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Magnetic seed localization for soft tissue lesions in breast patients: Clinical effectiveness, cost-effectiveness, and guidelines

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Abbreviations

BMI	Body mass index
CI	Confidence interval
cm	centimeter
Magseed	Magnetic seeds
mm	millimeter

Context and Policy Issues

Magnetic seed, also known as Magseed needle with magnetic marker system, was first approved by Health Canada in April 2014 and used to localize non-palpable breast lesions.[1,2] It consists of a magnetic marker, the size of a grain of rice, which can be detected using the Sentimag® probe during surgery.[2] The magnetic seeds can be inserted up to 30 days prior to surgery using a needle and guided imaging of a mammogram.[2,3] However, non-magnetic tools will need to be used while the Sentimag® probe is being used to detect the magnetic seeds. In the Netherlands, there is another magnetic seed localization technology known as MaMaLoc; however, this is not yet available in Canada.[4]

The use of wire localization is the most commonly used option and has documented effectiveness and safety.[5] However, since the wire is external, it may dislodge and can cause discomfort.[3,5] Additionally, since it needs to be placed ahead of the surgery, there needs to be coordination between wire insertion and surgery.[3,5] Radioactive seed localization will result in exposure to radioactivity.[3] Using magnetic seeds for localization can avoid these disadvantages.[3]

CADTH previously reviewed preoperative seed placement for breast cancer surgery; however, the focus of that report was on the use of radioactive seeds.[6]

The purpose of this report is to review the clinical and cost-effectiveness of magnetic seed localization of non-palpable breast lesions, as well as the guidelines for its use.

Research Questions

1. What is the clinical effectiveness of magnetic seed localization for non-palpable breast lesions in breast surgery patients?
2. What is the cost-effectiveness of magnetic seed localization for non-palpable breast lesions in breast surgery patients?
3. What are the evidence based guidelines regarding the use of magnetic seed localization for non-palpable breast lesions in breast surgery patients?

Key Findings

Five primary studies were identified for the use of magnetic seeds for localization of non-palpable breast lesions in breast cancer patients; however, these studies were all single-arm non-randomized trials with less than 200 patients, some fewer than 50. This makes it difficult to determine how this technique compares to the current standard for effectiveness and safety. Overall, the studies suggest this technique is effective and safe with surgeons indicating they are satisfied and able to adopt this technique.

No cost-effectiveness studies and evidence-based guidelines were identified for the use of magnetic seed localization for non-palpable breast lesions in breast surgery patients;

therefore, no conclusion can be made on the comparative cost on the use of magnetic seed localization.

With a paucity of evidence and all identified studies having methodological flaws, the effectiveness, safety and the use of magnetic seeds for localization of non-palpable breast lesions in breast cancer patients remains uncertain. Additionally, all studies identified were conducted outside of Canada which may not inform Canadian policy and decision makers on the use of this technique in the Canadian population.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Ovid MEDLINE, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, 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 seed localization and breast lesions. No filters were applied to limit the retrieval by study type. The search was also limited to English language documents published between January 1, 2009 and April 22, 2019.

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.

Table 1: Selection Criteria

Population	Breast surgery patients with non-palpable lesions (i.e., tumours or other lesions)
Intervention	Magnetic seed (also called MagSeed) localization for non-palpable breast lesions
Comparator	Q1: Wire localization; radioactive seeds; any comparator; no comparator Q2: Wire localization; radioactive seeds; any comparator Q3: No comparator
Outcomes	Q1: Clinical effectiveness (i.e., treatment success, harms) Q2: Cost-effectiveness Q3: guidelines
Study Designs	HTA/systematic reviews/meta-analyses; RCTs; non-randomized studies; economic evaluations; evidence-based guidelines

HTA =health technology assessments; RCT = randomized controlled trials

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2009. Guidelines with unclear methodology and abstracts for conferences were also excluded.

Critical Appraisal of Individual Studies

Primary studies were critically appraised using Downs and Black.[7] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 67 citations were identified in the literature search. Following screening of titles and abstracts, 48 citations were excluded and 19 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant articles, 14 publications were excluded for various reasons, and 5 publications met the inclusion criteria and were included in this report. This comprised of five non-randomized studies. Appendix 1 presents the PRISMA[8] 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

Five non-randomized studies were identified for this report and all were single-arm studies.[9-13] One study was a retrospective study from March 2017 to August 2017[10] while the other four studies were prospective observational cohort studies.[9,11-13]

Country of Origin

Two studies were from the United States,[10,12] one from the United Kingdom,[9] one from Slovakia[11] and one from the Netherlands.[13]

Patient Population

For the study by Harvey et al., 29 adult females with core biopsy-proven breast cancer were included who have a mean age of 54 years (range 37 to 75 years old).[9] In the study by Lamb et al., there were 188 women with a mean age of 59 years (range 22 to 89 years old) included who underwent localization with magnetic markers at the institution.[10] Pohlodek et al. included ten patients with a mean age of 49 years.[11] Price et al. included 64 patients with a mean age of 58 years (range 25 to 86 years old), who underwent Magseed localization.[12] Schermers et al. included 15 females with unifocal non-palpable breast cancer who needed primary surgical treatment without neo-adjuvant chemotherapy.[13] No information on age of the included participants was provided for the study by Schermers et. al.[13]

Interventions and Comparators

All five studies were single arm studies and utilized magnetic seeds for the localization of the non-palpable breast lesion.[9-13]

Outcomes

The primary outcome for the Harvey et. al. study was clinically significant migration of the magnetic seeds, which was defined to be 10 mm or more.[9] Magnetic seeds were placed at least two days and up to 30 days prior to the procedure.[9] Additional secondary outcomes included accuracy of magnetic seed placement, depth of seed placement, seed integrity, safety, tolerability and ease of transcutaneous detection of the magnetic seed.[9] Lamb et al. assessed technical success of the localization of the magnetic seed, which was defined as within one cm of the target on post-procedural mammogram, retrieval of magnetic seed at surgery, and complications.[10] Pohlodek et. al. considered the following outcomes: localization of impalpable lesions, detection of magnetic seed, complications, adverse events, and migration of magnetic seed.[11] Price et al. assessed the success of localization of the magnetic seed, localization of magnetic seed within 1 mm of target, and complications.[12] In the study by Schermers et. al., the outcomes were localization of magnetic markers less than one mm median distance, identification of the magnetic marker, and surgeon's satisfaction.[13]

Summary of Critical Appraisal

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

All of the studies identified for this report were single-arm and non-randomized, making it difficult to conclude the clinical and comparative effectiveness as well as the safety of the use of magnetic seeds for localization without a comparison.[9-13] The objectives and methods were clearly stated in all of the studies.[9-13] Four of the studies included less than 100 patients[9,11-13] while one of them had just under 200 patients.[10] Small sample sizes may limit the generalizability of results. All of the studies were conducted outside of Canada, which may not be relevant for the Canadian population.[9-13]

Descriptive statistics were used in all of the studies and were appropriate since these were all single-arm, non-comparative studies.[9-13] Only one study declared no conflicts of interest[9] and this information was not available in two studies.[10,12] Two studies declared conflicts of interest where one study was funded but the manufacturers of Magseed[11] and the other included three authors were inventors of the magnetic marker localization technology.[13] Lamb et al. conducted a retrospective study, which may be difficult to control for confounders.[10]

Summary of Findings

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

Clinical Effectiveness of Magnetic Seed Localization

The identified studies have similar conclusions demonstrating how magnetic seeds are effective and safe for localization of non-palpable breast lesions; however, it is worth noting that these studies all have methodological limitations and are of low quality.[9-13] One study detected no migration for the pre- and post-mammogram as all (100%) of them were within 10 mm (95% confidence interval [CI] 88% to 100%) with 27 of 29 (93%) Magseeds (95% CI 78% to 98%) placed at target lesion while the other two seeds were at 2 mm and 3 mm of target lesions.[9] The magnetic seeds were placed with a median of five days prior to surgery (range 1 to 15 days) and no complications or adverse events were observed due to magnetic seed placement of the surgery.[9] Technical success, defined to be placement of

magnetic seed within 1 cm of the target, occurred in 206 of 213 markers (96.7%) with 7 (3.3%) beyond 1 cm of the target.[10] All magnetic seeds (213 of 213) were removed successfully at surgery and no complications were observed.[10] Localization and detection of all magnetic seeds was reported in the study by Pohlodek et. al. and no migration nor complications were observed.[11] In one study, all magnetic seeds were successful for localization of non-palpable breast lesions within 1 cm of target but only 70% of all magnetic seeds were within 1 mm of target.[12] All magnetic seeds were successfully retrieved and three complications (4%) were reported including post-operative hematoma, post-operative infection, and pneumothorax, which was likely due to difficulty in finding the magnetic seed.[12] One study had all magnetic seeds localized within a median of sub-millimeter, ie. less than one millimeter, and successful identification of the marker in all patients (15 of 15).[13] The study also assessed surgeon's satisfaction with the magnetic seed technology and overall the surgeons seemed satisfied and reported that they are able to adopt this new technology.[13]

Cost-Effectiveness of Magnetic Seed Localization

No studies were identified for the cost-effectiveness of magnetic seed localization for soft tissue lesions in breast surgery patients; therefore, no summary can be provided.

Guidelines

No guidelines were identified for the cost-effectiveness of magnetic seed localization for soft tissue lesions in breast surgery patients; therefore, no summary can be provided.

Limitations

A limited number of studies of low methodological quality were identified indicating the paucity of evidence that evaluates the effectiveness and safety of the use of magnetic seeds for the localization of non-palpable breast lesions, making it difficult to make evidence-informed decisions on the use of such technology. Additionally, without comparative studies, especially to the current methods, it is not possible to select between the different techniques.[9-13] The investigators of two studies were affiliated with the manufacturer of the technique.[11,13] The use of magnetic seeds for localization of non-palpable breast lesions is quite new, which is likely why there is a paucity of evidence.

Since no cost-effectiveness studies or evidence-based guidelines were identified, there is limited evidence to inform clinical decisions.

Conclusions and Implications for Decision or Policy Making

Five non-randomized, single-arm studies were identified to be relevant in the search for the use of magnetic seeds for the localization of non-palpable breast lesions.[9-13]

The available evidence indicates that magnetic seeds are effective and safe for the localization of non-palpable breast lesions in patients with breast cancers. Findings indicated that magnetic seeds are relatively safe considering there were very few reported adverse events. Surgeons have also indicated their satisfaction with this technique. However, these findings were based on low quality evidence with methodological flaws. The paucity of available evidence may limit the usefulness of these findings. Since this is a relatively new technique for localization of non-palpable breast lesions in breast cancer patients, further research, particularly comparative studies with existing techniques, would

be needed to determine comparative effectiveness. This would be useful for policy makers in determining the appropriate technique for use.

No cost-effectiveness studies or evidence-based guidelines were identified. Therefore, no conclusions regarding the cost-effectiveness or recommended use can be provided. The paucity of evidence suggests the need for further research comparing the use of magnetic seeds to current techniques for the localization of breast lesions and may help determine its place in therapy for this setting and help reduce uncertainty.

References

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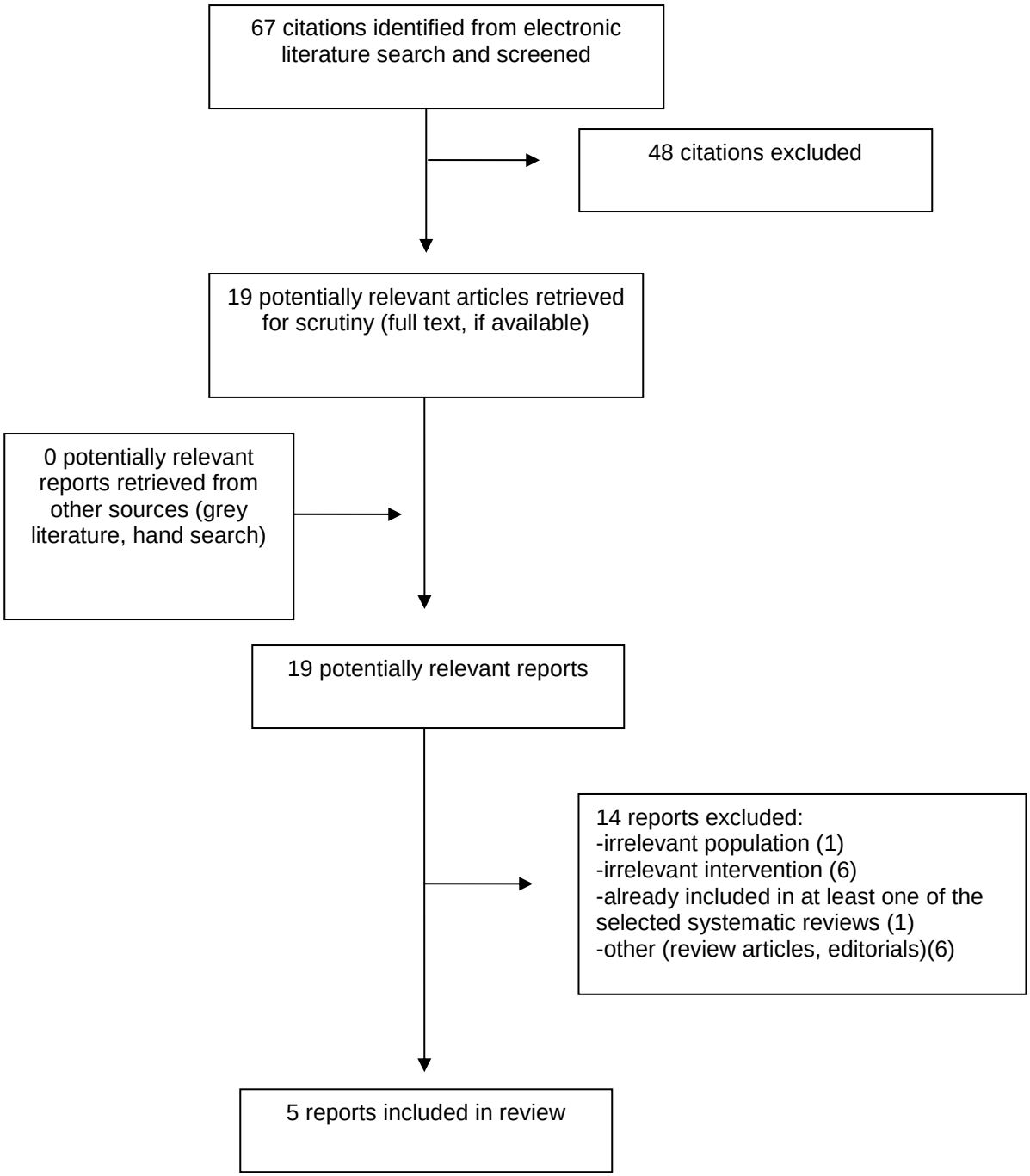
11. Pohlodek K, Foltin M, Meciarova I, Ondrias F. Simultaneous use of magnetic method in localization of impalpable breast cancer and sentinel lymph nodes detection: initial experience. *Nanomedicine.* 2018;13(24):3075-3081.
12. Price ER, Khoury AL, Esserman LJ, Joe BN, Alvarado MD. Initial clinical experience with an inducible magnetic seed system for preoperative breast lesion localization. *Am J Roentgenol.* 2018;210(4):913-917.
13. Schermers B, van der Hage JA, Loo CE, et al. Feasibility of magnetic marker localisation for non-palpable breast cancer. *Breast.* 2017;33:50-56.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Harvey 2018[9] **United Kingdom**	Two-centre, open-label, single arm cohort study 29 patients were included	Adult (18 years or older) female patients with core biopsy-proven breast cancer Exclusion: a pacemaker or implanted device in the chest wall, nickel allergy, pregnancy or lactation, known coagulopathy or current anticoagulant medication, neoadjuvant chemotherapy and Sienna injection in the previous 6 months Age: mean 54 years old (range 37 to 75) BMI: 28.3 kg/m^2 (range 20.3 to 42.2)	Magseeds inserted into the centre of the target lesions	Primary outcome: distribution of seed migration to estimate risk of markers migrating a clinically significant distance (10 mm or more) Secondary outcome: accuracy of initial placement, depth of seed placement and ease of transcutaneous detection, seed integrity, safety and tolerability Minimum two days up to 30 days
Lamb 2018[10] **United States**	Single-arm, retrospective study from March 2017 to August 2017	Patients who underwent image-guided wireless needle localization with magnetic markers 188 Women (mean age 59 years old, range 22 to 89 years old)	Image-guided localization with Magseend	Technical success defined as placement of the magnetic marker within 1 cm of the target on post-procedural mammogram Retrieval of Magseed at surgery Complications
Pohlodek 2018[11] **Slovakia**	Observational single-center, single-arm cohort study	10 patients Mean age: 48.76 years old Mean BMI: 24.9	Localization with Magseed	• Localization of impalpable lesions • Detection of Magseed • Complications and adverse events • Migration of Magseed
Price 2018[12] **United States**	Observational single-arm cohort study October 2016 to	64 patients who underwent Magseed localization	Magseed localization	• Localization of Magseed • Localization of Magseed within

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	February 2017	Mean age: 58 years old (range 25 to 86 years old)		target (1 mm) • Complications
Schermers 2017[13] **The Netherlands**	Single-arm, observational cohort study	15 females Inclusion: unifocal, non-palpable breast cancer, scheduled for primary surgical treatment without neo-adjuvant chemotherapy	Magnetic marker localization (MaMaLoc)	• Localization of magnetic markers (sub-millimetre median distance) • Identification of magnetic marker • Surgeon's satisfaction

BMI = body mass index

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using Downs and Black[7]

Strengths	Limitations
Harvey, 2018[9]	
• Objectives, outcomes and methods were clearly stated. • Statistical analyses seems appropriate for the type of study (descriptive analyses). • Clearly defined population who are the ones that would be of interest for this clinical question. • All patients who were recruited were included in the analyses. • No dropouts or withdrawals from the study. • Authors declared no conflicts of interest.	• Small sample size (29). • Open-label study, single arm study with no comparison. • Conducted in the UK, may not be applicable for the Canadian healthcare system.
Lamb, 2018[10]	
• Objectives and methods were clearly stated. • Statistical analyses were descriptive and seemed appropriate for this type of study.	• Retrospective study with no comparator. • Outcomes were not clearly stated in the methods. • Inclusion and exclusion criteria were not clearly detailed in the methods. • Single arm with no comparator. • 188 patients in the study, small sample. • Conducted in the United States, may not be applicable for the Canadian healthcare system. • Duration of follow-up was unclear. • No information on conflicts of interest.
Pohlodek, 2018[11]	
• Objectives and methods were clearly stated. • Descriptive statistics were provided. • Conflict of interest information was documented.	• Outcomes were not clearly documented. • Single arm, non-randomized study. • Small study of 10 women. • Observational, descriptive study. • No details on follow-up. • Conducted in Slovakia, which may not be representative of the health system in Canada. • Funded by Sysmex Europe GmbH, which is the company that manufacturers Magseed.
Price, 2018[12]	
• Objectives and methods were clearly stated. • Descriptive statistics were provided, which seems appropriate for an observational study.	• Outcomes were not clearly documented. • Single arm, non-randomized study. • Small study of 64 women. • Observational, descriptive study. • No details on follow-up. • No information on conflict of interest.
Schermers, 2017[13]	
• Objectives and methods were clearly stated. • When descriptive statistics were provided, which seems appropriate for an observational study. • Conflict of interest and funding information were provided.	• Outcomes were not clearly documented. • Single arm, non-randomized study. • Small study of 15 women. • Observational, descriptive study. • The descriptive statistics were not very consistent, ie. Not always

	provided. • No details on follow-up. • Three of the authors are the inventors of the magnetic marker localization technology.

UK = United Kingdom

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Harvey, 2018[9]	
• Migration: no migration for 100% of participants between the two mammograms (all migration were within 10 mm distance, 95% CI 88% to 100%) • Accuracy of placement: 27/29 (93%) Magseeds were place directly at target lesion (95% CI 78% to 98%) with the other two seeds at 2 mm and 3 mm from target lesion. • Magseeds were placed with a median of 5 days before surgery (range 1 to 15 days) • No complications or adverse events were observed due to seed placement or the surgery.	*"In conclusion, Magseed is a feasible means of localizing breast lesions and is safe to deploy. It is commercially available in Europe and the US and has been used in over 3000 patients. Studies are ongoing in the US and Europe to demonstrate its effectiveness in the setting of lumpectomy surgery. It will improve radiological and surgical scheduling and give surgeons intraoperative directional determination of the cancer site using the Sentimag probe."* (*p535*)[9]
Lamb, 2018[10]	
• Technical success (placement of Magseed within 1 cm of the target): 206 of 213 markers (96.7%) with 7 (3.3%) markers were more than 1 cm from target • Retrieval at surgery: all (213/213) were successfully removed at surgery • Complications: none were observed	*"The present study shows that needle localization with nonradioactive magnetic markers is a safe, feasible, and effective method for image-guided surgical excision of breast lesions."* (*p945*)[10]
Pohlodek, 2018[11]	
• Localization of impalpable lesions: all were localized with Magseed • Detection with Sentimag system: all accurately detected • Complications or adverse events: none were reported due to seed placement or to surgery • Migration of Magseed: not observed	*"To the best of our knowledge, this is the first feasibility report describing the clinical experience of the simultaneous use of the Magseed and Sienna/Sentimag system. All our first ten patients with impalpable breast tumors could be accurately localized with the magnetic method."* (*p3079*)[11]
Price, 2018[12]	
• Localization: successful for all Magseeds • Placement: all placed within 1 cm of target with 70% of seeds within 1 mm of target • Retrieval of Magseed: successful for all • Complications: 3 operative complications were reported (post-operative hematoma, post-operative infection, and pneumothorax); pneumothorax was likely due to Magseed due to difficulty in finding the seed	*"In our early experience, this nonradioactive inducible magnetic seed localization system provided an effective means for preoperative localization of nonpalpable breast lesions."* (*p915*)[12]
Schermers, 2017[13]	
• localization of magnetic markers: all patients were had markers placed within a median of sub-millimetre • Identification of magnetic marker: successful in all patients (15/15, 100%) • Surgeon's satisfaction: overall the surgeons seemed satisfied and able to adopt this new technology	*"In conclusion, we have shown that intra-operative localisation of non-palpable breast cancer using the MaMaLoc technology in this pilot study was both feasible and safe. Radiologists could adapt to the technology in the current clinical workflow. Repeated mammography showed that migration of the magnetic marker was negligible. The magnetic marker identification rate was 100% and participating surgeons were positive about the prospects of this novel technology."* (*p55*)[13]

CI = confidence interval

Appendix 5: Additional References of Potential Interest

Magnetic Marker Techniques using Systems other than Magseed in a Non-Clinical Setting

Nicolae A, Dillon J, Semple M, Hong NL, Ravi A. Evaluation of a ferromagnetic marker technology for intraoperative localization of nonpalpable breast lesions. *Am J Roentgenol*. 2019;212(4):727-733.

Magseed Combined with Other Localization Techniques

Hersi AF, Eriksson S, Ramos J, Abdsaleh S, Warnberg F, Karakatsanis A. A combined, totally magnetic technique with a magnetic marker for non-palpable tumour localization and superparamagnetic iron oxide nanoparticles for sentinel lymph node detection in breast cancer surgery. *Eur J Surg Oncol*. 2019;45(4):544-549.