Systematic review

Meta-analysis of sentinel lymph node biopsy in breast cancer using the magnetic technique

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Background: **The standard for sentinel lymph node biopsy (SLNB), the dual technique (radiolabelled tracer and blue dye), has several drawbacks. A novel magnetic technique without these drawbacks has been evaluated in a number of clinical trials. It uses a magnetic tracer and a handheld magnetometer to identify and excise sentinel lymph nodes. A systematic review and meta-analysis was performed to assess the performance and utility of the magnetic in comparison to the standard technique.**

Methods: **MEDLINE, PubMed, Embase and the Cochrane online literature databases were used to identify all original articles evaluating the magnetic technique for SLNB published up to April 2016. Studies were included if they were prospectively conducted clinical trials comparing the magnetic with the standard technique for SLNB in patients with breast cancer.**

Results: **Seven studies were included. The magnetic technique was non-inferior to the standard technique ($z = 3·87$, $P < 0·001$), at a 2 per cent non-inferiority margin. The mean identification rates for the standard and magnetic techniques were 96·8 (range 94·2–99·0) and 97·1 (94·4–98·0) per cent respectively (risk difference (RD) 0·00, 95 per cent c.i. −0·01 to 0·01; $P = 0·690$). The total lymph node retrieval was significantly higher with the magnetic compared with the standard technique: 2113 (1·9 per patient) *versus* 2000 (1·8 per patient) (RD 0·05, 0·03 to 0·06; $P = 0·003$). False-negative rates were 10·9 (range 6–22) per cent for the standard technique and 8·4 (2–22) per cent for the magnetic technique (RD 0·03, 0·00 to 0·06; $P = 0·551$). The mean discordance rate was 3·9 (range 1·7–6·9) per cent.**

Conclusion: **The magnetic technique for SLNB is non-inferior to the standard technique, with a high identification rate but with a significantly higher lymph node retrieval rate.**

Paper accepted 30 June 2016

Published online 9 September 2016 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.10283

Introduction

The standard technique for sentinel lymph node biopsy (SLNB) is the dual technique, consisting of subareolar, periareolar or peritumoral injections of technetium-labelled nanocolloid (radiolabelled tracer) and blue dye[1]. The dual technique has a sentinel node identification rate of 96·4 per cent, with a false-negative rate of 7·3 per cent[2]. However, it has several drawbacks. The radiolabelled tracer (technetium-99 m) and its parent isotope (molybdenum-99) have relatively short half-lives of 6 and 66 h respectively, requiring frequent supply from nuclear medicine centres. There are logistical challenges caused by strict guidelines for the transport, handling and disposal of the radiolabelled tracers[3,4]. The blue dye can obscure the surgical field and frequently leaves a blue skin stain, which can take months to fade, or can be permanent. There is also an up to 0·9 per cent risk of an adverse reaction to blue dye[5] and, as a result, some centres have stopped using blue dye routinely. These drawbacks have limited the uptake of SLNB worldwide. Although the incidence of cancer is rising, the use of SLNB has reached a plateau, with around 60 per cent of an estimated 500 000 patients with breast cancer in developed countries having access to it[3]. This value falls to 5 per cent in China and is even lower in developing countries[6].

Alternative methods for performing SLNB are therefore needed and several techniques are currently being evaluated[7]. A novel magnetic technique is most promising, using a superparamagnetic iron oxide (SPIO) magnetic tracer injected into the breast and a handheld magnetometer used during the operation. Proof of principle was demonstrated using a prototype magnetometer[8] and this research led to the development of a handheld magnetometer and magnetic tracer that are certified for use in Europe, Australia and New Zealand (Conformité Européene (CE)- and Administration Therapeutic Goods (ATG)-certified). The shelf-life of the magnetic tracer is several years, but most importantly it is not radioactive and can be administered by the surgeon. It is brown or black and can also result in a colour change in the sentinel node, depending on the timing of injection and dose used. Non-inferiority compared with the standard technique was first demonstrated in the SentiMAG Multicentre Trial[9], a first-in-woman trial. Since then, several additional clinical trials have evaluated this technique. In this systematic review and meta-analysis, the performance and utility of the magnetic technique were evaluated and compared with of the standard technique.

Methods

Search strategy and selection criteria

Using MEDLINE, PubMed, Embase and the Cochrane online literature databases, a literature search was conducted to identify all published evidence, up to April 2016, on the use of the magnetic technique for SLNB in patients with breast cancer. The medical subject heading (MeSH) terms used were ['breast cancer' AND 'sentinel lymph node biopsy' AND ('nanoparticle*' OR 'magnet*' OR 'magnetic*' OR 'sentimag')]. Search strategies were adapted to each database's search engine and no further search restrictions were applied. All articles were reviewed based on title and abstract, and those meeting the inclusion criteria were reviewed in full. References of included articles were searched manually for new articles. The final search was performed on 30 April 2016.

Studies were included if they fulfilled the following inclusion criteria: prospectively conducted clinical trials using the magnetic technique; comparing the magnetic technique with the standard technique (using either radiolabelled tracer or blue dye alone, or a combination of both) for SLNB in patients with breast cancer; obtained ethical approval; and performed an appropriate sample size calculation. Articles without available full text were excluded, as were conference proceedings, review articles, case reports, editorial reports and letters to the editor.

Data extraction

Each study was evaluated for eligibility by two reviewers, who extracted study characteristics and outcomes for all selected studies. A third reviewer verified the accuracy of the extracted data. The first author of each study was contacted for clarification if this was required. False-negative rates were calculated for all studies and defined as the ratio of missed involved nodes relative to the total number of involved nodes retrieved during SLNB, expressed as a percentage. Reported concordance and reverse concordance were checked for accuracy, and calculated for studies that did not report them. The term concordance was defined as the total number of successful SLNB procedures or nodes identified by both the standard (radioisotope and blue dye or radioisotope alone) and magnetic techniques, divided by the total number of successful SLNB procedures or nodes identified with the standard technique. Reverse concordance was defined as the total number of successful SLNB procedures or nodes identified by both the standard and magnetic techniques, divided by the total number of successful SLNB procedures or nodes identified with the magnetic technique[10].

Quality assessment

The quality of studies was assessed using a modified version of the Consolidated Standards of Reporting Trials (CONSORT) for non-inferiority and equivalency trials. Seven criteria were used to assess the quality of the non-inferiority trials using a modified CONSORT checklist, as discussed by Mounsey and colleagues[11]. Studies were included if they covered at least four of seven criteria. Two reviewers performed the assessment independently. In case of disagreement, a consensual decision was reached with the senior author.

Statistical analysis

All extracted data were tabulated and presented as means and percentages. Numerators and denominators were provided to address the outcomes of included studies. The R package was used for the quantitative analyses[12]. For sentinel lymph node (SLN) identification, the Cochran–Mantel–Haenszel method was used to test for an association between the two techniques. A similar method was used for lymph node retrieval and false-negative rate, across all studies. The fixed-effect model was used to calculate the pooled outcome. The probability for each variable was computed and the risk difference (RD) with 95 per cent c.i. was calculated for binary data variables. For a comparison of the magnetic technique against the standard technique for each study, the χ^2 test was used. A maximum I^2 value of 30 per cent identified low heterogeneity. Study-result heterogeneity was shown in forest plots, displaying the RD estimates of different outcomes. In case of high heterogeneity, a random-effects model was used[13,14].

Using the pooled identification rate for all patients, non-inferiority for SLNB rate with the magnetic technique to the standard technique was calculated at a 2 per cent non-inferiority margin[15].

Funding and risk of vested interest bias

The declared conflicts of interest, acknowledgements, sources of funding and potential vested interests were tabulated for each study. First authors were contacted to verify this information. Online trial registration databases were searched for any relevant study information, and trial registration information was tabulated for each study.

Results

Selection of studies

A total of 610 articles were identified from the literature search (*Fig. 1*). After reviewing the titles and abstracts, 599 articles were excluded, leaving a total of 11 articles for full-text review. One study[16] was excluded as there was no documentation of ethics approval. Three more feasibility studies[4,17,18] were excluded owing to lack of an appropriate sample size calculation. Seven articles[9,19–24] matched the inclusion criteria and were available for meta-analysis.

Quality assessment

The quality of the six non-inferiority trials[9,19–23] was assessed using the modified CONSORT checklist. These six studies described the rationale for using a non-inferiority design and the non-inferiority margin used. All six studies formulated the hypothesis and statistical analysis correctly, and performed a sample size calculation. Per-protocol analysis was used for all studies as all patients included received both treatments. These six studies satisfied all quality criteria set by the modified CONSORT checklist. One article[24] reported a feasibility study that was set up in a similar way to the non-inferiority trials, and was therefore assessed using the CONSORT checklist. This study scored 6 of 7 (it did not recruit the 115 preset cohort size) and was not considered of high quality for execution. The mean score for all studies was 6·9 of 7 (*Table 1*).

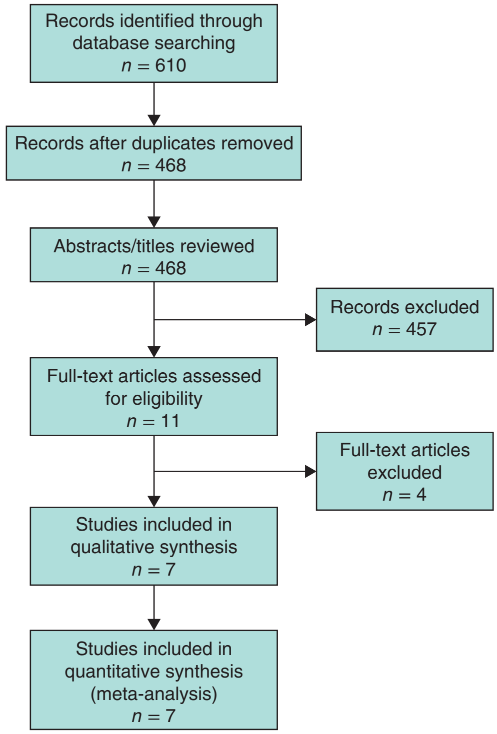

Fig. 1 PRISMA diagram showing selection of articles for review

Study characteristics

The seven studies included a total of 1118 patients and 1122 SLNB procedures. All studies were published between 2014 and 2016, and included 1041 patients (93·1 per cent) with invasive breast cancers. SLNB was performed in combination with breast-conserving surgery in 772 patients (69·1 per cent) (*Table 2*), with mastectomy in 175 patients (15·7 per cent), alone in 20 patients (1·8 per cent) and type of surgery was unknown for 151 patients (13·5 per cent). A total of 2298 SLNs were excised, giving a mean lymph node retrieval rate of 2·1 nodes per patient (*Table 3*).

Sentinel lymph node biopsy procedure

All studies used 2·0 ml of magnetic tracer (Sienna+®; Endomagnetics, Cambridge, UK) administered as a subareolar or periareolar, subcutaneous injection during the procedure, as described in the SentiMAG Multicentre Trial[9] (*Table 2*). For the standard technique, three studies[9,23,24] administered Patent Blue V (Guerbet, Villepinte, France) in accordance with each centre's protocol, subsequent to the radiolabelled tracer injection, which was followed by a 5-min massage. One study[19] used methylene blue in accordance with each centre's protocol

Table 1 Modified version of the Consolidated Standards of Reporting Trials for non-inferiority or equivalency trials according to recommendations by Mounsey *et al.*[11]

	Douek *et al.*[9]	Thill *et al.*[21]	Rubio *et al.*[20]	Pinero-Madrona *et al.*[19]	Ghilli *et al.*[22]	Houpeau *et al.*[24]*	Karakatsanis *et al.*[23]
Rationale for using a non-inferiority or equivalence design	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Non-inferiority margin based on clinical and statistical reasoning	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Correctly formulated hypothesis and statistical analysis	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sample size calculation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Non-inferiority trial similar to the trial(s) comparing standard treatment with placebo	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Per-protocol analysis used	Yes	Yes	Yes	Yes	Yes	Yes	Yes
High-quality overall design and execution	Yes	Yes	Yes	Yes	Yes	No	Yes

*Feasibility trial executed in similar way to the other non-inferiority trials.

(manufacturer not specified), and three studies[20–22] did not administer any additional blue dye and used only radiolabelled tracer. All studies injected radiolabelled tracer in accordance with each centre's standard of care, with no standardization of technique or dose of radioisotope between centres. Specification of the tracer and method of injection was provided in six studies[9,20–24], in which technetium-99 was injected either subareolarly or peritumorally. Three studies[9,19,20] used the standard technique only after SLNB had been performed with the magnetometer and for *ex vivo* verification. The other four studies[21–24] used the magnetometer simultaneously with the standard technique.

Four studies[20–22,24] performed lymphoscintigraphy before SLNB, in two studies[9,19] lymphoscintigraphy was not reported, and in the remaining study[23] lymphoscintigraphy was not undertaken routinely. Two studies[20,24] blinded the surgeons to the lymphoscintigraphy results until SLNB had been performed with the magnetic technique.

Identification and node retrieval rate

The mean SLNB identification rate for the pooled data, using the standard and magnetic techniques combined, was 98·8 (range 98·1–100) per cent (*Table 3*). The mean SLNB identification rates for the standard and magnetic techniques alone were 96·8 (94·2–99·0) and 97·1 (94·4–98·0) per cent respectively. There was no heterogeneity for identification rates ($I^2 = 0$ per cent), and the overall fixed-effect model showed no significant difference between the two techniques (RD 0·00, 95 per cent c.i. −0·01 to 0·01; $P = 0{\cdot}690$) (*Fig. 2a*). With a non-inferiority margin of 2 per cent, the pooled data showed that the magnetic technique was non-inferior to the standard technique ($z = 3{\cdot}87$, $P < 0{\cdot}001$).

The mean lymph node retrieval rate per patient was 2·1 (range 1·8–2·5) nodes with the standard and magnetic techniques combined, 1·8 (1·6–2·0) nodes with the standard technique and 1·9 (1·6–2·2) nodes with the magnetic technique (*Table 3*). The studies showed high heterogeneity ($I^2 = 70$ per cent); hence a random-effects model was used. The total number of lymph nodes retrieved was significantly higher with the magnetic technique (2113 *versus* 2000 with standard technique) (RD 0·05, 0·03 to 0·06; $P = 0{\cdot}003$) (*Fig. 2b*).

Mean concordance and mean reverse concordance rates were 98·2 (range 96·1–99·3) and 97·9 (95·7–99·4) per cent respectively. Nodal concordance was 95·5 (90·2–98·5) per cent and reverse nodal concordance was 90·3 (83·0–94·5) per cent (*Table 3*).

Histopathology

A total of 323 patients (28·9 per cent) had involved sentinel nodes (micrometastasis or macrometastasis), 14 patients (1·3 per cent) had isolated tumour cells and the histological status of nodes was unknown[19] for two patients (0·2 per cent). One study[20] reported on the number of involved nodes, specifying micrometastases, macrometastases and isolated tumour cells. Three studies[9,23,24] provided information only on patients with micrometastases and macrometastases, and the other three studies[19,21,22] reported the number of patients with involved nodes without specifying micrometastatic or macrometastatic involvement. The total number of involved nodes in two studies[9,20] was retrieved from source trial data.

The total number of involved nodes in all studies was 430 (18·7 per cent), of which 36 (1·6 per cent) were missed by the magnetic technique and 47 (2·0 per cent) by the standard technique. Mean false-negative rates were 10·9 (range

Table 2 Study characteristics

Reference	Study type	No. of patients initially recruited (SLNB procedures)	Breast-conserving surgery*	No. of patients with axillary metastasis*	No. of patients with invasive cancer*	Standard technique	Magnetic technique
Douek *et al.*[9]	Non-inferiority cohort study	161 (170)	92 of 160 (57·5)	35 of 160 (21·8)	146 of 160 (91·3)	Patent Blue V (by only 5 of 7 centres, 1 of 7 used it selectively; subareolar injection) Technetium-99 m tracer (subareolar, 1 centre also used peritumoral–subdermal injection)	Periareolar–subcutaneous injection 2 ml Sienna+® (diluted with 3 ml saline), during surgery a minimum of 5 min before SLNB procedure
Thill *et al.*[21]	Non-inferiority cohort study	150 (–)	154 (102·6)†	35 (23·3)	131 (87·3)	Technetium-99 m tracer only (periareolar or peritumoral–subdermal injection)	Subareolar injection 2 ml Sienna+® (diluted with 3 ml saline), during surgery a minimum of 20 min before SLNB procedure
Rubio *et al.*[20]	Non-inferiority cohort study	120 (–)	103 (85·8)	36 (30·0)	108 (90·0)	Technetium-99 m tracer only (subareolar injection)	Subareolar injection 2 ml Sienna+® (diluted with 3 ml saline), during surgery a minimum of 20 min before SLNB procedure
Pinero-Madrona *et al.*[19]	Non-inferiority cohort study	181 (–)	130 (71·8)	60 (33·1)	180 (99·4)	Methylene blue (use depending on centre) Radiolabelled tracer (type not stated)	Subareolar injection 2 ml Sienna+® (diluted with 3 ml saline), during surgery a minimum of 20 min before SLNB procedure
Ghilli *et al.*[22]	Non-inferiority cohort study	199 (203)	190 of 193 (98·4)	57 of 193 (29·5)	182 of 193 (94·3)	Technetium-99 m tracer only (periareolar or peritumoral–subdermal injection)	Subareolar injection 2 ml Sienna+® (diluted with 3 ml saline, according to manufacturer's instructions), during surgery a minimum of 20 min before SLNB procedure
Houpeau *et al.*[24]	Feasibility cohort study	115 (–)	103 of 108 (95·4)	46 of 108 (42·6)	105 of 108 (97·2)	Technetium-99 m tracer (periareolar injection) Patent Blue V sodium salt); one-quarter of centres used it only if there was no sentinel node detected on lymphoscintigraphy	Periareolar injection 2 ml Sienna+® (diluted with 3 ml saline), during surgery
Karakatsanis *et al.*[23]	Non-inferiority cohort study	206 (206)	154 (74·8)	54 (26·2)	189 (91·7)	Technetium-99 m tracer (subareolar, subdermal or subcutaneous) Patent Blue V sodium salt	Subareolar injection 2 ml Sienna+® (diluted with 3 ml saline), during surgery a minimum of 20 min before SLNB procedure

*Values in parentheses are percentages, based on number of patients actually included in studies. †Number of patients having breast-conserving procedures exceeded number of recruited patients in published report. SLNB, sentinel lymph node biopsy; n.s., not stated.

Table 3 Study outcomes

	No. of patients	SLNB identification rate (%)				LNs retrieved per patient†			False-negatives (%)		Concordance by patient	Reverse concordance by patient
Reference	(SLNB procedures)	Total	STD	MG	Discordance (%)*	Total	STD	MG	STD	MG	(node) (%)	(node) (%)
Douek *et al.*[9]	160 (160)	98·1 (157 of 160)	95·0 (152 of 160)	94·4 (151 of 160)	6·9 (11 of 160)	2·5	1·9	2·0	22 (15 of 67)	22 (15 of 67)	96·1 (90·2)	96·7 (83·0)
Thill *et al.*[21]	150 (150)	98·7 (148 of 150)	97·3 (146 of 150)	98·0 (147 of 150)	2·0 (3 of 150)	1·9	1·8 (1–9)	1·9 (1– 9)	9 (4 of 45)	4 (2 of 45)	99·3 (98·5)	98·6 (92·9)
Rubio *et al.*[20]	120 (120)	98·3 (118 of 120)	94·2 (113 of 120)	96·7 (116 of 120)	5·8 (7 of 120)	2·4	1·9‡	2·2‡	6 (2 of 36)	3 (1 of 36)	98·2 (96·1)	95·7 (83·7)
Pinero-Madrona *et al.*[19]	181 (181)	98·3 (178 of 181)	97·8 (177 of 181)	97·2 (176 of 181)	1·7 (3 of 181)	1·8 (1–5)	1·6	1·6	12 (9 of 76)	9 (7 of 76)	98·9 (95·4)	99·4 (92·2)
Ghilli *et al.*[22]	193 (197)	100 (197 of 197)	99·0 (195 of 197)	98·0 (193 of 197)	3·1 (6 of 197)	1·9	1·8(1·0) (0–4)	1·8(1·0) (0–4)	6 (5 of 77)	5 (4 of 77)	97·9 (95·6)	98·9 (94·5)
Houpeau *et al.*[24]	108 (108)	98·1 (106 of 108)	95·4 (103 of 108)	97·2 (105 of 108)	3·7 (4 of 108)	2·1(0·9)	2·0(1·0)	1·9(1·0)	11 (7 of 61)	2 (1 of 61)	99·0 (97·4)	97·1 (90·4)
Karakatsanis *et al.*[23]	206 (206)	99·5 (205 of 206)	97·1 (200 of 206)	97·6 (201 of 206)	4·9 (10 of 206)	2·0	1·8	1·8	7 (5 of 68)	9 (6 of 68)	98·0 (95·9)	97·5 (93·9)
Overall	1118 (1122)	98·8 (1109 of 1122)	96·8 (1086 of 1122)	97·1 (1089 of 1122)	3·9 (44 of 1122)	2·1	1·8	1·9	10·9 (47 of 430)	8·4 (36 of 430)	98·2 (95·5)	97·9 (90·3)

*Calculated for intraoperative results and per procedure. †Lymph nodes (LNs) retrieved during sentinel lymph node biopsy (SLNB). ‡Median. STD, standard technique; MG, magnetic technique.

6–22) per cent for the standard technique and 8·4 (2–22) per cent for the magnetic technique. The weighted mean discordance was 3·9 (range 1·7–6·9) per cent (*Table 3*). There was a trend towards a lower false-negative rate in favour of the magnetic technique, but this was not statistically significant (RD 0·03, 95 per cent c.i. 0·00 to 0·06; $P = 0{\cdot}551$); there was no heterogeneity ($I^2 = 0$ per cent).

Complication rate

SLNB-related adverse events were recorded in all studies[9,19–24]. Douek and colleagues[9] reported blue urticaria in two patients, and an adverse event that could have been related to either the magnetic tracer or blue dye in one patient. Ghilli *et al.*[22] documented brown skin staining (71 of 150 patients), which disappeared over time (15), attenuated (50), enlarged (1) or remained unchanged (5). Thill and co-workers[21] did not report any dye- or tracer-related adverse events, Rubio and colleagues[20] reported grey staining in 20 of 105 patients, and Pinero-Madrona *et al.*[19] noted transient staining in an unknown number of patients. Houpeau and colleagues[24] reported postoperative brown dermal pigmentation (22 of 108 patients). Karakatsanis *et al.*[23] documented discoloration in 66 (35·5 per cent) of 186 patients during follow-up between 0 and 3 months, 39 (21·0 per cent) after 12 months and 16 (8·6 per cent) after 15 months, following which discoloration was noted to be smaller and paler. None of the studies reported MRI artefacts as an adverse event. However, one study[23] reported a magnetometer count in all patients with cutaneous discoloration noted during follow-up, which is expected to cause MRI artefacts.

Disadvantages of the magnetic technique were discussed in six studies[9,19,20,22–24], such as the relatively large diameter of the magnetometer's handheld probe resulting in larger surgical incisions, the time-consuming frequent balancing of the magnetic baseline level required for a correct localization, the requirement for use of plastic alternatives instead of standard surgical retractors, and the role of lymphoscintigraphy in successful SLN localization.

Conflicts of interest and vested interest bias

All studies received free magnetic tracer and handheld magnetometers on loan from the manufacturer or

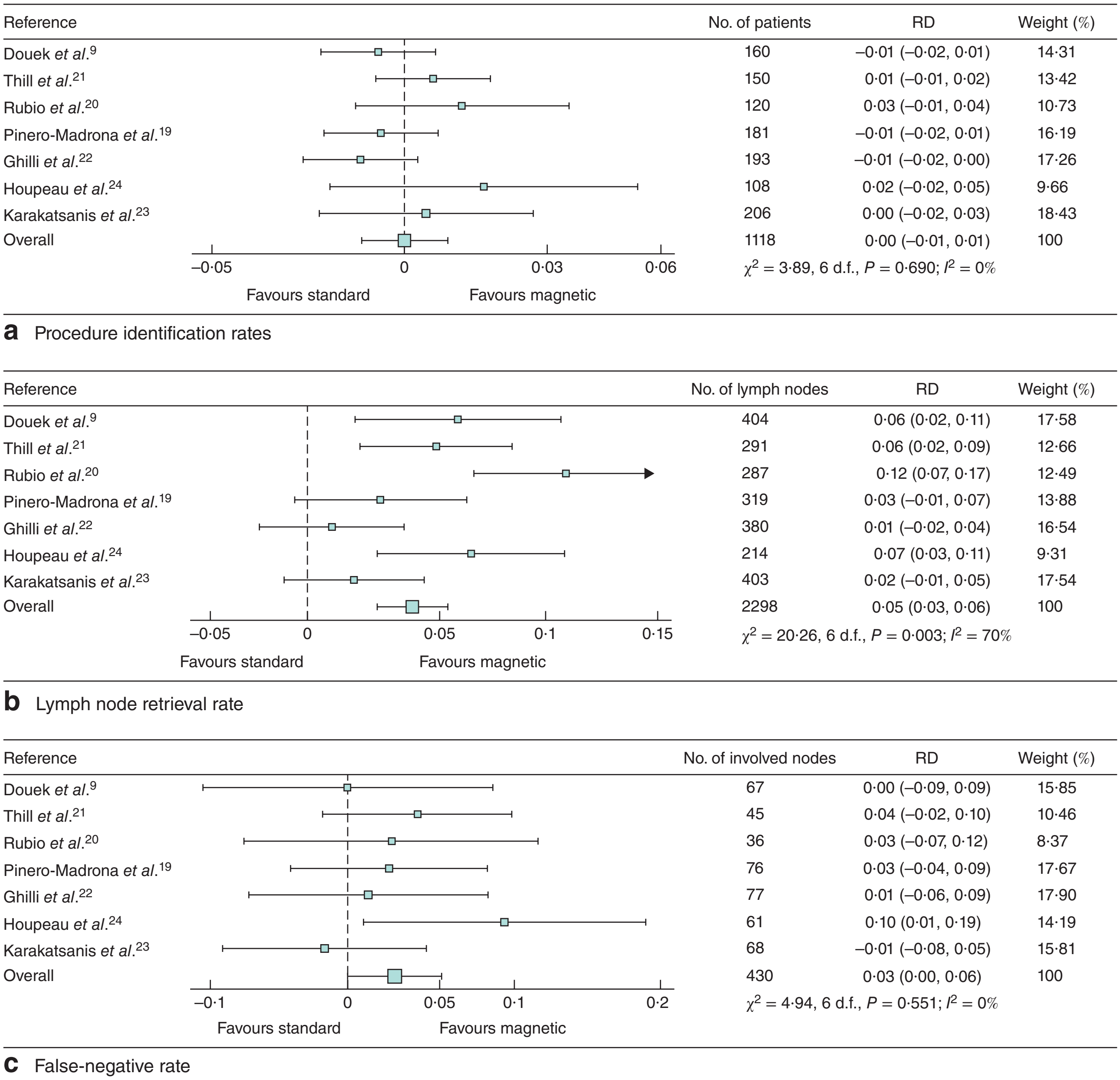

Fig. 2 **a** Risk difference (RD) analysis of sentinel lymph node (SLN) biopsy identification rates by magnetic *versus* standard technique (fixed-effect model); **b** RD analysis of total lymph nodes excised using magnetic *versus* standard technique (random-effects model); **c** RD analysis of discordant identification of involved nodes (false-negatives) using magnetic *versus* standard technique (fixed-effect model). RD values are shown with 95 per cent confidence intervals

distributor. The first-in-woman study, the SentiMAG Multicentre Trial[9], was funded via an unrestricted educational grant from the manufacturer, but was sponsored academically with no commercial involvement at any stage of the trial design, management, analysis or publication. This study had a Trial Management Committee and an Independent Data Monitoring Committee. It received purely academic input from the Professor of Physics at University College London and one of the inventors of the handheld magnetometer (Q. Pankhurst). In one study[21] the first author received consultant and speaker honoraria. Involvement of industry in the process of data analysis or the actual writing (including revision of the English language) of the published manuscript occurred in two studies[21,22]. One study[24] was supported by Sysmex Europe (Norderstedt, Germany), which accompanied surgeons as an observer for the first five patients in each centre. In a further two reports[22,23] the sponsor of the trial was not noted. The potential conflicts of interest and risk of vested interest bias are summarized in *Table S1* (supporting information).

Discussion

The mean sentinel node identification rates were high with both the standard and magnetic technique, (96·8 and 97·1 per cent respectively) and the magnetic technique was non-inferior to the standard technique at a 2 per cent non-inferiority margin. This identification rate is in line with the high identification rates observed with the standard dual technique in the AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery) Trial (97·3 per cent)[25] and in a large systematic review (96·4 per cent)[2]. However, in the present analysis lymph node retrieval was significantly higher with the magnetic technique (2113 nodes *versus* 2000 nodes with standard technique; RD 0·05, 95 per cent c.i. 0·03 to 0·06; $P = 0{\cdot}003$), which is undesirable, but there is no evidence of any negative impact of this on morbidity[26]. Although not significant, the false-negative rate for the magnetic technique was lower than that of the standard technique, which could be explained by the higher lymph node retrieval. The false-negative rates obtained with both the magnetic and standard techniques (8·4 and 10·9 per cent respectively) are high but cannot be compared with the rate of 7·3 per cent for the standard technique reported in a previous meta-analysis[2], as this was analysed against axillary clearance. If the observed reduction in the false-negative rate is real, then 22 759 patients (McNemar test, with 90 per cent power and 5 per cent significance) would be needed, rather than the 1118 patients recruited in the seven studies so far, to demonstrate that the magnetic technique does indeed have a lower false-negative rate.

Complications and adverse reactions were reported in all studies. Brown and grey skin coloration at the magnetic tracer injection site was reported by five studies (179 of 549 patients)[19,20,22–24]. Most studies reported attenuation of skin coloration, but in one study[22] the staining remained unchanged or enlarged (6 of 150 patients). This was due to residual magnetic tracer at the injection site, which can cause MRI void artefacts; this complication was not reported by any of the studies and became apparent more recently[27]. In most countries breast MRI is not used routinely in patients with early breast cancer and the magnetic tracer is not visible on conventional imaging (mammography or ultrasonography), or on conventional histology. However, in some countries (such as Germany), breast MRI is used routinely, although this was not reported as an issue in the Central European Study[21]. Subareolar injections may have a higher risk of void artefacts than intratumoral or peritumoral injections of small magnetic tracer volumes, because the tumour area is excised. All seven studies used the original 2 ml of magnetic tracer and dilution described by Douek and colleagues[9]. However, it is feasible to perform SLNB using lower doses injected intratumorally, although this may influence identification rates negatively[4]. With greater use of 3-tesla MRI, void artefacts may have a negative clinical impact. More research should clarify the patient cohort eligible for the magnetic technique and optimize the amount of magnetic tracer required. Based on current evidence, the magnetic technique should not be used in patients undergoing SLNB before primary chemotherapy (if MRI is used to assess response to treatment), those undergoing breast MRI surveillance (such as *BRCA* mutation carriers) or those with a mammographically occult tumour at diagnosis, in whom MRI may be required for further assessment or follow-up imaging.

Lymphoscintigraphy cannot be undertaken without radioisotope tracer. Even though the need for lymphoscintigraphy for successful SLN localization has been subject to debate, if needed this procedure can be replaced by preoperative SLN localization on MRI, a technique for which feasibility was demonstrated recently[28,29]. Lymphoscintigraphy is no longer performed routinely, as shown here: only five of the included studies[20–24] reported using it in a proportion or the whole cohort of patients. Furthermore, in two studies[20,24] the surgeons were blinded to the lymphoscintigraphy results in order not to bias them.

The diameter of the magnetometer probe used in the existing studies was relatively large. The manufacturer has resolved this and reduced the probe size in the current version of the magnetometer. However, other disadvantages, such as the need for frequent balancing of the magnetic baseline level and the requirement for use of plastic retractors during surgery, are difficult to resolve and unavoidable.

Another concern with the magnetic technique is the maximum depth at which the magnetic signal can be detected, both transcutaneously and after incision. The magnetometer does not reach the same depth as a γ probe, which can have consequences for the identification of deeper nodes, as demonstrated in the recently published MELAMAG Trial[30]. Patients with melanoma who required SLNB in the axillary basin had a lower SLN identification rate than those who underwent SLNB in the groin basin, seemingly owing to SLNs being located deeper in the axilla compared with the groin.

There is strong evidence that studies funded by industry produce a more favourable outcome for their product[31]. An important bias of all included studies was that they received equipment support from industry. Two studies[21,24] were supported financially by industry; in one of these the first author[21] received honoraria. One of the studies supported by industry[21] had the highest identification rates for the magnetic technique (98·0 per cent) in 150 patients. Only three[9,20,24] of seven studies included in this meta-analysis were registered online. Every-Palmer and Howick[31] suggested that trial registration should be mandatory to improve evidence-based medicine.

The meta-analysis by Kim *et al.*[2] included 69 studies and 10 454 patients. It showed that the use of a radiolabelled tracer combined with blue dye had higher identification rates and also led to lower false-negative rates than use of the radiolabelled tracer alone. Only four studies[9,19,23,24] included in the present systematic review used blue dye subsequent to the radiolabelled tracer, and at centres where blue dye was normally used for standard SLNB. Comparison of the magnetic technique with use of radioisotope alone would be expected to result in a lower rate of discordance between the two techniques, given that similar injection sites are used (subareolar, peritumoral or intratumoral), but this approach does not reflect current practice because the dual technique is regarded as the standard of care[2]. Studies that used blue dye, even those with a protocol-driven requirement to carry out the procedure initially with the magnetic technique[9], suffer from bias as the operator cannot ignore the presence of blue dye during SLN identification. Furthermore, the distinct use of both γ probe and magnetometer devices becomes more difficult when both are available in the operating room. This might explain why the highest identification rates were obtained in the studies[21–24] that performed the SLNB procedures with both the magnetometer and γ probes simultaneously. Different ways of administering the magnetic tracer, waiting time, the surgeon's experience in using the magnetometer, and the surgeon's learning curve can all have a considerable effect on identification rates[2,18]. Furthermore, the blue dye, radioisotope and magnetic tracer may be competing for lymph nodes (depending on which dye is injected first), and there are differences in injection sites, which also have a negative impact on discordance.

Owing to the absence of radioisotope and nuclear medicine dependence, the magnetic technique should in theory be cheaper than the standard technique. A detailed cost-effectiveness analysis is required before clinical implementation. No cost-effectiveness analysis has yet compared the magnetic technique with the standard technique.

Teshome *et al.*[32] reviewed some of the published trials comparing the magnetic technique with the standard technique, and performed a meta-analysis showing a strong agreement between both techniques in identifying SLNs by patient (prevalence-adjusted bias-adjusted κ (PABAK) 0·94, 95 per cent c.i. 0·89 to 0·98) and detecting malignant SLNs by patient (PABAK 0·89, 0·84 to 0·95), and a moderate to substantial agreement for SLN detection by node (PABAK 0·68, 0·54 to 0·82). The authors stated that all trials used the same method of identification. The optimal approach is to use the magnetic technique first to demonstrate that it works and then use the γ probe to confirm whether any nodes were missed. This approach was used in only three[9,19,20] of the studies included in the present meta-analysis. The other four studies[21–24] used the magnetometer simultaneously with the standard technique. The statistical analysis used by Teshome *et al.*[32] assumes that the two SLNB techniques are independent of each other, which is not the case when the techniques are used synchronously on the same patients. The RD and fixed-effect model used here provide a more powerful test, which does not make this assumption. With respect to blue dye, it is not possible to blind the surgeon. This inability to blind the surgeon was confirmed using the Cochran–Mantel–Haenszel test for association in this meta-analysis. Furthermore, Teshome *et al.*[32] did not consider or assess potential vested interest bias in their review.

In addition to their study of 206 patients, Karakatsanis and colleagues[23] performed a meta-analysis of the magnetic technique compared with the dual standard technique including the same articles as analysed here. The Nordic study meta-analysis found similar SLN identification rates (98·0 and 97·3 per cent for the SPIO and standard technique respectively; fixed odds ratio (OR) 1·10, 95 per cent c.i. 0·67 to 1·79; $P = 0{\cdot}71$) and concordance rates per patient ($Z = 0{\cdot}22$, $P = 0{\cdot}82$) for both techniques. Furthermore, a higher nodal detection rate was found for the magnetic technique (97·3 *versus* 91·9 per cent; OR 1·84, 1·37 to 2·47; $P < 0{\cdot}001$). The statistical methods used by Karakatsanis *et al.*[23] were appropriate but they did not consider the importance of potential bias or evaluate complication rates across the studies.

The aforementioned biases can be resolved with a non-commercial RCT[33], in which the magnetic technique is compared with the dual technique and specific requirements are set for participating centres, to ensure sufficient experience with both techniques before randomization. This is a simple approach given the ease of patient recruitment observed in all studies and the fact that end-points are self-evident at the end of the SLNB procedure. There have been no published studies using the magnetic technique alone, but a weakness of such a cohort trial would be lack of comparative data on the standard technique. It is no longer ethical to require formal axillary lymph node dissection to assess the false-negative rate of the magnetic technique. After publication of a RCT, a phase IV postmarketing registry could provide valuable additional prospective data on the magnetic technique. This approach would also provide feedback to the manufacturer in line with their responsibilities. The results of this meta-analysis suggest the magnetic technique to be feasible, but its performance should now be evaluated in a non-commercial RCT before clinical implementation.

Acknowledgements

A.Z. and M.C.L.P. are joint first authors of this article.
Disclosure: The authors declare no conflict of interest.

References

1 Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T *et al.* Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *Lancet Oncol* 2007; **8**: 881–888.

2 Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer* 2006; **106**: 4–16.

3 Rescigno J, Zampell JC, Axelrod D. Patterns of axillary surgical care for breast cancer in the era of sentinel lymph node biopsy. *Ann Surg Oncol* 2009; **16**: 687–696.

4 Ahmed M, Anninga B, Goyal S, Young P, Pankhurst QA, Douek M *et al.* Magnetic sentinel node and occult lesion localization in breast cancer (MagSNOLL Trial). *Br J Surg* 2015; **102**: 646–652.

5 Barthelmes L, Goyal A, Newcombe RG, McNeill F, Mansel RE; NEW START and ALMANAC study groups. Adverse reactions to patent blue V dye – the NEW START and ALMANAC experience. *Eur J Surg Oncol* 2010; **36**: 399–403.

6 Leong SP, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS *et al.* Is breast cancer the same disease in Asian and Western countries? *World J Surg* 2010; **34**: 2308–2324.

7 Ahmed M, Purushotham AD, Douek M. Novel techniques for sentinel lymph node biopsy in breast cancer: a systematic review. *Lancet Oncol* 2014; **15**: e351–e362.

8 Joshi T, Pankhurst Q, Hattersley S, Brazdeikis A, Hallcraggs M, Devita E *et al.* Magnetic nanoparticles for detecting sentinel lymph nodes. *Eur J Surg Oncol* 2007; **33**: 1135.

9 Douek M, Klaase J, Monypenny I, Kothari A, Zechmeister K, Brown D *et al.* Sentinel node biopsy using a magnetic tracer *versus* standard technique: the SentiMAG Multicentre Trial. *Ann Surg Oncol* 2014; **21**: 1237–1245.

10 Sondak VK, King DW, Zager JS, Schneebaum S, Kim J, Leong SP *et al.* Combined analysis of phase III trials evaluating [^{99m}Tc]tilmanocept and vital blue dye for identification of sentinel lymph nodes in clinically node-negative cutaneous melanoma. *Ann Surg Oncol* 2013; **20**: 680–688.

11 Mounsey A, Viera AJ, Dominik R. 7 questions to ask when evaluating a noninferiority trial. *J Fam Pract* 2014; **63**: E4–E8.

12 R Core Team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing: Vienna, 2015.

13 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7**: 177–188.

14 Walker GA, Shostak J. *Common Statistical Methods for Clinical Research with SAS Examples*. SAS Institute: Cary, 2010.

15 Schuirmann DJ. Confidence interval methods for bioequivalence testing with binomial end-points. *Proceedings – Biopharmaceutical Section, American Statistical Association, Baltimore*, 1999; 227–232.

16 Barranger E, Delmas M, Ihrai T, Flipo B, Darcourt J. Sentinel node biopsy in breast cancer using magnetic tracer: preliminary study. *Gynecol Obstet Fertil* 2014; **42**: 490–493.

17 Coufal O, Fait V, Lzicarova E, Chrenko V, Zaloudik J. [SentiMag – the magnetic detection system of sentinel lymph nodes in breast cancer.] *Rozhl Chir* 2015; **94**: 283–288.

18 Shiozawa M, Lefor AT, Hozumi Y, Kurihara K, Sata N, Yasuda Y *et al.* Sentinel lymph node biopsy in patients with breast cancer using superparamagnetic iron oxide and a magnetometer. *Breast Cancer* 2013; **20**: 223–229.

19 Pinero-Madrona A, Torro-Richart JA, de Leon-Carrillo JM, de Castro-Parga G, Navarro-Cecilia J, Dominguez-Cunchillos F *et al.* Superparamagnetic iron oxide as a tracer for sentinel node biopsy in breast cancer: a comparative non-inferiority study. *Eur J Surg Oncol* 2015; **41**: 991–997.

20 Rubio IT, Diaz-Botero S, Esgueva A, Rodriguez R, Cortadellas T, Cordoba O *et al.* The superparamagnetic iron oxide is equivalent to the Tc99 radiotracer method for identifying the sentinel lymph node in breast cancer. *Eur J Surg Oncol* 2015; **41**: 46–51.

21 Thill M, Kurylcio A, Welter R, van Haasteren V, Grosse B, Berclaz G *et al.* The Central-European SentiMag study: sentinel lymph node biopsy with superparamagnetic iron oxide (SPIO) *vs.* radioisotope. *Breast* 2014; **23**: 175–179.

22 Ghilli M, Carretta E, Di Filippo F, Battaglia C, Fustaino L, Galanou I *et al.* The superparamagnetic iron oxide tracer: a valid alternative in sentinel node biopsy for breast cancer treatment. *Eur J Cancer Care (Engl)* 2015; [Epub ahead of print].

23 Karakatsanis A, Christiansen PM, Fischer L, Hedin C, Pistioli L, Sund M *et al.* The Nordic SentiMag trial: a comparison of super paramagnetic iron oxide (SPIO) nanoparticles *versus* Tc and patent blue in the detection of sentinel node (SN) in patients with breast cancer and a meta-analysis of earlier studies. *Breast Cancer Res Treat* 2016; **157**: 281–294.
24 Houpeau JL, Chauvet MP, Guillemin F, Bendavid-Athias C, Charitansky H, Kramar A *et al.* Sentinel lymph node identification using superparamagnetic iron oxide particles *versus* radioisotope: the French Sentimag feasibility trial. *J Surg Oncol* 2016; **113**: 501–507.
25 Straver ME, Meijnen P, van Tienhoven G, van de Velde CJ, Mansel RE, Bogaerts J *et al.* Sentinel node identification rate and nodal involvement in the EORTC 10981-22023 AMAROS trial. *Ann Surg Oncol* 2010; **17**: 1854–1861.
26 Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM *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.
27 Huizing E, Anninga B, Young P, Monypenny I, Hall-Craggs M, Douek M. Analysis of void artefacts in post-operative breast MRI due to residual SPIO after magnetic SLNB in SentiMAG Trial participants. *Eur J Surg Oncol* 2015; **41**: S18.
28 Pouw JJ, Grootendorst MR, Bezooijen R, Klazen CA, de Bruin WI, Klaase JM *et al.* Preoperative sentinel lymph node localization in breast cancer with superparamagnetic iron oxide-MRI: the SentiMAG Multicentre Trial imaging sub protocol. *Br J Radiol* 2015; **88**: 20150634.
29 Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C *et al.* The sentinel node in breast cancer – a multicenter validation study. *N Engl J Med* 1998; **339**: 941–946.
30 Anninga B, White SH, Moncrieff M, Dziewulski P, LC Geh J, Klaase J *et al.*; MELAMAG Multicentre Trialists Group. Magnetic technique for sentinel lymph node biopsy in melanoma: the MELAMAG Trial. *Ann Surg Oncol* 2016; **23**: 2070–2078.
31 Every-Palmer S, Howick J. How evidence-based medicine is failing due to biased trials and selective publication. *J Eval Clin Pract* 2014; **20**: 908–914.
32 Teshome M, Wei C, Hunt KK, Thompson A, Rodriguez K, Mittendorf EA. Use of a magnetic tracer for sentinel lymph node detection in early-stage breast cancer patients: a meta-analysis. *Ann Surg Oncol* 2016; **23**: 1508–1514.
33 Anninga B, Ahmed M, Douek M. Magnetic guidance for cancer surgery. *Br J Surg* 2015; **102**: e12–e14.

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Table S1 Potential conflicts of interest and risk of vested interest bias (Word document)

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