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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Intraoperative Mammography for Breast Cancer Surgery: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	April 22, 2019
Report Length:	27 Pages

CADTH

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Cite As: Intraoperative mammography for breast cancer surgery: a review of clinical effectiveness, cost-effectiveness, and guidelines. Ottawa: CADTH 2019 Apr (CADTH rapid response report: summary with critical appraisal).

ISSN: 1922-8147 (online)

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

Abbreviations

BCS	breast conserving surgery
CI	95% confidence interval
CSR	conventional specimen radiography
DCIS	ductal carcinoma *in situ*
GSE	gross specimen examination
IBC	invasive breast cancer
IO	intraoperative
IOSM	intraoperative specimen mammography
IOSR	intraoperative radiography
IOUS	intraoperative ultrasound
MRI	magnetic resonance imaging
OR	operating room
RCT	randomized controlled trial
SSM	standard specimen mammography

Context and Policy Issues

Breast cancer is one of the most common cancers among women in Canada and is the second leading cause of death from cancer in this population.[1] As of 2017, an estimated 26,300 new cases of breast cancer were diagnosed annually in Canada.[1] When patients are diagnosed with early stage breast cancer, breast-conserving surgery may be offered (following an assessment of risk factors) as an alternative to mastectomy.[2] The goal of breast-conserving surgery is to excise cancerous tissue with adequate disease-free (i.e., negative) margins, in order to control disease, limit recurrence, maximize disease survival rates, and maintain cosmetic integrity of the breast.[2,3] Standard of care requires excised specimens to be prepared and transferred to a pathology laboratory for evaluation or margin status assessment.[2] Excised specimens with disease close to or at the boundary (i.e., positive margins) are an indication for re-excision, cavity shaving, or re-operation.[2] To minimize the probability of recalling patients for repeat surgeries on a different day following pathology assessment, intraoperative assessment of excised specimens is being explored.[2]

With intraoperative margin assessment, the probability of residual disease at or near the boundaries of the excised specimen may be determined in real-time within the operating room while the patient is under anesthesia.[4] Intraoperative margin assessment can inform surgical decision-making and may potentially decrease the incidence of re-excisions[5] without significantly increasing operating time.[6] Different radiology options for intraoperative margin assessment are available, such as conventional specimen radiography (CSR), standard specimen mammography (SSM), intraoperative specimen mammography (IOSM), and intraoperative ultrasound (IOUS). CSR and SSM involve the acquisition of two-dimensional radiographic images of excised specimens outside the operating room with or without compression to confirm the presence of the target lesion or cancerous tissue and to assess the margin status.[5] Images are reviewed by radiologists and the results are conveyed to surgeons. With IOSM, radiographic images of excised specimens are acquired inside or adjacent to the operating room and are immediately interpreted by surgeons with or without the support of radiologists.[5] Similarly, IOUS involves the acquisition of ultrasonographic images of excised specimen inside the operating room for immediate interpretation by surgeons with or without radiologists.[7] IOSM and IOUS both allow surgeons to assess margin status in real-time within the operating environment, and each

technique has advantages and disadvantages.[5,7,8] IOUS does not involve x-rays or other forms of harmful radiation and may be more accessible (physically and financially) than IOSM.[9] Notwithstanding these benefits, sonographically occult lesions (i.e., undetectable or not easily visualized with ultrasound) and microcalcifications present a challenge to IOUS, thereby potentially limiting the technique's clinical effectiveness and its impact on decision-making by surgeons.[9] While IOSM may detect microcalcifications, the technique's sensitivity decreases in dense breast parenchyma.[10] As such, there remains uncertainty regarding the comparative clinical effectiveness of various intraoperative margin status assessment techniques and their impact on clinical decision-making.

The objective of this report is to assess the comparative clinical effectiveness and cost-effectiveness of intraoperative imaging with mammography (i.e., intraoperative specimen mammography or intraoperative mammography) for breast cancer surgery, and to evaluate relevant evidence-based guidelines.

Research Questions

1. What is the clinical effectiveness of intraoperative imaging with mammography for breast cancer surgery?
2. What is the cost-effectiveness of intraoperative imaging with mammography for breast cancer surgery?
3. What are the evidence-based guidelines regarding intraoperative imaging for breast cancer surgery?

Key Findings

Seven studies including one randomized controlled trial[5] and six retrospective studies[6,11-15] provided evidence of limited quality on the clinical effectiveness of intraoperative specimen mammography (IOSM).

The clinical effectiveness evidence was sparse and results were inconclusive, primarily due to heterogeneity in the designs of the studies, lack of consistency in the terminology used to describe the interventions, and lack of details in describing the image acquisition techniques. Insufficient information was provided to ascertain whether comparable interventions were used across the studies. The interventions were identified as IOSM, digital IOSM, or intraoperative radiography and the comparators included standard specimen mammography, conventional specimen radiography, intraoperative ultrasound, gross specimen examination, and frozen section analysis. Furthermore, definitions of the outcome measures were not universal.

Findings in support of IOSM were as follows: IOSM was as accurate as SSM in detecting target lesions within excised specimen in one randomized controlled trial involving 44 patients who primarily had invasive breast cancer; and in a retrospective database review, the use of IOSM in 26 patients to guide select shave margins in sonographically occult lesions significantly decreased re-excision rates relative to intraoperative ultrasound in 63 patients or gross specimen examination in 38 patients. Neither of these studies were conducted in Canada.

No relevant economic analyses or evidence-based guidelines regarding the use of intraoperative mammography for breast cancer surgery were identified.

Caution is advised in interpreting the information presented in this report due to the aforementioned heterogeneity among the studies, included studies' lack of clarity in describing the interventions, and the paucity of evidence derived from the Canadian population. Economic evaluations and evidence-based guidelines are needed, and additional studies evaluating the comparative clinical effectiveness of IOSM in Canada would enhance the value of the clinical evidence.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to guidelines for the third research question only. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and March 21, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients undergoing surgery for breast cancer
Intervention	Intraoperative mammography
Comparator	Q1, 2: Intraoperative ultrasound, no intraoperative imaging, postoperative imaging of specimen Q3: Not required
Outcomes	Q1: Clinical effectiveness (e.g., tumour delineation, image resolution, outcome margins, quality of specimen, reduced patient "call backs" for further surgery) Q2: Cost-effectiveness Q3: Guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, if they were duplicates or if they were published prior to 2009. Economic evaluations that reported only on costs without an assessment of costs relative to clinical benefits, and guidelines with unclear methodology, were excluded.

Critical Appraisal of Individual Studies

The included randomized controlled trial (RCT) and non-randomized studies were critically appraised by one reviewer using the Downs and Black checklist.[16] Summary scores were

not calculated for the included studies; rather, a review of the strengths and limitations of each included study was narratively described.

Summary of Evidence

Quantity of Research Available

A total of 266 citations were identified in the literature search. Following the screening of titles and abstracts, 241 citations were excluded, and 25 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search for full text review. After screening the full-text versions of the 30 potentially relevant articles, 23 papers were excluded for various reasons, while seven studies which met the inclusion criteria were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection. One additional reference of potential interest is provided in Appendix 5.

Summary of Study Characteristics

A total of seven studies evaluating the clinical effectiveness of IOSM were identified. A detailed summary of the characteristics of included studies is presented in Appendix 2.

Study Design

One randomized controlled trial[5] and six retrospective chart or database review studies[6,11-15] were included. No relevant economic evaluations or evidence-based guidelines were found.

Country of Origin

Three of the studies were published by authors in Canada,[11-13] two were published in the United States,[5,6] and one each was published in Germany[14] and the United Kingdom.[15] Two of the Canadian studies were published by the same group of authors during the same period;[11,12] however, any overlap in the patient populations would have been minimal as one study recruited patients diagnosed with pure ductal carcinoma *in situ* (DCIS)[11] while the other recruited patients with invasive breast cancer (IBC).[12] Two of the studies were published in 2018,[6,11] three were published in 2016,[5,12,14] one each in 2013[13] and 2012.[15]

Patient Population

All of the studies involved patients requiring breast-conserving surgery for breast cancer. Two retrospective studies enrolled patients with DCIS only.[11,14] Patients who had neoadjuvant therapy, were missing pathology reports, had no tumor in the resection specimen, or were evaluated with frozen sections were excluded from one of the studies that was conducted in Canada.[11] Patients with missing images, those without evidence of microcalcification or those who had undergone mastectomy were excluded from the study that was conducted in Germany.[14]

Three studies enrolled patients with IBC. One retrospective study enrolled patients in the United Kingdom with palpable unifocal IBC,[15] while the RCT enrolled patients in the United States with IBC primarily, along with patients who had DCIS, unidentified abnormal mammograms, or atypia.[5] A retrospective database review that was conducted in Canada enrolled patients who primarily had nonpalpable, biopsy-proven IBC.[12]

One retrospective study enrolled patients in Canada with nonpalpable breast cancer and excluded patients who had a mastectomy, did not have pre-operative needle localization, were younger than 18 years, or were male.[13] Another enrolled patients in the United States with sonographically occult lesions in stages 0 to III.[6]

Patients were recruited from a variety of settings: a university hospital's interdisciplinary breast care centre in Germany,[14] outpatient breast clinics associated with a tertiary care hospital in the United States,[5] a breast surgery unit in the United Kingdom,[15] and a community hospital.[6] Two studies that were conducted in Canada included patients treated at 14 urban and community facilities across a single province, Alberta.[11,12] The third Canadian study recruited patients from a tertiary care hospital.[13]

Interventions and Comparators

The intervention in the RCT,[5] and four retrospective studies was identified as IOSM or digital IOSM.[6,11-13] The remaining retrospective studies identified the intervention as IOSR.[14,15] IOSR was included as an intervention in this report because the term was used interchangeably with IOSM in the literature. The images were acquired in the operating room and evaluated by a surgeon with[5] or without[5,6] consulting with a radiologist. In the final retrospective study, the images were reviewed remotely by a radiologist who conveyed the results verbally by telephone to the surgeon on an as-needed basis.[13] The qualifications of the individuals who evaluated the images were not disclosed in two retrospective studies.[11,12]

For the purposes of this report, "no intraoperative imaging" was considered to include imaging conducted outside the operating room as well as techniques that did not involve imaging. The authors of the RCT compared digital IOSM used by surgeons (with or without the aid of radiologists) to SSM used by radiologists on images acquired outside the operating room.[5] For SSM, while the patients remained under anesthesia, excised specimen were taken to the radiology department for imaging and interpretation by radiologists and results were reported to the surgeon in the operating room.[5] One retrospective study compared digital IOSM conducted by a surgeon who consulted with a radiologist as needed via telephone to conventional specimen radiography (CSR) conducted by radiologists on images acquired outside the operating room.[13] Three of the retrospective studies compared IOSM to IOUS and gross specimen examination (GSE) conducted within the operating room.[6,11,12] GSE involved visual inspection of sliced pieces of excised specimens.[12] One of these studies also included frozen section analysis and a combination of techniques as comparators.[12]

None of the included studies evaluated postoperative imaging as a comparator. Postoperative imaging was understood to involve diagnostic imaging following the conclusion of surgery.

Outcomes

The outcomes of interest were target lesion detection rate[5] margin status assessment,[5,6,11-15] and accuracy of margin status assessment relative to pathology.[6,11-15]

Target lesion detection

The target lesion detection rate refers to the proportion of specimen in which the intervention detected a known primary lesion.[5] This outcome was reported in the RCT.[5]

Incidence of positive, close, or negative margins

Margin status assessment involved the classification of a specimen's margin as positive, close, or negative for disease. The outcome measures that reflected the failure or success of the primary excision or surgery were the proportions (or incidence) of excised specimen with positive or negative margins, respectively. These outcome measures were reported by authors of the RCT,[5] and two retrospective comparative reviews.[13,15] Two studies included an intermediate measure of close margins.[5,13]

The distance of disease from the specimen's boundary was the primary method used to classify specimens. The thresholds that were used to determine margin status varied across the studies. A "positive" margin was defined as one with disease at the specimen's boundary (i.e., "at ink"),[5,13] within 2 mm of the boundary for palpable unifocal IBC,[15] or within 5 mm for DCIS.[15] A "close" margin was one in which disease was within 0.2 mm[5] or 1 mm[13] of the boundary but not at the boundary. A "negative" margin was one in which disease was found at 2 mm or more,[5] or at 1mm or more[13] from the boundary. In the RCT, the authors did not indicate what the status of the margin was when disease was found between 0.2 mm and 2 mm of the boundary.[5]

Incidence of positive margins, close margins, re-operations, or re-excision following pathology assessment

The accuracy of margin status assessment by an intervention was determined through comparison with findings from pathology. Outcome measures that reflected an intervention's accuracy in assessing margin status included incidence of positive margins determined at pathology,[11-13,15] incidence of positive and close margins determined at pathology,[13,14] and incidence of re-excisions following pathology.[6,11,13-15]

Definitions of margin status varied across the group of studies that reported on the accuracy of margin status assessment. A "positive" margin was defined as one with disease at the specimen's boundary (i.e., "at ink"),[6,12,13] within 2 mm of the boundary,[6,11,12,14,15] or within 5 mm of the boundary for DCIS.[15] A "close" margin was one in which disease was within 1 mm of the boundary but not at the boundary.[13] A "negative" margin was one in which disease was found at 1 mm or more from the boundary.[13]

Authors of one study indicated that surgeons required cavity shaves or re-excision (i.e., the removal of additional tissue from the cavity) if a margin was positive following pathology assessment.[15] Others suggested that re-excisions were conducted at the discretion of the surgeon following pathology assessment.[12,13]

Summary of Critical Appraisal

A summary of the critical appraisal of the studies is summarized below and additional details regarding the strengths and limitations of the included publications are available in Appendix 3.

Randomized controlled trial

The randomized controlled trial[5] had numerous strengths related to reporting, external validity, and internal validity. With regard to reporting, the study objective, patients' characteristics, inclusion criteria, exclusion criteria, interventions, and main outcomes were described clearly. Patients were treated at outpatient breast clinics associated with one tertiary care hospital strengthening external validity of the results. Internal validity was

strengthened by the use of accurate outcome measures, by recruiting patients for both groups over the same time period and from the same source, and by randomly assigning patients to the intervention and the comparator.

Regarding limitations, the authors did not report exact probability values (*P* values) for any of the outcomes of interest, estimates of the random variability in the data, or on adverse events. Although patients were recruited from outpatient breast clinics associated with a tertiary care hospital, it remains unclear whether patients who were included were representative of the entire population from which they were selected. Blinding of patients, outcomes assessors, compliance with the intervention and comparators, impact of potential confounders, and statistical power were not discussed. Importantly, data from 42% (i.e., 32 out of 76) of eligible patients were excluded from the analysis of margin status evaluation primarily due to benign pathology.

Retrospective comparative studies

Strengths common to the retrospective comparative studies[6,11-15] were that the authors clearly described their objectives, patients' characteristics, inclusion criteria, exclusion criteria, and main outcomes. All but one[6] listed potential principal confounders.[11-15] External validity was assured by enrolling patients who were treated at facilities that were representative of where patients are treated. All of the authors used appropriate statistical tests to assess the main outcomes and did not conduct unplanned subgroup analyses, thereby mitigating risk of bias. The authors limited confounding by enrolling patients for all interventions from the same sources. Two of the Canadian studies enrolled patients from a single database that included 14 facilities from the same province.[11,12]

With regard to limitations, none of the studies provided adequate details (such as radiographic settings) about the interventions, nor did they discuss adverse events. With regard to external validity, it remains unclear in all of the studies whether the patients who were enrolled were representative of the entire population from which they were sampled. As such care must be taken in generalizing the findings. Two of the studies enrolled patients from two distinctly separate time periods (prior to and after the introduction of intervention of interest), thereby potentially increasing the risk of confounding due to changes in the experience levels of the surgeons or other changes in standard care over time.[13,15] The authors of one of these studies suggested that the risk of bias may be negligible given that surgeries were conducted by seasoned surgeons and as such, their performance would have been stable across both enrollment periods.[15] Three studies[6,13,15] did not provide estimates of the random variability in the main outcomes, although two of them reported on the statistical significance of the difference between the intervention and comparators.[13,15] Despite being retrospective, two of the studies were insufficiently powered; the rest did not discuss statistical power relevant to the outcomes of interest.[11,13,14]

Summary of Findings

Rapid Response reports are organized so that the evidence for each research question is presented separately.

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

Clinical effectiveness of intraoperative mammography

Target lesion detection rate

Results from the RCT suggest that IOSM (performed by surgeons within the operating room) was equally as effective at detecting lesions as SSM images (acquired and evaluated by radiologists outside the operating room).[5] Both techniques enabled operators to detect 97% of 22 primary target lesions in each group.[5]

Incidence of positive, close, or negative margins

The RCT reported that with the aid of IOSM, surgeons assessed 9%, 32%, or 59% of 22 excised specimens as having positive, close, or negative margins, respectively.[5] In comparison, radiologists using SSM images acquired outside the operating room determined that 18%, 14%, or 68% of a mutually exclusive set of 22 specimens had positive, close, or negative margins, respectively.[5] Margins were classified as "positive" if disease was detected "at ink" (i.e., at the specimen's boundary), "close" if disease was within 0.2 mm of the boundary but not at ink, and "negative" if disease was found at 2 mm or further from the boundary.[5] The patients had surgery primarily for IBC and less often for DCIS, atypia, and benign lesions.[5] Both techniques classified fewer margins as positive relative to pathology assessment. The incidence of positive margins detected at pathology was 18.2% and 22.7% in the groups that were evaluated by IOSM and SSM, respectively. Since the assessments were conducted in mutually exclusive groups of patients, a comparison of these detection rates does not provide an adequate assessment of the techniques' relative clinical effectiveness.

There was a significantly higher rate of cavity shaves (due to positive margins) among patients with palpable unifocal IBC who were assessed with IOSR compared to those assessed with GSE.[15] These results reflect measurements taken of specimens from two distinct groups of patients at different periods. Margins were classified as "positive" if IBC was detected within 2 mm of the boundary or if DCIS was detected within 5 mm of the boundary.

In a cohort of 214 patients with nonpalpable breast cancer, there was a significantly lower rate of positive margins among patients who were assessed with digital IOSM compared to those assessed with CSR.[13] When close margins were added, the different in incidence rates was not statistically significant.[13] IOSM images were interpreted by surgeons in the operating with the support of remote radiologists as needed while CSR images were interpreted by radiologists outside the operating room.[13] A "positive" margin was defined as one with disease "at ink", a "close" margin was one with disease within 1 mm of the boundary but not at the boundary, and a "negative" margin was one with disease at 1mm or more from the boundary.[13]

The two retrospective studies went on to report on the impact that intraoperative margin assessment had on incidence of positive margins[15] and re-operation rates[13] following pathology assessment.

Incidence of positive margins, close margins, re-operations rates, or re-excision rates following pathology assessment

In one retrospective study involving 181 patients who had partial mastectomy for sonographically occult breast cancer, a smaller proportion of patients who were assessed with IOSM needed re-excisions following pathology assessment compared with those assessed with IOUS or GSE.[6] While IOSM resulted in fewer positive margins at pathology

compared with CSR, the impact on re-operation rates following pathology assessment was not statistically significant.[13] Results from two retrospective studies from the same authors suggested that IOSM may have no statistically significant effect on the odds of detecting positive margins relative to the wire localization technique.[11,12] In the cohort of patients with pure DCIS, surgeons using IOUS and GSE reduced the odds of a positive margin (identified via pathology) compared with the wire localization technique while the odds of detecting positive margins with IOSM were not statistically different compared with the wire localization technique.[11] IOSM and IOUS had no statistically significant effect on re-excision rates relative to wire localization while GSE reduced the odds of re-excisions.[11] In the cohort of patients with IBC (with or without DCIS), IOSM and IOUS had no statistically significant effect on the odds of detecting positive margins relative to the wire localization technique, while GSE and frozen section techniques significantly reduced those odds.[12] IOUS was evaluated in groups that were at least a third smaller than the comparator groups.[11,12]

Despite higher incidence of cavity shaves with IOSR, the incidence of re-excisions (following the detection of positive margins at pathology) was not statistically different between patients with palpable unifocal IBC who were imaged with IOSR or patients evaluated with GSE.[15] One retrospective study involving patients with calcification-involved DCIS reported that an IOSR margin of 3.5 Fmm or less significantly increased the risk of positive histological margins.[14] Consequently, the authors recommended a lower threshold of 4 Fmm for classifying negative margins.

Cost-Effectiveness

No relevant evidence regarding the cost-effectiveness of intraoperative mammography for breast cancer surgery was identified; therefore, no summary can be provided.

Guidelines

No evidence-based guidelines regarding intraoperative imaging for breast cancer surgery were identified; therefore, no summary can be provided.

Limitations

The primary limitations to the body of evidence on clinical effectiveness are the heterogeneity in the designs of the studies, lack of consistency in the terminology used to describe the interventions, lack of details in describing the image acquisition techniques, the paucity of evidence derived from the Canadian population. These limitations hinder synthesis of the data and warrant the use of caution when interpreting the results of this report.

With regard to heterogeneity, among other weaknesses, the seven studies that reported on the clinical effectiveness of IOSM followed diverse protocols, included patients with diverse types of breast cancers, and used a range of methods. Some studies restricted their patient cohorts to those with DCIS[11,12,14] or IBC[15] only, while others included both.[5] Cancers varied by palpability (e.g., palpable,[15] nonpalpable[13]), radio-opacity (e.g., sonographically occult),[6] calcification, focality (e.g., unifocal)[15] and stage (e.g., 0 to III).[6] The surgical procedures also varied from excisional biopsy to gross resection. There was a lack of consistency in protocols involving IOSM. Studies varied in the preparation of the specimen, acquisition of IOSM images, interpretation of the images, and in thresholds for determining margin status. The intervention under review was identified as IOSM, digital IOSM, or IOSR. Without details on the image acquisition settings or systems used, it was not possible to ascertain

whether the interventions used across the studies were comparable. The authors reported outcomes as incidence rates, and odds ratios, making it all the more challenging to compare findings across the studies. Some authors reported on the margin status as evaluated by the intervention, while others reported on the accuracy of margin status assessment as determined at pathology.

Given that four of the seven studies were conducted outside Canada, the outcomes may not be easily replicated in Canada. Information from more Canadian sources or country-specific analyses may have improved the generalizability of the findings to patients living in Canada.

Finally, there were no economic evaluations to guide implementation decisions, nor evidence-based guidelines.

Conclusions and Implications for Decision or Policy Making

In this review, there was a limited quantity and quality of evidence on the clinical effectiveness of IOSM, no evidence on cost-effectiveness, and no relevant evidence-based guidelines. A total of seven studies were included: one randomized controlled trial,[5] and six retrospective studies.[6,11-15] Two of the studies were published by the same group of authors who reviewed charts of patients treated during the same time period; however the authors enrolled patients with different indications.[11,12]

The results were sparse and generally inconclusive, stemming from the heterogeneity of the studies, lack of consistency in the terminology used to describe the interventions, and lack of details in describing the image acquisition techniques. The clinical impact of margin status assessment varied with study parameters such as patient population and comparators. For example, while digital IOSM results better reflected pathology findings than CSR in a cohort of 214 patients with nonpalpable breast cancer, there was no significant difference in the rate of re-operation between the IOSM and CSR groups following pathology assessment.[13] Conversely, in a cohort of patients who had partial mastectomy for sonographically occult breast cancer, a smaller proportion of patients that were assessed with IOSM needed re-excisions following pathology assessment compared with those assessed with IOUS or GSE.[6]

Caution is advised in interpreting the information presented here due to the variability in the included study designs, the included studies' lack of clarity in describing the interventions, and the paucity of evidence derived from the Canadian population.[13] Additional comparative studies evaluating the clinical effectiveness of IOSM in Canada would enhance the applicability of the evidence.

When contemplating the cost-effectiveness of IOSM in Canada, decision-makers may need to consider, among other things, how the technology will be incorporated into the clinical pathway.

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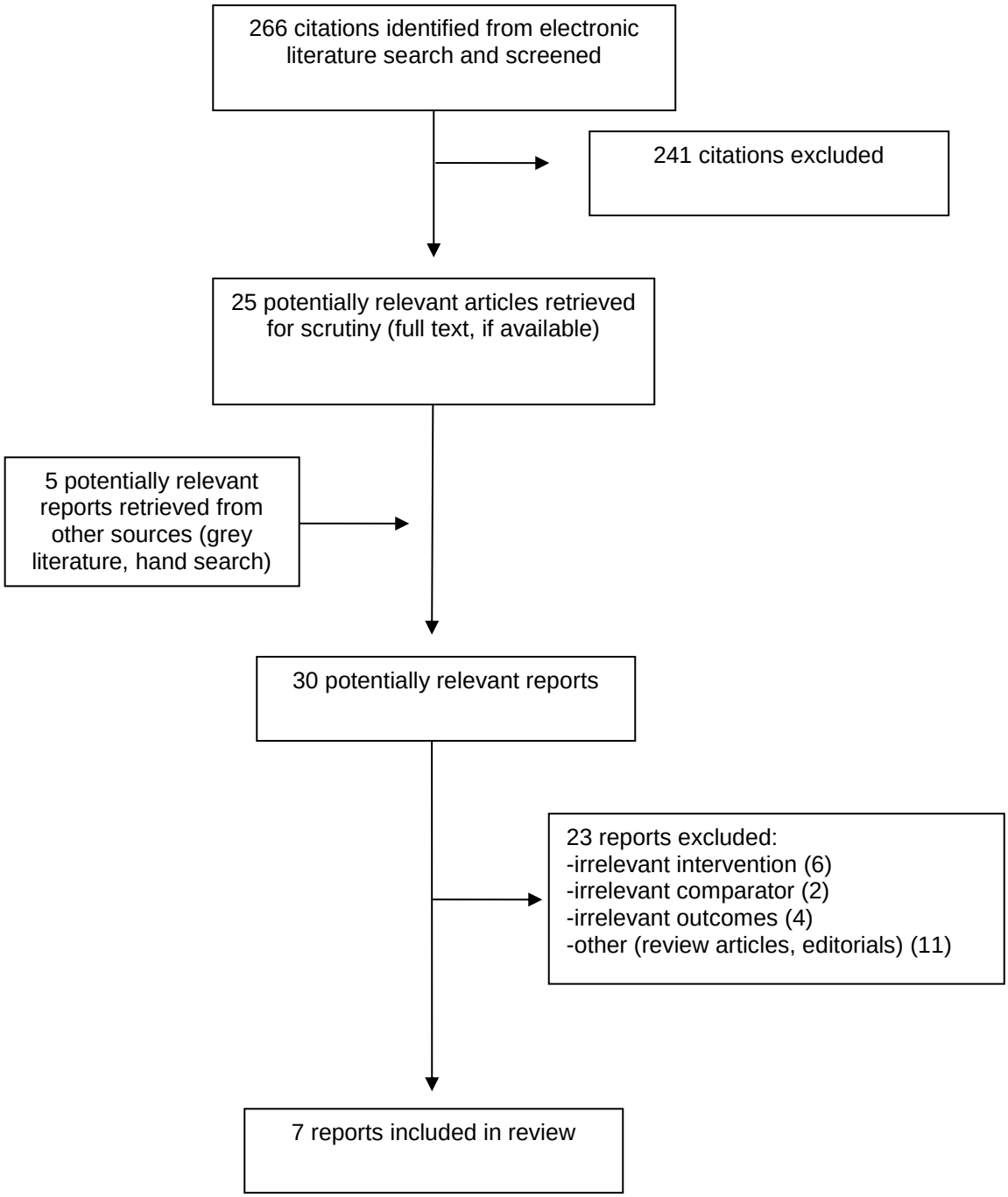
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Intraoperative specimen mammography (IOSM)				
Randomized controlled trial				
Miller, 2016,[5] United States	Randomized controlled trial	76 patients (age >18 years) requiring wire-localized lumpectomy for biopsy-proven IBC or DCIS (n=53), excisional biopsy following an abnormal mammogram (n=7), or atypia (n=12) between March 2013 and May 2015 Exclusion criteria: 4 patients because wire-localized excision could not be conducted Mean age (n=72): 58 years (range, 36 to 79)	IOSM-digital with the Faxitron system (n=22); surgeons interpreted the images SSM (n=22) conducted and interpreted by radiologists outside the OR Reference standard: pathology + visual inspection	Target lesion detection rate; incidence of positive and close margins; diagnostic test accuracy of margin status assessment relative to pathology Interpretation time, total operating time, and total procedure time were not included in this review
Retrospective comparative studies				
Larson, 2018,[6] United States	Retrospective chart review	181 patients who had partial mastectomy for sonographically occult grade 0 to III breast cancer between January 2013 and January 2014 at a single community hospital Exclusion criteria: NR Mean age: NR	IOSM images acquired with the Faxitron system and interpreted by a staff surgeon (n=26) to guide cavity shave margins. IOUS (n=63) GSE conducted outside the OR (n=38) was used to guide cavity shave margins. IOSM was acquired to confirm the marking clip but not used to assess shave margins in sonographically occult lesions	Incidence of re-excisions
Laws, 2018,[11] Canada	Retrospective population-based database review	646 patients who had wire-localized BCS for pure DCIS diagnosed	The interventions were: Single view intact	Incidence of positive margins (odds ratio) relative to wire

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		by core biopsy between January 2010 and December 2014 at any of 14 institutions in a single province Exclusion criteria: missing pathology reports, no DCIS or IBC in the resection specimen, and use of frozen section Mean age: 58.6 years (range, 27 to 86)[a]	IOSM (system NR) with (n=42) or without (n=284) macroscopic pathology IOUS (system NR) performed by the surgeon with (n=4) or without (n=17) other methods GSE with (n=42) or without (n=23) IOSM Wire localization (n=220)	localization; incidence of re-excisions (odds ratio) relative to wire localization
Lange, 2016,[14] Germany	Retrospective single cohort chart review	132 patients with calcification-associated DCIS treated with BCS between January 2009 and December 2011 at a university hospital's interdisciplinary breast care centre Exclusion criteria: NR Mean age (n=91): 57.7 ± 9.3 years	IOSR with ventro-dorsal projections (n=91) Reference standard: histology (n=91)	Incidence of positive and close margins, re-excisions and successful re-excisions; Diagnostic test accuracy of assessing margin status relative to histology
Laws, 2016,[12] Canada	Retrospective population-based database review	2304 patients with nonpalpable, biopsy-proven IBC who had wire-localized BCS between January 2010 and December 2014 at any of 14 institutions in a single province Exclusion criteria: neoadjuvant therapy, missing pathology reports, no tumor in the resection specimen, DCIS alone Mean age (n=1649): 62.7 years (range, 35 to 93)	1165 specimens were intraoperatively assessed with the following interventions: IOSM (system NR) (n=400) IOUS (system NR) (n=10) GSE with the fresh specimens sliced and visually inspected (n=560) Frozen section analysis where the specimens were microscopically	Incidence of positive margins (odds ratio) relative to wire localization

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
			inspected (n=55) Combination of techniques (n=140) Wire localization (n=479) Reference standard: pathology with a negative margin ≥ 2 mm for DCIS and no tumour at ink for IBC	
Kim, 2013,[13] Canada	Retrospective chart review	214 consecutive patients with nonpalpable breast lesions undergoing wire or seed localized BCS between December 2007 and July 2009 (n=108 cases) using CSR and from August 2009 and March 2011 (n=108 cases) at a single tertiary care hospital; following core biopsy, mammography, ultrasound, or MRI Exclusion criteria: Patients who had a mastectomy; did not have pre-operative needle localization, males, or < 18 years old Mean age (n=201): 59.6 years	IOSM-digital (n=96) with image interpretation conducted by the surgeon with or without a radiologist via telephone CSR (n=105) with single standard compression images acquired and outside the OR and evaluated by radiologists	Incidence of positive margins, positive or close margins, re-operations Mean operating time was reported but not included in this review
Layfield, 2012,[15] United Kingdom	Retrospective chart review	224 female patients undergoing BCS for palpable unifocal invasive carcinoma between October 2003 and April 2005 and between April 2006 and October 2007	IOSR with a Faxitron system from April 2006 to October 2007 (n=113) Mean age: 59.64 (range, 25 to 90) GSE by surgeons or	Incidence of cavity shaves, positive margins/re-excisions, diagnostic test accuracy of margin status assessment Findings involving the weight of excised

Table 2: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		Exclusion criteria: patients for whom excised specimen weight was not available Age: Reported for sub-groups	trainees from October 2003 to April 2005 (n=111) Reference standard: histology Mean age: 59.87 years (range, 28 to 90)	specimen were not included in the report

BCS = breast-conserving surgery; CSR = conventional specimen radiography; DCIS = ductal carcinoma in situ; GSE = gross specimen examination; IBC = invasive breast cancer; IOSR = intraoperative radiography; IOSM = intraoperative specimen mammography; IOSM-digital = digital IOSM; IOUS = intraoperative ultrasound; MRI = magnetic resonance imaging; NR = not reported; OR = operating room; SSM = standard specimen mammography.

[a] Calculated from table 1.[11]

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[16]

Strengths	Limitations
Randomized controlled trial	
Miller, 2016[5]	
Reporting • The objective of the study was clearly described • The main outcomes were clearly described in the methods section • The characteristics of the patients included in the study were clearly described • The interventions of interest were clearly described • The inclusion and exclusion criteria were clearly described • Distributions of principal confounders in each group were clearly described • The main findings of the study were clearly described • Characteristics of patients lost to follow-up were described External validity – representativeness of the findings • The staff, places, and facilities where the patients were treated were representative of the treatment the majority of patients received Internal validity – bias • No retrospective unplanned subgroup analyses were reported • The main outcome measures were accurate Internal validity – confounding • Patients in both groups were recruited from the same source • Patients in both groups were recruited over the same time period • Patients were randomized to intervention groups	Reporting • The study did not provide estimates of the random variability in the data for the main outcomes. Confidence intervals for the main outcomes were not reported. • Probability values were not reported • Adverse events were not reported External validity • It was unclear whether the patients who were asked to participate were representative of the population from which they were recruited. The study did not report on the proportion of the source population from which the patients were derived. • It was unclear whether the patients who agreed to participate were representative of the entire population from which they were recruited. A comparison of the characteristics of those who were invited and those who enrolled in the study was not presented. Internal validity – bias • Appropriate statistical tests were used to assess the time-related outcomes, but not applied to the outcomes of interest for the present review • Blinding of patients and outcomes assessors was not discussed • Compliance with the intervention and comparator were not discussed Internal validity - confounding • Although an account was made of patients who were lost to follow-up, a comparison of the characteristics of the general, invited, enrolled, and analyzed populations was not documented • Although the distribution of confounders was described, there was insufficient consideration of their impact Power • Statistical power was not discussed
Retrospective comparative studies	
Larson, 2018[6]	
Reporting • The objective of the study was clearly described • The main outcomes were clearly described in the introduction or methods sections	Reporting • The interventions of interest were not clearly described • Distributions of principal confounders in each group were not discussed

Table 3: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[16]

Strengths	Limitations
• The characteristics of the patients included in the study were clearly described • The main findings of the study were clearly described <u>External validity</u> • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of patients receive <u>Internal validity – bias</u> • No retrospective unplanned subgroup analyses were reported • The statistical tests used to assess the main outcomes were appropriate <u>Internal validity – confounding</u> • Patients in all groups were enrolled from the same source • Patients in all groups were enrolled over the same time period	• Adverse events were not reported • Estimates of the random variability in the data for the main outcomes were not reported <u>External validity</u> • It was unclear whether the patients who were asked to participate were representative of the population from which they were recruited. The study did not report on the proportion of the source population from which the patients were derived. • It was unclear whether the patients who agreed to participate were representative of the entire population from which they were recruited. A comparison of the characteristics of those who were invited and those who enrolled in the study was not presented. <u>Internal validity - confounding</u> • No consideration was given to confounding <u>Power</u> • Statistical power was not discussed.
Laws, 2018[11]	
<u>Reporting</u> • The objective of the study was clearly described • The main outcomes were clearly described in the introduction or methods sections • The characteristics of the patients included in the study were clearly described • Distributions of principal confounders in each group were clearly described • The main findings of the study were clearly described • The study provides estimates of the random variability in the data for the main outcomes. Confidence intervals for the main outcomes were reported <u>External validity</u> • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of patients received <u>Internal validity – bias</u> • No retrospective unplanned subgroup analyses were reported • The statistical tests used to assess the main outcomes were appropriate <u>Internal validity – confounding</u> • Patients in all intervention groups were recruited from the same source	<u>Reporting</u> • The interventions of interest were not clearly described • Adverse events were not reported <u>External validity</u> • It was unclear whether the patients who were asked to participate were representative of the population from which they were recruited. The study did not report on the proportion of the source population from which the patients were derived. • It iwas unclear whether the patients who agreed to participate were representative of the entire population from which they were recruited. A comparison of the characteristics of those who were invited and those who enrolled in the study was not presented. <u>Internal validity - confounding</u> • Although an account was made of patients who were lost to follow-up, a comparison of the characteristics of the general, invited, enrolled, and analyzed populations was not documented. <u>Power</u> • Statistical power was not discussed

Table 3: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[16]

Strengths	Limitations
• Patients in all intervention groups were recruited over the same time period • The impact of confounding factors was considered	
Lange, 2016[14]	
Reporting • The objective of the study was clearly described • The main outcomes were clearly described in the introduction or methods sections • The characteristics of the patients included in the study were clearly described • The interventions of interest were clearly described • Distributions of principal confounders in each group were clearly described • The main findings of the study were clearly described • The study provided estimates of the random variability in the data for the main outcomes. Confidence intervals for the main outcomes were reported External validity • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of patients receive Internal validity – bias • No retrospective unplanned subgroup analyses were reported • The statistical tests used to assess the main outcomes were appropriate Internal validity – confounding • Patients in both groups were recruited from the same source • Patients in both groups were recruited over the same time period • There was adequate consideration for confounding in the analyses from which the findings were drawn	Reporting • Adverse events were not reported External validity • It was unclear whether the patients who were asked to participate were representative of the population from which they were recruited. The study did not report on the proportion of the source population from which the patients were derived. • It was unclear whether the patients who agreed to participate were representative of the entire population from which they were recruited. A comparison of the characteristics of those who were invited and those who enrolled in the study was not presented. Internal validity – bias • Blinding of patients and outcomes assessors was not discussed Power • Statistical power was not discussed
Laws, 2016[12]	
Reporting • The objective of the study was clearly described • The main outcomes were clearly described in the introduction or methods sections • The characteristics of the patients included in the study were clearly described • Distributions of principal confounders in each group were clearly described • The main findings of the study were clearly described • The study provides estimates of the random variability in the data for the main outcomes. Confidence intervals for the	Reporting • The interventions of interest were not clearly described • Adverse events were not reported External validity • It was unclear whether the patients who were asked to participate were representative of the population from which they were recruited. The study did not report on the proportion of the source population from which the patients were derived. • It was unclear whether the patients who agreed to

Table 3: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[16]

Strengths	Limitations
main outcomes were reported External validity • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of patients received Internal validity – bias • No retrospective unplanned subgroup analyses were reported • The statistical tests used to assess the main outcomes were appropriate Internal validity – confounding • Patients in all intervention groups were recruited from the same source • Patients in all intervention groups were recruited over the same time period • The impact of confounding factors was considered	participate were representative of the entire population from which they were recruited. A comparison of the characteristics of those who were invited and those who enrolled in the study was not presented. Internal validity - confounding • Although an account was made of patients who were lost to follow-up, a comparison of the characteristics of the general, invited, enrolled, and analyzed populations was not documented. Power • The study lacked statistical power to asses intraoperative ultrasound adequately
Kim, 2013[13]	
Reporting • The objective of the study was clearly described • The main outcomes were clearly described in the introduction or methods sections • The characteristics of the patients included in the study were clearly described • Distributions of principal confounders in each group were clearly described • The main findings of the study were clearly described External validity • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of patients received Internal validity – bias • No retrospective unplanned subgroup analyses were reported • The statistical tests used to assess the main outcomes were appropriate Internal validity – confounding • Patients in both groups were recruited from the same source	Reporting • The interventions of interest were not clearly described • Adverse events were not reported • Estimates of the random variability in the data for the main outcomes were not reported External validity • It was unclear whether the patients who were asked to participate were representative of the population from which they were recruited. The study did not report on the proportion of the source population from which the patients were derived. • It was unclear whether the patients who agreed to participate were representative of the entire population from which they were recruited. A comparison of the characteristics of those who were invited and those who enrolled in the study was not presented. Internal validity – bias • Blinding of patients and outcomes assessors was not discussed Internal validity - confounding • Patients were recruited over two distinct periods • Although an account was made of patients who were lost to follow-up, a comparison of the characteristics of the general, invited, enrolled, and analyzed populations was not documented.

Table 3: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[16]

Strengths	Limitations
	Power • The study was powered to detect differences in operative time, an outcome that was not included in this review
Layfield, 2012[15]	
Reporting • The objective of the study was clearly described • The main outcomes were clearly described in the introduction or methods sections • The interventions of interest were clearly described • Distributions of principal confounders in each group were clearly described • The main findings of the study were clearly described External validity • The staff, places, and facilities where the patients were treated, were representative of the treatment the majority of patients received Internal validity – bias • The statistical tests used to assess the main outcomes were appropriate	Reporting • The characteristics of the patients included in the study were not clearly described • Adverse events were not reported • Estimates of the random variability in the data for the main outcomes were not reported External validity • It was unclear whether the patients who were asked to participate were representative of the population from which they were recruited. The study did not report on the proportion of the source population from which the patients were derived. • It was unclear whether the patients who agreed to participate were representative of the entire population from which they were recruited. A comparison of the characteristics of those who were invited and those who enrolled in the study was not presented. Internal validity – bias • The time period between the intervention and outcome was not the same for all patients as data was collected at different periods Internal validity - confounding • Patients were recruited over two distinct periods Power • The study was insufficiently powered to detect differences in re-excision rates

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Randomized controlled trial	
Miller, 2016[5]	
IOSM (n=22) vs. SSM (n=22) Target lesion detection rate: 97% (34/35) vs. 97% (35/36); *P*=NR[a] *Intraoperative assessment*[b] Incidence of positive margins: 9% (2/22) vs. 18% (4/22)[c] Incidence of close margins: 32% (7/22) vs. 14% (3/22)[c] Incidence of negative margins: 59% (13/22) vs. 68% (15/22)[c] Incidence of close and negative margins: 95.5% (21/22) vs. 81.8% (21/22) *Pathology assessment*[b] Incidence of positive margins based on pathology: 18.2% (4/22) vs. 22.7% (5/22) Incidence of close and negative margins based on pathology: 81.8% (18/22) vs. 77.3% (17/22) The statistical significance of the differences was not reported. These results suggest that while IOSM and SSM accurately detected the target lesions, the techniques identified fewer positive margins than pathology. Excluded from analysis (n=28): IOSM could not be conducted in 1 patient due to equipment malfunction; 17 were benign; 10 did not have intraoperative margin interpretation Interpretation time, total operating time, total procedure time, and post-hoc concordance results were not included in this review.	*"…[IOSM] enabled accurate identification of the target within the excision specimen ... by the operating surgeon when compared to radiologist interpretation with SSM"* (p. 518)
Retrospective comparative reviews	
Larson, 2018[6]	
IOSM (n=26) vs. IOUS vs. GSE (n=38) relative to histology Incidence of positive margins/re-excisions at pathology: 3.9% (1/26) vs. 12.7% (8/63) vs. 21.1% (8/38); suggesting that IOSM reduces the need for re-excisions[d]	"*Radiographically guided shave margins were associated with lower re-excision rates compared to shave margins based on GSE. Specifically, use of IOSM to guide select shave margins in sonographically occult lesions significantly decreases re-excision rates."* (p. 821)
Laws, 2018[11]	
IOSM (n=326) vs. IOUS (n=21) vs. GSE (n=65) **Odds of detecting positive margins relative to wire localization (odds ratio)** IOSM with or without pathology (n=326): 0.90 (CI, 0.56 to 1.41); *P*=0.650 IOUS (n=21): 0.50 (CI, 0.28 to 0.89); *P*=0.018	*"Current utilization of intraoperative margin assessment techniques does not appear to reduce positive margins or re-excision rates overall. Surgeons should be aware of the limitations of specimen mammography for margin assessment; additional investigation of other techniques such as macroscopic margin assessment by a pathologist is warranted."* (p. 1210)

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
GSE (n=65): 0.54 (CI, 0.37 to 0.80); *P*=0.002 These results suggest that IOSM had no effect on the odds of detecting positive margins relative to wire localization while IOUS and GSE decreased the odds of detecting positive margins relative to wire localization **Odds of re-excisions relative to wire localization (odds ratio)** IOSM (n=326): 1.46 (CI, 0.85 to 2.52); *P*=0.166 IOUS (n=21): 0.66 (CI, 0.35 to 1.23); *P*=0.193 GSE (n=65): 0.61 (CI, 0.39 to 0.97); *P*=0.036 These results suggest that there was no significant difference in the re-excision rates between IOSM or IOUS and wire localization while the re-excision rate with GSE was lower relative to wire localization Excluded from analysis: patients with missing pathology reports (n=2), no malignancy in the excised specimen (n=51), and use of frozen section (n=5)	
Lange, 2016[14]	
IOSR (n=91) vs. histology (n=91) **Histology results** Incidence of positive and close margins: 51.6% (47/91) Incidence of re-excision: 49.5% (51/91) Incidence of successful re-excisions: 37.3% (19/51) **Risk of histologically positive margins for radiological specimen margins ≤3.5 Fmm** OR: 1.72 (CI, 1.06 to 2.77); *P*=0.02 suggesting that an IOSR margin of ≤3.5 Fmm significantly increased the risk of positive histological margins =In multivariate analysis, for IOSR margins <4 Fmm, the increase in the risk of positive histological margins was not statistically significant (*P*=0.066). Excluded from analysis (n=41): missing images, absence of microcalcification, or initial mastectomy	"*The results of our study suggest that a 4.0 Fmm radiological margin is acceptable because the rates of involved margins were 61.8% and 36.1% for radiological margins of <3.5 Fmm and >3.5 Fmm respectively. Consequently, we recommend intraoperative re-excision in cases of radiological margins <4 Fmm."* (p. 77)
Laws, 2016[12]	
IOSM (n=400) vs. IOUS (n=10) vs. GSE (n=560) vs. frozen section (n=55) **Incidence of positive margins relative to wire localization (odds ratio)** IOSM (n=400): 1.23 (CI, 0.84 to 1.81); *P* =0.29 IOUS (n=10): 1.09 (CI, 0.50 to 2.37); *P*=0.83 GSE (n=560): 0.56 (CI, 0.39 to 0.81); *P*=0.002 Frozen section (n=55): 0.43 (CI, 0.19 to 0.98); *P*=0.046 The results suggested that IOSM and IOUS had no significant effect on the odds of positive margins relative to wire localization, while	*"…both gross assessment by pathologist and frozen section analysis significantly reduced the odds of a positive margin [over wire localization alone], while IOSM and IOUS did not demonstrate an effect on margin status. Future prospective study using standardized protocols for individual techniques and immediate re-excisions is needed to refine optimal margin assessment methods."* (p. 3295)

Table 4: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
GSE and frozen section significantly reduced the odds of detecting positive margins Excluded from analysis: Patients with neoadjuvant therapy (n=22), missing pathology reports (n=9), no malignancy in the excised specimen (n=14), DCIS alone (n=610)	
Kim, 2013[13]	
IOSM-digital (n=96) vs. CSR (n=105) Incidence of positive margins: 12.7% (10/96) vs. 26.6% (25/105); *P*=0.023 Incidence of positive or close margins: 25.3% (20/96) vs. 37.2% (35/105); *P*=0.094 Incidence of re-operations: 14.6% (14/96) vs. 17.1% (18/105); *P*=0.641 While IOSM-digital (with external interpretation by a radiologist) resulted in fewer positive margins at pathology compared with CSR, the difference in re-operation rates was not statistically significant Excluded from analysis: did not have pre-operative wire localization (n=2), had mastectomy (n=3), had bilateral benign disease (n=1), did not include mammographic specimen assessment (n=9) Mean operating time was reported but not included in this review	*"The use of [IOSM-digital], [] produced a lower number of positive and close surgical margins in comparison to CSR. [IOSM-digital] can be readily integrated into routine care, enabling the surgical team to perform and interpret specimen radiographs rapidly and make immediate surgical decisions based on these images."* (p. 709)
Layfield, 2012[15]	
IOSR (n=104) vs. GSE (n=107) Incidence of cavity shaves: 30.8% (32/104) vs. 8.4% (9/107); *P*=0.001; the introduction of IOSR led to a significant increase in the proportion of cavity shaves following primary excisions Incidence of positive margins (i.e., failed IO specimen assessment) following histological evaluation of the primary excised specimen: 29.8% (31/104) vs. 24% (26/107); *P*=0.60 These results suggest that there was no statistically significant difference in detection of positive margins at pathology. Data from 13 patients who were lost to follow-up were excluded from the analysis	Introduction of IOSR did not have a positive impact on the incidence of positive margins at pathology despite a higher incidence of cavity shaves.

CI = 95% confidence interval; CSR = conventional specimen radiography; GSE = gross specimen examination; IO = intraoperative; IOSM = intraoperative mammography; IOSR = intraoperative radiography; IOUS = intraoperative ultrasound; NR = not reported; SSM = standard specimen mammography.

[a] Included feedback from radiologists, as needed

[b] Evaluated two mutually exclusive populations

[c] These proportions do not reflect the diagnostic accuracy values presented

[d] *P* = 0.03 for the difference between IOSM and GSE

Appendix 5: Additional References of Potential Interest

Guidelines with Unclear Methodology

Appavoo S, Aldis A, Causer P, et al. CAR practice guidelines and technical standards for breast imaging and intervention. Ottawa (ON): Canadian Association of Radiologists; 2016: https://car.ca/wp-content/uploads/Breast-Imaging-and-Intervention-2016.pdf. Accessed 2019 Apr 22.

Kuerer HM, Smith BD, Chavez-MacGregor M, et al. DCIS margins and breast conservation: MD Anderson Cancer Center multidisciplinary practice guidelines and outcomes. J Cancer. 2017;8(14):2653-2662.
PubMed: PM28928852

Diagnostic Test Accuracy Studies

Buggi F, Mingozzi M, Curcio A, et al. Intra-operative radiological margins assessment in conservative treatment for non-palpable DCIS: correlation to pathological examination and re-excision rate. SpringerPlus. 2013 Dec;2(1):243.
PubMed: PM23741658

Ihrai T, Quaranta D, Fouche Y, et al. Intraoperative radiological margin assessment in breast-conserving surgery. Eur J Surg Oncol. 2014 Apr;40(4):449-453.
PubMed: PM24468296

Pop MM, Cristian S, Hanko-Bauer O, Ghiga DV, Georgescu R. Obtaining adequate surgical margin status in breast-conservation therapy: intraoperative ultrasound-guided resection versus specimen mammography. Clujul medical (1957). 2018;91(2):197-202.
PubMed: PM29785158