, PI, TMG (Norwich and Norfolk University Hospitals, Norwich, UK); katalin.zechmeister@nnuh.nhs.uk.

Key: CI - Chief Investigator; PI - Principal Investigator; TMG - Trial Management Group; STAT - Statistician; CTM - Clinical Trial Manager; CTC - Clinical Trial Co-ordinator; PA - Patient Advocate (Independent Cancer Patient Voice); DMC - Data Monitoring Committee.

Surgical Collaborators

Guy's & St Thomas' Hospitals, London, UK: Mr W Al Sarakbi; wail.alsarakbi@gstt.nhs.uk. Mr H Hamed; hisham.hamed@gstt.nhs.uk. Mr M Kontos; michalis.kontos@gstt.nhs.uk. Mr T Kontoulis; theodoros.kontoulis@gstt.nhs.uk. Mr T Kovacs; tibor.kovacs@gstt.nhs.uk. Mr Y Masannat; yazanmas@hotmail.com. Miss A Suyoi; amalinda.suyoi@gstt.nhs.uk.

Medisch Spectrum Twente, Enschede, The Netherlands: Dr J Gerritsen; j.gerritsen@mst.nl. Dr W Mastboom; w.mastboom@mst.nl. Dr P Steenvoorde; p.steenvoorde@mst.nl. Dr E B van Duyn; e.vanduyn@mst.nl.

University Hospital of Wales at Llandough, Cardiff, UK: Ms E Davies; eleri.davies8@wales.nhs.uk. Mr S Goyal; sumit.goyal@wales.nhs.uk. Prof. H Sweetland; sweetland@cf.ac.uk. Prof. R E Mansel; manselre@cf.ac.uk.

Norwich and Norfolk University Hospitals, Norwich, UK: Mr M Hussein; maged.hussein@nnuh.nhs.uk. Mr Gabor Peley; gabor.peley@nnuh.nhs.uk. Mr S Pain; simon.pain@nnuh.nhs.uk.

University of Sheffield, Sheffield, UK: Miss V Chandran; vidya.Chandran@sth.nhs.uk Prof M Reed; m.w.reed@sheffield.ac.uk.

Royal Cornwall Hospitals NHS Trust, Truro, Cornwall, UK: Mr I Abbas; imran.abbas@rcht.cornwall.nhs.uk; Mr I Brown; iain.brown@rcht.cornwall.nhs.uk. Mr M El-Gammel; mohsen.elgammal@rcht.cornwall.nhs.uk. Miss R English; rachel.english@rcht.cornwall.nhs.uk. Miss P King; polly.King@rcht.cornwall.nhs.uk.

Research Nurses

Joann McGrath (Norwich and Norfolk University Hospitals, Norwich, UK); joann.mcgrath@nnuh.nhs.uk. Laura McCabe (University of Sheffield, Sheffield, UK); l.mccabe@sheffield.ac.uk. Sadie Mitchell (Royal Cornwall Hospitals NHS Trust, Truro, Cornwall, UK); sadie.mitchell@rcht.cornwall.nhs.uk. Chris Morris (University Hospital of Wales at Llandough, Cardiff, UK); christine.morris3@wales.nhs.uk. Rachael Reid (Ninewells Hospital and Medical School, Dundee, UK); rachaelreid@nhs.net. Anja Stam (Medisch Spectrum Twente, Enschede, The Netherlands); researchbureau.heelkunde@mst.nl.

Data Monitoring Committee (independent)

Dr Jane Warwick, Imperial College London, Senior Lecturer in Clinical Trials Statistics, UK DMC. Dr Jurgen Fütterer, University Medical Centre Nijmegen, Body and Interventional Radiologist, The Netherlands DMC. Miss Zoe Winters, Senior Lecturer in Surgery, Bristol University, Consultant Surgeon, UK DMC.

REFERENCES

1. Cabanas RM. An approach for the treatment of penile carcinoma. *Cancer.* 1977;39:456–66.
2. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. *J Natl Cancer Inst.* 2006;98:599–609.
3. Cody HS III, Fey J, Akhurst T, et al. Complementarity of blue dye and isotope in sentinel node localization for breast cancer: univariate and multivariate analysis of 966 procedures. *Ann Surg Oncol.* 2001;8:13–9.
4. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. *J Clin Oncol.* 2005;23:7703–20.
5. Straver ME, Meijnen P, van Tienhoven G, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. *Ann Surg Oncol*. 2010;17:1854–61.
6. Goyal A, Newcombe RG, Chhabra A, Mansel RE. Factors affecting failed localisation and false-negative rates of sentinel node biopsy in breast cancer: results of the ALMANAC validation phase. *Breast Cancer Res Treat.* 2006;99:203–8.
7. White V, Harvey JR, Griffith CD, Youssef M, Carr M. Sentinel lymph node biopsy in early breast cancer surgery: working with the risks of vital blue dye to reap the benefits. *Eur J Surg Oncol*. 2011;37:101–8.
8. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg.* 1994;220:391–8; discussion 398–401.
9. Joshi T, Pankhurst QA, Hattersley S, et al. Magnetic nanoparticles for detecting cancer spread. *Breast Cancer Res Treat.* 2007;1006(Suppl. 1):S129.
10. Johnson L, Douek M. Magnetic sentinel lymph node detection for breast cancer. *Cancer Res.* 2010;70:140s.

11. Gunasekera UA, Pankhurst QA, Douek M. Imaging applications of nanotechnology in cancer. *Target Oncol.* 2009;4:169–81.
12. Johnson L, Gunasekera A, Douek M. Applications of nanotechnology in cancer. *Discov Med.* 2010;9:374–9.
13. Johnson L, Pinder SE, Douek M. Deposition of superparamagnetic iron-oxide nanoparticles in axillary sentinel lymph nodes following subcutaneous injection. *Histopathology*. 2013;62:481–6.
14. Motomura K, Ishitobi M, Komoike Y, et al. SPIO-enhanced magnetic resonance imaging for the detection of metastases in sentinel nodes localized by computed tomography lymphography in patients with breast cancer. *Ann Surg Oncol*. 2011;18:3422–9.
15. Cserni G, Bianchi S, Boecker W, et al. Improving the reproducibility of diagnosing micrometastases and isolated tumor cells. *Cancer.* 2005;103:358–67.
16. Newcombe RG. Improved confidence intervals for the difference between binomial proportions based on paired data. *Stat Med.* 1998;17:2635–50.
17. Wishart GC, Loh SW, Jones L, Benson JR. A feasibility study (ICG-10) of indocyanine green (ICG) fluorescence mapping for sentinel lymph node detection in early breast cancer. *Eur J Surg Oncol*. 2012;38:651–6.
18. Motomura K, Inaji H, Komoike Y, Kasugai T, Noguchi S, Koyama H. Sentinel node biopsy guided by indocyanine green dye in breast cancer patients. *Jpn J Clin Oncol.* 1999;29:604–7.
19. Takeuchi M, Sugie T, Abdelazeem K, et al. Lymphatic mapping with fluorescence navigation using indocyanine green and axillary surgery in patients with primary breast cancer. *Breast J*. 2012;18:535–41.
20. Sugie T, Sawada T, Tagaya N, et al. Comparison of the indocyanine green fluorescence and blue dye methods in detection of sentinel lymph nodes in early-stage breast cancer. *Ann Surg Oncol*. 2013;20:2213–8.
21. Abe H, Mori T, Umeda T, et al. Indocyanine green fluorescence imaging system for sentinel lymph node biopsies in early breast cancer patients. *Surg Today*. 2011;41:197–202.
22. Hojo T, Nagao T, Kikuyama M, Akashi S, Kinoshita T. Evaluation of sentinel node biopsy by combined fluorescent and dye method and lymph flow for breast cancer. *Breast*. 2010;19:210–3.
23. Troyan SL, Kianzad V, Gibbs-Strauss SL, et al. The FLARE intraoperative near-infrared fluorescence imaging system: a first-in-human clinical trial in breast cancer sentinel lymph node mapping. *Ann Surg Oncol.* 2009;16:2943–52.
24. van der Vorst JR, Schaafsma BE, Verbeek FP, et al. Randomized comparison of near-infrared fluorescence imaging using indocyanine green and 99(m) technetium with or without patent blue for the sentinel lymph node procedure in breast cancer patients. *Ann Surg Oncol*. 2012;19:4104–11.