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Magnetic Techniques in Breast Cancer Surgery

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Abstract

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Preoperative tumor localization and axillary mapping in breast cancer surgery are integral for successful breast conserving surgery and axillary staging. They can be performed with a variety of markers and tracers, including magnetic seeds and a liquid sentinel node tracer containing superparamagnetic iron oxide (SPIO) nanoparticles. Although numerous studies have demonstrated the safety and efficacy of both magnetic seeds and SPIO in breast cancer surgery, further research is needed to optimize their application and maximize their potential benefits.

Paper I presents a systematic review and meta-analysis of studies that have investigated the role of SPIO for sentinel lymph node biopsy (SLNB). The findings confirm that SPIO performs comparably to radioisotope while highlighting knowledge gaps regarding the optimal dose, timing, and site of SPIO injection to minimize side-effects and facilitate tailoring of treatment.

Paper II reports a pragmatic, multicenter randomized clinical trial comparing the use of magnetic seed and SPIO to conventional guidewire and SPIO in non-palpable breast tumors. In 426 patients, both methods demonstrated equivalent re-excision rate, SLN detection, and resection ratio. However, the combination of magnetic seed and SPIO resulted in shorter operative times, fewer failed localizations and improved surgical logistics.

Paper III presents the results of a prospective cohort study that investigated the feasibility and efficacy of SPIO for SLNB in patients undergoing primary systemic therapy (PST) for breast cancer. The results showed that SPIO performed comparably to radioisotope (RI) but detected more sentinel lymph nodes and demonstrated a higher detection rate of metastatic sentinel lymph nodes. The findings suggest that SPIO injection before PST is both feasible and beneficial for enhancing axillary mapping in this patient population, though further studies are needed to refine the optimal timing of administration.

Paper IV consists of a health economic analysis of the trial from Paper II. It explores the financial implications of the implementation of a magnetic marker compared to the guidewire. Through a cost-minimization approach that considered all direct and indirect costs, the study demonstrated that although the magnetic marker is more expensive as a device, incorporating it in the Swedish healthcare system is more cost-effective than the guidewire.

Keywords: Breast Cancer, Breast Conserving Surgery, Sentinel Lymph Node, Sentinel Lymph Node Detection, Superparamagnetic Iron Oxide Nanoparticles, SPIO, Magnetic Seed, Guidewire, Targeted Axillary Dissection, Cost-Minimization, Health Economy

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To the patients we heal and those we lose—
May the number of the former grow and the latter diminish

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I. Pantiora E, Tasoulis MK, Valachis A, Eriksson S, Kühn T, Karakatsanis A, Rubio IT. Evolution and refinement of magnetically guided sentinel lymph node detection in breast cancer. Br J Surg 2022. doi: 10.1093/bjs/znac426.

II. Pantiora E*, Jazrawi A*, Hersi A-F, Abdsaleh S, Ahlstedt H, Molnar E, Wärnberg F, Eriksson S#, Karakatsanis A#. Effect of magnetic marker vs Guide wire localization of non-palpable breast cancer in combination with magnetic sentinel lymph node dissection. An open-label, phase 3, pragmatic randomised controlled trial. JAMA Surg 2024. doi: 10.1001/jamasurg.2023.6520

III. Pantiora E, Wärnberg F, Eriksson S#, Karakatsanis A#. Magnetic guided surgery following primary systemic therapy for breast cancer. Implications for enhanced axillary mapping. Br J Surg 2024 https://doi.org/10.1093/bjs/znae008

IV. Pantiora E, Sampaio F, Jazrawi A,Wärnberg F, Eriksson S #, Karakatsanis A#. Magnetic seed vs guidewire breast cancer localization with magnetic lymph node detection: a cost-minimization analysis.

Contents

Abbreviations

AJCC	American Joint Committee on Cancer
ALND	Axillary lymph node dissection
ARV	Actual resection volume
ASTRO	American Society for Radiation Oncology
BCS	Breast-conserving surgery
BD	Blue dye
CI	Confidence interval
CONSORT	Consolidated standards for reporting trials
DCIS	Ductal carcinoma in situ
FNA	Fine needle aspiration
FNR	False-negative rate
HBOC	Hereditary breast and ovarian cancer
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
ICG	Indocyanine green
IONs	Iron oxide nanoparticles
IQR	Interquartile range
ITT	Intention to treat
LN	Lymph node
MINORS	Methodological Index for Non-randomized Studies
MRI	Magnetic resonance imaging
NOS	Newcastle- Ottawa scale
NSABP	National Surgical Adjuvant Breast and Bowel Project
OR	Operating room
ORV	Optimal resection volume
PP	Per protocol
PRECIS-2	PRagmatic-Explanatory Continuum Indicator Summary 2
PRISMA	Preferred Reporting Items for Systematic reviews and meta-analyses
PST	Primary Systemic Treatment
QoL	Quality of Life
QUADAS	Quality Assessment for Diagnostic Accuracy Studies
RCC	Regional Cancer Centre

RI	Radioactive isotope
ROBINS-I	Risk Of Bias In Non-randomized Studies of Interventions
RR	Risk ratio
SD	Standard deviation
SEER	Surveillance, Epidemiology, and End Results Program
SSO	Society of Surgical Oncology
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SPIO	Superparamagnetic iron oxide
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
TAD	Targeted Axillary Dissection
Tc-99	Technetium- 99
TNM	Tumour Nodes Metastases
WHO	World Health Organizationα

1 Introduction

Breast cancer is one of the most extensively researched malignancies, representing a field in which significant advancements in both detection and treatment have been achieved. Once considered an incurable illness, breast cancer has emerged in contemporary medical discourse as one of the malignancies associated with a favourable prognosis. The increase in survival has been attributed to the early detection of the disease and recent advancements in systemic treatment. The targeted and extensive use of systemic therapies has allowed a substantial de-escalation of surgical interventions while the development of new technologies facilitates more precise surgery, to ensure quality of life (QoL) for these patients without compromising oncological outcomes.

2 Breast Cancer

2.1 Overview and Epidemiology

Breast cancer is the most common malignancy in women, excluding non-melanoma skin cancer with over 2.3 million cases diagnosed worldwide in 2020 [1]. The number is projected to exceed 3 million by 2040, making breast cancer a leading cause of morbidity among the female population [1]. Although its incidence has been rising steadily by approximately 0.4% per year since 2010, the mortality of the disease has been declining, with an overall decrease that reached 43% in 2020 reflecting improvements in screening and management [2]. The incidence rate of breast cancer in Sweden has increased from 117.2 cases per 100.000 women in 1992 to 190.9 cases per 100.000 women in 2022 according to Swedish Regional Cancer Centre (RCC)[3]. This increase could be partially attributed to overdiagnosis as well as the overall increase in life expectancy in the past decades[4]. However, the notable increase of breast cancer in adolescent and young adults globally, suggests a genuine increase in the incidence of the disease [5,6]. Following international trends, the relative 5-year survival for women between the ages of 30-89 with breast cancer reached 86% in 2020 irrespective of stage or biological subtype[7].

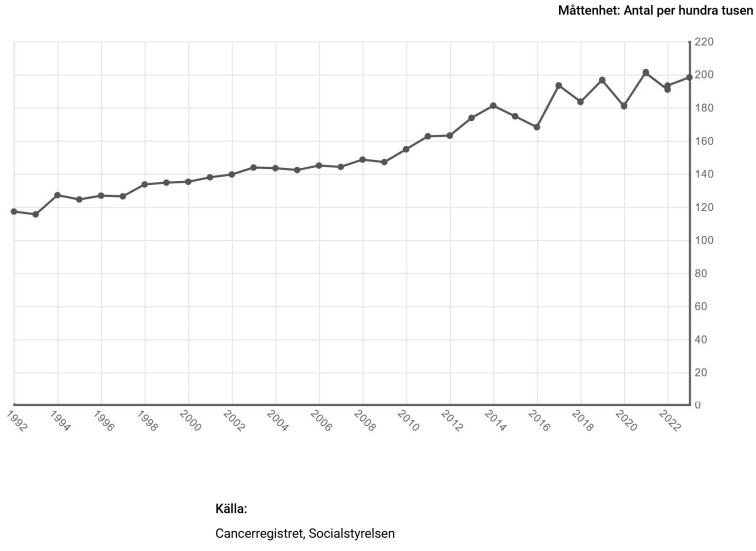

Fig 1. New cases of breast cancer diagnosed in Sweden between 1992- 2022 per 100.000 women
Source: RCC https://vardenisiffror.se/

Although breast cancer primarily affects women, 0.5- 1% of cases occur in men [8]. Established risk factors include female sex and increasing age. The estimated lifetime risk of breast cancer in women globally is approximately 13% [9]. Another important risk factor is the presence of a germline pathogenic variant in genes related to hereditary breast and ovarian cancer syndrome (HBOC). High-risk genes, such as the well-known BRCA1 and BRCA2 are associated with a lifetime risk of breast cancer that exceeds 60%, whilst moderate-risk genes increase the risk by two- to fourfold[10,11]. Although HBOC accounts for less than 10% of all cases, patients with suggestive family history or clinical features are routinely tested for these genetic mutations to guide treatment alternatives and risk-reduction strategies[12]. Aside from the presence of pathogenic mutations, family history, hormonal influences, as well as previous chest wall radiation increase the risk of breast cancer[13]. Additionally, environmental and lifestyle factors such as pesticide exposure, industrial pollutants, air pollution, exogenous hormones, non-parity, alcohol intake, and lack of physical activity have been linked to increased breast cancer risk[14–17].

2.2 Subtypes and Staging

Breast cancer is a heterogeneous disease comprising various morphological and molecular subtypes. Advances in molecular classification have led to

more targeted treatment which has led to an increase in overall survival rates and QoL. The primary classification system of breast cancer is based on the presence of hormone receptors (HR) -estrogen receptor (ER) and progesterone receptor (PR)- and human epidermal growth factor subtype 2 (HER2) receptor expression. These are single gene classifiers and provide predictive value but also guide systemic treatment decisions. Based receptor status, the World Health Organization (WHO), classifies invasive breast tumours into the following categories:

1. HR+ HER2- (Luminal A or B): Represents ~70% of breast cancers and typically has a more indolent course
2. HR+ HER2+: Less common but benefits from both endocrine therapy and anti-HER2-targeted treatments.
3. HR- HER2+: Aggressive but highly responsive to HER2-targeted therapies.
4. HR- HER2- (Triple-negative breast cancer, TNBC): Lacks ER, PR, and HER2 expression, often associated with poorer prognosis but may respond to immunotherapy and chemotherapy.

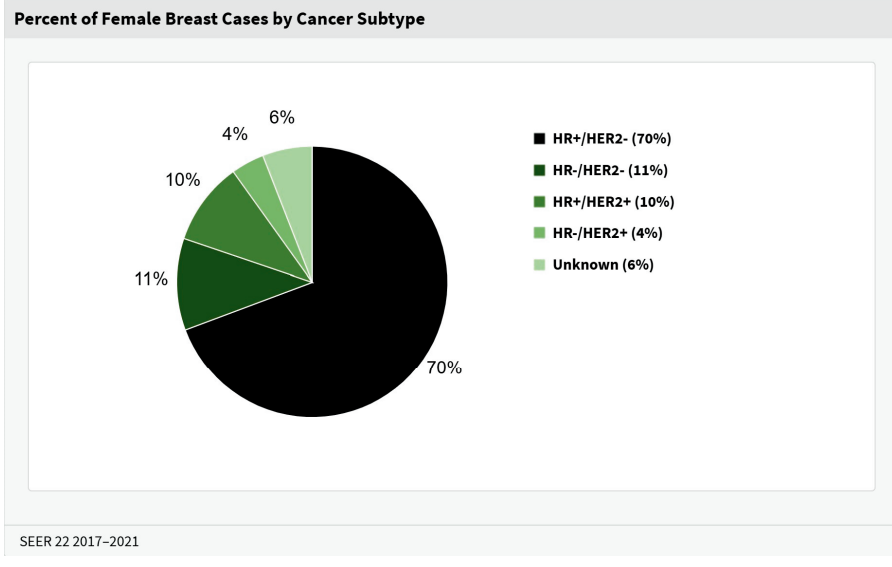

Fig 2. Percent of Female breast cancer cases by subtype

5-Year Relative Survival Percent, Female Breast Subtypes by SEER Combined Summary Stage

Subtype	Localized	Regional	Distant
HR+/HER2-	100.0%	90.5%	35.4%
HR-/HER2-	92.0%	66.8%	14.3%
HR+/HER2+	99.3%	90.4%	45.8%
HR-/HER2+	97.3%	84.2%	39.7%
Unknown	96.6%	77.4%	16.8%
Total	99.6%	86.7%	31.9%

SEER 22 (Excluding IL/MA) 2014–2020

Fig 3. 5-year relative survival percent by subtype and stage
Source: National Cancer Institute Female Breast Cancer Subtypes — Cancer Stat Facts

HR+/HER2- breast cancers represent approximately 70% of all breast tumours as seen in Figure 2 and are considered to have a more indolent course. However, biology is not the only important factor regarding survival outcomes. In Figure 3, where survival rates are depicted by both subtype and stage, it becomes evident that stage is a determining factor of prognosis even in more aggressive subtypes.

While receptor status is a key determinant of treatment decisions, additional markers help refine prognosis and predict therapy response. The protein ki-67 which is found on proliferating cells but not resting cells, was one of the first markers used to distinguish luminal A (low proliferation) from luminal B (high proliferation) [18–20]. However, ki- 67 use is restricted by interlaboratory variability and the lack of a distinct cut-off value, which leaves a substantial group of patients in a “grey zone”, regarding treatment decisions [20]. Multigene prognostic arrays like Oncotype DX®, MammaPrint®, PAM-50 ROR®, EndoPredict®, and the Breast Cancer Index® are used to assess recurrence risk, addressing the limitations of ki-67. All of these markers, along with the specific morphological characteristics of a tumour are assessed when the decision for systemic treatment is made [21].

The most widely accepted system of breast cancer staging is the one proposed by the American Joint Committee on Cancer (AJCC) which incorporates:

- T (Tumour size and invasion)
- N (Nodal involvement)
- M (Presence of distant metastases)

The TNM system of classification utilizes clinical and radiological evaluation to assess the clinical TNM status of a tumour and combines this information with the pathological findings for T and N status that are available after resection and microscopic examination of the primary tumour. In the 8th and most recent edition of the AJCC classification, the aforementioned biomarkers are incorporated in the clinical and pathologic TNM and formulate a Pathologic Prognostic Stage Group [22].

2.3 Principles of Breast Cancer Treatment

Breast cancer management consists of locoregional and systemic treatment. Locoregional treatment includes breast and axilla surgery which will be discussed in detail in the following sections as well as radiation therapy. Radiation therapy can be targeted towards the remaining breast parenchyma after BCS , the chest wall after mastectomy when indicated and even the regional lymph node stations[23–25].

The field of systemic treatment in breast cancer is broad and continuously evolving, with more targeted treatments being added to our therapeutic armamentarium constantly. Briefly it can be summarized in four major categories which include endocrine treatment, chemotherapy, targeted anti HER2 drug therapy and immunotherapy. The choice of treatment is based on tumour morphological characteristics, molecular subtype and stage [26]. Given the high toxicity that accompanies a lot of these treatments, patient comorbidities should be considered during the decision-making process. Systemic treatment can be administered as adjuvant to surgery or, under certain indications, as neoadjuvant treatment, otherwise called primary systemic treatment (PST). In the PST setting, tumour response is evaluated, and adjuvant treatment can be escalated in poor responders to improve overall survival. Furthermore, PST allows for de-escalation of surgery both in the breast and the axilla [26].

3 Breast Cancer Surgical Treatment

3.1 Evolution of Surgical Treatment

Breast cancer surgery has undergone significant transformation over the past century, shifting from highly radical procedures to more conservative approaches that prioritize both oncological safety and quality of life.

Although reports of breast tumours can be found dating to Ancient Egypt [27], surgical treatment of breast cancer varied largely with no technique being able to offer a substantial cure. In the late 19th century, William Halsted, a prominent surgeon from Johns Hopkins Hospital Medical School in Baltimore, introduced a surgical procedure that included the removal of all breast tissue along with the pectoralis major muscle and axillary lymph nodes. This procedure was based on the theory that breast cancer spreads locally. Halsted published in 1894 a cohort of 50 patients treated with this procedure, managing for the first time to demonstrate a three-year local recurrence as low as 6% and a three-year overall survival rate of 45% [28]. This procedure which was named radical mastectomy or 'Halsted mastectomy' was universally accepted as the gold standard of breast cancer treatment for several decades. A more conservative approach sparing the pectoralis major muscle being introduced nearly 50 years later, in 1948 by Patey and Dyson[29]. This novel approach, called the modified radical mastectomy was the first step toward the evolution of breast conserving surgery (BCS).

During the 1970s, advances in radiotherapy along with the introduction of endocrine therapy for breast cancer, steered scientific interest towards a more systemic approach to breast cancer and the subsequent de-escalation of surgical techniques. The National Surgical Breast and Bowel Project (NSABP) led by the American surgeon Bernard Fisher conducted the first trials that established the safety of breast conservation combined with radiotherapy for the treatment of early breast cancer [30]. Their findings were further supported by a contemporary trial conducted by Veronezi et al in Milan [31], establishing breast conservation, usually in the form of quadrantectomy as an equal alternative to mastectomy. Both studies have published results based on twenty years of follow-up, reaffirming their initial findings [32,33].

Since then, breast conservation has evolved immensely with the introduction of oncoplastic techniques aiming to facilitate breast conservation in

patients with larger tumours or smaller breasts and optimize the cosmetic and functional outcomes[34–37]. At the same time, the Society of Surgical Oncology (SSO) along with the American Society of Radiation Oncology (ASTRO) issued a consensus stating that acceptable margins for invasive breast cancer constitute "no ink on tumour", meaning microscopically clear margins and 2mm for pure ductal cancer in situ (DCIS) [38]. The establishment of these margins allows for precision surgery which spares breast tissue for a better cosmetic and functional outcome without compromising oncological outcomes.

3.2 The importance of lesion localization in Breast Conserving Surgery

The implementation of screening protocols for breast cancer along with the improvement of imaging techniques has led to an increase in diagnosis of breast cancer at an earlier stage [39–41].

Consequently, a large proportion of breast tumours diagnosed today are relatively small and not palpable, and thus appropriate for BCS. During the first and second quarters of 2024, screening-detected breast cancer represented 68.6% of all new diagnoses in Sweden, and in reports from 2023, 90.2% of tumours smaller than 30mm were treated with BCS across the country while this percentage was as high as 98.7% in Uppsala [42,43]. These data demonstrate the dominant role of BCS in surgical practice in Sweden.

In the era of precision surgery, a non-palpable tumour requires preoperative localization under radiologic guidance to assist the surgeon in accurate and safe excision. Successful localization is defined by correctly identifying the tumour and removing it with clear margins, whilst avoiding the excision of unnecessary healthy tissue. An ideal localization marker should accurately guide the surgeon to identify the lesion, without misleading them into larger-than-necessary excisions. At the same time, it should be made of materials appropriate for in vivo use, without significant side-effects whilst being easy to use and affordable.

3.2.1 Lesion localization with Guidewire

Since its introduction in the late 1970s, the guidewire has been the standard of care for breast lesion localization[44,45]. It is an inexpensive and widely available method with which most radiologists and surgeons are familiar. A steel guidewire with a hooked end is inserted by the radiologist under ultrasound or stereotactic guidance through the lesion and the surgeon excises the tissue

surrounding the guidewire. The specimen is then controlled by mammogram to ensure that the lesion is included, and the radiological margins are adequate.

Guidewire localization has been the gold standard of breast lesion localization for many years, but it is not without disadvantages. The way the guidewire is inserted by the radiologist is not always convenient for the surgeon, who may have to excise a larger specimen to remove the wire, especially when the insertion point is not close to the skin incision. Furthermore, various complications have been reported regarding this technique, including wire transection and retention of wire fragments in the breast or migration with damage to the surrounding structures[46–48].

One of the most apparent disadvantages of this technique is the logistical challenges that it poses in theatre planning. A guidewire is usually inserted on the day of the surgery which may cause delays that affect the workload of radiologists and surgeons and increase the financial burden on the healthcare system.

3.2.2 Wireless Lesion localization

Alternative methods of breast lesion localization have been developed to address the issues occurring with the guidewire. Since the early 2000s, various technologies have been employed and new localization techniques in the form of a small marker that is detected using a handheld probe have been studied. One of the first non-wire markers introduced in the early 2000s was radioactive seed localization (RSL), which uses 125I seeds for lesion localization, with many studies confirming favorable outcomes compared to guidewire localization[49–52].

The strict regulations regarding radioactive materials and technical difficulties that surround the use of radioactive seeds led to the development of non-radioactive markers such as radiofrequency (RFID) tags[53,54], radar reflectors [55,56], and magnetic seeds [57–60].

Despite the technology they employ, all wireless methods are based on decoupling lesion localization from surgery and facilitating theatre logistics.

3.3 Axillary Surgery

3.3.1 Sentinel Lymph Node Biopsy in upfront surgery

Axillary Lymph Node Dissection (ALND) of levels I/II was the only available management of the axilla in upfront surgery for breast cancer patients regardless of the clinical lymph node status until the late 1990s. The NSABP B-04 and the NSABP B-32 trials demonstrated that Sentinel Lymph Node Biopsy

(SLNB) has similar oncological outcomes and lower morbidity compared to ALND, establishing SLNB as the gold standard in axillary management of early breast cancer by 2010 [30,61].

In NSABP B-32, the sentinel node was detected by using a blue dye (BD) and Technetium-99 (Tc-99), a radioisotope (RI) tracer [61]. Since then, axillary mapping and sentinel lymph node (SLN) detection have been traditionally performed using RI with or without BD [62]. Although very accurate and reliable, this combination poses challenges due to restricted access to nuclear medicine facilities, strict regulations regarding radioactive material transportation and disposal, as well as the rare but severe allergenic reactions caused by BD. Furthermore, the short half-life of both tracers limits their administration on the day of surgery, complicating logistics around theatre planning.

More tracers have been developed in recent years, including carbon nanoparticles [63], Indocyanine green (ICG)[64,65], and Superparamagnetic Iron Oxide Nanoparticles (SPIO)[66–68] as non-radioactive alternatives with comparable performance.

3.3.2 Axillary Staging after Primary Systemic Treatment

The management of the axilla after PST is a currently evolving field, with surgical de-escalation being a priority for ongoing trials. So far, studies have shown that the false negative rate (FNR) for SLNB is comparable to upfront surgery, so SLNB is recommended to all patients with clinically negative axilla (cN0) at diagnosis who remain cN0 after PST (ycN0) [69].

The case of clinically positive lymph node (LN) at diagnosis has been rather challenging and traditionally ALND was performed in all those patients regardless of their response to PST. A direction towards de-escalation was taken after data demonstrated that axillary response usually aligns with the response rate of the primary tumour and the notion of SLNB in patients with complete radiologic response was explored [70,71]. The ACOSOG Z1071 was the first trial that examined the role of SLNB in this setting and demonstrated acceptable false negative rates (9.8%) when certain criteria were met, specifically the use of dual tracer and the removal of at least two lymph nodes [72]. The investigators further demonstrated that the false negative rate was lowest (6.8%) in the cases where the pathologic node was clipped before PST administration and then removed together with all sentinel nodes, a method that is called Targeted Axillary Dissection (TAD)[73]. Subsequent trials, with the most prominent being the SENTINA and SN-FNAC trials showed similar results regarding the safety of SLNB in the neoadjuvant setting[74,75]. All these studies were conducted using BD and RI as tracers, so the performance of the

previously mentioned non-radioactive techniques has not been determined in the neoadjuvant setting.

Patients with poor response or the presence of metastatic nodes after neoadjuvant treatment are subdued to ALND, however, ongoing studies are investigating further de-escalation even in this subgroup[76].

4 Magnetic Techniques in Breast Cancer Surgery

4.1 Magnetic Seeds

The Magseed® (Endomag, Cambridge, UK) is a magnetic marker that is 5mm long and has a diameter of 0.9mm. It is made of surgical stainless steel, a material that has ferromagnetic properties. Ferromagnetism is one of the three major classifications of magnetism, the other two being diamagnetism and paramagnetism [77].

Ferromagnetic materials, when exposed in an external magnetic field, are strongly attracted to the strongest part of the field. They retain their magnetic properties even in the absence of a magnetic field [78].

Diamagnetic materials tend to be repelled by an applied magnetic field and move away from the strongest part of the field, while paramagnetic materials are weakly attracted toward an external magnetic field but in contrast to ferromagnetic materials lose their magnetism when the field is removed[79,80].

Stainless steel is one of few materials that have ferromagnetic properties and is simultaneously safe for in vivo use. These properties make it an ideal candidate for the development of a wireless and non-radioactive marker for lesion localization.

The Magseed ® (Endomag, Cambridge, UK) magnetic marker system is completed by the Sentimag® (Endomag, Cambridge, UK) probe which generates an alternating magnetic field. The Magseed® magnetic marker is deployed under either ultrasound (US) or mammographic guidance. The needle delivery system and markers are visible under both modalities. Magseed® is not suitable for MRI-guided deployment because the needle delivery system is not MRI-compatible. Using the delivery system, the marker is placed percutaneously in the breast days to weeks before surgery. A postplacement mammogram can be used to confirm that the marker is in the desired position in the breast.

During surgery, the Sentimag® probe generates an alternating magnetic field around the marker. The magnetic signature generated by the marker is then detected by a sensitive magnetometer in the probe. The unit displays a numerical reading and emits an audible tone that increases in frequency (pitch)

with the marker's proximity to the probe. Once the marker has been localized, it is excised with the lesion. The efficacy of Magseed® as a marker for breast lesion localization has been shown in institutional and observational studies, but there are no data from randomized trials [57,59,60,81].

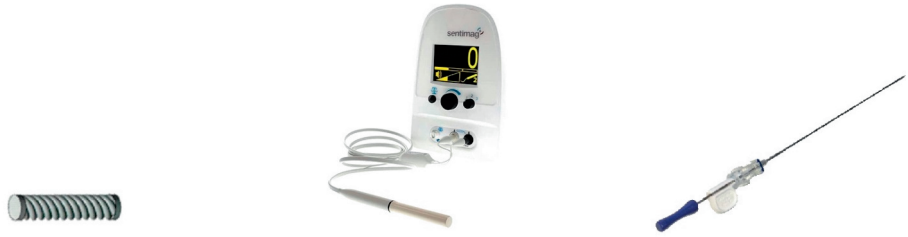

Fig 4. The Magseed® marker, Sentimag® probe and delivery system

4.2 Superparamagnetic Iron Oxide (SPIO) Nanoparticles

Iron Oxide Nanoparticles (IONs) are iron compounds smaller than 100 nanometers in diameter. They are found in nature and have been extensively researched for medical purposes due to their unique magnetic abilities and their biocompatibility [82]. SPIO nanoparticles are superparamagnetic IONs, meaning that they become transiently magnetized when an external magnetic field is applied, but do not retain their magnetism outside the field. They are usually coated in organic material to improve their stability and biocompatibility within the body and have been investigated as a contrast agent for Magnetic Resonance Imaging (MRI) for diagnostic purposes, targeted delivery for drugs, as well a magnetic hyperthermia and thermoablation for cancer treatment [82,83].

SPIO nanoparticles tend to accumulate in lymph nodes through the process of phagocytosis by macrophages, a characteristic that makes them an ideal tracer for SLNB. The first SPIO approved in Europe for SLNB (Sienna, Endomag, Cambridge, UK) was diluted with normal saline (2+3 ml). Further advances allowed for production of SPIO that did not require dilution (Magtrace®, Endomag, Cambridge, UK) a liquid suspension of carboxy dextran-coated iron oxide nanoparticles. Each milliliter of Magtrace ® contains approximately 28 mg of iron. The iron oxide nucleus has a diameter of 7nm, and along with the coating, the total diameter is 60nm.

According to commercial indication, 1-2ml of Magtrace® can be injected either in the subareolar region or around the breast lesion, up to several weeks preoperative and the SLNs that have absorbed it can be detected with the Sentimag® probe that was described previously. The probe applies a magnetic field and the SPIO nanoparticles become transiently magnetic and induce a signal similar to the Magseed®.

SPIO nanoparticles have shown comparable performance to RI ± BD as an SLN tracer with the additional advantage of a wider timeframe for preoperative administration. Furthermore, since it does not contain radiation, it does not require the strict regulation of RI [66,67]. Recent studies have investigated the use of SPIO within a wider timeframe and different doses with promising results[84–87].

5 Aims

5.1 Paper I

To analyse the available data on SPIO in breast cancer surgery, evaluate its performance as a tracer in SLNB, and identify factors associated with its effectiveness. Finally, to evaluate the role of the magnetic technique in addressing tailored patient needs and identify knowledge gaps.

5.2 Paper II

To determine whether the combination of a paramagnetic seed and superparamagnetic iron oxide (SPIO) is equivalent to the guidewire and SPIO for breast cancer localization and sentinel lymph node detection (SLNB) in non-palpable breast tumours.

5.3 Paper III

To investigate the width of the timeframe within SPIO can be administered in patients undergoing PST without affecting negatively nodal detection, and the concordance of SPIO and radioisotope-based detection in this subset of patients.

5.4 Paper IV

To evaluate the financial consequences of the implementation of the magnetic technique in clinical practice and compare the total costs of the technique to the traditional guidewire.

6 Patients and Methods

6.1 Patient inclusion criteria

6.1.1 Paper I

This paper is a meta-analysis of published studies.

6.1.2 Paper II

Women aged 18 years or older with biopsy-proven non palpable invasive T1-T3 breast cancer on preoperative imaging or ductal carcinoma in situ (DCIS) who were scheduled for BCS and SLNB. Patients with clinical evidence of axillary lymph node metastases, previous breast or axillary surgery, inability to autonomously consent, and contraindication to MRI or SPIO, were excluded.

6.1.3 Paper III

Patients with breast cancer and cN0/cN1 axillae, intended for PST (chemotherapy, targeted treatment, or endocrine therapy) with curative intent, were included in the study. Participant enrollment occurred at Uppsala University Hospital between January 2020 and October 2022. Exclusion criteria included inflammatory cancer, distant metastases at diagnosis, tumour progression during PST, or surgery before the completion of PST for any reason (PST adverse effects, patient preference). For cN+-to-ycN0 patients, the decision to proceed with TAD was made after discussion at the multidisciplinary meeting and subsequent patient consent, as TAD was not yet included in the Swedish National Guidelines during enrollment period. Patients who opted for upfront ALND were also excluded. Only patients who converted to ycN0 and were scheduled for SLNB or TAD were included in the analysis.

6.1.4 Paper IV

The health economic analysis was performed on patient data from the Magtotal RCT which is the paper II of this thesis.

6.2 Study Design and Setting

6.2.1 Paper I

Systematic review and meta/analysis of both prospective and retrospective observational studies, as well as comparative trials.

6.2.2 Paper II

Phase 3, pragmatic, equivalence, 2-arm, open-label, randomized clinical trial. It was conducted at three university and/or community hospitals in Sweden from May 2018 to May 2022.

6.2.3 Paper III

The study design involved a prospective analysis of patients with non-metastatic, non-inflammatory breast cancer intended for primary systemic therapy (PST) with curative intent. The research was conducted at Uppsala University Hospital between January 2020 and October 2022.

6.2.4 Paper IV

The health economic analysis of the randomized trial that compared the use of magnetic seed to guidewire included a cost-minimization analysis using micro-costing to identify and assign value to all relevant costs for the localization procedure.

6.3 Methods and Considerations

6.3.1 Paper I

The data for systematic review and meta-analysis were accrued from various institutions, and the literature search encompassed PubMed, MEDLINE, abstracts from congress volumes, and citation searches. Additional data were requested from the authors of source studies when required. The study design and setting thus involved a comprehensive review of relevant literature from multiple sources, reflecting a wide range of real-world clinical settings and research environments.

The methods employed in the study included a systematic literature review, data extraction, and analyses. The researchers utilized the PRISMA statement for the literature search, the studies were screened independently by two authors and the data were stored in a preformed worksheet using Microsoft

Excel. The DerSimonian Laird random-effects model was selected for the meta-analysis.

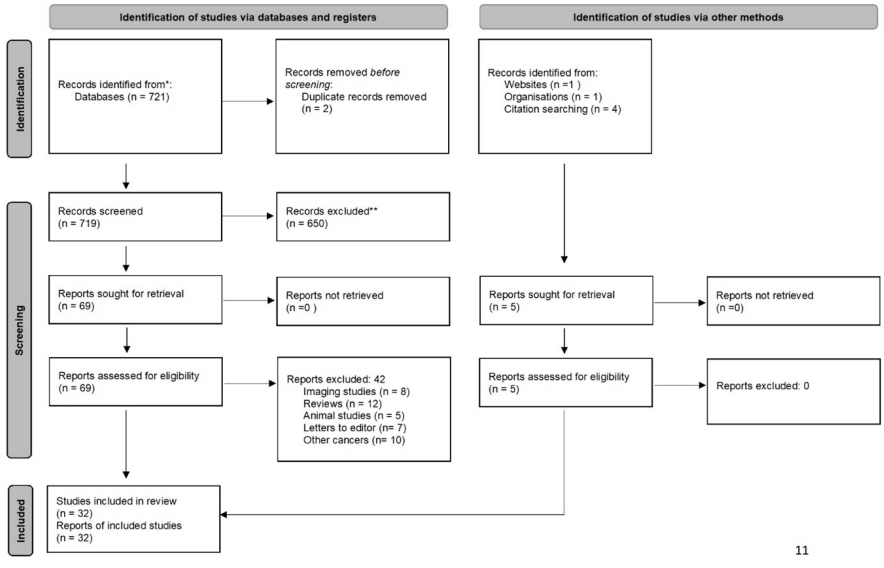

Fig 5. PRISMA 2022 flow diagram for new systematic reviews

Considerations in the study encompassed the assessment of bias using the appropriate validated tools, depending on the type of study. The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)[88] and Methodological Index for Non-Randomized Studies (MINORS)[89] were used to assess bias in comparative studies, while the MINORS tool for single-arm studies was used in non-comparative studies. Assessment of studies reporting on MRI outcomes was performed with the Newcastle–Ottawa Scale (NOS)[90] , and the quality assessment tool for diagnostic accuracy studies (QUADAS-2)[91] was used in studies reporting on diagnostic accuracy. Two authors conducted independently these assessments and differences were resolved after thorough discussion. Additionally, the study involved sensitivity analyses, subgroup and meta-regression analyses, evaluation of heterogeneity, and examination of publication bias. These methodological considerations ensured a comprehensive and rigorous approach to data analysis and interpretation.

6.3.2 Paper II

In this study, participants were randomly assigned in a 1:1 ratio to receive either a paramagnetic seed or a guidewire. Randomization was performed using the randomizeR package of R statistical software. The trial took place in

three hospitals in Sweden (Akademiska University Hospital, Uppsala; Västmanlands Hospital, Västerås; and Sahlgrenska University Hospital, Gothenburg). In the experimental arm, lesion localization was performed with the Magseed® magnetic marker, and in the control arm, with a guidewire. All patients received 1 to 1.5 mL of SPIO (Magtrace®), dorsally to the tumour. In line with the pragmatic nature of the trial, marker placement and SPIO injection could be performed by either the radiologist or the surgeon, at the same time or on different occasions, according to local routines and adapted to each case. Previous experience with the technique was not required for participating radiologists and surgeons, nor was a specific professional level necessary. Guidewire placement was placed exclusively by a radiologist on the day of the surgery or a day before. Localization was verified radiologically in both arms and specimen radiography was performed in all cases.

The extent of pragmatism was quantified using the PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) score, a tool used to facilitate the design of pragmatic trials[92].PRECIS-2 evaluates the applicability of a trial within 10 domains and produces a PRECIS-2 wheel, as shown in the table below (Table 1) as well as Figure 6.

Table 1. PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) score

Domain	**Score**	**Rationale**
Eligiblity criteria	5	Patients with breast tumours that need localisation- Exclusion criteria related to reaction to the material and not the delivery of the technique.
Recruitment Path	5	Recruitment performed during routine clinic appointment for surgery planning.
Setting	4	Study conducted in two university and one county hospital, with various case volumes and level of experience. However, all three centres are in the same country.
Organisation intervention	5	No prior training or additional resources needed for and of the disciplines involved in the trial.
Flexibility-delivery	5	No monitor or specific advice on co-intervention.
Flexibility -adherence	5	No special adherence measures.
Follow up	4	A 2 year follow up which is not routine in usual care and QoL measurements.
Outcome	5	Primary outcomes are directly relevant to participants
Analysis	5	All available data used

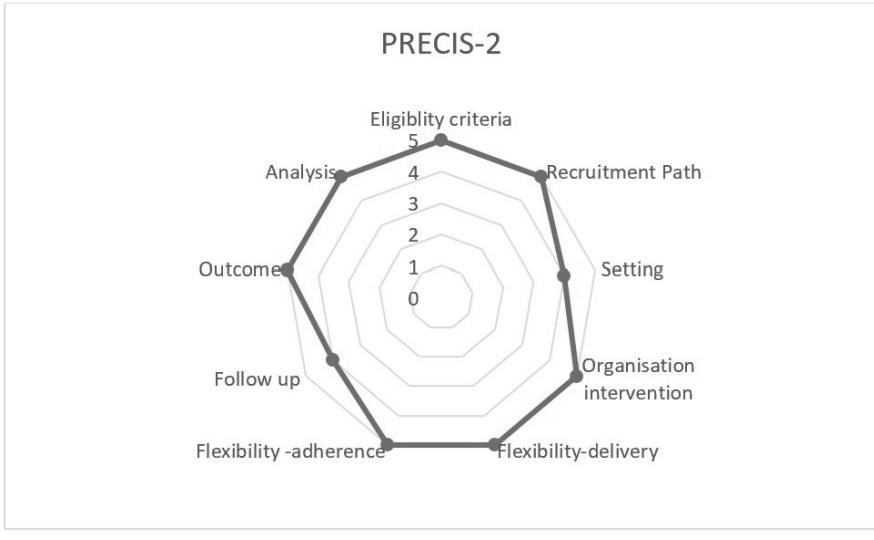

Figure 6. PRagmatic-Explanatory Continuum Indicator Summary 2 (PRECIS-2) wheel

6.3.3 Paper III

The study included cN0/1-to-ycN0 patients undergoing SLNB or TAD. Patients with up to three radiologically suspicious lymph nodes without palpable lymphadenopathy were subjected to a biopsy (FNA or core biopsy) of the most prominent node. In cases of pathologic confirmation of metastasis, or high clinical suspicion despite negative biopsy, the node was clipped with a conventional marker or later on in the study with a Magseed®. The decision for de-escalation of axillary treatment in patients with proven metastasis was taken at the multidisciplinary meeting.

All patients received SPIO either before primary systemic therapy (PST) or before surgery, and radioisotope on the day of surgery. In cases where the response to treatment was monitored with MRI, SPIO was injected after the last MRI was performed to avoid artifacts in imaging, but a seed could be placed in the axilla before initiation of treatment as it does not affect breast imaging. During surgery, all sentinel nodes and the clipped node were detected using the Sentimag® probe, and all nodes were controlled ex-vivo both with the magnetic and the radioisotope probe, and the results were recorded to examine concordance. A specimen mammogram was performed to verify the presence of the clipped node. The axilla was then controlled with the radioisotope probe and any additional radioactive nodes were removed.

The study aimed to investigate the width of the timeframe of SPIO administration in patients undergoing PST and the concordance of SPIO and

radioisotope-based detection. The study also considered the feasibility of SPIO administration before PST and the potential implications of magnetic-guided surgery for enhanced axillary mapping.

6.3.4 Paper IV

The study included the population of the Magtotal RCT that is described in paper II. In summary, patients with non-palpable cTis-T3N0 lesions that were planned for BCS and SLNB were randomized to receive either a magnetic seed and SPIO or a guidewire and SPIO. The magnetic seed could be deployed by either a breast radiologist or a surgeon, but the guidewire could only be placed by a radiologist.

Costs were estimated from a Swedish healthcare system perspective, which is universal, and taxpayer funded. A bottom-up approach (micro-costing) was used to identify all relevant costs and assign monetary value. The costs that were considered were: the cost of each device, the cost of the radiologist and radiology nurse time, the cost of a referral to radiology department, the cost of theatre coordinators time and the total operating room (OR) time. Information about the cost of the devices as well as procedural costs including the hourly rates of all involved healthcare personnel were obtained by invoice review and personnel interviews. All costs were collected in 2022 Swedish krona (SEK), and converted to 2022 EURO (€) using the EPPI cost conversion database[93]. The analysis was performed with and without accounting for OR planning to make the results more generalisable in different clinical settings.

Given the comparable clinical outcomes of the two devices, a cost-minimization approach was deemed appropriate for this analysis. One way sensitivity analysis was performed, using two different scenarios, i) all localizations (magnetic seed and guidewire) and SPIO administration were performed by a radiologist, ii) magnetic seed localizations that could be performed under ultrasound guidance were performed by a surgeon.

6.4 Endpoints and Statistical Analyses

6.4.1 Paper I

The detection rate for SPIO per patient was the primary point of this meta-analysis. This was described as the ratio of patients where at least one SLN was identified using SPIO to the total number of patients that underwent SLND.

Secondary endpoints included detection rate per sentinel lymph node (SLN), i.e. the proportion of SLNs detected by SPIO divided by the total

number of SLNs retrieved; SLN yield, which was defined as the average number of SLNs removed. Other secondary endpoints focused on the frequency and factors increasing SPIO-induced skin discoloration, imaging artifacts in postoperative MRI due to SPIO remnants in the breast tissue, and cost-effectiveness. The concordance between SPIO and radioactive tracers was also analyzed in comparative studies.

The concordance between the two methods was defined as the number of patients in whom both SPIO and RI were successful, divided by the number of patients in whom RI was successful.

$$\text{Concordance} = \frac{SPIO+RI}{RI}$$

Reverse concordance was defined as the number of patients in whom both techniques were successful, divided by the number of patients in whom SPIO was successful.

$$\text{Reverse concordance} = \frac{SPIO + RI}{SPIO}$$

In the case of equally performing tracers, the number of LNs detected with each method should be the same. That leads to a difference between concordance and reverse concordance that equals 0. If one of the tracers performs better than the other, then the concordance rate will favor one of the tracers. The difference between the concordance and the reverse concordance was selected as effect size and was retrieved from comparative studies with a paired design.

Statistical analyses involved the calculation of effect sizes, and the DerSimonian Laird random-effects model was selected to provide more conservative estimates and account for potential heterogeneity in the data. Leave-one-out meta-analyses were conducted for sensitivity, and separate analyses were performed for detection rates in the presence of metastasis. The study included studies that used different types of SPIO, different probes, and a variety of SPIO solutions in different doses. There was also wide variation in the timing of SPIO administration and the clinical setting (upfront surgery *versus* PST), and the site of injection (subareolar/periareolar *versus* peritumoural). Subgroup and meta-regression analyses were performed for all these parameters. Heterogeneity was evaluated using the I^2 statistic, and examination of publication bias using funnel plots and Egger's test. Meta-analyses were undertaken using appropriate statistical methods in Stata release 17 (StataCorp,

College Station, TX, USA). These analyses provided a robust framework for interpreting the data and drawing meaningful conclusions from the study.

6.4.2 Paper II

The primary outcome of this trial was the resection ratio for each localization method in patients with negative margins. The resection ratio was calculated by dividing the actual resection volume (ARV) which was calculated using specimen weight with the optimal resection volume (ORV). ORV was calculated for each tumour based on the radiological dimensions of the tumour (in cases of discordance between different modalities, the largest dimension was used) using the volume calculation formula for ellipsoid tumours, $V = \frac{4\pi r1r2r3}{3}$ where r1= x radius +1cm, r2=y radius+1cm, r3= y radius +1cm. In all dimensions, 1 cm is added as it is the universally accepted macroscopic margin for breast lesions. Optimally, the ratio ARV/ORV should be as close to 1 as possible to ensure that no unnecessary tissue is removed which may jeopardize the cosmetic and functional outcomes of a breast-conserving operation.

Secondary outcomes included SLN detection rate, adverse events, time to specimen excision total operative time, and ease of implementation by all involved healthcare practitioners. Patient-reported outcomes and quality of life evaluation, as well as patient-reported experience measures and cost-effectiveness analyses, will be analyzed separately.

The sample size was calculated based on the principle of equivalence, allowing for the detection of a significant difference in resection ratios of 0.3 adjusted for a non-inferiority margin of 4% for re-excision rates and SLN detection. The literature suggests a resection ratio for the guidewire between 2 and 2.8. To obtain robust results, this was lowered to 1.8 and a 1.5 resection ratio was accepted for the total magnetic technique stemming from the previous pilot study [58]. The two-sided p-value is set at 0.05 and power to 80%. An additional 10% of the sample size calculation will be recruited as inflation to pragmatic settings and tolerance.

Descriptive statistics were performed. Continuous variables were controlled for normality using the Kolmogorov Smirnoff and Shapiro-Wilk tests. For normally distributed data, means and standard deviation (SD) were calculated whereas median with interquartile range (iqr) or range were used to summarize variables without normal distribution. Detection of significance between groups for these variables was performed using the student´s t-test or the Mann-Whitney test. Intention-to-treat (ITT) and per-protocol (PP) analyses were performed for primary outcomes and PP analyses for secondary outcomes. The discordance between ITT and PP groups was assessed using

the McNemar test for paired nominal data. Statistical significance was set at p=0.05 with 95% confidence intervals (CI).

6.4.3 Paper III

The study endpoints included successful sentinel lymph node detection, concordance per procedure, and the number of sentinel lymph nodes retrieved per technique. Statistical analysis was performed using McNemar's test for paired comparisons and Fisher's test for non-paired comparisons. Continuous variables were summarized as mean (standard deviation, SD) or median (interquartile range, iqr; range), as appropriate. The correlation of outcomes with the timeframe of SPIO administration was assessed by Kendall's tau (τ) and Spearman's rho (ρ). Multivariable analysis was performed if statistically significant differences were seen in univariable analysis, and statistical analysis was performed with SPSS v28 and Stata v17. The manuscript was prepared and reported according to the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) statement.

6.4.4 Paper IV

This within-trial health economic evaluation was performed on data provided by the RCT presented in paper II [94]. The present study is reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [95].

The endpoint of this study was to compare the costs associated with magnetic seed localization plus SPIO versus guideline localization plus SPIO for SLNB in non-palpable breast tumours. The analysis was performed from the perspective of the Swedish public healthcare system using a cost-minimization framework, as clinical outcomes between the two methods were equivalent.

Cost components included device costs (magnetic seed and guidewire), personnel costs (time-dependent salaries of radiology staff, surgeons, OR personnel and coordinators) and additional indirect costs based on localization procedure and logistical expenses. All costs were collected in 2022 Swedish krona (SEK) and converted to 2022 EURO (€) using the EPPI cost conversion database[93]. All costs are summarized in Table 3.

Table 3: Resources, unit costs and total costs

	Magseed			Guidewire			Source of unit cost
	Frequency	**Unit cost**	**Total**	**Frequency**	**Unit cost**	**Total**	
Material costs							
Device cost	215	278	59770	208	38	7904	per invoice
Delivery costs		none	none		none	none	per invoice
Deployment cost							
Radiology (physician and nurse) time*	203*4 min	1.7/min	1362,1	208*15 min	1.7/min	5304	hourly rate of a consultant breast radiologist salary from salary logs
Surgeon time*	12	0	0		NA	0	performed during the preoperative consultation
Referral to Radiology	203	265	53795	208	265	55120	Hospital invoicing system
Capital		0	0		0	0	
OR list planning							
Surgical coordinators' time**	0	0	0	42**	96.11	4036,6	hourly rate of three breast coordinators from salary logs
Operation time (median, in minutes) *	215*69 min	37.1/min	550378,5***	208*75.5 min	37.1/min	582618,4***	
Total cost excluding device cost			605535,6			647079	
Total cost including device cost			665305,6			654983	

*: Time is provided in minutes; respective monetary costs are multiplied by the respective cost/minute. **: For the surgical coordinator time, the extra time required responds to every fifth patient and corresponds to one working hour for three breast nurses/ OR coordinators. ***: Number of procedures multiplied by procedural time multiplied by cost per minute.

Bootstrapping with 1000 iterations was performed to estimate the 95% Cis and improve the robustness of the results. Significance was set at a two-sided p value of < 0.05 and analysis was performed with SPSS 28 and STATA v17 software.

Sensitivity analyses were conducted to account for variations in practice. The two scenarios that were examined were (1) assuming all localizations were performed by radiologists, and (2) assuming all ultrasound guided magnetic seed placements were performed by surgeons during the preoperative consultation.

6.5 Ethical considerations, ethics committee approval, and trial registration

All the studies that involved human participants were approved by the ethics committee in Uppsala and conducted according to the Helsinki Declaration. Project I was a meta-analysis of published studies and was exempt from ethical approval. Project II and Project III were registered in a public trial registry with the following identification numbers: Project II: ISRCTN.org Identifier: ISRCTN11914537, Project III: NCT05985551. Project IV was a predefined secondary analysis of Project II and is included in the ethical approval that covers project II.

The studies were sponsored by Uppsala University and Uppsala University Hospital, and supported by institutional grants from Uppsala University, Västmanlands Cancer Foundation, Swedish Breast Cancer Association and the Centre for Clinical Research Region Västmanland. Magseed® and Magtrace® were provided by Endomag (Cambridge, UK).

7 Results

7.1 Paper I

Overall, 32 studies met the criteria for inclusion in qualitative and quantitative synthesis. Of these, 20 were comparative studies (SPIO versus RI ± BD), and 19 had a paired design. Three studies were focused on the neoadjuvant setting, but only one of them had clear information about the lymph node status before systemic treatment. Four studies included only data on postoperative MRI artifacts and one study had only information on skin discoloration. Only one study had a randomized design, but the randomization was between different doses of SPIO, not between SPIO and RI +/- BD. Finally, one study investigated the concept of delayed SLNB, i.e. SPIO administration outside of the 7-day proposed timeframe in the setting of DCIS.

The primary endpoint of the meta-analysis was the detection rate for superparamagnetic iron oxide (SPIO) per patient. This was 98.7% (95% CI 98.1-99.2) across the 27 studies that reported it, with a low heterogeneity (I^2=25%, p=0.119). Across the comparative studies (n=20) the polled detection rate was 97.5% (95% CI 96.8-98.1) for SPIO and 96.5 % (95% CI 95.7- 97.2) for RI ± BD but the difference was not significant (RR 1.006, 95 percent c.i. 0.992 to 1.019; P = 0.376; I^2 = 28.7%). The detection rate for patients with metastatic lymph nodes was 99.4 (97.8 to 100) percent for SPIO and 97.0 (92.8 to 99.7) percent for RI ± BD and did not reach a significant difference (RR 1.006, 0.982 to 1.031; P = 0.637; I2 = 0 percent).A subgroup analysis that looked into the effect of SPIO type, dose, injection site, probe type, and neoadjuvant therapy demonstrated that preoperative injection (>24h) and use of SPIO in the setting of delayed SLND was associated with better node detection compared to RI ±BD. These results are shown in detail in the manuscript.

The nodal detection rate was reported in 19 of the comparative studies and it was 94.1 % (91.8 -96.1) for SPIO and 83.5% (78.7- 87.9) for RI ±BD, a significant difference (RR 1.098, 95 percent CI 1.058 to 1.140; P < 0.001), but the heterogeneity among the studies was rather high (I^2 = 85.2%).

Dates for the estimation of concordance and reverse concordance were available in 19 comparative studies. The concordance rate was 99% (95%CI 98.2-99.6) and the reverse concordance rate was 97.1 (95%CI 95.2-98.6). The difference was not significant (p= 0.656) and the heterogeneity among the

studies was moderate (I^2 = 59.6%). The concordance rates were not affected by any of the factors examined in the subgroup analysis, but the reverse concordance rates were affected by the factors that were found to increase SPIO detection rate (preoperative administration and delayed SLNB).

Information about skin discoloration could be retrieved from 12 studies. Overall, the prevalence of skin discoloration was 30.8% ranging from 0 to 84.4%, and a heterogeneity of 96% and was reported mainly after breast conservative surgery. Subgroup analysis showed that lower discoloration rates were related to lower SPIO doses, peritumoral injection, and preoperative injection (>24h). These associations were not retained on meta-regression, a finding that suggests that a combination of the three is the most effective way to reduce skin discoloration.

Four studies provided information on MRI artifacts and all of the patients apart from six had received 2ml SPIO diluted in 3ml of saline via a subareolar injection. MRI artifacts were present in 61% of patients for up to 46 months after SPIO injection. Subgroup analysis showed an association with BCS (70% versus 21% in mastectomy, $p<0.001$, 95% CI: 28-70). The small number of studies, high heterogeneity (I^2=90%), and the high selection bias did not allow for further analyses.

7.2 Paper II

In total, 426 women were randomized in two arms of 213 participants. As the study allowed for tolerance during the covid-19 pandemic, to facilitate theatre planning, in the per-protocol analysis, the total magnetic arm included 215 participants, while the guidewire included 208. The difference between ITT and PP allocation was -0.9% on the McNemar test (95% CI, -2.6%, 0.8%, p=0.34), however all analyses for primary outcomes were conducted in both ITT and PP. The flow diagram of the trial is shown below (Fig 7).

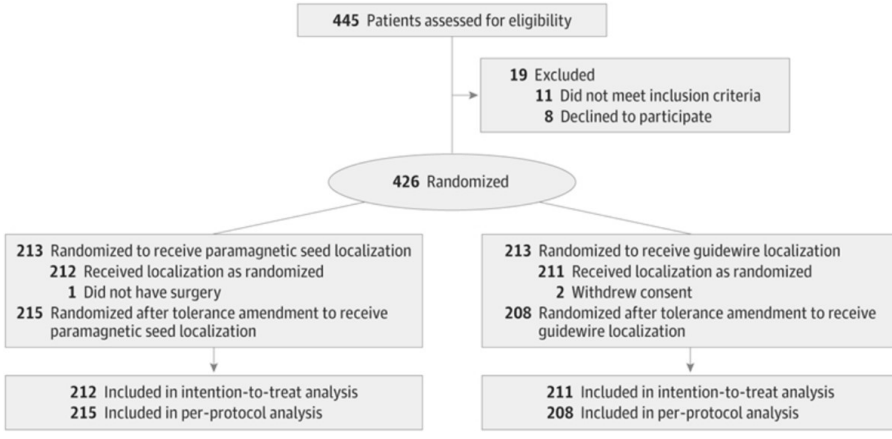

Fig 7. Magtotal Trial Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram

The re-excision rate was 2.90% (95% CI, 1.60%-4.80%), and the median (IQR) resection ratio was 1.96 (1.15-3.44). No differences were found between the guidewire and the seed in re-excisions (6 of 211 [2.84%] vs 6 of 209 [2.87%]; difference, −0.03%; 95% CI, −3.20% to 3.20%; P = .99) or resection ratio (median, 1.93; IQR, 1.18-3.43 vs median, 2.01; IQR, 1.11-3.47; P = .70). Resection ratio was related to body mass index, type of surgery and recruiting site on multivariable analyses and can be seen in table 2.

Table 2. Univariate and Multivariable Analysis for Resection Ratio

Table 2. Univariate and Multivariable Analysis for the Resection Ratio

	Univariate analysis		Multivariable analysis	
Site/variable	Resection ratio (IQR)	*P* value	β coefficient (95% CI)	*P* value
Per intention-to-treat analysis				
Magnetic marker	2.01 (1.11-3.47)	.70[a]	NA	NA
Guidewire	1.93 (1.18-3.43)			
Per-protocol analysis				
Magnetic marker	1.97 (1.11-3.46)	.82[a]	NA	NA
Guidewire	1.96 (1.22-3.48)			
Recruiting site			1.269 (0.763-1.775)	<.001
Uppsala	1.45 (0.78-2.13)	<.001[b]	1 [Reference]	NA
Västerås	3.33 (2.13-5.39)		2.478 (1.650-3.036)	<.001
Gothenburg	2.87 (2.00-4.38)		1.729 (0.805-2.653)	<.001
Body mass index[c]	0.307 (0.213-0.395)[d]	<.001[d]	0.181 (0.101-0.260)	<.001
Palpable lesion				
No	2.00 (1.18-3.52)	.03[a]	−0.957 (−2.491-0.577)	.22
Diffusely palpable lesion	1.60 (0.90-2.23)			
Preoperative MRI				
Yes	2.55 (1.50-4.27)	<.001[a]	−0.156 (−1.115-0.802)	.75
No	1.61 (0.95-2.83)			
Multifocal disease				
No	1.98 (1.18-3.46)	.13[a]	NA	NA
Yes	1.37 (0.56-3.15)			
Histology				
IDC (NST)	1.95 (1.15-3.54)	.53[b]	NA	NA
ILC	2.00 (1.04-2.81)			
DCIS	2.25 (1.57-3.06)			
Other	1.79 (1.07-2.85)			
Type of breast-conserving surgery			1.188 (0.475-1.901)	<.001
Simple WLE	2.07 (1.26-3.60)	<.001[b]	1 [Reference]	NA
OPBCS level I	1.37 (0.70-1.85)		−0.029 (−1.105-1.047)	.96
OPBCS level II	2.69 (1.05-5.57)		4.916 (3.367-6.466)	<.001
Overall	1.96 (1.15-3.44)			

SLN detection was 98.1% in the Magtotal arm *versus* 99% in the Guidewire arm (difference, -0.9; 95% CI, -3.6% to 1.8%, p=0.72) and was not affected by the presence of metastatic nodes.

The study also found that the seed and SPIO resulted in shorter operative times (69 [56-86] minutes vs 75.5 [59-101] minutes; P = .03) and increased satisfaction among healthcare practitioners.

7.3 Paper III

After screening, 128 patients met the eligibility criteria. Of those, 113 were available for analysis at the end of neoadjuvant treatment. SPIO was administered within a timeframe that ranged from 0 to 248 days, with a median of 3 days. Axillary mapping with SPIO was performed within a week from the operation in 66.4% of the patients, and longer than a week in 33.6%.

Successful SLNB was noted in 97.3% of patients with SPIO, 91.2% for RI (difference 6.2%, 95% CI -0.8, 13.2, p=0.057) and 100% for combined methods. SLN detection was not affected by any of the baseline factors in logistic regression for either method, but increased BMI negatively affected SLN detection with SPIO in univariable analysis. SLN detection was increased with the addition of SPIO to RI (difference 8.8%, 95% CI 2.4, 15.0; p<0.001) but not vice versa. Concordance per procedure was 97.1% (95% CI 93.8, 100) for isotope (SPIO+RI/RI) and 90.9% (95% CI 85.5, 96.3) for SPIO (SPIO+RI/SPIO) and was not affected by the timing of SPIO injection (Kendall's tau: 0.027, 95% CI -0.098, 0.151; p=0.746).

SPIO was more successful in the identification of ≥2 LNs (84.1% vs 77%) compared to RI, and the combination of the two methods was successful in 90.3% of the patients. Age and BMI were inversely related to the probability of retrieving ≥2 LNs with SPIO, but they affected RI only in univariable analysis and not in logistic regression. Similarly, SPIO succeeded in 55.8% of the patients identifying 3 LNs while RI succeeded in 48.7%. The combination was again more successful than either method separately, at 66.4%.

The difference in the median yield of nodes was significant between the two methods, with SPIO retrieving a median (IQR) of 3 (2,3) and isotope a median (IQR) of 2 (2,3) (p<0.001). The combination led to a median number of nodes retrieved of 3(2,4), which was significantly higher than any method separately (p<0.001).

In node-positive patients that converted to node-negative after PST and were subjected to TAD, the detection rate was 100% for SPIO and 82% for RI (difference 18%, 95% CI 2, 34; p=0.016). The index node was SPIO-positive in 94% of the patients and radioactive in 67% (difference 27%, 95% CI 7, 48; p=0.007). SPIO had a significantly higher median yield of LNs even in this setting compared to RI [3 (3,5) vs 2 (2,3); p<0.001].

Within the cohort, 19 patients had a median (iqr) of 1(1,2) metastatic node. More nodes were detected even in this group with SPIO compared to RI (median [iqr] 3 (2,4) vs 2 [2,3]; p=0.01) and more metastatic SLNs (median [iqr] 1 (1,2) vs 1 (0,1); p=0.005).

The study concluded that injection of SPIO before primary systemic therapy is feasible and does not affect concordance with radioisotope. SPIO performed comparably to radioisotope but detected more sentinel lymph nodes and had a higher detection rate of metastatic sentinel lymph nodes.

7.4 Paper IV

The detailed trial results are reported in paper II. The main characteristics of the current analysis population are shown in table 4.

Table 4. Patient characteristics

		Allocation arm				
		Guidewire		Magnetic marker		p-value
Age (median, iqr)		67	(56, 72)	64	(56, 69)	.082†
Body Mass Index, BMI (kg/m^2) (median, iqr)		26.1	(23.7, 29.7)	26.7	(24.1, 29.9)	.332†
Screening detected lesion (n, %)	No	16	7,8%	18	8,9%	.859*
	Yes	188	92,2%	194	91,1%	
Lateralization (n, %)	Right Breast	95	48,7%	100	47,4%	.843*
	Left Breast	100	51,3%	111	52,6%	
Lesion Size (mm) (median, iqr)		10	(8, 15)	11	(8, 15)	.138*
Type of surgery	WLE	180	84,9%	169	81,3%	.46*
	OPBCS	24	11,3%	26	12,5%	
	TM	8	3,8%	13	6,3%	

WLE: Wide local excision, OPBCS: Oncoplastic breast conserving surgery, TM: Therapeutic Mammoplasty

Magnetic seeds were placed (median [iqr]) 5 [1,8] days ahead of surgery, with a median (iqr) of 4 (3,5) minutes required for the localisation session, most often (189 of 215; 92.2%) under ultrasound guidance and as a single localisation session (184 of 215; 85.6%). With the exception of ultrasound guidance, there were significant differences with the guidewire (table 5)

Table 5. Patterns of lesion localization and SPIO administration

		Guidewire		Magnetic marker		p-value
Localization modality (n, %)	Ultrasound	194	93.3%	189	92.2%	.71*
	Stereotactic	14	6.7%	16	7.8%	
Days from localization to surgery (median, iqr)		0	0	5	(1,8)	<.001†
Time for lesion localization (min) (median, iqr)		10	(10,11)	4	(3,5)	<.001†
SPIO administration (n, %)	Surgeon	85	40.6%	29	13.5%	<.001*
	Radiologist	123	59.4%	186	86.5%	
Lesion localised by (n, %)	Surgeon	0	0.0%	12	5.6%	<.001*
	Radiologist	208	100.0%	203	94.4%	
Days from SPIO injection to surgery (median, iqr)		7	(0,15)	6	(1,8)	.041†
Single localization procedure (breast & axilla) (n, %)	Yes	74	33.7%	184	85.6%	<.001*
	No	138	66.3%	31	14.4%	

*: Fisher's exact test, †: Mann Whitney U-test.

Cost- Minimization Analysis

Base case analysis

In the unadjusted analysis, the mean total cost was €3274 for magnetic seed localization and €3337 for guidewire localization, with a mean difference of -€63 (95% CI: -€302 to €174; p = 0.599), indicating no statistically significant difference.

After adjusting for localization method, breast surgery type, and single localization or not , the mean total cost was €3123 for the magnetic seed group and €3514 for the guidewire group. This reflected a statistically significant cost reduction of -€391 (95% CI: -€360 to -€422; p = 0.002), representing an 11.1% decrease in costs associated with magnetic seed localization. The results are shown in Table 6.

Table 6. Cost minimisation analysis.

	Unadjusted analysis			Adjusted analysis			
	Mean (95% CI)	Marginal Difference (95% CI)	p-value	b Coefficient (95% CI)	Marginal Means (95% CI)	Difference (95% CI)	p-value
Localization device							
Guide-wire	3337 (3151, 3524)	Ref. [0]		Ref. [0]	3514 (3333, 3696)	Ref. [0]	
Seed	3274 (3124, 3160)	-63 (-302, 174)	0.599*	-0.118 (-0.192,-0.044)	3123 (2973, 3273)	-391 (-360, -422)	0.002**
Type of Breast Surgery							
WLE	3126 (3010, 3241)	Ref. [0]		Ref. [0]	3137 (3024, 3250)	Ref. [0]	
OP-BCS	3722 (3365, 4078)	604 (144, 1064)	<0.001*	0.156 (0.055,0.256)	3666 (3321, 4010)	528 (297, 760)	0.003**
TM	5232 (4560,5903)	2106 (1280, 2932)	<0.001	0.493 (0.342,0.643)	5135 (4387, 5884)	1998 (1362,2634)	<0.001**
Single localization session							
Yes	3015 (1180)	Ref. [0]		Ref. [0]	2988 (2820, 3157)	Ref. [0]	
No	3498 (1230)	481 (243, 720)	<0.001*	0.164 (0.087,0.240)	3519 (3361, 3678)	531 (521, 541)	<0.001**

Trial-based, Unadjusted and Adjusted Cost Minimisation Analysis. Monetary units are Euros (€). Mean values are presented with 95% CI (confidence intervals). The adjusted analysis is performed with a generalized linear model (gamma family, log link). Ref.: reference category, OPBCS: oncoplastic breast conserving surgery, TM: therapeutic mastopexy/mammaplasty, WLE: wide local excision. *: regression analysis, **: generalised linear regression model.

Sensitivity analyses

Sensitivity analyses confirmed the robustness of these findings. Under the assumption that all localizations were performed by radiologists, no significant difference was observed between groups ($p = 0.601$). However, when the assumption that surgeons performed all magnetic seed placements where feasible was applied, a statistically significant cost advantage emerged in favour of magnetic seeds ($p = 0.007$). Adjusted sensitivity models consistently showed a reduction in total costs with magnetic seed localization.

8 Discussion

8.1 Paper I

Breast cancer surgery has developed immensely in the past decades. The implementation of screening protocols has led to earlier detection of breast cancer and at the same time, the advancements in systemic treatment have resulted in a favorable prognosis and allowed for de-escalation of surgical treatment. Breast cancer surgery nowadays is not exclusively focused on oncological outcomes but also strives for a balance between safe tumour excision and preservation of function and cosmesis regarding both breast and axillary management.

Axillary clearance is reserved for specific cases and has been replaced by SLNB, the removal of the first lymph nodes that drain the breast. This technique allows for accurate staging of the axilla while minimizing the risk of lymphedema. One of the tracers used for the detection of SLNs is based on SPIO, which gather on the lymph nodes and remain there for a longer period than the isotope and BD, allowing for axillary mapping within a wider timeframe. SPIO has been used for the past ten years in different solutions, and a variety of doses and has been injected either peritoumorally or in the subareolar region of the breast on the day of the surgery or a few days before surgery. The only concerns that have been raised regarding SPIO are the possible artifacts on postoperative MRI and the skin discoloration that may occur.

The first project aimed to gather and review the available studies in which SPIO was investigated either on its own or in comparison to isotope. A meta-analysis of the studies was undertaken, with further subgroup analysis to obtain a clear picture of the evidence, evaluate the evolution of the technique, and identify knowledge gaps or areas that need further investigation.

The results of the meta-analysis demonstrate that SPIO is comparable to isotope in terms of SLN detection and seems to retrieve more nodes, without exceeding the clinically safe threshold. The performance of SPIO was not affected by lower doses. An important finding of the meta-analysis was that preoperative injection of SPIO (> 24 hours) was not only feasible and safe but enhanced the performance of the tracer for node detection. An extended timeframe for administration of up to 47 days before surgery has already been investigated with success in the setting of delayed SLNB in patients with

DCIS and raises the question of whether this timeframe can be extended even more[85]. Regarding postoperative MRI artifacts and skin discoloration, the results of the meta-analysis suggest that lower doses and peritumoral injection minimize these adverse effects, as the bulk of the SPIO is removed with the tumour. The studies that reported such results were however highly heterogeneous and more studies with more specific inclusion criteria and standardized reporting are needed before any conclusions are drawn.

In conclusion, this meta-analysis has confirmed that SPIO is a comparable tracer to isotope, but more studies are needed to establish the optimal dose and location of administration to minimize skin discoloration and artifacts without compromising the tracer's performance level. Future studies should also explore the wide timeframe of administration as this would be useful in different clinical settings, such as PST.

8.2 Paper II

As breast cancer surgery evolves, new technologies are being developed to facilitate precision surgery and de-escalation. Patients with early breast cancer are now opting for BCS, as it is proven to equal safety and better quality of life. BCS requires accurate localization of the tumour for excision with adequate margins but not unnecessary tissue removal. Guidewire localization prevailed for decades, but logistical challenges led to the development of other techniques that can detach preoperative localization from surgery. Magnetic markers satisfy this condition as they can be placed in the breast weeks before surgery and are moreover easier to handle than radioactive seeds that require specific and strict policies for safe disposal. Previous studies studied the efficacy and safety of magnetic markers but randomized data comparing magnetic markers to guidewire localization are lacking [57,59,60,81,96]. Furthermore, the combination of magnetic markers and SPIO for a totally magnetic technique has not been adequately investigated and has been met with scepticism due to fear of overlapping signals around the tumour. The second project aimed to compare guidewire localization with SPIO-guided SLNB to a totally magnetic technique for breast and axillary management. The results of this trial showed that the two markers are equal in terms of re-excision rates and volume of resection regardless of the level of experience of the radiologist and surgeon. The overlapping signal did not seem to affect the resected volume as with this technique SPIO is injected dorsally to the tumour and enhances the magnetic signal from the seed without creating too much "noise" around it. Moreover, in the centre with the highest level of experience with the technique, seed localization led to the lowest reported resection ratio, without

increasing the re-excision rates. This indicates that while the technique is safe for even inexperienced surgeons, it offers a possibility of even more precise surgery with experience.

The study also found that the magnetic technique resulted in shorter operative times and increased satisfaction among healthcare practitioners. The pragmatic design ensured external validity, and that the intervention could be implemented with ease and flexibility and could be adapted to different institutional routines.

In conclusion, a totally magnetic technique is an effective and safe option for breast tumour localization and SLNB, with the advantages of shorter operative time, more successful localization, and more flexible planning.

8.3 Paper III

As discussed previously, SPIO is comparable to RI ± BD regarding sentinel node detection in patients with early breast cancer. Furthermore, it can be administered within a wider timeframe, a quality that facilitates logistics and motivates further exploration of the use of SPIO in various clinical settings. This was first investigated in the setting of patients with DCIS, where performance of SLNB without confirmation of invasive disease is often unnecessary. The ability of SPIO to remain in the sentinel nodes for extended periods, allowed for preoperative axillary mapping followed by the excision of DCIS and subsequent axillary surgery only if invasive cancer was confirmed on the specimen. This was examined in the SentiNot study, which recently published an interim analysis with promising results and demonstrated that SPIO injection can be safely performed up to 47 days before axillary surgery[85]. Despite this evolution and the current evidence regarding the efficacy and the possibilities of SPIO, it has not been adequately investigated in longer periods or the setting of primary systemic treatment (PST).

De-escalation of axillary management after PST from axillary clearance to SLNB or TAD has raised concerns regarding the risk of high false negative rates due to fibrotic alterations in the lymphatic system. A double tracer for minimizing false negatives is recommended alongside clipping of biopsy-proven metastatic nodes for safe evaluation of response to PST. RI ± BD is the currently recommended tracer in patients undergoing PST. The third project focused on exploring a wider timeframe for SPIO administration and the effect that this would have on sentinel node detection and SPIOs concordance with isotope in a patient group where axillary staging is challenging.

The study concluded that the injection of SPIO before primary systemic therapy is feasible and does not affect concordance with radioisotope.

Furthermore, SPIO performed comparably to RI but detected more sentinel nodes and had a higher detection rate of metastatic SLNs. These findings suggest the potential utility of SPIO in enhancing axillary mapping in patients undergoing primary systemic therapy for breast cancer.

8.4 Paper IV

Preoperative breast lesion localization has been paramount to successful BCS. The use of guidewire for localization was practically the only method available for many decades. However, the guidewire poses several logistical challenges, leading to the development of wireless technologies which aim to decouple tumour localization from surgery and facilitate preoperative planning. These technologies rely on the insertion of a seed with specific properties (radioactivity, magnetism, radar reflection etc) which will then be detected intraoperatively with a probe. Numerous studies have demonstrated equal outcomes in terms of successful localization, specimen excision with negative margins and ease-of -use. However, as with any new method that is introduced, the financial consequences are always considered. Given that healthcare resources are limited, in the absence of a dramatically significant difference in clinical outcomes, any new technology needs to be evaluated for cost-effectiveness before any decision is made about adopting it.

The magnetic marker has shown equal performance to the guidewire in all clinical parameters while facilitating logistics and streamlining the process of theater planning. The high cost of the device, however, especially when compared to the guidewire has raised concerns regarding wide implementation. The present study demonstrated that despite the higher cost of the device, the magnetic seed resulted in overall reduced costs.

When considering the adoption of a new method or procedure, all direct and indirect costs should be considered as these seemingly small variables can shift the balance in a healthcare system. This analysis did not include the healthcare personnel preference in a “willingness-to-pay” fashion, as it focused on more objective outcomes, but this aspect is also a factor that needs to be factored in during policy decision making. Investing in methods and technologies that facilitate and streamline procedures will increase productivity and reduce overall costs in the long run.

Furthermore, the magnetic marker is shown in previous studies to reduce anxiety in patients[81]. This is understandable as the guidewire needs to be inserted on the day of the surgery or at earliest the day before. Inserting the wire the same day as the surgery will generate stress to the patient, especially if the localization is cumbersome and might result in surgery cancellation or

compromised outcomes. On the other hand, inserting the guidewire the day before will cause discomfort and movement restriction.

9 Future Perspectives

The first project, which was a meta-analysis of available studies that investigated SPIO as a tracer for sentinel node detection in breast cancer, identified several knowledge gaps and areas for future research. One of the main areas for future research is the investigation of the optimal dose and site of injection for SPIO to minimize skin staining and MRI artifacts while maintaining high detection rates. Another quality that separates SPIO from other tracers is the long timeframe within which it can be administered without any compromise in detection rate or nodal yield. This advantage of SPIO has only recently been explored in the setting of DCIS, but there are many areas where it could be utilized to facilitate logistics, decrease costs, and enhance patient safety and experience.

Recent studies like the SOUND and INSEMA RCTs have demonstrated the feasibility of SLNB omission in patients with small tumours and clinically negative axilla [97,98]. Though local recurrence rates were very low, and the OS was not affected by the omission of axillary surgery, postoperative staging does not always agree with clinical stage and lymph node status might be important for decisions regarding adjuvant treatment. In such cases, SPIO could be preoperatively injected and delayed SLNB could be performed without compromising detection of SLNs.

Given the high heterogeneity found in many of the studies and the variations in reporting especially for subjective outcomes, such as skin discoloration or MRI artifacts, the study highlighted the need for well-designed prospective trials to improve the level of evidence for the magnetic technique and to address existing evidence heterogeneity. The study also recommended the use of standardized reporting of outcomes to facilitate comparison and meta-analysis of future studies.

The second project compared a totally magnetic technique for breast tumour localization and SLNB to the traditional guidewire localization and demonstrated similar re-excision rates and resection volumes but shorter operative time and fewer failed localizations with the magnetic marker. Furthermore, the healthcare disciplines involved expressed a more positive experience with the magnetic marker than with the guidewire.

The future perspectives of the study may include further investigations and developments in the field of breast cancer localization and sentinel lymph node detection using magnetic seeds and SPIO. An ongoing analysis of the data obtained in the trial is a cost-effectiveness analysis to assess the economic implications of implementing the magnetic seed technique compared to the guidewire method, including considerations of healthcare resource utilization and patient outcomes. Furthermore, an analysis of patient-centered outcomes is undertaken and will be published separately. In this, patient-reported outcomes and experiences are investigated to understand the impact of the magnetic technique on patient satisfaction, quality of life, and psychological well-being compared to traditional localization methods.

Other potential future perspectives could involve longer-term follow-up to assess the oncological outcomes, such as LLR, distant metastasis, and OS, and evaluate the impact of the magnetic technique on long-term clinical outcomes. Another perspective for consideration is the conduct of comparative studies with larger sample sizes and in diverse clinical settings to further validate the findings and assess the generalizability of the results across different patient populations and healthcare systems. Lastly, future research should be directed into exploring advancements in magnetic localization technologies and techniques, including the development of new paramagnetic seeds, imaging modalities, and surgical tools to enhance the precision and efficiency of breast cancer localization and SLNB.

The third project suggests that the concept of delayed sentinel lymph node detection through a wide timeframe between SPIO administration and sentinel lymph node detection, as introduced in the SentiNot study, can be applicable in the setting of PST. This could potentially facilitate logistics and enhance axillary mapping. However, the study also acknowledges certain limitations and suggests that the implementation of a prolonged timeframe needs to be tested in a dedicated trial. Additionally, the study notes that SPIO administration before PST precludes the possibility of MRI monitoring, which is currently a popular strategy. Therefore, future research may focus on addressing these limitations and further exploring the potential applications of SPIO in the context of breast cancer treatment.

The fourth project demonstrates that the adoption of a magnetic technique in breast cancer surgery has the potential to be more cost-effective than a guidewire. The magnetic marker and SPIO are both detected by the same probe, minimizing the use of appliances in the OR. The only other technology that offers the same possibility is the use of radioactive seeds and RI. However, this alternative is restricted by the need of nuclear oversight which limits accessibility, strict safety protocols, and recurrent shortages. Furthermore, RI

has a short half-life which limits administration to the day of surgery or the day before. This technique lacks therefore the unique flexibility that magnetic technology provides. The next step would be to delineate the optimal pathway of use, that will increase effectiveness and reduce costs.

Further analyses that capture and assign value to indirect and less objective costs such as healthcare personnel preference or patient comfort should be conducted. The study was carefully conducted in a way that provides ground for analyses tailored to different clinical settings and financial environments.

10 Conclusions

This thesis explores the clinical and economic implications of magnetic techniques in breast cancer surgery, focusing on the use of Magseed ® for breast lesion localization and SPIO for SLNB. Across four comprehensive studies, the findings demonstrate that these magnetic techniques offer a safe, effective, and feasible alternative to conventional methods while providing additional logistical and economic benefits.

Collectively, the findings of this thesis underscore the clinical and economic viability of magnetic techniques in breast cancer surgery. They offer a safe and effective alternative to conventional approaches while addressing logistical challenges and enhancing patient care. Future research should focus on optimizing SPIO dosing and exploring the numerous possibilities that this technique offers in tailoring breast surgery. By continuing to innovate and evaluate, magnetic technologies hold the potential to improve surgical precision and patient outcomes while ensuring sustainable healthcare practices.

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12 Appendices

12.1 Appendix 1: Supplementary material for paper I

Table 7: MINORS criteria for comparative studies

Study ID	Aim	Inclusion	Prospective	Endpoints	Endpoint assessment	Follow-up	Loss <5%	Sample size	Control group	Contemporary group	Group Equivalence	Statistical Analyses	Total
Douek et al, 2014 (3)	2	1	2	2	2	2	2	2	2	2	2	2	**23**
Thill et al, 2014 (4)	2	1	2	2	2	2	2	1	2	2	2	2	**22**
Rubio et al, 2014 (35)	2	2	2	2	2	1	2	0	2	2	2	1	**20**
Rubio et al, 2015 (5)	2	2	2	2	2	2	2	1	2	2	2	2	**23**
Pineiro et al, 2015 (6)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Ghilli et al, 2015 (7)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Coufal et al, 2015 (8)	2	2	2	2	2	1	2	0	2	2	2	1	**20**
Ahmed et al, 2015 (36)	2	1	2	2	2	2	2	0	2	2	2	2	**21**
Houpeau et al, 2016 (9)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Karakatsanis et al, 2016 (10)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Karakatsanis et al, 2017 (11)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Karakatsanis et al, 2018 (20)	2	2	2	2	2	2	2	0	2	2	2	2	**22**
Karakatsanis et al, 2019 (19)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Alvarado et al, 2019 (16)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Taruno et al, 2019 (37)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Makita et al, 2020 (48)	2	2	2	2	2	2	2	0	2	2	2	2	**22**
Hamzah et al, 2020 (38)	2	2	2	2	2	2	2	0	2	2	2	0	**20**
Rubio et al, 2020 (17)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Hersi et al, 2021 (18)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Giménez-Climent et al, 2021 (39)	2	2	2	2	2	2	2	0	2	2	2	2	**22**

Table 8: ROBINS-I tool

Study ID	Confounding bias	Selection bias	Classification of interventions bias	Deviation from interventions bias	Missing data bias	Measurement of outcomes bias	Report bias	Overall
Douek et al, 2014 (3)	Low	Low	Low	Low	Moderate	Low	Low	**Low**
Thill et al, 2014 (4)	Low	Low	Low	Low	Moderate	Low	Low	**Low**
Rubio et al, 2014 (35)	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	**Moderate**
Rubio et al, 2015 (5)	Low	Low	Low	Low	Low	Low	Low	**Low**
Pineiro et al, 2015 (6)	Low	Low	Low	Low	Moderate	Low	Low	**Low**
Ghilli et al, 2015 (7)	Low	Low	Low	Low	Low	Low	Low	**Low**
Coufal et al, 2015 (8)	Moderate	Moderate	Serious	Moderate	Critical	Serious	Moderate	**Moderate**
Ahmed et al, 2015 (36)	Moderate	Low	Low	Low	Low	Low	Low	**Low**
Houpeau et al, 2016 (9)	Low	Low	Low	Low	Low	Low	Low	**Low**
Karakatsanis et al, 2016 (10)	Low	Low	Low	Low	Low	Moderate	Low	**Low**
Karakatsanis et al, 2017 (11)	Low	Low	Low	Low	Low	Low	Moderate	**Low**
Karakatsanis et al, 2018 (20)	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Moderate	**Moderate**
Karakatsanis et al, 2019 (19)	Low	Moderate	Low	Low	Moderate	Low	Low	**Low**
Alvarado et al, 2019 (16)	Low	Low	Low	Low	Low	Low	Low	**Low**
Taruno et al, 2019 (37)	Low	Low	Low	Low	Low	Moderate	Low	**Low**
Makita et al, 2020 (48)	Low	Low	Moderate	Moderate	Moderate	Moderate	Low	**Moderate**
Hamzah et al, 2020 (38)	Moderate	Low	Moderate	Moderate	Moderate	Serious	Low	**Moderate**
Rubio et al, 2020 (17)	Low	Moderate	Low	Low	Low	Low	Low	**Low**
Hersi et al, 2021 (18)	Low	Low	Low	Low	Low	Low	Low	**Low**
Giménez-Climent et al, 2021 (39)	Moderate	Low	Low	Low	Low	Low	Low	**Low**

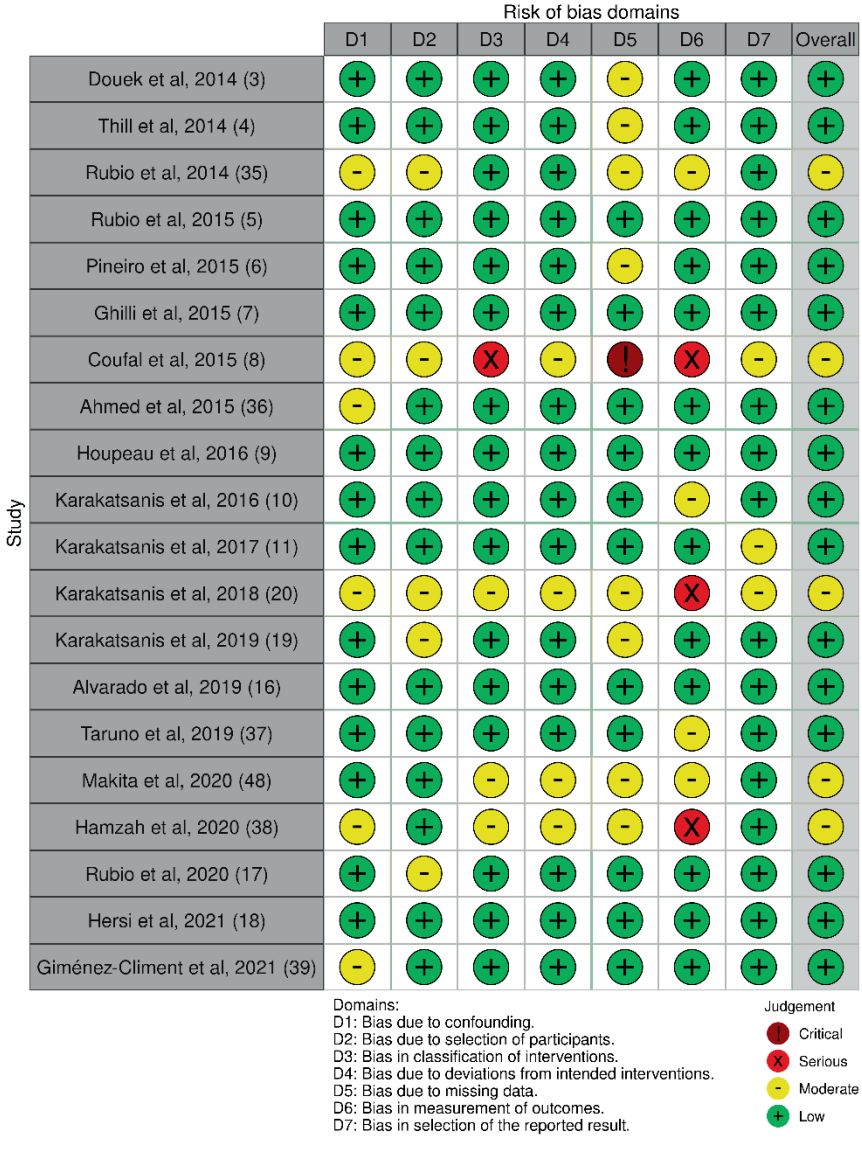

Fig 8. Risk-of-bias plot for the ROBINS-I tool of comparative studies

Table 9: MINORS criteria for single-arm studies

Study ID	Aim	Inclusion	Prospective	Endpoints	Endpoint assessment	Follow-up	Loss <5%	Sample size	Total
Hersi et al, 2019 (23)	2	2	2	2	2	2	2	0	**14**
Lorek et al, 2019 (42)	2	2	1	1	2	2	1	0	**11**
Man et al, 2019 (43)	2	2	1	2	2	2	2	0	**13**
Vural et al, 2019 (44)	2	2	2	2	2	2	2	0	**14**
Bazire et al 2019 (45)	2	1	0	2	2	1	1	0	**9**
Pohlodek et al, 2019 (46)	2	2	1	2	2	2	2	0	**13**
Kurylcio et al, 2021 (47)	2	2	1	1	1	1	2	0	**10**

Table 10: Risk-of-Bias (RoB) assessment for single-arm studies

Study ID	Sampling bias	Selection bias	Deviation from interventions bias	Missing data bias	Measurement of outcomes bias	Report bias	Overall
Hersi et al, 2019 (23)	High	Low	Low	Some concerns	Some concerns	Some concerns	**Moderate**
Lorek et al, 2019 (42)	Some concerns	Low	Some concerns	High	High	No information	**High**
Man et al, 2019 (43)	Some concerns	Some concerns	Some concerns	Some concerns	High	Some concerns	**Moderate**
Vural et al, 2019 (44)	Some concerns	Some concerns	Low	No information	Some concerns	Low	**Moderate**
Bazire et al 2019 (45)	High	Low	No information	High	High	Low	**High**
Pohlodek et al, 2019 (46)	Some concerns	Some concerns	No information	Low	Some concerns	Some concerns	**Moderate**
Kurylcio et al, 2021 (47)	Some concerns	Some concerns	No information	No information	No information	High	**High**

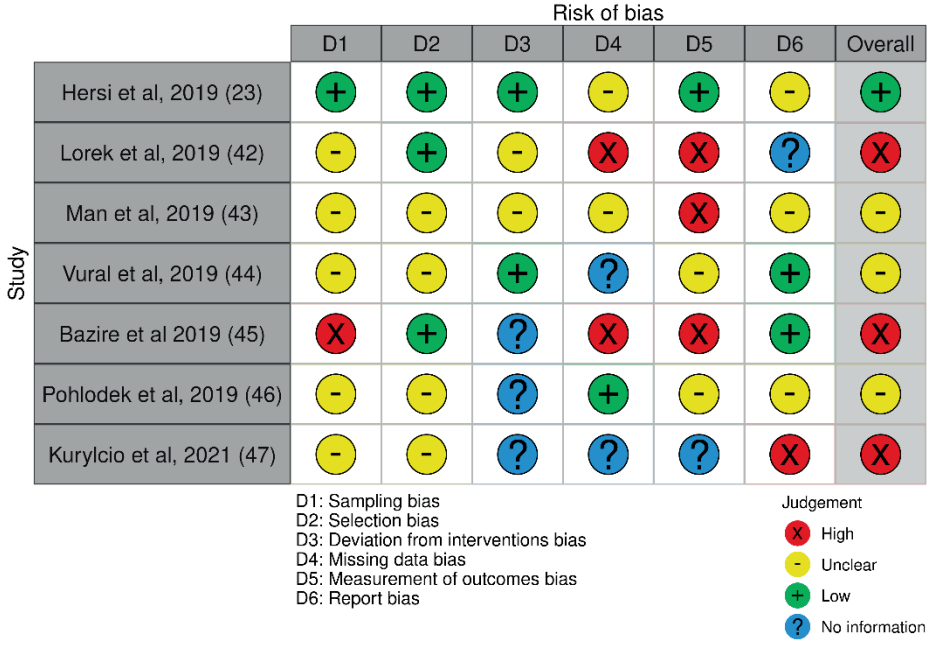

Fig 9: Risk-of-bias plot for single-arm studies

Table 11: Newcastle-Ottawa (NOS) criteria for studies on MRI artifacts

Study ID	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability	Standardised Assessment of outcome with independency	Adequacy of follow-up	Lost to follow-up (less than 10% and reported)	
Krischner et al, 2018 (12)	--	--	*	*	--	--	*	--	**3**
Aribal et al, 2021 (13)	--	--	*	*	--	--	*	--	**3**
Chapman et al, 2021 (14)	--	--	*	*	--	--	*	--	**3**
Christenhuz et al, 2022 (15)	--	--	*	*	*	*	*	--	**5**

Table 12: QUADAS-2 tool for studies on MRI artifacts

Study ID	Patient selection	Index test	Reference Standard	Flow and timing	Overall
Krischner et al, 2018 (12)	High	High	No information	No information	High
Aribal et al, 2021 (13)	High	High	High	High	High
Chapman et al, 2021 (14)	High	High	No information	No information	High
Christenhuz et al, 2022 (15)	High	High	High	High	High

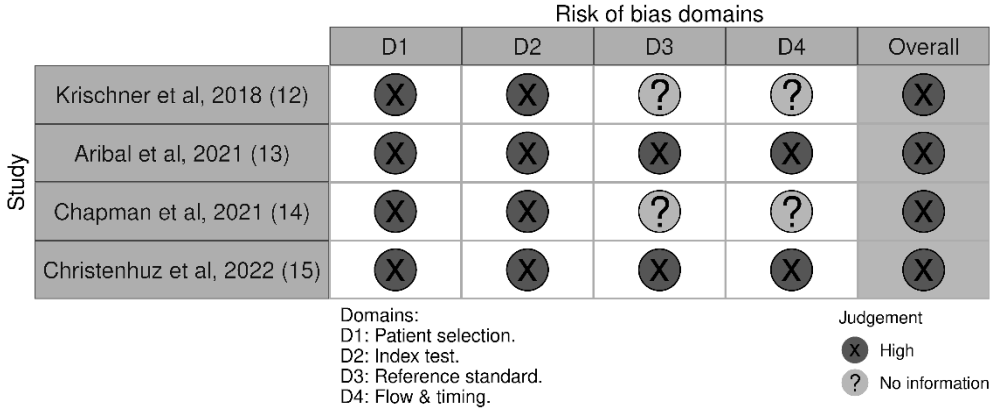

Fig 10: Risk-of-bias plot for the QUADAS-2 tool of studies for MRI artifacts

Do Superparamagnetic Iron Oxide nanoparitcles (SPIO) perform comparably to Isotope with or without blue dye (RI+/-BD) for standard SLN detection in patients with breast cancer?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Superparamagnetic Iron Oxide nanoparticles (SPIO)	Isotope with or without blue dye (RI+/-BD)	Relative (95% CI)	Absolute (95% CI)		
Detection Rate												
20	observational studies	not serious	not serious	not serious	not serious	none	2370/2430 (97.5%)	2320/2404 (96.5%)	**RR 1.01** (0.99 to 1.02)	**10 more per 1.000** (from 10 fewer to 19 more)	⊕⊕⊕⊕ High	IMPORTANT
Concordance between SPIO and RI+/-BD												
19	observational studies	not serious	not serious	not serious	not serious	none	2123/2144 (99.0%)	2123/2186 (97.1%)	**Rate difference -0.003** (-0.009 to 0.015)	**-- per 1.000** (from -- to --)	⊕⊕⊕⊕ High	IMPORTANT
Number of SLNs												
19	observational studies	serious[a]	serious[a]	not serious	serious[a]	strong association	4201/4536 (92.6%)*	3926/4592 (85.5%)*	**RR 1.10** (1.06 to 1.14)	**68 more per 1.000** (from 43 more to 94 more)	⊕⊕◯◯ Low	NOT IMPORTANT
							94.1% (pooled weighted rate)	83.5% (pooled weighted rate)		**67 more per 1.000** (from 42 more to 92 more)		

Fig 11: GRADE recommendations

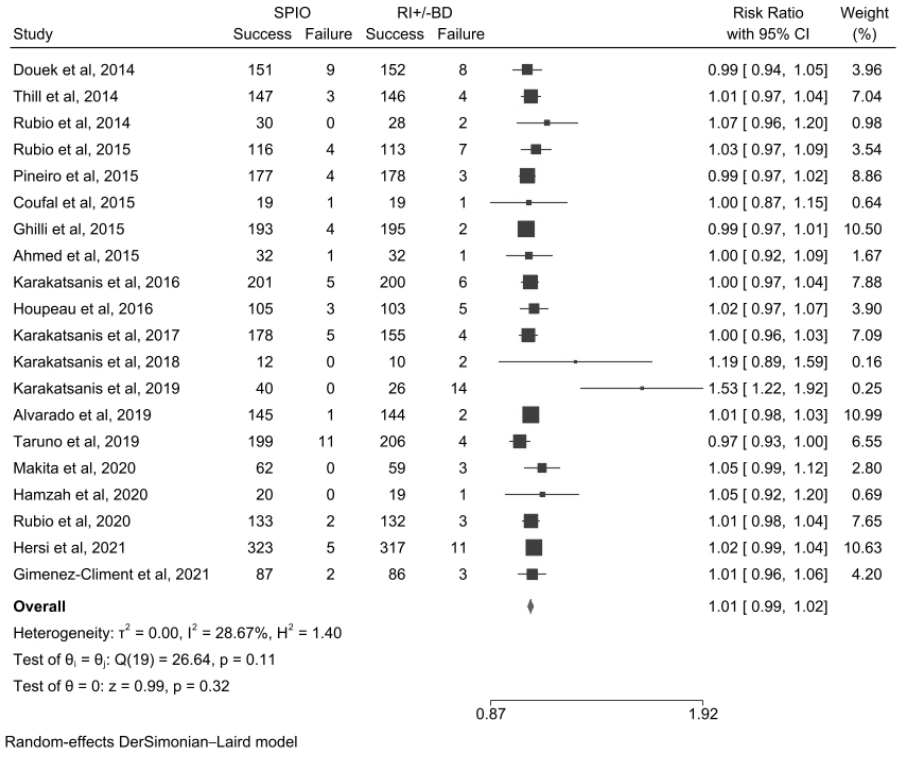

Fig 12: Forest plot for detection rate (per patient/procedure)

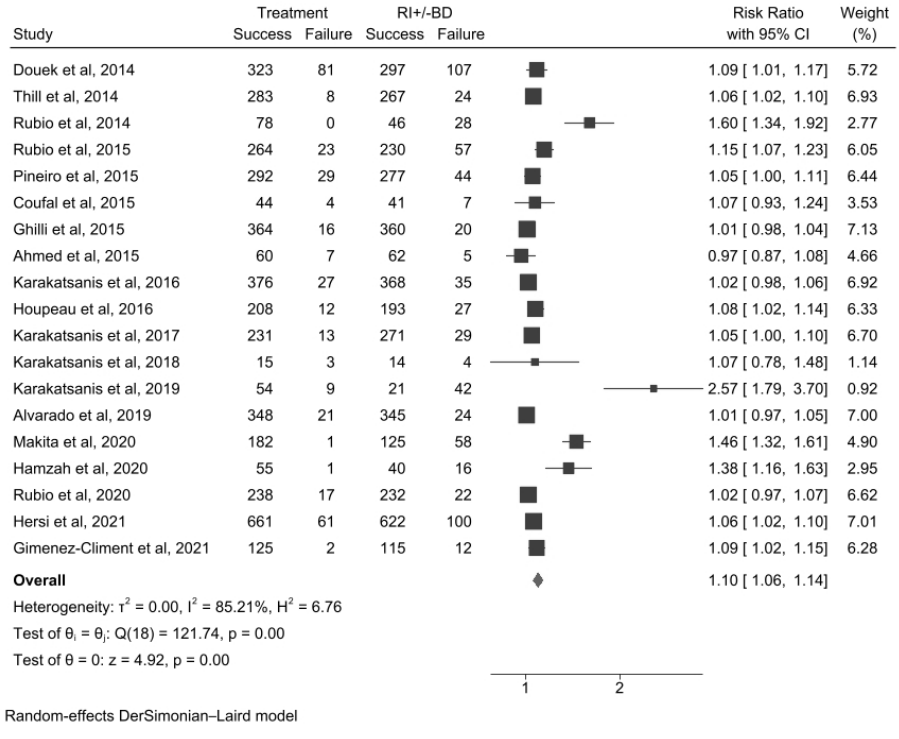

Fig 13: Forest plot for nodal detection rate

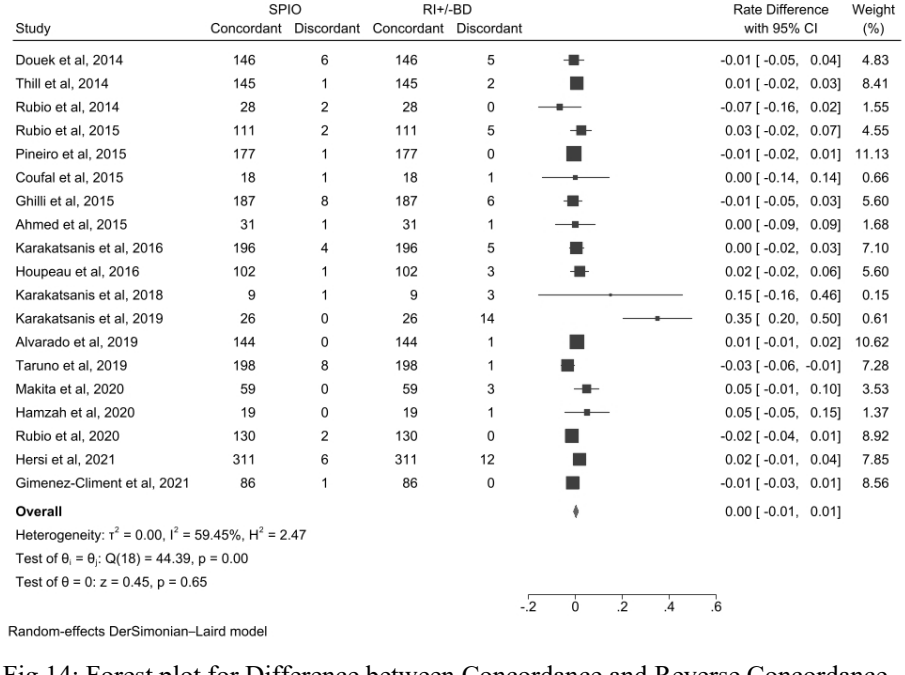

Fig 14: Forest plot for Difference between Concordance and Reverse Concordance

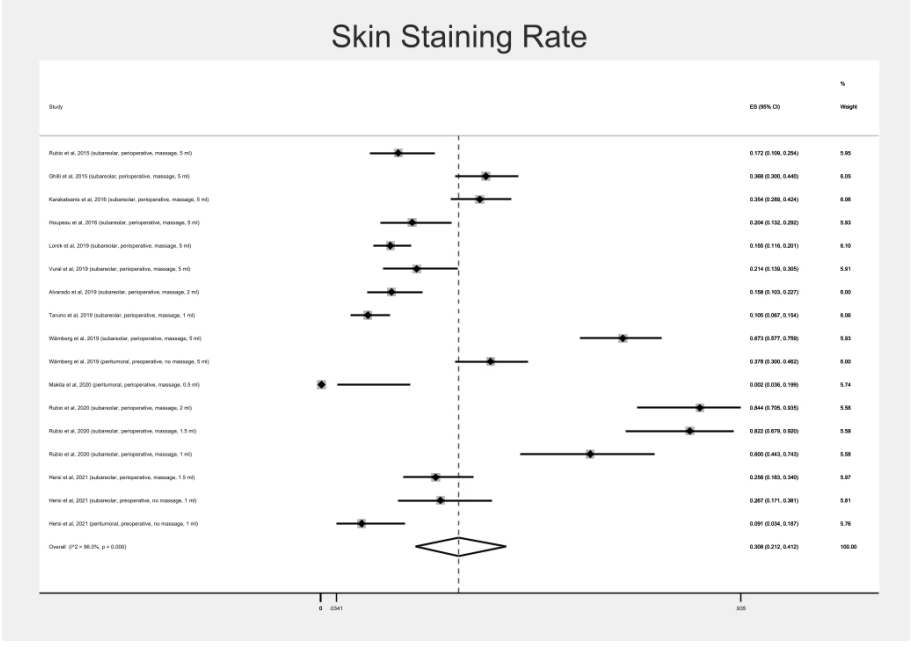

Figure 15: Forest plot for SPIO-induced skin staining

12.2 Appendix 2: Supplementary material for paper II

Table 13: Resection ratio per site and type of surgery

	Overall	Guidewire	Magnetic marker	p-value
Entire trial	1.96 (1.14, 3.46)	1.96 (1.22, 3.48)	1.97 (1.11, 3.46)	.96
Uppsala	1.45 (.78, 2.13)	1.59 (.77, 2.15)	1.26 (.78, 2.07)	.08
WLE (n=170)	1.48 (.85, 2.13)	1.60 (.98, 2.17)	1.29 (.76, 2.05)	
OPBCS Level I (n=47)	1.26 (.68, 1.73)	1.46 (.69, 1.81)	1.15 (.69, 1.60)	
OPBCS Level II (n=18)	1.87 (.88, 7.40)	1.38 (.49, 41.79)	2.13 (1.08, 13.21)	
Västerås	3.33 (2.13, 5.39)	3.21 (1.60, 4.79)	3.46 (2.50, 5.75)	.92
WLE (n=105)	3.42 (2.19, 5.21)	3.33 (1.82, 4.79)	3.44 (2.47, 5.78)	
OPBCS Level I	-	-	-	
OPBCS Level II (n=2)	4.21 (2.85, 5.57)	-	4.21 (2.85, 5.57)	
Gothenburg	2.87 (2.00, 4.38)	2.88 (2.05, 4.38)	2.77 (1.86, 4.63)	.91
WLE (n=71)	2.78 (2.00, 4.27)	2.88 (2.22, 4.20)	2.57 (1.73, 4.27)	
OPBCS Level I (n=3)	3.18 (3.00, 6.62)	-	3.18 (3.00, 6.62)	
OPBCS Level II (n=1)	5.27 (5.27, 5.27)	-	5.27 (5.27, 5.27)	

Legend: Resection Ratios per received marker (per protocol analysis) in subgroups by site and type of surgery. Resection ratio is summarized as median (interquartile range, iqr). OPBCS: oncoplastic breast conserving surgery, WLE: wide local excision. p-value: independent medians test.

Table 14: Type of complication per received localization device. Analysis per protocol. P-value: Fisher's exact test

(n.%)	Per protocol intervention		p-value
	Guidewire	Magnetic marker	
None	193 (92.8)	194 (90.2)	.53
Symptomatic breast seroma	3 (1.4)	1 (0.5)	
Breast hematoma	2 (1.0)	4 (1.9)	
Symptomatic axillary seroma	0 (0.0)	1 (0.5)	
Axillary hematoma	2 (1.0)	1 (0.5)	
Breast infection	5 (2.4)	3 (1.4)	
Axillary infection	1 (0.5)	2 (0.9)	
Delayed wound healing	0 (0.0)	3 (1.4)	
Postoperative bleeding in the breast	1 (0.5)	4 (1.9)	
Pain at SPIO injection site	1 (0.5)	1 (0.5)	
Superficial venous thrombosis	0 (0.0)	1 (0.5)	

Table 15: Health care practitioner's experience with each marker

	Paramagnetic seed	Guidewire	p-value
Ease of logistics and planning (theatre coordinators)	10 (10,10)	6 (4,8)	<.001
Ease of localisation (radiologists)	7 (7,9)	7 (7,7)	<.001
Ease of intraoperative detection (surgeons)	9 (8,10)	7 (7,8)	<.001

Legend: Responses to Likert items with range 0-10, higher score denotes higher satisfaction. Likert scores are summarized as median (iqr). p-value: independent sample medians test.

12.3 Appendix 3: Supplementary material for paper IV

Table 16: Unadjusted analysis for the main trial and the sensitivity analyses

A: Type of device					
	Guide-wire	Magnetic Marker		Difference (95%) CI	p-value
1. In-trial results					
Mean (SD)	3337 (1350)	3274 (1105)		-63 (-302, 174)	0.599*
Mean (95 % CI)	3337 (3151, 3524)	3274 (3124, 3160)			
Median (IQR)	3034 (2663, 3696)	3031 (2518, 3696)			0.886**
Bootstrapped Mean (95% CI)	3337 (3157, 3527)	3274 (3127, 3423)		-63 (-303, 173)	0.596*
Bootstrapped Median (95% CI)	3043 (2857, 3175)	3031 (2909, 3227)			
2. Sensitivity Analysis 1					
Mean (SD)	3620 (1350)	3556 (1105)		-63 (-302, 175)	0.601*
Mean (95 % CI)	3620 (3433, 3806)	3556 (3406, 3706)			
Median (IQR)	3316 (2663, 4340)	3313 (2800, 3978)			0.886**

Bootstrapped Mean (95% CI)	3620 (3439, 3810)	3556 (3410, 3705)		-63 (-303, 173)	0.596*
Bootstrapped Median (95% CI)	3316 (3139, 3457)	3313 (3191, 3509)			
3. Sensitivity Analysis 2					
Mean (SD)	3618 (1350)	3287 (1119)		-330 (-570, -90)	0.007*
Mean (95 % CI)	3618 (3432, 3805)	3287 (3138, 3439)			
Median (IQR)	3297 (2663, 4340)	3022 (2528, 3694)			0.056**
Bootstrapped Mean (95% CI)	3618 (3438, 3810)	3254 (3140, 3296)		-330 (-571, -95)	0.011*
Bootstrapped Median (95% CI)	3297 (3101, 3457)	3022 (2903, 3296)			
B: Type of surgery					
	WLE	OPBCS	TM	Difference (95%) CI	
1. In-trial results					
Mean (SD)	3126 (1087)	3730 (1284)	5232 (1475)	604 (144, 1064) // 2106 (1280, 2932)	<0.001*
Mean (95 % CI)	3126 (3010, 3241)	3722 (3365, 4078)	5232 (4560, 5903)		
Median (IQR)	2934 (2359, 3583)	3266 (2751, 4371)	4848 (4168, 5710)		<0.001**

Bootstrapped Mean (95% CI)	3126 (3020, 3240)	3730 (3383, 4104)	5232 (4639, 5863)	604 (251, 1006) // 2106 (1481, 2817)	<0.001*
Bootstrapped Median (95% CI)	2934 (2828, 3031)	3266 (3053, 3942)	4848 (4269, 5546)		
2. Sensitivity Analysis 1					
Mean (SD)	3408 (1087)	4013 (1284)	5515 (1475)	604 (144, 1065) // 2106 (1280, 2933)	<0.001*
Mean (95 % CI)	3408 (3293, 3524)	4012 (3648, 4378)	5515 (4843, 6187)		
Median (IQR)	3216 (2641, 3865)	3548 (3033, 4653)	5131 (4455, 5993)		<0.001**
Bootstrapped Mean (95% CI)	3408 (3302, 3523)	4012 (3666, 4387)	5515 (4922, 6146)	604 (251, 1006) // 2106 (1481, 2818)	<0.001*
Bootstrapped Median (95% CI)	3216 (3112, 3313)	3548 (3335, 4225)	5131 (4554, 5828)		
3. Sensitivity Analysis 2					
Mean (SD)	3276 (1105)	3857 (1326)	5349 (1521)	580 (106, 1055) // 2073 (1221, 2925)	<0.001*
Mean (95 % CI)	3276 (3158, 3393)	3857 (3480, 4234)	5349 (-4657, -5268)		
Median (IQR)	3022 (-2503, -3732)	(-2942, -4365)	(-4839, -5993)		<0.001**
Bootstrapped Mean (95% CI)	3276 (3169, -3390)	3857 (-3427, -4156)	5349 (-4732, -5982)	2073 (1416, 2799)	<0.001*

Bootstrapped Median (95% CI)	3022 (-2902, -3161)	3435 (-3180, -4009)	4839 (-4365, -5828)		
C: Single localisation session					
	No	Yes		Difference (95% CI)	
1. In-trial results					
Mean (SD)	3498 (1230)	3015 (1180)		481 (243, 720)	<0.001*
Mean (95 % CI)	3498 (3345, 3652)	3015 (2833, 3196)			
Median (IQR)	3237 (2683, 3976)	2737 (2225, 3543)			<0.001**
Bootstrapped Mean (95% CI)	3498 (3233, 3527)	3015 (2857, 3186)		481 (245, 705)	<0.001*
Bootstrapped Median (95% CI)	3237 (3058, 3453)	2737 (2477, 2869)			
2. Sensitivity Analysis 1					
Mean (SD)	3781 (1230)	3297 (1180)		481 (243, 720)	<0.001*
Mean (95 % CI)	3781 (3636, 3934)	3297 (3116, 3479)			
Median (IQR)	3520 (2952, 4258)	3019 (2507, 3825)			<0.001**
Bootstrapped Mean (95% CI)	3781 (3626, 3931)	3297 (3130, 3563)		481 (245, 705)	<0.001*

Bootstrapped Median (95% CI)	3520 (3340, 3735)	3019 (2765, 3152)			
3. Sensitivity Analysis 2					
Mean (SD)	3585 (1277)	3250 (1181)		332 (88, 576)	0.008*
Mean (95 % CI)	3585 (3425, 3744)	3250 (3068, 3431)			
Median (IQR)	3337 (2706, 4049)	2904 (2428, 3694)			0.006**
Bootstrapped Mean (95% CI)	3585 (3427, 3739)	3250 (3084, 3422)		332 (94, 561)	0.007*
Bootstrapped Median (95% CI)	3337 (3101, 3496)	2904 (2744, 3139)			

Table 17: Unadjusted and adjusted sensitivity analysis.

	Unadjusted analysis			Adjusted analysis			
	Mean (95% CI)	Marginal Difference (95% CI)	p-value	Coefficient (95% CI)	Marginal Means (95% CI)	Difference (95% CI)	p-value
Sensitivity analysis 1							
Localization device							
Guidewire	3620 (3433, 3806)	Ref. [0]		Ref. [0]	3798 (3618, 3978)	Ref. [0]	
Seed	3556 (3406, 3706)	-63 (-302, 175)	0.601	-0.110 (-0.178, -0.041)	3403 (3253, 3554)	-394 (-365, 424)	0.002
Type of Breast Surgery							
WLE	3408 (3293, 3524)	Ref. [0]		Ref. [0]	3415 (3307, 3533)	Ref. [0]	
OPBCS	4012 (3648, 4378)	604 (144,1065)		0.144 (0.051, 0.236)	3948 (3607, 4290)	528 (301, 756)	0.002
TM	5515 (4843, 6187)	2106 (1280,2933)	<0.001	0.461 (0.322, 0.599)	5421 (4695, 6147)	2001 (1388, 2614)	<0.001
Single localization session							
Yes	3297 (3116, 3479)	Ref. [0]		Ref. [0]	3269 (3100, 3439)	Ref. [0]	
No	3781 (3636, 3934)	481 (243, 720)	<0.001	0.151 (0.081, 0.222)	3803 (3645, 3960)	533 (521, 546)	<0.001

Sensitivity analysis 2							
Localiza-tion device							
Guidewire	3618 (3432, 3805)	Ref. [0]		Ref. [0]	3791 (3611, 3985)	Ref. [0]	
Seed	3287 (3138, 3439)	-330 (-570, -90)	0.007	-0.118 (-0.260, -0.117)	3145 (3000, 3289)	-653 (-696, -611)	<0.001
Type of Breast Surgery							
WLE	3276 (3158, 3393)	Ref. [0]		Ref. [0]	3415 (3307, 3533)	Ref. [0]	
OPBCS	3857 (3480, 4234)	580 (106, 1055)		0.146 (0.049, 0.242)	3948 (3607, 4290)	528 (301, 756)	0.003
TM	5349 (-4657, -5268)	2073 (1221, 2925)	<0.001	0.488 (0.344, 0.632)	5421 (4695, 6147)	2001 (1388, 2614)	<0.001
Single localization session							
Yes	3250 (3068, 3431)	Ref. [0]		Ref. [0]	3156 (2988, 3325)	Ref. [0]	
No	3585 (3425, 3744)	332 (88, 576)	<0.001	0.151 (0.081, 0.222)	3659 (3498, 3820)	503 (495, 510)	<0.001

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Systematic Review

Evolution and refinement of magnetically guided sentinel lymph node detection in breast cancer: meta-analysis

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Abstract

Background: Superparamagnetic iron oxide nanoparticles (SPIO) have been used as a tracer for sentinel lymph node (SLN) localization in breast cancer, demonstrating comparable performance to the combination of radioisotope (RI) and blue dye (BD).

Methods: A systematic literature search and meta-analysis with subgroup and meta-regression analysis were undertaken to update the available evidence, assess technique evolution, and define knowledge gaps. Recommendations were made using the GRADE approach.

Results: In 20 comparative studies, the detection rate was 97.5 per cent for SPIO and 96.5 per cent for RI ± BD (risk ratio 1.006, 95 per cent c.i. 0.992 to 1.019; $P = 0.376$, high-certainty evidence). Neoadjuvant therapy, injection site, injection volume or nodal metastasis burden did not affect the detection rate, but injection over 24 h before surgery increased the detection rate on meta-regression. Concordance was 99.0 per cent and reverse concordance 97.1 per cent (rate difference 0.003, 95 per cent c.i. −0.009 to 0.015; $P = 0.656$, high-certainty evidence). Use of SPIO led to retrieval of slightly more SLNs (pooled mean 1.96 *versus* 1.89) with a higher nodal detection rate (94.1 *versus* 83.5 per cent; RR 1.098, 1.058 to 1.140; $P < 0.001$; low-certainty evidence). In meta-regression, injection over 24 h before surgery increased the SPIO nodal yield over that of RI ± BD. The skin-staining rate was 30.8 per cent (very low-certainty evidence), and possibly prevented with use of smaller doses and peritumoral injection.

Conclusion: The performance of SPIO is comparable to that of RI ± BD. Preoperative injection increases the detection rate and nodal yield, without affecting concordance. Whether skin staining and MRI artefacts are reduced by lower dose and peritumoral injection needs to be investigated.

Introduction

Assessment of sentinel lymph node (SLN) status remains a significant component of breast cancer management, being routine practice in the majority of patients with a clinically negative axilla[1]. Radioisotopes (RIs) and blue dye (BD) have been the preferred tracers for SLN localization during the past two decades. This procedure, however, poses challenges not only associated with the regulations for manipulation and disposal of the radioactive materials, but also in terms of administration logistics. Conventional tracers are subject to limitations related to patient management, especially owing to the restricted time frame from injection to surgery[2]. New methods have consequently been developed to fill this gap.

Superparamagnetic iron oxide nanoparticles (SPIO) have been tested as SLN localization tracer in multiple studies and meta-analyses. Many trials[3–10] have shown high concordance with conventional localization techniques and non-inferiority to RI ± BD regarding the detection rate. Several studies[7,10,11] have reported skin staining, mainly after breast-conserving surgery. In addition, concerns have been raised regarding potential artefacts in postoperative MRI[12–15]. The technique has evolved in recent years, showing promising results with smaller doses of SPIO, injected not only in the subareolar region[16,17] but also close to the tumour[18]. The efficacy of injection in different time frames has also been tested, ranging from intraoperative administration to up to several weeks before surgery[19–21]. At the

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same time, the introduction of paramagnetic markers for the localization of impalpable lesions[22,23] offers the option of an integrated platform for breast and axillary procedures[24]. In this setting, the only consideration is that the use of metallic instruments interferes with the magnetic signal, and so plastic or titanium instruments need to be used instead.

The aim of this systematic review and meta-analysis was to examine the available data on SPIO in breast cancer surgery, the performance of SPIO as a tracer in SLN biopsy (SLNB), and to investigate factors associated with technique refinement. Finally, the role of the magnetic technique in addressing tailored patient needs and knowledge gaps was evaluated.

Methods

Endpoints

The primary endpoint for this meta-analysis was the detection rate for SPIO per patient, defined as the proportion of patients with at least one SLN detected successfully by the magnetic technique divided by the total number of patients. As a second primary endpoint, factors that influence the detection rate were investigated. Secondary endpoints were: detection rate per SLN, defined as the proportion of SLNs detected successfully by the magnetic technique divided by the total number of SLNs retrieved; SLN yield, expressed as the average (pooled mean) number of SLNs retrieved; prevalence of SPIO-induced skin staining, defined as documented skin staining after SPIO injection and associated factors; SPIO-induced artefacts in postoperative MRI; and cost-effectiveness. Finally, in comparative studies, the concordance between SPIO and RI was analysed. For the latter, concordance was defined as the proportion of the number of patients in whom SPIO and RI were both successful, divided by the number of patients in whom RI was successful.

$$\text{Concordance} = \frac{SPIO + RI}{RI}$$

Reverse concordance was defined as the proportion of the number of patients in whom SPIO and RI were both successful, divided by the number of patients in whom SPIO was successful.

$$\text{Reverse concordance} = \frac{SPIO + RI}{SPIO}$$

For tracers performing in an equivalent manner, the assumption is that they should be successful in the same patients, that is $N_{(SPIO+RI)} = N_{SPIO} = N_{RI}$, meaning that the rate difference (RD = concordance – reverse concordance) should be 0. However, if one of the two tracers performs better than another single tracer, that is, if $N_{RI} \neq N_{SPIO}$, then concordance rates may be high or low, although this may not be clinically relevant. Therefore, RD was selected as effect size and was retrieved from comparative studies with a paired design. Pooled proportions and risk ratios (RRs) in comparative studies, with 95 per cent confidence intervals, were calculated to express the other outcomes. In studies in which BD was used as an adjunct for both SPIO and RI, successful detection was considered with the addition of BD for both tracers.

The findings of the meta-analysis were summarized in the form of clinical questions according to the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool[25] by two authors. Lack of evidence in clinically relevant questions was defined as a knowledge gap after discussion among the authors.

Literature search

A PubMed and MEDLINE search was performed using the search terms 'magnetic technique', 'superparamagnetic iron oxide nanoparticles', 'sentinel lymph node', 'breast cancer' according to the PRISMA statement[26]. A parallel search of other literature sources, including abstracts from congress volumes and citation searches, was undertaken. Authors of source studies were contacted for additional data, if deemed necessary. Single-arm, prospective, and retrospective cohort studies, and comparative, randomized and non-randomized trials were included if they provided data on the primary endpoint of the meta-analysis. For comparative trials, an isotope tracer was required as control. Any studies comparing SPIO with exclusive use of BD were excluded. Preclinical data, studies with fewer than 10 participants, and studies reporting on systems that were not available commercially at the time of publication were excluded. The literature search ended in February 2022.

Data extraction and analyses

Included studies were screened independently by two authors and the data were stored in a preformed worksheet (Microsoft® Excel; Microsoft, Redmond, WA, USA). The DerSimonian Laird random-effects model was selected *a priori*[27]. Reported effect sizes were calculated from the results of the entire source study and leave-one-out meta-analyses were performed for sensitivity. Separate analyses for detection rates and in the presence of metastasis were undertaken for the available comparative studies. Heterogeneity was evaluated by means of the I^2 statistic[28]. Subgroup and meta-regression analyses were performed for type of SPIO, type of probe, dose of SPIO, timing of SLNB (upfront or after neoadjuvant therapy), site of injection (subareolar or periareolar *versus* peritumoral) and timing of injection (perioperative, suggesting intraoperative and less than 24 h before surgery; preoperative, more than 24 h before surgery). For this, studies reporting on distinct subgroups were split into respective subgroups. Publication bias was examined by inspection of funnel plots and Egger's test for small studies effect[29]. Meta-analyses were undertaken in Stata® release 17 (StataCorp, College Station, TX, USA). For pooled rates of proportions, such as detection rates and skin staining, single-arm studies of SPIO and the SPIO arm of comparative trials were analysed using the metaprop command[30]. For these studies, meta-regression was performed with the metareg command[31].

Bias assessment

The Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)[32] and Methodological Index for Non-Randomized Studies (MINORS)[33] tools were used to assess bias in the included comparative studies. Single-arm studies were assessed using the MINORS tool for single-arm studies. The observational studies addressing MRI outcomes were assessed by means of the Newcastle–Ottawa Scale (NOS) for cohort studies[34], and the quality assessment tool for diagnostic accuracy studies (QUADAS-2) for studies of diagnostic accuracy[35]. These assessments were carried out by two authors and consensus was reached after discussion. For the studies reporting on detection rates, the MINORS version was selected for the manuscript, for uniformity of presentation and the conduct of meta-regression analyses that would allow insight on whether reported outcomes might be affected by study quality.

Results

The systematic literature review identified 32 studies that were appropriate for inclusion in qualitative and quantitative synthesis (*Fig. S1*). Twenty studies[3–11,16–20,36–42] were comparative (SPIO *versus* RI ± BD), of which 19 undertook concomitant administration of SPIO and RI ± BD in the same patients (paired design), whereas 7 were non-comparative[24,43–48]. Of these, two trials[10,18] overlapped as the study by Hersi *et al.*[18] was a patient-level meta-analysis including the outcomes of Karakatsanis *et al.*[10]. The overlapping patient group was removed from the study by Hersi *et al.*[18], to avoid duplication. Three studies[36,40,48] presented dedicated data on SLNB after neoadjuvant treatment, but only one[40] reported clearly on the original nodal status. Furthermore, one study[41] was used only to discuss discolouration data, and four[12–15] were dedicated to reporting MRI artefacts. There was only one randomized trial[17], which compared different doses of SPIO; no other randomized trials comparing SPIO with RI ± BD could be retrieved. Finally, one trial (SentiNot)[19] examined the role of SPIO in the context of delayed SLNB, in patients initially operated for ductal carcinoma *in situ* (DCIS). In this study, SPIO was injected peritumorally in the breast during the breast procedure and the patient was taken to delayed SLNB in another session, only if underlying invasive cancer was found in the specimen. The RI was injected before delayed SLNB in the previous excision site and the subareolar region or, in the event of mastectomy, intradermally near the scar or the areola[19]. All included studies are summarized in *Tables 1* and *2*, with the respective MINORS and NOS scores for study quality. A detailed assessment of study quality and the risk of bias assessed using MINORS and ROBINS-I for studies reporting on detection rates, and NOS and QUADAS-2 for studies reporting on MRI artefacts, is available in *Table S1*.

Detection rate

The pooled SLN detection rate for SPIO across all studies (27 in total, 20 comparative and 7 non-comparative) was 98.7 (95 per cent c.i. 98.1 to 99.2) per cent, with low heterogeneity ($I^2 = 25.0$ per cent, $P = 0.119$). For this outcome, meta-regression analysis showed that a lower MINORS score was significantly associated with higher reported detection rates (exp(b) = 0.9992, 95 per cent c.i. 0.9982 to 0.9998; $P = 0.013$; $I^2 = 16.9$ per cent). Across 20 comparative studies, the pooled detection rate was 97.5 (96.8 to 98.1) per cent for SPIO and 96.5 (95.7 to 97.2) per cent for RI ± BD, but the difference was not significant (RR 1.006, 95 per cent c.i. 0.992 to 1.019; $P = 0.376$; $I^2 = 28.7$ per cent) (*Fig. S2*). The results were independent of pN status. For pN+ disease, across 16 comparative studies the pooled detection rate was 99.4 (97.8 to 100) per cent for SPIO and 97.0 (92.8 to 99.7) per cent for RI ± BD, indicating comparable performance (RR 1.006, 0.982 to 1.031; $P = 0.637$; $I^2 = 0$ per cent). Leave-one-out meta-analysis did not affect the results.

Subgroup analyses showed that probe type, SPIO type, SPIO dose, neoadjuvant therapy, and type of study design did not influence outcomes, whereas peritumoral injection was associated with a trend for better detection for SPIO over RI ± BD. SPIO demonstrated improved detection over RI ± BD after preoperative injection and in the setting of SentiNot, which examined the feasibility of delayed SLNB. These effects were retained on meta-regression analysis. There was no heterogeneity ($I^2 = 0$ per cent). The results are summarized in *Table 3*.

Nodal retrieval and nodal detection rate

Data from 24 studies were available for this analysis. In crude analysis, the pooled mean number of SLNs retrieved per procedure with the magnetic technique was 2.3. The pooled nodal detection rate was 96.0 (95 per cent c.i. 93.5 to 98.1) per cent, but the results were highly heterogeneous ($I^2 = 95.3$ per cent). No subgroup analyses were attempted.

Across 19 comparative studies, the nodal detection rate was significantly higher for SPIO than for RI ± BD (94.1 (91.8 to 96.1) *versus* 83.5 (78.7 to 87.9) per cent; RR 1.098, 95 per cent c.i. 1.058 to 1.140; $P < 0.001$), but with marked heterogeneity ($I^2 = 85.2$ per cent) (*Fig. S3*). Leave-one-out meta-analysis did not change the outcome. However, crude pooled analysis showed that this difference was not clinically relevant when examining the pooled mean number of SLNs identified and excised for SPIO and RI ± BD (1.93 *versus* 1.85 respectively). In meta-regression analysis, use of the Sentimag® probe, preoperative SPIO injection, SLND after neoadjuvant therapy, and delayed SLNB were associated with a higher nodal detection rate for SPIO over RI ± BD (*Table 4*). Type of SPIO, SPIO dose, SPIO injection site, and type of study (paired *versus* non-paired comparative) were not significant. There was high heterogeneity ($I^2 = 70.0$ per cent) and the Egger test demonstrated a small studies effect ($\beta 1 = 1.83$, $P < 0.001$), which mandates that these findings are interpreted with caution.

Concordance

Only 19 studies with a paired design were appropriate for examination of concordance. The pooled concordance rate ($\frac{SPIO+\ RI}{RI}$) was 99.0 (95 per cent c.i. 98.2 to 99.6) per cent ($I^2 = 34.2$ per cent, $P = 0.073$) and the reverse concordance rate ($\frac{SPIO+\ RI}{SPIO}$) was 97.1 (95.2 to 98.6) per cent ($I^2 = 75.0$ per cent, $P < 0.001$). The pooled difference was −0.003 (95 per cent c.i. −0.009 to 0.015; $P = 0.656$), with moderate heterogeneity ($I^2 = 59.5$ per cent) (*Fig. S4*). Leave-one-out meta-analysis did not affect this outcome. In subgroup and meta-regression analysis, concordance was not affected by any factor. Reverse concordance, as expected, was decreased by the factors that increased SPIO detection over RI ± BD, subsequently affecting the RD. Indeed, subgroup and meta-regression analysis for the difference verified that preoperative SPIO injection and delayed SLN biopsy (SLNB) (SentiNot) detection affected this outcome (*Table 5* and *Fig. S4*). The very high collinearity between SPIO detection and reverse concordance, however, limits the size of explained variance by the meta-regression model. Indeed, the adjusted R^2 value was 0 per cent, suggesting that the difference between concordance and reverse concordance probably stems from the fact that the detection rate was higher with use of SPIO than with RI ± BD for preoperative SPIO detection and the SentiNot technique.

Skin staining and MRI artefacts

Data for skin staining were available in 12 studies[5,7,9,10,13–15,33,36,38,40,44] with a maximum follow-up of 3 years. The prevalence of skin staining was 30.8 (95 per cent c.i. 21.2 to 41.2) per cent, but ranged from 0 to 84.4 per cent, with very high heterogeneity ($I^2 = 96$ per cent) (*Fig. S5*). Skin staining was reported almost exclusively (over 95 per cent) after breast-conserving surgery. In subgroup analysis, the lowest discolouration rates came with a lower SPIO dose, peritumoral injection, and preoperative injection without the need to massage. No significant associations could be demonstrated on meta-regression analysis for each factor separately, suggesting that reducing skin

Table 1 Characteristics of the comparative studies included in the systematic review and meta-analysis

Reference	Data accrual	SLNB procedures	SPIO	Injection volume (ml)	Injection site	Timing of injection	MINORS score
Douek *et al.*[3]	Prospective, non-randomized	160	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	23
Thill *et al.*[4]	Prospective, non-randomized	150	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	22
Rubio *et al.*[36]‡	Prospective, non-randomized	30	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	20
Rubio *et al.*[5]	Prospective, non-randomized	120	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	23
Piñeiro-Madrona *et al.*[6]	Prospective, non-randomized	181	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	24
Ghilli *et al.*[7]	Prospective, non-randomized	197	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	24
Coufal *et al.*[8]	Prospective, non-randomized	20	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	20
Ahmed *et al.*[37]	Prospective, non-randomized	32	Sienna+®	0.5 ml SPIO	Peritumoral	Peroperative	21
Houpeau *et al.*[9]	Prospective, non-randomized	108	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	24
Karakatsanis *et al.*[10]	Prospective, non-randomized	206	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	24
Karakatsanis *et al.*[11]*	Prospective, non-randomized	339	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar/ peritumoral	Peroperative/ preoperative	24
Karakatsanis *et al.*[20]	Prospective, non-randomized	12	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Preoperative	22
Karakatsanis *et al.*[19]§	Prospective, non-randomized	40	Sienna+®	2 ml SPIO	Subareolar/ peritumoral	Preoperative	24
Alvarado *et al.*[16]	Prospective, non-randomized	146	Magtrace®	2 ml SPIO	Subareolar	Peroperative	24
Taruno *et al.*[38]†	Prospective, non-randomized	210	Ferucarbutran	1 ml SPIO	Subareolar	Peroperative	24
Makita *et al.*[42]†	Prospective, non-randomized	69	Ferucarbutran	0.5 ml SPIO	Subareolar/ peritumoral	Peroperative	22
Hamzah *et al.*[39]	Prospective, non-randomized	20	Magtrace®	2 ml SPIO	Subareolar	Peroperative	20
Rubio *et al.*[17]	Prospective, randomized	135	Magtrace®	SPIO in different doses	Subareolar	Peroperative	24
Hersi *et al.*[18]	Prospective, non-randomized	328	Magtrace®	SPIO in different doses	Subareolar/ peritumoral	Peroperative/ preoperative	24
Giménez-Climent *et al.*[40]‡	Prospective, non-randomized	89	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	22
Wärnberg *et al.*[41]¶	Prospective, observational	340	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar/ peritumoral	Peroperative/ preoperative	20

*Head-to-head comparison between superparamagnetic iron oxide nanoparticles (SPIO) and radioisotope. All other studies had a within-patient comparison design—all patients received both tracers ± blue dye and paired comparisons were made. †Used Tokyo probe; the Sentimag® system (Endomag, Cambridge, UK) was used in all other studies. ‡Sentinel lymph node biopsy (SLNB) after neoadjuvant treatment. §Delayed SLNB after primary surgery for ductal carcinoma *in situ* (SentiNot study). ¶Reported only skin-staining outcomes. MINORS, Methodological Index for Non-Randomized Studies. Sienna+® (Endomag, Campbridge, UK); Magtrace® (Endomag, Cambridge, UK).

staining is probably best achieved by a combination of these factors (*Table 6*). Two studies[17,41] included patient-reported outcomes, which showed that the majority of patients did not consider staining to be a problem.

Four retrospective[12–15] reports with a total of 97 patients were available on MRI artefacts after SPIO-guided SLND. The results were pooled from the source studies to analyse the role of SPIO dose, injection site, and type of surgery, stratified per study. Apart from six patients who received an intratumoral injection of 0.1 ml, all others had received 2 ml SPIO in a total volume of 5 ml in the subareolar area. Artefacts were present in 61 (95 per cent c.i. 50 to 70) per cent up to 46 months after SPIO administration. In univariable analyses, artefacts were more common after breast-conserving surgery than mastectomy (70 *versus* 21 per cent; difference 49 (95 per cent c.i. 28 to 70) per cent; $P < 0.001$). For the six patients with a 0.1-ml intratumoral

Table 2 Characteristics of the non-comparative studies included in the systematic review and meta-analysis

Reference	Data accrual	Procedures	SPIO	Injection volume (ml)	Injection site	Timing of injection	Study quality score
Detection rate and skin staining							
Hersi *et al.*[24]‡	Prospective, observational	32 SLNB	Magtrace®	2 ml SPIO	Peritumoral	Peroperative	14
Lorek *et al.*[43]§	Retrospective	303 SLNB	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	11
Man *et al.*[44]	Retrospective	333 SLNB	Magtrace®	2 ml SPIO	Subareolar	Peroperative	13
Vural and Yilmaz[45]	Prospective, observational	104 SLNB	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	14
Bazire *et al.*[46]¶	Retrospective	288 SLNB	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	9
Pohlodek *et al.*[47]‡	Retrospective	38 SLNB	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	13
Kurylcio *et al.*[48]#	Retrospective	76 SLNB	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	10
SPIO artefacts on postoperative MRI							
Krischer *et al.*[12]	Retrospective	23 MRI	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	3†
Aribal *et al.*[13]	Retrospective	36 MRI	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	3†
Chapman *et al.*[14]	Retrospective	21	Sienna+®	2 ml SPIO diluted in 3 ml NaCl or local anaesthetic	Subareolar	Peroperative	3†
Christenhusz *et al.*[15]	Retrospective	76	Sienna+®	2 ml SPIO in 3 ml NaCl subareolar or 0.1 ml intratumoral	Subareolar/ intratumoral	Peroperative	5†

*Methodological Index for Non-Randomized Studies score, except †Newcastle–Ottawa Scale score. ‡Examined the combination of superparamagnetic iron oxide nanoparticles (SPIO) with a paramagnetic seed for tumour localization. §Primary endpoint was complications of SPIO sentinel lymph node dissection (SLND) procedures. ¶Primary endpoint was the safety of postoperative radiotherapy after SPIO SLND procedures. #SLND after neoadjuvant treatment. SLNB, sentinel lymph node biopsy.

Table 3 Subgroup and meta-regression analysis examining factors for successful superparamagnetic iron oxide nanoparticle-guided sentinel lymph node detection

	Subgroup analysis		Meta-regression analysis	
	Risk ratio	*P*	Coefficient b	*P*
Probe				
Sentimag®	1.007 (0.994, 1.019)	0.289		
Tokyo probe	1.003 (0.924, 1.088)	0.941		
SPIO				
Ferucarbutran	1.003 (0.924, 1.088)	0.941		
Magtrace®	1.010 (0.992, 1.029)	0.277		
Sienna + ®	1.004 (0.988, 1.021)	0.598		
Injection site			–0.0083 (–0.0663, 0.0498)*	0.781
Subareolar	1.000 (0.991, 1.010)	0.957		
Peritumoral	1.118 (0.982, 1.272)	0.091		
Timing of injection			0.0544 (0.0042, 0.1045)†	0.034
Peroperative	0.999 (0.990, 1.008)	0.819		
Preoperative	1.116 (1.020, 1.222)	0.017		
Setting				
After neoadjuvant therapy	1.021 (0.975, 1.069)	0.375		
Upfront	1.005 (0.992, 1.018)	0.442		
Comparison				
Paired	1.007 (0.995, 1.020)	0.251		
Unpaired	0.956 (0.893, 1.024)	0.197		
Subgroup			–0.3627 (–0.5967, –0.1287)‡	0.002
Standard SLNB	1.002 (0.993, 1.011)	0.661		
Delayed SLNB	1.528 (1.216, 1.922)	< 0.001		
Injection volume (ml)				
0.5	1.032 (0.981, 1.086)	0.227		
1.0	1.016 (0.968, 1.067)	0.522		
1.5	0.988 (0.959, 1.017)	0.407		
2.0	1.042 (0.974, 1.115)	0.231		
5.0	1.000 (0.988, 1.013)	0.959		

Values in parentheses are 95% confidence intervals. Coefficient for *subareolar injection, †preoperative injection or ‡standard sentinel lymph node dissection. SPIO, superparamagnetic iron oxide nanoparticles; SLNB, sentinel lymph node biopsy.

Table 4 Subgroup and meta-regression analysis of nodal detection rate

	Subgroup analysis		Meta-regression analysis	
	Risk ratio	P	Coefficient b	P
Probe			0.3566 (0.1641, 0.5490)*	<0.001
Sentimag®	1.072 (1.038, 1.108)	<0.001		
Tokyo probe	1.456 (1.318, 1.608)	<0.001		
SPIO			−0.0019 (−0.1593, 0.1555)	0.981
Ferucarbutran	1.456 (1.318, 1.608)	<0.001		
Magtrace®	1.066 (1.010, 1.126)	0.021		
Sienna+®	1.078 (1.032, 1.126)	0.001		
Injection site			0.0395 (−0.1173, 0.1963)	0.622
Peritumoral	1.303 (1.008, 1.683)	0.043		
Subareolar	1.082 (1.043, 1.122)	<0.001		
Timing of injection			0.1473 (0.0371, 0.2574)†	0.009
Preoperative	1.284 (1.095, 1.507)	0.002		
Peroperative	1.070 (1.033, 1.109)	<0.001		
Setting			−0.1179 (−0.2231, −0.0127)‡	0.028
Upfront	1.078 (1.039, 1.118)	<0.001		
After neoadjuvant therapy	1.308 (0.894, 1.912)	0.167		
Comparison			−0.1258 (−0.2685, 0.0169)	0.084
Paired	1.097 (1.057, 1.139)	<0.001		
Unpaired	0.930 (0.841, 1.029)	0.158		
Subgroup			−0.8075 (−1.2011, −0.4139)§	<0.001
Standard SLNB	1.080 (1.044, 1.118)	<0.001		
Delayed SLNB	2.571 (1.788, 3.699)	<0.001		
Injection volume (ml)			0.0092 (−0.0365, 0.05489)	0.693
0.5	1.188 (0.796, 1.772)	0.400		
1.0	1.128 (1.053, 1.207)	0.001		
1.5	1.001 (0.926, 1.083)	0.970		
2.0	1.175 (1.025, 1.346)	0.021		
5.0	1.069 (1.031, 1.110)	<0.001		

Values in parentheses are 95% confidence intervals. Coefficient for *Tokyo probe, †preoperative injection, ‡upfront surgery or §standard sentinel lymph node biopsy. SPIO, superparamagnetic iron oxide nanoparticles; SLNB, sentinel lymph node biopsy.

Table 5 Subgroup and meta-regression analysis for rate difference (concordance – reverse concordance)

	Subgroup analysis		Meta-regression analysis	
	Rate difference	P	Coefficient b	P
Probe				
Sentimag®	−0.002 (−0.009, 0.004)	0.502		
Tokyo probe	−0.004 (−0.084, 0.076)	0.922		
SPIO				
Ferucarbutran	−0.004 (−0.084, 0.076)	0.922		
Magtrace®	−0.010 (−0.022, 0.001)	0.078		
Sienna+®	−0.004 (−0.021, 0.013)	0.642		
Injection site				
Peritumoral	−0.120 (−0.020, 0.063)	0.099		
Subareolar	0.001 (−0.006, 0.007)	0.846		
Timing of injection			−0.0558 (−0.0904, −0.0212)*	0.002
Preoperative	−0.122 (−0.219, −0.025)	0.014		
Peroperative	0.001 (−0.005, 0.008)	0.655		
Setting				
Upfront	−0.002 (−0.009, 0.004)	0.454		
After neoadjuvant therapy	0.021 (−0.020, 0.063)	0.312		
Subgroup			0.2957 (0.1440, 0.4473)†	<0.001
Standard SLNB	−0.0001 (−0.007, 0.006)	0.890		
Delayed SLNB	−0.350 (−0.498, −0.202)	<0.001		
Injection volume (ml)				
0.5	−0.035 (−0.080, 0.011)	0.132		
1.0	−0.016 (−0.067, 0.034)	0.524		
1.5	0.011 (−0.022, 0.044)	0.516		
2.0	−0.011 (−0.024, 0.003)	0.121		
5.0	−0.001 (−0.007, 0.010)	0.518		

Values in parentheses are 95% confidence intervals. Coefficient for *preoperative injection or †standard sentinel lymph node dissection. SPIO, superparamagnetic iron oxide nanoparticles; SLNB, sentinel lymph node biopsy.

SPIO injection, the incidence of MRI artefact was 0 per cent, compared with 65 per cent after a subareolar injection of 2 ml SPIO and 3 ml sodium chloride (difference 65 (55.0 to 75) per cent; $P = 0.003$). In an analysis of artefacts after breast-conserving surgery (78 patients), the effect was similar (0 *versus* 76 per cent; difference 76 (67 to 86) per cent; $P < 0.001$).

Table 6 Subgroup and meta-regression analysis for superparamagnetic iron oxide nanoparticle-induced skin staining

	Skin staining (%)	Coefficient b	P
Injection volume (ml)		–0.0061 (–0.0816, 0.0693)*	0.863
0.5	0 (0, 19.9)		
1.0	25.2 (9.4, 41.0)		
1.5	43.3 (37.0, 49.5)		
2.0	32.1 (26.9, 37.2)		
5.0	31.3 (20.5, 42.1)		
Injection site		0.2390 (–0.2178, 0.6958)†	0.279
Subareolar	36.6 (25.8, 47.3)		
Peritumoral	15.4 (0, 36.2)		
Massage		0.0344 (–0.4202, 0.4891)‡	0.873
Yes	34.7 (22.7, 46.6)		
No	24.4 (6.3, 42.6)		

Values in parentheses are 95% confidence intervals. Coefficient for *lower superparamagnetic iron oxide nanoparticle volume, †subareolar injection or ‡perioperative injection with massage.

Aggregated artefact rates ranged from 46 to 100 per cent among studies, owing to small numbers, high level of selection bias, and significant heterogeneity ($I^2 = 90$ per cent). In terms of qualitative and quantitative artefact characteristics, the studies used different, non-standardized classifications, which precluded any further analyses.

Health economic outcomes

Three studies reported on health economic outcomes. In an exploratory analysis from the Swedish MONOS trial[11], switching from RI to SPIO would result in an average procedure-related cost reduction of €27 (€252 to €225; reduction 10.7 (95 per cent c.i. 7.2 to 15.2) per cent), whereas with preoperative, in-office SPIO administration, the average savings were €352.7 per procedure, owing to avoidance of nuclear medicine charges and theatre delays. A pilot study from Germany[49] also showed that SPIO-guided SLNB shortened the preoperative care pathway without affecting operating time or reimbursement. The authors concluded that the technique yielded the potential to reduce costs and improve patient experience. Finally, the SentiNot interim analysis[19] showed that, by SPIO allowing upfront SLNB to be avoided in patients with high-risk DCIS, a mean reduction of €448 (95 per cent c.i. €151 to 746) per patient, corresponding to a reduction of 8.5 per cent (€4813 *versus* 5261; $P = 0.003$), was achieved for the entire study. This reduction was even more significant for women with DCIS (and not invasive tumours) who would have undergone SLNB (mean cost saving €1296 (€3990 *versus* 5286), 24.5 per cent; $P < 0{\cdot}001$). No other relevant data could be retrieved during the systematic review.

Evidence summary, knowledge gaps, and research priorities

Summarizing the evidence according to GRADE (*Table S2*), in the setting of upfront SLNB for breast cancer, SPIO performed comparably and was concordant in terms of detection rate with RI ± BD, independently of nodal status (high-certainty evidence), retrieving slightly more SLNs (low-certainty evidence). The latter was an outcome with marked heterogeneity and may depend on other factors, such as differences in study protocols (for example registration of *ex vivo* signal with registration of more nodes as magnetic or removal of palpable lymph nodes) that are difficult to account for. Regardless, the average numbers of SLNs retrieved were similar and there should be no concern about the removal of an excessively larger number of SLNs. Interestingly, SPIO yielded a higher detection rate when administered more than 24 h before surgery, a property that should be capitalized on, as it may have the potential to provide logistical advantages, and possibly contain costs. Another point of interest from this meta-analysis is that studies with a higher risk of bias, such as retrospective analyses, and those without a control group, smaller numbers or without standardized reporting of outcomes (corresponding to a lower MINORS score), reported higher detection rates, suggesting that only well designed prospective trials are expected to improve the level of evidence for the magnetic technique.

In the present meta-analysis, skin staining after SPIO injection occurred in approximately 30 per cent of patients. The existing evidence was heterogeneous in outcomes, but also in type and duration of follow-up. Reported skin staining rates were much lower after injection of smaller volumes deep in the parenchyma and close to the tumour. The strength of recommendations is currently low owing to data heterogeneity, but, given that smaller volumes or peritumoral injection did not have adverse effects on SLN detection, this is something that should be considered. Further studies need to take these parameters into account, and provide structured follow-up and reporting of skin staining.

Regarding the presence of MRI artefacts, only retrospective reports[12–14] were identified. It would appear that residual SPIO in the parenchyma is expected to produce artefacts in the ipsilateral breast and predominantly at the injection site. Reassuringly, the contralateral breast or other surrounding structures are not affected. The results of the meta-analysis suggest that a small injection volume in the part of the breast that will be removed may address this concern. The evidence is, however, very limited. The quality of the identified studies precludes definitive conclusions or clear recommendations. Therefore, prospective observational studies should examine the outcome of MRI artefacts in relation to different doses and injection sites, and interpret the findings in a standardized and clinically relevant manner. Currently, there are two ongoing prospective studies[17,50] dedicated to investigating MRI artefacts after SPIO injection, one after subareolar and the other after peritumoral SPIO administration in doses of 2.0, 1.5, and 1.0 ml.

Although dedicated studies examining SPIO-guided SLND after neoadjuvant therapy were restricted, subgroup and meta-regression analyses demonstrated that SPIO performed comparably to RI in this setting. The lack of structured reports on node status before neoadjuvant therapy is a serious limitation, as no detailed conclusions can be drawn. More, well structured studies in this setting should add to the existing body of evidence. No data exist regarding the use of SPIO for SLND in pregnant

patients with breast cancer, as pregnancy was an exclusion criterion in all the prospective trials identified.

Discussion

RI ± BD has long served as the standard tracer for SLNB in patients with breast cancer. Its known restrictions, including challenging logistics, restricted access and, in the case of the dye, anaphylactic reactions, have motivated research for new techniques. The magnetic technique with SPIO is one such method. Two previous meta-analyses[10,51] have already shown non-inferiority and reached similar conclusions, despite using different methodology. Therein, all included studies had a paired design, that is patients acted as their own controls, and all had received a perioperative subareolar injection of 5 ml (2 ml SPIO, diluted with 3 ml sodium chloride 0.9 per cent) followed by a 5-min massage. Since then, more studies have been added to the literature, evaluating SPIO as the sole tracer for SLNB, or examining the effect of different doses, injection sites in the breast, and time frames of administration. In the present meta-analysis, data synthesis verified that SPIO performs comparably to RI ± BD, regardless of dose or injection site. Both detection rates and concordance were comparable, suggesting that SPIO is a valid alternative to RI ± BD. The difference noted in nodal detection rate suggests that SPIO retrieves more SLNs, but crude analysis showed that the numerical difference is not relevant, and that SPIO-guided SLND does not result in excessive node retrieval.

A novel finding of this meta-analysis is that the preoperative injection of SPIO is not only feasible, but also increases SLN detection. Although injection more than 24 h before surgery was shown to increase detection over peroperative or intraoperative administration, the optimal or maximum interval between SPIO administration and surgery still needs to be defined. It seems that extending the time before surgery allows increased SPIO concentration in the SLN, facilitating identification, a finding in line with experimental data[52]. Several studies[11,18] have reported on a time frame that extends up to 27 days in upfront SLNB. This has already been capitalized on in the SentiNot study, which explored the feasibility of delayed SLNB in women with a preoperative diagnosis of DCIS, in whom successful SLNB was performed up to 47 days after SPIO injection[19]. This is a property unique to SPIO and further investigation in other clinical scenarios, such as the neoadjuvant therapy setting, could provide with interesting implementations, such as SPIO administration already before the induction of neoadjuvant therapy, both in terms of clinical outcomes but also in cost containment. Recently, the feasibility of minimally invasive magnetic axillary mapping was demonstrated in the phase II MagUS study[53], in which a group of patients were mapped with SPIO injection before neoadjuvant therapy. At surgery when SLNB or targeted axillary dissection was performed, the magnetic SLNs were still visualized on MRI, without tracer migration, and had good concordance with the isotope.

Skin staining and MRI artefacts have been the main concern regarding the SPIO technique, mostly after breast conservation. The present results suggest that staining is less with a smaller dose and a peritumoral injection can address this, as the bulk of SPIO is removed during surgery. Because there is an absolute correlation between SPIO staining and magnetic signal[10], a similar association could be expected for MRI artefacts. The available evidence, however, stems from studies with a high risk of bias, reporting outcomes after injection of 5 ml, which is no longer used. In a study from the Netherlands[15], it was shown that no artefacts were present in patients who had received a peritumoral, lower-volume SPIO injection. This is in line with the hypothesis that residual SPIO is related to the presence of artefacts. Therefore, removing this area should address such concerns. However, this is only a hypothesis that needs to be confirmed; currently, this topic is viewed as the most important knowledge gap to be addressed. Results from the PostMAG MRI study[50] and the SUNRISE trial[17] are expected to provide more insight, as these studies are examining the same question after 2.0-, 1.5-, and 1.0-ml injections, but the injection was peritumoral in PostMAG MRI and subareolar in SUNRISE. At the same time, the results suggest that further research on SPIO is required to achieve high detection rates and, at the same time, minimize the risk of skin staining and MRI artefacts.

Apart from binary meta-analyses, the magnetic technique has shown comparable performance to RI ± BD or indocyanine green in network meta-analyses[10,51,54]. However, the present work provides an updated and comprehensive review of current knowledge and provides information on the outcomes associated with use of different SPIO products, probes, doses, injection timings, and injection sites, thus contributing to the refinement of the technique. The available evidence has been evaluated according to the standardized GRADE approach, which defines the level of evidence and strength of recommendations. Interestingly, the GRADE outcomes have highlighted that, although there are no clinically relevant differences in detection rates and node retrieval between comparative and non-comparative studies, the level and strength of evidence will increase only if further research is performed in well designed prospective trials, instead of small, non-controlled studies. The latter should merely serve as pilot projects that will assess the feasibility of larger trials or report on off-label uses.

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The risk-of-bias plots in the *supplementary material* were created with the robvis tool[55]. The review was not registered in a public registry.

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS* online.

Data availability

The review protocol, template data collection forms, data extracted from included studies, and data used for all analyses can be accessed upon reasonable request.

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Evolution and refinement of magnetic-guided sentinel lymph node detection in breast cancer: meta-analysis

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Supplementary Materials - Index

Supplementary Figures and Tables

Supplementary Tables

Table S1: Risk of bias assessment for the included studies

1. **Studies on detection rate**

1.a: Comparative studies.

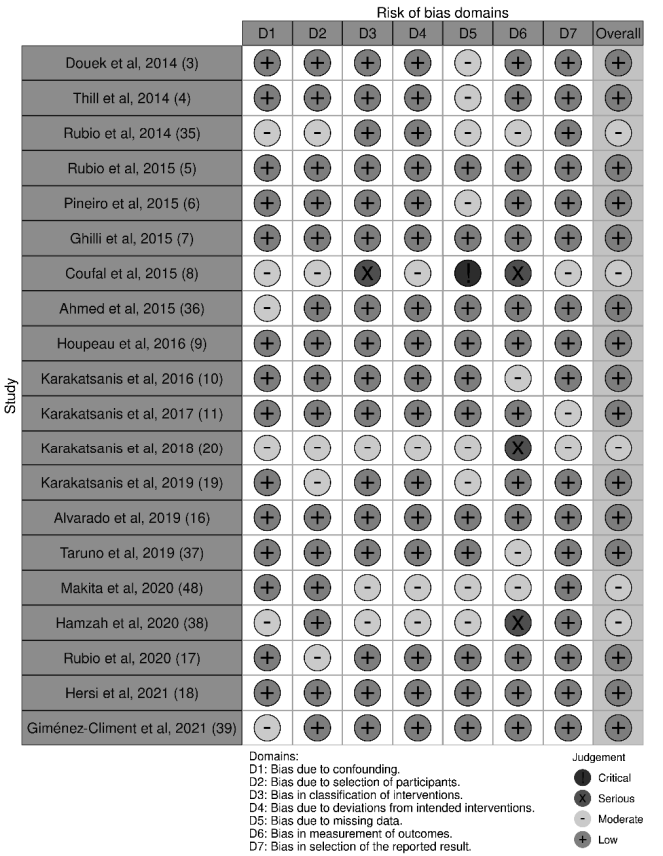
1.a.(i): Detailed MINORS criteria

Study ID	Aim	Inclusion	Prospective	Endpoints	Endpoint assessment	Follow-up	Loss <5%	Sample size	Control group	Contemporary group	Group Equivalence	Statistical Analyses	Total
Douek et al, 2014 (3)	2	1	2	2	2	2	2	2	2	2	2	2	**23**
Thill et al, 2014 (4)	2	1	2	2	2	2	2	1	2	2	2	2	**22**
Rubio et al, 2014 (35)	2	2	2	2	2	1	2	0	2	2	2	1	**20**
Rubio et al, 2015 (5)	2	2	2	2	2	2	2	1	2	2	2	2	**23**
Pineiro et al, 2015 (6)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Ghilli et al, 2015 (7)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Coufal et al, 2015 (8)	2	2	2	2	2	1	2	0	2	2	2	1	**20**
Ahmed et al, 2015 (36)	2	1	2	2	2	2	2	0	2	2	2	2	**21**
Houpeau et al, 2016 (9)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Karakatsanis et al, 2016 (10)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Karakatsanis et al, 2017 (11)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Karakatsanis et al, 2018 (20)	2	2	2	2	2	2	2	0	2	2	2	2	**22**
Karakatsanis et al, 2019 (19)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Alvarado et al, 2019 (16)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Taruno et al, 2019 (37)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Makita et al, 2020 (48)	2	2	2	2	2	2	2	0	2	2	2	2	**22**
Hamzah et al, 2020 (38)	2	2	2	2	2	2	2	0	2	2	2	0	**20**
Rubio et al, 2020 (17)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Hersi et al, 2021 (18)	2	2	2	2	2	2	2	2	2	2	2	2	**24**
Giménez-Climent et al, 2021 (39)	2	2	2	2	2	2	2	0	2	2	2	2	**22**

1.a.(ii): ROBINS-I tool

Study ID	Confounding bias	Selection bias	Classification of interventions bias	Deviation from interventions bias	Missing data bias	Measurement of outcomes bias	Report bias	Overall
Douek et al, 2014 (3)	Low	Low	Low	Low	Moderate	Low	Low	**Low**
Thill et al, 2014 (4)	Low	Low	Low	Low	Moderate	Low	Low	**Low**
Rubio et al, 2014 (35)	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	**Moderate**
Rubio et al, 2015 (5)	Low	Low	Low	Low	Low	Low	Low	**Low**
Pineiro et al, 2015 (6)	Low	Low	Low	Low	Moderate	Low	Low	**Low**
Ghilli et al, 2015 (7)	Low	Low	Low	Low	Low	Low	Low	**Low**
Coufal et al, 2015 (8)	Moderate	Moderate	Serious	Moderate	Critical	Serious	Moderate	**Moderate**
Ahmed et al, 2015 (36)	Moderate	Low	Low	Low	Low	Low	Low	**Low**
Houpeau et al, 2016 (9)	Low	Low	Low	Low	Low	Low	Low	**Low**
Karakatsanis et al, 2016 (10)	Low	Low	Low	Low	Low	Moderate	Low	**Low**
Karakatsanis et al, 2017 (11)	Low	Low	Low	Low	Low	Low	Moderate	**Low**
Karakatsanis et al, 2018 (20)	Moderate	Moderate	Moderate	Moderate	Moderate	Serious	Moderate	**Moderate**
Karakatsanis et al, 2019 (19)	Low	Moderate	Low	Low	Moderate	Low	Low	**Low**
Alvarado et al, 2019 (16)	Low	Low	Low	Low	Low	Low	Low	**Low**
Taruno et al, 2019 (37)	Low	Low	Low	Low	Low	Moderate	Low	**Low**
Makita et al, 2020 (48)	Low	Low	Moderate	Moderate	Moderate	Moderate	Low	**Moderate**
Hamzah et al, 2020 (38)	Moderate	Low	Moderate	Moderate	Moderate	Serious	Low	**Moderate**
Rubio et al, 2020 (17)	Low	Moderate	Low	Low	Low	Low	Low	**Low**
Hersi et al, 2021 (18)	Low	Low	Low	Low	Low	Low	Low	**Low**
Giménez-Climent et al, 2021 (39)	Moderate	Low	Low	Low	Low	Low	Low	**Low**

Risk-of-bias plot for the ROBINS-I tool of comparative studies



1.b: Single-arm studies.

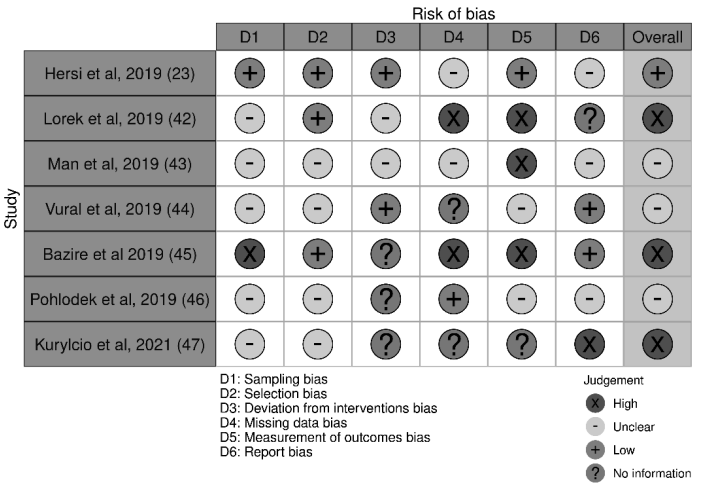
1.b.(i): Detailed MINORS criteria

Study ID	Aim	Inclusion	Prospective	Endpoints	Endpoint assessment	Follow-up	Loss <5%	Sample size	Total
Hersi et al, 2019 (23)	2	2	2	2	2	2	2	0	**14**
Lorek et al, 2019 (42)	2	2	1	1	2	2	1	0	**11**
Man et al, 2019 (43)	2	2	1	2	2	2	2	0	**13**
Vural et al, 2019 (44)	2	2	2	2	2	2	2	0	**14**
Bazire et al 2019 (45)	2	1	0	2	2	1	1	0	**9**
Pohlodek et al, 2019 (46)	2	2	1	2	2	2	2	0	**13**
Kurylcio et al, 2021 (47)	2	2	1	1	1	1	2	0	**10**

1.b.(ii): Risk-of-Bias (RoB) assessment

Study ID	Sampling bias	Selection bias	Deviation from interventions bias	Missing data bias	Measurement of outcomes bias	Report bias	Overall
Hersi et al, 2019 (23)	High	Low	Low	Some concerns	Some concerns	Some concerns	**Moderate**
Lorek et al, 2019 (42)	Some concerns	Low	Some concerns	High	High	No information	**High**
Man et al, 2019 (43)	Some concerns	Some concerns	Some concerns	Some concerns	High	Some concerns	**Moderate**
Vural et al, 2019 (44)	Some concerns	Some concerns	Low	No information	Some concerns	Low	**Moderate**
Bazire et al 2019 (45)	High	Low	No information	High	High	Low	**High**
Pohlodek et al, 2019 (46)	Some concerns	Some concerns	No information	Low	Some concerns	Some concerns	**Moderate**
Kurylcio et al, 2021 (47)	Some concerns	Some concerns	No information	No information	No information	High	**High**

Risk-of-bias plot for single-arm studies



2. Studies on MRI artifacts

2.a: Newcastle-Ottawa Scale (NOS) criteria

Study ID	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability	Standardised Assessment of outcome with independency	Adequacy of follow-up	Lost to follow-up (less than 10% and reported)	
Krischner et al, 2018 (12)	--	--	*	*	--	--	*	--	**3**
Aribal et al, 2021 (13)	--	--	*	*	--	--	*	--	**3**
Chapman et al, 2021 (14)	--	--	*	*	--	--	*	--	**3**
Christenhuz et al, 2022 (15)	--	--	*	*	*	*	*	--	**5**

2.b: QUADAS-2 tool

Study ID	Patient selection	Index test	Reference Standard	Flow and timing	Overall
Krischner et al, 2018 (12)	High	High	No information	No information	High
Aribal et al, 2021 (13)	High	High	High	High	High
Chapman et al, 2021 (14)	High	High	No information	No information	High
Christenhuz et al, 2022 (15)	High	High	High	High	High

Risk-of-bias plot for the QUADAS-2 tool of studies for MRI artifacts

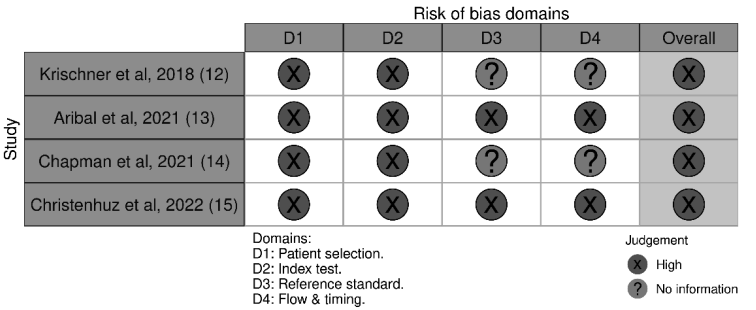


Table S2: GRADE recommendations

Do Superparamagnetic Iron Oxide nanoparitcles (SPIO) perform comparably to Isotope with or without blue dye (RI+/-BD) for standard SLN detection in patients with breast cancer?

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Superparamagnetic Iron Oxide nanopartcles (SPIO)	Isotope with or without blue dye (RI+/-BD)	Relative (95% CI)	Absolute (95% CI)		
Detection Rate												
20	observational studies	not serious	not serious	not serious	not serious	none	2370/2430 (97.5%)	2320/2404 (96.5%)	**RR 1.01** (0.99 to 1.02)	**10 more per 1.000** (from 10 fewer to 19 more)	⨁⨁⨁⨁ High	IMPORTANT
Concordance between SPIO and RI+/-BD												
19	observational studies	not serious	not serious	not serious	not serious	none	2123/2144 (99.0%)	2123/2186 (97.1%)	**Rate difference -0.003** (-0.009 to 0.015)	**-- per 1.000** (from – to –)	⨁⨁⨁⨁ High	IMPORTANT
Number of SLNs												
19	observational studies	serious[a]	serious[a]	not serious	serious[a]	strong association	4201/4536 (92.6%)*	3926/4592 (85.5%)*	**RR 1.10** (1.06 to 1.14)	**68 more per 1.000** (from 43 more to 94 more)	⨁⨁◯◯ Low	NOT IMPORTANT
							94.1% (pooled weighted rate)	83.5% (pooled weighted rate)		**67 more per 1.000** (from 42 more to 92 more)		

CI: confidence interval; **RR:** risk ratio, **SLN:** sentinel lymph node

Explanations

a. Heterogeneity in definition of SLN across studies (only tracer-active, tracer and/or BD active, tracer inactive but palpable, etc.). *: crude proportion rates

Figure S1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

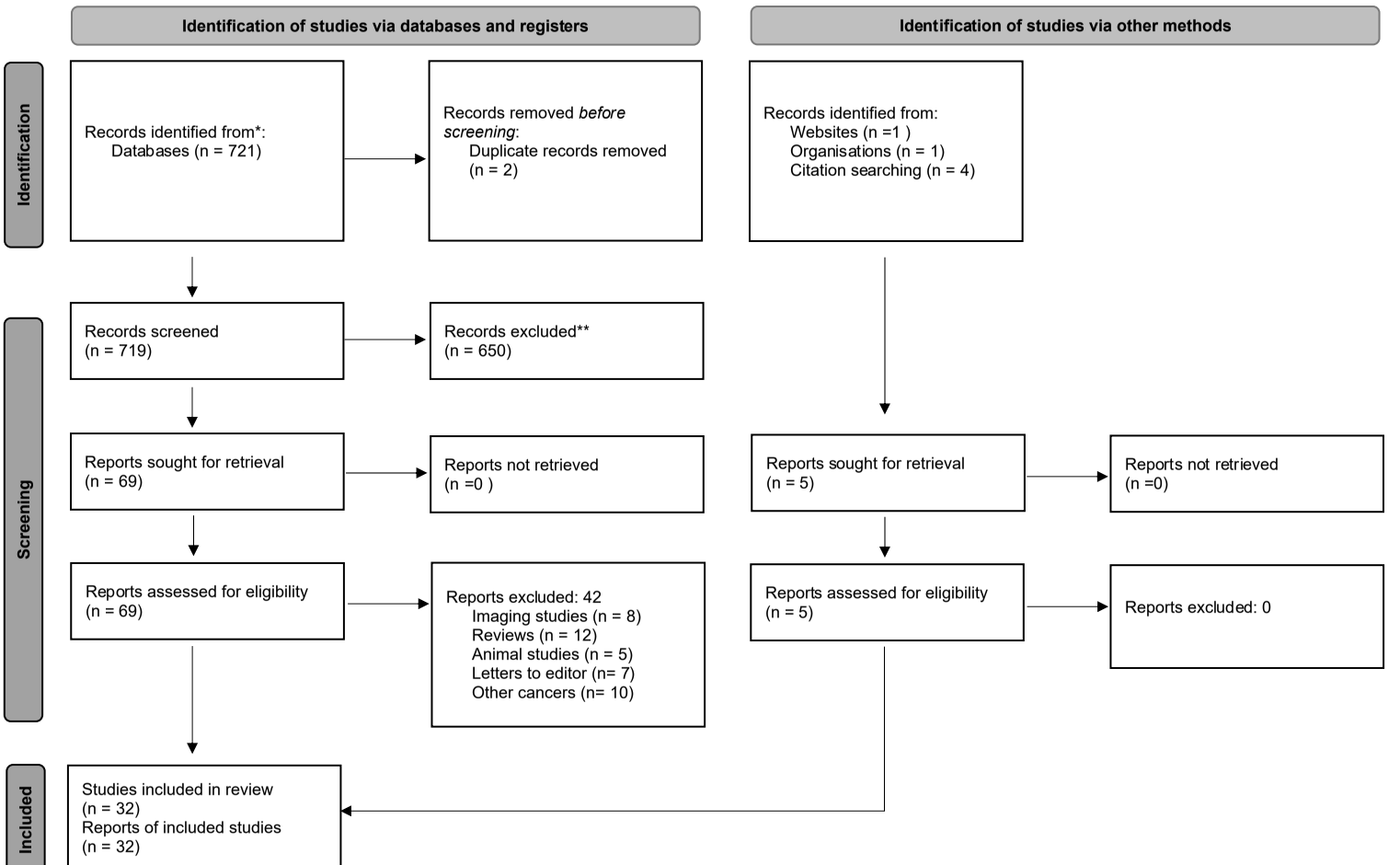


Figure S2: Forest plot for Detection rate (per patient/procedure)

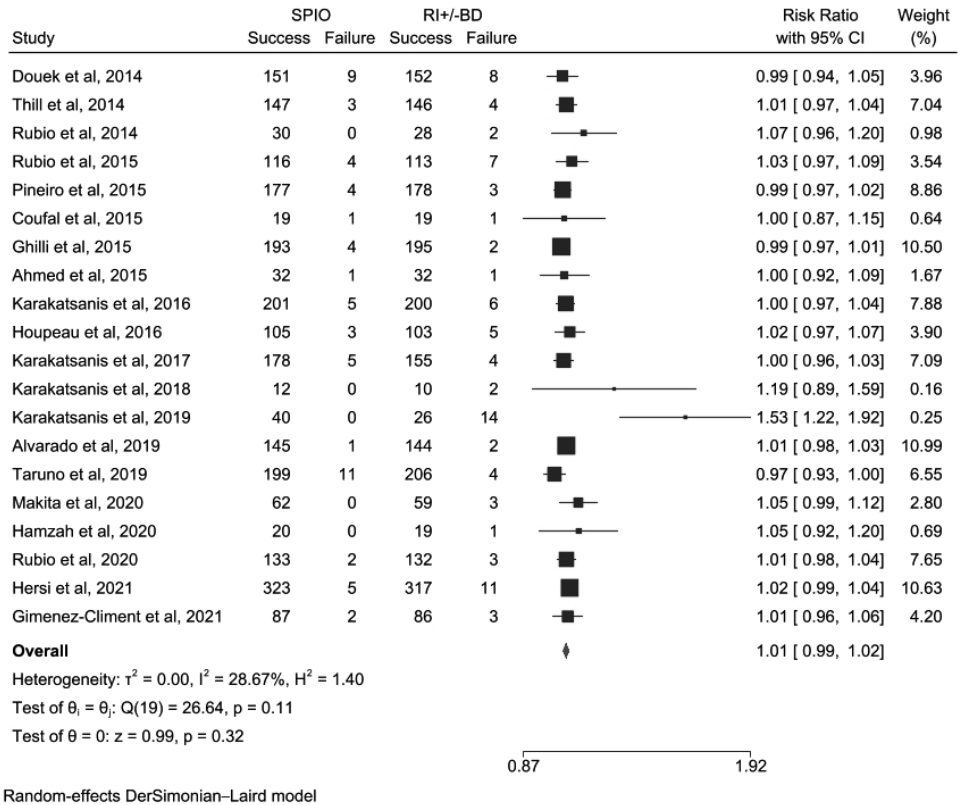


Figure S3: Forest plot for Nodal detection rate

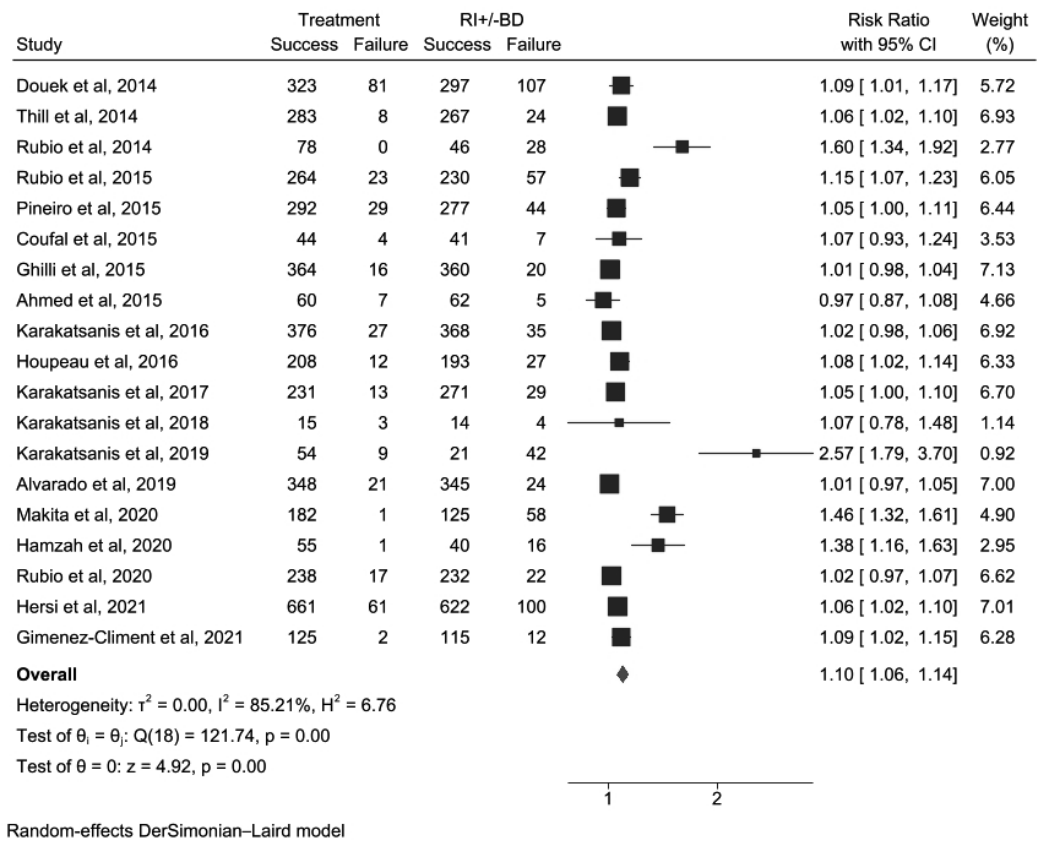


Figure S4: Forest plot for Difference between Concordance and Reverse Concordance

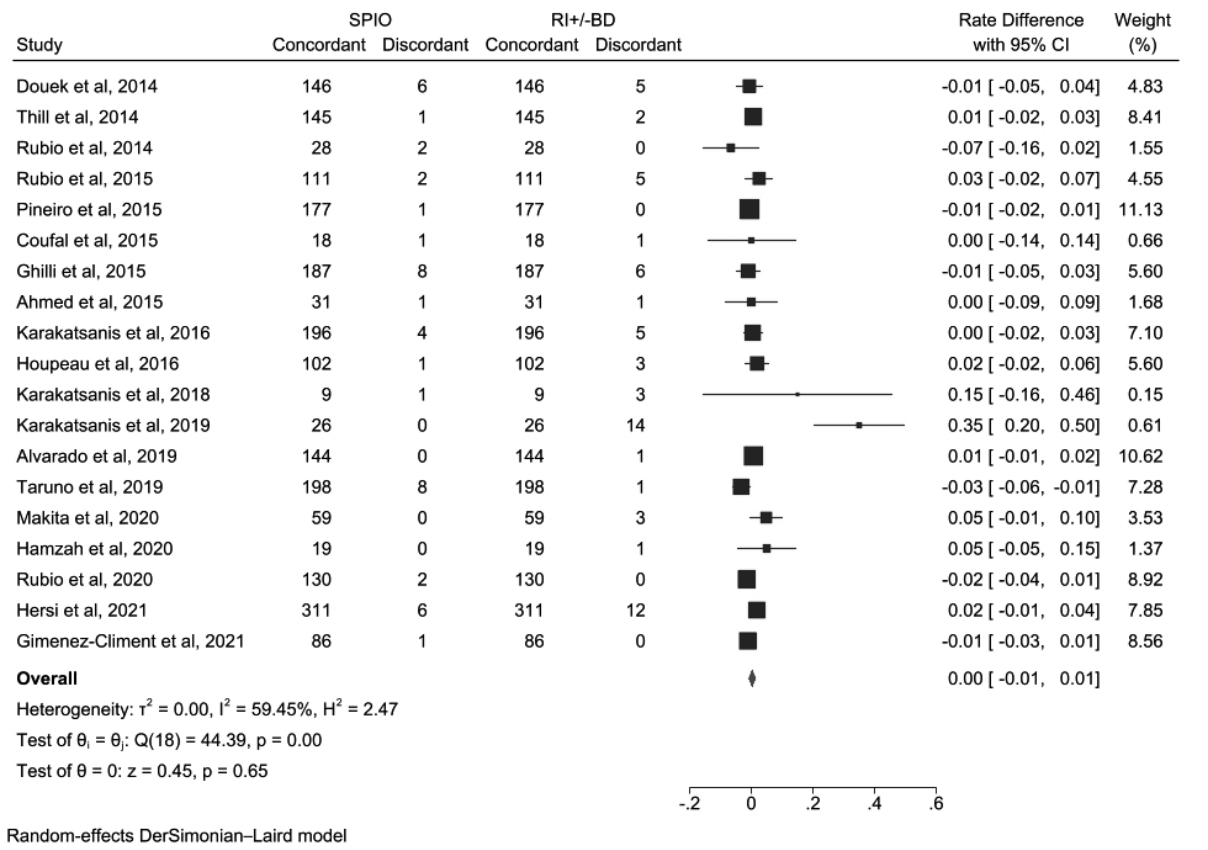
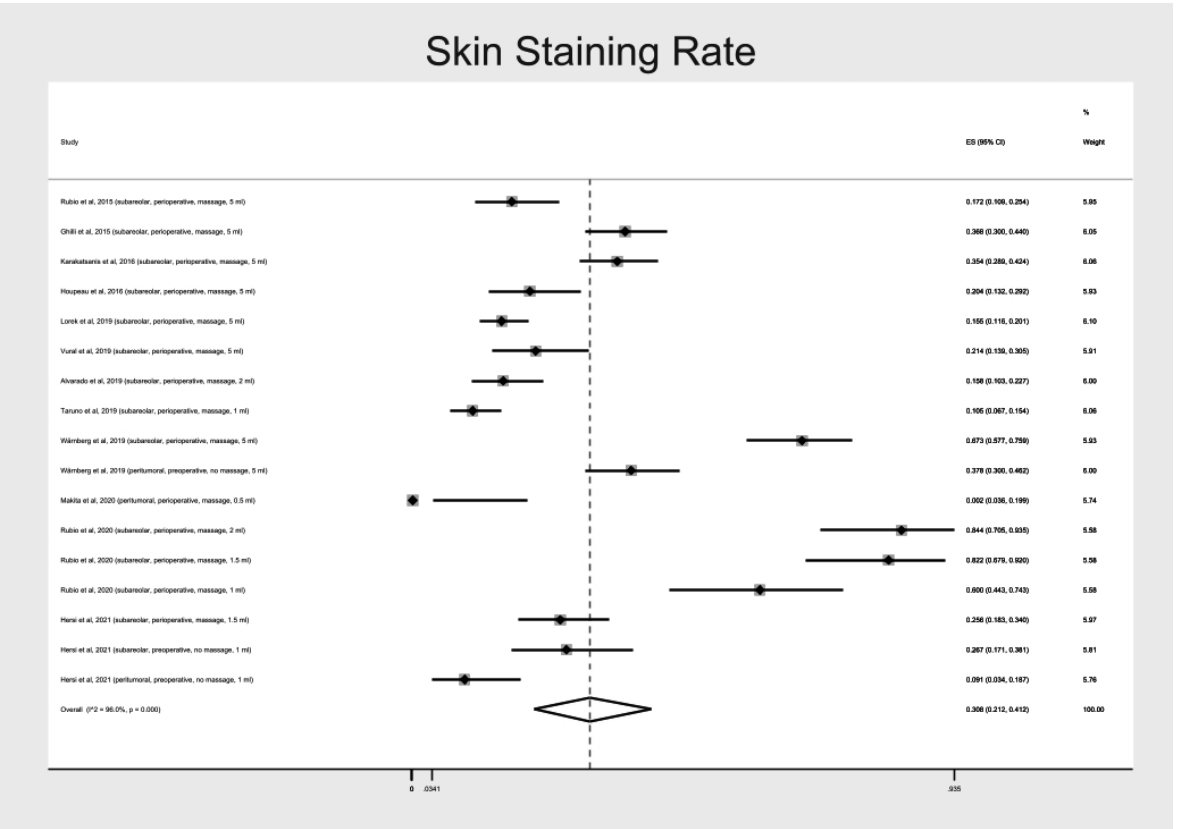


Figure S5: Forest plot for SPIO-induced skin staining



PRISMA 2020 Main Checklist

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1, Row 1-2
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 3, Row 86-98
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 3, Rows 99-102
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4, Rows 136-146
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4, Rows 136-146
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4, Rows 136-146
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4, Rows 136-146
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 4, Rows 149-150

Topic	No.	Item	Location where item is reported
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Pages 4-5, Rows 151-164
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Pages 4-5, Rows 151-164
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Supplement Table 1
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Pages 4-5, Rows 151-164
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Pages 4-5, Rows 151-164
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Pages 4-5, Rows 151-164
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Pages 4-5, Rows 151-164
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Pages 4-5, Rows 151-164
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Pages 4-5, Rows 151-164
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Pages 4-5, Rows 151-164
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 5, Rows 166-176

Topic	No.	Item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 4, Rows 131-133
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 5, Rows 179-198; Figure 1 (PRISMA flowchart)
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	No such studies were found
Study characteristics	17	Cite each included study and present its characteristics.	Table 1; Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Supplement Table 1
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1; Table 2
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Page 5-8, Rows 200-293
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 5-8, Rows 200-293
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 5-8, Rows 200-293
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 5-8, Rows 200-293
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Supplement Table 1
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 8-9, Rows 295-336

Topic	No.	Item	Location where item is reported
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 1, Rows 340-354
	23b	Discuss any limitations of the evidence included in the review.	Page 9, Rows 369-370; Page 9-10, Rows 375-376
	23c	Discuss any limitations of the review processes used.	Page 10, Rows 389-394
	23d	Discuss implications of the results for practice, policy, and future research.	Page 10, Rows 394-401
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 10; Rows 404-412
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 10; Rows 404-412
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Not relevant as not performed
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 10; Rows 404-412
Competing interests	26	Declare any competing interests of review authors.	Page 10; Rows 404-412
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 10; Rows 404-412

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	No
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	No
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	Yes
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes

Topic	No.	Item	Reported?
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Paper II

JAMA Surgery | Original Investigation

Magnetic Seed vs Guidewire Breast Cancer Localization With Magnetic Lymph Node Detection
A Randomized Clinical Trial

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IMPORTANCE Guidewires have been the standard for breast lesion localization but pose operative and logistic challenges. Paramagnetic seeds have shown promising results, but to the authors' knowledge, no randomized comparison has been performed.

OBJECTIVE To determine whether the combination of a paramagnetic seed and superparamagnetic iron oxide (SPIO) is equivalent to guidewire and SPIO for breast cancer localization and sentinel lymph node detection (SLND).

DESIGN, SETTING, AND PARTICIPANTS This was a phase 3, pragmatic, equivalence, 2-arm, open-label, randomized clinical trial conducted at 3 university and/or community hospitals in Sweden from May 2018 to May 2022. Included in the study were patients with early breast cancer planned for breast conservation and SLND. Study data were analyzed July to November 2022.

INTERVENTIONS Participants were randomly assigned 1:1 to a paramagnetic seed or a guidewire. All patients underwent SLND with SPIO.

MAIN OUTCOMES AND MEASURES Re-excision rate and resection ratio (defined as actual resection volume / optimal resection volume).

RESULTS A total of 426 women (median [IQR] age, 65 [56-71] years; median [IQR] tumor size, 11 [8-15] mm) were included in the study. The re-excision rate was 2.90% (95% CI, 1.60%-4.80%), and the median (IQR) resection ratio was 1.96 (1.15-3.44). No differences were found between the guidewire and the seed in re-excisions (6 of 211 [2.84%] vs 6 of 209 [2.87%]; difference, −0.03%; 95% CI, −3.20% to 3.20%; $P = .99$) or resection ratio (median, 1.93; IQR, 1.18-3.43 vs median, 2.01; IQR, 1.11-3.47; $P = .70$). Overall SLN detection was 98.6% (95% CI, 97.1%-99.4%) with no differences between arms (203 of 207 [98.1%] vs 204 of 206 [99.0%]; difference, −0.9%; 95% CI, −3.6% to 1.8%; $P = .72$). More failed localizations occurred with the guidewire (21 of 208 [10.1%] vs 4 of 215 [1.9%]; difference, 8.2%; 95% CI, 3.3%-13.2%; $P < .001$). Median (IQR) time to specimen excision was shorter for the seed (15 [10-22] minutes vs 18 [12-30] minutes; $P = .01$), as was the total operative time (69 [56-86] minutes vs 75.5 [59-101] minutes; $P = .03$). The experience of surgeons, radiologists, and surgical coordinators was better with the seed.

CONCLUSIONS AND RELEVANCE The combination of SPIO and a paramagnetic seed performed comparably with SPIO and guidewire for breast cancer conserving surgery and resulted in more successful localizations, shorter operative times, and better experience.

TRIAL REGISTRATION ISRCTN.org Identifier: ISRCTN11914537

Visual Abstract
Invited Commentary
Supplemental content

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Breast cancer screening, along with the improvement of imaging, have led to an increase in breast cancer diagnosis at a presymptomatic stage.[1] In the majority of these cases, breast-conserving surgery is feasible, but preoperative tumor localization is required.

The guidewire has been the most extensively used method of breast tumor localization due to its low cost and ease of use.[2,3] However, complications such as dislocation, migration, and patient discomfort have been described.[4-7] Apart from these complications, guidewire localization is restricted to the day of surgery, posing logistical challenges. These issues have led to the development of novel, wire-free localization devices[8] such as radioiodine seeds,[9-11] radar reflectors,[12,13] radiofrequency tags,[14,15] and paramagnetic/magnetic seeds.[16,17]

Most of these patients are clinically node negative and undergo sentinel lymph node dissection (SLND), which has traditionally been performed with a radioisotope (RI) with or without blue dye (BD). Although highly reliable, this combination poses challenges due to restricted access to nuclear medicine facilities, strict regulations, and risk of allergic reaction to BD, whereas the short half-life of the RI limits administration on the day of surgery or the day before, complicating logistics. Superparamagnetic iron oxide (SPIO) nanoparticles have shown comparable performance with an RI with or without BD with the additional advantage of a wider time frame of preoperative administration.[18-20] Perceived drawbacks of the method are skin staining and artifacts on postoperative magnetic resonance imaging (MRI)[21,22]; a recent meta-analysis,[20] however, suggests that peritumoral SPIO administration could address these concerns, without any compromise of SLN detection outcomes.

Previous large cohort studies have shown that paramagnetic seeds are advantageous in terms of operating time and ease of logistics compared with the guidewire and with comparable re-excision rates and specimen sizes; this, however, has not been validated in randomized clinical trials (RCTs).[16,23] At the same time, combining seeds with SPIO for a totally magnetic technique encompassing tumor localization and SLN detection has been investigated in small studies.[24,25] The technique was found feasible with the possible advantages of simplified logistics, as the localization procedure and tracer injection are detached from the day of surgery and, possibly, increased patient and physician satisfaction. Furthermore, both seed and SPIO are detectable by the same probe, avoiding multiple equipment in the operating room. Therefore, an RCT would elucidate these questions.

Key Points

Question Is the combination of paramagnetic seed and superparamagnetic iron oxide (SPIO) equivalent to guidewire and SPIO for breast cancer localization and sentinel lymph node detection (SLND)?

Findings This randomized clinical trial including 426 patients from 3 hospitals in Sweden found that a totally magnetic technique was equivalent to the combination of guidewire and SPIO in re-excision frequency, specimen volumes, and SLND. In addition, seed and SPIO resulted in shorter operative times and increased satisfaction among health care practitioners.

Meaning A totally magnetic technique is an effective option for breast cancer localization and SLND.

Methods

In the interest of higher external validity, the Magnetic Marker to Detect Primary Lesion and Sentinel Node in Breast Cancer (MAGTOTAL) trial was designed as a phase 3, open-label, pragmatic trial including centers with different levels of experience with the magnetic technique (Supplement 1). The trial was approved by the Uppsala Regional ethics committee and registered to a publicly available database. Enrollment took place between May 1, 2018, and May 1, 2022, at 3 hospitals in Sweden (Akademiska University Hospital, Uppsala; Västmanlands Hospital, Västerås; and Sahlgrenska University Hospital, Gothenburg). Adult patients with nonpalpable ductal cancer in situ (DCIS) or T1 to T3 invasive breast cancer who were scheduled to receive breast-conserving surgery and SLND were eligible for inclusion in the trial. Patients with small, diffusely palpable lesions requiring preoperative localization or multifocal/multicentric lesions amenable to breast conservation were also included. Exclusion criteria included intolerance or hypersensitivity to iron or dextran compounds, iron overload disease, pregnancy and lactation, inability to provide informed consent, and pacemakers or implantable devices in the ipsilateral chest-wall or shoulder. Participant race and ethnicity were not collected because there is not any known interaction between these and the outcomes examined in the trial. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines for pragmatic trials.[26]

After oral and written informed consent, participants were randomly assigned with an allocation ratio of 1:1 in blocks of 8. The randomization was performed using the randomizeR package of R statistical software, version 3.5.1 (R Project for Statistical Computing).[27] The sequence was concealed in opaque envelopes until the intervention was assigned. During the COVID-19 pandemic, the protocol was amended to allow for tolerance and ensure that scheduled surgery would not be affected by randomization.

In the experimental arm, lesion localization was performed with the Magseed marker (Endomag), a 5-mm paramagnetic seed used for the localization of breast cancer lesions, and in the control arm, with a guidewire (Bard Peripheral Vascular Inc). Regardless of randomization, because SPIO dose and injection timing do not affect SLN detection, patients received 1 to 1.5 mL of Magtrace (Endomag), a nonradioactive liquid tracer containing iron oxide nanoparticles, dorsally to the tumor, at any point between the preoperative visit for surgical planning to the day of surgery, either simultaneously with lesion localization or not.[20] Following trial pragmatism, the placement of the marker and the administration of SPIO were to be performed according to local routines or case-by-case convenience, meaning that surgeons or radiologists could insert the paramagnetic marker with or without simultaneous injection of the liquid tracer preoperatively, whereas guidewires were exclusively inserted by a breast radiologist on the day of

the surgery or the day before. Both methods of localization were performed under local anesthesia, and accurate localization was verified radiologically. There were no prerequisites such as medical professional level (resident, fellow, consultant), minimum experience, or a completed learning curve for participating radiologists and surgeons. Specimen radiography was performed as per routine, and SLND was performed with the SentiMag probe (Endomag), a probe that can detect both the paramagnetic marker and the liquid tracer, adhering to the 10% of the maximum signal cutoff rule, to complete the procedure. Due to the nature of the intervention, masking was not possible.

The primary outcome measure was resection ratio for each marker in patients with negative margins. The resection ratio was defined as the actual resection volume (ARV) divided by the optimal resection volume (ORV), the latter being the assessed volume needed to excise the lesion with 1-cm margins. The ARV was derived from the fresh specimen weight with concomitant volume calculation, and the ORV was calculated based on preoperative radiology; in cases of discordance between different modalities, the largest measurement was used. Negative margins were defined as "no tumor on ink" for invasive cancer and 2 mm for DCIS. Secondary outcomes included SLN detection rate, adverse events, time to specimen excision, operative time, and ease of implementation by all involved health care practitioners (surgeons, radiologists, surgical coordinators), assessed by Likert scales (scored 0-10, with a higher score denoting higher satisfaction). A prespecified longitudinal analysis of patient-reported outcomes and quality of life evaluation as well as patient-reported experience measures and cost-effectiveness analyses will be reported elsewhere.

Statistical Analysis

According to the Swedish Breast Cancer Registry, the 3 participating sites had comparable re-excision frequencies, with a documented average between 4% and 7%. Therefore, a clinically meaningful improvement based solely on a new device was not expected. However, placing the paramagnetic marker and injecting SPIO in the same location could cause an overlapping signal, possibly leading to excision of larger specimens, a concern that would not apply with the guidewire. Available literature suggests that the resection ratio for guidewire-based excision ranges between 1.9 and 2.8.[23,28] The MAGTOTAL pilot study suggested that the totally magnetic technique for nonpalpable tumor localization and magnetic SLND used in the trial had a resection ratio of 1.5,[25] whereas a nonrandomized comparison of guidewires and paramagnetic seeds with isotope-based SLND found comparable ratios (1.92 vs 1.67) with comparable re-excision rates (14 vs 16%).[23] In the absence of established reference values, we assumed a 2-sided equivalence of 0.3 difference in resection ratio as clinically meaningful (corresponding to a 30% difference in excised volume), with a 2-sided *P* value set at .05 and power of 80%, corresponding to 191 patients per arm. This population also satisfied the hypothesis of noninferiority in re-excision rates for a standard of 4% by a 5% margin, and an additional 10% was included per arm.

Table 1. Patient Characteristics

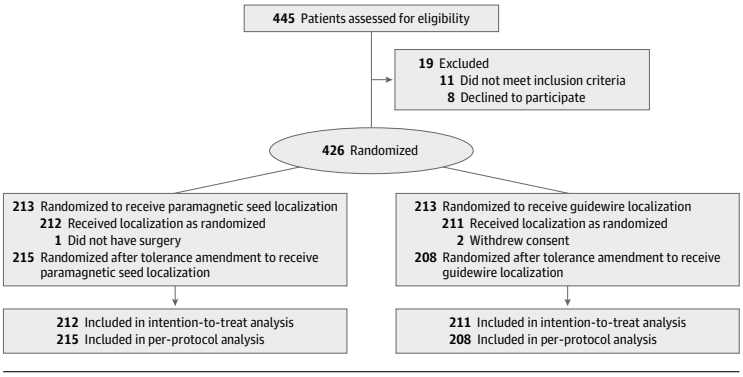
Characteristic	Allocation arm	
	Guidewire	Magnetic marker
Recruiting site, No. (%)		
Uppsala	121 (57.1)	115 (54.5)
Västerås	53 (25.0)	54 (25.6)
Gothenburg	38 (17.9)	42 (19.9)
Age, median (IQR), y	67 (56-72)	64 (56-70)
Body mass index, median (IQR)[a]	26.1 (23.8-29.8)	26.7 (24.1-29.8)
Screening detected lesion, No. (%)		
No	16 (7.6)	18 (8.5)
Yes	195 (92.4)	193 (91.5)
Palpable lesion, No. (%)		
No	199 (94.3)	196 (92.9)
Diffusely palpable	12 (5.7)	15 (7.1)
Preoperative MRI, No. (%)		
No	133 (75.1)	115 (66.5)
Yes	44 (24.9)	58 (33.5)
Lateralization, No. (%)		
Right breast	104 (49.5)	101 (47.9)
Left breast	106 (50.5)	110 (52.1)
Location, No. (%)		
Upper outer quadrant	119 (56.1)	115 (54.8)
Upper inner quadrant	33 (15.6)	40 (19.0)
Lower inner quadrant	22 (10.4)	20 (9.5)
Lower outer quadrant	29 (13.7)	20 (9.5)
Central/retroareolar	7 (3.3)	15 (7.1)
Multifocal/multicentric	2 (0.9)	1 (0)
Lesion size, median (IQR), mm	10 (8-15)	11 (8-15)
Histology, No. (%)		
IDC (NST)	170 (80.2)	174 (84.1)
ILC	27 (12.7)	16 (7.7)
DCIS	3 (1.4)	3 (1.4)
Other[b]	12 (5.7)	14 (6.8)
Nuclear grade, No. (%)		
Grade 1	52 (25.2)	63 (31.5)
Grade 2	123 (59.7)	105 (52.5)
Grade 3	31 (15.0)	32 (16.0)
Intrinsic subtype, No. (%)		
Luminal A	138 (69.0)	117 (59.7)
Luminal B, *ERBB2* negative	41 (20.5)	62 (31.6)
Luminal B, *ERBB2* enriched	4 (2.0)	6 (3.1)
Basal-like, *ERBB2* enriched	5 (2.5)	3 (1.5)
Triple-negative breast cancer	12 (6.0)	8 (4.1)
Primary systemic therapy		
Yes	7 (3.3)	7 (3.3)
No	205 (96.7)	204 (96.7)
Type of surgery		
Simple WLE	180 (84.9)	169 (81.3)
OPBCS level I	24 (11.3)	26 (12.5)
OPBCS level II	8 (3.8)	13 (6.3)

Abbreviations: DCIS, ductal cancer in situ; IDC (NST), invasive ductal cancer (nonspecific type); ILC, invasive lobular cancer; MRI, magnetic resonance imaging; OPBCS, oncoplastic breast-conserving surgery; WLE, wide local excision.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Other refers to mucinous breast cancer, medullary breast cancer, tubular breast cancer.

Figure. MAGTOTAL Trial Consolidated Standards of Reporting Trials (CONSORT) Flow Diagram



Continuous variables were summarized as means with SD or medians with IQR, depending on data distribution. Comparisons were performed using a *t* test for means and the Mann-Whitney *U* test or the Kruskal-Wallis test for medians. Likert items were analyzed as ordinal data (median, IQR) and compared with nonparametric tests, as appropriate. Categorical variables were summarized as numbers and proportions with 95% CIs and comparisons were performed with Fisher exact test for unpaired data (Wald test for differences) and McNemar test for paired data. Multivariable regression analysis was performed if significant univariate associations of clinically relevant variables were demonstrated. Intention-to-treat and per-protocol analyses were performed for the primary end points, and per-protocol analyses were performed for the secondary end points. Effect sizes (odds ratios [ORs] for logistic regression and β coefficients for linear regression) were reported with 95% CIs. Analyses were performed with Stata 17 (StataCorp) and SPSS, version 28 (IBM Corp).

Results

Of the 445 assessed patients, 430 were deemed eligible. After consent withdrawal from 4 patients, 426 women (median [IQR] age, 65 [56-71] years; median [IQR] tumor size, 11 [8-15] mm) were randomly assigned to 2 well-balanced arms of 213 participants (**Table 1**). In the per-protocol analysis, the totally magnetic arm included 215 participants whereas the guidewire arm included 208 (**Figure**); however, the discordance was not significant (McNemar test: difference, −0.9%; 95% CI, −2.6% to 0.8%; *P* = .34).

Re-excision Rates, Resection Ratios, and SLND Outcomes

The overall re-excision rate was 2.90% (95% CI, 1.60%-4.80%). No differences were found between the guidewire and the paramagnetic seed (intention-to-treat analysis, 6 of 211 [2.84%] vs 6 of 209 [2.87%]; difference, −0.03%; 95% CI, −3.20% to 3.20%; *P* = .99 and per-protocol analysis, 6 of 206 [2.91%] vs 6 of 214 [2.84%]; difference, 0.07%; 95% CI, −3.10% to 3.30%; *P* = .95). Only the recruiting site was associated with re-excision rate in the univariable analysis (Uppsala: 0.9%; 95% CI, 0.2-2.7; Västerås, 3.8%; 95% CI, 1.3-8.7; Gothenburg, 7.6%; 95% CI, 3.2-15.0; *P* = .004), with logistic regression suggesting similar outcomes (1 [Reference] for free margins Uppsala; Västerås: OR, 0.219; 95% CI, 0.039-1.215; *P* = .08; Gothenburg: OR, 0.104; 95% CI, 0.020-0.529; *P* = .006).

The median (IQR) overall resection ratio was 1.96 (1.15-3.44). The outcomes were equivalent between the guidewire and the paramagnetic seed (intention-to-treat analysis: median, 1.93; IQR, 1.18-3.43 vs median, 2.01; IQR, 1.11-3.47; *P* = .70; per-protocol analysis: median, 1.96; IQR, 1.22-3.48 vs median, 1.97; IQR, 1.11-3.46; *P* = .82). In univariable analyses, resection ratio was associated with body mass index, recruiting site, diffusely palpable lesion, preoperative MRI, and type of breast conservation. In multivariable analyses, only body mass index, type of breast conservation, and recruiting site were found to affect the resection ratio (**Table 2**). Sites interacted with re-excision rates and were a surrogate of experience with the magnetic technique and (possibly) different operating styles; further analyses conducted showed that in the center with the longest experience with the probe, resection ratios and re-excision rates were the lowest. In this setting, the resection ratio for the paramagnetic seed was 0.3 lower than the guidewire (1.26 vs 1.57), but this did not reach statistical significance (eTable 1 in Supplement 2).

Overall SLN detection was (98.6%; 95% CI, 97.1%-99.4%). SLN detection rates were similar between the experimental and the control arms (203 of 207 [98.1%] vs 204 of 206 [99.0%]; difference, −0.9%; 95% CI, −3.6% to 1.8%; *P* = .72). A median (IQR) of 2 (1-3) SLNs were retrieved in both arms (*P* = .68). The prevalence of metastasis was also comparable (32 of 212 [15.1%] vs 21 of 204 [10.3%]; difference, −4.8%; 95% CI, −11.7% to 2.1%; *P* = .19) and did not affect detection rates or nodal yield.

Procedural Outcomes and Patterns of Implementation

Median (IQR) time to specimen excision was significantly shorter for the paramagnetic marker (15 [10-22] minutes vs

Table 2. Univariate and Multivariable Analysis for the Resection Ratio

Site/variable	Univariate analysis Resection ratio (IQR)	*P* value	Multivariable analysis β coefficient (95% CI)	*P* value
Per intention-to-treat analysis				
Magnetic marker	2.01 (1.11-3.47)	.70[a]	NA	NA
Guidewire	1.93 (1.18-3.43)			
Per-protocol analysis				
Magnetic marker	1.97 (1.11-3.46)	.82[a]	NA	NA
Guidewire	1.96 (1.22-3.48)			
Recruiting site			1.269 (0.763-1.775)	<.001
Uppsala	1.45 (0.78-2.13)	<.001[b]	1 [Reference]	NA
Västerås	3.33 (2.13-5.39)		2.478 (1.650-3.036)	<.001
Gothenburg	2.87 (2.00-4.38)		1.729 (0.805-2.653)	<.001
Body mass index[c]	0.307 (0.213-0.395)[d]	<.001[d]	0.181 (0.101-0.260)	<.001
Palpable lesion				
No	2.00 (1.18-3.52)	.03[a]	−0.957 (−2.491-0.577)	.22
Diffusely palpable lesion	1.60 (0.90-2.23)			
Preoperative MRI				
Yes	2.55 (1.50-4.27)	<.001[a]	−0.156 (−1.115-0.802)	.75
No	1.61 (0.95-2.83)			
Multifocal disease				
No	1.98 (1.18-3.46)	.13[a]	NA	NA
Yes	1.37 (0.56-3.15)			
Histology				
IDC (NST)	1.95 (1.15-3.54)	.53[b]	NA	NA
ILC	2.00 (1.04-2.81)			
DCIS	2.25 (1.57-3.06)			
Other	1.79 (1.07-2.85)			
Type of breast-conserving surgery			1.188 (0.475-1.901)	<.001
Simple WLE	2.07 (1.26-3.60)	<.001[b]	1 [Reference]	NA
OPBCS level I	1.37 (0.70-1.85)		−0.029 (−1.105-1.047)	.96
OPBCS level II	2.69 (1.05-5.57)		4.916 (3.367-6.466)	<.001
Overall	1.96 (1.15-3.44)			

Abbreviations: DCIS, Ductal cancer in situ; IDC (NST), invasive ductal cancer (nonspecific type); ILC, invasive lobular cancer; MRI, magnetic resonance imaging; reference category; NA, not applicable; OPBCS, oncoplastic breast-conserving surgery; WLE, wide local excision.

[a] Mann-Whitney *U* test.

[b] Kruskal-Wallis test.

[c] Calculated as weight in kilograms divided by height in meters squared.

[d] Spearman ρ (95% CI in parentheses).

18 [12-30] minutes; *P* = .01) as was the total operative time (69 [56- 86] minutes vs 75.5 [59-101] minutes; *P* = .03) (**Table 3**). These outcomes were associated with type of breast surgery on univariable analysis, too. Multivariable regression demonstrated that the use of a paramagnetic marker for lesion localization still resulted in shorter excision and operative times.

The rate of failed localizations in the trial was 5.9% (95% CI, 3.9-8.6). There were significantly more failed localizations in the guidewire arm compared with the paramagnetic marker (21 of 208 [10.1%] vs 4 of 215 [1.9%]; difference, 8.2%; 95% CI, 3.3%-13.2%; *P* < .001). From the 4 failed seed localizations, 1 was due to failed deployment and a guidewire was used instead; 3 were intraoperative due to superficial lesions, with the seed dislocated during dissection; in all cases, the tumor was identified with the SPIO magnetic signal. In the guidewire arm (n = 21), 8 localizations failed preoperatively due to tumor location or dense parenchyma and were replaced with a seed, and the remaining 13 were intraoperative dislocations, where resection was guided by the magnetic signal and brown staining of the SPIO. Re-excision was more common in failed localizations (2 of 25 [8%] vs 10 of 395 [2.5%]), but the difference was not significant (5.5%; 95% CI, −5.3% to 16.2%; *P* = .11) and did not differ per localization technique. Postoperative SPIO-induced skin staining at the postoperative visit was 10.5% (95% CI, 7.7%-13.8%) and was associated only with nonradiology-guided, free-hand peritumoral injection (17 of 108 [15.7%] vs 27 of 313 [8.6%]; difference, 7.1%; 95% CI, 0.04%-15.6%; *P* = .04; OR, 1.979; 95% CI, 1.032-3.795; *P* = .04). The rate of postoperative complications was 8.6% (95% CI, 6.1%-11.7%) and did not differ between the paramagnetic marker and the guidewire in frequency (9.8% vs 7.3%; difference, 2.5%; 95% CI, −3.3% to 8.3%; *P* = .45) or type (eTable 2 in Supplement 2).

There was significant variability in how lesion localization and SPIO administration were implemented (**Table 4**). However, none of these interacted with re-excision rates, resection ratios, or SLN detection. The localization time was shorter in the totally magnetic arm (median [IQR], 4 [3-5] minutes) than the guidewire arm (median [IQR], 5 [5-6] minutes) across all centers (*P* < .001).

Ease of Implementation

All the disciplines involved graded their experience on a Likert scale of 0 to 10 with higher scores denoting higher satisfaction. Overall, 15 surgeons, 4 radiologists, and 6 surgical coordinators were involved. Satisfaction was higher with the paramagnetic marker across all disciplines, with the difference

Table 3. Univariate and Multivariable Regression for Time To Specimen Excision and Operative Time

Marker/surgery type	Univariate analysis		Multivariable analysis	
	Median (IQR)	*P* value	β coefficient (95% CI)	*P* value[a]
Time to specimen excision, min				
Type of marker			3.768 (1.623-5.917)	.001
Magnetic marker	15 (10-22)	.01[b]	1 [Reference]	NA
Guidewire	18 (12-30)		3.763 (1.613-5.913)	.001
Type of breast-conserving surgery			4.913 (2.895-6.931)	<.001
Simple WLE	16 (11-24.5)	.01[c]	1 [Reference]	NA
OPBCS level I	20 (14-30)		5.079 (1.819-8.339)	.002
OPBCS level II	30 (11.5-36)		9.656 (4.831-14.479)	<.001
Total operative time, min				
Type of marker			10.227 (4.634-15.820)	<.001
Magnetic marker	69 (56- 86)	.03[b]	1 [Reference]	NA
Guidewire	75.5 (59-101)		10.442 (4.873-16.011)	<.001
Type of breast-conserving surgery			23.121 (17.782-28.460)	<.001
Simple WLE	69 (55-86)	<.001[c]	1 [Reference]	NA
OPBCS level I	78.5 (66-103)		15.505 (6.969-24.041)	<.001
OPBCS level II	115 (102-143)		54.236 (41.505-66.967)	<.001

Abbreviations: NA, not applicable; OPBCS, oncoplastic breast-conserving surgery; WLE, wide local excision.

[a] *P* value refers to the outcomes of the multivariable regression analysis (linear regression).

[b] Mann-Whitney *U* test.

[c] Kruskal-Wallis test.

Table 4. Patterns of Lesion Localization and Superparamagnetic Iron Oxide (SPIO) Administration

Localization/administration	Guidewire	Magnetic marker	*P* value
Localization modality, No. (%)			
Ultrasound	194 (93.3)	189 (92.2)	.71[a]
Stereotactic	14 (6.7)	16 (7.8)	
Days from localization to surgery, median (IQR)	0	5 (1-8)	<.001[b]
Time for lesion localization, median (IQR), min	5 (5-6)	4 (3-5)	<.001[b]
SPIO administration, No. (%)			
Surgeon[c]	86 (40.6)	22 (10.5)	<.001[a]
Radiologist	126 (59.4)	188 (89.5)	
SPIO volume, mL, No. (%)			
1.0	187 (89.0)	195 (92.9)	.23[a]
1.5	23 (11.0)	15 (7.1)	
Days from SPIO injection to surgery, median (IQR)	7 (0-15)	6 (1-8)	.04[b]
Single localization procedure (breast and axilla), No. (%)			
Yes	74 (34.9)	180 (85.3)	<.001[a]
No	138 (65.0)	31 (14.7)	

[a] Fisher exact test.

[b] Mann-Whitney *U* test.

[c] Surgeon denotes free-hand SPIO injection around the tumor.

being more pronounced for surgeons and coordinators (eTable 3 in Supplement 2).

Discussion

In this pragmatic, multicenter RCT, a paramagnetic marker was equivalent to the guidewire in terms of re-excision rates and excess tissue removal regardless of physician experience or localization routines. These results corroborate findings from previous cohort studies[16,23,29] and provide stronger evidence. Moreover, the implementation of a totally magnetic technique for lesion removal and SLND was favorable compared with the guidewire in terms of shorter operative times and easier logistics, as shown by the preferences of all health care practitioners that were involved.

One of the concerns expressed regarding the combination of a paramagnetic marker for lesion localization and a peritumoral SPIO injection was that the overlapping signal might lead to the excision of larger specimens.[24] Clearly, the combination is successful, regardless of SPIO injection location (subareolar or intraparenchymal in another quadrant of the breast), as smaller studies that tried to address this concern have suggested.[24,30] Reassuringly, resection ratios in this RCT were similar between the trial arms, regardless of previous physician experience or practice patterns, suggesting that adaptation is safe. Moreover, in the center with the highest experience, the resection ratio in the totally magnetic arm was 0.3 lower (1.26 vs 1.57) and one of the lowest reported in the literature with only 0.9% re-excisions. Although this did not reach statistical significance, it is indicative of how familiarization with the technique yields potential for precision surgery and

resection of smaller specimens. It seems that the totally magnetic technique for nonpalpable tumor localization used in the MAGTOTAL trial allows for the creation of a magnetic halo around the lesion, with the seed placed in the anterior aspect of the tumor, whereas the brown staining from SPIO in the surrounding tissue enables additional intraoperative visual navigation. This technique had lower failed localization rates than the guidewire, a finding similar to previous nonrandomized comparisons.[16] Furthermore, injecting SPIO close to the tumor, especially under ultrasonographic guidance, results in reduced skin staining because the bulk of SPIO is removed. This may contribute to minimizing postoperative MRI artifacts, which has been a concern with SPIO-guided SLND.[21,22] Currently, this hypothesis is being investigated in a prospective study from our group.[31]

Previous studies have investigated solely magnetic lesion localization and others solely magnetic SLN detection; the outcomes were comparable with the guidewire and, respectively, RI with or without BD.[16,20] Paramagnetic markers and SPIO both have the benefit of decoupling the respective procedure from the day of surgery[17,32,33]; however, if not combined, this benefit is not being fully utilized. In this RCT, the combination was successful and was positively met by all health care professionals involved in planning and performing breast cancer surgery. The present RCT showed that the totally magnetic technique for nonpalpable tumor localization is currently the only wire- and RI-free technique, to the authors' knowledge, where both lesion localization and SLN detection can be performed with the same probe, suggesting that the technique can be implemented in any setting.

Strengths and Limitations

Multiple, nonrandomized comparisons of the paramagnetic seed to the guidewire that had suggested similar outcomes served in providing baseline comparative evaluation. Therefore, an RCT was necessary for a definitive comparison of main efficacy and safety aspects, as suggested by the Idea, Development, Exploration, Assessment, and Long-term Follow-Up (IDEAL) Framework.[34] The trial did not investigate superiority, but equivalence, as the rationale that a device per se can improve outcomes had not been demonstrated in similar trials[11]; however, because the investigated technique had other presumed benefits, an RCT was necessary, as relevant literature suggests.[35] The pragmatic design ensures the external validity and that the intervention can be implemented with ease and flexibility and without expertise or previous familiarization.

On the other hand, the trial has several limitations. Differences in surgical style are hard to account for, which may be the reason for differences among sites, but, reassuringly, not between trial arms. Moreover, the inherent inability to mask the intervention may account for performance bias and the Pygmalion effect, but we chose end points that would minimize this as we investigated both re-excision and excess excision of healthy tissue at the same time.[36] Finally, cost efficacy analyses are still pending, but the shorter localization and operating time, along with the ease of preoperative planning, may compensate for the higher cost of the device.

Conclusions

In this RCT, a paramagnetic marker was equivalent to the guidewire in re-excisions and excised specimen volumes, with advantages of shorter operative time, safer localization, and preferable logistics. Additionally, familiarization with the technique may offer the potential for more precise surgery. Moreover, a totally magnetic technique for lesion localization and SLND relieves the health care system from the restrictions posed by guidewire localization or radioisotope-based methods, making it an attractive alternative for numerous and diverse clinical settings.

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Supplementary Online Content

Pantiora E, Jazrawi A, Hersi AF, et al. Magnetic seed vs guidewire breast cancer localization with magnetic lymph node detection: a randomized clinical trial. *JAMA Surg*. Published online December 27, 2023. doi:10.1001/jamasurg.2023.6520

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1: Resection ratio per site and type of surgery

	Overall	Guidewire	Magnetic marker	p-value
Entire trial	1.96 (1.14, 3.46)	1.96 (1.22, 3.48)	1.97 (1.11, 3.46)	.96
Uppsala	1.45 (.78, 2.13)	1.59 (.77, 2.15)	1.26 (.78, 2.07)	.08
WLE (n=170)	1.48 (.85, 2.13)	1.60 (.98, 2.17)	1.29 (.76, 2.05)	
OPBCS Level I (n=47)	1.26 (.68, 1.73)	1.46 (.69, 1.81)	1.15 (.69, 1.60)	
OPBCS Level II (n=18)	1.87 (.88, 7.40)	1.38 (.49, 41.79)	2.13 (1.08, 13.21)	
Västerås	3.33 (2.13, 5.39)	3.21 (1.60, 4.79)	3.46 (2.50, 5.75)	.92
WLE (n=105)	3.42 (2.19, 5.21)	3.33 (1.82, 4.79)	3.44 (2.47, 5.78)	
OPBCS Level I	-	-	-	
OPBCS Level II (n=2)	4.21 (2.85, 5.57)	-	4.21 (2.85, 5.57)	
Gothenburg	2.87 (2.00, 4.38)	2.88 (2.05, 4.38)	2.77 (1.86, 4.63)	.91
WLE (n=71)	2.78 (2.00, 4.27)	2.88 (2.22, 4.20)	2.57 (1.73, 4.27)	
OPBCS Level I (n=3)	3.18 (3.00, 6.62)	-	3.18 (3.00, 6.62)	
OPBCS Level II (n=1)	5.27 (5.27, 5.27)	-	5.27 (5.27, 5.27)	

Legend: Resection Ratios per received marker (per protocol analysis) in subgroups by site and type of surgery. Resection ratio is summarized as median (interquartile range, iqr). OPBCS: oncoplastic breast conserving surgery, WLE: wide local excision. p-value: independent medians test.

eTable 2. Type of complication per received localization device. Analysis per protocol. P-value: Fisher's exact test

(n.%)	Per protocol intervention		p-value
	Guidewire	Magnetic marker	
None	193 (92.8)	194 (90.2)	.53
Symptomatic breast seroma	3 (1.4)	1 (0.5)	
Breast hematoma	2 (1.0)	4 (1.9)	
Symptomatic axillary seroma	0 (0.0)	1 (0.5)	
Axillary hematoma	2 (1.0)	1 (0.5)	
Breast infection	5 (2.4)	3 (1.4)	
Axillary infection	1 (0.5)	2 (0.9)	
Delayed wound healing	0 (0.0)	3 (1.4)	
Postoperative bleeding in the breast	1 (0.5)	4 (1.9)	
Pain at SPIO injection site	1 (0.5)	1 (0.5)	
Superficial venous thrombosis	0 (0.0)	1 (0.5)	

eTable 3. Health care practitioners' experience with each marker

	Paramagnetic seed	Guidewire	p-value
Ease of logistics and planning (theatre coordinators)	10 (10,10)	6 (4,8)	<.001
Ease of localisation (radiologists)	7 (7,9)	7 (7,7)	<.001
Ease of intraoperative detection (surgeons)	9 (8,10)	7 (7,8)	<.001

Legend: Responses to Likert items with range 0-10, higher score denotes higher satisfaction. Likert scores are summarized as median (iqr). p-value: independent sample medians test.

Paper III

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Original Article

Magnetically guided surgery after primary systemic therapy for breast cancer: implications for enhanced axillary mapping

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Preliminary results presented to the 13th European Breast Cancer Conference (EBCC-13), Barcelona, Spain, November 2022 (https://doi.org/10.1016/S0959-8049(22)01422-8).

Abstract

Background: Superparamagnetic iron nanoparticles perform comparably to radioisotope ± blue dye for sentinel lymph node detection in breast cancer, even when injected up to 8 weeks before surgery. Using superparamagnetic iron nanoparticles for sentinel lymph node detection after primary systemic therapy, and the maximum time frame of superparamagnetic iron nanoparticle administration have not been investigated.

Methods: This cohort study included cN0/1-to-ycN0 patients undergoing sentinel lymph node detection or targeted axillary dissection. All patients received superparamagnetic iron nanoparticles either before primary systemic therapy or before surgery, and radioisotope on the day of surgery.

Results: For 113 patients analysed, superparamagnetic iron nanoparticles were injected a median of 3 (range 0–248) days before surgery, with a 97.4% detection rate compared with 91.2% for radioisotope ($P = 0.057$). Concordance for radioisotope was 97.1% and this was not affected by timing of superparamagnetic iron nanoparticle injection (Kendall's tau 0.027; $P = 0.746$). The median sentinel lymph node yield was 3 (interquartile range (i.q.r.) 2–3) for superparamagnetic iron nanoparticles and 2 (i.q.r. 2–3) for radioisotope ($P < 0.001$). In targeted axillary dissection, detection was 100% for superparamagnetic iron nanoparticles and 81.8% for radioisotope ($P = 0.124$). The index node was magnetic in 93.9% and radioactive in 66.7% ($P = 0.007$), an outcome that was not affected by any factors. For patients with metastases, superparamagnetic iron nanoparticle detection was 100% and radioisotope-based detection was 84.2% ($P = 0.083$), with superparamagnetic iron nanoparticles detecting more metastatic sentinel lymph nodes (median of 1 (i.q.r. 1–2) for superparamagnetic iron nanoparticles compared with a median of 1 (i.q.r. 0–1) for radioisotope; $P = 0.005$).

Conclusion: Injection before primary systemic therapy is feasible and does not affect concordance with radioisotope. Superparamagnetic iron nanoparticles perform comparably to radioisotope, but detect more sentinel lymph nodes and have a higher rate of detection of metastatic sentinel lymph nodes.

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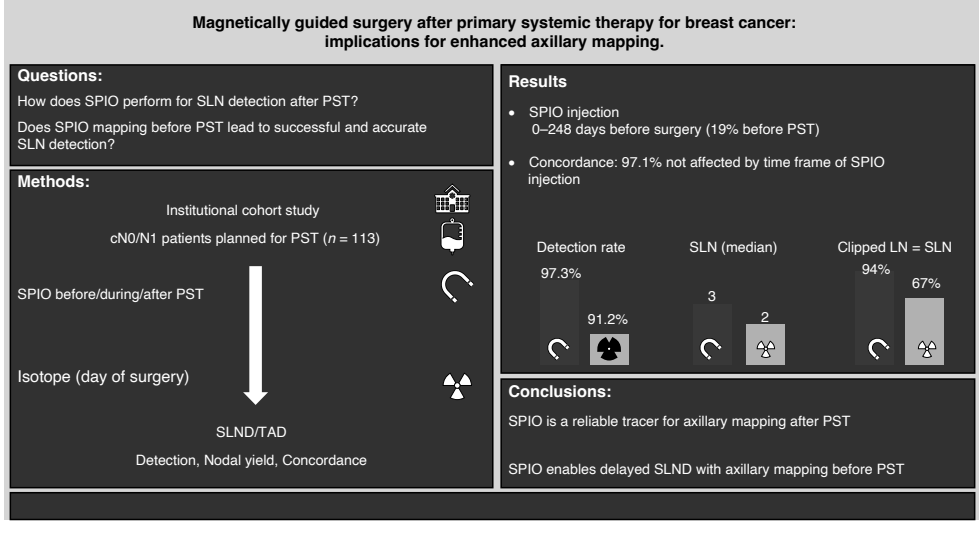
Graphical Abstract



Introduction

Superparamagnetic iron nanoparticles (SPIO) have shown comparable performance to radioisotope ± blue dye for sentinel lymph node (SLN) detection (SLND) in breast cancer, with the convenience of easier accessibility, disposal, and administration days before surgery[1]. Moreover, SPIO provide the possibility for delayed SLND, as demonstrated in the SentiNot study. In that study, SLND using SPIO was still feasible weeks after primary breast surgery for ductal carcinoma *in situ*, in the cases where specimen pathology demonstrated invasive cancer[2,3]. However, the role of SPIO for SLND after primary systemic therapy (PST) has not been extensively investigated.

Current evidence suggests that radioisotope-based SLND is the accepted standard after PST. Radioisotope-based dual mapping is specifically recommended for cN+-to-ycN0 patients, when SLN biopsy or targeted axillary dissection (TAD) is performed, as the number of SLN retrieved has been inversely linked to the false negative rate[4–8]. Apart from the logistic benefits of SPIO, with administration before PST, an additional aspect of interest is the ability to map the axilla before the fibrotic changes and lymphatic remodelling induced by chemotherapy occur, a concern mainly in patients who are initially cN+[9]. This mandates investigating that SPIO remain detectable after a prolonged interval of administration and that they do not migrate to higher nodal echelons. While preliminary data suggest feasibility[10], the aim of this study was to investigate the width of time frame of SPIO administration for patients undergoing PST and the concordance of SPIO and radioisotope-based detection.

Methods

Inclusion process

This study considered patients with non-metastatic, non-inflammatory breast cancer and cN0/cN1 axillae, intended for PST (chemotherapy, targeted therapy, or endocrine therapy) with curative intent, recruited at Uppsala University Hospital between January 2020 and October 2022. Tumour progression during PST and surgery before the completion of PST for any reason (for example PST adverse effects and patient preference) were exclusion criteria. For cN+-to-ycN0 patients, a decision regarding TAD was taken after discussion at the multidisciplinary meeting, followed by patient consent, as, during the enrolment interval, TAD was not yet included in the Swedish National Guidelines. Patients who opted for upfront axillary lymph node dissection were also excluded from this study. The final study cohort consisted of ycN0 patients, scheduled for either SLND alone or TAD.

Procedures

Initial diagnostic workup consisted of mammogram, breast/axillary ultrasonography, and core biopsy. In cases with a single palpable axillary lymph node or up to three suspicious axillary lymph nodes on ultrasonography in the absence of palpable lymphadenopathy, the most prominent lymph node was sampled by either fine-needle aspiration or core biopsy, according to radiologist preference. The lymph nodes were clipped during the same session at the discretion of the radiologist with a conventional marker. If fine-needle aspiration or core biopsy was negative, but clinical suspicion was high (BI-RADS 5, corresponding to a lymph node with metastatic features), removal was *a priori* intended. For patients with biopsy-proven metastatic lymph nodes, but without bulky axillary lymphadenopathy, a discussion regarding the possibility of de-escalation in the case of response to treatment took place in the multidisciplinary meeting. Initially, conventional clips were placed and replaced with paramagnetic clips (Magseed®; Endomag, Cambridge, UK) before surgery, but, later in this study, paramagnetic clips were used directly for biopsy-proven metastatic lymph nodes. This practice extended to patients in need of MRI monitoring, with the exception of axillary

tail tumours[11]. For patients requiring MRI monitoring, SPIO (Magtrace®; Endomag; 1 ml) were administered peritumorally or in the clip of the residual tumour after PST completion and before surgery, either during the preoperative surgical consultation or during lesion localization by the radiologist. If MRI monitoring was not necessary, SPIO were injected peritumorally before or after PST initiation. All patients received radioisotope on the day of surgery (40 mBq) or the day before (60 mBq), divided into two doses (periareolar and at the tumour bed), according to local routines. Axillary surgery (SLND or TAD) was performed under magnetic probe guidance (Sentimag®; Endomag) and the resected lymph nodes were controlled for magnetic and then radioactive signal *ex vivo*. Upon completion of the procedure with the magnetic probe, the axilla was controlled with the radioisotope probe and any additional lymph nodes with a radioactive, but not magnetic, signal were removed. Clinically enlarged and suspicious lymph nodes were also removed in line with preoperative patient consent. Accordingly, in TAD cases, if less than two SLN were retrieved and the index node was detected, enlarged lymph nodes detected during surgery or axillary lymph node dissection were removed, as long as patient consent was obtained before surgery. Frozen-section or one-step nucleic-acid amplification were not performed.

Study endpoints

Successful SLND was defined as the retrieval of at least one SLN with the respective technique. Concordance per procedure was defined as the proportion of procedures with at least one concordant SLN for both tracers divided by the procedures with at least one SLN detected with the radioisotope ((SPIO and radioisotope)/radioisotope). Reverse concordance per procedure was defined respectively ((SPIO and radioisotope)/SPIO). The number of SLN retrieved per technique was documented. Nodal and reverse concordance were calculated similarly. This study was registered in clinicaltrials.gov (NCT05985551) and undertaken to inform the design of the SENTINEO study (NCT05625698).

Sample size, statistical analysis, and reporting

For SPIO administration before PST to be clinically meaningful, SPIO detection should be comparable to radioisotope-based detection and with high concordance that would be unaffected by the timing of administration. For that, a maximum absolute value of 0.3 was set as the tolerance margin for Spearman's rho correlation coefficient and a maximum discordance of 8% in detection rates, presuming non-inferior detection rate for SPIO by 5%. The sample size satisfying both conditions was 114 patients. Sample size calculations were performed using G*Power version 3 (Dusseldorf University) and STATA version 16.

Categorical variables are summarized as *n* (%) with 95% confidence intervals. Paired comparisons were performed using McNemar's test and non-paired comparisons were performed using Fisher's test. Continuous variables are summarized as median (interquartile range (i.q.r.)) or median (range). Comparisons were made with the respective parametric or non-parametric test. Correlation of outcomes with the timing of SPIO administration was assessed using Kendall's tau and Spearman's rho. Multivariable analysis was performed if statistically significant differences were seen in the univariable analysis and regression models included the clinically relevant variables that were found to have significant interaction on univariable analysis. For these outcomes, standard and exponentiated B (expB) coefficients with 95% confidence intervals are reported for linear and logistic regression, respectively. Statistical analysis was performed using SPSS® (IBM, Armonk, NY, USA; version 28) and Stata (StataCorp, College Station, TX, USA; version 17). Reported tests and *P* values are two-sided, unless stated otherwise. Continuity corrections were not performed. The manuscript was prepared and reported according to the STROBE statement[12].

Table 1 Study population characteristics

Age (years), median (i.q.r.)	56 (45–68)
BMI (kg/m^2) median (i.q.r.)	25.1 (22.9–28.8)
Tumour size at baseline (mm), median (i.q.r.)	30 (22–42.5)
T stage before PST	
cT1	22 (19.6)
cT2	78 (69.7)
cT3	12 (10.7)
cT4	1 (0.9)
N stage before PST	
cN0	81 (71.1)
cN1	33 (28.9)
Histology	
IDC (NST)	103 (91.2)
ILC	7 (6.2)
Other (mucinous, medullar, metaplastic)	3 (2.7)
Receptor status	
HR+HER2−	41 (36.3)
HR+HER2+	17 (15.0)
HR−HER2+	17 (15.0)
HR−HER2−	38 (33.7)
Type of PST	
Chemotherapy ± targeted therapy	87 (77.7)
Endocrine therapy	25 (22.3)
Duration of PST (days), median (i.q.r.)	
Chemotherapy ± targeted therapy	145 (142–145)
Endocrine therapy	50 (45–91)

Values are *n* (%) unless otherwise indicated. i.q.r., interquartile range; PST, primary systemic therapy; IDC, invasive ductal cancer; NST, non-special type; ILC, invasive lobular cancer; HR, hormone receptor; HER2, human epidermal growth factor receptor 2.

Results

In total, 128 patients were eligible for this study. After PST completion, eight patients had a non-complete radiologic axillary response, six patients opted for axillary lymph node dissection, and one patient withdrew consent, leaving 113 patients for analysis (*Table 1*). Administration of SPIO was performed less than or equal to 1 week before surgery for 75 patients (66.4%) and greater than 1 week before surgery for 38 patients (33.6%; with 18.6% of patients receiving SPIO before the start of PST), at a median of 3 (range 0–248) days before surgery for the entire cohort.

At least one SLN was detected for 110 patients (97.3%) with SPIO and for 103 patients (91.2%) with radioisotope (difference 6.2%, 95% c.i. −0.8% to 13.2%; $P = 0.057$), whereas the combination of SPIO + radioisotope was successful for all patients (100%). Successful SPIO detection interacted negatively with higher BMI and administration on the day of surgery in the univariable analysis, but the effect was not retained in logistic regression, whereas radioisotope-based detection did not interact with any baseline factor. The addition of SPIO to radioisotope significantly increased the overall detection rate (difference 8.8%, 95% c.i. 2.4% to 15.0%; $P < 0.001$), but the addition of radioisotope to SPIO did not significantly improve overall detection (difference 2.7%, 95% c.i. −11.9% to 6.5%; $P = 0.125$). At least one SLN was concordant for SPIO and radioisotope in 100 of 113 procedures (88.5%, 95% c.i. 82.2% to 94.8%). The procedural concordance for radioisotope ('magnetic and isotopic/isotopic') was 97.1% (95% c.i. 93.8% to 100%) and the procedural concordance for SPIO

('magnetic and isotopic/magnetic') was 90.9% (95% c.i. 85.5% to 96.3%). Procedural concordance did not correlate with timing of SPIO injection (Kendall's tau 0.027, 95% c.i. −0.098 to 0.151; $P = 0.746$).

Looking specifically into the successful identification of greater than or equal to two SLN (*Table 2*), SPIO were successful for 84.1% of patients and radioisotope was successful for 77.0% of patients (difference 7.1%, 95% c.i. −0.6% to 14.8%; $P = 0.049$). For both SPIO and radioisotope, only older age, higher BMI, and use of preoperative endocrine therapy interacted with probability for retrieval of less than two SLN. In logistic regression, none of these factors retained significance for radioisotope, but older age (Exp(B) = 0.922, 95% 0.871, 0.976; $P = 0.005$) and higher BMI (Exp(B) = 0.830, 95% 0.737, 0.935; $P = 0.002$) retained this effect for SPIO. Clinical axillary status at baseline (cN0 *versus* cN1) did not interact with the outcomes. The combination of SPIO + radioisotope detected greater than or equal to two SLN for 90.3% of patients, significantly different compared with SPIO only (difference 6.2%, 95% c.i. 0.9% to 11.5%; $P = 0.008$) or radioisotope only (difference 13.3%, 95% c.i. 6.1% to 20.3%; $P < 0.001$).

Setting the threshold to greater than or equal to three SLN, SPIO were successful for 55.8% of patients and radioisotope was successful for 48.7% of patients (difference 7.1%, 95% c.i. −2.6% to 16.7%; $P = 0.122$). The combination of SPIO + radioisotope was successful for 66.4% of patients, significantly higher than for SPIO only (difference 10.6%, 95% c.i. 4.9% to 16.3%; $P < 0.001$) or radioisotope only (difference 17.7%, 95% c.i. 9.8% to 25.6;% $P < 0.001$).

A total of 356 SLN were identified with either SPIO or radioisotope. Out of these, 314 were detected by SPIO and 266 were detected by radioisotope; 226 SLN were concordant for SPIO and radioisotope. Thus, the nodal detection rate was 88.5% for SPIO and 75.0% for radioisotope (difference 13.5%, 95% c.i. 7.1% to 19.9%; $P < 0.001$).

Table 2 Patients with different numbers of sentinel lymph nodes excised per technique

	Concordant*	SPIO only	Radioisotope only	SPIO + radioisotope combined
0	13 (11.5)	3 (2.7)	10 (8.8)	0 (0.0)
≥1	100 (88.5)	110 (97.3)	103 (91.2)	113 (100.0)
≥2	76 (67.3)	95 (84.1)	87 (77.0)	102 (90.3)
≥3	38 (33.6)	63 (55.8)	55 (48.7)	75 (66.4)

Values are *n* (%). *For concordant cases, 0 denotes a successful procedure, but no concordant sentinel lymph nodes. SPIO, superparamagnetic iron oxide nanoparticles.

The median SLN yield was three (i.q.r. 2–3) for SPIO and two (i.q.r. 2–3) for radioisotope, resulting in a significant difference ($P < 0.001$). The median number of SLN for the combination of SPIO + radioisotope was three (i.q.r. 2–4), higher than for any single tracer ($P < 0.001$), whereas a median of two (1–3) SLN were concordant for SPIO and radioisotope. The nodal concordance was 85.0% (95% c.i. 80.1% to 89.0%) for radioisotope and the reverse concordance (SPIO) was 72.0% (95% c.i. 66.7% to 76.9%).

For cN+-to-ycN0 patients undergoing TAD (33 patients), the detection rate was 100% for SPIO (33 patients) and 82% for radioisotope (27 patients) (difference 18%, 95% c.i. 2% to 34%; $P = 0.016$). The index node was retrieved in all cases and was SPIO-positive in 31 (94%) and radioactive in 22 (67%) (difference 27%, 95% c.i. 7% to 48%; $P = 0.007$), an outcome that was not affected by age, BMI, type of PST, or time from SPIO and radioisotope injection to surgery. Overall, the median number of SLN identified using SPIO was higher than that identified using radioisotope (3 (i.q.r. 3–5) *versus* 2 (i.q.r. 2–3), respectively; $P < 0.001$). Specifically the TAD technique, compared with SLND, retrieved more SLN for SPIO (median of 3 (i.q.r. 3–5) *versus* 2 (i.q.r. 2–3), respectively; $P < 0.001$), but not for radioisotope (median of 2 (i.q.r. 2–3) for both; $P = 0.875$), whereas the number of concordant SLN did not differ (median of 2 (i.q.r. 2–3) *versus* 1 (i.q.r. 2–3) respectively; $P = 0.273$).

A median of one (i.q.r. 1–2) axillary metastasis was found in 19 patients (17%). For greater than or equal to one SLN, SPIO detection was 19 of 19 (100%) and radioisotope-based detection was 16 of 19 (84%) (difference 16%, 95% c.i. −0.6% to 32.2%; $P = 0.083$), for greater than or equal to two SLN, SPIO detection was 18 of 19 (95%) and radioisotope-based detection was 15 of 19 (79%) (difference 16%, 95% c.i. −0.6% to 32.2%; $P = 0.083$), and, for greater than or equal to three SLN, SPIO detection was 13 of 19 (68%) and radioisotope-based detection was nine of 19 (47%) (difference 21%, 95% c.i. 2.7% to 39.4%; $P = 0.046$). In this subgroup of ypN+ patients, SPIO detected more SLN than radioisotope (median of 3 (i.q.r. 2–4) *versus* 2 (i.q.r. 2–3) respectively; $P = 0.010$) and more metastatic SLN than radioisotope (median of 1 (i.q.r 1–2) *versus* 1 (i.q.r. 0–1) respectively; $P = 0.005$). From those patients that underwent completion axillary lymph node dissection, additional metastatic nodes were found in one patient (4%).

Time from SPIO administration to surgery did not affect the number of SPIO SLN (Spearman's rho 0.053, 95% c.i. −0.138 to 0.241; $P = 0.575$) or nodal concordance (Spearman's rho −0.022, 95% c.i. −0.220 to 0.177; $P = 0.821$). In univariable analysis, the number of SPIO SLN interacted with patient age, BMI, and positive clinical nodal status at baseline (*Table 3*). Linear regression showed a persisting negative effect between number of SPIO SLN and BMI,

Table 3 Factors affecting numbers of sentinel lymph nodes identified per technique

	Univariable analysis		Multivariable analysis	
	Spearman's rho (95% c.i.)	P	Coefficient b (95% c.i.)	P
SPIO				
Age	−0.022 (−0.447,−0.096)	0.003	−0.018 (−0.036,0.000)	0.055
BMI	−0.334 (−0.498,−0.147)	<0.001	−0.090 (−0.141,−0.038)	<0.001
cN stage	0.245 (0.056,0.416)	0.009	0.758 (0.134,1.383)	0.018
Radioisotope				
Age	−0.171 (−0.350,0.019)	0.069	−0.009 (−0.026,0.009)	0.318
BMI	−0.334 (−0.497,−0.147)	<0.001	−0.051 (−0.101,−0.002)	0.041
cN stage	−0.013 (−0.204,0.178)	0.890	−0.031 (−0.629,0.568)	0.919

Multivariable analysis is linear regression for the factors with significant correlation. SPIO, superparamagnetic iron oxide nanoparticles; cN stage, clinical node stage at presentation.

and a positive interaction between number of SPIO SLN and positive axillary status at baseline. The number of radioisotope SLN interacted with BMI only, an effect retained on multivariable analysis, with higher BMI resulting in retrieval of less radioisotope SLN.

All patients who received SPIO before PST (21 patients; median of 135 (i.q.r. 120–140) days) had successful magnetic SLND, whereas radioisotope was successful for 17 of 21 (difference 19%, 95% c.i. 2.3% to 35.8%; $P = 0.046$). For these 21 patients, a median of 3 (i.q.r. 2–3) SPIO SLN were retrieved and the median number of concordant SLN was two (i.q.r. 1–3). The median magnetic count of the retrieved SLN for these patients was lower compared with that for the rest of the cohort (1430 *versus* 2523 respectively; $P = 0.002$), but there was no difference in the median magnetic count of the first SLN detected (4100 *versus* 3873 respectively; $P = 0.567$).

One patient who received SPIO 2 days before surgery presented with mild skin staining that disappeared at 4 weeks after surgery. No other adverse events were reported.

Discussion

For this well-defined cohort of patients undergoing SLND or TAD after PST, it was shown that SPIO performed comparably to radioisotope, but detected more SLN and had a higher rate of detection of metastatic SLN. Moreover, administration before PST did not affect concordance with radioisotope, meaning that SPIO provide the possibility of mapping the axilla before PST.

Axillary mapping after PST has been established as the standard of care, as the feasibility and accuracy of the procedure have been demonstrated for both cN0 and cN+-to-ycN0 patients in larger studies[4,6,13,14]. Initial concerns have largely been abandoned, as it has been shown that ypN is a stronger prognosticator than cN[15,16]. In two meta-analyses, conducted in 2009 and 2022, the pooled SLND rate was, however, 90.9% and 90.6% respectively, with significant heterogeneity ($I^2 = 89\%$)[17,18]. While no difference in this outcome was reported with regard to baseline axillary status, previous literature suggests that radioisotope ± blue dye outperforms blue dye alone[4,5,13,14,19]. In the present study, SPIO detection was very high and was not affected by baseline axillary status, a finding consistent with previous reports[20], whereas radioisotope-based detection was comparable to the available literature[17]. The negative interaction between high BMI and SPIO detection does not seem to be tracer-specific, as high BMI has been identified as a challenge for other tracers as well[18,21]. Additionally, the detection rate of SPIO was comparable to that of the combination of SPIO + radioisotope, suggesting a potential advantage over radioisotope in its use as sole tracer. This is an advantage compared with other isotope-free tracers, such as blue dye, which performs worse than radioisotope[4,5,19], or indocyanine green, which performs comparably to radioisotope, but without any benefit compared with the combination of indocyanine green + radioisotope[22].

With regard to SLND after PST, a concern beyond detection is accuracy, especially for cN+-to-ycN0 patients, for whom false negative rates under 10% have repeatedly been associated with the retrieval of greater than or equal to three SLN[4,6,14]. The introduction of TAD has facilitated this and decreased false negative rates even more[5–7], but surgeons often encounter the phenomenon of retrieving less than three SLN in these patients. Institutional reports suggest that three SLN may not be an absolute cut-off, but it is unclear whether higher axillary recurrences were observed with the retrieval of only one SLN *versus* two SLN[23]. However, adequate nodal yield should not aim at the prevention of axillary recurrence, but accurate staging. This is important, as residual disease may affect treatment decisions[24–27] and prompt completion axillary dissection, until the role of radiotherapy has been elucidated[28]. The use of SPIO resulted in high detection rates, retrieving a median of three SLN, regardless of baseline cN. The clipped lymph node was an SLN for SPIO in 94% of cases, whereas it was an SLN for radioisotope in only 67% of cases, the latter being consistent with previous studies[29]. Interestingly, despite the fact that the combination of SPIO + radioisotope had a higher probability of retrieving more SLN, this was not significant for patients with malignant SLN. This observation is important, as it may hint at possibilities for more accurate axillary staging. Such a finding could be explained by the fact that SPIO is taken up by tissue macrophages in the lymph node and that SPIO maps SLN before the fibrotic effect of PST, the latter contributing to SLND failure[9]. This should be viewed as hypothesis generating and should be tested in a dedicated trial.

A novel finding of this study is that axillary mapping before PST is feasible and does not affect procedural accuracy. Indeed, no association between timing of SPIO administration and concordance between radioisotope and SPIO could be found, thus satisfying the primary outcome of this study. Moreover, the detection rate and the nodal yield for the patients receiving SPIO before PST were comparable to those for the rest of the cohort. The median magnetic count was lower for 'all SLN', but not for the 'first SLN', and the values allowed for easy detection. These data not only corroborate previous reports and meta-analyses regarding SPIO as a tracer for SLN after PST[1,20] but suggest that the concept of delayed SLND through a wide time frame between SPIO administration and SLND, introduced in the SentiNot study[2,3], can be applicable in the setting of PST, facilitating logistics and potentially enhancing axillary mapping.

This study has certain limitations. It is a feasibility study, primarily assessing the interplay between the timing of SPIO administration and concordance between SPIO and radioisotope, as the latter was administered according to clinical routine. The outcomes are interesting and clearly suggest that SPIO can be used for SLND after PST, but the implementation of a prolonged time frame needs to be tested in a dedicated trial. Moreover, SPIO administration before PST precludes the possibility of MRI monitoring, currently a popular strategy[30]. This, reassuringly, does not constitute a major limitation, as the literature suggests that MRI is not superior to ultrasonography when assessing the response in the breast[31,32] or the axilla[33]. Moreover, a recent meta-analysis suggests that contrast-enhanced mammography, a modality that does not interfere with SPIO, seems to yield comparable diagnostic accuracy to MRI during PST[34]. Thus, the potential of axillary mapping with SPIO before PST should be explored, especially in light of the findings of the present study. Finally, this is a single-centre study, from an institute with extensive experience with the magnetic technique, suggesting that the results should be externally validated. Currently, the SENTINEO pilot study[35] is accruing data and a multicentre trial is being planned.

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E.P. and S.E. share first authorship. S.E. and A.K. had access to the full study data and made the decision to submit for publication.

Author contributions

Eirini Pantiora (Conceptualization, Data curation, Formal analysis, Investigation, Writing—original draft, Writing—review & editing), Staffan Eriksson (Formal analysis, Investigation, Resources, Supervision, Writing—review & editing), Fredrik Wärnberg (Conceptualization, Investigation, Methodology, Supervision, Writing—review & editing), and Andreas Karakatsanis (Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Writing—review & editing)

Disclosure

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Data availability

An application for data sharing can be made available upon reasonable request following contact with the corresponding author.

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Paper IV

Magnetic seed vs guidewire breast cancer localization with magnetic lymph node detection: a cost-minimization analysis

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Abstract

Background

Magnetic seeds have comparable performance to guidewires in breast lesion localization with the advantages of shorter operative time, facilitated logistics and higher staff satisfaction. However, the higher cost of the device remains an issue, meaning the health economy studies in this field are needed to inform on this question.

Methods

This is a predefined health economic analysis of a pragmatic randomized controlled trial (RCT) including 426 patients (median [iqr] age 65 [56, 71] years; Body Mass Index 26.6 [24.0,29.8] kg/m2; tumour size 11 [8, 15] mm) with non-palpable breast cancer, randomized to either a magnetic seed or a guidewire, whereas sentinel lymph node detection was performed using superparamagnetic iron oxide nanoparticles, enabling a totally magnetic approach. A cost minimization analysis was conducted, from a healthcare system perspective, using unadjusted and adjusted analyses of costs.

Results

The unadjusted analysis did not show any difference in incremental costs (guidewire €3337 vs seed €3274; difference -63 [95% CI -302, 174], p-value=0.599). However, in the adjusted analysis including marker, type of breast surgery performed and single-session lesion and SLN localisation, showed that the seed was associated with reduced costs (guidewire €3514 vs seed €3123; difference -391 [95% CI -360, -422], p=0.002), corresponding to a 11.1% reduction. Sensitivity analyses did not change direction of outcome.

Conclusion

In this predefined health economic analysis of an RCT, the use of magnetic seeds resulted in incremental cost containment, despite the increased cost of the device. Contributing factors included shorter localization and operation time and process streamlining.

Introduction

Breast conserving surgery (BCS) with preoperative lesion localization and sentinel lymph node dissection (SLND) has become the mainstay treatment of early-stage, non-palpable breast cancer[1,2]. Guidewire localization has been the standard localization since the introduction of BCS[3]. While affordable and accessible, the guidewire poses challenges in scheduling, as it has to be inserted on the day of surgery. The need to de-couple preoperative localization from surgery led to the development of wireless localization devices [4,5]. These include often a seed or tag that can be placed days before surgery and is detected intraoperatively by a probe[6–9]. At the same time, SLND has traditionally relied on the use radioactive isotope (RI) which has a high identification rate. However, use of radioactive materials is dictated by strict regulations, the need of nuclear oversight and recurring production shortages[10,11]. Furthermore, RI has a short half-life, posing the same logistical challenges as the guidewire(ref).

Amongst the new technologies, the Magseed© (Endomag, UK), a 5-mm ferromagnetic marker for lesion localization and Magtrace© (Endomag, UK), a superparamagnetic iron oxide nanoparticle (SPIO) suspension for SLND, have been extensively studied and adopted in clinical routine[12–15]. Recently, the Magtotal randomized controlled trial (RCT) compared a totally magnetic technique (seed for the tumor, SPIO for SLN) to guidewire and SPIO; whilst the main outcomes of volumes excised, re-excision rates and complications were equivalent, the magnetic marker resulted in less localisation failures, shorter operating time, and higher preference by healthcare practitioners [16].

Cost-effectiveness is crucial for the evaluation and selection of new technologies in surgery. The aim of this predefined secondary health economic analysis was to conduct a cost-minimization of the magnetic marker against the previous standard of the guidewire, to provide insights on its economic impacts.

Methods

Study design

This study is a within-trial health economic evaluation, conducted from a healthcare system perspective, based on data from the Magtotal RCT[16]. This pragmatic RCT was conducted in three hospitals in Sweden between May 1, 2018, and May 1, 2022. Seed placement and SPIO injection could be done by either a breast radiologist or a surgeon during the preoperative consultation, but guidewire placement could only be performed by a radiologist. The trial was approved by the Uppsala Regional Ethics Committee and registered at ISRCTN (ID: ISRCTN11914537). The

present work is reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement[17].

Study Population and procedure

The trial included adults with non-palpable cTis-T3N0 breast cancer who were scheduled to undergo BCS and SLND, randomly allocated (1:1 ratio) to either a magnetic seed and SPIO or guidewire for tumour localisation and SPIO for SLND. A full report on inclusion criteria is reported in the published results of the trial[16]. All patients provided written informed consent.

Comparators

The ferromagnetic seed is compared to the guidewire which is the standard of care localization method. The wire used in the trial was the Hawkins™ Hardwire BLN with echogenic tip, (Argon ©, USA)

Data collection

Sample characteristics

Patient age, body mass index (BMI), and tumor characteristics (laterality, size, histology, receptor status), type of radiologic workup and receipt of primary systemic therapy were collected as baseline characteristics. Preoperative volumetry was performed to define the optimal resection volume (ORV), which was the volume required to remove the tumour with 1-cm macroscopic margins. Localization time and personnel, time from localization to surgery, operative time and type of surgery were prospectively documented.

The primary outcomes were positive margins and the resection ratio (volume excised/ORV) in patients with negative margins. Secondary outcomes included successful SLND, adverse events, failed localization, operative time and ease of implementation by healthcare practitioners. Patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) data were also collected and will be reported elsewhere.

Resource use and costs

Costs were estimated from a Swedish healthcare system perspective, which is universal and publicly funded, with each Region as the payer. The cost analysis used a bottom-up approach (micro-costing) to accurately identify, measure, and assign value to specific cost items such as the cost of the device, cost of personnel time, and operating theatre (OR) costs [18].

Moreover, the satisfaction of surgeons, radiologists and nurses/ OR coordinators had been collected prospectively and reported in the trial[16]. For the coordinators, we sought to explore the reasons behind satisfaction with each marker. When a patient had to receive a guidewire, that would result in rescheduling of the weekly theatre list to avoid i) either one late start (meaning an average theatre delay by 90 minutes (accounting for lesion localisation, transfer from radiology to the day-surgery department, admission and preparation for anaesthesia) for every fifth operating list, or ii) that the patient that would receive a guidewire would have to wait more days from the preoperative appointment to surgery. The first outcome would have an impact on productivity, whereas the second would lead to higher risk of breaching the interval between diagnosis and treatment required by the Standardized Pathway (Standardiserad Vårdförlopp, SVF), that is implemented in Sweden for all cancer patients[19]. That was compensated with extra meetings to mitigate these risks. The extra time required for rescheduling was estimated to correspond to the total of one hour for each of the three coordinators.

The trial protocol allowed for the implementation of local routines in the localization procedure, leading to a variation in the timing and the setting of seed placement and SPIO injection. Seed localization could be performed by the surgeon under ultrasound guidance during preoperative planning, whereas SPIO injection could be performed under ultrasound or free-hand by the surgeon. When localization was performed by a radiologist, this was done under ultrasound or stereotactic guidance, with the aid of a radiology nurse. Guidewire placement required an additional 5-10 min to stabilise and secure the guidewire, a procedure not required in seed localizations. In both arms, post-localization mammograms were performed to ensure correct placement. Intraoperatively, the guidewire was identified through direct visual inspection, whereas the seed was localized with the use of the same probe that was used for SLND (Sentimag©, Endomag, UK). Intraoperative specimen radiology was performed in all cases to ensure presence of the marker and the lesion in the specimen, and additional cavity shavers were taken when needed.

The cost of the additional time of healthcare professionals was estimated, considering the hourly salary of all healthcare personnel involved sourced from salary logs including employee insurance benefits. Since SPIO was already routinely used in all three hospitals and was used in both trial

arms, its cost was not included in this analysis[20]. Finally, despite more failed localisations in the guidewire arm, these instances were not included in the analysis, as wires were either replaced with seeds or, in cases of intraoperative dislocation, the peritumoral magnetic signal and the tissue discoloration from SPIO guided the excision.

Information on the cost of each device was obtained by reviewing invoices from the recruitment period to capture the pricing. Further information regarding deployment and surgical operative times required for each procedure were prospectively registered during the trial. The time spent preparing for localization, as well as the time required to perform post-localization mammogram, clean up the room and register the procedure, was equal between the two methods and therefore not included in the analysis. Localization and operative time data were included in the RCT outcomes. Respective hourly salaries were used to estimate the cost of the time of the two techniques. The cost/minute for operating theatre use is registered in the hospital operational system and was retrieved from the patient logs.

Total costs were estimated including material costs (cost of device), the deployment costs, and OR time. Costs were collected in 2022 Swedish krona (SEK), and converted to 2022 EURO (€) using the EPPI cost conversion database [21]. All resources used, unit costs and total costs are shown in Table 1.

Given that the nature of the intervention did not have long-term effects, the time-horizon of the analysis was the period from lesion localization and axillary mapping, and included the immediate postoperative period, which is universally defined as 30 days (ref.22).

Data analysis

The trial reported equivalence for the primary outcome of re-excision (per protocol analysis 2.91% for guidewire vs 2.84% for the magnetic marker; difference, 0.07%; 95% CI, −3.10% to 3.30%; P = 0.95), and complications (7.3% for the magnetic marker vs 9.8% for the guidewire; difference -2.5%; 95% CI, −8.3% to 3.3%; P = 0.45) whereas, despite that failed localisations were more frequent with the guidewire than the magnetic marker (10.1% vs 1.9%; difference, 8.2%; 95% CI, 3.3%-13.2%; P < .001), the peritumoral SPIO injection could guide specimen resection[16]. Moreover, preliminary data on quality of life and PROs have not shown any difference[22]. Therefore, a Cost-Minimization Analysis (CMA) was considered the most appropriate approach and the primary objective was to determine which intervention was less costly.

Descriptives

Continuous variables were summarized as either mean (standard deviation; SD and/or 95% confidence intervals, 95% CI) or median (interquartile range; iqr), as appropriate. Bootstrapping with 1000 iterations was performed to account for uncertainty, and the subsequent means and medians were presented with 95% CI. Unadjusted comparisons were performed with linear regression and the marginal differences with 95% CI were reported.

Analysis of cost data

To identify the cost of the implementation of the seed, regardless of the perceived ease of logistics, we adopted a stepped procedure comparing the cost analyses with the monetary costs associated with OR scheduling. Given the interaction between costs and time, and since time was affected by a single localisation session (both device and SPIO at the same session) and type of BCS (simple wide local excision [WLE], level I oncoplastic breast surgery [OPBCS] or therapeutic mammaplasty/mastopexy [TM]), we employed a generalized linear model to fit the cost data using a gamma distribution and a log-link. A two-sided p-value of <0.05 was considered significant. SPSS 28 and Stata v17 software were used for the analysis.

Sensitivity analysis

We performed the following deterministic sensitivity analyses: i) incremental costs if all localizations had been performed by radiologists and ii) incremental costs if all the magnetic seeds in patients that were deployed under ultrasonographic (but not stereotactic) guidance had been performed by surgeons. These two scenarios reflect the predominant routine practice patterns in the USA, the UK and large parts of Europe and, respectively, in Central Europe such as Germany, Austria or Switzerland[23].

Results

Detailed trial results have been reported elsewhere [16]. The population consisted of 426 patients (median [iqr] age 65 [56, 71] years; Body Mass Index 26.6 [24.0,29.8] kg/m^2; tumor size 11 [8, 15] mm) and the main characteristics are summarised in Table 2.

Magnetic markers were placed (median [iqr]) 5 [1,8] days ahead of surgery, with a median (iqr) of 4 (3,5) minutes required for the localisation session, most often (189 of 215; 92.2%) under

ultrasound guidance and as a single localisation session (184 of 215; 85.6%). With the exception of ultrasound guidance, there were significant difference with the guidewire (Table 3).

Cost minimization analysis

Base case analysis

The unadjusted analysis did not show any difference in incremental costs (guidewire €3337 vs seed €3274; difference -63 [95% CI -302, 174], p-value=0.599). However, in the adjusted analysis including marker (guidewire or seed), type of breast surgery performed (WLE vs OPBCS vs TM) and single localisation (yes/no), showed that the seed was associated with reduced costs (guidewire €3514 vs seed €3123; difference -391 [95% CI -360, -422], p=0.002), corresponding to a 11.1% reduction. The results are shown in Table 4.

Sensitivity analyses

Looking into the sensitivity analyses, the results were not different: If the radiologists had performed all the localisations, that would have not resulted in a cost difference either (magnetic marker €3556 [3406, 3706] vs guidewire €3620 [3433, 3806]; p=0.601]. Finally, if surgeons had placed all the magnetic markers in cases where ultrasound guidance was feasible, the cost difference would have been marginally significant in favour of the magnetic marker (€3287 [3138, 3439]) against the guidewire (€3618 [3432, 3805]) (p=0.007). Full details are provided in the Supplement, Table 1. On the other hand, both adjusted sensitivity analyses (Supplement, Table 2) still demonstrated that the magnetic marker was associated with incremental cost reduction.

Discussion

The Magtotal RCT corroborated previous observational data showing that the magnetic marker has equal performance to the guidewire regarding successful localization and re-excision rates, with the additional advantage of facilitating logistics by de-coupling lesion localization and SLN mapping from surgery [9,12,24]. Furthermore, the use of magnetic markers is related to increased physician satisfaction and decreased patient anxiety[25]. Despite these findings, there have been concerns regarding the cost of the seed, which is significantly higher than that of a guidewire. This health economic analysis of the Magtotal RCT demonstrates that replacing the guidewire with a magnetic seed, enabling a totally magnetic technique for lesion localisation and SLND, decreased

the cost of the procedure. Furthermore, the magnetic seed was preferred by healthcare personnel as it streamlined theatre planning procedures and increased productivity[16].

The incremental cost reduction associated with the magnetic seed suggests that the higher device cost was mitigated by the shorter OR time, the ease of planning and the decoupling of lesion localisation and SLN mapping from the day of surgery, in a single session and within a very wide timeframe. The analysis did not include the cost of SPIO and the Sentimag© probe since they were used for SLND in both arms. However, previous head-to-head comparisons have demonstrated reduced costs with SPIO instead of radioisotope, especially when SPIO is administered before the day of surgery[14,15]. Moreover, the integration of SPIO for SLND effectively eliminates the necessity for multiple devices, contributing to capital costs reduction and accelerates the depreciation of equipment. Interestingly, the only alternative option currently for single-probe lesion and SLN detection, is the combination of RI and radioactive seeds. However, this requires nuclear medicine oversight (which suggests challenging access, especially in the global setting), and generates costs related to transportation, storage and disposal of radioactive materials as shown in other studies[26,27]. Moreover, the short half-life of the isotope would limit preoperative single session localization and axillary mapping either on the day of surgery or the afternoon before, resulting in less flexibility compared to the Magtotal technique.

Numerous studies have demonstrated clinical equivalence and highlighted the logistical advantages of various wireless markers [6–8,28–33]. Furthermore, a recently published study suggests that these technologies may offer a more sustainable profile compared to guidewires[34]. Despite these promising developments, the existing literature remains deficient in addressing the financial implications of implementing wireless markers across various healthcare settings. Therefore, the study findings are important, as the main prohibiting factor for adopting wireless technologies is the concern over the higher costs. Moreover, it covers a question that has not been widely addressed previously, as relevant literature has explored the cost-effectiveness of radioactive seeds in different financial environments, but, to the best of the authors' knowledge, there is only one published study on magnetic markers that looks into a budget impact analysis [26,27,35,36].

Strengths and limitations

The main strength of the present study is that results are derived from a prospectively curated database of a pragmatic RCT, which minimizes selection or procedure bias. Moreover, the analysis captured the indirect costs that accompany breast lesion localization and the way these affect theatre planning and resource allocation. The use of magnetic markers diminished the time theatre co-ordinators spent each week to arrange the theatre lists in a way that no delays would

occur due to same-day localization. Additionally, performing a cost-minimization analysis based on actual costs allows for results that are not based on assumptions. On the other hand, the type of analysis performed allows for insights in different healthcare settings and the breakdown of the data may provide a ground for further studies in diverse settings.

Given the fact that in Sweden, around 2/3 of new breast cancers are diagnosed via screening and require localization, relying solely on guidewires would severely affect production[37]. Acknowledging that this may not be the case internationally, the present analysis is specifically examining the incremental costs of a combined technique for lesion and SLN localization that is flexible and applicable in any setting, suggesting that appropriate reimbursement strategies could address practice variations. Moreover, the fact that patients who received a guidewire were not scheduled as first cases in the operating list did not allow for the capture of the extra costs associated with treatment delay. However, this decision was made to prevent delays in the operating theatre, in line with the pragmatic trial character. Finally, we did not monetize healthcare provider satisfaction through a "willingness-to-pay" approach. Instead, we explored the reasons associated with satisfaction as they were more objective.

Conclusion

The results of the economic analysis showed that, despite the increased cost of the device, the use of a magnetic marker resulted in cost containment. It is already established that they are comparable in terms of re-excision rates and specimen resection ratio and the magnetic marker has gained in favor as it facilitates theatre planning and can be adapted to different hospital settings. In this study, the use of a magnetic marker was related to shorter localization and operating times which compensated for the total cost. The technique was also significantly favored by all involved healthcare professionals as it removed planning limitations and increased efficiency.

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Tables

Table 1. Resources, unit costs and total costs.

	Magseed			Guidewire			Source of unit cost
	Frequency	**Unit cost**	**Total**	**Frequency**	**Unit cost**	**Total**	
Material costs							
Device cost	215	278	59770	208	38	7904	per invoice
Delivery costs		none	none		none	none	per invoice
Deployment cost							
Radiology (physician and nurse) time*	203*4 min	1.7/min	1362,1	208*15 min	1.7/min	5304	hourly rate of a consultant breast radiologist salary from salary logs
Surgeon time*	12	0	0		NA	0	performed during the preoperative consultation
Referral to Radiology	203	265	53795	208	265	55120	Hospital invoicing system
Capital		0	0		0	0	
OR list planning							
Surgical coordinators' time**	0	0	0	42**	96.11	4036,6	hourly rate of three breast coordinators from salary logs? Statistics Sweden
Operation time (median, in minutes)*	215*69 min	37.1/min	550378,5***	208*75.5 min	37.1/min	582618,4***	xxx
Total cost excluding device cost			605535,6			647079	
Total cost including device cost			665305,6			654983	

All costs are in Euros (€), 2022. *: Time is provided in minutes; respective monetary costs are multiplied by the respective cost/minute. ** : For the surgical coordinator time, the extra time required for the guidewire responds to every fifth patient and corresponds to one working hour for three breast nurses / OR coordinators.

***: Number of procedures multiplied by procedural time multiplied by cost per minute

Table 2. Trial population characteristics

		Allocation arm				
		Guidewire		Magnetic marker		p-value
Age (median, iqr)		67	(56, 72)	64	(56, 69)	.082†
Body Mass Index, BMI (kg/m²) (median, iqr)		26.1	(23.7, 29.7)	26.7	(24.1, 29.9)	.332†
Screening detected lesion (n,%)	No	16	7,8%	18	8,9%	.859*
	Yes	188	92,2%	194	91,1%	
Lateralization (n,%)	Right Breast	95	48,7%	100	47,4%	.843*
	Left Breast	100	51,3%	111	52,6%	
Lesion Size (mm) (median, iqr)		10	(8, 15)	11	(8, 15)	.138*
Type of surgery	WLE	180	84,9%	169	81,3%	.46*
	OPBCS	24	11,3%	26	12,5%	
	TM	8	3,8%	13	6,3%	

Key input variables of the trial population. Results are presented per protocol. BMI: body mass index; iqr: interquartile range; OPBCS: Oncoplastic breast conserving surgery (corresponding to oncoplastic lumpectomy); TM: Therapeutic mastopexy/mammaplasty; WLE: wide local excision. †: Mann Whitney U test; *: Fisher's exact test.

Table 3. Patterns of lesion localisation and SPIO administration.

		Guidewire		Magnetic marker		p-value
Localization modality (n, %)	Ultrasound	194	93.3%	189	92.2%	.71*
	Stereotactic	14	6.7%	16	7.8%	
Days from localization to surgery (median, iqr)		0	0	5	(1,8)	<.001†

Time for lesion localization (min) (median, iqr)		10	(10,11)	4	(3,5)	<.001†
SPIO administration (n, %)	Surgeon	85	40.6%	29	13.5%	<.001*
	Radiologist	123	59.4%	186	86.5%	
Lesion localised by (n, %)	Surgeon	0	0.0%	12	5.6%	<.001*
	Radiologist	208	100.0%	203	94.4%	
Days from SPIO injection to surgery (median, iqr)		7	(0,15)	6	(1,8)	.041†
Single localization procedure (breast & axilla) (n, %)	Yes	74	33.7%	184	85.6%	<.001*
	No	138	66.3%	31	14.4%	

Implementation patterns of lesion localisation and SPIO administration in the trial. Iqr: interquartile range; ml: millilitre; SPIO: superparamagnetic iron oxide.; "Surgeon" denotes free-hand SPIO injection around the tumor. *: Fisher's exact test, †: Mann Whitney U-test.

Table 4. Cost minimization analysis.

	Unadjusted analysis			Adjusted analysis			
	Mean (95% CI)	Marginal Difference (95% CI)	p-value	b Coefficient (95% CI)	Marginal Means (95% CI)	Difference (95% CI)	p-value
Localization device							
Guide wire	3337 (3151, 3524)	Ref. [0]		Ref. [0]	3514 (3333, 3696)	Ref. [0]	
Seed	3274 (3124, 3160)	-63 (-302, 174)	0.599*	-0.118 (-0.192, -0.044)	3123 (2973, 3273)	-391 (-360, -422)	0.002**
Type of Breast Surgery							
WLE	3126 (3010, 3241)	Ref. [0]		Ref. [0]	3137 (3024, 3250)	Ref. [0]	

OPBCS	3722 (3365, 4078)	604 (144, 1064)	<0.001*	0.156 (0.055, 0.256)	3666 (3321, 4010)	528 (297, 760)	0.003**
TM	5232 (4560, 5903)	2106 (1280, 2932)	<0.001	0.493 (0.342, 0.643)	5135 (4387, 5884)	1998 (1362, 2634)	<0.001**
Single localization session							
Yes	3015 (1180)	Ref. [0]		Ref. [0]	2988 (2820, 3157)	Ref. [0]	
No	3498 (1230)	481 (243, 720)	<0.001*	0.164 (0.087, 0.240)	3519 (3361, 3678)	531 (521, 541)	<0.001**

Trial-based, Unadjusted and Adjusted Cost Minimization Analysis. Monetary units are Euros (€). Mean values are presented with 95% CI (confidence intervals). The adjusted analysis is performed with a generalized linear model (gamma family, log link). Ref.: reference category, OPBCS: oncoplastic breast conserving surgery, TM: therapeutic mastopexy/mammaplasty, WLE: wide local excision. *: regression analysis, **: generalised linear regression model.

Magnetic seed vs guidewire breast cancer localization with magnetic lymph node detection: a cost-minimisation analysis

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Supplementary Material.

Table S1: Unadjusted analysis for the main trial and the sensitivity analyses.

Table S2: Unadjusted and adjusted sensitivity analysis. Sensitivity analysis 1 denotes all magnetic seeds placed by radiologists. Sensitivity analysis 2 denotes all magnetic seeds placed by surgeons, along with SPIO administration, for all tumours detactable on ultrasound.

Supplement: CHEERS Checklist

Table S1: Unadjusted analysis for the main trial and the sensitivity analyses.

A: Type of device					
	Guidewire	Magnetic Marker		Difference (95%) CI	p-value
1. In-trial results					
Mean (SD)	3337 (1350)	3274 (1105)		-63 (-302, 174)	0.599*
Mean (95 % CI)	3337 (3151, 3524)	3274 (3124, 3160)			
Median (IQR)	3034 (2663, 3696)	3031 (2518, 3696)			0.886**
Bootstrapped Mean (95% CI)	3337 (3157, 3527)	3274 (3127, 3423)		-63 (-303, 173)	0.596*
Bootstrapped Median (95% CI)	3043 (2857, 3175)	3031 (2909, 3227)			
2. Sensitivity Analysis 1					
Mean (SD)	3620 (1350)	3556 (1105)		-63 (-302, 175)	0.601*
Mean (95 % CI)	3620 (3433, 3806)	3556 (3406, 3706)			
Median (IQR)	3316 (2663, 4340)	3313 (2800, 3978)			0.886**
Bootstrapped Mean (95% CI)	3620 (3439, 3810)	3556 (3410, 3705)		-63 (-303, 173)	0.596*
Bootstrapped Median (95% CI)	3316 (3139, 3457)	3313 (3191, 3509)			
3. Sensitivity Analysis 2					
Mean (SD)	3618 (1350)	3287 (1119)		-330 (-570, -90)	0.007*
Mean (95 % CI)	3618 (3432, 3805)	3287 (3138, 3439)			
Median (IQR)	3297 (2663, 4340)	3022 (2528, 3694)			0.056**
Bootstrapped Mean (95% CI)	3618 (3438, 3810)	3254 (3140, 3296)		-330 (-571, -95)	0.011*
Bootstrapped Median (95% CI)	3297 (3101, 3457)	3022 (2903, 3296)			
B: Type of surgery					
	WLE	OPBCS	TM	Difference (95%) CI	
1. In-trial results					
Mean (SD)	3126 (1087)	3730 (1284)	5232 (1475)	604 (144, 1064) // 2106 (1280, 2932)	<0.001*
Mean (95 % CI)	3126 (3010, 3241)	3722 (3365, 4078)	5232 (4560, 5903)		
Median (IQR)	2934 (2359, 3583)	3266 (2751, 4371)	4848 (4168, 5710)		<0.001**

Bootstrapped Mean (95% CI)	3126 (3020, 3240)	3730 (3383, 4104)	5232 (4639, 5863)	604 (251, 1006) // 2106 (1481, 2817)	<0.001*
Bootstrapped Median (95% CI)	2934 (2828, 3031)	3266 (3053, 3942)	4848 (4269, 5546)		
2. Sensitivity Analysis 1					
Mean (SD)	3408 (1087)	4013 (1284)	5515 (1475)	604 (144, 1065) // 2106 (1280, 2933)	<0.001*
Mean (95 % CI)	3408 (3293, 3524)	4012 (3648, 4378)	5515 (4843, 6187)		
Median (IQR)	3216 (2641, 3865)	3548 (3033, 4653)	5131 (4455, 5993)		<0.001**
Bootstrapped Mean (95% CI)	3408 (3302, 3523)	4012 (3666, 4387)	5515 (4922, 6146)	604 (251, 1006) // 2106 (1481, 2818)	<0.001*
Bootstrapped Median (95% CI)	3216 (3112, 3313)	3548 (3335, 4225)	5131 (4554, 5828)		
3. Sensitivity Analysis 2					
Mean (SD)	3276 (1105)	3857 (1326)	5349 (1521)	580 (106, 1055) // 2073 (1221, 2925)	<0.001*
Mean (95 % CI)	3276 (3158, 3393)	3857 (3480, 4234)	5349 (-4657, -5268)		
Median (IQR)	3022 (-2503, -3732)	(-2942, -4365)	(-4839, -5993)		<0.001**
Bootstrapped Mean (95% CI)	3276 (3169, -3390)	3857 (-3427, -4156)	5349 (-4732, -5982)	2073 (1416, 2799)	<0.001*
Bootstrapped Median (95% CI)	3022 (-2902, -3161)	3435 (-3180, -4009)	4839 (-4365, -5828)		
C: Single localisation session					
	No	Yes		Difference (95% CI)	
1. In-trial results					
Mean (SD)	3498 (1230)	3015 (1180)		481 (243, 720)	<0.001*
Mean (95 % CI)	3498 (3345, 3652)	3015 (2833, 3196)			
Median (IQR)	3237 (2683, 3976)	2737 (2225, 3543)			<0.001**
Bootstrapped Mean (95% CI)	3498 (3233, 3527)	3015 (2857, 3186)		481 (245, 705)	<0.001*
Bootstrapped Median (95% CI)	3237 (3058, 3453)	2737 (2477, 2869)			
2. Sensitivity Analysis 1					
Mean (SD)	3781 (1230)	3297 (1180)		481 (243, 720)	<0.001*
Mean (95 % CI)	3781 (3636, 3934)	3297 (3116, 3479)			
Median (IQR)	3520 (2952, 4258)	3019 (2507, 3825)			<0.001**
Bootstrapped Mean (95% CI)	3781 (3626, 3931)	3297 (3130, 3563)		481 (245, 705)	<0.001*

Bootstrapped Median (95% CI)	3520 (3340, 3735)	3019 (2765, 3152)			
3. Sensitivity Analysis 2					
Mean (SD)	3585 (1277)	3250 (1181)		332 (88, 576)	0.008*
Mean (95 % CI)	3585 (3425, 3744)	3250 (3068, 3431)			
Median (IQR)	3337 (2706, 4049)	2904 (2428, 3694)			0.006**
Bootstrapped Mean (95% CI)	3585 (3427, 3739)	3250 (3084, 3422)		332 (94, 561)	0.007*
Bootstrapped Median (95% CI)	3337 (3101, 3496)	2904 (2744, 3139)			

Table S2: Unadjusted and adjusted sensitivity analysis.

	Unadjusted analysis			Adjusted analysis			
	Mean (95% CI)	Marginal Difference (95% CI)	p-value	Coefficient (95% CI)	Marginal Means (95% CI)	Difference (95% CI)	p-value
Sensitivity analysis 1							
Localization device							
Guidewire	3620 (3433, 3806)	Ref. [0]		Ref. [0]	3798 (3618, 3978)	Ref. [0]	
Seed	3556 (3406, 3706)	-63 (-302, 175)	0.601	-0.110 (-0.178, -0.041)	3403 (3253, 3554)	-394 (-365, -424)	0.002
Type of Breast Surgery							
WLE	3408 (3293, 3524)	Ref. [0]		Ref. [0]	3415 (3307, 3533)	Ref. [0]	
OPBCS	4012 (3648, 4378)	604 (144, 1065)		0.144 (0.051, 0.236)	3948 (3607, 4290)	528 (301, 756)	0.002
TM	5515 (4843, 6187)	2106 (1280, 2933)	<0.001	0.461 (0.322, 0.599)	5421 (4695, 6147)	2001 (1388, 2614)	<0.001
Single localization session							
Yes	3297 (3116, 3479)	Ref. [0]		Ref. [0]	3269 (3100, 3439)	Ref. [0]	
No	3781 (3636, 3934)	481 (243, 720)	<0.001	0.151 (0.081, 0.222)	3803 (3645, 3960)	533 (521, 546)	<0.001
Sensitivity analysis 2							

Localization device							
Guidewire	3618 (3432, 3805)	Ref. [0]		Ref. [0]	3791 (3611, 3985)	Ref. [0]	
Seed	3287 (3138, 3439)	-330 (-570, -90)	0.007	-0.118 (-0.260, -0.117)	3145 (3000, 3289)	-653 (-696, -611)	<0.001
Type of Breast Surgery							
WLE	3276 (3158, 3393)	Ref. [0]		Ref. [0]	3415 (3307, 3533)	Ref. [0]	
OPBCS	3857 (3480, 4234)	580 (106, 1055)		0.146 (0.049, 0.242)	3948 (3607, 4290)	528 (301, 756)	0.003
TM	5349 (-4657, -5268)	2073 (1221, 2925)	<0.001	0.488 (0.344, 0.632)	5421 (4695, 6147)	2001 (1388, 2614)	<0.001
Single localization session							
Yes	3250 (3068, 3431)	Ref. [0]		Ref. [0]	3156 (2988, 3325)	Ref. [0]	
No	3585 (3425, 3744)	332 (88, 576)	<0.001	0.151 (0.081, 0.222)	3659 (3498, 3820)	503 (495, 510)	<0.001

Unadjusted and Adjusted Cost Minimisation Sensitivity Analysis. Sensitivity analysis 1 denotes all magnetic seeds placed by radiologists. Sensitivity analysis 2 denotes all magnetic seeds placed by surgeons, along with SPIO administration, for all tumours detactable on ultrasound.

Monetary units are Euros (€). Mean values are presented with 95% CI (confidence intervals). The adjusted analysis is performed with a generalized linear model (gamma family, log link). Ref.: reference category, OPBCS: oncoplastic breast conserving surgery, TM: therapeutic mastopexy/mammaplasty, WLE: wide local excision. *: regression analysis, **: generalised linear regression model.