Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Wire-Free, Nonradioactive Localization Techniques to Guide Surgical Excision of Nonpalpable Breast Tumours: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

The standard treatment for nonpalpable breast tumours is to surgically remove them. But because these tumours are so small, it is necessary to pinpoint their location before surgery by implanting a marker inside the tumour using mammogram or ultrasound guidance. This procedure is called localization. The current localization techniques used in Ontario are wire-guided localization and radioactive seed localization, both of which have some limitations. Wire-free, nonradioactive localization is a new type of localization that overcomes these limitations. Two types are now being used at some hospitals in Ontario: magnetic seed localization and reflector-guided localization.

This health technology assessment looked at how safe and effective wire-free, nonradioactive localization techniques to guide surgical removal of nonpalpable breast tumours are. It also looked at the budget impact of publicly funding wire-free, nonradioactive localization techniques and at the experiences, preferences, and values of people who have undergone a localization procedure for the excision of a nonpalpable breast tumour.

What Did This Health Technology Assessment Find?

Wire-free, nonradioactive localization of a nonpalpable breast tumour likely reduces the risk of re-excision (additional surgery) or has the same risk as wire-guided and radioactive seed localization. The rates of postoperative complications and operation time are about the same for wire-free, nonradioactive localization and conventional localization techniques. Overall, the wire-free, nonradioactive localization devices evaluated in this health technology assessment are effective and safe for the localization of nonpalpable breast tumours and are reasonable alternatives to wire-guided and radioactive seed localization.

We were unable to determine the cost-effectiveness of wire-free, nonradioactive localization techniques. We estimate that publicly funding these techniques for the surgical excision of nonpalpable breast tumours over the next 5 years will cost an additional $7.73 million.

People with experience of undergoing a localization procedure reported valuing surgical interventions that are clinically effective, timely, and patient centred. They responded positively to the potential public funding of wire-free, nonradioactive localization techniques and felt that equitable access should be a requirement of implementation.

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Abstract

Background

The current standard treatment for nonpalpable breast tumours is surgical excision; however, it is nearly impossible to locate these small masses during surgery. Therefore, a marker must be implanted into the abnormal tissue under mammography or ultrasound guidance prior to surgery to guide the surgeon to the location of the tumour. Two techniques to localize nonpalpable breast tumours are currently used in Ontario: wire-guided localization and radioactive seed localization. However, these techniques have some limitations. New wire-free, nonradioactive technologies that address these limitations are now available. We conducted a health technology assessment of wire-free, nonradioactive localization techniques available in Canada that are used to localize nonpalpable breast tumours for surgical excision. This report includes an evaluation of the effectiveness, safety, and budget impact of publicly funding these techniques, as well as an evaluation of patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the ROBINS-I tool and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search, and we analyzed the budget impact of publicly funding wire-free, nonradioactive localization techniques to guide surgical excision of nonpalpable breast tumours in Ontario. We did not conduct a primary economic evaluation because of the limited data available to use as model inputs. To contextualize the potential value of wire-free, nonradioactive localization techniques, we spoke with people who had undergone a localization procedure for the surgical excision of a nonpalpable breast tumour.

Results

We included 16 studies in the clinical evidence review, of which 15 were comparative studies and one was a single-arm study. The results of our analysis of the comparative studies suggest that the re-excision rate for the wire-guided, nonradioactive devices included in this review is either lower or not different from the rate for conventional localization methods (GRADE: Moderate/Low). We found no difference in postoperative complications or operation time between the new and the conventional techniques (GRADE: Moderate). In a feasibility study of a newly developed magnetic seed device in Ontario, no patient required re-excision (GRADE: not assessed). Our economic evidence review identified two costing studies that found that wire-free, nonradioactive localization techniques were more expensive than wire-guided and radioactive seed localization. We were unable to identify any published cost-effectiveness evidence for wire-free, nonradioactive localization techniques. The annual budget impact of publicly funding wire-free, nonradioactive localization techniques in Ontario over the next 5 years ranges from an additional $0.51 million in year 1 to an additional $2.61 million in year 5, for a total 5-year budget impact of $7.73 million. The people we spoke with who had undergone a localization procedure reported valuing surgical interventions that are clinically effective, timely, and patient centred. They responded positively to the potential public funding of wire-free, nonradioactive localization techniques and felt that equitable access should be a requirement of implementation.

Conclusions

The wire-free, nonradioactive localization techniques included in this review are effective and safe methods for the localization of nonpalpable breast tumours and are reasonable alternatives to wire-guided and radioactive seed localization. We estimate that publicly funding wire-free, nonradioactive localization techniques in Ontario would result in an additional cost of $7.73 million over the next 5 years. Broad access to wire-free, nonradioactive localization techniques may have a positive impact on patients undergoing surgical excision for a nonpalpable breast tumour. People with lived experience of a localization procedure value surgical interventions that are clinically effective, timely, and patient centred. They also value equitable access to surgical care.

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Objective

This health technology assessment evaluates the effectiveness and safety of wire-free, nonradioactive localization techniques to guide surgical excision of nonpalpable breast tumours for adults with breast cancer. It also evaluates the budget impact of publicly funding these techniques and the experiences, preferences, and values of people who have undergone a localization procedure for the excision of a nonpalpable breast tumour.

Background

Health Condition

Breast cancer is the second most common cancer in Canadian women, following nonmelanoma skin cancer.[1] Breast cancer arises in the lining cells of the milk ducts (85% of cases) or in the lobules (15% of cases) in the glandular tissue of the breast.[2] Initially, the cancerous cells are confined to the duct or lobule and may not cause any symptoms as the tumour is very small at first. Ductal carcinoma in situ (DCIS) is a premalignant tumour that starts in the milk ducts. This type is usually not palpable (i.e., not able to be felt upon physical examination) and is often found via mammogram through participation in a breast cancer screening program. DCIS is noninvasive, meaning that the cancer has not spread beyond the milk ducts into healthy breast tissue. It is considered "stage 0" breast cancer because it has not spread but carries the risk of becoming invasive. In invasive breast cancer, cancerous cells spread to other breast tissue and may spread to the nearby lymph nodes and beyond to other organs in the body, increasing a person's risk of dying from metastatic cancer (cancer that has spread from one location to other parts of the body).

Breast cancer occurs owing to mutations in genes responsible for regulating the growth of cells and keeping them healthy. Certain inherited gene mutations, such as those in breast cancer susceptibility gene 1 (*BRCA1*) and breast cancer susceptibility gene 2 (*BRCA2*), increase the risk of developing breast cancer. Nonheritable genetic mutation can also occur during a person's life as a result of aging and other factors.[3]

Clinical Need and Target Population

Breast cancer in women is a major health burden worldwide. The estimated incidence of female breast cancer in Ontario in 2020 was 11,945.[4] More than one-third of all cases diagnosed annually are nonpalpable.[5] The increasing implementation of breast cancer screening programs combined with the use of advanced imaging modalities will further increase the number of people diagnosed with nonpalpable tumours.[5] In addition to detecting cancer, breast cancer screening also detects noncancerous and atypical lesions, which may also require localization for surgical resection and accurate diagnosis.

Screening mammography has allowed the detection of breast cancer at an earlier stage, when the tumour is not yet palpable and is associated with a more favourable survival outcome.[6] Although it is uncommon to detect nonpalpable breast tumours outside of screening programs, they may be detected if the cancer causes symptoms such as nipple pain or discharge, a change in breast skin colour or thickness, or swollen lymph nodes under the arm, and the person seeks medical advice for such symptoms.

Surgical Excision of Nonpalpable Tumours

The current standard treatment for nonpalpable breast tumours is lumpectomy, meaning the surgical excision (removal) of the tumour. This is considered breast-conserving surgery. Breast-conserving surgery can also be offered to some people with palpable tumours.

The goal of surgical excision of a nonpalpable tumour is to remove all abnormal tissue, as well as a thin layer of healthy tissue around it to ensure that the remaining breast tissue is free of cancerous cells. However, it is a challenging procedure because it is nearly impossible to accurately locate these small masses during surgery, as they cannot be seen or felt upon physical examination and the breast lacks anatomical landmarks to match with presurgical imaging. Therefore, it is necessary to pinpoint the tumour site by implanting a marker within the abnormal tissue under stereotactic mammography or ultrasound guidance prior to surgery. The precision of the localization technique is an important factor in the success of the excision and enables the surgeon to remove the tumour with optimal cosmetic outcomes, minimal morbidity, and less chance of cancer recurrence. In this context, the adoption of innovative methods that may improve outcomes is essential for the care of people with nonpalpable breast tumours.

With breast-conserving treatment, patients may also receive neoadjuvant chemotherapy (i.e., chemotherapy given before surgery) or radiation therapy on the breast following surgery. Neoadjuvant chemotherapy for breast cancer is used to down-stage (shrink) the tumour in the breast and axilla to facilitate breast conservation and is now being offered to select patients.[7] Almost all lumpectomy patients should be considered for adjuvant radiation to optimize outcomes.

Surgical Margin Status

A key element of surgical excision involves checking the margins (i.e., the edges or border) of the removed tumour to see if cancerous cells are present at the margin or very close to it. To examine surgical margins, the pathologist uses a special type of ink to mark the margins of the tumour and determine whether all the tumour has been completely removed. A positive margin means that cancerous cells are present at the edge of the lumpectomy specimen, which may mean that cancerous cells are still present in the patient's breast. This can lead to additional surgeries, treatment delay, additional stress for patients, and increased health care costs.[8]

Margin status serves as a surrogate marker for possible residual disease in the breast and has an impact on the risk of tumour recurrence. It has been shown that the presence of a positive margin is associated with a two-fold increase in the risk of breast cancer recurrence compared with a negative margin.[9] A 2014 consensus guideline on margins for breast-conserving surgery by the Society of Surgical Oncology and the American Society for Radiation Oncology defines a positive margin for invasive cancer as "ink on tumour," which differs from the definition provided in their previous guideline. The adoption of the 2014 guideline was associated with a major change in practice and a decrease in rates of reoperation.[10] For DCIS, this guideline recommends the use of a 2 mm clear margin as the standard for an adequate margin when treatment includes whole breast irradiation. This guideline has been widely adopted in Canada.[11]

In the United Kingdom, the Association of Breast Surgeons consensus statement advises a 1 mm minimum clear radial margin to be achieved after breast-conserving surgery for early invasive breast cancer and for carcinoma in situ of the breast.[12]

Studies have shown that taking additional tissue circumferentially around the cavity left by lumpectomy (also known as cavity shave margins) can reduce the rates of positive margins and re-excision. Two randomized controlled trials of patients with stages 0 to III breast cancer have demonstrated that resection of cavity shave margins significantly reduced the rates of positive margins and re-excision in patients undergoing partial mastectomy (surgery to remove part of the breast).[13,14]

Breast Cancer Treatment Plan

When a breast lesion is found through a mammogram, other imaging test, or physical examination, the radiologist performs a biopsy (takes a sample of tumour tissue) in a radiology suite to determine if the cells are cancerous, and the patient is scheduled for surgical excision of the tumour. At the time of surgery, a sentinel lymph node biopsy is also performed for most clinically node-negative patients (i.e., those with no clinical signs of lymph node metastases). This is done because the sentinel lymph node is the first lymph node on the pathway from the breast to the axilla and is where cancer cells typically spread first. If the result of the pathological examination of the biopsy specimen shows that the tissue is cancerous, a multidisciplinary team specialized in various areas of breast cancer treatment such as surgical oncology, breast radiology, radiation oncology, pathology, and plastic surgery work together to create the patient's overall treatment plan, which will include different types of treatments. Treatment options and recommendations are based on a consideration of many factors, including the following:

- Tumour subtype
- Tumour stage
- Lymph node status
- Hormone receptor status (estrogen or progesterone receptor positive)
- Human epidermal growth factor receptor 2 (HER2) status
- Genetic information
- The patient's age
- The patient's general health
- The patient's menopausal status
- The patient's treatment preferences

Treatments for breast cancer can be local (directed to the breast) or systemic (affecting the whole body). Surgery and radiation are local treatments, whereas drugs are considered systemic therapies because they can reach cancer cells anywhere in the body. Drug treatments for breast cancer include chemotherapy, hormone therapy, targeted therapy, and immunotherapy. Targeted therapies are used for people with an inherited *BRCA1* or *BRCA2* gene mutation, those with hormone-receptor-positive breast cancer, and those with HER2-enriched breast cancer.

For details on current treatments for breast cancer, please refer to the treatment map provided by Cancer Care Ontario.[11]

Current Tumour Localization Options

Two techniques to localize nonpalpable breast tumours are currently used in Ontario hospitals: wire-guided localization and radioactive seed localization using radioactive iodine 125. Localization devices are implanted by radiologists in the radiology department under imaging guidance.

Wire-guided localization was invented more than 40 years ago and has been shown to be a safe and effective procedure for preoperative localization of nonpalpable breast tumours. With this method, a wire is placed in the breast tumour percutaneously (through the skin), with the distal part of the wire positioned within the abnormal tissue and the proximal part of the wire remaining outside the breast.[15]

The wire is implanted on the day of surgery to minimize the risk of displacing, kinking, or fracture. When this technique is used, the departments of radiology and surgery must coordinate scheduling so that the two procedures can be performed in sequence on the same day.[15] If the radiology and surgical sites are in different locations, patients are transferred from radiology to the surgical site after the wire has been implanted. This transfer can increase the risk of the wire becoming dislodged or fractured. Further, since part of the wire must remain outside the breast to guide the surgical trajectory, some patients may experience discomfort and anxiety.

Radioactive seed localization is an alternative that addresses these limitations. Its advantage over wire-guided localization is that the radioactive seed is placed entirely within the breast and can be placed up to 1 week prior to surgery, which provides scheduling flexibility by decoupling the radiology and surgical visits. However, the technique requires compliance with regulatory and safety requirements for the use, handling, and disposal of radioactive materials, which adds to the procedural and programmatic complexity.[15]

Health Technology Under Review

During scoping for this health technology assessment, we identified several techniques for the preoperative localization of nonpalpable breast tumours. However, some are not in use in Ontario, and some are not licensed by Health Canada. Therefore, we focused on the new wire-free, nonradioactive technologies that are licensed by Health Canada and have been adopted by some hospitals in Ontario: magnetic seed localization systems and the reflector-guided localization system.

The devices used in these procedures are inserted into the tumour in the radiology department under mammography or ultrasound guidance, as with the wire-guided and radioactive seed localization techniques. First, as with the wire-guided and radioactive seed localization techniques, the radiologist uses a small needle to inject a local anesthetic medication into the area of the breast being targeted. Then, under imaging guidance, the radiologist inserts a needle into the target lesion. Once the position of the needle is confirmed on the mammogram or ultrasound, the radiologist implants the localization device through the needle and then removes the needle. The position of the device cannot be changed once implanted. Post-procedure mammogram is used to document the position of the device in relation to the target lesion.[16]

Since wire-free devices are implanted entirely within the breast and cannot be seen, the surgeon uses a specific handheld probe in the operating room to identify the location of the device and to remove both the tumour and the device. Wire-free techniques enable the surgeon to choose the

most cosmetically appropriate incision, whereas with wire-guided localization, the surgeon must follow the path of the wire. Wire-free devices can also be implanted weeks prior to surgery. [16]

Magnetic Seed Localization Systems

Magnetic seeds are one of the latest technological evolutions to overcome the limitations of radioactive seed localization. Magnetic seed localization is similar to radioactive seed localization but without the need to handle and dispose of radioactive materials. In this technique, a small metal marker called a "seed" is implanted into the tumour by the radiologist under imaging guidance up to 30 days before surgery. During surgery, the seed is detected by a handheld probe that detects magnetic response and transforms it into audible and visual signals to guide the surgeon to the location of the seed and tumour. Two localization systems based on magnetism are currently used in some Ontario hospitals for the localization of nonpalpable breast tumours: Magseed and the magnetic occult lesion localization instrument, or MOLLI.

MAGSEED

The Magseed marker is a 5 mm long "seed" made of paramagnetic steel and iron oxide. During surgery, the seed's location is detected by the Sentimag probe, which is a handheld magnetometer. The probe generates an alternating magnetic field that transiently magnetizes the iron oxide particles within the seed and detects the seed's location. The probe then displays a numerical count and produces an audio tone related to the strength of the magnetic field and the distance of the seed from the probe.[17] In the absence of the Sentimag signal, the Magseed marker is inert (i.e., nonmagnetic and therefore inactive).

MAGNETIC OCCULT LESION LOCALIZATION INSTRUMENT

The MOLLI localization procedure involves the implantation of a 3.2 mm long, gold-coated ferromagnetic marker into the tumour. The MOLLI marker produces a persistent magnetic field that is measured using a handheld probe.[18] The probe consists of two magnetometers that can detect the magnetic field produced by the MOLLI marker. The probe then translates the magnetic signal into audiovisual feedback. The audio signal increases in frequency as the surgeon approaches the seed with the probe, while the visual feedback shows the proximity of the probe to the seed in millimeters on an ergonomically designed mountable tablet. The system is not substantially affected by the operating room environment or by surgical equipment such as the electrocautery devices commonly involved in breast-conserving surgery.[18]

Reflector-Guided Localization System

The Scout radar localization system includes a radiofrequency reflector, a handheld device, and a console. The reflector is an infrared-activated, electromagnetic wave device that is inserted into the tumour. The reflector is 12 mm long (including 4 mm antennas on each side) and contains infrared light receptors and a transistor switch. The reflector is made of nitinol, which is not radioactive.[19] When receiving an infrared light pulse emitted by the handheld device, the infrared light receptors close the transistor switch connected to the antennas and reflect a wave signal to the handheld device. This combination of electromagnetic wave and infrared light technology allows the location of the reflector to be detected. Audible feedback from the console increases in cadence as the handheld device nears the reflector.

Within this report, the Scout radar localization system will be referred to as "reflector" to better describe its mechanism of action and for ease of reading.

Regulatory Information

Health Canada and the US Food and Drug Administration have approved the following wire-free, nonradioactive localization devices for the surgical excision of nonpalpable breast tumours:

- Magseed needle with magnetic marker system, licence no. 97204, Endomagnetics Ltd., Jeffreys Building, Cowley Road, Cambridge, Cambridgeshire, United Kingdom, CB4 0WS
- MOLLI introducer and MOLLI marker, licence no. 106152, MOLLI Surgical Inc., 22 St. Clair Avenue East, Suite 1500, Toronto, ON, Canada, M4T 2S3
- Scout surgical guidance system, licence no. 106201, Merit Medical Systems, Inc., 6 Journey, Suite 125, Aliso Viejo, CA, United States, 92656

Ontario and Canadian Context

Wire-guided localization is currently in use in most Ontario hospitals. Some centres in Ontario are also using radioactive seed localization, including the Ottawa Hospital,[20] North York General Hospital,[21,22] London Health Sciences Centre,[23] and Hamilton Health Sciences.[24,25]

Breast Imaging Kingston at Kingston Health Sciences Centre in southeastern Ontario[26] and Sioux Lookout Meno Ya Win Health Centre[27] in northwestern Ontario have recently purchased the Endomag system (a new brand identity for Endomagnetics) to perform breast tumour localization with Magseed.

Alberta Health Services has conducted a two-stage health technology evaluation trial of Sentimag with Magseed and Magtrace. The trial first evaluated clinical feasibility (with three arms of 10 patients each) at two high-volume surgery sites in Edmonton and Calgary and then evaluated provincial scalability with Grand Prairie Regional Hospital to inform imminent clinical and operational decision-making.[28]

Sunnybrook Health Sciences Centre has transitioned to MOLLI[29] and, in collaboration with Princess Margaret Hospital and North York General Hospital, is currently evaluating the clinical and health economic outcomes associated with the use of MOLLI through a nonrandomized, multicentre registry (NCT04893421). The study compares MOLLI with the centre's two standard localization techniques (i.e., wire-guided and radioactive seed localization). The expected completion date is December 31, 2023.

MOLLI Surgical has also established a partnership with the CAN Health Network (a national partnership of leading Canadian health organizations) to evaluate the feasibility and economic impact of implementing the MOLLI system in Canada.[30]

Some hospitals in Ontario are also using the Scout radar localization system. A Canadian registry study is currently being undertaken to evaluate the utility of this system (NCT04815291).

We did not identify any Canadian practice guideline for the use of the new wire-free, nonradioactive localization devices to guide surgical excision of nonpalpable breast tumours.

Expert Consultation

We engaged with experts in the specialty areas of breast surgical oncology and breast interventional radiology to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42022334004), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the clinical effectiveness and safety of wire-free, nonradioactive localization techniques to guide surgical excision of nonpalpable breast tumours compared with wire-guided or radioactive seed localization?

Methods

Clinical Literature Search

We performed a clinical literature search on May 4, 2022, to retrieve studies published from January 1, 2014, until the search date. Since no comparative studies for the new devices included in this review were published before 2018, searching the literature from January 2014 seemed appropriate given that the first approval of such devices by the US Food and Drug Administration (FDA) was granted in 2014. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[31]

We created database auto-alerts in MEDLINE and Embase, and monitored them until August 15, 2022. We also performed a targeted grey literature search of the International HTA Database, HTA organizations, and regulatory agencies websites, as well as clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from January 1, 2014, to May 4, 2022
- Randomized controlled trials, comparative observational studies, health technology assessments, and systematic reviews of new localization devices (i.e., magnetic seed or reflector) with reported outcomes of interest for this review
- Where no published comparative studies of devices of interest were available, single-arm studies of those devices were included

Exclusion Criteria

- Editorials, commentaries, case reports, conferences abstracts, editorials, letters, commentaries, and narrative reviews
- Single-arm studies (however, see exception under "Inclusion Criteria")
- Animal and in vitro studies

PARTICIPANTS

Inclusion Criteria

- Adult patients undergoing surgical excision of nonpalpable breast tumours (i.e., lumpectomy, partial or segmental mastectomy, quadrantectomy)
- Studies that included patients with nonpalpable and palpable tumours were included if the proportion of palpable tumours was clearly stated and did not exceed 20% of the sample size

Exclusion Criteria

- Adult patients undergoing surgical excision of palpable breast tumours or surgical excision of axillary lymph nodes localized with localization devices

INTERVENTIONS

Inclusion Criteria

- Wire-free, nonradioactive localization techniques (i.e., magnetic seed localization systems or the reflector-guided localization system)

Exclusion Criteria

- Carbon nanoparticle suspension (CNS)
- Cryo-assisted localization (CAL)
- EnVisio Surgical Navigation System
- Hematoma-directed ultrasound-guided localization
- Intraoperative ultrasound-guided surgery (IOUS)
- Magnetic marker localization (MaMaLoc)
- Methylene blue
- Radio-guided occult lesion localization (ROLL)
- Radiofrequency identification (RFID) tag system (LOCalizer)
- Sirius Pintuition (navigational system)

COMPARATORS

Inclusion Criteria

- Wire-guided localization
- Radioactive seed localization

Exclusion Criteria

- Techniques other than wire-guided and radioactive seed localization

OUTCOME MEASURES

- Re-excision rate
- Technical outcomes
- Successful placement of device in target tissue
- Failure to implant the device

- Failure to detect the device
- Device dislodgement or migration
- Operation time (duration of surgical procedure)
- Postoperative complications
- Patient and clinician satisfaction related to the use of a specific device
- Patient quality of life

Literature Screening

Two reviewers conducted an initial screening of titles and abstracts using Covidence[32] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. One reviewer then examined the full-text articles and selected studies eligible for inclusion. A single reviewer examined the reference lists of all included studies.

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source: citation information, year of publication, country
- Methods: study design, intervention and comparators, study period, participant characteristics, types of surgeries, reporting of missing data
- Outcomes: outcomes measured, number of participants for each outcome, outcome definition, unit of measurement

We contacted study authors to provide clarification as needed.

Statistical Analysis

For re-excision rate, we meta-analyzed the data from observational studies to obtain a pooled estimate for comparison between the interventions of interest and either wire-guided or radioactive seed localization for surgical excision of nonpalpable breast tumours. We performed a quantitative synthesis of the individual studies using STATA, version 11.2.[33] We also assessed data for the presence and extent of statistical heterogeneity among studies. And we undertook a descriptive summary of the outcomes for which meta-analysis was not possible.

Critical Appraisal of Evidence

For nonrandomized observational studies, we assessed risk of bias using the ROBINS-I tool[34] (Appendix 2), and for one noncomparative study, we assessed risk of bias using the Joanna Briggs Institute critical appraisal tool for case series studies.[35]

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[36] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence. We used the approach described by Schünemann and colleagues when applying the ROBINS-I tool as a part of GRADE's certainty rating process.[37]

Results

Clinical Literature Search

The database search of the clinical literature yielded 400 citations published between January 1, 2014, and May 4, 2022, including grey literature searches and after duplicates were removed. We screened the abstracts of these 400 studies and excluded 377. We assessed the full text of 23 articles and excluded a further eight. We identified one additional eligible study from other sources, including database alerts (monitored until August 15, 2022). In total, we included 16 articles in the qualitative synthesis and 12 articles in the quantitative synthesis.

See Appendix 3 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

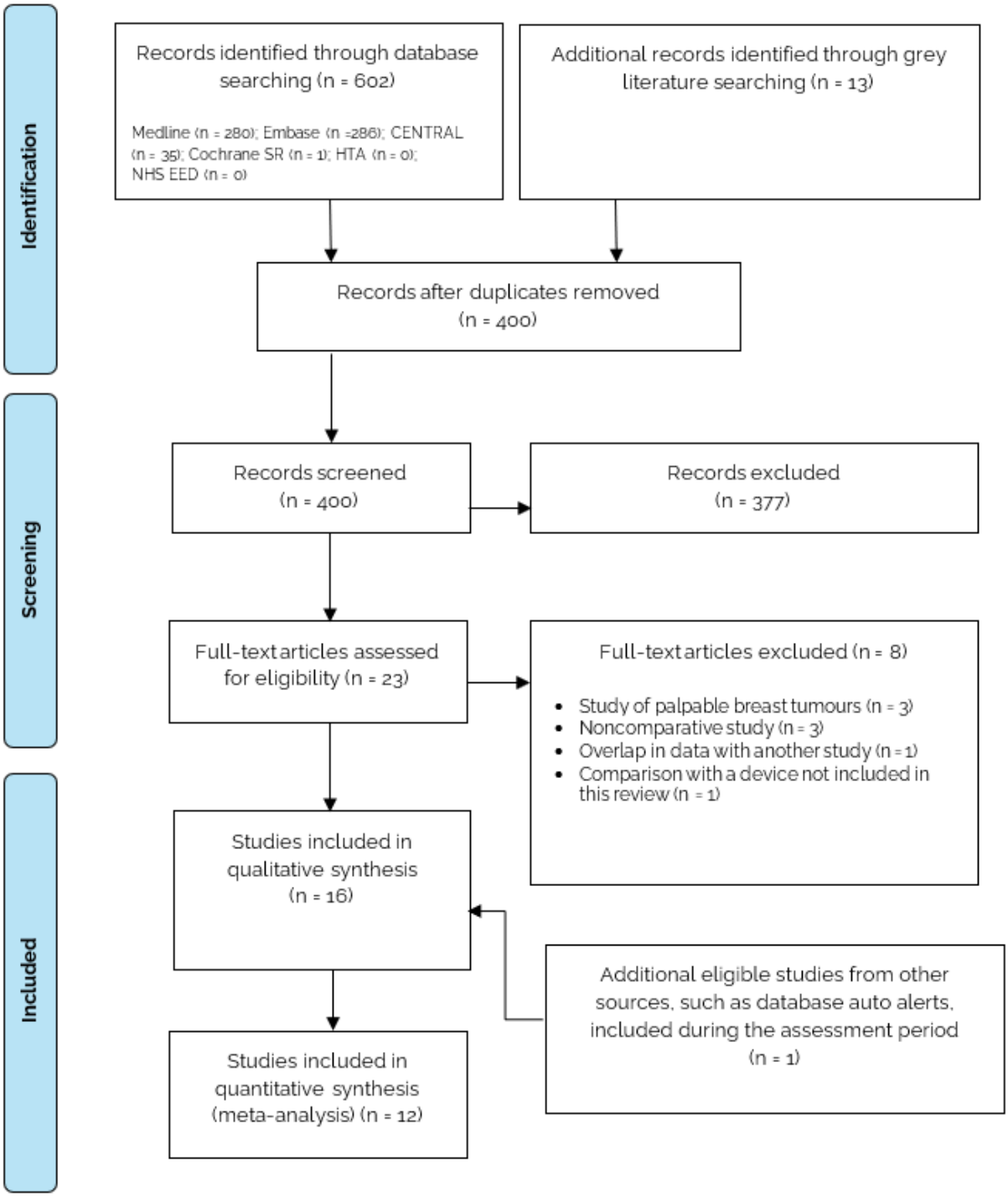

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

PRISMA flow diagram showing the clinical search strategy. After removing duplicates, the database search of the clinical literature yielded 400 citations published between January 1, 2014, and May 4, 2022. We screened the abstracts of 400 studies and excluded 377. We assessed the full text of 23 articles and excluded a further eight. We identified one additional eligible study from other sources. In total, we included 16 articles in the qualitative synthesis and 12 articles in the quantitative meta-analysis.

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[38]

Risk of Bias in the Included Studies

For nonrandomized comparative studies, we determined the risk of bias for four comparisons using the ROBINS-I tool: magnetic seed versus wire-guided localization, magnetic seed versus radioactive seed localization, reflector-guided versus wire-guided localization, and reflector-guided versus radioactive seed localization.[34]

For studies that compared magnetic seed with wire-guided localization, the overall risk of bias was low for re-excision rate and moderate for technical outcomes, operation time, and postoperative complications.[39-46] (Appendix 2, Tables A1 to A6).

For the study that compared magnetic seed with radioactive seed localization, we determined the risk of bias as low for re-excision rate. We could not assess the risk of bias for technical outcomes, operation time, or postoperative complications owing to lack of data.[42] (Appendix 2, Table A7).

For studies that compared reflector-guided with wire-guided localization,[47-52] the overall risk of bias was serious for re-excision rate because in some studies, additional margins or tissue segments were resected after initial lumpectomy in patients who had received reflector-guided localization, which likely reduced the re-excision rate for the reflector group in these studies. We could not assess the risk of bias for technical outcomes in these studies owing to lack of data. The risk of bias for operation time was moderate because additional margins or tissue segments were resected in patients who had received reflector-guided localization, which may have increased the operation time for this group. Also, the authors of one study stated that patients with more extensive disease were more likely to receive wire-guided than reflector-guided localization.[50] This decision likely increased the operation time for the wire-guided group in this study. We determined the overall risk of bias for postoperative complications as moderate since not all studies reported postoperative complications (Appendix 2, Tables A8 to A13).

For studies that compared reflector-guided with radioactive seed localization,[47,51,52] we determined the overall risk of bias for re-excision rate as serious because in one study, additional margins or tissue segments were resected in patients who had received radioactive seed localization, which likely reduced the re-excision rate in this group. We could not assess risk of bias for technical outcomes owing to lack of data. We determined the risk of bias for operation time as moderate since in one study, more patients in the radioactive seed localization group also underwent sentinel lymph node biopsy than in the reflector-guided group.[51] We determined the overall risk of bias for postoperative complications as moderate since not all studies reported postoperative complications (Appendix 2, Table A14).

We determined the risk of bias for the noncomparative study, a single-arm study of magnetic seed localization using the magnetic occult lesion localization instrument (MOLLI),[53] with the Joanna Briggs Institute critical appraisal tool for case series studies.[35] We determined the risk of bias as low. We did not use GRADE to assess the quality of this evidence, as the data were noncomparative.

Tables A16 to A19 in Appendix 2 provide the GRADE ratings for each outcome reported in the comparative studies.

Magnetic Seed Versus Wire-Guided or Radioactive Seed Localization

We identified no randomized controlled trials comparing magnetic seed with wire-guided or radioactive seed localization. Nine observational studies, including three prospective studies[39,46,54] and six retrospective studies[40-45], reported clinical outcomes for magnetic seed compared with wire-guided localization. One of these studies had three arms comparing magnetic seed with wire-guided and radioactive seed localization.[42] This study reported only re-excision rate; it did not report technical outcomes, operation time, or postoperative complications. All included studies comparing magnetic seed with wire-guided or radioactive seed localization used the Magseed magnetic seed localization system.

CHARACTERISTICS OF INCLUDED STUDIES

The study population of these studies was patients with nonpalpable breast tumours with a mean or median age ranging from 59 to 64 years. The six retrospective studies compared a cohort of patients who underwent magnetic seed localization with a historical cohort of patients who underwent wire-guided localization.[41-45,54]

The largest study was a prospective cohort study conducted in the United Kingdom, which compared magnetic seed with wire-guided localization (the iBRA-NET Localisation Study) and reported the results of lumpectomies performed for unifocal unilateral breast tumours less than 50 mm in size.[39]

The study by Liang et al[42], which was conducted in a large academic centre and had the longest study duration, included a large cohort of patients who underwent magnetic seed, wire-guided, or radioactive seed localization between 2011 and 2019. The three groups did not differ with respect to age or neoadjuvant chemotherapy. Benign lesions were excluded from the analysis of positive margin and re-excision rates. A few years after the study had begun, a change to the definition of positive margin was provided in an updated guideline[55]. As a result, before the adoption of the updated guideline, more patients in the wire-guided and radioactive seed groups underwent re-excision than would have based on the new guideline. Further, the use of magnetic seed localization started after the adoption of the new guideline.

Table 1 provides the characteristics of the studies comparing magnetic seed with wire-guided or radioactive seed localization. Table 2 provides the definitions of positive margin used across studies to determine whether patients required re-excision.

Table 1: Characteristics of Included Studies: Magnetic Seed Versus Wire-Guided or Radioactive Seed Localization

Author, year, country	Study design, comparison	Surgical procedure	Study period	Participants, N	Participant age, mean (SD/range)
Dave et al, 2022,[39] United Kingdom	Multicentre (35 units) prospective cohort Magseed vs. WGL	Lumpectomy for single unifocal unilateral lesions < 50 mm Mammoplasty	Aug. 2018–Aug. 2020	*Consecutive patients:* 2,300 Magseed: 946 WGL: 1,170 *Single unifocal unilateral lesions < 50 mm:* 1,746 Magseed: 743 WGL: 1,003	*Total population* Magseed: 59.9 y (10.4 y) WGL: 60.4 y (10.6 y) *P* = .210
Kelly et al, 2022,[41] United States	Single-centre retrospective Magseed vs. WGL	Lumpectomy Lumpectomy plus axillary surgery Excisional biopsy	Magseed: Mar. 2017–Oct. 2018 WGL: Oct. 2015–Dec. 2016 (during this period, only WGL was performed)	*Consecutive patients:* 1,219 Magseed: 600 (608 lesions) WGL: 619 (628 lesions) *Single cancerous lesion* Magseed: 377 WGL: 369	*Total population* Magseed: 59 y (23–91 y) WGL: 59 y (20–92 y) *P* = .992
Liang et al, 2022,[42] United States	Single-centre retrospective 3-arm study conducted at a large academic cancer centre Magseed vs. WGL vs. RSL	Segmental mastectomy or excisional biopsy for unilateral single and multiple lesions (For patients with multiple lesions, the largest lesion was used for analysis)	2011–2019	Total: 1,835 Magseed: 561 WGL: 825 RSL: 449	*Median (range)* Magseed: 61 y (23–87 y) WGL: 59 y (20–89 y) RSL: 59 y (33–85 y) *P* = .06
Ross et al, 2022,[44] United Kingdom	Single-centre prospective Magseed vs. retrospective WGL	Wide local excision Reconstructive surgery	Magseed: Dec. 2017–Dec. 2019 WGL: Jan. 2016–Dec. 2019	Magseed: 255 WGL: 460 *Single Magseed for lesions* Magseed: 250	Magseed: 60.9 y (37–83 y) WGL: 60.6 y (28–86 y)

Author, year, country	Study design, comparison	Surgical procedure	Study period	Participants, N	Participant age, mean (SD/range)
Redfern and Shermis, 2022,[43] United States	Single-centre retrospective Magseed vs. WGL	Lumpectomy Excisional biopsy	Magseed: Aug. 2017–Sep. 2018 WGL: Jan. 2016–Aug 2017 (period just before adoption of Magseed)	*Consecutive patients* Magseed: 148 WGL: 148 *Lumpectomy* Magseed; 117 WGL: 104	*Median (range)* Magseed: 62 y (52–70 y) WGL: 59 y (42–67 y) *P* = .08
Kabeer et al, 2022,[40] United Kingdom	Single-centre prospective Magseed vs. retrospective WGL	Wide local excision (Magseed 83%, WGL 85%) Mammoplasty	Magseed: Jul. 2019–Feb. 2020 WGL: Jan. 2018–Aug. 2018	Magseed: 105 WGL: 133 (same inclusion/ exclusion criteria as Magseed used to select WGL cohort) Multiple lesions requiring ≥ 2 localization devices were excluded	*Median (range)* Magseed: 64 y (34–87 y) WGL: 60 y (28–82 y) *P* = .050
Micha et al, 2021,[54] United Kingdom	Single-centre (2 hospital sites) prospective	Wide local excision Mammoplasty	Jan. 2018–Jan. 2019	*Consecutive patients* Magseed: 128 WGL: 168	Magseed: 61.3 y (11.6 y) WGL: 59.6 y (10.9 y) *P* = .604
Sreedhar et al, 2021,[45] New Zealand	Single centre retrospective	Wide local excision	Magseed: May 2017–Jan. 2020 WGL: Jan. 2013–May 2017	*Consecutive patients* Magseed: 23 WGL: 15	All patients: 61.7 y
Zacharioudakis et al, 2019,[46] United Kingdom	Two-centre prospective	Wide local excision	Oct. 2017–Sep. 2018	*Consecutive patients* Magseed: 104 WGL: 96 Patients who required bracketing were excluded	Magseed: 60.9 y WGL: 61.7 y *P* = .586

Abbreviations: RSL, radioactive seed localization; WGL, wire-guided localization; y, years.

Table 2: Definition of Positive Margin Used Across Studies: Magnetic Seed Versus Wire-Guided or Radioactive Seed Localization

Author, year	Definition of positive margin
Studies conducted in the United Kingdom	
Dave et al, 2022[39]	< 1 mm from inked margin
Ross et al, 2022[44]	< 1 mm from inked margin
Kabeer et al, 2022[40]	< 1 mm from inked margin
Micha et al 2021,[54]	< 1 mm from inked margin
Zacharioudakis et al, 2019[46]	< 1 mm from inked margin
Studies conducted in the United States	
Kelly et al, 2022[41]	0 mm from inked margin < 2 mm from inked margin for pure DCIS
Liang et al, 2022[42]	Previous practice guideline: < 2 mm for both invasive and DCIS Updated practice guideline: 0 mm from inked margin or < 2 mm from inked margin for pure DCIS
Redfern and Shermis, 2022[43]	< 2 mm from inked margin

Abbreviation: DCIS, ductal carcinoma in situ.

RE-EXCISION RATE

Magnetic Seed Versus Wire-Guided Localization

Seven studies reported on the rate of re-excision after initial surgical excision.[39,40,42-46] These studies reported re-excision rate on a per-patient basis, and we used the reported data to conduct a meta-analysis. Figure 2 provides a pooled summary estimate for re-excision rate for the studies comparing magnetic seed with wire-guided localization.

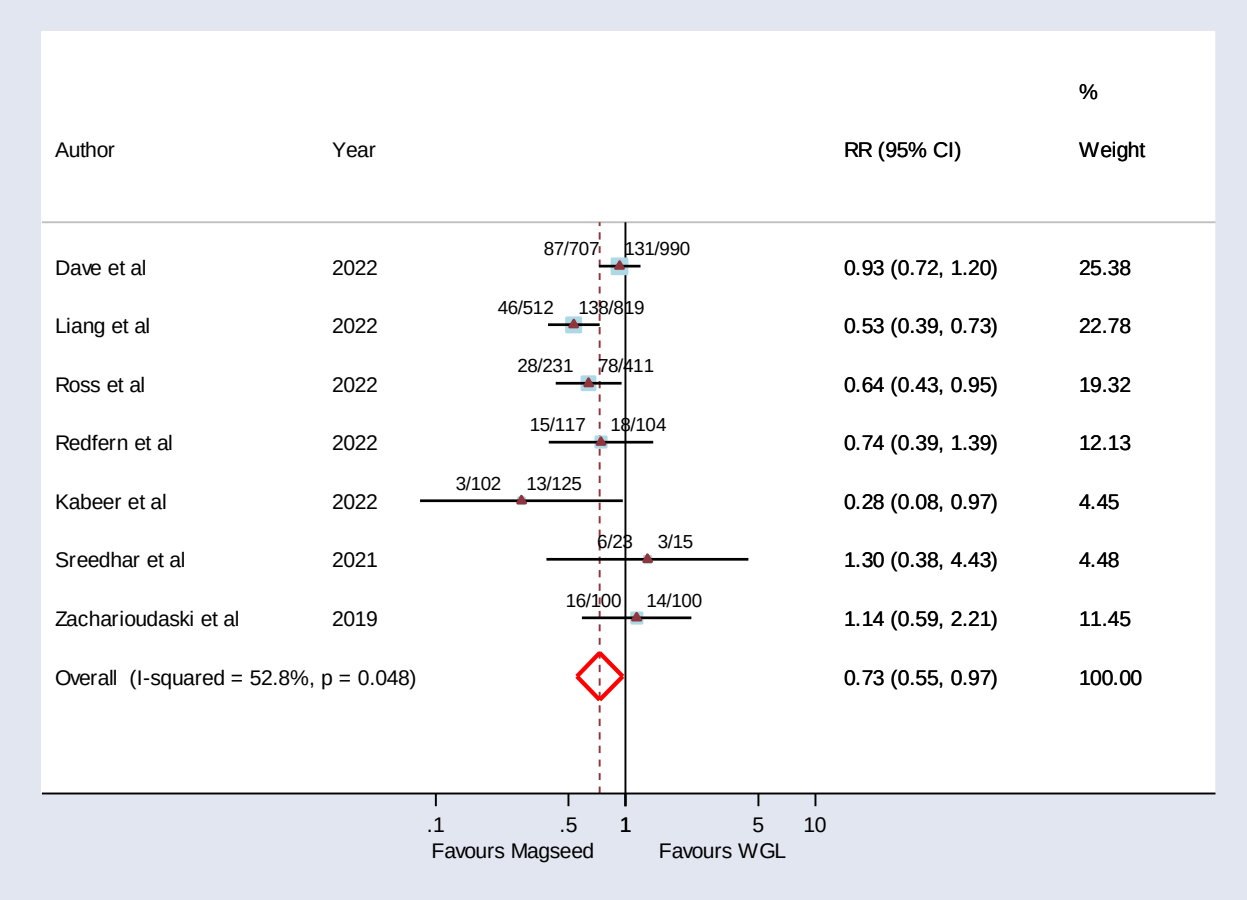

Figure 2: Re-excision Rate: Magnetic Seed Versus Wire-Guided Localization

Abbreviations: CI, confidence interval; RR, relative risk; WGL, wire-guided localization.

The pooled summary estimate of 0.73 (95% confidence interval [CI], 0.55–0.97) shows that patients in whom a breast tumour was localized with magnetic seed localization had a lower rate of re-excision compared with those who had undergone wire-guided localization. The overall rates of re-excision for magnetic seed and wire-guided localization were 11.3% and 15.4%, respectively. Heterogeneity among studies was not considerable (GRADE: Moderate).

The two prospective studies found no difference in re-excision rate between magnetic seed and wire-guided localization.[39,46]. The re-excision rates for magnetic seed and wire-guided localization were 12.3% and 13.2%, respectively (*P* = .574), in the study by Dave et al,[39] and 16% and 14%, respectively (*P* = .692), in the study by Zacharioudakis et al.[46]

The studies by Kabeer et al[40] and Liang et al[42] had the largest effect sizes. In Kabeer et al,[40] the rate of re-excision was 2.9% in the magnetic seed group compared with 10.4% in the wire-guided group (*P* = .030). For the wire-guided group, the authors selected a historical cohort deemed potentially suitable for magnetic seed localization. Patients with multiple lesions requiring two or more wires and those with a depth of tumour from the skin of more than 3 cm on ultrasound or more than 7 cm deep

in the central breast on mammogram were excluded from the wire-guided group based on the same exclusion criteria used for the magnetic seed group. Liang et al[42] also found a difference in re-excision rate favouring magnetic seed (9% vs. 16.8%, $P < .000$), although this difference may in part be due to the change in the definition of positive margin in the updated practice guideline published in the middle of the study, which likely favoured the magnetic seed group.

Sreedhar et al[45] found a relatively lower re-excision rate for the wire-guided versus the magnetic seed group (magnetic seed: 26%, wire-guided: 20%, $P = .666$). This study was conducted in a rural area in which the hospital had only one surgeon proficient in the localization techniques, so all patients in this study were treated by this surgeon. Although the goal of the study was primarily to assess lymph node biopsy using the Sentimag probe, the authors also reported on magnetic seed and wire-guided localization. The results of this study may not be generalizable to urban hospitals.

We also considered whether cavity shaving or resection of additional margins was performed equally across both groups. We considered this because randomized controlled trials have shown that cavity shaving significantly reduced the rates of positive margins and re-excision in breast cancer patients undergoing partial mastectomy.[13,14] Thus, if more patients in one group underwent additional resection after initial lumpectomy than the other, the intervention could not be considered equal across both groups, and the re-excision rate would be biased (i.e., in favour of the group in which more patients underwent additional resection). Meta-analysis of the three studies that reported on resection of additional margins did not show a difference between the two groups (risk ratio [RR], 0.98; 95% CI, 0.92—1.05)[39,40,43] Figure 3 shows the percentages of patients who underwent cavity shaving or resection of additional margins.

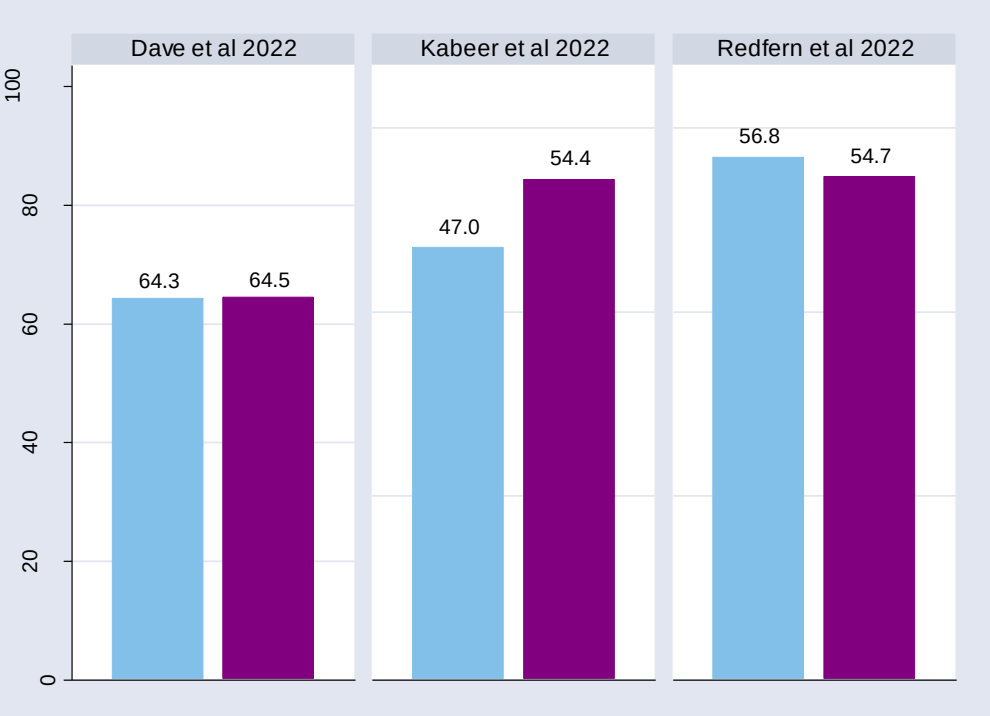

Figure 3: Additional Margins Resected: Magnetic Seed Localization Versus Wire-Guided Localization

Note: Blue bars indicate magnetic seed localization; purple bars indicate wire-guided localization.

Magnetic Seed Versus Radioactive Seed Localization

We included one study that compared the re-excision rate of patients who had undergone magnetic seed localization with that of patients who had undergone radioactive seed localization.[42] In this study, the re-excision rate for patients with a positive or close margin was lower in those who had undergone magnetic seed localization than in those who had undergone radioactive seed localization. In the magnetic seed localization group, 46 of 512 patients (9%) required re-excision compared with 71 of 449 (15.8%) in the radioactive seed localization group (RR, 0.71; 95% CI, 0.56–0.90) (GRADE: Low).

This study did not report comparisons of technical outcomes, operation time, or postoperative complications.

TECHNICAL OUTCOMES

All studies reported on the most common technical outcomes: successful device implantation, device dislodgement or migration, device detection issues, and device retrieval. However, three studies did not report technical outcomes for wire-guided localization.[42,44,45] We determined the GRADE for technical outcomes in these studies as Moderate.

One prospective study, which had the largest sample size, reported a higher rate of successful device implantation (P = .032) and a lower rate of device migration (P = .039) for magnetic seed compared with wire-guided localization.[39] The remaining studies reported no difference in technical outcomes between the two localization techniques (Table 3).

Table 3: Technical Outcomes: Magnetic Seed Versus Wire-Guided or Radioactive Seed Localization

Author, year	Successful device implantation, N (%)	Device dislodgement or migration, N (%)	Magnetic seed detection issues, N (%)	Successful device retrieval, N (%)
Dave et al, 2022[39]	*Lumpectomy for a single focal lesion* Magseed: 15/913 (1.64) WGL: 23/1,162 (1.98) *P* = .032 *All patients* Magseed: 905/946 (99.8) WGL: 1,150/1,170 (99.1) *P* = .048	Magseed: 4/946 (0.4) WGL: 16/1,170 (1.4) *P* = .039	Magseed: 8/946 (0.84)	NR
Kelly et al, 2022[41]	NR (10 localizations with Magseed displacement and subsequent WGL were excluded from analysis)	NR	NR	Magseed: 608/608 (100) WGL: 628/628 (100)
Liang et al, 2022[42]	560/561 (99.8) WGL: NR RSL: NR	Magseed: 0/561 (0) WGL: NR RSL: NR	Magseed: 0/561 (0)	Magseed: 561/561 (100) WGL: NR RSL: NR
Ross et al, 2022[44]	Magseed: 250/255 (98) WGL: NR	Magseed: 3/255 (1.2) WGL: NR	Magseed: 0/255 (0)	Magseed: 255/255 (100) WGL: NR
Redfern and Shermis, 2022[43]	Magseed: 148/148 (100) WGL: 148/148 (100) *P* = 1.000	Magseed: 3/148 (2) WGL: 2/148 (2) *P* = 1.000	NR	Magseed: 146/148 (99.3) WGL: 146/148 (99.3) *P* = 1.000
Kabeer et al, 2022[40]	Magseed: 104/105 (99) WGL: 133/133 (100)	Magseed: 5/105 (4.9) WGL: 0/133 (0)	Magseed: 1/105 (1)	Magseed: 105/105 (100) WGL: 133/133 (100)

Author, year	Successful device implantation, N (%)	Device dislodgement or migration, N (%)	Magnetic seed detection issues, N (%)	Successful device retrieval, N (%)
Micha et al, 2021[54]	Magseed: 127/128 (99) WGL: 168/168 (100)	Magseed: 0/128 (0) WGL: 0/168 (0) *P* = 1.000	NR	*Retrieved with initial specimen* Magseed: 121/128 (94.5) (2 retrieved through cavity shave; 3 found out of specimen WGL: 163/168 (97) *P* = .315
Sreedhar et al, 2021[45]	NR	Magseed: 0/23 (0) WGL: NR	NR	NR
Zacharioudakis et al, 2019[46]	Magseed: 102/104 (98.1) WGL: 100/100 (100)	Magseed: 2/104 (1.9) WGL: 0/96 (0)	Magseed: 2/104 (1.9)	Magseed: 100/100 (100) WGL: 100/100 (100)

Abbreviations: NR, not reported; RSL, radioactive seed localization; WGL, wire-guided localization.

OPERATION TIME

One prospective and two retrospective studies reported a comparison of operation time between magnetic seed and wire-guided localization.[39,41,43] The mean or median operation time varied across studies partly because of the use of different definitions of operation time and variation in surgical expertise or procedural protocols across study sites. We determined the GRADE for operation time as Moderate.

The prospective study by Dave et al[39] reported that lumpectomy for a unifocal unilateral lesion took about the same amount of time for the magnetic seed and the wire-guided localization groups. In the study by Kelly et al,[41] more bracketing (placing more than one localization device to delineate the boundaries of a large lesion) was performed in the wire-guided group than in the magnetic seed group (13.5% vs. 7.9%, *P* = .001), but the authors stratified the data for operation time by subgroup and adjusted for differences between groups. For lumpectomy alone, the mean operation time was shorter in the magnetic seed group than in the wire-guided group (42.3 min vs. 46.9 min, *P* = .017). However, for excisional biopsy, benign lesions, and atypia (abnormal cells) the mean operation time was longer in the magnetic seed group than in the wire-guided group. In the study by Redfern and Shermis,[43] the operation time for both the magnetic seed and the wire-guided groups was considerably longer than those reported by other studies. This was because the authors defined operation time as "time from patient entry to OR [operating room] to the time of exiting OR," which could have included the time taken for all procedures that take place in the operating room (e.g., patient preparation, administration of anesthesia), not just the surgical excision itself. Table 4 provides the operation times for studies comparing magnetic seed with wire-guided localization.

Table 4: Operation Time: Magnetic Seed Versus Wire-Guided Localization

Author, year	Definition of operation time	Operation time, minutes
Dave et al, 2022[39]	Time for surgical procedure	Median (IQR) *Lumpectomy for unifocal unilateral lesions* Magseed: 60.5 (50–81) WGL: 60 (45–82) *P* = 1.000
Kelly et al, 2022[41]	Number of minutes from surgical incision to end of surgery	Mean (range) *Lumpectomy alone including bracketed lesions* Magseed: 42.3 (19–84) WGL: 46.9 (14–118) *P* = .017 *Lumpectomy alone excluding bracketed lesions* Magseed: 41.4 WGL: 43.4 *P* = .249 *Lumpectomy plus axillary surgery* Magseed: 65.6 (24–178) WGL: 61.3 (13–123) *P* = .096 *Excisional biopsy* Magseed: 37 (10–86) WGL: 31.9 (8–86) *P* < .001 *Benign lesions* Magseed: 37.2 WGL: 33.7 *P* = .011 *Atypia* Magseed: 36.7 WGL: 29.8 *P* < .001 Note: Bilateral lesions and excisions combined with other procedures were excluded from calculation
Liang et al, 2022[42]	NR	NR
Ross et al, 2022[44]	NR	Median (range) *Wide local excision and excisional biopsy* Magseed: 45 (35–60) WGL: NR

Author, year	Definition of operation time	Operation time, minutes
Redfern and Shermis, 2022[43]	Time from patient entry to OR to the time of exiting OR	Median (IQR) *Lumpectomy* Magseed: 138 (114–156) WGL: 138 (114–168 *P* = .24 *Entire cohort* Magseed: 124 (100–153) WGL: 124 (100–153) *P* = .420
Kabeer et al, 2022[40]	NR	NR
Micha et al, 2021[54]	NR	NR
Sreedhar et al, 2021[45]	NR	NR
Zacharioudakis et al, 2019[46]	NR	NR

Abbreviations: NR, not reported; OR, operating room; WGL, wire guided localization.

POSTOPERATIVE COMPLICATIONS

Three studies reported on postoperative complications for both magnetic seed and wire-guided localization.[39,45,54] One study reported this outcome only for magnetic seed localization.[44] No studies reported a difference in postoperative complications between the magnetic seed and wire-guided localization groups. The most commonly reported postoperative complications were hematoma formation and seroma formation (presence of blood and fluid, respectively) in the cavity where the tumour was excised. The incidence of hematoma following tumour removal was reported as 0.3% to 0.78% for magnetic seed localization and 0.3% to 0.6% for wire-guided localization. The prospective study by Dave et al[39] reported all postoperative complications encountered in both groups and found no difference between groups. One study reported on postoperative complications using the Clavien-Dindo classification system and reported no difference between groups for postoperative complications rated Clavien-Dindo grade 3 or higher. We determined the GRADE for postoperative complications as Moderate.

Table 5 shows the postoperative complications reported by studies comparing magnetic seed with wire-guided localization.

Table 5: Postoperative Complications: Magnetic Seed Versus Wire-Guided Localization

Author, year	Bleeding or hematoma, N (%)	Seroma	Other
Dave et al, 2022[39]	*Hematoma requiring aspiration in clinic* Magseed: 3/946 (0.3) WGL: 8/1,170 (0.7) *P* = .364 *Hematoma requiring surgical evacuation* Magseed: 3/946 (0.3) WGL: 4/1,170 (0.3) *P* = 1.000	*Seroma requiring aspiration* Magseed: 14/946 (1.5) WGL: 25/1,170 (2.1) *P*= .264	*Minor wound infection requiring oral antibiotic* Magseed: 14/946 (1.5) WGL: 27/1,170 (2.3) *P* = .170 *Major wound infection requiring IV antibiotic* Magseed: 3/946 (0.3) WGL: 7/1.170 (0.6) *P* = .527 *Major wound infection requiring drainage/debridement* Magseed: 1/946 (0.1) WGL: 4/1,170 (0.3) *P* = .388 *In-hospital complication including systemic complications such as DVT, PE, or MI* Magseed: 6/946 (0.7) WGL: 4/1,170 (0.3) *P* = .349 *Unexpected readmission to hospital within 30 days* Magseed: 7/946 (0.8) WGL: 11/1,170 (1) *P* = .676
Kelly et al, 2022[41]	NR	NR	NR
Liang et al, 2022[42]	NR	NR	NR
Ross et al, 2022[44]	*Bleeding* Magseed: 1/255 (0.4) WGL: NR	Magseed: 0/255 (0) WGL: NR	*Syncopal episode during insertion* Magseed: 1/255 (0.4) WGL: NR
Redfern and Shermis, 2022[43]	NR	NR	NR
Kabeer et al, 2022[40]	NR	NR	NR

Author, year	Bleeding or hematoma, N (%)	Seroma	Other
Micha et al, 2021[54]	Magseed: 1/128 (0.78) WGL: 1/168 (0.6)	NR	NR
Sreedhar et al, 2021[45]	NR	NR	*Clavien-Dindo grade* ≥ *3* Magseed: 0/23 (0) WGL: 1/15 (7.14) *P* = .213
Zacharioudakis et al, 2019[46]	NR	NR	NR

Abbreviations: DVT, deep vein thrombosis; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; WGL, wire-guided localization.

PATIENT AND CLINICIAN SATISFACTION

One prospective cohort study reported on patient and clinician satisfaction using the System Usability Scale questionnaire.[54] The study included 128 patients who underwent magnetic seed localization and 168 patients who underwent wire-guided localization. The majority of patients underwent wide local excision (83% in the magnetic seed cohort and 85% in wire-guided cohort); the rest underwent mammoplasty. Lesion bracketing was more frequently performed in the wire-guided cohort than in the magnetic seed cohort. Eleven consultant radiologists/radiographers and seven consultant surgeons were involved in the study.

In the magnetic seed and wire-guided cohorts, 80% and 57% of patients responded to the pain question, 78% and 56% responded to the discomfort question, and 78% and 57% responded to the anxiety question, respectively. The study reported a difference between groups in the experience of anxiety in the time between localization and surgery favouring magnetic seed (*P* = .009) but no difference between groups in the pain associated with the localization procedure or in feelings of discomfort in the time between localization and surgery (GRADE: Moderate).

Patients who underwent wire-guided localization reported being mostly satisfied with having the localization procedure on the same day as surgery, but opinions among patients who underwent magnetic seed localization were divided (i.e., some wanted to have both procedures on the same day, and others wanted them on separate days). Most patients in both cohorts said that if localization and surgery needed to be done on different days, the localization procedure should be coordinated with the time of another appointment at the hospital.

Of the radiologists, 77% and 88% responded to a question about ease of radiological localization for magnetic seed and wire-guided localization, respectively. Of the surgeons, 90% and 82% responded to a question about ease of transcutaneous localization for magnetic seed and wire-guided localization, respectively. And 89% and 81% of surgeons responded to a question about ease of intraoperative localization for magnetic seed and wire-guided localization, respectively. Both radiology and surgical staff were more satisfied with magnetic seed than with wire-guided localization (GRADE: Moderate).

Table 6 summarizes the results for patient satisfaction, and Table 7 summarizes the results for clinician (i.e., radiologist and surgeon) satisfaction.

Table 6: Patient Satisfaction: Magnetic Seed Versus Wire-Guided Localization

Responses on a 5-point scale	5	4	3	2	1
Pain during localization	No pain				Very painful
Magseed vs. WGL	30% vs. 30%	37% vs. 39%	21% vs. 22%	10% vs. 6%	2% vs. 3%
Being comfortable between localization and surgery	Very comfortable				Very uncomfortable
Magseed vs. WGL	62% vs. 43%	23% vs. 32%	13% vs. 19%	2% vs. 4%	0% vs. 2%
Anxiety between localization and surgery	No anxiety				Very anxious
Magseed vs. WGL	63% vs. 38%	16% vs. 24%	12% vs. 22%	5% vs. 6%	4% vs. 8%

Abbreviation: WGL, wire-guided localization.

Table 7: Clinician Satisfaction: Magnetic Seed Versus Wire-Guided Localization

Clinician ratings	Very easy	Fairly easy	Fairly difficult	Difficult	Unable to localize
Ease of localization procedure					
Magseed vs. WGL	52% vs. 28%	35% vs, 28%	4% vs. 0%	1% vs. 3%	–
Ease of transcutaneous localization					
Magseed vs. WGL	54% vs. 20%	31% vs. 45%	5% vs. 17%	8% vs. 14%	–
Ease of intraoperative localization					
Magseed vs. WGL	40% vs. 21%	41% vs. 46%	8% vs. 14%	7% vs. 11%	4% vs. 8%

Abbreviation: WGL, wire-guided localization.

We identified no studies comparing magnetic seed with wire-guided or radioactive seed localization that evaluated patient quality of life.

Magnetic Seed Localization: Noncomparative Data

We identified one small noncomparative feasibility study conducted in Canada that reported on magnetic seed localization using the MOLLI system.[53] This study had a small sample size of 20

patients (mean age 60.3 years [SD 13 years]) who underwent lumpectomy for premalignant and malignant breast tumours. The results of this study showed 100% success in implantation, no device detection issues, and 100% successful device retrieval. No devices migrated or were dislodged. Pathological examination showed that all surgical margins were negative, and no patients required re-excision after initial lumpectomy. Tables 8 and 9 list the technical and clinical outcomes, respectively.

We did not use GRADE to assess the quality of this evidence, as the data were noncomparative.

Table 8: Technical Outcomes: Magnetic Seed Localization Using MOLLI

Author, year	Successful implantation, N (%)	Device dislodged/ migrated, N (%)	Magnetic seed detection issues, N (%)	Successful device retrieval, N (%)
Look Hong et al, 2020[53]	20/20 (100)	0/20 (0)	0/20 (0)	20/20 (100)

Table 9: Clinical Outcomes: Magnetic Seed Localization Using MOLLI

Author, year	Operative time (min), mean (SD/range)	Positive margin, N (%)	Re-excision rate, N (%)	Postoperative complications
Look Hong et al, 2020[53]	Time from sedation to removal of specimen: 36.3 (16.6/21–80)	0/20 (0)	0/20 (0)	0/20 (0)

Reflector-Guided Versus Wire-Guided or Radioactive Seed Localization

We identified no randomized controlled trials comparing reflector-guided with wire-guided or radioactive seed localization. Six retrospective studies reported on clinical outcomes for reflector-guided versus wire-guided localization.[47-52] Three studies[47,51,52] had three arms comparing reflector-guided, wire-guided, and radioactive seed localization.

CHARACTERISTICS OF INCLUDED STUDIES

The study population of the six retrospective studies included patients with a nonpalpable breast tumour.[47-52] The mean or median age ranged from 57.1 years to 66 years in the reflector-guided groups, from 59.5 years to 61 years in the wire-guided groups, and from 51.4 years to 69 years in the radioactive seed groups. These studies compared a cohort of patients who had undergone reflector-guided localization with historical cohorts of patients who had undergone wire-guided or radioactive seed localization.

Table 10 provides the study characteristics of the included studies.[47-52] Table 11 provides the definition of positive margin used in two studies to determine which patients would require re-excision.[47,49] (This definition was not reported in the others.)

Table 10: Characteristics of Included Studies: Reflector-Guided Versus Wire-Guided or Radioactive Seed Localization

Author, year, country	Study design, Comparison	Surgical procedure	Study Period	Participants, N	Participant age
Farha et al, 2022,[48] United States	Single-centre retrospective Reflector vs. WGL	Surgical excision	Jul. 1, 2017–Jun. 30, 2019	Reflector: 64 WGL: 48	NR
Chagpar et al, 2021,[47] United States	10 centres, retrospective collection of data from 2 previous RCTs Reflector vs. WGL vs. RSL	Patients with residual nonpalpable tumour after lumpectomy for cancer	2011–2013, 2017–2018	Reflector: 7 WGL: 465 RSL: 50	*Median (range NR)* Reflector: 57.5 y WGL: 61 y RSL: 67 y *P* = .160
Misbach et al, 2021,[50] United States	Single-centre retrospective Reflector vs. WGL	Partial mastectomy ± sentinel lymph node surgery or excisional biopsy	Reflector: Feb. 1, 2016–Jun. 16, 2019 WGL: Oct. 4, 2018–Jan. 21, 2019	Reflector: 61 (70 lesions) WGL: 63 (78 lesions)	*Mean (range)* Reflector: 57.1 y (32–80 y) WGL: 59.8 y (41–88 y)
Srour et al, 2021,[52] United States	Single-centre retrospective, 3 arms Reflector vs. WGL vs. RSL	Partial mastectomy or breast biopsy for multiple lesions	Jul. 2017–Jul. 2018	Reflector: 16 WGL: 41 RSL: 11	*Mean (SD)* Reflector: 60.38 y (14.73 y) WGL: 59.93 y (15.14 y) RSL: 51.36 y (11.84 y) *P* = .202
Srour et al, 2020,[51] United States	Single-centre retrospective, 3 arms Reflector vs. WGL vs. RSL	Partial mastectomy or breast biopsy for single lesions	Jul. 2017–Jul. 2018	Reflector: 108 WGL: 126 RSL: 59	*Median (range)* Reflector: 66 y (25–89 y) WGL: 59.5 y (26–89 y) RSL: 69 y (38–87 y) *P* = .010
Lee et al, 2020,[49] United States	Single-centre retrospective, 3 arms Reflector vs. WGL vs. RFID	Lumpectomy Patients who required bracketed localization or had cancers greater than 60 mm from the skin on imaging were excluded from the study	Reflector: Nov. 2018–Feb. 2019 WGL: Jan. 2018–Aug 2018	Reflector: 21 WGL: 50	*Mean (SD)* Reflector: 63.4 y (12.1 y) WGL: 60.7 y (11.4 y)

Abbreviations: NR, not reported; RFID, radiofrequency identification; RSL, radioactive seed localization; SD, standard deviation; WGL, wire-guided localization; y, years.

Table 11: Definition of Positive Margin Reported in Two Studies: Reflector-Guided Versus Wire-Guided or Radioactive Seed Localization

Author, year	Definition
Chagpar et al, 2021[47]	0 mm from inked margin for invasive carcinoma < 2 mm from inked margin for DCIS
Lee et al, 2020[49]	0 mm from inked margin (based on final shaved margin)

Abbreviation: DCIS, ductal carcinoma in situ.

RE-EXCISION RATE

Reflector-Guided Versus Wire-Guided Localization

Five studies reported on the rate of re-excision.[47-49,51,52] These studies reported re-excision rate on a per-patient basis, and we used the reported data to conduct a meta-analysis. Figure 4 provides a pooled summary estimate for re-excision rate for the studies comparing reflector-guided with wire-guided localization.

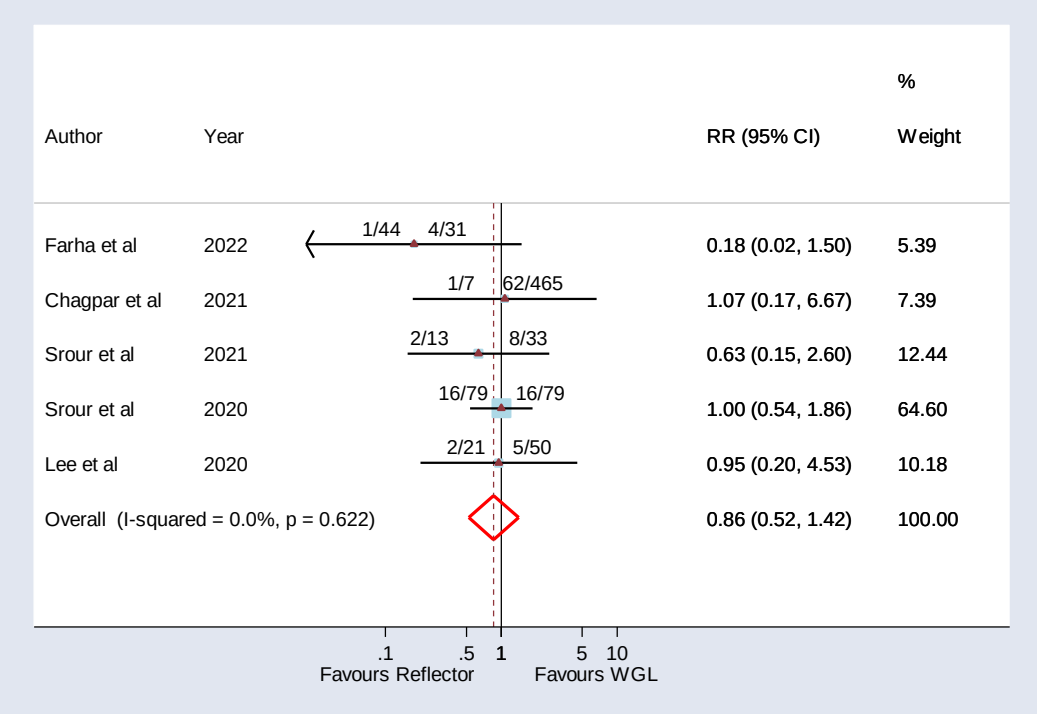

Figure 4: Re-excision Rate: Reflector-Guided Versus Wire-Guided Localization

Abbreviations: CI, confidence interval; RR, relative risk; WGL, wire-guided localization.

The pooled summary estimate of 0.86 (95% CI, 0.52—1.42) shows that there was no difference in re-excision rate between the reflector-guided and wire-guided groups. There was also no

heterogeneity among the studies. The overall rates of re-excision for reflector-guided and wire-guided localization were 13.4% and 14.4%, respectively (GRADE: Low).

We also considered whether the resection of additional margins was performed equally across both groups and found that three studies reported a difference between groups.[47,51,52] Meta-analysis of these studies showed a difference (RR, 1.79; 95% CI, 1.37–2.34) that likely benefited the reflector-guided group, as more of these patients underwent resection of additional margins following initial lumpectomy, resulting in a lower re-excision rate for this group (Figure 5).

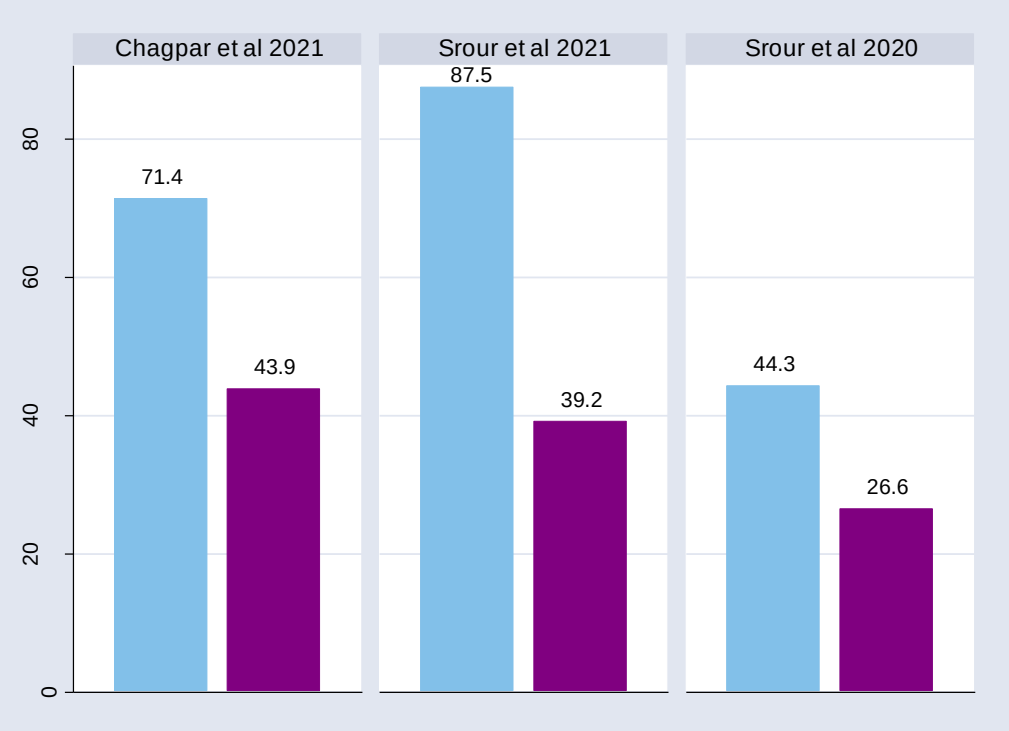

Figure 5: Additional Margins Resected: Reflector-Guided Versus Wire-Guided Localization

Note: Blue bars indicate reflector-guided localization; purple bars indicate wire-guided localization.

Reflector-Guided Versus Radioactive Seed Localization

Three studies that each had three arms reported on the rate of re-excision among patients who had undergone reflector-guided or radioactive seed localization.[47,51,52] These studies reported re-excision rate on a per-patient basis, and we used the reported data to conduct a meta-analysis. Figure 6 provides a pooled summary estimate for re-excision rate for the studies comparing reflector-guided with radioactive seed localization, which shows no difference between groups (RR, 0.76; 95% CI, 0.37–1.57).

The overall re-excision rates for reflector-guided and radioactive seed localization were 19.2% and 13.3%, respectively (GRADE: Low). There was no difference in the resection of additional or selected margins between the two groups (RR, 1.22; 95% CI, 0.81–1.84).

The GRADE for technical outcomes could not be assessed as they were not reported. We determined the GRADE for operation time and postoperative complications as Moderate.

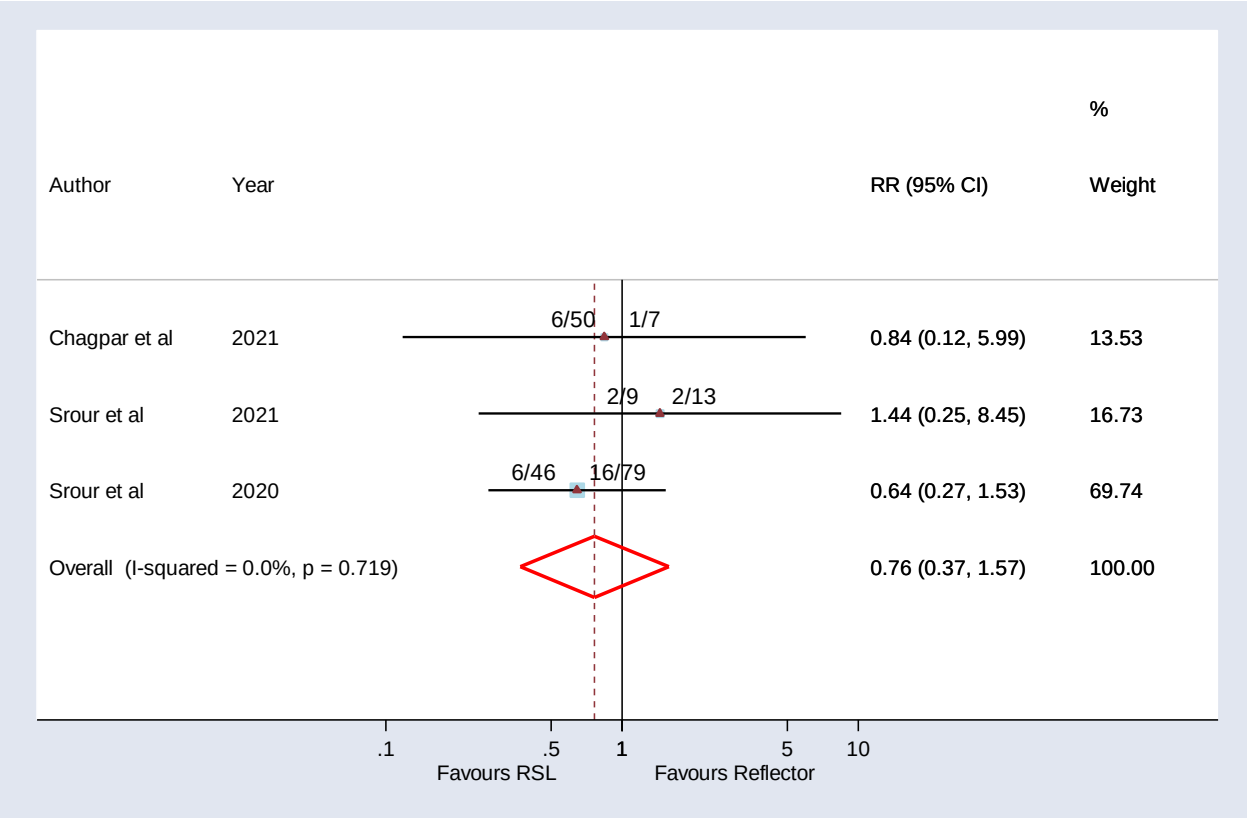

Figure 6: Re-excision Rate: Reflector-Guided Versus Radioactive Seed Localization

Abbreviations: CI, confidence interval; RR, relative risk; RSL, radioactive seed localization.

TECHNICAL OUTCOMES

No studies comparing reflector-guided with wire-guided or radioactive seed localization reported comparative data on technical outcomes. One study reported technical outcomes for reflector-guided localization alone,[50] and one study reported only that all devices had been successfully retrieved[49] (Table 12).

The GRADE for technical outcomes could not be assessed owing to lack of data.

Table 12: Technical Outcomes: Reflector-Guided Versus Wire-Guided or Radioactive Seed Localization

Author, year	Successful device implantation, N (%)	Device dislodgement or migration, N (%)	Reflector detection issues, N (%)	Successful device retrieval, N (%)
Farha et al, 2022[48]	NR	NR	NR	NR
Chagpar et al, 2021[47]	NR	NR	NR	NR
Misbach et al, 2021[50]	Reflector: 59/61 (96.7) WGL: NR	Reflector: 1/61 (1.6) WGL: NR	3/61 (4.9) WGL: NR	Reflector: 61/61 (100) WGL: NR
Srour et al, 2021[52]	NR	NR	NR	NR
Srour et al, 2020[51]	NR	NR	NR	NR
Lee et al, 2020[49]	NR	NR	NR	Reflector: 21/21 (100) WGL: 50/50 (100)

Abbreviations: NR, not reported; WGL, wire-guided localization.

OPERATION TIME

Four studies comparing reflector-guided with wire-guided or radioactive seed localization reported on operation time.[49-52] However, only two studies[49,50] defined operation time, stating whether it was calculated based on time required for the surgical procedure or time from entering to exiting the operating room. No studies reported a difference in operation time between groups. The median or mean operation time for patients localized with a single device ranged from 50 to 80.8 minutes for reflector-guided localization and from 47 to 77.6 minutes for wire-guided localization. One study reported median operation time when multiple devices were used but did not find a difference between groups (reflector-guided: 76 min; wire-guided: 60 min).[52] We determined the GRADE for operation time as Moderate.

Table 13 shows the reported operation times for studies comparing reflector-guided with wire-guided or radioactive seed localization.

Table 13: Operation Time: Reflector-Guided Versus Wire-Guided or Radioactive Seed Localization

Author, year	Operation time, minutes
Farha et al, 2022[48]	NR
Chagpar et al, 2021[47]	NR
Misbach et al, 2021[50]	Total operation time for patients localized with a single device undergoing partial mastectomy with or without sentinel lymph node and excisional biopsy (patients localized with multiple devices were excluded for the calculation of operation time) Operation time defined as "length of surgery" Median (range) Reflector: 61 (17–135) WGL: 47 (23–123) *P* = .073
Srour et al, 2021[52]	Total operation time for patients localized with multiple devices undergoing partial mastectomy, breast biopsy, or other procedure Operation time not defined Median (range) *Hospital setting* Reflector: 76 (47–123) WGL: 60 (41–197) RSL: 89 (32–120) *P* = .705
Srour et al, 2020[51]	Total operation time for patients localized with a single device undergoing partial mastectomy, breast biopsy, or other procedure Operation time not defined Median (range) *Hospital setting* Reflector: 50 (17–118) WGL: 50 (20–122) RSL: 59.5 (33–106) *P* = .108 *Ambulatory setting* Reflector: 56.5 (35–67) WGL: 45 (24–127) RSL: 50 (18–85) *P* = .715

Author, year	Operation time, minutes
Lee et al, 2020[49]	Patients undergoing lumpectomy for single breast cancer (patients who required bracketed localization or had cancers greater than 60 mm from the skin on imaging were excluded from the study) Operation time defined as "time from incision to closure" Mean (SD) Reflector: 80.8 (25.9) WGL: 77.6 (30.5) *P* = .910

Abbreviations: NR, not reported; RSL, radioactive seed localization; WGL, wire-guided localization.

POSTOPERATIVE COMPLICATIONS

The incidence of hematoma and seroma following tumour removal for patients who had undergone reflector-guided localization ranged from 0.0% to 1.6% and from 0% to 3.3%, respectively. The incidence of hematoma following tumour removal for patients who had undergone wire-guided localization ranged from 0.9% to 1.59%. Only one study reported the incidence of seroma among patients who had undergone wire-guided localization: 1.59%.[51] No studies reported a difference between the two groups for postoperative complications (Table 14).

We determined the GRADE for postoperative outcomes as Moderate.

Table 14: Postoperative Complications: Reflector-Guided Versus Wire-Guided or Radioactive Seed Localization

Author, year	Bleeding or hematoma, N (%)	Seroma, N (%)	Other
Farha et al, 2022[48]	No significant bleeding or hematoma in either group	NR	NR
Chagpar et al, 2021[47]	*Bleeding or seroma* Reflector: 0/7 (0) WGL: 4/465 (0.9) RSL: 0/50 (0) *P* = .629	NR	NR
Misbach et al, 2021[50]	Reflector: 1 (1.6) WGL: NR	Reflector: 2 (3.3) WGL: NR	*Cellulitis* Reflector: 2 (3.3) WGL: NR
Srour et al, 2021[52]	NR	NR	30-day complications *Lymphedema* Reflector: 0/16 (0) WGL: 1/41 (2.4) RSL: 0/11 (0) *Infection* Reflector: 0/16 (0) WGL: 0/41 (0) RSL: 1/11 (9.1) *P* = 1.000
Srour et al, 2020[51]	*Hematoma requiring intervention* Reflector: 1/108 (0.93) WGL: 2/126 (1.59) RSL: 1/59 (1.69)	*Breast seroma requiring aspiration* Reflector: 0/108 (0) WGL: 2/126 (1.59) RSL: 0/59 (0)	Overall 30-day complications (*P* = .965) *Infection* Reflector: 3/108 (2.78) WGL: 2/126 (1.59) RSL: 1/59 (1.69) *Medical complications (apnea, pacemaker, or UTI)* Reflector: 1/108 (0.93) WGL: 0/126 (0) RSL: 0/59 (0)
Lee et al, 2020[49]	NR	NR	NR

Abbreviations: NR, not reported; RSL, radioactive seed localization; UTI, urinary tract infection; WGL, wire-guided localization.

We identified no studies comparing reflector-guided with wire-guided or radioactive seed localization that evaluated patient or clinician satisfaction or patient quality of life.

Ongoing Studies

We are aware of one nonrandomized, multicenter, sequential-arm registry study evaluating the clinical and health economic outcomes of breast tumour localization with MOLLI in Ontario (NCT04893421).[21] Patients are currently being enrolled across three surgical sites (Sunnybrook Health Sciences Centre [primary site], Princess Margaret Cancer Centre, and North York General Hospital). The study started on May 16, 2021, and is scheduled to be completed by December 2023. The study is collecting patient- and system-related outcome measures for patients undergoing wire-guided or radioactive seed localization first (the two techniques currently in use at these hospitals). Following transition to the MOLLI system, the study will compare the outcomes of MOLLI with the collected outcomes of wire-guided and radioactive seed localization.

Discussion

We have summarized the results of studies comparing the new wire-free, nonradioactive techniques available in Canada to localize nonpalpable breast tumours for surgical excision with two conventional techniques currently in use in clinical practice in Ontario (i.e., wire-guided localization and radioactive seed localization). We did not include a comparison between wire-guided and radioactive seed localization since there is sufficient evidence that there are no differences between these methods with respect to re-excision rate, operation time, or postoperative complications.[56] We did not assess the comparative effectiveness of the devices included in this review, as we found no published randomized controlled trials evaluating these devices.

Overall, we found that the wire-free, nonradioactive localization techniques we reviewed are effective and safe methods for localizing nonpalpable breast tumours. As we found slightly better outcomes or no difference in the outcomes associated with the use of these techniques and those associated with wire-guided or radioactive seed localization, they have the potential for use as alternative to wire-guided or radioactive seed localization.

We identified comparative data for magnetic seed localization only in studies using the Magseed system. The risk of re-excision after initial lumpectomy when the tumour was localized with magnetic seed was reduced by 27% compared with wire-guided localization (RR, 0.73; 95% CI, 0.55–0.97). One study also showed a lower re-excision rate for magnetic seed compared with radioactive seed localization (9% vs. 15.8%; RR, 0.71 [95% CI, 0.56–0.90]). One study found a difference between the magnetic seed cohort and the wire-guided cohort in reported anxiety between the time of localization and time of surgery favouring magnetic seed (P = .009). Both radiology and surgical staff reported greater satisfaction with magnetic seed than with wire-guided localization. We did not identify any comparative data for the MOLLI system but did include noncomparative data from a single-arm feasibility study of the MOLLI system, which found 100% successful implantation and retrieval rates, no device migration, and a 0% re-excision rate.[53]

Reflector-guided localization was associated with a similar re-excision rate to that of wire-guided localization (RR, 0.86; 95% CI, 0.52–1,42), although in some studies more patients in the reflector-guided group underwent additional resection of breast tissue after initial lumpectomy to locate the localization device or biopsy clip or to remove additional abnormal tissue or calcifications identified through intraoperative palpation.[51,52]. This likely helped reduce the re-excision rate in this group.

Operation time and postoperative complications did not differ between the two groups. Of note, technical outcomes were not reported in the studies comparing reflector-guided with wire-guided or radioactive seed localization, and the reason for this is unclear. No difference in re-excision rate was found between reflector-guided and radioactive seed localization (RR, 0.76; 95% CI, 0.37–1.57).

Wire-free localization techniques provide some benefits over wire-guided and radioactive seed localization, as they allow the localization and surgical procedures to be done on different days, which can improve scheduling efficiency and workflow in both the radiology and surgical departments (e.g., the surgery schedule will not be at risk of delays that might arise from delays in the localization procedure). Radioactive seed localization has been adopted as the localization technique of choice at some centres in Ontario. Although evidence supports the safety and effectiveness of this technique, and it avoids potential complications associated with wire-guided localization, it requires strict regulation and radiation safety precautions and may have limited availability in some areas.

Wire-free, nonradioactive localization devices also have some limitations compared with wire-guided localization. For example, magnetic seeds cannot be placed under magnetic resonance imaging (MRI) and can create artifacts on MRI if the breast is imaged after implantation. Reflector-guided systems may disengage if in close proximity to electrocautery equipment,[49] and hematomas can obscure the reflector signal; thus, this technique may not be appropriate when it is known that a large hematoma is present.[50]

Strengths and Limitations

A strength of this study is our stringent inclusion and exclusion criteria. We included only studies of nonpalpable breast tumours, and the results of our analysis are directly related to patients diagnosed with a suspicious lesion through mammographic screening, as most lesions detected through screening are nonpalpable.

One limitation is the poorly reported technical outcomes in studies comparing reflector-guided with wire-guided and radioactive seed localization, which prevented us from being able to provide a complete picture of the true effectiveness of reflector-guided localization.

Conclusions

Overall, the wire-free, nonradioactive localization techniques we reviewed are effective and safe methods to guide surgical excision of nonpalpable breast tumours.

Compared with wire-guided localization, magnetic seed localization:

- Likely reduces re-excision rates (GRADE: Moderate)
- Likely results in little to no difference in technical outcomes, operation time, and postoperative complications (GRADE: Moderate)
- Likely reduces patients' feelings of anxiety (GRADE: Moderate)
- Likely increases surgeon and radiologist satisfaction (GRADE: Moderate)
- Likely results in little to no difference in patients' feelings of pain or discomfort in the time between localization and surgery (GRADE: Moderate)

Compared with radioactive seed localization, magnetic seed localization:

- May reduce re-excision rates (GRADE: Low)

Compared with wire-guided localization, reflector-guided localization:

- May have similar re-excision rates (GRADE: Low)
- Likely results in little to no difference in operation time and postoperative complications (GRADE: Moderate)

Compared with radioactive seed localization, reflector-guided localization:

- May have similar re-excision rates (GRADE: Low)
- Likely results in little to no difference in operation time and postoperative complications (GRADE: Moderate)

Economic Evidence

Research Question

What is the cost-effectiveness of wire-free, nonradioactive localization techniques to guide surgical excision of nonpalpable breast tumours compared with wire-guided or radioactive seed localization?

Methods

Economic Literature Search

We performed an economic literature search on May 4, 2022, to retrieve studies published from January 1, 2014, until the search date. We searched the literature from January 1, 2014, since 2014 corresponds to the first US Food and Drug Administration approval of a wire-free, nonradioactive localization device. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them until August 15, 2022. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See the clinical literature search for further details on methods used. See Appendix 1 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from January 1, 2014, to May 4, 2022
- Cost-benefit analyses, cost-effectiveness analyses, cost-minimization analyses, cost-utility analyses, cost-consequence analyses, budget impact analyses, or systematic reviews of economic analyses

Exclusion Criteria

- Studies in which the outcomes of interest are not reported or cannot be extracted
- Nonsystematic reviews, editorials, case reports, commentaries, conference abstracts, letters, and unpublished studies
- Noncomparative costing studies, feasibility analyses

POPULATION

Inclusion Criteria

- Adult patients undergoing surgical excision of nonpalpable breast tumours (i.e., lumpectomy, partial or segmental mastectomy, quadrantectomy)

Exclusion Criteria

- Adult patients undergoing surgical excision of palpable breast tumours or surgical excision of axillary lymph nodes localized with localization devices

INTERVENTIONS

Inclusion Criteria

- Wire-free nonradioactive localization techniques

Exclusion Criteria

- Carbon nanoparticle suspension (CNS)
- Cryo-assisted localization (CAL)
- EnVisio Surgical Navigation System
- Hematoma-directed ultrasound-guided localization
- Intraoperative ultrasound-guided surgery (IOUS)
- Magnetic marker localization (MaMaLoc)
- Methylene blue
- Radio-guided occult lesion localization (ROLL)
- Radiofrequency Identification (RFID) tag system (LOCalizer)
- Sirius Pintuition System (navigational system)

COMPARATORS

Inclusion Criteria

- Wire-guided localization
- Radioactive seed localization

Exclusion Criteria

- Techniques other than wire-guided and radioactive seed localization

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years, rate of re-excision, adverse events)
- Health care system outcomes (e.g., changes in operational capacity, staffing requirements)
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

We contacted study authors to provide clarification as needed.

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[57] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. We then assessed the applicability of each study to the research question (directly, partially, or not applicable).

Results

Economic Literature Search

The database search of the economic literature yielded 38 citations published between January 1, 2014, and May 4, 2022, after removing duplicates. We identified 14 additional studies from other sources, for a total of 52. In total, we identified two studies (a budget impact analysis and a cost-consequence analysis) that met our inclusion criteria. See Appendix 5 for a list of selected studies excluded after full-text review. Figure 7 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

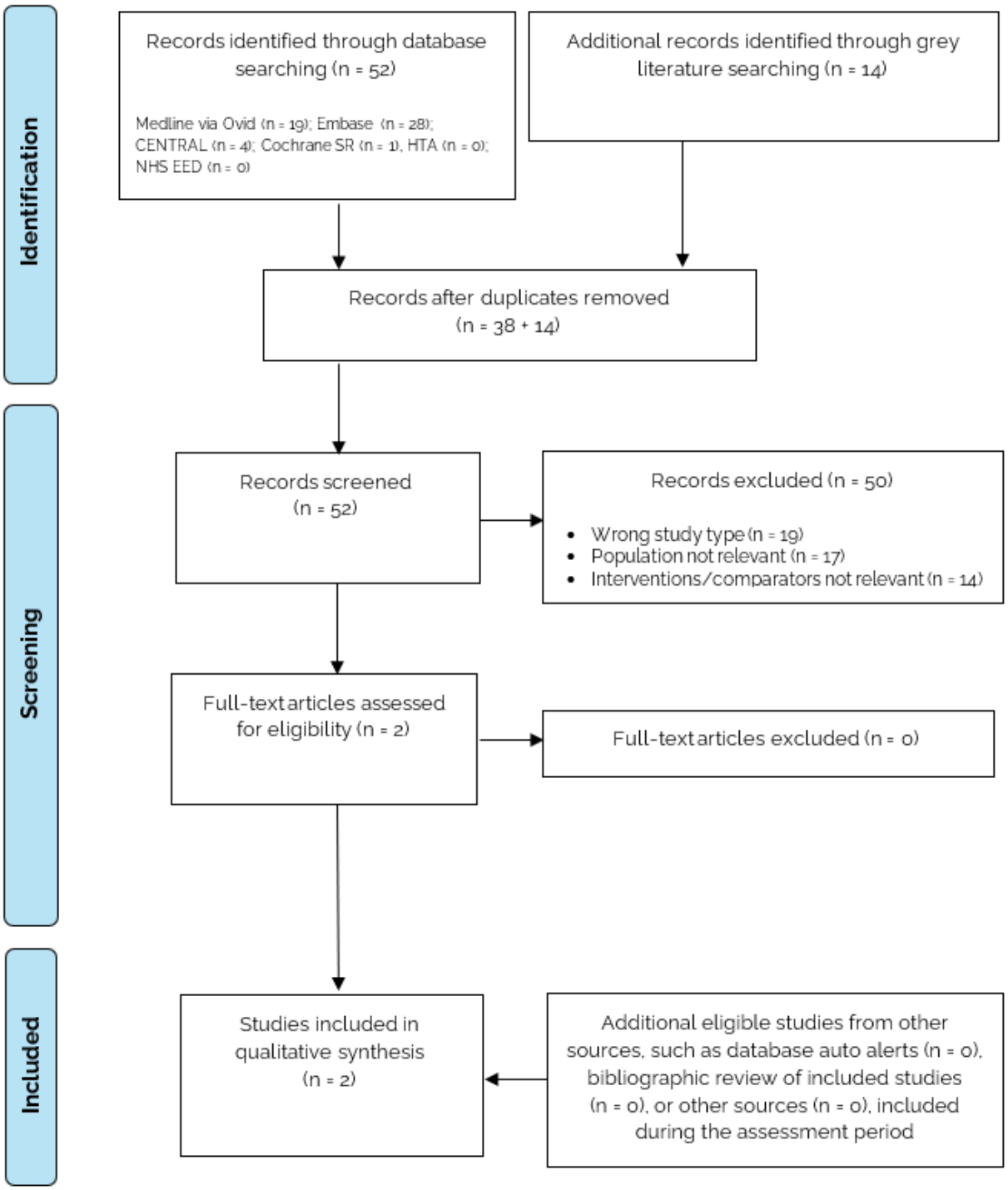

Figure 7: PRISMA Flow Diagram—Economic Search Strategy

PRISMA flow diagram showing the economic search strategy. The database search of the economic literature yielded 52 citations published between January 1, 2014, and May 4, 2022. We identified 14 additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 52 studies and excluded 50. We assessed the full text of two articles and did not exclude either one. In the end, we included two articles in the qualitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[38]

Overview of Included Economic Studies

We identified two relevant studies[45,58] published between January 1, 2014, and May 4, 2022. Table 15 describes the study design, population, interventions, comparators, and results of the included studies.

Note that we excluded four economic evaluations and one budget impact analysis of localization techniques as they did not include wire-free, nonradioactive comparators. Appendix 5 describes these excluded studies.

Lindenberg et al[58] conducted a model-based budget impact analysis to evaluate the per-patient and health care system–level costs of adding magnetic seed localization to the current standard of care (wire-guided and radioactive seed localization). The authors used a 5-year time horizon (2017–2022) and took the perspective of a public payer in the Netherlands. The study included material, personnel, and equipment costs related to localization (i.e., costs of surgery, pathology assessment, wire or seed placement, and purchasing localization equipment). For individuals receiving neoadjuvant chemotherapy (19% of patients) and undergoing either wire-guided or magnetic seed localization, a cost for the placement of an additional marker to monitor chemotherapy response was also included. The authors assumed that for all individuals requiring chemotherapy and receiving radioactive seed localization, the radioactive seed was considered to replace the marker to monitor chemotherapy response. The study also estimated the implementation costs (i.e., costs of licensing, training, and establishing internal procedures) related to starting a radioactive or magnetic seed localization program. The costs and resource use inputs were sourced from eight hospitals in the Netherlands. The cost of magnetic seed localization was assumed to range between €100 and €500 per seed. Costs were reported in 2017 euros (EUR).

The number of individuals requiring localization and the proportion receiving neoadjuvant chemotherapy were estimated from registry data. The authors assumed that all localization techniques would have the same clinical effectiveness based on several clinical studies that showed noninferiority among the localization techniques. They did not consider differences in rates of re-excision or adverse events. The authors noted that unlike wire-guided localization, the radioactive seed and magnetic seed localization techniques do not require patients to have the localization procedure and surgery on the same day.

The mean total cost per patient (in 2017 EUR) was estimated to be €2,617 for wire-guided localization, €2,834 for radioactive seed localization, and between €2,762 and €3,162 for magnetic seed localization. All three localization techniques had surgery and imaging costs of €2,173. Personnel costs were highest for radioactive seed localization at €321 compared to €279 for both wire-guided and magnetic seed localization. Material costs were €43 for wire-guided localization, €118 for radioactive seed localization, and between €112 and €512 for magnetic seed localization. The cost of the marker used to monitor chemotherapy response was €146. Per-patient equipment purchasing costs were €53 for radioactive seed localization and €49 for magnetic seed localization. Equipment costs were estimated by assuming that equipment would last five years. Yearly site implementation costs were €26,826 for radioactive seed localization and €2,794 for magnetic seed localization. Implementation costs were higher for radioactive seed localization as the authors estimated that establishing a radioactive seed localization program would require 322.75 staff hours compared to 24 hours for a magnetic seed localization program. Sensitivity analyses demonstrated

that budget impact analysis results were most sensitive to the cost of radioactive seed localization, the cost of magnetic seed localization, and the uptake of magnetic seed localization.

Sreedhar et al[45] conducted a retrospective cost-consequence analysis comparing magnetic seed localization with wire-guided localization in a rural New Zealand hospital. The authors also compared two sentinel lymph node biopsy techniques. The study was conducted between 2013 and 2020. The authors compared the rates of re-excision and adverse events between magnetic seed and wire-guided localization. The authors sourced the cost of magnetic seed and wire-guided localization from the hospital's finance department but did not report which cost components (e.g., personnel, material, overhead) were included. Costs were reported in 2019 New Zealand dollars (NZD). The authors also listed the cost of equipment, in 2016 NZD, required to conduct magnetic seed localization.

During the study period, 38 individuals required localization for nonpalpable breast tumours. Of these, 23 received magnetic seed localization and 15 received wire-guided localization. The rate of re-excision was 26% for magnetic seed localization and 20% for wire-guided localization. The difference in the rate of re-excision was not statistically significant. No adverse events were observed for individuals receiving magnetic seed localization, and one adverse event was recorded among individuals receiving wire-guided localization. The authors noted that before implementing a magnetic seed localization program, wire-guided localization required surgery dates to be planned around the visit schedule of an external radiology team and that individuals had to be transported across town with a wire extending from the breast skin. Since the magnetic seed can remain implanted in the breast for many weeks, magnetic seed localization increased the flexibility of surgical schedules. The study reported a cost per localization of $697.10 NZD for magnetic seed localization and $460.00 NZD for wire-guided localization. The cost to acquire the Sentimag localization system to conduct magnetic seed localization was $44,275 (in 2016 NZD).

Table 15: Results of Economic Literature Review—Summary

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Lindenberg et al, 2020,[58] Netherlands	Budget impact Model-based Public payer 5 y (2017–2022)	Individuals undergoing breast-conserving surgery for nonpalpable tumours	Intervention: MSL Comparators: WGL, RSL	Similar between MSL, WGL, and RSL	Average cost per patient (2017 EUR) MSL[a]: €2,762–€3,162 RSL: €2,834 WGL: €2,617	NA
Sreedhar et al, 2021,[45] New Zealand	Cost-consequence Retrospective Rural hospital 7 y (2013–2020)	Individuals undergoing localization for a nonpalpable breast tumour (N = 38) or for a sentinel lymph node biopsy (N = 116)	Intervention: MSL (N = 23) Comparator: WGL (N = 15)	Re-excision rate, N (%): • MSL: 6 (26%) • WGL: 3 (20%) Adverse events, N (%) • MSL: 0 (0%) • WGL: 1 (7%)	Average cost per patient (2019 NZD) MSL: $697.10 WGL: $460.00	NR

Abbreviations: EUR, euros; MSL, magnetic seed localization; NA, not applicable; NR, not reported; NZD: New Zealand dollars; RSL, radioactive seed localization; WGL, wire-guided localization; y, years.

[a]For magnetic seed localization, seed cost ranged from €100 to €500.

Applicability and Limitations of the Included Studies

Appendix 6 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. The populations and comparators of the studies by Lindenberg et al[58] and Sreedhar et al[45] matched the inclusion criteria of our economic evidence review. Lindenberg et al[58] was partially limited in its applicability to the Ontario setting since the costs and resource use parameters were based on data from a Dutch setting. Sreedhar et al[45] was not applicable because costs were sourced to reflect those incurred in a rural New Zealand hospital and the study did not report which cost components were included.

We did not assess the limitations of the included studies as they were deemed not to be directly applicable to the Ontario setting.

Discussion

We identified two studies that met our inclusion criteria.[45,58] The Dutch budget impact analysis conducted by Lindenberg et al[58] compared magnetic seed localization with wire-guided and radioactive seed localization. The study found that wire-guided localization was less costly than both radioactive seed and magnetic seed localization owing to lower material costs. Magnetic seed localization was found to be less costly than radioactive seed localization when the cost of the magnetic seed was less than €173. The study also demonstrated that the material and personnel costs directly associated with each localization technique were lower than the cost of surgery. This finding is likely attributable to the high cost of operating room time. The implementation costs required to establish a radioactive seed localization program were found to be higher than those required to establish a magnetic seed localization program owing to the increased regulatory requirements associated with handling radioactive seeds. The study was able to accurately assess the budget impact of introducing magnetic seed localization into the standard of care in the Netherlands, but the applicability of these results to an Ontario context remains uncertain owing to potential differences in unit costs, resource use, and clinical practice.

Sreedhar et al[45] conducted a retrospective analysis at a rural New Zealand hospital comparing magnetic seed localization with wire-guided localization. The study found that magnetic seed localization was more costly, by $237 NZD, than wire-guided localization. The study was unclear with regard to which components of localization were covered by cost estimates. Introducing magnetic seed localization allowed for increased flexibility in surgical schedules, which is likely to be applicable to other rural hospitals. Owing to the study's limitations and perspective (rural hospital), it is unlikely that these results are applicable to an Ontario context.

Strengths and Limitations

We conducted a review of the economic literature comparing wire-free, nonradioactive localization techniques with wire-guided and radioactive seed localization for surgical excision of nonpalpable breast tumours. Although we limited our search by starting from the year that the first wire-free, nonradioactive localization device received US Food and Drug Administration approval (which occurred before Health Canada approval), it is unlikely that we omitted relevant economic evaluations, as we were unable to identify relevant studies published prior to 2014 in the reference lists of the included studies. This review is limited in that the only wire-free, nonradioactive localization technique we were able to identify evidence for was magnetic seed localization. We were unable to source economic evidence for the reflector-guided localization technique.

Conclusions

We identified one budget impact analysis and one cost-consequence analysis that compared wire-free, nonradioactive localization techniques with wire-guided and radioactive seed localization. However, these two studies were limited in their applicability to an Ontario context. We were unable to identify any cost-effectiveness or cost-utility analyses comparing wire-free, nonradioactive localization techniques with wire-guided or radioactive seed localization.

Primary Economic Evaluation

We did not conduct a primary economic evaluation for the following reasons. First, we were unable to source estimates of health-related quality-of-life data for wire-free, nonradioactive localization techniques, which would be required to conduct a cost-utility analysis. Second, the clinical evidence review found that potential effectiveness outcomes such as accurate device placement, device migration, and operation time were deemed comparable between wire-free, nonradioactive localization techniques, wire-guided localization, and radioactive seed localization (GRADE: Low to Moderate). Third, the clinical evidence review found mixed evidence for the rate of re-excision, a potential effectiveness outcome in a cost-effectiveness analysis. Compared with wire-guided localization, magnetic seed localization was found to have a lower rate of re-excision with a relative risk of 0.73 (95% confidence interval [CI], 0.55–0.97; GRADE: Moderate). We identified one study that compared magnetic seed with radioactive seed localization.[42] The study estimated a risk ratio for re-excision of 0.71 (95% CI, 0.56–0.90; GRADE: Low) for magnetic seed localization compared with radioactive seed localization. The clinical evidence review found that the evidence for the re-excision rate of reflector-guided localization had serious limitations. Last, we were able to incorporate costs related to differences in clinical effectiveness between localization techniques (e.g., re-excision rate) in a budget impact analysis.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding wire-free, nonradioactive localization techniques to guide surgical excision of nonpalpable breast tumours?

Methods

Analytic Framework

We estimated the budget impact of publicly funding wire-free, nonradioactive localization techniques using the cost difference between two scenarios: (1) current clinical practice without public funding for wire-free, nonradioactive localization techniques (the current scenario) and (2) anticipated clinical practice with public funding for wire-free, nonradioactive localization techniques (the new scenario). We assumed that operational expenditures related to localization would be funded by the Ontario Ministry of Health and that capital expenditures would be funded through hospitals' global budgets. We considered only wire-free, nonradioactive localization techniques that have Health Canada approval and were deemed relevant by clinical experts. These include magnetic seed localization performed with either the Magseed system or the magnetic occult lesion localization instrument (MOLLI) and reflector-guided localization performed with the Scout radar localization system. Figure 8 presents the budget impact model schematic.

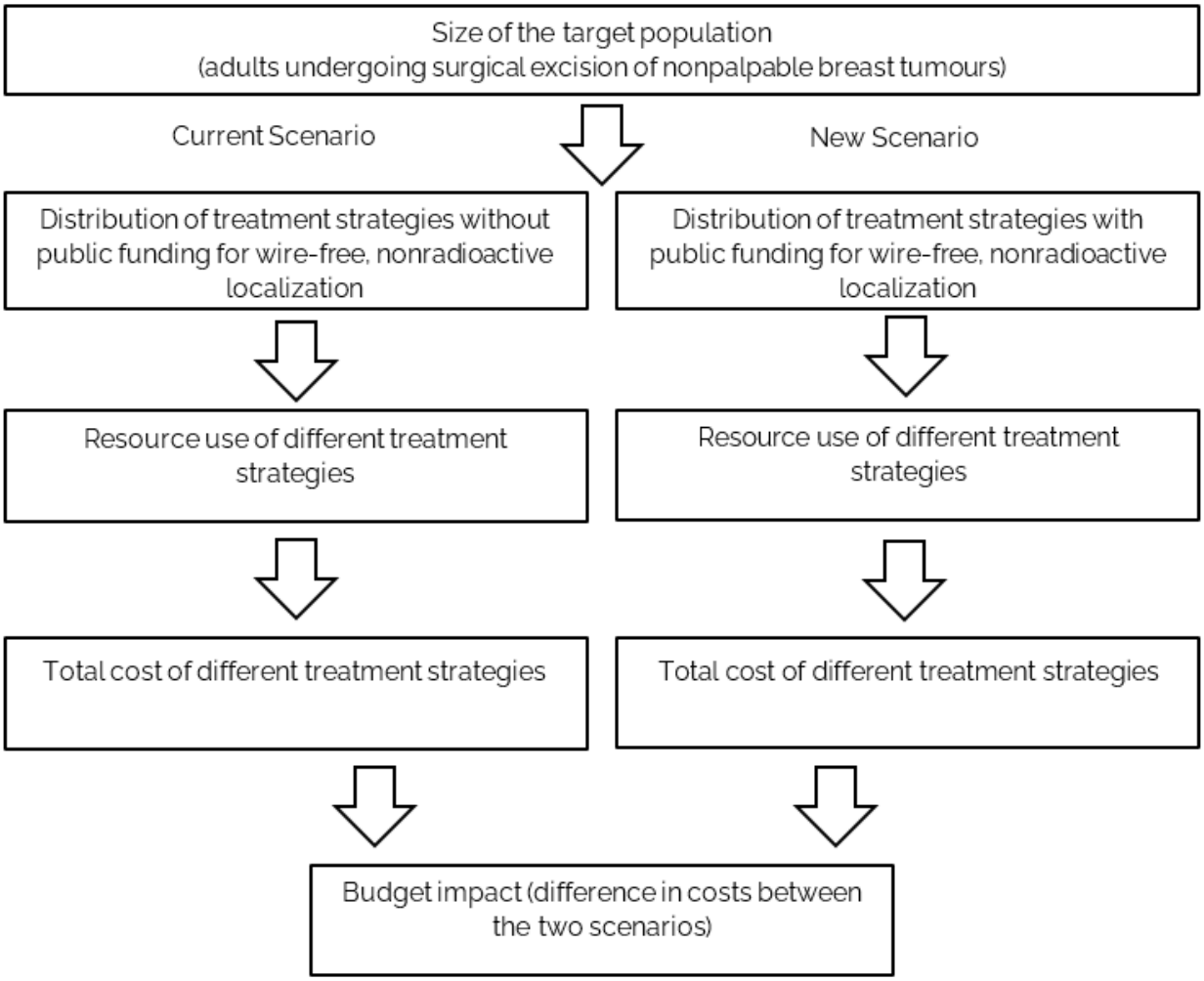

Figure 8: Schematic Model of Budget Impact

Flow chart describing the model for the budget impact analysis. The current scenario explores resource use and total costs without public funding for wire-free, nonradioactive localization techniques. The new scenario explores resource use and total costs with public funding for wire-free, nonradioactive localization techniques. The budget impact is the difference in cost between the two scenarios.

Key Assumptions

- We assumed no difference in the rate of adverse events between wire-free, nonradioactive localization techniques and wire-guided or radioactive seed localization. This assumption was based on our clinical evidence review, which found little to no difference in the rate of postoperative complications when comparing wire-free, nonradioactive localization techniques with wire-guided or radioactive seed localization (GRADE: Moderate)
- We did not consider differences in re-excision rate between wire-free, nonradioactive localization techniques and wire-guided or radioactive seed localization owing to mixed evidence on this outcome in the clinical evidence review
    - We relaxed this assumption in a scenario analysis that considered a different re-excision rate for each localization technique

- We assumed that surgery and operating room costs related to the surgical excision of nonpalpable breast tumours were not impacted by the method of localization except in the case of radioactive seed localization, which requires radiation-related monitoring
- We assumed that costs would remain constant throughout the study time horizon of 5 years

Target Population

The target population in our analysis was adults undergoing surgical excision of nonpalpable breast tumours. We estimated the number of localizations occurring in Ontario using administrative data from the Ontario Health Insurance Plan (OHIP) Schedule of Benefits database, accessed through IntelliHealth Ontario.[59]

First, we identified the number of patients undergoing surgical excision of breast tumours using the following two OHIP billing codes:

- R107: tumour or tissue for diagnostic biopsy and/or treatment, e.g., carcinoma, fibroadenoma or fibrocystic disease (single or multiple - same breast)
- R111: partial mastectomy or wedge resection for treatment of breast disease, with or without biopsy

Next, we identified the number of breast tumour localizations performed using the billing code E525, which can be claimed alongside R107 or R111 to indicate whether the procedure was done using wire-guided or radioactive seed localization:

- E525: after localization with mammographic wire or radioactive seeds

We sourced all patient visits with claims for any of the billing codes R111, R107, and E525 between January 1, 2014, and March 30, 2019 (the latest date we were able to source data for). During this period, when R107 was claimed, the localization billing code E525 was also used for 8.77% of patients. When R111 was claimed, billing code E525 was also used for 56.29% of patients. These percentages were consistent throughout the period for which data were available but varied by site. In 2018, we observed 7,339 visits for which billing code E525 was claimed. We also observed a consistent increase in the number of E525 claims year over year (2014 = 6,879; 2015 = 6,963; 2016 =7,180; 2017= 7,207; 2018= 7,339). We validated that OHIP billing codes were claimed during surgical excision of breast tumours using the Discharge Abstract Database, accessed through IntelliHealth Ontario (Appendix 8).[60,61]

Owing to the observed increase in the use of the E525 billing code, we predicted the number of localizations occurring during the 5-year model time horizon using a linear model. We calculated lower and upper 95% confidence intervals (CIs) for our predictions of number of localizations. We used the upper and lower CI estimates to conduct scenario analyses on the number of localizations predicted to occur in Ontario over the next 5 years (2023–2027). Table 16 provides our estimates. All analyses of IntelliHealth Ontario data were conducted using R.[62]

Table 16: Estimated Number of Localizations per Year

	Year 1 (2023)	Year 2 (2024)	Year 3 (2025)	Year 4 (2026)	Year 5 (2027)
Volume	7,829	7,931	8,033	8,135	8,237
Scenario: lower volume	7,153	7,160	7,168	7,175	7,182
Scenario: higher volume	8,506	8,702	8,899	9,096	9,293

Source: Data obtained from IntelliHealth Ontario.

Note: Volume predicted using a linear model. The number of localizations for the lower and higher volume scenarios were sourced using the lower and upper 95% CI of linear model predictions.

Current Intervention Mix

Although several Ontario sites are currently trialing or switching to wire-free, nonradioactive localization techniques,[63-66] the volume of wire-free, nonradioactive localization procedures is unknown and likely low. For the purpose of this analysis, we assumed that all patients in the current scenario would receive either wire-guided or radioactive seed localization as part of usual care. To estimate the proportion of patients receiving radioactive seed localization, we first identified sites currently using radioactive seed localization. Next, using IntelliHealth Ontario data,[60,61] we estimated that 15% of all localizations in the province are currently conducted at these sites.[23,67-70] Therefore, we assumed that 15% of localizations are currently being done with radioactive seed localization. We assumed that if wire-free, nonradioactive localization techniques were not publicly funded, the uptake of radioactive seed localization would increase to 20% after 5 years. This increase in uptake is due to clinician preference to stop using wire-guided localization.[71]

Uptake of the New Intervention and New Intervention Mix

We estimated the uptake of the new wire-free, nonradioactive localization techniques in Ontario to resemble uptake in the United Kingdom, which has a publicly funded health care system similar to Ontario's. Wire-free, nonradioactive localization techniques have had regulatory approval in the United Kingdom since 2017.[39] We based our uptake estimates on a survey of UK breast centres,[72] a National Institute for Health and Care Excellence (NICE) Medtech innovation briefing on magnetic seed localization,[73] and assumptions for the relative volume of sites that adopt innovative localization techniques. Appendix 7 provides a detailed description of our estimation of the uptake of wire-free, nonradioactive localization techniques.

Table 17 provides estimates for the expected uptake of wire-free, nonradioactive localization techniques in Ontario. Owing to the large degree of uncertainty surrounding future uptake, we conducted scenario analyses with lower and higher expected rates of uptake.

Table 17: Estimated Current and Future Uptake of Wire-Free, Nonradioactive Localization Techniques

	Year 1 (2023)	Year 2 (2024)	Year 3 (2025)	Year 4 (2026)	Year 5 (2027)
Current scenario					
Radioactive seed localization	15%	16%	18%	19%	20%
Wire-guided localization	85%	84%	82%	81%	80%
New scenario					
Radioactive seed localization	13%	11%	10%	8%	6%
Wire-guided localization	75%	65%	54%	44%	34%
Wire-free, nonradioactive localization	12%	24%	36%	48%	60%

Resources and Costs

We included material and labour costs related to localization for wire-guided localization, radioactive seed localization, and wire-free, nonradioactive localization techniques. Radiologist and medical radiation technologist time requirements for wire-guided and radioactive seed localization were sourced from a previously published budget impact analysis conducted at an Ontario hospital by Law et al.[70] We assumed that the radiologist and medical radiation technologist time requirements were the same for radioactive seed localization and wire-free nonradioactive localization techniques. This assumption aligns with the result of the budget impact analysis conducted in the Netherlands by Lindenberg et al.[58] We considered the additional labour costs of nuclear medical technologists, nursing, and pathology assistants for radioactive seed localization. We included labour costs related to radioactive seed loss, radioactive seed transection, and radioactive seed "near incidents" (i.e., events that require formal follow-up such as when a radioactive seed is presumed lost).

We sourced the costs of wire plus needle (for wire-guided localization) and radioactive seeds plus needle (for radioactive seed localization) from Law et al.[70] We selected preloaded radioactive seeds for the reference case analysis owing to the decreased risk of radiation exposure and reduced risk of seed loss associated with preloaded seeds compared with manually loaded seeds.[70] We used the material and labour costs of manually loaded radioactive seeds, which are manually loaded prior to localization, in a scenario analysis. We sourced material costs for wire-free, nonradioactive markers or seeds from Davis et al.[74] The authors reported a cost of $400 in 2021 USD for the Magseed seed and $450 in 2021 USD for the Scout radar localization reflector. We assumed that the material and labour costs of the three wire-free, nonradioactive localization devices (i.e., Magseed, MOLLI, and Scout) were equivalent and selected the midpoint of the Magseed and Scout costs. We conducted scenario analyses for a 20% increase and a 20% decrease in the cost of wire-free, nonradioactive markers or seeds.

We conducted scenario analyses for a range of prices of wire-free, nonradioactive markers or seeds. A localization might require the use of bracketing, in which multiple wires, markers, or seeds are needed to localize a single tumour. We estimated that the use of multiple wires, markers, or seeds would occur in 14% of all localizations (Appendix 7).[39,41-43,52,54] Thus, we multiplied the material costs for

wire and needle, radioactive seeds, and wire-free, nonradioactive markers or seeds by 1.14 to account for bracketing. We assumed that each localization was done for a single tumour.

We excluded operating room costs except for nursing labour associated with recording scintigraphic counts during the surgical procedure when radioactive seed localization is used. We assumed that operating room time was comparable between the three techniques. We did not consider additional room turnover costs associated with radioactive seed localization owing to limited data. Additionally, we expected that postoperative care would be similar for all techniques and thus did not consider these costs.

In our reference case analysis, we did not consider capital expenditures required to purchase localization equipment. However, we conducted a scenario analysis that did consider the capital expenditures required to purchase wire-free, nonradioactive localization equipment and radioactive seed localization equipment. We also included start-up costs required to store and handle radioactive seeds.[69] We did not consider the capital costs required to establish the nuclear medicine program required to conduct radioactive seed localization. We assumed that only sites with existing nuclear medicine programs would consider using radioactive seed localization. We excluded capital expenditures for wire-guided localization as the resources required to conduct wire-guided localization are unlikely to be acquired solely for the purpose of localization. For the capital expenditures scenario analysis, we followed Lindenberg et al[58] and a NICE Medtech innovation briefing[73] in assuming that the equipment required to conduct radioactive seed localization and wire-free, nonradioactive localization would have a life span of 5 years.

Patients receiving neoadjuvant chemotherapy prior to surgery commonly receive a biopsy clip to identify the location of the tumour after core biopsy.[75] Clinical experts indicated that wire-free, MRI-compatible nonradioactive localization devices can be used instead of a biopsy clip (email communication, June 15, 2022). We sourced the material and overhead costs of a biopsy clip from Lindenberg et al.[58] We sourced the frequency of neoadjuvant chemotherapy in Ontario (5.7%) from Powis et al.[76] We used the health care component of the Canadian Consumer Price Index to adjust costs to present values when they were not available in 2022 Canadian dollars.[77]

Table 18 provides the cost inputs for the reference case. Appendix 7 provides a detailed description of the components of each cost input and how each cost input was calculated.

Table 18: Reference Case Cost Inputs

Variable	Unit cost, $[a]	Duration or quantity	Total cost, $[a]	Reference
Wire-guided localization				
Wire and needle	27.84	1.14[b]	31.73	Law et al, 2021[70]
Additional disposables required for localization	33.78	1	33.78	Law et al, 2021[70]
Medical radiation technologist labour	50.10/h	40 min	33.40	CAMRT salary scale[78]; Law et al, 2021[70]

Variable	Unit cost, $[a]	Duration or quantity	Total cost, $[a]	Reference
Diagnostic radiologist labour	344.30/h	17.63 min	101.17	Law et al, 2021[70]; Zhang et al, 2017[69]
Transportation from breast imaging unit to surgical unit by porter	25.11/h	10 min	4.19	Law et al, 2021[70]; St. Joseph's Health Care job posting[79]
Radioactive seed localization				
Preloaded radioactive seed and needle	143.29	1.14[b]	163.35	Law et al, 2021[70]
Additional disposables required for localization	33.78	1	33.78	Law et al, 2021[70]
Medical radiation technologist labour	50.10/h	35 min	29.23	CAMRT salary scale[78]; Law et al, 2021[70]
Diagnostic radiologist labour	344.30/h	17.25 min	100.42	Law et al, 2021[70]; Zhang et al, 2017[69]
Nuclear medicine technologist labour	50.10/h	18.35 min	15.30	CAMRT salary scale[78]; Law et al, 2021[70]
Nursing labour for radioactive seed monitoring	52.67/h	3 min	2.63	Law et al, 2021[70]; Ontario Nursing Association[80]
Pathology assistant for seed retrieval and radiation survey	42.16/h	10 min	7.03	Law et al, 2021[70]
Seed loss, transection, or "near incidents"	30.10	1	30.10	Lindenberg et al, 2020[58]
Wire-free, nonradioactive localization				
Marker or seed	535.30	1.14[b]	610.24	Davis et al, 2021[74]
Additional disposables required for localization	33.78	1	33.78	Law et al, 2021[70]
Diagnostic radiologist labour	344.30/h	17.25 min	100.42	Law et al, 2021[70]; Zhang et al, 2017[69]
Medical radiation technologist labour	50.10/h	35 min	29.23	CAMRT salary scale[78]; Law et al, 2021[70]

Note: All labour costs except porter costs include 30% additional costs for benefits.

Abbreviation: CAMRT, Canadian Association of Medical Radiation Technologists.

[a]In 2022 Canadian dollars.

[b]The material costs for wires, radioactive seeds, and wire-free, nonradioactive markers or seeds have been multiplied by 1.14 to account for the 14% of localizations that we estimated would require bracketing.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and scenario analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our scenario analyses explored how the results were affected by varying input parameters and model assumptions. We coded the budget impact analysis deterministically using Microsoft Excel.[81] We provide the following results for the reference case analysis: provincial cost, cost per localization, and costs at a representative Ontario site. Table 19 provides the cost inputs for the scenario analyses. Appendix 7 provides a detailed description of the components of each cost input and how each cost input was calculated.

We conducted the following scenario analyses:

1. Low volume of localizations
    - We estimated a low volume of localizations from the lower 95% CI of the linear model used to estimate localization volume (reference case: year 1 = 7,829, year 2 = 7,931, year 3 = 8,033, year 4 = 8,135, year 5 = 8,237; scenario 1: year 1 = 7,153, year 2 = 7,160, year 3 = 7,168, year 4 = 7,175, year 5 = 7,182)
2. High volume of localizations
    - We estimated a high volume of localizations from the upper 95% CI of the linear model used to estimate localization volume (reference case: year 1 = 7,829, year 2 = 7,931, year 3 = 8,033, year 4 = 8,135, year 5 = 8,237; scenario 2: year 1 = 8,506, year 2 = 8,702, year 3 = 8,899, year 4 = 9,096, year 5= 9,293)
3. Increased uptake of wire-free, nonradioactive localization techniques
    - We assumed that the uptake of wire-free, nonradioactive localization techniques would increase by 15% each year (reference case: year 1 = 12%, year 2 = 24%, year 3 = 36%, year 4 = 48%, year 5 = 60%; scenario 3: year 1 = 15%, year 2 = 30%, year 3 = 45%, year 4 = 60%, year 5 = 75%)
4. Decreased uptake of wire-free, nonradioactive localization techniques
    - We assumed that the uptake of wire-free, nonradioactive localization techniques would increase by 9% each year (reference case: year 1 = 12%, year 2 = 24%, year 3 = 36%, year 4 = 48%, year 5 = 60%; scenario 4: year 1 = 9%, year 2 = 18%, year 3 = 27%, year 4 = 36%, year 5 = 45%)
5. Manually loaded radioactive seeds
    - We replaced the cost of acquiring preloaded radioactive seeds with the cost of manually loaded radioactive seed using costs sourced from Law et al[70] and Zhang et al[69]
6. Capital expenditures at a representative site
    - We used IntelliHealth Ontario data to estimate the volume of localizations occurring at a representative site (median site volume = 131 localizations, increasing each year by 1.3%) and evenly distributed the costs of capital expenditures across the localizations conducted over 5 years

7. Capital expenditures at a high-volume site
    - We used IntelliHealth Ontario data to estimate the volume of localizations occurring at a high-volume site (75th quantile volume = 197 localizations, increasing each year by 1.3%) and evenly distributed the costs of capital expenditures across the localizations conducted over 5 years
8. Capital expenditures at a low-volume site
    - We used IntelliHealth Ontario data to estimate the volume of localizations occurring at a low-volume site (25th quantile volume = 60 localizations, increasing each year by 1.3%) and evenly distributed the costs of capital expenditures across the localizations conducted over 5 years
9. Different re-excision rate for each localization technique
    - We used estimates of re-excision rates from our clinical evidence review (11.2% for wire-free, nonradioactive localization; 15.4%, for wire-guided localization; and 15.8% for radioactive seed localization; see Appendix 7 for detailed calculations). We sourced hospital costs of re-excision from the Ontario Case Costing Initiative database[82]
10. Higher cost to acquire wire-free, nonradioactive markers or seeds
    - We assumed a 20% higher cost to acquire wire-free nonradioactive markers or seeds (reference case: $610.24; scenario 10: $732.29)
11. Lower cost to acquire wire-free, nonradioactive markers and seeds
    - We assumed a 20% lower cost to acquire wire-free, nonradioactive markers or seeds (reference case: $610.24; scenario 11: $488.19)
12. Replacing biopsy clip placed after core biopsy with MRI-compatible wire-free, nonradioactive marker or seed
    - We assumed that 5.7% of individuals receiving neoadjuvant chemotherapy prior to surgery would receive a wire-free, nonradioactive marker or seed instead of a biopsy clip

Apart from the modifications listed above, the scenario analyses used the same model parameters as the reference case. Results for the capital expenditures scenario analyses are reported on a per-site level.

Table 19 provides the cost inputs for the scenario analyses. Appendix 7 provides a detailed description of the components of each cost input and how each cost input was calculated.

Table 19: Scenario Analysis Cost Inputs

Variable	Unit cost, $[a]	Duration or quantity	Total cost, $[a]	Reference
Incorporating the difference in re-excision rate between localization techniques				
Re-excision cost (breast-conserving surgery or mastectomy)	4,862.59	1	4,862.59	OCCI[82]; OHIP Schedule of Benefits[83]; Pataky et al, 2016[84]
Manually loaded radioactive seed				
Material cost of manually loaded seed	32.16	1.14[b]	36.66	Law et al, 2021[70]; Zhang et al, 2017[69]
Marker prior to neoadjuvant chemotherapy				
Additional cost for biopsy clip placed after core biopsy	239.93	1	239.93	Lindenberg et al, 2020[58]
Including capital expenditures				
Radioactive seed localization equipment	57,530.52	1	57,530.52	Zhang et al, 2017[69]
Wire-free, nonradioactive localization equipment	45,666.79	1	45,666.79	Lindenberg et al, 2020[58]

Abbreviations: OCCI: Ontario Case Costing Initiative; OHIP, Ontario Health Insurance Plan.

[a]In 2022 Canadian dollars.

[b]The material costs for wires, radioactive seeds, and wire-free, nonradioactive markers or seeds have been multiplied by 1.14 to account for the 14% of localizations that we estimated would require bracketing.

Results

Reference Case

Table 20 provides the results of the reference case analysis (see Appendix 9 for detailed results). We estimated that the cost of publicly funding wire-free, nonradioactive localization techniques would range from an additional $0.51 million in year 1 to $2.61 million in year 5, for a total of $7.73 million over 5 years. In the scenario in which wire-free, nonradioactive localization techniques were publicly funded, we estimated a decrease in labour-related costs (−$0.28 million) and an increase in material-related costs ($8.01 million). We estimated that 40,165 localizations would occur during the 5-year study period. When we considered that wire-free, nonradioactive localization techniques would be publicly funded, we estimated that 14,582 of the 40,165 localizations would be conducted using wire-free, nonradioactive localization techniques.

COST PER LOCALIZATION

We estimated the cost per localization to be $773.67 for wire-free, nonradioactive localization; $381.84 for radioactive seed localization; and $204.27 for wire-guided localization. Labour costs were $129.65 for wire-free, nonradioactive localization; $184.71 for radioactive seed localization; and $138.76 for wire-guided localization. Material costs were $644.02 for wire-free, nonradioactive localization; $197.13 for radioactive seed localization; and $65.51 for wire-guided localization. The higher material costs for wire-free, nonradioactive localization techniques were a result of the higher cost of markers or seeds used in these techniques compared with radioactive seeds and wires.

Table 20: Budget Impact Analysis Results—Reference Case

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Current scenario						
Total cost	1.81	1.85	1.90	1.94	1.98	9.46
RSL	0.45	0.48	0.55	0.59	0.63	2.70
WGL	1.36	1.36	1.35	1.35	1.35	6.76
New scenario						
Total cost	2.31	2.86	3.43	4.00	4.58	17.19
RSL	0.39	0.33	0.31	0.25	0.19	1.47
WGL	1.20	1.05	0.89	0.73	0.57	4.44
Wire-free, nonradioactive localization	0.73	1.47	2.24	3.02	3.82	11.28
Budget impact[b]						
Cost difference	0.51	1.01	1.53	2.06	2.61	7.73

Abbreviations: RSL: radioactive seed localization; WGL: wire-guided localization.

[a]In 2022 Canadian dollars.

[b]Results may appear inexact due to rounding.

COST OF LOCALIZATION AT A REPRESENTATIVE SITE

We estimated the 5-year cost, excluding capital expenditures, of conducting localization at a representative site (assuming an annual volume of 131 localizations per year, increasing each year by 1.3%) using wire-free, nonradioactive localization techniques to be $519,958. The cost would be $256,622 for radioactive seed localization and $137,283 for wire-guided localization.

Scenario Analyses

Table 21 provides the results of the scenario analyses. The estimates of the total budget impact over 5 years ranged from $4.69 million in scenario 9 (different re-excision rates) to $9.70 million in scenario 3 (increased uptake of wire-free, nonradioactive localization techniques). The model was sensitive to changes in assumptions regarding the uptake of wire-free, nonradioactive localization techniques,

the cost of a wire-free, nonradioactive marker or seed, the size of the population receiving localization, the re-excision rate, and the inclusion of capital expenditures.

In scenario 10 (20% higher cost to acquire wire-free, nonradioactive markers or seeds), the per-localization cost increased from $773.67 to $895.72. In scenario 11 (20% lower cost to acquire wire-free, nonradioactive markers or seeds), the per-localization cost was $651.62.

Including capital expenditures, which are funded through hospitals' global budgets, increased our estimates of the total budget impact compared with the reference case by 10% over 5 years. At a representative site, if capital expenditures are included, the cost of wire-free, nonradioactive localization would increase from $519,958 to $566,835, and the cost of radioactive seed localization would increase from $256,622 to $ $314,151 (Appendix 9, Table A22). For a site considering switching from wire-guided to wire-free, nonradioactive localization, the 5-year additional cost, including capital expenditures, would be $430,775. For a site considering switching from radioactive seed to wire-free, nonradioactive localization, the 5-year additional cost would be $252,408. As the number of localizations conducted at a site increases, capital expenditures are spread out over more cases, resulting in a lower per-localization capital expenditure cost. The scenario analyses of low-volume and high-volume sites demonstrate how the average number of localizations per site impacts the estimate of the cost of capital expenditures.

A site considering alternatives to radioactive seed localization could disinvest from that system and invest in a wire-free, nonradioactive localization system. The costs disinvested from a gamma detector ($57,530.52) could be used to purchase a wire-free, nonradioactive system ($46,879) (Appendix 9, Table A22).

In scenario 9 (lower re-excision rate for wire-free, nonradioactive localization techniques compared with wire-guided and radioactive seed localization), the 5-year budget impact decreased from $7.73 million to $4.69 million. In this scenario analysis, we estimated that there would be 625 fewer re-excisions over our 5-year time horizon.

Table 21: Budget Impact Analysis Results—Scenario Analyses

Scenario	Budget impact, $ million[a]						
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]	% Change[c]
Reference case	0.51	1.01	1.53	2.06	2.61	7.73	0%
1. Low volume of localizations	0.46	0.91	1.37	1.82	2.28	6.84	−11%
2. High volume of localizations	0.55	1.11	1.70	2.31	2.94	8.61	11%
3. Increased uptake of wire-free, nonradioactive localization techniques	0.63	1.27	1.92	2.59	3.28	9.70	26%
4. Decreased uptake of wire-free, nonradioactive localization techniques	0.38	0.75	1.14	1.54	1.94	5.75	−26%
5. Manually loaded radioactive seeds	0.53	1.06	1.61	2.18	2.76	8.14	5%
6. Capital expenditures scenario at a representative site	0.56	1.11	1.68	2.26	2.86	8.47	10%
7. Capital expenditures scenario at a high-volume site	0.54	1.08	1.63	2.19	2.77	8.22	7%
8. Capital expenditures scenario at a low-volume site	0.62	1.23	1.85	2.49	3.15	9.34	21%
9. Different re-excision rate for each localization technique	0.31	0.62	0.93	1.25	1.58	4.69	−39%
10. Higher cost to acquire wire-free, nonradioactive markers or seeds	0.62	1.25	1.89	2.54	3.21	9.51	23%
11. Lower cost to acquire wire-free, nonradioactive markers or seeds	0.39	0.78	1.18	1.59	2.01	5.95	−23%

Scenario	Budget impact, $ million[a]						
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]	% Change[c]
12. Replacing biopsy clip placed after core biopsy with MRI-compatible wire-free, nonradioactive marker or seed	0.49	0.99	1.49	2.01	2.54	7.53	−3%

[a]In 2022 Canadian dollars.

[b]Results may appear inexact due to rounding.

[c]Percent change calculated as the total budget impact of the scenario analysis divided by the total budget impact of the reference case.

Discussion

We conducted a budget impact analysis estimating the 5-year budget impact of publicly funding wire-free, nonradioactive localization techniques to guide surgical excision of nonpalpable breast tumours. We found that publicly funding these techniques in Ontario would increase the provincial budget over the next five years by $7.73 million.

The increased cost of adopting wire-free, nonradioactive localization techniques results primarily from the higher cost of the wire-free, nonradioactive markers or seeds compared with radioactive seeds and wires. In our scenario analyses, we found that the budget impact estimates were most sensitive to the cost of the wire-free, nonradioactive marker or seed; the uptake of wire-free, nonradioactive localization techniques; differing the re-excision rate between localization techniques; and the inclusion of capital expenditures.

Similar to Sreedhar et al,[45] we found that wire-free, nonradioactive localization techniques were more costly than wire-guided localization. Our findings that wire-free, nonradioactive localization techniques were more costly than radioactive seed localization are also comparable to those of Lindenberg et al.[58] Alberta Health Services is currently conducting a budget impact analysis comparing magnetic seed localization with radioactive seed and wire-guided localization (Alberta Health Services, email communication, March 16, 2022).

Wire-free, nonradioactive localization techniques have the potential to improve surgical efficiency because localization does not have to occur on the same day as surgery; rather, it can be performed several days prior to surgery. Sreedhar et al[45] found that unlinking radiology and surgical schedules allowed a rural New Zealand hospital to avoid the need to transport patients across town with wire extending from the breast skin.[45] Zhang et al[69] found that when implementing a radioactive seed localization program in an Ontario hospital, improved efficiency could be achieved by scheduling all localizations on a specific day of the week.[69] Owing to a lack of data, we were unable to quantify the health care system benefits of moving from wired to wire-free localization or to consider the potential quality-of-life improvements associated with wire-free, nonradioactive localization techniques.

Strengths and Limitations

Our analysis has several strengths. We sourced the number of localizations occurring in Ontario from Ontario administrative billing data, and we were able to validate the estimates using inpatient and outpatient visit data. We sourced costs to resemble inputs and resource use incurred in Ontario. We provided cost estimates at provincial, per-site, and per-localization levels. We conducted extensive scenario analyses to understand the impact of assumptions on our budget impact estimates.

Our analysis also has several limitations. Wire-free, nonradioactive localization techniques may be used to conduct procedures other than the localization of nonpalpable breast tumours, such as targeted axillary dissection of the lymph nodes.[73] These uses are outside the scope of our budget impact analysis and thus were not captured in our estimates of the use of wire-free, nonradioactive techniques in Ontario. Additionally, our analysis is limited in that the future uptake of wire-free, nonradioactive localization techniques is highly uncertain; however, we addressed this limitation by conducting scenario analyses on higher and lower uptake rates. Last, the capital expenditures scenario analyses are limited in that equipment purchased to conduct localization may be used for purposes other than those considered in our analyses. and high-volume sites may purchase more than one set of localization equipment.

Conclusions

We estimate that publicly funding wire-free, nonradioactive localization techniques to guide surgical excision of nonpalpable breast tumours over the next 5 years will range from an additional $0.51 million in year 1 to an additional $2.61 million in year 5, for a total 5-year budget impact of $7.73 million. We estimate that 40,165 localizations will occur in Ontario during this 5-year period. If wire-free, nonradioactive localization techniques are publicly funded, we estimate that 14,582 of the 40,165 total localizations will be conducted using wire-free, nonradioactive localization techniques. We estimate the per-localization cost of wire-free, nonradioactive localization techniques to be $773.67, compared with $381.84 for radioactive seed localization and $204.27 for wire-guided localization. We estimate the 5-year cost of conducting localization at a representative site (site volume = 131 localizations, increasing each year by 1.3%) using wire-free, nonradioactive localization techniques to be $519,958, compared with $256,622 for a site using radioactive seed localization and $137,283 for a site using wire-guided localization.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of people with lived experience of undergoing a localization procedure to guide the surgical excision of a nonpalpable breast tumour. Additionally, we examined patient and caregiver perceptions of wire-free, nonradioactive localization techniques.

Background

Exploring patient preferences and values provides unique information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and their personal environment. Engagement also provides insights into how a health condition is managed by the province's health care system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[85-87] Additionally, lived experience can provide information and perspective on the ethical and social implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of people with experience of undergoing a localization procedure for the surgical excision of a nonpalpable breast tumour via direct engagement. The initiative was led by the Patient and Public Partnering team at Ontario Health, and engagement with participants was completed through telephone interviews.

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people who have undergone a localization procedure to guide the surgical excision of a nonpalpable breast tumour in Ontario. We engaged with participants via phone interviews and email correspondence.

We conducted qualitative interviews, as this method of engagement allowed us to explore central themes in the experiences of people who have undergone a localization procedure for the surgical excision of a nonpalpable breast tumour, as well as the experiences of their families and caregivers.[88] The sensitive nature of exploring people's experiences of a health condition and their quality of life further support our choice of methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,[89-92] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed.

We approached a variety of partner organizations, clinical experts, and support groups in Ontario that support people seeking treatment for nonpalpable breast tumours with the goal of increasing public awareness of our engagement activity and connecting with people who wanted to share their lived experience.

Inclusion Criteria

We sought to speak with people who had undergone a localization procedure to guide the surgical excision of a nonpalpable breast tumour. Participants were not required to have had direct experience with wire-free, nonradioactive localization techniques, as we assumed that access to localization procedures could vary across the province.

Exclusion Criteria

We did not set exclusion criteria.

Participants

For this project, we spoke with 20 people in total, 19 of whom had received care for a nonpalpable breast tumour in Ontario. Eighteen had experience with the current standard of care for localization, which includes wire-guided and radioactive seed localization. One participant had experience with magnetic seed localization. We also spoke with one family member who provided insight from a caregiver's perspective.

Participants lived primarily in Southern Ontario, and there was equal representation of individuals from rural and urban settings. Additionally, some participants had received a benign diagnosis, whereas others had received a malignant diagnosis.

APPROACH

At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants verbally and, if requested, in a letter of information (Appendix 10). We then obtained participants' verbal consent before starting the interview. With the participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 20 to 60 minutes. The interview was semi-structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[19] The questions focused on the impact of being diagnosed with a nonpalpable breast tumour, participants' experiences of undergoing a localization procedure, and participants' perceptions of the benefits and limitations of broad access to wire-free, nonradioactive localization in Ontario. Appendix 11 provides our interview guide.

DATA EXTRACTION AND ANALYSIS

We used a modified version of grounded theory to analyze interview transcripts. The grounded theory methodology allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[93,94] We used the qualitative data analysis software program NVivo[95] to identify and interpret patterns in the data. The patterns we identified allowed us to describe the impact of undergoing localization to guide the

surgical excision of a nonpalpable breast tumour on the people we interviewed who had experienced this procedure, as well as on the family member we interviewed.

Results

CARE JOURNEY

Detection of Nonpalpable Breast Tumours

Nonpalpable breast tumours are characterized by their inability to be felt or seen during physical examination. In most cases, nonpalpable breast tumours are detected by medical imaging, and this was the case for the majority of those we interviewed. Several participants described the complex emotions they felt when they were called for additional screening after an abnormal finding.

> *I honestly felt disbelief because of not being able to feel anything and not having breast cancer in my family.*

> *I wasn't all that concerned with the initial callback because my mother had [had] two benign breast cysts. . . . Denial is a great thing.*

> *Actually, it was my very first mammogram! And so, the funniest thing about going the second time was that I had a lot of anxiety. And on that day, I was having a really tough time dealing with it and almost cancelled the appointment. I am so glad I did go for that second one because they told me that there was cancer.*

Following the initial mammogram, most participants reported undergoing additional diagnostic testing, with the most common tests being ultrasound imaging and wire-guided biopsy. A few participants reported having access to magnetic resonance imaging and genetic testing as well. Participants described their experience waiting for the results of the additional tests in the absence any signs or symptoms of breast cancer.

> *I found the waiting, especially for the results of the biopsy, to be one of the most anxious periods because I didn't have any symptoms. So, I felt fine, and yet I knew that the confirmation of a cancer diagnosis would mean big changes in my life, at least temporarily. There was nothing I could do at the time. Do you plan? What do you do? I found that several-week period very anxiety-producing.*

> *I really felt I had to wait until I knew what the results were. Intuitively you kind of feel like, "Well, if they're doing a biopsy, there must be something wrong." So, that's always going to cause some anxiety.*

> *You could tell by what he [the radiologist] was saying that something was there. He told me that he would give me my results within three days one way or the other, and I waited . . . and waited. . . . It was the worst three days of my life.*

In the transition from diagnostic testing to treatment, participants reported that care coordination among medical specialists (e.g., radiologists, breast surgeons) was timely and appropriate. The majority of those interviewed had access to a family doctor and highlighted the impacts, both positive and negative, of the patient–doctor partnership on their care journey.

> *My GP [general practitioner] is very good at getting me results quickly. So, I did get results from the ultrasound and maybe a copy of the report pretty quickly from him.*
>
> *We should be able to monitor our health through family doctors and nurse practitioners. Just going in and actually talking things through makes you feel as if your health care is being taken seriously, and you have the opportunity to actually discuss things that may not be significant right away.*
>
> *When that report came back to my family doctor, it was probably one of the worst experiences I've ever had with the doctor. So, when I had another appointment, I requested that the results go to my gynaecologist, who was kind enough to give me those results and refer me to a surgeon.*
>
> *The family doctor was very helpful. She took the time, without an appointment, to call me to go through and share similar patient experiences and diagnoses/prognoses.*

Access to Information and Shared Decision-Making

Some participants had prior knowledge of cancer care services and patient navigation tools through their professional backgrounds or experience as a caregiver. However, most first learned about the localization procedure and related treatment options around the time of diagnosis.

In both cases, participants highlighted the value of medical expertise and having access to information about the procedure. Some participants also sought out more information through online resources, which further encouraged help-seeking behaviour.

> *[The localization procedure] was reviewed with me when they did the biopsy test. They explained to me that if it was in fact cancer, they would put a seed for the surgeon to know where exactly it's located. It was very helpful! I have never gone through anything like this; I had no idea what I was heading for. Everything that they offered to me was very helpful, and I really appreciated it.*
>
> *I have a biology background, so I need to get as much information as possible on everything. I find the Mayo Clinic website to be really helpful; they have really detailed information on how the procedure goes and everything.*
>
> *I just wanted to understand. After everything that was new, I would get on my computer and research it.*
>
> *Actually, there was a* Time *magazine article that came out, and it was all about different breast tumours in their different stages. I read that to learn more about my own results.*

When exploring surgical options, those we spoke to relied primarily on the information and guidance provided by their surgeon. In other instances of shared decision-making, participants considered the general prognosis, the invasiveness of the surgery, and personal cosmetic preferences before proceeding with a surgical option.

> *They did all kinds of other testing, and then the surgeon explained the localization procedure. I wasn't quite fond of that, but I just wanted the tumour out. So, I said, "Whatever you're going to do to me, I'll participate."*
>
> *I kind of figured that it was best to go with the breast-conserving surgery. I thought that was the better option for me because I just couldn't imagine losing my breasts if I didn't have to.*
>
> *The deciding factor for me was when he [the surgeon] said that in terms of surviving cancer, it wasn't really that different whether I had a mastectomy or not, but there could be some impact from radiation. That helped me a great deal.*
>
> *I very seriously wanted to have a double mastectomy because I just wanted to be absolutely certain that I didn't have cancer. It was not something that was medically necessary, but it was something that I could opt for in terms of quality of life.*

LOCALIZATION

Most participants underwent wire-guided or radioactive seed localization in preparation for their breast-conserving surgery. Two participants had experience with more than one localization technique owing to a recurring nonpalpable breast tumour.

Participants who underwent wire-guided localization often arrived at the radiology unit in the morning in preparation for their breast surgery, which was typically scheduled in the afternoon.

> *So, that day my surgery was booked at 1:45 p.m., but I was told to be there earlier because I had two procedures: one was the wire localization, and the other one was the sentinel node. So, we actually had to be there at 7:00 a.m.*
>
> *You go first thing in the morning, you sit and wait, and then they call your name to do the localization. You come back out, and it's all taped to you . . . so you're being careful when you sit and wait. Then another procedure occurred at midday where they inject you with the dye. Then you've got to wait, wait, and wait. Finally, you go into surgery, which all went very smoothly.*

In contrast, participants who underwent radioactive or magnetic seed localization reported having the procedure two to seven days prior to their scheduled breast surgery.

> *You can get it done in advance. . . like, it's done a couple of days before surgery. I would check in and wait outside in the waiting room. Then I was led into a room . . . where there was a certain needle with pain medication, and at the same time at the end of the needle would be the radioactive seed. When they pulled out the needle, it left the seed in there. . . . This was actually really well done. Then I had to walk over to the other half of the hospital immediately after the placement to get a mammogram. After that, it's not even a week's wait.*

THE IMPACT OF LOCALIZATION ON PATIENTS AND CAREGIVERS

Physical Impacts

Most participants reported not experiencing complications following their localization procedure and felt that the procedure contributed to a positive surgical outcome. In cases of poor surgical outcomes (e.g., re-excision, lymphedema, surgical site infection, poor cosmesis), participants reported that although these outcomes had a considerable impact on their experience as a patient, they did not attribute these outcomes solely to the localization procedure.

> *Well, you know what? They go in there; they do what they can. The benefit is that it was a very successful surgery. We had very clear margins, we didn't have to do it again, I didn't have an infection, and I didn't have to go in and have drainage tubes put in. There were all kinds of things that went perfectly right.*

> *It did take two surgeries to get it all out because the margins weren't clear, but it wasn't a particularly traumatic situation.*

> *No, I didn't have any complications. No complications whatsoever, and it actually went pretty well. I mean, obviously it was like an outpatient surgery type of thing. The doctor came to see me afterwards and explained that she was pretty sure she got everything.*

> *No, there were no complications. This is day four after surgery, and I feel really good. It hasn't impacted my routine.*

However, pain management was a prominent theme, particularly for those who underwent wire-guided localization. Participants described not receiving anaesthetic for the procedure, as well as experiencing discomfort, and in some instances substantial pain, during the wire insertion.

> *I don't understand why there's no pain management throughout the whole thing. Even if I probably wouldn't have taken it, there should be some level of pain management offered. . . . The people were great, but this was something they do every day. For them, it's a procedure, and they do it all the time. For me, it was really scary without anaesthetic.*

> *For me, the localization was the worst part of the whole procedure because it was not only incredibly painful, but it was also because of the location of where they believed my tumour was. It really was a challenge.*

Many also described considerable discomfort following wire-guided localization, while they were awaiting surgery. Participants spoke of having an acute awareness of the risk of the wire dislodging or fracturing and having to limit their mobility following the procedure to reduce this risk. This experience negatively impacted their experience as a patient.

> *So, now they've inserted the wire into my breast—again, no anaesthetic—they just shove it in there, and you can feel it wrapping around this tumour. And then you go in and get this other procedure where you've got this wire taped to your tummy, and you really can't move around. Every time it does move, you can feel it pulling inside your breast.*

> *I had half of my procedure done at one hospital, and then they brought me to another hospital. I literally had to get on my hands [and position myself] upside down in the car; I recall that being very painful.*

> *That [wire-guided localization] certainly impacted my mobility throughout the day and made me feel more like a patient because I had that procedure, and I was in a gown unlike other people who were waiting for surgery, who were still dressed. So, that ended up being uncomfortable, but I wanted that surgery, so I just put up with it.*

Participants who underwent radioactive or magnetic seed localization described pain or discomfort during the procedure as moderate, and some indicated that they did not experience any discomfort. Overall, it appeared that participants who underwent wire-guided localization experienced more pain and discomfort than those who underwent radioactive or magnetic seed localization.

> *I must say, that was done with a very [minimal] amount of pain, really not much more than a needle prick. I have absolutely no complaints; there was no pain, no discomfort, no oozing, nothing.*

> *The only thing I found inaccurate was the level of pain. Actually, somebody told me that the pain was just going to be like a pinch, and it was a lot more painful than I expected it to be. It's still only for, like, 24 hours, but I was in more pain than I expected to be from it.*

> *It actually went very well. I did not have any pain whatsoever, and it wasn't uncomfortable. It was over within maybe 15, 20 minutes? It was just a procedure, and it was very easy.*

> *I mean, the needle for freezing always causes a little bit of discomfort, but afterwards there was nothing. I mean, I had a bruise, but yeah . . . it was pain free.*

All participants highlighted the importance of patient-centred care and believed that improved communication from the radiologist and other members of the care team could improve people's experience of the localization procedure.

> *The MRI biopsy was painful, but I was ready for it mentally and physically. I thought it [the localization procedure] would be similar, but it wasn't. Maybe a better description and preparation for people who are going to get the localization to better prepare [would help].*

> *I just think I was uninformed. I think [it would have helped] if I had talked to someone prior to that and known what was going to happen. Maybe it would have made me more anxious, but I think sometimes having the knowledge gives you more power over it.*

Emotional Impacts

Localization was often viewed as a step toward breast-conserving surgery, which helped participants process fears related to malignancy. Some participants said they had difficulty navigating the uncertainty of their diagnosis in the absence of physical symptoms and before any procedures had

been scheduled, with some reporting feeling unable to share their condition with family members or other support people. However, the localization procedure was seen as a confirmation of their condition that made them feel more comfortable sharing their health status with others.

> *I didn't want to tell my kids until I knew for sure. So, I was kind of hiding it from them, which was really hard to do sometimes.*

> *I had a daughter who was just finishing high school and one who was working. But I didn't want to scare them, so it was just my husband and [me] going through it all together.*

> *The part that was easier in the lumpectomy was that I knew what was going to happen next; I knew I was going to have surgery. I had so much more confusion about what was happening at the testing stages than I did in the actual surgical stages. I didn't like it. There's so much I didn't know precancer; postcancer, you know you have cancer and what you're dealing with.*

One participant spoke about how her mother's experience undergoing a wire-guided localization impacted her perception and experience of the procedure.

> *I remember, too, for my mother when she went through it [that] she came out of the hospital, and she was just as pale as a ghost. She said, "Oh my god, I never want to do anything like that again." And I recall that vividly. I don't know if part of me going into this was thinking that it was going to hurt, but I threw up after it was finished. I'm generally a pretty pain-tolerant person, but that was a very overwhelming experience to have done. . . . We made it through though.*

A few participants reported not having the details of the localization procedure explained to them (i.e., that localization and surgery are two separate procedures, that the localization procedure is conducted first, and that there is usually a wait time between localization and surgery) or could not recall if the details had been provided to them. These participants reported that this lack of communication negatively impacted their experience as a patient.

> *I was extremely anxious. I thought I was going for the surgery at that point, but it was much later in the day. Again, I think if he [the surgeon] [had] informed me of what was going to happen throughout the day, it would have probably helped with some of that anxiety.*

> *I thought maybe I was going to surgery, but there was no way of finding information; [the hospital is] not set up to do that. Nobody tells you this is step 1 of the 16-step process.*

Participants also highlighted that support from family members, friends, and online cancer survivor support groups helped them process the emotional impact of the localization procedure and subsequent medical interventions.

> *As far as support? Definitely my family; I have a very big family, and one of my nieces had gone through the process 13 years ago. She was very supportive of me.*

I'm married, and my husband is very supportive. And so are my children.

I relied on my family and direct circle of real friends. It's actually quite amazing how many people I actually already know that have been confronted with breast cancer; you tend to reach out to them.

I got together with a whole bunch of women who were breast cancer patients, and a lot of these people were doing exercise after breast cancer and chemo.

Impacts on Life and Work

Participants spoke about the impacts of treatment on their life in general and on their work life. Several participants spoke about the challenges of navigating the initial uncertainty when there was suspicion of a nonpalpable breast tumour. In the absence of other signs or symptoms, participants felt that this initial finding was disruptive to their lives and that the uncertainty surrounding the diagnosis made it challenging to plan. Participants reported having to cancel travel plans and adjust their work schedules to accommodate additional testing.

I had a trip planned with a choir that I belonged to. We were going to be touring Europe, and that had been planned for years. So, I mentioned that to the surgeon, and he said, "You want to get this taken care of. I'll sign whatever [needs] to be signed to say that." And you know, afterwards, when we talked about the wait time between appointments, the message was, "It's actually a very slowly growing tumour."

I remember calling her [a senior executive at work] to say, "I have had a diagnosis, and now I'm going to be seeing the oncologist to discuss with me what is going to happen next." I didn't tell my colleagues yet, just her. I remember people asking me when I got my diagnosis, "OK, so you're going to take a leave of absence now that you have a diagnosis?" And I remember being surprised because that had never occurred to me; it was important for me to keep on working.

Overall, participants felt supported by their social networks as they prepared for their breast-conserving surgery. They described instances where employers, family members, and friends helped them access care, travel to appointments, and understand preoperative care instructions.

I had a friend come with me to that first surgical appointment to meet with the breast surgeon and a couple of other appointments, too. My friend had done a lot of research, and so she asked all the questions, which was great. I didn't even think to do anything because I was in a weird headspace for a while there.

My husband is a biomedical technologist, so it was supportive not only having him there, but he knew so many staff members. I was very grateful and very, very lucky.

WIRE-FREE, NONRADIOACTIVE LOCALIZATION TECHNIQUES

All participants were presented with a general overview of the wire-free, nonradioactive localization techniques under review. They were then asked to share their perceptions of these procedures. They were also asked to consider, based on their lived experience and values, what impact access to this type of localization would have had on them and their families, and what impact it might have on others undergoing a localization procedure.

Perceived Benefits

Participants responded quite favourably to the idea of wire-free, nonradioactive localization being widely available. Key factors that informed this view were the perceptions that the technology would be clinically effective and minimally invasive.

> *It sounds like injecting a little seed is much more preferable to walking around with a wire. So, the caveat to this is, is the seed effective? As a patient, if it does do all those things [that it is supposed to do], then yeah! You're going to save time, and you won't have to do this other horrifying procedure.*

> *My mother-in-law had breast cancer about 10 years ago, and what they did back then was that they inserted wires into the breast, and for her, that was the most painful thing of the whole experience. Where now, they just insert this little seed that you don't even know is there. They've made great progress.*

The fact that wire-free, nonradioactive localization techniques allow the localization procedure to be decoupled from the surgical procedure was also viewed favourably. Although many participants reported valuing having fewer appointments, they also noted that in the early stages of treatment, patients are presented with a lot of information, which can be overwhelming. Thus, some participants felt that separating the localization procedure from the surgery could afford them more time to process information and advocate for their care preferences.

> *If there was a two- or three-day gap between the surgery and the implant, I probably would have been less anxious because after all that stuff that's going through your mind, you're not even thinking about outcomes and prognosis; you're just thinking about the process.*

> *So, would that mean the turnaround in the hospital on the day of the surgery would be a lot faster? I think that would have been amazing just because it was a very early morning to get everything going, which is fine, but the thought [of separating the localization procedure from the surgical procedure] would be of high interest.*

> *I'm very interested and given the delay and the fact that I had to show up for surgery 4 hours beforehand, if I had [had] an option about that prior to the procedure, and it wasn't linked to the date of the surgery, I would have very much welcomed that.*

Some participants felt that wire-free, nonradioactive localization techniques had the potential to improve care coordination between medical specialists. This view was expressed primarily by those who had undergone wire-guided localization, some of whom experienced delays on the day of their procedures. For example, one participant had not been informed of the need to arrive early for the localization procedure and nearly had the surgical procedure cancelled, and another's surgery was delayed owing to an unexpected change in the surgeon's schedule, leaving the participant alone and fasting for hours longer than had been planned. Lack of communication and delays were reported as having a negative impact on participants' experiences as a patient.

> *I was upset because. there was somebody that was meant to do this [wire-guided localization] for me. . . . I didn't know what happened that day in the hospital, but she*

> *[the radiologist] wasn't available, so they had somebody else doing it who was not a member of the regular staff. The whole thing wasn't how it should have been.*

Some participants also spoke about delays related to COVID-19 guidance for hospitals. These accounts were positioned as an example of how broad influences on a health care system can affect timely access to surgical care.

> *Because of COVID cancellations. I had to wait till the very last day of my window for the operation, and I did not have any communication in between. I called my surgeon's office every week.*

> *I wouldn't have wanted to wait that long for surgery, but back then, it was like 2 weeks, which is lucky. Now it's like months sometimes, especially with COVID.*

Additional Considerations

When considering the potential to decouple the localization procedure from the surgical procedure, a primary concern raised related to the amount of time between procedures. Many spoke of the psychological burden patients experience in the absence of signs or symptoms and how this may worsen if the localization procedure is scheduled weeks in advance of surgery.

> *I'm thinking that I'd like the idea of a gap between the implant and the surgery itself, but I don't like the idea of waiting for 30 days. I'd get too anxious, and I'd be worried about the progression of the cancer cells.*

> *Weeks with a localization seed in me? I would not like that at all! Also not being able to do what I want to do; you can't go into the pool, you can't go away, you can't jump. . . . For a couple of days, it's really no issue, but not more.*

> *I don't think I would have liked the procedures to be on separate days. It would have meant another trip to the hospital and a separate procedure. And knowing these seeds were there for all that time while waiting for the surgery would be a big issue for me.*

Participants emphasized the importance of patient-centred care, particularly with respect to communication. If the localization and surgical procedures are decoupled, participants felt it would be important for the health care team to clearly explain the purpose of the localization to the patient and to contextualize it within the patient's broader care journey. They felt that a better understanding of the localization technology, the pain management plan, and expected surgical outcomes would help patients advocate for care that aligns with their individual preferences. The general view among those we interviewed was that patient education and information-sharing must be a requirement for the implementation of broadly accessible wire-free, nonradioactive localization techniques, as clear communication encourages informed decision-making and the ability of patients to provide informed consent.

> *I think it's very important for patients to be their own advocate. You have to ask questions, and you have to advocate for yourself for the best kind of treatment. That is so, so very important. Communication is key because it relieves a lot of stress if you know what's going to happen.*

> *In some ways, you kind of just want to get it over with. You don't want to hang around for another 30 days before you have the surgery. But if you know the reason why you need to have that break in between, and you have that option, then that's a good thing.*
>
> *What's most important is communication and advocating for the best treatment that they can give you.*
>
> *I do not consider myself a collaborator in my treatment process. I consider myself the driver, and I expect enough information to be able to make a completely informed decision, and I will do the research to understand.*

Participants also reflected on the importance of equitable access to surgical care and what broad access to wire-free, nonradioactive localization techniques would look like in Ontario. Participants highlighted the impact of out-of-pocket costs on their care journey and that some patients may face barriers when trying to access care. The shared preference among those interviewed was to ensure equitable access to wire-free, nonradioactive localization techniques and not to exacerbate current gaps for underserved populations.

> *In theory, yeah, as long as you can afford it; can you afford the parking? Can you afford the time off? Is someone going to watch your kids? Can your husband take the time off to go with you? So, there's a whole bunch of "what ifs" around that question that have nothing to do with how I feel about having a little seed inside me for three days as opposed to a wire. In theory, I'll take the seed, but it is all the other economic factors around that that need to be considered.*
>
> *Like there's a numbing gel you can get if you can afford it, which we could, but I don't know what people who aren't able to afford it do because nobody asked if we could afford it.*
>
> *I guess the only issue for me is how available it will be and that's a part of why I put my hand up [to participate in this health technology assessment] because I don't live in a major center.*
>
> *You have to be able to drive or have somebody drive you, and that's just like a whole emotional burden on top of everything else you're going through. Costs can really add up if you're talking about being in a hospital environment for 6 hours. You need to pay for food, and if you're driving, then there's parking, etc.*

Discussion

The people we interviewed provided diverse perspectives on the potential for broad access to wire-free, nonradioactive localization techniques to be provided in Ontario. Direct engagement with participants diagnosed with a nonpalpable breast tumour allowed us to thoroughly examine the implications and impact of localization on their health, emotional well-being, and decision-making processes.

Owing to our outreach methodologies, most participants' experiences were with wire-guided or radioactive seed localization. There were few reports of re-excision or the use of multiple localization techniques. As a result, perspectives on wire-free, nonradioactive localization may have been limited.

Despite this limitation, the varied experiences and preferences of those interviewed provided robust narrative data on the current standard of care across Ontario. Participants were able to comment on many aspects of wire-free, nonradioactive techniques, including ethical implications and equitable access to care. In this way, direct engagement through interviews generated a thematic analysis of the diverse perspectives and values of people who have undergone a localization to guide the surgical excision of a nonpalpable breast tumour.

Conclusions

Broad access to wire-free, nonradioactive localization techniques has the potential to substantially impact the lives of people requiring the surgical excision of a nonpalpable breast tumour in Ontario. The people we interviewed responded positively to the potential public funding of wire-free, nonradioactive localization techniques, with perceived benefits focusing primarily on clinical effectiveness, pain management, minimal invasiveness, and scheduling flexibility.

Participants consistently reported feelings of anxiety and fear of malignancy at the time of diagnosis. They felt that wire-free, nonradioactive localization could help mitigate these feelings if the procedure and its role in the care journey are clearly explained to patients. Many participants said that patient education about the localization procedure is a key factor in a positive patient experience, as clear communication can ease anxiety and allow patients to make informed decisions about their care.

While decoupling the localization procedure from the surgical procedure was identified as a benefit, several participants raised concerns about the length of time between procedures, with some reporting that the psychological burden of a diagnosis could worsen during this time. Most reported preferring a minimal delay (i.e., days rather than weeks) between the localization and breast surgery.

Participants also emphasized the importance of equitable access to care. Several stated that efforts should be made to ensure people living in underserved communities are able to access the surgical care they need, including wire-free, nonradioactive localization.

Conclusions of the Health Technology Assessment

The wire-free, nonradioactive localization devices we reviewed are effective and safe for the localization of nonpalpable breast tumours for surgical excision. Compared with wire-guided or radioactive seed localization, magnetic seed localization likely reduces re-excision rate (GRADE: Moderate/Low) and likely results in no difference in postoperative complications or operation time (GRADE: Moderate). Magnetic seed localization also likely reduces patient anxiety in the time period between localization and surgery and likely increases clinician satisfaction (GRADE: Moderate). Reflector-guided localization may have a similar re-excision rate to those of wire-guided and radioactive seed localization (GRADE: Low) and likely has similar postoperative complications and operation time (GRADE: Moderate).

We were unable to determine the cost-effectiveness of wire-free, nonradioactive localization techniques. We estimate that publicly funding these techniques for the surgical excision of nonpalpable breast tumours over the next 5 years will cost an additional $7.73 million. Budget impact estimates were most sensitive to the cost of wire-free, nonradioactive markers or seeds, the uptake of wire-free, nonradioactive localization techniques, and different rates of re-excision for each localization technique.

People we spoke with who had experience of undergoing a localization procedure to guide the surgical excision of a nonpalpable breast tumour reported valuing surgical interventions that are clinically effective, timely, and patient centred. They responded positively to the potential public funding of wire-free, nonradioactive localization techniques and felt that equitable access should be a requirement of implementation.

Abbreviations

BIA	Budget impact analysis
BRCA1	Breast cancer susceptibility gene 1
BRCA2	Breast cancer susceptibility gene 2
CAMRT	Canadian Association of Medical Radiation Technologists
CCI	Canadian Classification of Health Interventions
CEA	Cost-effectiveness analysis
CI	Confidence interval
CPI	Consumer Price Index
DCIS	Ductal carcinoma in situ
FDA	US Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HER2	Human epidermal growth factor receptor 2
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
MOLLI	Magnetic occult lesion localization instrument
MRI	Magnetic resonance imaging
MSL	Magnetic seed localization
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OCCI	Ontario Case Costing Initiative
OHIP	Ontario Health Insurance Plan
OR	Odds ratio
QALY	Quality-adjusted life-year
RR	Relative risk *or* risk ratio
RSL	Radioactive seed localization
SD	Standard deviation
WGL	Wire-guided localization

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Market distribution: When evaluating more than two technologies, the market distribution is the proportion of the population that uses each technology.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Near incident: A situation in which a radioactive seed used in a radioactive seed localization procedure is thought to have been lost and requires formal follow-up.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Appendices

Appendix 1: Literature Search Strategies

Clinical Evidence Search

Search date: May 4, 2022

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2022>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 27, 2022>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 17>, Ovid MEDLINE(R) ALL <1946 to May 03, 2022>

Search strategy:

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1 Mastectomy, Segmental/ (27017)
2 (lumpectom* or ((segmentectom* or quadrantectom* or local excis*) and breast*) or ((limited resection* or local excis* or partial* or segmental*) adj3 mastectom*)).ti,ab,kf. (18230)
3 (breast* adj3 (conserv* or sparing)).ti,ab,kf. (34590)
4 exp Breast Neoplasms/su (105442)
5 (((breast* or mammar*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) and (preoperat* or pre-operat* or preop or pre-op or pre-surg* or presurg* or intraoperat* or intra-operat* or operat* or surg* or excis*)).ti,ab,kf. (178301)
6 Carcinoma, Intraductal, Noninfiltrating/su (4664)
7 (((carcinoma* adj3 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS) and (preoperat* or pre-operat* or preop or pre-op or pre-surg* or presurg* or intraoperat* or intra-operat* or operat* or surg* or excis*)).ti,ab,kf. (22438)
8 Breast/su (7399)
9 (((non-palp* or nonpalp* or impalp* or occult* or soft tissue*) and (breast* or mammar*)) or NPBL or NPBLs or NPBC).ti,ab,kf. (23140)
10 or/1-9 (264922)
11 Fiducial Markers/ (5071)
12 (((non-radioactive* or nonradioactive* or non-radioisotope* or non-nuclear* or nonnuclear* or non-radiat* or nonradiat* or non-isotop* or nonisotop* or non-ioni* or nonioni*) and (locali* or fiducial*)) or NWNI).ti,ab,kf. (4304)
13 ((wirefree* or wire-free* or wireless* or wire-less* or non-wire* or nonwire* or WF) and (locali* or fiducial*)).ti,ab,kf. (1789)
14 Magnets/ or Magnetics/ (65640)
15 ((magnet* or ferromagnet* or ferro-magnet* or electromagnet* or electro-magnet*) adj5 (locali* or marker* or seed* or fiducial*)).ti,ab,kf. (11233)
16 Radar/ (26330)
17 ((radar* or reflector * or infrared* or infra-red*) and (locali* or fiducial*)).ti,ab,kf. (10266)
18 (molli* or scout* or savi or magseed* or endomag*).ti,ab,kf. (13121)
19 (locali* adj (technique* or innovat* or technolog* or system$1)).ti,ab,kf. (4529)

20 or/11-19 (139258)
21 10 and 20 (1611)
22 21 use medall,coch,cctr,clhta,cleed (526)
23 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6067098)
24 22 not 23 (499)
25 exp Animals/ not Humans/ (16600697)
26 24 not 25 (486)
27 limit 26 to english language [Limit not valid in CDSR; records were retained] (467)
28 limit 27 to yr="2014 -Current" (316)
29 exp partial mastectomy/ (31820)
30 (lumpectom* or ((segmentectom* or quadrantectom* or local excis*) and breast*) or ((limited resection* or local excis* or partial* or segmental*) adj3 mastectom*)).tw,kw,kf. (18931)
31 (breast* adj3 (conserv* or sparing)).tw,kw,kf. (34805)
32 exp breast tumor/su (105365)
33 (((breast* or mammar*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) and (preoperat* or pre-operat* or preop or pre-op or pre-surg* or presurg* or intraoperat* or intra-operat* or operat* or surg* or excis*)).tw,kw,kf. (180348)
34 (((carcinoma* adj3 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS) and (preoperat* or pre-operat* or preop or pre-op or pre-surg* or presurg* or intraoperat* or intra-operat* or operat* or surg* or excis*)).tw,kw,kf. (22614)
35 breast/su (7399)
36 (((non-palp* or nonpalp* or impalp* or occult* or soft tissue*) and (breast* or mammar*)) or NPBL or NPBLs or NPBC).tw,kw,kf. (23303)
37 or/29-36 (267097)
38 fiducial marker/ (5071)
39 (((non-radioactive* or nonradioactive* or non-radioisotope* or non-nuclear* or nonnuclear* or non-radiat* or nonradiat* or non-isotop* or nonisotop* or non-ioni* or nonioni*) and (locali* or fiducial*)) or NWNI).tw,kw,kf,dv. (4309)
40 ((wirefree* or wire-free* or wireless* or wire-less* or non-wire* or nonwire* or WF) and (locali* or fiducial*)).tw,kw,kf,dv. (1798)
41 magnet/ or magnetism/ (42659)
42 ((magnet* or ferromagnet* or ferro-magnet* or electromagnet* or electro-magnet*) adj5 (locali* or marker* or seed* or fiducial*)).tw,kw,kf,dv. (11543)
43 telecommunication/ (31689)
44 ((radar* or reflector * or infrared* or infra-red*) and (locali* or fiducial*)).tw,kw,kf,dv. (10319)
45 (molli* or scout* or savi or magseed* or endomag*).tw,kw,kf,dv. (13311)
46 (locali* adj (technique* or innovat* or technolog* or system$1)).tw,kw,kf,dv. (4566)
47 or/38-46 (122568)
48 cancer localization/ (42193)
49 (non-radioactive* or nonradioactive* or non-radioisotope* or non-nuclear* or nonnuclear* or non-radiat* or nonradiat* or non-isotop* or nonisotop* or non-ioni* or nonioni*).tw,kw,kf,dv. (79932)
50 (wirefree* or wire-free* or wireless* or wire-less* or non-wire* or nonwire*).tw,kw,kf,dv. (42853)
51 ((magnet* adj5 (maker* or seed*)) or ferromagnet* or ferro-magnet* or electromagnet* or electro-magnet*).tw,kw,kf,dv. (108354)
52 (radar* or reflector* or infrared* or infra-red*).tw,kw,kf,dv. (362296)
53 or/49-52 (582039)

54 48 and 53 (221)
55 47 or 54 (122681)
56 37 and 55 (1654)
57 56 use emez (1132)
58 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (12510168)
59 57 not 58 (485)
60 (exp animal/ or nonhuman/) not exp human/ (11417620)
61 59 not 60 (460)
62 limit 61 to english language [Limit not valid in CDSR; records were retained] (436)
63 limit 62 to yr="2014 -Current" (286)
64 28 or 63 (602)
65 64 use medall (280)
66 64 use emez (286)
67 64 use coch (1)
68 64 use cctr (35)
69 64 use clhta (0)
70 64 use cleed (0)
71 remove duplicates from 64 (389)

Economic Evaluation and Cost-Effectiveness Search

Search date: May 4, 2022

Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2022>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 27, 2022>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 17>, Ovid MEDLINE(R) ALL <1946 to May 03, 2022>

Search strategy:

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1 Mastectomy, Segmental/ (27017)
2 (lumpectom* or ((segmentectom* or quadrantectom* or local excis*) and breast*) or ((limited resection* or local excis* or partial* or segmental*) adj3 mastectom*)).ti,ab,kf. (18230)
3 (breast* adj3 (conserv* or sparing)).ti,ab,kf. (34590)
4 exp Breast Neoplasms/su (105442)
5 (((breast* or mammar*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) and (preoperat* or pre-operat* or preop or pre-op or pre-surg* or presurg* or intraoperat* or intra-operat* or operat* or surg* or excis*)).ti,ab,kf. (178301)
6 Carcinoma, Intraductal, Noninfiltrating/su (4664)
7 (((carcinoma* adj3 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS) and (preoperat* or pre-operat* or preop or pre-op or pre-surg* or presurg* or intraoperat* or intra-operat* or operat* or surg* or excis*)).ti,ab,kf. (22438)

8 Breast/su (7399)
9 (((non-palp* or nonpalp* or impalp* or occult* or soft tissue*) and (breast* or mammar*)) or NPBL or NPBLs or NPBC).ti,ab,kf. (23140)
10 or/1-9 (264922)
11 Fiducial Markers/ (5071)
12 (((non-radioactive* or nonradioactive* or non-radioisotope* or non-nuclear* or nonnuclear* or non-radiat* or nonradiat* or non-isotop* or nonisotop* or non-ioni* or nonioni*) and (locali* or fiducial*)) or NWNI).ti,ab,kf. (4304)
13 ((wirefree* or wire-free* or wireless* or wire-less* or non-wire* or nonwire* or WF) and (locali* or fiducial*)).ti,ab,kf. (1789)
14 Magnets/ or Magnetics/ (65640)
15 ((magnet* or ferromagnet* or ferro-magnet* or electromagnet* or electro-magnet*) adj5 (locali* or marker* or seed* or fiducial*)).ti,ab,kf. (11233)
16 Radar/ (26330)
17 ((radar* or reflector * or infrared* or infra-red*) and (locali* or fiducial*)).ti,ab,kf. (10266)
18 (molli* or scout* or savi or magseed* or endomag*).ti,ab,kf. (13121)
19 (locali* adj (technique* or innovat* or technolog* or system$1)).ti,ab,kf. (4529)
20 or/11-19 (139258)
21 10 and 20 (1611)
22 21 use coch,clhta,cleed (1)
23 economics/ (263736)
24 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (980696)
25 economics.fs. (467389)
26 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1149886)
27 exp "costs and cost analysis"/ (655553)
28 (cost or costs or costing or costly).ti. (312158)
29 cost effective*.ti,ab,kf. (412707)
30 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (269977)
31 models, economic/ (15315)
32 markov chains/ or monte carlo method/ (99813)
33 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (58502)
34 (markov or markow or monte carlo).ti,ab,kf. (164146)
35 quality-adjusted life years/ (50780)
36 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (100035)
37 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (168781)
38 or/23-37 (3113672)
39 21 and 38 (92)
40 39 use medall,cctr (28)
41 22 or 40 (29)
42 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (6067098)
43 41 not 42 (29)
44 limit 43 to english language [Limit not valid in CDSR; records were retained] (29)
45 limit 44 to yr="2014 -Current" (24)
46 exp partial mastectomy/ (31820)

47 (lumpectom* or ((segmentectom* or quadrantectom* or local excis*) and breast*) or ((limited resection* or local excis* or partial* or segmental*) adj3 mastectom*)).tw,kw,kf. (18931)
48 (breast* adj3 (conserv* or sparing)).tw,kw,kf. (34805)
49 exp breast tumor/su (105365)
50 (((breast* or mammar*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or pre-cancer* or precancer* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) and (preoperat* or pre-operat* or preop or pre-op or pre-surg* or presurg* or intraoperat* or intra-operat* or operat* or surg* or excis*)).tw,kw,kf. (180348)
51 (((carcinoma* adj3 (intraductal* or ductal*)) or ductal hyperplasia* or DCIS) and (preoperat* or pre-operat* or preop or pre-op or pre-surg* or presurg* or intraoperat* or intra-operat* or operat* or surg* or excis*)).tw,kw,kf. (22614)
52 breast/su (7399)
53 (((non-palp* or nonpalp* or impalp* or occult* or soft tissue*) and (breast* or mammar*)) or NPBL or NPBLs or NPBC).tw,kw,kf. (23303)
54 or/46-53 (267097)
55 fiducial marker/ (5071)
56 (((non-radioactive* or nonradioactive* or non-radioisotope* or non-nuclear* or nonnuclear* or non-radiat* or nonradiat* or non-isotop* or nonisotop* or non-ioni* or nonioni*) and (locali* or fiducial*)) or NWNI).tw,kw,kf,dv. (4309)
57 ((wirefree* or wire-free* or wireless* or wire-less* or non-wire* or nonwire* or WF) and (locali* or fiducial*)).tw,kw,kf,dv. (1798)
58 magnet/ or magnetism/ (42659)
59 ((magnet* or ferromagnet* or ferro-magnet* or electromagnet* or electro-magnet*) adj5 (locali* or marker* or seed* or fiducial*)).tw,kw,kf,dv. (11543)
60 telecommunication/ (31689)
61 ((radar* or reflector * or infrared* or infra-red*) and (locali* or fiducial*)).tw,kw,kf,dv. (10319)
62 (molli* or scout* or savi or magseed* or endomag*).tw,kw,kf,dv. (13311)
63 (locali* adj (technique* or innovat* or technolog* or system$1)).tw,kw,kf,dv. (4566)
64 or/55-63 (122568)
65 cancer localization/ (42193)
66 (non-radioactive* or nonradioactive* or non-radioisotope* or non-nuclear* or nonnuclear* or non-radiat* or nonradiat* or non-isotop* or nonisotop* or non-ioni* or nonioni*).tw,kw,kf,dv. (79932)
67 (wirefree* or wire-free* or wireless* or wire-less* or non-wire* or nonwire*).tw,kw,kf,dv. (42853)
68 ((magnet* adj5 (maker* or seed*)) or ferromagnet* or ferro-magnet* or electromagnet* or electro-magnet*).tw,kw,kf,dv. (108354)
69 (radar* or reflector* or infrared* or infra-red*).tw,kw,kf,dv. (362296)
70 or/66-69 (582039)
71 65 and 70 (221)
72 64 or 71 (122681)
73 54 and 72 (1654)
74 Economics/ (263736)
75 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (142062)
76 Economic Aspect/ or exp Economic Evaluation/ (522402)
77 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1170775)
78 exp "Cost"/ (655553)
79 (cost or costs or costing or costly).ti. (312158)
80 cost effective*.tw,kw,kf. (422606)

81 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw,kf. (280724)
82 Monte Carlo Method/ (77756)
83 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (61926)
84 (markov or markow or monte carlo).tw,kw,kf. (167628)
85 Quality-Adjusted Life Years/ (50780)
86 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (103524)
87 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (189796)
88 or/74-87 (2666939)
89 73 and 88 (98)
90 89 use emez (63)
91 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (12510168)
92 90 not 91 (32)
93 limit 92 to english language [Limit not valid in CDSR; records were retained] (32)
94 limit 93 to yr="2014 -Current" (28)
95 45 or 94 (52)
96 95 use medall (19)
97 95 use emez (28)
98 95 use coch (1)
99 95 use cctr (4)
100 95 use cleed (0)
101 95 use clhta (0)
102 remove duplicates from 95 (38)

Grey Literature Search

Performed: May 11–13, 2022

Websites searched: Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, Health Technology Assessment Database, Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services (AGENAS), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used: lumpectomy, lumpectomies, non-palpable, breast conserving, localization, localisation, fiducial, magseed, scout, molli, magnet AND breast, radar AND breast, seed* AND breast marker AND breast*, wirefree, wire-free, non-wire, non-radioactive, nonradioactive, non-radioisotope* or non-nuclear* or nonnuclear* or non-radiat* or nonradiative, ferromagnet, ferro-magnet, electromagnetic, electro-magnetic, infrared, infra-red

Clinical results (included in PRISMA): 13

Economic results (included in PRISMA): 14

Ongoing HTAs (PROSPERO/EUnetHTA/): 0

Ongoing RCTs (clinicaltrials.gov): 36

Appendix 2: Critical Appraisal of Clinical Evidence

Table A1: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Magnetic Seed Versus Wire-Guided Localization—Re-excision Rate

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Dave et al, 2022[39]	Low	Low	Low	Low	Low	Low	Low
Liang et al, 2022[42]	Low	Moderate[b]	Low	No info	Low	Low	Low
Ross et al, 2022[44]	Low	Low	Low	No info	Low	Low	Low
Redfern and Shermis, 2022[43]	Low	Low	Low	Low	Low	Low	Low
Kabeer et al, 2021[40]	Low	Low	Low	Low	Low	Low	Low
Sreedhar et al, 2021[45]	Low	Low	Low	No info	Low	Low	Low
Zacharioudakis et al, 2019[46]	Low	Low	Low	No info	Low	Low	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]Moderate owing to selection bias that occurred after the start of the intervention or analysis, as stated in the ROBINS-I guideline. A few years after the study had begun, a change to the definition of "positive margin" was provided in an updated guideline. As a result, before the adoption of the updated guideline, more patients in the wire-guided and radioactive seed groups underwent re-excision than would have based on the new guideline. Further, the use of magnetic seed localization started after adoption of the new guideline.

Table A2: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Magnetic Seed Versus Wire-Guided Localization—Successful Device Implantation

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Dave et al, 2022[39]	Low	Low	Low	Low	Low	Low	Low
Kelly et al, 2022[41]	No info	No info	No info	No info	No info	No info	Serious[b]
Liang et al, 2022[42]	No info	No info	No info	No info	No info	No info	Cannot be assessed
Ross et al, 2022[44]	No info[c]	No info[c]	No info[c]	No info[c]	No info[c]	No info[c]	Cannot be assessed[c]
Redfern and Shermis, 2022[43]	Low	Low	Low	Low	Low	Low	Low
Kabeer et al, 2021[40]	Low	Low	Low	Low	Low	Low	Low
Micha et al, 2021[54]	Low	Low	Low	Low	Low	Low	Low
Sreedhar et al, 2021[45]	No info	No info	No info	No info	No info	No info	No info
Zacharioudakis et al, 2019[46]	Low	Low	Low	Low	Low	Low	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]Excluded from the analysis 10 magnetic seed localizations in which seeds were displaced and tumours subsequently localized with wire.

[c]No information for control group.

Table A3: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Magnetic Seed Versus Wire-Guided Localization—Device Dislodgement/Migration

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Dave et al, 2022[39]	Low	Low	Low	Low	Low	Low	Low
Kelly et al, 2022[41]	No info	No info	No info	No info	No info	No info	No info
Liang et al, 2022[42]	No info	No info	No info	No info	No info	No info	Cannot be assessed
Ross et al, 2022[44]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be assessed[b]
Redfern and Shermis, 2022[43]	Low	Low	Low	Low	Low	Low	Low
Kabeer et al, 2021[40]	Low	Low	Low	Low	Low	Low	Low
Micha et al, 2021[54]	Low	Low	Low	Low	Low	Low	Low
Sreedhar et al, 2021[45]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be assessed[b]
Zacharioudakis et al, 2019[46]	Low	Low	Low	Low	Low	Low	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]No information for control group.

Table A4: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Magnetic Seed Versus Wire-Guided Localization—Successful Device Retrieval

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Dave et al, 2022[39]	No information	No info	No info	No info	No info	No info	No info
Kelly et al, 2022[41]	Low	Low	Low	Low	Low	Low	Low
Liang et al, 2022[42]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be assessed[b]
Ross et al, 2022[44]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be assessed[b]
Redfern and Shermis, 2022[43]	Low	Low	Low	Low	Low	Low	Low
Kabeer et al, 2021[40]	Low	Low	Low	Low	Low	Low	Low
Micha et al, 2021[54]	Low	Low	Low	Low	Low	Low	Low
Sreedhar et al, 2021[45]	No info	No info	No info	No info	No info	No info	No info
Zacharioudakis et al, 2019[46]	Low	Low	Low	Low	Low	Low	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]No information for control group.

Table A5: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Magnetic Seed Versus Wire-Guided Localization—Operation Time

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Dave et al, 2022[39]	Low	Low	Low	Low	Low	Low	Low
Kelly et al, 2022[41]	Low	low	Low	Low	Low	Low	Low
Liang et al, 2022[42]	No info	No info	No info	No info	No info	No info	No info
Ross et al, 2022[44]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be assessed[b]
Redfern and Shermis, 2022[43]	Low	Low	Low	Low	Low	Low	Low
Kabeer et al, 2021[40]	No info	No info	No info	No info	No info	No info	No info
Micha et al, 2021[54]	No info	No info	No info	No info	No info	No info	No info
Sreedhar et al, 2021[45]	No info	No info	No info	No info	No info	No info	No info
Zacharioudakis et al, 2019[46]	No info	No info	No info	No info	No info	No info	No info

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]No information for control group.

Table A6: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Magnetic Seed Versus Wire-Guided Localization—Postoperative Complications

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Dave et al, 2022[39]	Low	Low	Low	Low	Low	Low	Low
Kelly et al, 2022[41]	No info	No info	No info	No info	No info	No info	No info
Liang et al, 2022[42]	No info	No info	No info	No info	No info	No info	No info
Ross et al, 2022[44*]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be assessed[b]
Redfern and Shermis, 2022[43]	No info	No info	No info	No info	No info	No info	No info
Kabeer et al, 2021[40]	No info	No info	No info	No info	No info	No info	No info
Micha et al, 2021[54]	No info	No info	No info	No info	No info	No info	No info
Sreedhar et al, 2021[45]	Low	Low	Low	Low	Low	Low	Moderate[c]
Zacharioudakis et al, 2019[46]	No info	No info	No info	No info	No info	No info	No info

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]No information for control group.

[c]No details provided for comparison of postoperative complications.

Table A7: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Magnetic Seed Versus Radioactive Seed Localization (Liang et al, 2022)

	Pre-intervention		At intervention	Post-intervention			
Outcome	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Re-excision rate	Low	Moderate[b]	Low	No info	Low	Low	Low
Technical outcomes	No info[c]	No info[c]	No info[c]	No info[c]	No info[c]	No info[c]	Cannot be assessed[c]
Operation time	No info	No info	No info	No info	No info	No info	No info
Adverse events	No info	No info	No info	No info	No info	No info	No info

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

Source: Liang et al 2022.[42]

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]Moderate owing to selection bias that occurred after the start of the intervention or analysis, as stated in the ROBINS-I guideline. A few years after the study had begun, a change to the definition of "positive margin" was provided in an updated guideline. As a result, before the adoption of the updated guideline, more patients in the wire-guided and radioactive seed groups underwent re-excision than would have based on the new guideline. Further, the use of magnetic seed localization started after adoption of the new guideline.

[c]No information for control group.

Table A8: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Reflector-Guided Versus Wire-Guided Localization—Re-excision Rate

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Farha et al, 2022[48]	Moderate[b]	Low	Low	Low	Low	Low	Moderate[c]
Chagpar et al, 2021[47]	Low	Low	Low	Serious[d]	Low	Low	Low
Srour et al, 2021[52]	Low	Low	Low	Serious[d]	Low	Low	Low
Srour et al, 2020[51]	Low	Low	Low	Serious[d]	Low	Low	Low
Lee et al, 2020[49]	Low	Low	Low	Moderate[e]	Low	Low	Moderate[f]

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]Patients with lesions deeper than 5 cm or lesions needing bracketing were localized only with wire, and the number of such cases was not reported.

[c]Unclear whether there were any differences in baseline characteristics or clinicopathological factors, as these were not reported.

[d]The difference between arms of the studies was significant with respect to resection of additional margins or segments.

[e]Margin positivity was based on final shaved margin.

[f]Cavity shave margin reported for total population, not for each group.

Table A9: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Reflector-Guided Versus Wire-Guided Localization—Successful Device Implantation

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Farha et al, 2022[48]	No info	No info	No info	No info	No info	No info	No info
Chagpar et al, 2021[47]	No info	No info	No info	No info	No info	No info	No info
Misbach et al, 2021[50]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be assessed[b]
Srour et al, 2021[52]	No info	No info	No info	No info	No info	No info	No info
Srour et al, 2020[51]	No info	No info	No info	No info	No info	No info	No info
Lee et al, 2020[49]	No info	No info	No info	No info	No info	No info	No info

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]No information for control group.

Table A10: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Reflector-Guided Versus Wire-Guided Localization—Device Dislodgement/Migration

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Farha et al, 2022[48]	No info	No info	No info	No info	No info	No info	No info
Chagpar et al, 2021[47]	No info	No info	No info	No info	No info	No info	No info
Misbach et al, 2021[50]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be assessed[b]
Srour et al, 2021[52]	No info	No info	No info	No info	No info	No info	No info
Srour et al, 2020[51]	No info	No info	No info	No info	No info	No info	No info
Lee et al, 2020[49]	No info	No info	No info	No info	No info	No info	No info

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]No information for control group.

Table A11: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Reflector-Guided Versus Wire-Guided Localization—Successful Device Retrieval

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Farha et al, 2022[48]	No info	No info	No info	No info	No info	No info	No info
Chagpar et al, 2021[47]	No info	No info	No info	No info	No info	No info	No info
Misbach et al, 2021[50]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be assessed[b]
Srour et al, 2021[52]	No info	No info	No info	No info	No info	No info	No info
Srour et al, 2020[51]	No info	No info	No info	No info	No info	No info	No info
Lee et al, 2020[49]	Low	Low	Low	Low	Low	Low	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]No information for control group.

Table A12: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Reflector-Guided Versus Wire-Guided Localization—Operation Time

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Farha et al, 2022[48]	No info	No info	No info	No info	No info	No info	No info
Chagpar et al, 2021[47]	No info	No info	No info	No info	No info	No info	No info
Misbach et al, 2021[50]	Moderate[b]	Low	Low	Low	Low	Low	Low
Srour et al, 2021[52]	Moderate[c]	Low	Low	Low	Low	Low	Low
Srour et al, 2020[51]	Moderate[c]	Low	Low	Low	Low	Low	Low
Lee et al, 2020[49]	Low	Low	Low	Low	Low	Low	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]Authors stated that patients with more extensive disease were more likely to be directed to wire-guided rather than reflector-guided localization. This likely increased operation time in the wire-guided localization group.

[c]The difference between arms of the studies was significant with respect to resection of additional margins or segments, which likely increased operation time in the reflector group.

Table A13: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Reflector-Guided Versus Wire-Guided Localization—Postoperative Complications

	Pre-intervention		At intervention	Post-intervention			
Author, year	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Farha et al, 2022[48]	No info	No info	No info	No info	No info	No info	No info
Chagpar et al, 2021[47]	Moderate[b]	Low	Low	Low	Low	Low	Low
Misbach et al, 2021[50]	No info[c]	No info[c]	No info[c]	No info[c]	No info[c]	No info[c]	Cannot be assessed[c]
Srour et al, 2021[52]	Moderate[b]	Low	Low	Low	Low	Low	Low
Srour et al, 2020[51]	Moderate[b]	Low	Low	Low	Low	Low	Low
Lee et al, 2020[49]	No info	No info	No info	No info	No info	No info	No info

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]The difference between arms of the studies was significant with respect to resection of additional margins or segments, which likely impacted the frequency of postoperative complications among the groups.

[c]No information for control group.

Table A14: Risk of Bias[a] Among Nonrandomized Trials (ROBINS-I Tool) of Reflector-Guided Versus Radioactive Seed Localization

	Pre-intervention		At intervention	Post-intervention			
Outcome	Confounding	Study participation selection	Classification of interventions	Deviations from intended intervention	Missing data	Measurement of outcomes	Selection of reported results
Re-excision rate (3 studies)	Low	Low	Low	Serious[b]	Low	Low	Low
Technical outcomes (no studies)	No info	No info	No info	No info	No info	No info	No info
Operation time (2 studies)	Moderate[c]	Low	Low	Low	Low	Low	Low
Adverse events (3 studies)	Moderate[d]	Low	Low	Low	Low	Low	Low

Abbreviation: ROBINS-I, Risk of Bias in Non-randomized Studies—of Interventions.

[a]Possible risk-of-bias levels: low, moderate, serious, critical, no information.

[b]In one study, significantly more additional margins or segments were resected in patients localized with radioactive seed, which likely favored this group.

[c]In one study, significantly more additional margins or segments were resected in patients localized with radioactive seed, which likely increased operation time in this group. Also in this study, the number of other procedures performed in the radioactive seed group was twice that of those in the reflector group.

[d]In one study, significantly more additional margins or segments were resected in patients localized with radioactive seed, which likely impacted the frequency of postoperative complications in this group.

Table A15: Risk of Bias for Case Series[a] (Joanna Briggs Institute Critical Appraisal Tool for Case Series Studies)—MOLLI

Question[a]	Answer
Were there clear criteria for inclusion in the case series?	Yes
Was the condition measured in a standard, reliable way for all participants included in the case series?	Yes
Were valid methods used for identification of the condition for all participants included in the case series?	Yes
Did the case series have consecutive inclusion of participants?	Unclear
Did the case series have complete inclusion of participants?	Unclear
Was there clear reporting of the demographics of the participants in the study?	Yes
Was there clear reporting of clinical information of participants?	Yes
Were the outcomes of follow-up results of cases clearly reported?	Yes
Was there clear reporting of the presenting site's/clinic's demographic information?	Yes
Was statistical analysis appropriate?	Yes

[a]Possible answers: yes, no, unclear, not applicable.

Table A16: GRADE Evidence Profile for the Comparison of Magnetic Seed Versus Wire-Guided Localization

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Re-excision rate							
2 (prospective) 5 (retrospective)	No serious limitations	Serious limitations (−1)[a]	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Successful implantation							
3 (prospective) 2 (retrospective)	Serious limitations (−1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Device dislodgement/migration							
3 (prospective) 2 (retrospective)	Serious limitations (−1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Successful device retrieval							
2 (prospective) 3 (retrospective)	Serious limitations (−1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Operation time							
1 (prospective) 2 (retrospective)	Serious limitations (−1)[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Adverse events							
2 (prospective) 1 (retrospective)	Serious limitation (−1)[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Patient/radiologist/surgeon satisfaction							
1 (prospective)	Serious limitation (−1)[e]	Cannot be assessed	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]Variation existed among studies with respect to eligibility for re-excision based on the use of different local guidelines and a change in practice guideline during the conduct of one study, which may have impacted the outcome measurement.

[b]Some studies reported for the intervention group but not for the control group.

[c]The definition of operation time varied across studies.

[d]Not all postoperative complications were reported by all studies.

[e]Low rate of patient response, as some patient questionnaires were missed at both study sites. More lesions were bracketed in the wire-guided group than in the magnetic seed group.

Table A17: GRADE Evidence Profile for the Comparison of Magnetic Seed Versus Radioactive Seed Localization

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Re-excision rate							
1 (retrospective)	No serious limitations	Cannot be evaluated[b]	Very serious limitations (−2)[a]	No serious limitations	Undetected	None	⊕⊕ Low
Technical outcomes							
1 (retrospective)	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	No info[b]	Cannot be evaluated
Operation time							
1 (retrospective)	No info	No info	No info	No info	No info	No info	Cannot be evaluated
Adverse events							
1 (retrospective)	No info	No info	No info	No info	No info	No info	Cannot be evaluated

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]The practice guideline used to determine eligibility for re-excision changed during the conduct of the study.

[b]One study only.

[c]No information for intervention and/or control groups.

Table A18: GRADE Evidence Profile for the Comparison of Reflector-Guided Versus Wire-Guided Localization

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Re-excision rate							
5 (retrospective)	Very serious limitations (−2)[a, b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕ Low
Technical outcomes							
No comparative study	Cannot be evaluated	Cannot be evaluated	Cannot be evaluated	Cannot be evaluated	Cannot be evaluated	None	Cannot be evaluated
Operation time							
4 (retrospective)	Serious limitations (−1)[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate
Adverse events							
3 (retrospective)	Serious limitations (−1)[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⊕⊕⊕ Moderate

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]There was a significant difference and an imbalance between groups in deviation from intended intervention in three studies.

[b]In one study, cavity shave margin was reported only for the total population, not just for patients with cancer.

[c]In some studies, significantly more additional margins or segments were resected in patients localized with reflector, which likely increased the operation time in this group, In one study, patients with more extensive disease were more likely to be directed to wire-guided than reflector-guided localization, which likely increased operation time in the wire-guided group.

[d]Not all common postoperative complications were reported by all studies.

Table A19: GRADE Evidence Profile for the Comparison of Reflector-Guided Versus Radioactive Seed Localization

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Re-excision rate							
3 (retrospective)	Very serious limitations (−2)[a]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁ Low
Technical outcomes							
No comparative study	Cannot be evaluated	Cannot be evaluated	Cannot be evaluated	Cannot be evaluated	Cannot be evaluated	None	Cannot be evaluated
Operation time							
2 (retrospective)	Serious limitations (−1)[b]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate
Adverse events							
3 (retrospective)	Serious limitations (−1)[d]	No serious limitations	No serious limitations	No serious limitations	Undetected	None	⨁⨁⨁ Moderate

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]There was a significant difference and an imbalance between groups in deviation from intended intervention in three studies.

[b]Studies did not define operation time (i.e., start and stop time). The inclusion of patients with single or multiple devices varied among studies. In one study, the frequency of other procedures performed in addition to lumpectomy was different between groups.

[d]Not all common postoperative complications were reported by all studies.

Appendix 3: Selected Excluded Studies—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Choe AI, Ismail R, Mack J, Walter V, Yang AL, Dodge DG. Review of variables associated with positive surgical margins using Scout reflector localizations for breast conservation therapy. Clin Breast Cancer. 2022;22(2):e232-38.	Included patients with palpable tumours
Webster AJ, Kelly BN, McGugin C, Coopey SB, Smith BL, Gadd MA, Specht MC. Comparison of wireless localization alternatives with wire localization for nonpalpable breast lesions. J Am Coll Surg. 2022;234(6):1091-99.	Overlap of population included in Kelly et al, 2022[41]
Murphy E, Quinn E, Stokes M, Kell M, Barry M, Flanagan F, Walsh SM. Initial experience of magnetic seed localization for impalpable breast lesion excision: First 100 cases performed in a single Irish tertiary referral centre. Surgeon. 2022;20(30)e36-42.	Single-arm study
Powell M, Gate T, Kalake O, Ranjith C, Pennick MO. Magnetic seed localization (Magseed) for excision of impalpable breast lesions: the North Wales experience. Breast J. 2021;27(6):529-36.	Single-arm study
Tsui HL, Fung EPY, Kwok KM, Wong LKM, Lo LW, Mak WS. Magnetic marker wireless localisation versus radioguided localisation of nonpalpable breast lesions. Hong Kong Journal of Radiology. 2021;24(4):247-56.	Wrong comparator
Wazir U, Kasem I, Michell MJ, Suaris T, Evans D, Malhotra A, Mokbel K. Reflector-guided localisation of non-palpable breast lesions: a prospective evaluation of the SAVI SCOUT(®) System. Cancers. 2021;13(10): 2409.	Single-arm study
Tingen JS, McKinley BP, Rinkliff JM, Cornett WR, Lucas C. Savi Scout radar localization versus wire localization for breast biopsy regarding positive margin, complication, and reoperation rates. Am Surg. 2020;86(8):1029-31.	Included patients with palpable tumours
Patel SN, Mango VL, Jadeja P, Friedlander L, Desperito E, Wynn R, et al. Reflector-guided breast tumor localization versus wire localization for lumpectomies: a comparison of surgical outcomes. Clin imaging. 2018;47:14-17.	Included patients with palpable tumours

Appendix 4: Selected Excluded Systematic Reviews—Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Athanasiou C, Mallidis E, Tuffaha H. Comparative effectiveness of different localization techniques for non-palpable breast cancer. A systematic review and network meta-analysis. Eur J Surg Oncol. 2022;48(1):53-9.	Included RCTs comparing any possible localization techniques. None evaluated comparisons of magnetic seed or reflector-guided localization with wire-guided or radioactive seed localization
Chan BK, Wiseberg-Firtell JA, Jois RH, Jensen K, Audisio RA. Localization techniques for guided surgical excision of non-palpable breast lesions. Cochrane Database Syst Rev. 2015(12):CD009206.	Included only RCTs comparing wire-guided localization versus another form of guided surgery. None evaluated comparisons of magnetic seed or reflector-guided localization with wire-guided or radioactive seed localization
Davey MG, O'Donnell JPM, Boland MR, Ryan EJ, Walsh SR, Kerin MJ, Lowery AJ. Optimal localization strategies for non-palpable breast cancers: a network meta-analysis of randomized controlled trials. Breast. 2022;62:103-13.	Included RCTs comparing any possible localization techniques. None evaluated comparisons of magnetic seed or reflector-guided localization with wire-guided or radioactive seed localization
Garzotto F, Comoretto RI, Michieletto S, Franzoso G, Lo Mele M, Gregori D, Bonavina MG, Bozza F, Caumo F, Saibene T. Preoperative non-palpable breast lesion localization, innovative techniques and clinical outcomes in surgical practice: a systematic review and meta-analysis. Breast. 2021;58:93-105.	Included 24 prospective and retrospective studies of all possible localization techniques published until February 2021. Only four of the included studies are the same as those included in our review
Gera R, Tayeh S, Al-Reefy S, Mokbel K. Evolving role of Magseed in wireless localization of breast lesions: systematic review and pooled analysis of 1,559 procedures. Anticancer Res. 2020;40(4):1809-15.	Reported a pooled analysis of magnetic seed localization studies and a pooled analysis of wire-guided localization studies
Moreira IC, Ventura SR, Ramos I, Fougo JL, Rodrigues PP. Preoperative localisation techniques in breast conservative surgery: a systematic review and meta-analysis. Surg Oncol. 2020;35:351-73.	Included RCTs, prospective studies, and retrospective studies, but none evaluated comparisons of magnetic seed or reflector-guided localization with wire-guided or radioactive seed localization

Abbreviation: RCT, randomized controlled trial.

Appendix 5: Selected Excluded Studies—Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Law W, Look Hong N, Ravi A, Day L, Somani Y, Wright FC, et al. Budget impact analysis of preoperative radioactive seed localization. Ann Surg Oncol. 2021;28(3):1370-8.	Did not include wire-free, nonradioactive localization
Loving VA, Edwards DB, Roche KT, Steele JR, Sapareto SA, Byrum SC, et al. Monte Carlo simulation to analyze the cost-benefit of radioactive seed localization versus wire localization for breast-conserving surgery in fee-for-service health care systems compared with accountable care organizations. AJR Am J Roentgenol. 2014;202(6):1383-8.	Did not include wire-free, nonradioactive localization
Postma EL, Koffijberg H, Verkooijen HM, Witkamp AJ, van den Bosch MA, van Hillegersberg R. Cost-effectiveness of radioguided occult lesion localization (ROLL) versus wire-guided localization (WGL) in breast conserving surgery for nonpalpable breast cancer: results from a randomized controlled multicenter trial. Ann Surg Oncol. 2013;20(7):2219-26.	Did not include wire-free, nonradioactive localization
Wright CM, Moorin RE, Saunders C, Marinovich ML, Taylor DB. Cost-effectiveness of radioguided occult lesion localization using 125I seeds versus hookwire localization before breast-conserving surgery for non-palpable breast cancer. Br J Surg. 2021;108(7):843-50.	Did not include wire-free, nonradioactive localization
Zhang Y, Seely J, Cordeiro E, Hefler J, Thavorn K, Mahajan M, et al. Radioactive seed localization versus wire-guided localization for nonpalpable breast cancer: a cost and operating room efficiency analysis. Ann Surg Oncol. 2017;24(12):3567-73.	Did not include wire-free, nonradioactive localization

Appendix 6: Results of Applicability Checklists for Studies Included in the Economic Literature Review

Table A20: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Wire-Free, Nonradioactive Localization Techniques

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment[a]
Lindenberg et al, 2020,[58] Netherlands	Yes	Yes	Partially	Yes, public payer	Yes	NA	NA	Yes	Partially applicable
Sreedhar et al, 2021,[45] New Zealand	Yes	Yes	Partially	Yes, rural hospital	Unclear	Unclear	NA	Unclear	Not applicable

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Appendix 7: Detailed Budget Impact Analysis Model Inputs

Wire-Guided Localization Cost Items

WIRE AND NEEDLE: $27.84 2022 CAD

We sourced a material cost for wire and needle of $25.75 2016 CAD from Law et al[70] (Table 2, p. 1375). Adjusting for inflation using the health care component of the Consumer Price Index (CPI)[77] (CPI 2022/CPI 2016 = 134.8%/124.7% = 108.1%), we arrived at a cost of $27.84 2022 CAD.

ADDITIONAL DISPOSABLES REQUIRED FOR LOCALIZATION: $33.78 2022 CAD

We sourced a cost for additional disposables required for localization of $31.25 2016 CAD from Law et al[70] (Table 2, p. 1375). This cost includes "basic biopsy tray, gloves, steri-strips, scalpel, hypodispensible needle, blunt needle, syringe, lidocaine and sterile gauze," as well as "additional needle guide for mammographic procedures." Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2016 = 134.8%/124.7% = 108.1%), we arrived at a cost of $33.78 2022 CAD.

MEDICAL RADIATION TECHNOLOGIST—HOURLY SALARY INCLUDING BENEFITS: $50.10 2022 CAD; TIME REQUIRED TO CONDUCT A WIRE-GUIDED LOCALIZATION: 40 MINUTES

We sourced the hourly salary of a medical radiation technologist from the salary scale of the Canadian Association of Medical Radiation Technologists (CAMRT).[78] We used the hourly salary of a medical radiation technologist working at the University Health Network Radiation Therapy Unit (midpoint of the salary scale, step 4, p. 13): $38.34 2021 CAD. Following Law et al,[70] we assumed a 30% additional cost for benefits to arrive at an hourly salary including benefits of $49.84 2021 CAD ($38.34 × 1.3). Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2021 = 134.8%/134.1% = 100.5%), we arrived at an hourly salary including benefits of $50.10 2022 CAD.

We sourced the time required for a medical radiation technologist to conduct a wire-guided localization from Law et al.[70] The study provides time requirements stratified by whether the wire was inserted under ultrasound or mammographic guidance but does not provide an overall time requirement. However, the authors do provide a total cost for medical radiation technologist labour ($32 2016 CAD; Table 4, p. 1375) and an hourly salary for a medical radiation technologist ($48 CAD 2016; p. 1374). Thus, we were able to estimate a time of 40 minutes (0.666 h) required for a medical radiation technologist to conduct a wire-guided localization ($32 labour cost/$48 hourly salary).

RADIOLOGIST—HOURLY SALARY INCLUDING BENEFITS: $344.30 2022 CAD; TIME REQUIRED TO CONDUCT A WIRE-GUIDED LOCALIZATION: 17.63 MINUTES

We sourced the hourly salary of a radiologist of $245 2016 CAD from Zhang et al[69] (p. 3568). Following Law et al,[70] we assumed a 30% additional cost for benefits to arrive at an hourly salary including benefits of $318.50 2016 CAD ($245 × 1.3). Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2016 = 134.8%/124.7% = 108.1%), we arrived at an hourly salary including benefits of $344.30 2022 CAD.

We sourced the time required for a radiologist to conduct a wire-guided localization from Law et al.[70] As with our calculation for the medical radiation technologist time requirement, we divided the

labour cost ($92; Table 4, p. 1375) by the hourly salary estimate ($313, p. 1374) to arrive at a time requirement of 17.63 minutes (0.293 h).

PORTER—HOURLY SALARY: $25.11 2022 CAD; PATIENT TRANSPORTATION TIME: 10 MINUTES

Patients who receive wire-guided localization must be transported from the imaging department where they underwent localization to the surgical unit. We sourced the hourly salary of a porter from an Ontario hospital job posting: $25.11.[79] We did not include an additional 30% for benefits as the posting excluded benefits. Law et al[70] estimate that it takes 10 minutes for a porter to transfer a patient (p. 1375).

Radioactive Seed Localization Cost Items

PRELOADED RADIOACTIVE SEED AND NEEDLE: $143.29 2022 CAD

We sourced a material cost for a preloaded seed and needle of $132.55 2016 CAD from Law et al[70] (Table 2, p. 1375). Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/ CPI 2016 = 134.8%/124.7% = 108.1%), we arrived at a cost of $143.29 2022 CAD.

ADDITIONAL DISPOSABLES REQUIRED FOR LOCALIZATION: $33.78 2022 CAD

We sourced a cost for additional disposables required for localization of $31.25 2016 CAD from Law et al[70] (Table 2, p. 1375). This cost includes "basic biopsy tray, gloves, steri-strips, scalpel, hypodispensible needle, blunt needle, syringe, lidocaine and sterile gauze," as well as "additional needle guide for mammographic procedures." Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2016 = 134.8%/124.7% = 108.1%), we arrived at a cost of $33.78 2022 CAD.

MEDICAL RADIATION TECHNOLOGIST—HOURLY SALARY INCLUDING BENEFITS: $50.10 2022 CAD; TIME REQUIRED TO CONDUCT A RADIOACTIVE SEED LOCALIZATION: 35 MINUTES

Our method of sourcing the hourly salary of a medical radiation technologist including benefits is described above (p. 107).

To estimate the time required for a medical radiation technologist to conduct a radioactive seed localization, we used an approach similar to that used for wire-guided localization. Law et al[70] provide time requirements stratified by whether the seed was inserted under ultrasound or mammographic guidance but do not provide an overall time requirement. However, the authors do provide a total cost for medical radiation technologist labour ($28 2016 CAD) and an hourly salary for a medical radiation technologist ($48 2016 CAD). Thus, we were able to estimate a time of 35 minutes (0.583 h) required for a medical radiation technologist to conduct a radioactive seed localization ($28 labour cost/$48 hourly salary).

RADIOLOGIST—HOURLY SALARY INCLUDING BENEFITS: $344.30 2022 CAD; TIME REQUIRED TO CONDUCT A RADIOACTIVE SEED LOCALIZATION: 17.25 MINUTES

Our method of sourcing the hourly salary for a radiologist including benefits is described above (p. 107).

We sourced the time required for a radiologist to conduct a radioactive seed localization from Law et al.[70] As with our calculation for the medical radiation technologist time requirement, we divided the labour cost ($90) by the hourly salary estimate ($313; p. 1374) to arrive at a time requirement of 17.25 minutes (0.287 h).

NUCLEAR MEDICINE TECHNOLOGIST—HOURLY SALARY INCLUDING BENEFITS: $50.10 2022 CAD; TIME REQUIRED FOR SEED INTAKE AND DISPOSAL, AUDITS, AND QUALITY CONTROL: 18.35 MINUTES

We assumed that the hourly salary of a nuclear medicine technologist would be the same as that of a medical radiation technologist because the Government of Canada Job Bank groups nuclear medicine technologists with medical radiation technologists,[96] and, for several jurisdictions in Canada, the CAMRT salary scale groups radiation technologists with nuclear medicine technologists.[78] The CAMRT salary scale does not include an entry for nuclear medicine technologists for the province of Ontario.

Law et al[70] indicate that it takes 1 hour of nuclear medicine technologist time per week to conduct seed intake, disposal, and audits (p. 1376). The Ottawa site at which Law et al conducted their study performed 170 radioactive seed localizations in 1 year (p. 1370). These figures result in a time requirement per localization of 18.35 minutes (52 h/170 procedures).

NURSE—HOURLY SALARY INCLUDING BENEFITS: $52.67 2022 CAD; TIME REQUIRED TO RECORD SCINTIGRAPHIC COUNTS: 30 MINUTES

We sourced the hourly salary of a full-time registered nurse (midpoint of 5 years' seniority) of $40.59 2022 CAD from the Ontario Nurses' Association.[80] Following Law et al,[70] we assumed a 30% additional cost for benefits to arrive at an hourly salary including benefits of $52.67 ($40.59 × 1.3).

We sourced the time required to record scintigraphic counts of 30 minutes from Law et al[70] (p. 1376).

PATHOLOGY ASSISTANT—HOURLY SALARY: $42.16 2022 CAD; TIME REQUIRED TO COMPLETE SEED RETRIEVAL AND PERFORM RADIATION SURVEY: 10 MINUTES

We sourced the hourly salary of a pathology assistant of $39 2016 CAD from Law et al[70] (p. 1376). Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2016 = 134.8%/124.7% = 108.1%), we arrived at an hourly wage of $42.16 2022 CAD.

Law et al[70] estimate that it takes 10 minutes to conduct a radiation survey and complete seed retrieval (p. 1376).

Wire-Free, Nonradioactive Localization Cost Items

WIRE-FREE, NONRADIOACTIVE MARKER OR SEED: $535.30 2022 CAD

We sourced the cost of a wire-free, nonradioactive marker or seed from Davis et al (p. 544).[74] The authors reported a cost of $450 in 2021 USD for the Scout marker and $400 in 2021 USD for the Magseed seed. We used purchasing power parity (PPP) estimates for Canada (PPP 2021: 1.253) to convert this amount to 2021 CAD. This resulted in estimates of $563.85 2021 CAD for a Scout marker and
$501.20 2021 CAD for a Magseed seed. We selected the midpoint of these costs to arrive at an

estimated cost of $532.52 2021 CAD for a wire-free, nonradioactive marker or seed. Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2021 = 134.8%/134.1% = 100.5%), we arrived at a cost of $535.30 2022 CAD. Owing to the large degree of uncertainty around Canadian costs, we conducted scenario analyses with 20% higher and 20% lower costs for wire-free, nonradioactive markers or seeds.

ADDITIONAL DISPOSABLES REQUIRED FOR LOCALIZATION: $33.78 2022 CAD

We sourced a cost for additional disposables required for localization of $31.25 2016 CAD from Law et al[70] (Table 2, p. 1375). This cost includes "basic biopsy tray, gloves, steri-strips, scalpel, hypodispensible needle, blunt needle, syringe, lidocaine and sterile gauze," as well as "additional needle guide for mammographic procedures." Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2016 = 134.8%/124.7% = 108.1%), we arrived at a cost of $33.78 2022 CAD.

MEDICAL RADIATION TECHNOLOGIST—HOURLY SALARY INCLUDING BENEFITS: $50.10 2022 CAD; TIME REQUIRED TO CONDUCT A WIRE-FREE, NONRADIOACTIVE LOCALIZATION: 35 MINUTES

Our method of sourcing the hourly salary of a medical radiation technologist including benefits is described above (p. 107).

We assumed that wire-free, nonradioactive localization would require the same amount of time as radioactive seed localization (see p. 108 for our calculation). This assumption aligns with the analysis conducted by Lindenberg et al.[58]

RADIOLOGIST—HOURLY SALARY INCLUDING BENEFITS: $344.30 2022 CAD; TIME REQUIRED TO CONDUCT A WIRE-FREE, NONRADIOACTIVE LOCALIZATION: 17.25 MINUTES

Our method of sourcing the hourly salary for a radiologist including benefits is described above (p. 107).

We assumed that wire-free, nonradioactive localization would require the same amount of time as radioactive seed localization (see p. 108 for our calculation). This assumption aligns with the analysis conducted by Lindenberg et al.[58]

Scenario Analysis Cost Items

MANUALLY LOADED RADIOACTIVE SEED AND NEEDLE: $26.45 2022 CAD

We sourced a material cost for a manually loaded seed and needle of $24.47 2016 CAD from Zhang et al ($18.76 + $5.71).[69] Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2016 = 134.8%/124.7% = 108.1%), we arrived at a cost of $26.45 2022 CAD.

RADIOLOGIST—HOURLY SALARY INCLUDING BENEFITS: $344.30 2022 CAD; TIME REQUIRED TO MANUALLY LOAD A SEED: 1 MINUTE; LABOUR COST FOR A MANUALLY LOADED SEED: $5.71 2022 CAD

Our method of sourcing the hourly salary for a radiologist including benefits is described above (p. 107).

We sourced a time required to manually load a seed of 1 minute from Law et al.[70]

We arrived at the labour cost for a manually loaded seed ($5.71 2022 CAD) by dividing the hourly salary by 60 minutes.

RE-EXCISION (BREAST-CONSERVING SURGERY OR MASTECTOMY): $4,862.59 2022 CAD

We estimated the inpatient expenditures associated with re-excision by querying the Ontario Case Costing Initiative (OCCI) database[82] for the Canadian Classification of Health Interventions (CCI) procedure codes for breast-conserving surgery and mastectomy.

We identified the CCI codes for breast-conserving surgery from our IntelliHealth Ontario analysis (1YM87UT,1YM87UTXXE, 1YM87LA).[82] The OCCI provides an estimate for breast-conserving surgery of $3,301.44 2018 CAD. This amount includes the costs of inpatient visits, ambulatory visits, and day surgery.

We sourced the CCI codes for mastectomy from the *Quality-Based Procedures Clinical Handbook for Cancer Surgery* (1YM89LAXXE, 1YM91LA, 1YM91LAPM, 1YM91LATP, 1YM91LAXXA, 1YM91LAXXE, 1YM91TR, 1YM91TRXXA, 1YM91TRXXE, 1YM91WP, 1YM91WPXXA, 1YM91WPXXE).[97] Querying the OCCI for these CCI codes generated an estimate for the cost of mastectomy of $5,261.78 2018 CAD.

Pataky et al (p. 316)[84] report that re-excision occurred following mastectomy 52.7% of the time. We used a weighted average of the costs of breast-conserving surgery and mastectomy to estimate a re-excision cost of $4,334.54 2018 CAD ($3,301.44 × [1 − 52.7%] + $5,261.78 × 52.7%). Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2018 = 134.8%/128.1% = 105.2%), we arrived at a cost of $4,561.25 2022 CAD.

We sourced physician fees from the OHIP Schedule of Benefits[83]: billing code R111 ($269.40) is used for breast-conserving surgery, and billing code R108 ($330) is used for mastectomy. We assigned a weighted average of the two billing codes based on the rate of re-excision reported in Pataky et al.[84] We estimated the physician cost for re-excision to be $301.34 2022 CAD ($269.40 × [1 − 52.7%] + $330.00 × 52.7%).

We thus estimated the total cost of re-excision to be $4,862.59 2022 CAD ($4,561.25 + $301.34).

CAPITAL EXPENDITURES FOR RADIOACTIVE SEED LOCALIZATION: $57,530.52 2022 CAD

We sourced the cost of a probe ($50,000 2016 CAD) from Zhang et al[69]; this was the cost of purchasing the Neoprobe Gamma Detection System (GDS) Control Module by Mammotome. We sourced a total start-up cost of $3,220 2016 CAD from Zhang et al[69] (p. 3571); this cost included the costs of a safe to store radioactive seeds, a radiation detector to locate lost seeds, and long-term storage containers. We thus estimated the total capital expenditure for radioactive seed localization to be $53,220 2016 CAD. Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2016 = 134.8%/124.7% = 108.1%), we arrived at a cost of $57,530.52 2022 CAD.

CAPITAL EXPENDITURES FOR WIRE-FREE, NONRADIOACTIVE LOCALIZATION: $46,879.33 2022 CAD

We sourced capital expenditures for wire-free, nonradioactive localization from Lindenberg et al,[58] who provide a per-patient equipment cost of €49 (Appendix 4, Excel spreadsheet "Cost information") 2018 EUR. They assumed 116 localizations conducted at a single site per year and a 5-year amortization period for the probe (Appendix 4, Excel spreadsheet "Cost information"). This results in a probe cost of €28,420 2018 EUR (€49 × 116 × 5). We converted this amount into Canadian dollars

using PPP estimates for Canada (PPP 2018: 1.207) and the Netherlands (PPP 2018: 0.77) and arrived at a cost of $44,549.27 2018 CAD. Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2018 = 134.8%/128.1% = 105.2%), we arrived at a cost of $46,879.33 2022 CAD.

BIOPSY CLIP PLACED AFTER CORE BIOPSY PRIOR TO NEOADJUVANT CHEMOTHERAPY: $239.93 2022 CAD

We sourced the cost of a neoadjuvant chemotherapy marker from Lindenberg et al,[58] who provide an estimate of €146 2018 EUR. We converted this amount into Canadian dollars using PPP estimates for Canada (PPP 2018: 1.207) and the Netherlands (PPP 2018: 0.77) and arrived at a cost of $228 2018 CAD. Adjusting for inflation using the health care component of the CPI[77] (CPI 2022/CPI 2018 = 134.8%/128.1% = 105.2%), we arrived at a cost of $239.93 2022 CAD.

SEED LOSS, TRANSECTION, AND NEAR INCIDENTS: $30.10 2022 CAD PER LOCALIZATION

We included radiology, nuclear medicine technologist, and pathology labour costs related to radioactive seed loss, transection, and "near incidents" as reported by Lindenberg et al.[58] The authors define a "near incident" as a situation in which a seed is thought to have been lost and requires formal follow-up "in view of radioactivity regulations."

Lindenberg et al[58] reported that seed loss and transection require two days of work and that near incidents require 6 hours of work. The five participating hospitals conducting radioactive seed localization in this study reported that seed loss, transection, and near incidents occurred once or twice a year. Using the average number of localizations conducted at single site per year reported by the authors of 116 (Appendix 4, Excel spreadsheet "Cost"), we estimated the probability of seed loss, transection, or a near incident to be 0.34% (2/[116 × 5]).

We sourced the time requirement of 20 hours (14 hours [2 workdays] + 6 hours) to address a seed loss, transection, and near incident from Lindenberg et al.[58] We multiplied the hourly salary of a radiologist, medical radiation technologist, and pathologist ($344.30, $50.10, and $42.16, respectively) by 20 hours to arrive at an estimated cost of addressing a seed loss, transection, and near incident of $8,731.20 2022 CAD. We multiplied this figure by the probability of seed loss, transection, or near incident (0.34%) to arrive at a cost per localization of $30.10 2022 CAD.

This amount is comparable to the labour cost associated with seed loss, transection, or near incident reported by Lindenberg et al[58] of €23 2018 EUR ($36.05 2022 CAD; Appendix 2, "Detailed Description of Intervention Costs").

We did not consider the potential risk of loss of licence or inability to perform other nuclear medicine procedures as a result of radioactive seed loss.[70]

Uptake of Wire-Free, Nonradioactive Localization Techniques

We estimated the uptake of wire-free, nonradioactive localization techniques to resemble uptake in the United Kingdom, a jurisdiction where a wire-free, nonradioactive localization technique (Magseed) was approved in 2017.[39] The Medtech innovation briefing on Magseed by the National Institute for Health and Care Excellence (NICE) published in 2020 stated that 42 National Health Service (NHS) trusts are currently using Magseed.[73] There are 209 nonambulatory trusts in the NHS, many of which include more than one hospital.[98] A 2019 survey of 98 UK breast units found that 82 sites used wire-guided localization, 9 used magnetic seed localization, and the remaining 7 used other localization techniques.[72]

We are uncertain about the relative volume of sites that have adopted wire-free, nonradioactive localization techniques compared with those using wire-guided localization. From IntelliHealth Ontario data,[60,61] we found that between January 1, 2014, and March 30, 2019, sites that conduct radioactive seed localization on average conducted 2.66 more localizations than sites not using radioactive seed localization. We therefore assumed that UK sites using wire-free, nonradioactive localization techniques are conducting 2.66 more localizations over the same amount of time than sites that are not.

According to the 2019 survey of UK breast units,[72] about 22% of localization procedures performed in the United Kingdom as of 2019 were done using wire-free, nonradioactive techniques ([9/98 × 2.66]/[9/98 × 2.66 + 91/98]). This results in a yearly increase of 11% since 2017 (22%/2).

Using the results from the NICE Medtech innovation briefing on Magseed,[73] we found that an estimated 40% of localizations are conducted using wire-free, nonradioactive localization ([42/209 × 2.66]/[42/209 × 2.66 + 167/209]). This results in a yearly increase of 13% since 2019 (40%/3). We assumed the midpoint between the two estimates for a yearly increase of 12% (year 1 = 12%, year 2 = 24%, year 3 = 36%, year 4 = 48%, year 5 = 60%). Owing to the large degree of uncertainty in market share estimates, we also include results for models using yearly increases of 9% and 15%.

We assumed that wire-free, nonradioactive localization techniques would take market share equally from wire-guided and radioactive seed localization. For example, in year 1 in the scenario of no funding for wire-free, nonradioactive localization, the uptake of wire-guided localization was 85% and the uptake of radioactive seed localization was 15%. In year 1 in the scenario of funding for wire-free, nonradioactive localization, the uptake of wire-free, nonradioactive localization was 13%. Of the remaining 87% market share, 12% of localizations would be done using radioactive seed localization (87% × 15%), and 75% would be done using wire-guided localization (87% × 85%).

Rate of Bracketing

We estimated the rate of bracketing (the use of multiple seeds, markers, or wires to localize a single tumour) from the six studies included in the clinical evidence review that reported number of wires, seeds, or markers used per patient:

- Dave et al, 2022[39]: 2% (49/2,116)
- Kelley et al, 2022[41]: 11% (133/1,236)
- Liang et al, 2022[42]: 28% (517/1,836)
- Micha et al, 2021[54]: 16% (44/276)
- Redfern and Shermis, 2022[43]: 8% (24/296)
- Srour et al, 2021[52]: 25% (23/91)
- 6 studies combined: 14% (790/5,851)

Rate of Re-excision

We sourced estimates of the rate of re-excision from the clinical evidence review. We assumed that all wire-free, nonradioactive localization techniques would have the same rate of re-excision as magnetic seed localization (highest-evidence GRADE):

- Wire-free, nonradioactive localization: 11.2%
- Wire-guided localization: 15.4%
- Radioactive seed localization: 15.8% (wire-free, nonradioactive localization rate of re-excision/risk ratio of re-excision comparing wire-free, nonradioactive localization with radioactive seed localization = 11.2%/0.71)

We did not consider using different rates of re-excision in the reference case for the following reasons: (1) the clinical evidence for the rate of re-excision associated with reflector-guided localization had serious limitations (GRADE: Low), and (2) the clinical evidence for rate of re-excision comparing magnetic seed localization with radioactive seed localization is based on a single study (GRADE: Low).

Notes

- PPP estimates were sourced from the Organisation for Economic Co-operation and Development[99]
- CPI calculations may seem imprecise due to rounding
- We used the health care component of the CPI[77] (2016: 124.7; 2018: 128.1; 2021: 134.1; February 2022: 134.8)

Appendix 8: Validation of Population Estimates

To validate that the OHIP billing codes were claimed during the surgical excision of breast tumours, we matched claims to same-day surgeries and inpatient visits sourced from the Discharge Abstract Database accessed through IntelliHealth Ontario.[60,61] We were able to match 99% of patient visits with an inpatient visit or same-day procedure according to OHIP billing codes. We matched patient visits to the primary treatment received using the Canadian Classification of Health Interventions (CCI) codes. We found that when OHIP billing code E525 was claimed, the primary treatment was a surgical breast intervention. The following CCI codes were used in more than 5% of visits for which OHIP billing code E525 was also claimed:

- 1YM87UT: excision partial, breast, using open approach with localization device (e.g., needle hook, radioactive seed, wire) with simple apposition (e.g., suturing)
- 1YM87UTXXE: excision partial, breast, using open approach with localization device (e.g., needle hook, radioactive seed, wire) with local flap (to close defect)
- 1YM87LA: excision partial, breast, using open approach with simple apposition (e.g., suturing)
- 1YM87LAXXE: excision partial, breast, using open approach with local flap (to close defect)

Appendix 9: Detailed Reference Case Results

Table A21: Detailed Budget Impact Analysis Results—Reference Case

	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Current scenario						
Total RSL	0.45	0.48	0.55	0.59	0.63	2.70
RSL labour	0.22	0.23	0.27	0.29	0.30	1.31
RSL material	0.23	0.25	0.29	0.30	0.32	1.40
Total WGL	1.36	1.36	1.35	1.35	1.35	6.76
WGL labour	0.92	0.92	0.91	0.91	0.91	4.59
WGL material	0.44	0.44	0.43	0.43	0.43	2.17
New scenario						
Total RSL	0.39	0.33	0.31	0.25	0.19	1.47
RSL labour	0.19	0.16	0.15	0.12	0.09	0.71
RSL material	0.2	0.17	0.16	0.13	0.1	0.76
Total WGL	1.2	1.05	0.89	0.73	0.57	4.44
WGL labour	0.81	0.72	0.6	0.5	0.39	3.02
WGL material	0.38	0.34	0.28	0.23	0.18	1.42
Total WFNRL	0.73	1.47	2.24	3.02	3.82	11.28
WFNRL labour	0.12	0.25	0.37	0.51	0.64	1.89
WFNRL material	0.61	1.23	1.86	2.51	3.18	9.39
Budget impact[b]						
Total cost difference	0.51	1.01	1.53	2.06	2.61	7.73
Cost difference, labour	−0.02	−0.04	−0.06	−0.08	−0.1	−0.28
Cost difference, material	0.52	1.05	1.59	2.14	2.71	8.01

Abbreviations: RSL, radioactive seed Localization; WGL, wire-guided localization; WFNRL: wire-free, nonradioactive localization.

[a]In 2022 Canadian dollars.

[b]Results may appear inexact due to rounding.

Table A22: Detailed Capital Expenditures at a Representative Site

	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b]
Number of localizations	131	133	134	136	138	672
Capital costs, RSL			$57,530.52			
Capital costs, WFNRL			$46,879.33			
Per-localization capital costs, RSL[a]			$85.60			
Per-localization capital costs, WFNRL[a]			$69.75			
Wire-guided localization costs						
Total	$26,759	$27,108	$27,457	$27,805	$28,154	$137,283
Labour	$18,178	$18,414	$18,651	$18,888	$19,125	$93,256
Material	$8,582	$8,694	$8,805	$8,917	$9,029	$44,027
Capital expenditures	$0	$0	$0	$0	$0	$0
Radioactive seed localization costs						
Total	$61,235	$62,032	$62,830	$63,628	$64,426	$314,151
Labour	$24,197	$24,512	$24,828	$25,143	$25,458	$124,138
Material	$25,824	$26,160	$26,497	$26,833	$27,170	$132,485
Capital expenditures	$11,214	$11,360	$11,506	$11,652	$11,798	$57,529
Wire-free, nonradioactive localization costs						
Total	$110,488	$111,928	$113,367	$114,806	$116,246	$566,835
Labour	$16,984	$17,205	$17,427	$17,648	$17,869	$87,134
Material	$84,367	$85,466	$86,565	$87,664	$88,763	$432,825
Capital expenditures	$9,137	$9,256	$9,375	$9,494	$9,613	$46,877

Note: All costs in 2022 Canadian dollars.

[a]Per-localization capital costs estimated by dividing capital expenditures by the total number of localizations occurring over the lifetime of the equipment (5 years).

[b]Results may appear inexact due to rounding.

Appendix 10: Letter of Information

LETTER OF INFORMATION

Ontario Health

Ontario Health is conducting a review of **Wire-Free, Nonradioactive Localization Techniques**. The purpose is to understand whether this should be publicly funded in Ontario.

An important part of this review involves gathering perspectives of patients, family members, and caregivers with experience undergoing a localization for the surgical removal of a nonpalpable breast tumour.

WHAT DO YOU NEED FROM ME

- ✓ Willingness to share your story
- ✓ 20-40 minutes of your time for a phone
- ✓ Permission to audio- (not video-) record the interview

WHAT YOUR PARTICIPATION INVOLVES

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 20-40 minutes. It will be held over the telephone. With your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about surgical options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

CONFIDENTIALITY

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however, no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project completion, the records will be destroyed.

RISKS TO PARTICIPATION

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experiences.

IF YOU ARE INTERESTED, PLEASE CONTACT US BEFORE JULY 15, 2022:

Appendix 11: Interview Guide

Introduction

Thank you – again, if at any point you would like for me to pause or to completely stop the recording, please do not hesitate to let me know. Now before we begin, I would like to see if you have any questions regarding the project or our work at Ontario Health in general?

Description of Ontario Health: Ontario Health is a government agency, which can be viewed as an extension of the Ministry of Health and Long-Term Care. The role of the Health Technology Assessment program is to use scientific methods to analyze evidence and assess new and existing health care services and medical devices. Our reviews cover three (3) domains of evidence: clinical, economic impact, and preferences and values. In addition, each health technology assessment includes recommendations for the Ministry on whether these health services and/or medical devices should be publicly funded.

The aim of the Patient and Public Partnering team is to ensure that equal consideration is given to the lived experience and preferences of patients, families, and caregivers through evidence generation.

Description of Technology Under Review: For this health technology assessment, we are reviewing innovative localization systems that are wire-free, and nonradioactive. The current care standard in Ontario is to use wire- and radioactive seed-guided localization techniques. The devices under review use different technology (e.g., radar or magnetic) and involve implanting the device into the breast and the surgeon using a specific hand-held probe to find its location during breast-conserving surgery. The devices can be implanted weeks prior to the scheduled surgery, and this has been advertised as a potential benefit for patients.

Aim of Direct Engagement: the goal of today's interview is to learn from your experience undergoing a localization and to get a better understanding of your values, decision-making, and preferences in relation to wire-free, nonradioactive localization systems.

Journey to Findings

- I'd like to start by asking you to please describe the events that led to the diagnosis of a nonpalpable tumour?
    - Probes/prompts: Routine mammogram?
    - Probes/prompts: Barriers to access?
    - Probes/prompts: Self-advocacy? Support team?

Access to Information

- Once the finding was confirmed, what information about the localization procedure was available to you?
    - Probes/prompts: Thoughts or feelings?
    - Probes/prompts: Primary source of information? Was it accessible?
    - Probes/prompts: Access to informal sources of information (e.g., social media groups)?

Impact of Localization procedure

- How was your experience undergoing the localization procedure?
  Probes/prompts: Was the localization performed on the same day as the surgery?
  Probes/Prompts: Required travel? Timing?
  Probes/Prompts: Barriers?
  Probes/Prompts: Surgical outcomes? Comfort?
  Probes/Prompts: Impact on decision-making across your care journey? Preferences?

Broad Access to Wire-Free, Nonradioactive Localization Techniques

- Does broad access to innovative localization techniques align with your preferences and values? Why or why not?
  Probes/Prompts: Perceived impacts (i.e., emotional, physical, or work-life)?

- Would you have any concerns with publicly funding broad access to innovative localization systems? Why or why not?
  Probes/Prompts: Perceived barriers (i.e., access, equity, or care)?

Conclusion

- Thank you - those are all the questions that I have today but is there anything else you would like to add?

- Finally, do you have any questions for me?

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