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SUMMARY WITH CRITICAL APPRAISAL

Magnetic Localization System for Sentinel Lymph Node Biopsy: A Review of the Diagnostic Accuracy, Cost-Effectiveness, and Guidelines

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Abbreviations

BD	Blue dye
CI	Confidence interval
DCIS	Ductal carcinoma in situ
ER	Estrogen receptor
HER-2	Human epidermal growth factor receptor-2
ISPOR	Professional Society for Health Economics and Outcomes Research
NMA	Network meta-analysis
PR	Progesterone receptor
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RR	Risk ratio
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
SPIO	Superparamagnetic iron oxide
Tc	Technetium-99

Context and Policy Issues

Breast cancer is the most common type of cancer in Canadian women and the second leading cause of death from cancer.[1] As of 2019, it was estimated that approximately one in eight Canadian women develop breast cancer during their lifetime, while around one in 33 Canadian women die from breast cancer.[1] Breast cancer most commonly affects women over the age of 40,[2] with the median age at diagnosis 62 years (based on data from the United States).[3] Breast cancer also affects men, albeit less commonly, accounting for around 0.2% of all newly diagnosed cancers.[4]

In patients with breast cancer, involvement of axillary lymph nodes is an indicator of poor prognosis.[5] Staging of axillary lymph nodes has become the standard of care[6] in clinically node-negative breast cancer (i.e., no signs of metastases in axillary lymph nodes). Tumor cells from the breast drain to the same few lymph nodes, which are termed sentinel lymph nodes (SLNs).[7] The most common current approach to staging axillary lymph nodes involves a biopsy of the SLNs.[7] This technique is called sentinel lymph node biopsy (SLNB). SLNB alone provides adequate information for staging of the axillary lymph nodes.[6] The information from SLNB can then be used to guide further treatment.

SLNB involves injecting one or two tracers into the breast near the tumor or under the areolar plexus.[7] The tracer enters the lymphatic channels and first drains to the SLNs.[7] The SLNs are then identified based on presence of the tracer, removed, and tested for the presence of cancer.[7] Common tracers include blue dye (BD), the radioisotope technetium-99 (Tc), or a combination of the two (Tc/BD).[7] When using BD, the SLNs are identified by making an incision in the axilla and identifying blue lymph nodes at the end of a lymphatic channel for removal. When Tc is used, a gamma probe is used to detect areas of maximum radioactivity in the axilla (a “hot spot”).[7] An incision can then be made at the “hot spot” and the SLN(s) can be removed.[7] Using Tc exposes patients and healthcare providers to radioactivity, and there are also concerns about the supply of Tc.[8] Use of BDs carries a risk of adverse effects, such as severe anaphylaxis or skin necrosis.[7] Therefore, alternative methods for SLNB may be desirable. One such approach involves magnetic localization. This procedure uses superparamagnetic iron oxide (SPIO; brand name Magtrace, previously Sienna) as a tracer. The presence of SPIO in SLNs can then be detected using a magnetic probe (Sentimag), and the SLNs can be removed for further testing.[7]

The aim of the report is to summarize the diagnostic accuracy, safety, and cost-effectiveness of SLN detection using a magnetic localization system and to summarize existing guidelines on this topic.

Research Questions

1. What is the diagnostic accuracy of magnetic localization systems for sentinel node biopsies in patients with breast cancer?
2. What is the safety of magnetic localization systems for sentinel node biopsies in patients with breast cancer?
3. What is the cost-effectiveness of magnetic localization systems for sentinel node biopsies in patients with breast cancer?
4. What are the evidence-based guidelines regarding the use of sentinel lymph node localization techniques for sentinel node biopsies in patients with breast cancer?

Key Findings

One systematic review with network meta-analysis and three non-randomized studies were identified regarding the diagnostic accuracy and safety of magnetic localization systems for sentinel lymph node biopsy. Evidence from one systematic review with network meta-analysis and three non-randomized studies suggested that the detection rate for sentinel lymph node biopsy with magnetic localization systems (using a superparamagnetic iron oxide tracer) was similar, or non-inferior, to sentinel lymph node biopsy using the radioisotope method (technetium-99 with or without blue dye). The network meta-analysis found that there was no statistically significant difference in false negative rate between these two methods, but there were no data on the false positive rate. The comparative safety of magnetic localization systems was difficult to establish due to limitations in how adverse effects were reported in eligible studies. However, magnetic localization systems for sentinel lymph node biopsy appeared to be generally safe based on the available information. The main safety concern with this procedure appeared to be skin staining/discolouration. Studies with explicit and detailed comparisons of adverse effects for magnetic localization systems versus the radioisotope method (technetium-99) with or without blue dye will be helpful in clarifying the comparative safety of this technique for sentinel lymph node biopsy.

No cost-effectiveness evidence or guidelines were identified. Therefore, the cost-effectiveness of magnetic localization systems for sentinel lymph node biopsy, and recommendations regarding the use of magnetic localization systems for this procedure, are unclear.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH

(Medical Subject Headings), and keywords. The main search concepts were magnetic localization systems and sentinel lymph node biopsy for breast cancer. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2015 and January 28, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Primary studies were excluded if they were already part of an included systematic review, and systematic reviews were excluded if they were fully captured in a more recent and comprehensive systematic review.

Table 1: Selection Criteria

Population	Q1-4: Patients with breast cancer
Intervention or Index Test	Q1-4: Sentinel lymph node localization using magnetic tracer or magnetic localization system (brand name: Magtrace or Magtrace with Sentimag) also known as super paramagnetic iron-oxide nano-particles
Comparator or Reference Standard	Q1 (Reference Standard): histological confirmation Q1-3 (Comparator): Sentinel lymph node localization using radioactive isotopes such as technetium99 with or without blue dye, or blue dye alone Q4: Not applicable
Outcomes	Q1: Diagnostic accuracy (e.g., tumour identification; detecting cancer spread/detection rate; sensitivity and specificity) Q2: Safety; adverse outcomes (e.g., interference with follow up tests) Q3: Cost-effectiveness Q4: Recommendations regarding the use of sentinel lymph node localization techniques for sentinel biopsies
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published before 2015. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included systematic review and network meta-analysis was critically appraised by one reviewer using the Professional Society for Health Economics and Outcomes Research (ISPOR) checklist[9] and included nonrandomized studies were appraised by one reviewer using the Quality of Assessment of Diagnostic Accuracy Studies (QUADAS) 2 tool.[10] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 456 citations were identified in the literature search. Following screening of titles and abstracts, 415 citations were excluded and 41 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search for full-text review. Of these potentially relevant articles, 36 publications were excluded for various reasons, and four publications[11-14] met the inclusion criteria and were included in this report. These comprised one systematic review with network meta-analysis (NMA)[11] and three non-randomized studies.[12-14] Appendix 1 presents the PRISMA flowchart of the study selection. Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One systematic review with NMA was eligible for inclusion.[11] This NMA was published in 2019 and the search included articles published up to November 2017. The aim was to compare novel and conventional SLNB techniques. The authors included 35 cohort studies in total, seven of which were relevant for this report (four comparing magnetic localization systems [with SPIO tracer] to Tc and three comparing magnetic localization systems [with SPIO tracer] to Tc/BD).

Three prospective, non-randomized studies investigating diagnostic test accuracy were eligible for inclusion.[12-14] The studies by Alvarado et al. and Taruno et al.[13,14] were non-inferiority studies comparing the performance of magnetic localization systems (with SPIO) to the radioisotope method (with Tc/BD) for SLNB in the same patient (i.e., patients received both techniques and performance of techniques was compared). In the other non-randomized study by Karakatsanis et al.,[12] one hospital conducted all SLNBs using magnetic localization (with SPIO), while another hospital conducted all SLNBs using the radioisotope method (with Tc/BD), and the performance of the techniques was compared between the two hospitals.

Country of Origin

The systematic review with NMA was conducted in Singapore (eligible studies were conducted in France, Italy, Germany, Japan, Netherlands, Spain, Sweden, and United Kingdom).[11] One non-randomized study was conducted in the United States,[13] one in Japan,[14] and the other in Sweden.[12]

Patient Population

The systematic review with NMA[11] provided little detail on patient or study characteristics. The mean age of patients was 57 years old and the sex of patients was not described.

The patients in Alvarado et al.[13] had primary invasive breast cancer or ductal carcinoma in situ (DCIS) and were clinically node-negative. The mean age of included patients was 61 years. Approximately 84% of eligible patients were estrogen receptor (ER) positive, 64%

were progesterone receptor (PR) positive, and 10% were human epidermal growth factor receptor-2 (HER2) positive. The sex of patients was not explicitly described.

In Taruno et al.,[14] patients were females who had been diagnosed with breast cancer and were clinically node-negative. The median age of patients was 57 years.

In the study by Karakatsanis et al.,[12] patients had early breast cancer (invasive tumors [T1 to T3] or DCIS) without suspicion of metastasis on axillary ultrasound. The mean age in the SPIO arm was 64 years and the mean age in the Tc arm was 65 years. The sex of patients was not explicitly described.

Interventions and Comparators

The eligible systematic review with NMA[11] made separate comparisons for magnetic localization with SPIO versus the radioisotope method with Tc alone, and for magnetic localization with SPIO versus the radioisotope method with Tc/BD. The authors also compared each of SPIO, Tc, and Tc/BD, to BD alone as the reference standard. No further details about the techniques were provided.

In Alvarado et al.,[13] the intervention was magnetic localization (Magtrace [SPIO] with Sentimag) and the comparator was the radioisotope method (Tc sulfur colloid) with isosulfan BD. All patients received SPIO, Tc, and BD. SPIO was injected in the subareolar region at least 20 minutes before the SLNB. BD was then injected. Magnetic and radioisotope counts were recorded at the injection site using both the magnetic probe and gamma probe, then the incision was made. After the incision was made, SLNs were first identified using the Sentimag (either by the probe or visual confirmation of the black/brown node) and a magnetic count was taken both in vivo and ex vivo. A radioisotope count was also taken both in vivo and ex vivo. Nodes identified by Sentimag, the gamma probe, or visual confirmation, were excised. Nodes that were clinically suspicious were also excised. Pathological assessment was performed for all nodes.

Taruno et al.[14] used SPIO coated with carboxydextran as a magnetic tracer (Resovist) and a magnetic probe developed at University of Tokyo, for detection, as well as Tc. Both Tc and SPIO were administered into areolar tissue up to 24 hours before the surgery. Before the surgery, BD was administered in all patients. To detect SLNs, the magnetic probe was used first, followed by detection of SLNs using Tc. Pathological assessment of excised nodes was not described.

In the Karakatsanis et al. study,[12] the magnetic localization arm received SPIO either one to four weeks before the surgery or around one hour before surgery (at least 20 minutes before surgery). In the magnetic localization arm, BD was administered 10 minutes before skin incision only if the transcutaneous magnetic signal was deemed inadequate by the operator. In the radioisotope arm, Tc was injected on the morning of the surgery, or the day before. BD was injected routinely for patients in the radioisotope arm (no further details provided). In both arms, transcutaneous counts were recorded using the appropriate probe before the incision. Locations with the highest signals were marked and considered SLNs. Nodes with 10% or more of the highest signal, or those that were blue or brown, were also considered SLNs. Signals were recorded in situ and ex vivo. All excised nodes were examined histologically.

Outcomes

The outcomes in the eligible systematic review with NMA[11] were the detection rate and false negative rate. The authors did not specify if their analysis was per patient or per node.

In the Alvarado et al. study,[13] the primary outcome was the node detection rate (number of lymph nodes identified by a method as a proportion of the number of lymph nodes detected). The authors tested non-inferiority of magnetic localization (with SPIO) compared to the radioisotope method (with Tc/BD), and used a non-inferiority margin of 5% between the detection rate of the magnetic localization system and the radioisotope method.

The primary outcome in the Taruno et al. study[14] was the detection rate per patient. The authors also measured the concordance between magnetic localization (with SPIO) and the radioisotope method (with Tc/BD) and side effects after the procedure. A detection rate over 90% in the magnetic localization group was used as the non-inferiority threshold.

Karakatsanis et al.[12] compared the procedure detection rate between magnetic localization (with SPIO) and the radioisotope method (Tc/BD). The authors also compared skin staining in the magnetic localization arm over a median of 398 days. Finally, in the magnetic localization arm, the authors compared the detection rate based on the timing of SPIO administration (preoperative versus perioperative), but these were not compared with Tc/BD.

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Systematic Review with Network Meta-Analysis

The eligible systematic review with NMA[11] reported on relevant interventions and outcomes. The authors conducted a comprehensive search and performed a thorough critical appraisal of included studies (judging eligible studies to be at low or moderate risk of bias). The analysis preserved within-study randomization and the authors checked for consistency in direct and indirect treatment comparisons. The results were generally well-reported, with a graphical representation of the network, and contrasts between interventions and associated 95% confidence intervals in a table. The results of the individual studies were not reported.

The primary concern with this NMA was that there was minimal information provided on the characteristics of patients in the eligible studies, as well as details about conduct of the individual studies themselves. This made it difficult to judge whether there were concerns related to heterogeneity and transitivity. The authors tested for consistency between the direct and indirect comparisons; however, they did not appear to test for statistical heterogeneity in the pairwise comparisons nor discuss any clinical heterogeneity between studies. While the authors stated they used a meta-regression model, there was no detail provided about the model.

Due to the lack of detail about the patient population in the NMA, it was not possible to determine the generalizability of the results to the Canadian context.

Non-randomized studies

There were concerns related to selection bias in all three nonrandomized studies. In the studies by Alvarado et al.[13] and Taruno et al.,[14] it was unclear whether consecutive patients were enrolled. In the study by Karakatsanis et al.,[12] separate groups of patients received each technique depending on which hospital they attended, and thus patients were not randomized. Confounding may also be a concern in this study, as there were some differences between the two groups (difference between groups in body-mass index was statistically significantly different, while there were differences between groups in cancer subtype and age that were not statistically significant but could be important) and few potential confounders were reported (raising possibility of residual confounding). There were no concerns related to applicability of the patient population in any of the studies.

Both Alvarado et al.[13] and Taruno et al.[14] were conducted in an unblinded fashion and the authors employed SPIO and Tc consecutively in the same patients. This could introduce bias, since the assessors would have known the results of one technique when performing another. Further, in all three nonrandomized studies, the reference test was performed after the SLNB technique was employed. Since SLNB techniques result in staining of the SLN, those performing the reference test may have had knowledge of the results of the SLNB method, which may have also introduced bias. The timing of administration in the study by Karakatsanis et al.[12] varied, with some patients receiving SPIO around one hour before surgery and some patients receiving one to four weeks before the procedure. The authors noted differences in detection rate based on timing of SPIO; however, they only compared the difference in detection rate in the SPIO arm and did not compare the detection rates based on SPIO timing directly to the detection rate using Tc. Thus, whether timing of SPIO resulted in a meaningful difference in detection rate compared to Tc was unclear.

The patients in the Karakatsanis et al. study[12] were consecutively enrolled in Sweden, while the patients in the Alvarado et al. study[13] were enrolled from multiple centers in the United States (unclear if consecutive). The median age of patients in these studies were 61 years and 64 years, respectively. The median age at diagnosis in the United States is 62 years,[3] suggesting the results from these studies may be generalizable in a Canadian context. Patients in the Taruno et al. study had a median age of 57,[14] which was slightly younger, though comparable to the median age at diagnosis in the United States. However, this trial was conducted in Japan and employed a SPIO tracer (Resovist) and probe developed at University of Tokyo. This system appears to be different from Magtrace/Sentimag and does not appear to be available in Canada. As such, the applicability of this study in a Canadian context was less clear.

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

Diagnostic accuracy

Detection rate

The systematic review and NMA by Mok et al.[11] reported no difference in detection rate for magnetic localization with SPIO compared to the radioisotope method with Tc alone (risk ratio [RR] 0.99, 95% confidence interval [CI] 0.93 to 1.06) or with Tc/BD (RR 1.01, 95% CI 0.95 to 1.07). This systematic review and NMA also reported differences in detection rate between each technique and BD alone as a comparator. The detection rate was statistically significantly greater for both SPIO (RR 1.09, 95% CI 1.01 to 1.18) and Tc alone (RR 1.09,

95% CI 1.04 to 1.15) compared to BD alone. The detection rate for Tc/BD was also greater compared to BD alone but the difference was non-significant (RR 1.09, 95% CI 0.98 to 1.16). Alvarado et al. found that magnetic localization with SPIO was non-inferior to the radioisotope method with Tc/BD (absolute difference in node detection rate = 0.8%, P for non-inferiority = 0.0065).[13] There was no statistical comparison between magnetic localization and the radioisotope method for the outcome of patient detection rate; however, the patient detection rate for magnetic localization was 99.3% (95% CI 98.0 to 100) and the patient detection rate for the radioisotope method was 98.6% (95% CI 96.7 to 100). Taruno et al. also reported that magnetic localization with SPIO was non-inferior to the radioisotope method with Tc/BD (absolute difference in patient detection rate = -3.3%, 95% CI -6.9 to 0.2).[14] Finally, Karakatsanis et al.[12] found no difference in node detection between magnetic localization with SPIO and the radioisotope method with Tc/BD (absolute difference in node detection rate = -1.3%, P = 0.537).

False negative rate

Mok et al.[11] found no statistically significant difference in false negative rate between magnetic localization with SPIO and the radioisotope method with Tc alone (RR 0.84, 95% CI 0.36 to 1.93). This systematic review and NMA also reported differences in false negative rate between each technique and BD alone as a comparator. There was a statistically significant reduction in false negative rate for Tc alone versus BD (RR 0.44, 95% CI 0.20 to 0.96), while there was a non-significant reduction for SPIO versus BD (RR 0.45, 95% CI 0.14 to 1.45) and for Tc/BD versus BD (RR 0.57, 95% CI 0.13 to 2.51).

Concordance

Taruno et al. reported that the concordance between magnetic localization with SPIO and the radioisotope method with Tc/BD was 96.1% (198/206 patients).[14]

Safety

Alvarado et al. reported 69 adverse events in the overall study population (146 patients) and noted that 9 were serious (no further detail provided).[13] These authors reported that 10 patients experienced ecchymosis or bruising. They also reported that 24 (16.3%) patients had adverse events related to the magnetic tracer (23 of these patients [15.6%] had breast discoloration or hyperpigmentation). There was no information on whether this was transient or permanent. Taruno et al. reported that a skin tattoo related to SPIO remained in 22/210 patients (10%) 1 month after the procedure.[14] Finally, Karakatsanis et al.[12] found that 73 patients (39.9%) in the magnetic localization arm had skin staining, which faded slowly over time but was still present in 66 patients 15 months after the procedure. The authors also noted that more patients that had a perioareolar injection experienced staining (58/73 patients) compared to peritumoral injection (15/73 patients).

Cost-effectiveness

No relevant evidence regarding the cost-effectiveness of magnetic localization systems for sentinel node biopsies in patients with breast cancer was identified; therefore, no summary can be provided.

Guidelines

No relevant guidelines regarding use of sentinel node localization techniques for sentinel node biopsies in patients with breast cancer were identified; therefore, no summary can be provided.

Limitations

A central challenge with the current evidence base related to magnetic localization systems was the lack of economic evaluations that compared the cost-effectiveness of magnetic localization to the radioisotope method. There were also no guidelines available on the use of magnetic localization systems for SLNB in patients with breast cancer.

Eligible studies focused primarily on detection rate, and false negative rate; however, there were no data on false positive rates. Since avoiding unnecessary harm from subsequent procedures/tests is a goal of SLNB, data on false positive rates would be informative for decision-makers. The comparative safety of magnetic localization systems was also difficult to establish based on the evidence in this review. Eligible studies did not include explicit comparisons of adverse effects for each procedure. Studies that reported safety generally only reported on rates of skin staining attributed to SPIO or reported adverse effects in aggregate.

There were also challenges in the evidence base related to generalizability. The patient characteristics were not well-described for the studies in the Mok et al. NMA,[11] making it unclear whether the results in this NMA were applicable to the Canadian context. It also made it difficult to determine whether there was a specific population or subtype of cancer where magnetic localization was particularly useful. Further, one of the eligible studies[14] used a tracer system developed by a group in Japan, which appears to not be available in Canada. Therefore, it was unclear whether the findings are relevant to the Canadian context. Finally, Taruno et al. only enrolled women in their trial; therefore, the generalizability of the findings of this study to men with breast cancer is unclear. The other eligible studies did not report the sex of participants, and therefore the generalizability of these studies with respect to sex is also unclear,

Conclusions and Implications for Decision or Policy Making

This report identified one systematic review with NMA[11] and three non-randomized studies[12-14] examining diagnostic accuracy and safety of magnetic localization systems for SLNB. There was no evidence on cost-effectiveness of magnetic localization systems and no guidelines on the use of magnetic localization systems for SLNB in patients with breast cancer.

The NMA and non-randomized studies all reported that for SLNB, the detection rate for magnetic localization was similar, or non-inferior, to the detection rate for the radioisotope method with Tc alone or Tc/BD. The NMA also reported that the detection rates for magnetic localization or the radioisotope method were both greater than the detection rate using BD alone. The NMA by Mok et al.,[11] found that the false negative rate for magnetic localization was similar to the false negative rate for the radioisotope method with Tc alone. The false negative rate for the radioisotope method using Tc alone was lower compared to BD alone, while the false negative rate for magnetic localization or the radioisotope method using Tc/BD may be lower compared to BD alone, but the differences were not statistically significant. The included studies all had limitations. In the NMA by Mok et al.,[11] clinical and statistical heterogeneity across studies was not reported in detail, making it difficult to judge whether it was appropriate to perform NMA with these studies (subsequently making it difficult to judge the validity of NMA results). In the non-randomized studies, the primary concern was the possibility of bias due to lack of blinding, which reduced confidence in the results of these studies. Despite these limitations, the available evidence suggested that

magnetic localization systems may be comparable to the radioisotope method (with Tc or Tc/BD) in terms of detection rate and false negative rate. Since there were no data on false positive rates, future studies of magnetic localization systems could consider comparisons of techniques with respect to these outcomes.

The available studies concluded that magnetic localization systems appeared to be generally safe. The main safety concern from the SPIO tracer appeared to be skin staining from the procedure. The included studies either reported adverse effects in aggregate, or only reported skin staining related to SPIO specifically. They did not provide comparisons of adverse effects between SPIO and Tc. One of the theoretical advantages of using SPIO as a tracer is avoidance of allergic reactions to BD and avoidance of radiation; however, eligible studies did not examine this. It may therefore be helpful for future studies to provide and report more detailed comparisons of adverse effects between SPIO and Tc or Tc/BD, to gain further understanding of the comparative safety of SPIO.

The cost-effectiveness of magnetic localization systems was unclear. Since the diagnostic accuracy of magnetic localization systems appeared to be comparable to that of the radioisotope method (with Tc or Tc/BD), cost-effectiveness data for magnetic localization systems would be particularly helpful to decision-makers. One of the eligible non-randomized studies[12] compared the cost per procedure (cost of visit + cost of tracer) for magnetic localization (using SPIO) to the radioisotope method (using Tc/BD) and found magnetic localization was €27 cheaper than the radioisotope method (€225 for magnetic localization vs. €252 for radioisotope). However, costing varies by jurisdiction and this study was conducted in Sweden, and there were no cost-effectiveness data related to magnetic localization systems. Therefore, there is a need for cost-effectiveness data for magnetic localization systems compared to the radioisotope method (using Tc or Tc/BD). This would further clarify the role of magnetic localization systems in SLNB for decision-makers looking to implement this technology.

No guidelines were identified on use of magnetic localization systems for SLNB in patients with breast cancer. Future guidelines on SLNB may consider incorporating recommendations on the role of magnetic localization systems for SLNB in patients with breast cancer.

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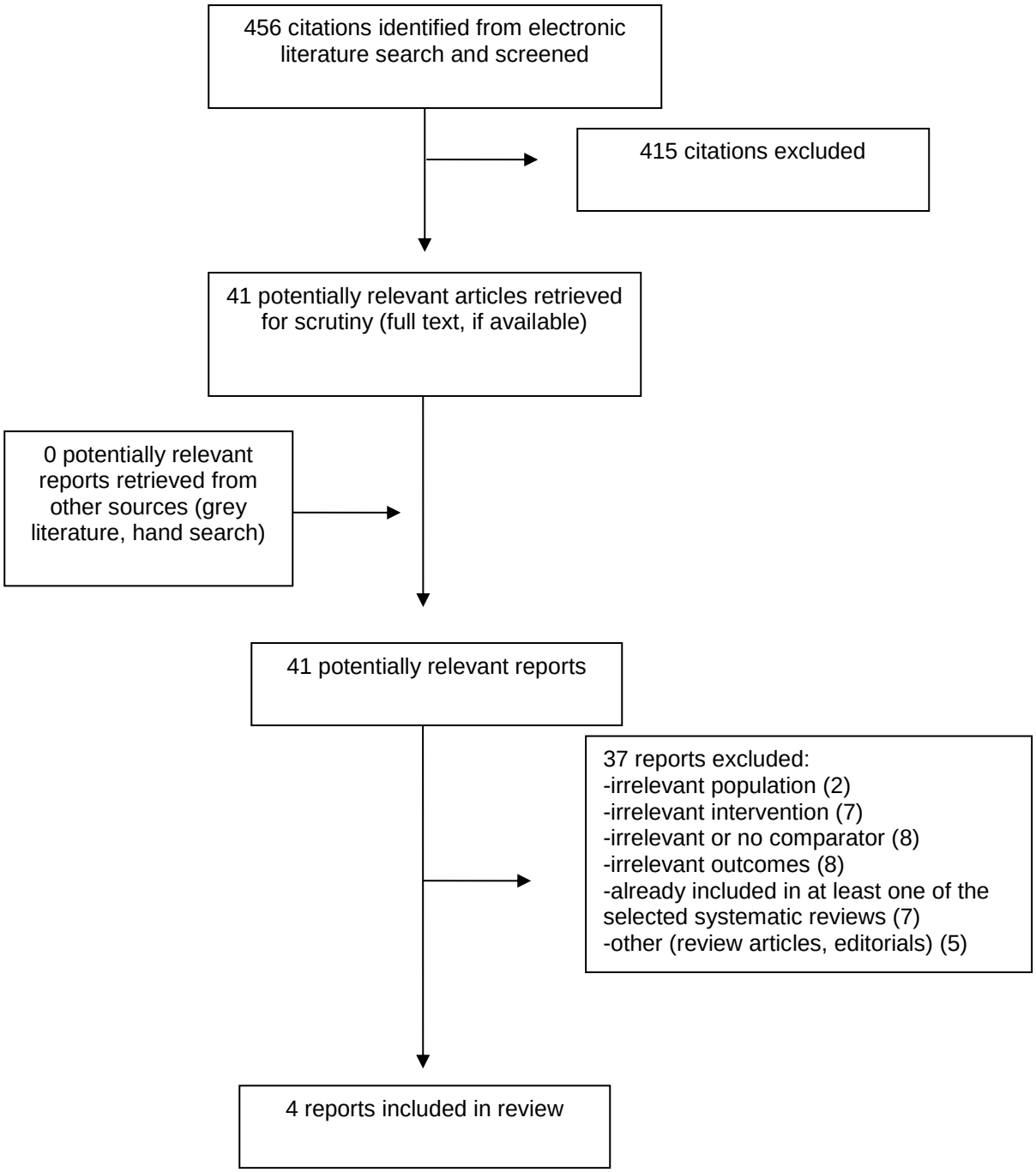
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Review and Network Meta-Analysis

First Author, Publication Year, Country	Objective, Study Designs, Databases Searched, Search Date, Number of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Mok et al. 2019[11] **Country** Singapore	**Objective** Compare performance of BD alone or in combination with Tc with novel techniques (SPIO, ICG, or CEUS), for SLN detection in breast cancer **Databases** Pubmed, Embase, Cochrane Library, China Knowledge Research Integrated Database, Clinicaltrials.gov, OpenGrey **Studies** Total of 35 studies (n=4244 patients), compared novel techniques with BD +/- Tc; all studies used a cohort design 7 of the studies (n=1116 subjects) were relevant to this report (i.e., compared SPIO with Tc +/- BD specifically) **Search date** November 31, 2017	Mean age = 57 years Sex of participants not reported	**Intervention** SLN detection using SPIO **Comparator** SLN detection using Tc, Tc/BD 3 studies involved combination Tc/BD; 4 studies involved Tc only	**Outcomes** Detection rate, false negative rate

BD = blue dye; CEUS = contrast-enhanced ultrasound imaging; ICG = indocyanine green fluorescence; SLN = sentinel lymph node; SPIO = superparamagnetic iron oxide; Tc = technetium-99.

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design, Eligibility Criteria	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Alvarado et al. 2019[13] **Country** United States	Prospective, open-label, paired comparison, non-inferiority study **Inclusion criteria** Diagnosis of primary invasive breast cancer or ductal carcinoma in situ who were clinically node-negative, ≥18 years or older, ECOG status 0 to 2, node-negative axilla **Exclusion criteria** Pregnant, lactating, hypersensitivity or intolerance to isosulfan blue dye, iron, dextran compounds or Magtrace; previous axillary surgery, reduction mammoplasty or impaired lymphatic function (surgeon's judgment); previous radiation to the affected breast or axilla; a recent injection of ferumoxytol; iron overload disease; or implantable device in the chest wall, such as a pacemaker	n=160 patients Mean age 61 years (SD 12.3, range 35 to 88) 113 (83.7%) patients were ER positive 87 (64%) patients were PR positive 13 (10%) patients were HER2 positive Sex of participants not reported	**Intervention** SLN detection with SPIO (Magtrace) **Comparator** SLN detection with Tc/BD All patients underwent SLN detection with both SPIO (Magtrace) and Tc/BD All excised nodes underwent pathologic assessment; only histologically confirmed nodes were included in study analysis	**Primary outcome** SLN detection rate (number of lymph nodes identified by a specific method as a proportion of the total number of nodes detected) **Other outcomes** Safety A post-operative follow-up visit was carried out 6 to 22 days after the procedure Non-inferiority margin of 5%
Taruno et al. 2019[14] **Country** Japan	Prospective, multicenter study **Inclusion criteria** Female, ≥20 years old, diagnosed with breast cancer, clinically node negative **Exclusion criteria** Intolerance or hypersensitivity to iron compounds or carboxydextran,	n=220 patients (100% female) Median age 57 years (range 33 to 94 years)	**Intervention** SLN detection using SPIO (Resovist) **Comparator** SLN detection using Tc+BD All patients underwent SLN detection with both Tc+BD and SPIO (Resovist)	**Primary outcome** SLN detection rate per patient **Secondary outcome** Concordance of detection, side effects directly after surgery "If we assume that the detection rate of the RI method is 97%, then the noninferiority threshold is 90%,

First Author, Publication Year, Country	Study Design, Eligibility Criteria	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	pregnancy or lactation, pacemaker or other ferrous metal-containing devices in the chest wall, breast implant insertion, liver failure, and renal failure			meaning that any results above 90% will be viewed as noninferior to the radioisotope method" (p. 1393)
Karakatsanis et al. 2017[12] **Country** Sweden	Prospective cohort study (conducted at two hospitals, one using SPIO and one using Tc + BD) **Inclusion criteria** Patients with early breast cancer and scheduled for primary surgery with SLN biopsy, invasive tumors (T1 to T3) or ductal carcinoma in situ without suspicion of metastasis on axillary ultrasound imaging **Exclusion criteria** Pacemaker or other implantable metallic device in the chest, allergy or intolerance to iron and dextran compounds, haemochromatosis, pregnant or lactating	**SPIO arm** (n=183 patients and 184 procedures) Mean age 64 years Preoperative injection in 108 patients and perioperative in 76 patients Luminal A: 78/183 (46%) Luminal B/HER2-: 46/183 (25%) Luminal B/HER+: 20/183 (11%) HER2+/non-luminal: 6/183 (3.3%) Triple-negative: 13/183 (7.1%) Unknown: 21/183 (11%) Sex of participants not reported **Tc arm** (n=155 patients and 159 procedures) Mean age 65 years Luminal A: 92/155 (59%) Luminal B/HER2-: 29/155 (19%) Luminal B/HER+: 10/155 (6.5%) HER2+/non-luminal: 4/155 (2.6%) Triple-negative: 12/155 (7.7%) Unknown:	**Intervention** SLN detection using SPIO (Sienna+) **Comparator** SLN detection using Tc + BD All nodes retrieved were examined with haematoxylin and eosin staining In the SPIO arm, BD was also administered if the transcutaneous signal was deemed inadequate by the operator	**Primary outcome** SLN detection rate per procedure **Secondary outcome** Cost per patient Follow-up was performed every 3 months in patients enrolled in the SPIO arm in order to assess the size and fading of skin staining in the postoperative period

First Author, Publication Year, Country	Study Design, Eligibility Criteria	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		12/155 (7.7%) Sex of participants not reported		

BD = blue dye; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; HER2 = human epidermal growth factor; PR = progesterone receptor; SPIO = superparamagnetic iron oxide; Tc = technetium-99.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Critical Appraisal of Network Meta-Analysis using ISPOR Questionnaire[9]

Question	Mok 2019[11]		
	Strength	Weakness	Comment
Relevance			
Is the population relevant?	Unclear		Minimal information included on characteristics of patients that were part of eligible studies
Are any critical interventions missing?	Yes	—	
Are any relevant outcomes missing?	Yes	—	
Is the context (e.g., settings and circumstances) applicable to your population?	Unclear		Minimal information provided on context
Credibility			
Did the researchers attempt to identify and include all relevant randomized controlled trials?	Yes	—	Comprehensive search strategy
Do the trials for the interventions of interest form one connected network of randomized controlled trials?	Yes	—	
Is it apparent that poor-quality studies were included, thereby leading to bias?	Yes	—	Included studies had low or moderate risk of bias as reported by study authors
Is it likely that bias was induced by selective reporting of outcomes in the studies?	Yes	—	
Are there systematic differences in treatment effect modifiers across the different treatment comparisons in the network?	Unclear		Patient characteristics not reported in detail
If yes, were these imbalances in effect modifiers across the different treatment comparisons identified prior to comparing individual study results?	Unclear		Patient characteristics not reported in detail
Analysis			
Were statistical methods used that preserve within-study randomization (no naive comparisons)?	Yes	—	
If both direct and indirect comparisons are available for pairwise contrasts, was agreement in treatment effects evaluated or discussed?	Yes	—	
In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?	Unclear		
With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network	Unclear		No evidence of statistical inconsistency; authors performed meta-regression but minimal information provided about

Question	Mok 2019[11]		
	Strength	Weakness	Comment
of trials, did the researchers attempt to minimize this bias with the analysis?			model and characteristics of eligible studies not provided in detail
Was a valid rationale provided for the use of random-effects or fixed-effects models?	Yes	—	
If a random-effects model was used, were assumptions about heterogeneity explored or discussed?	Unclear		Authors used meta-regression but minimal information provided on model, minimal information provided about included studies, and heterogeneity not discussed
If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Yes	—	Level of heterogeneity not mentioned, but authors performed meta-regression
Reporting Quality and Transparency			
Is a graphical or tabular representation of the evidence network provided with information on the number of randomized controlled trials per direct comparison?	Yes	—	
Are the individual study results reported?	—	No	
Are all pairwise contrasts between interventions, as obtained with the network meta-analysis, reported along with measures of uncertainty?	Yes	—	
Are results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?	Yes	—	Only forest plots provided, no effect estimates with confidence intervals are provided
Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?	—	No	Ranking provided but no measure of uncertainty
Is the impact of important patient characteristics on treatment effects reported?	—	No	
Are the conclusions fair and balanced?	Yes	—	
Conflict of Interest			
Were there any potential conflicts of interest?	Yes	—	
If yes, were steps taken to address these?	N/A		

ISPOR = Professional Society for Health Economics and Outcomes Research.

Table 5: Critical Appraisal of Primary Studies Using QUADAS-2[10]

Item	Alvarado 2019[13]	Taruno 2019[14]	Karakatsanis 2017[12]
Patient selection: risk of bias	Unclear	Unclear	High
Patient selection: concerns regarding applicability	Low	Low	Low
Index test: risk of bias	High	High	Low
Index test: concern regarding applicability	Low	Low	Low
Reference standard: risk of bias	High	High	High
Reference standard: concerns regarding applicability	Low	Low	Low
Flow and timing: risk of bias	Low	Low	Low

QUADAS = Quality Assessment of Diagnostic Accuracy Studies.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings of Included Network Meta-Analysis

Study	Intervention/ Comparison	Outcome	Findings	Authors' Conclusions
Mok et al. 2019[11]	SPIO	Pooled detection rate and 95% CI	97.4% (96.3 to 98.6)	"SPIO performed significantly better than BD in terms of detection rate. Although the risk ratio compared with BD for false-negative rate was not statistically significant, a 55 per cent decrease on the point estimate suggested a promising direction for the use of SPIO in sentinel lymph node biopsy." (*p450*) Authors only commented on comparison of each method to BD alone Authors did not comment specifically on comparison between SPIO and Tc or SPIO and Tc/BD
	Tc		96.5% (95.2 to 97.9)	
	Tc/BD		96.7% (94.3 to 99.1)	
	SPIO	Pooled false negative rate and 95% CI	4.0% (1.9 to 6.1)	
	Tc		2.6% (0.7 to 4.6)	
	Tc/BD		5.5% (0.9 to 10.2)	
	SPIO vs. Tc	Detection rate (RR and 95% CI)	0.99 (0.93 to 1.06)	
		False negative rate (RR and 95% CI)	0.84 (0.36 to 1.93)	
	SPIO vs. Tc/BD	Detection rate (RR and 95% CI)	1.01 (0.95 to 1.07)	
		False negative rate (RR and 95% CI)	No data	
	SPIO vs. BD as comparator	Detection rate (RR and 95% CI)	1.09 (1.01 to 1.18)	
	SPIO vs. BD as comparator	False negative rate (RR and 95% CI)	0.45 (0.14 to 1.45)	
	Tc vs. BD as comparator	Detection rate (RR and 95% CI)	1.09 (1.04 to 1.15)	
	Tc vs. BD as comparator	False negative rate (RR and 95% CI)	0.44 (0.20 to 0.96)	
	Tc/BD vs. BD as comparator	Detection rate (RR and 95% CI)	1.09 (0.98 to 1.16)	
	Tc/BD vs. BD as comparator	False negative rate (RR and 95% CI)	0.57 (0.13 to 2.51)	

BD = blue dye; CI = confidence interval; RR = risk ratio; SPIO = superparamagnetic iron oxide; Tc = technetium-99.

Table 7: Summary of Findings of Included Primary Studies

Study	Intervention/ Comparison	Outcome	Findings	Authors' Conclusions
Alvarado et al. 2019[13]	SPIO	Node detection rate (95% CI)	94.3% (91.9 to 96.7)	"We show the Magtrace tracer to be noninferior to radioisotope combined with blue dye for sentinel node detection in early-stage breast cancer" (*p3513*)
	Tc/BD		93.5% (91.0 to 96.0)	
	Tc alone		91.6% (no CI provided)	
	SPIO vs. Tc/BD	Difference in node detection rate (p value for non-inferiority)	0.8% (P = 0.0065 for non-inferiority)	
	SPIO	Patient detection rate (95% CI)	99.3% (98.0 to 100)	
	Tc/BD		98.6% (96.7 to 100)	
	Tc alone		95.9% (no CI provided)	
	Overall study population	Safety	69 adverse events in 56 patients, 9 of which were serious Ecchymosis or bruising occurred in 10 patients (6.8%) Authors did not break down adverse events by group except for hyperpigmentation (reported below)	
			23 (15.6%) patients had breast discoloration or hyperpigmentation due to magnetic tracer	
Taruno et al. 2019[14]	SPIO	Patient detection rate (95% CI)	94.8% (91.6 to 98)	"SLNB using the Resovist magnetic nanoparticles and a newly developed handheld probe can be considered as an equivalent method to the conventional radioisotope method." (*p1395*)
	Tc/BD		98.1% (95.9 to 100)	
	SPIO vs. Tc/BD	Difference in patient detection rate (95% CI)	-3.3% (-6.9 to 0.2)	
		Concordance	96.1%	
	SPIO	Safety	Skin tattoo remained in 22/210 patients (10%) 1 month after procedure	
Karakatsanis et al. 2017[12]	SPIO	Node detection rate	95.6%	"The use of SPIO alone is a safe alternative, with results comparable to those of the standard dual technique using Tc and blue dye." (*p1675*)
	Tc/BD		96.9%	
	SPIO vs. Tc/BD	Difference in patient detection rate	-1.3%, P = 0.537	

Study	Intervention/ Comparison	Outcome	Findings	Authors' Conclusions
	SPIO	Safety	"73 SPIO patients (39.9%) presented with skin staining that faded slowly in size and colour over time" (p. 1682) 58/73 who developed staining had periareolar injection, 15/73 had peritumoral injection Staining still present in 66 patients (36.1%) at 15 months	
	SPIO vs. Tc/BD	Cost (mean cost of tracer and injection expenses per procedure)	Tracer and injection €225 for SPIO vs. €252 for Tc/BD	

BD = blue dye; CI = confidence interval; SPIO = superparamagnetic iron oxide; Tc = technetium-99.

Appendix 5: Additional References of Potential Interest

Studies investigating safety of SLN detection using SPIO that did not include a comparator

Bazire L, Alran S, El Bamrani S, et al. Radiation therapy after sentinel lymph node biopsy for early stage breast cancer using a magnetic tracer: results of a single institutional prospective study of tolerance. *Cancer Radiotherapie*. 2019;23(1):23-27.

Krischer B, Forte S, Niemann T, Kubik-Huch RA, Leo C. Feasibility of breast MRI after sentinel procedure for breast cancer with superparamagnetic tracers. *Eur J Surg Oncol*. 2018;44(1):74-79.

Lorek A, Stojcev Z, Zarebski W, Kowalczyk M, Szyluk K. Analysis of postoperative complications after 303 sentinel lymph node identification procedures using the SentiMag method in breast cancer patients. *Med Sci Mon*. 2019;25:3154-3160.

Meta-analyses with full overlap with included network meta-analysis

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