Ontario Health
Cancer Care Ontario

Guideline 1-25 GL

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

Preoperative Breast Magnetic Resonance Imaging Guideline

Derek Muradali, Glenn G. Fletcher, Erin Cordeiro, Samantha Fienberg, Ralph George, Supriya Kulkarni, Jean Seely, Rola Shaheen, Andrea Eisen, and the Preoperative Breast MRI Expert Panel

Report Date: March 24, 2023

The evidence base for this guideline is Evidence Summary 1-25 ES plus some additional analysis of the data in the current document. 1-25 ES is available at https://www.cancercareontario.ca/sites/ccocancercare/files/assets/pebc1-25es.pdf

For information about this document, please contact Derek Muradali, the lead author, through the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the OH (CCO) website at https://www.cancercareontario.ca/en/guidelines-advice or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Muradali D, Fletcher GG, Cordeiro E, Fienberg S, George R, Kulkarni S, et al. Preoperative Breast Magnetic Resonance Imaging Guideline. Toronto (ON): Ontario Health (Cancer Care Ontario); 2023 March 24. Program in Evidence-Based Care Guideline No.: 1-25 GL.

PUBLICATIONS RELATED TO THIS REPORT

Muradali D, Fletcher GG, Cordeiro E, Fienberg S, George R, Kulkarni S, Seely JM, Shaheen R, Eisen A. Preoperative Breast Magnetic Resonance Imaging: An Ontario Health (Cancer Care Ontario) Clinical Practice Guideline. Current Oncology 2023; 30(7):6255-6270. https://doi.org/10.3390/curroncol30070463

Eisen A, Fletcher GG, Fienberg S, George R, Holloway C, Kulkarni S, Seely JM, Muradali D. Breast Magnetic Resonance Imaging for Preoperative Evaluation of Breast Cancer: A Systematic Review and Meta-Analysis. Canadian Association of Radiologists Journal. 2023;0(0). https://journals.sagepub.com/doi/10.1177/08465371231184769

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Preoperative Breast Magnetic Resonance Imaging Guideline

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For background, potential benefits and harms, key evidence associated with each recommendation, and technical and implementation considerations see Section 2.

GUIDELINE OBJECTIVES

To make recommendations about whether preoperative breast magnetic resonance imaging (MRI) should be added to conventional imaging (mammography and/or ultrasound) in patients with newly diagnosed breast cancer, and to make recommendations about specific indications if evidence allows.

TARGET POPULATION

Patients diagnosed with breast cancer of any stage for which additional information on disease location or extent in the breast obtained prior to surgery may influence staging, treatment, or prognosis. The guideline does not address patients diagnosed with breast cancer but without an identified cancerous lesion in the breast (occult breast cancer).

INTENDED USERS

1. Radiologists, surgeons, and other clinicians involved in determining extent of disease and treatment of patients diagnosed with breast cancer.
2. Members of the Breast Cancer Advisory Committee, Ontario Health (Cancer Care Ontario) (OH [CCO]) staff, and others involved in the review and update of the Breast Cancer Pathway Map [see https://www.cancercareontario.ca/en/pathway-maps/breast-cancer].

RECOMMENDATIONS

Recommendation 1
Preoperative breast MRI ***should be considered*** on a case-by-case basis in patients diagnosed with breast cancer for whom additional information about disease extent could influence treatment. The ensuing decision of whether to conduct MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences. Stronger recommendations for specific situations are provided in Recommendations 2 and 3.
Qualifying Statements for Recommendation 1
• Benefits and harms (see Key Evidence and Table 2-1) may vary depending on patient and disease characteristics such as breast density, tumour size, tumour stage, number and distribution of tumours (multicentric or multifocal), subtype of cancer, type of surgery being considered or preferred, adjuvant treatment, and patient factors/comorbidities. • System issues such as MRI availability may result in treatment delays that may modify the decision. • "Treatment" in the recommendation includes surgery as well as radiation and systemic treatment.

- In patients with strong preference for mastectomy or with contraindications to breast conserving surgery (BCS), MRI is unlikely to change surgical planning in the ipsilateral breast. Breast MRI may still impact treatment if mammographically occult contralateral breast cancer (CBC) is detected.
- Contrast-enhanced mammography (contrast-enhanced spectral mammography, contrast-enhanced digital mammography), diffusion-weighted imaging (DWI) MRI, magnetic resonance spectroscopy, or other advanced imaging techniques are known to provide additional information beyond that of conventional imaging and be suitable instead of or in addition to CE-MRI. Potential adverse effects due to contrast agent and radiation exposure vary among these techniques, whereas many other potential benefits and harms in Table 2-1 would be relevant. These are mentioned briefly in the systematic review, but evaluation was outside of scope. They are less widely available and there is much less evidence regarding their effect on patient outcomes.

Recommendation 2

Preoperative breast MRI ***is recommended*** in patients diagnosed with invasive lobular carcinoma (ILC) for whom additional information about disease extent could influence treatment. The decision of whether to conduct MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences.

Qualifying Statements for Recommendation 2

- Risks and benefits will vary depending on patient and disease characteristics.
- System issues such as MRI availability may result in treatment delays that may modify the decision.

Recommendations related to MRI and treatment planning but without comparative studies in the Evidence Summary

Recommendation 3

Preoperative breast MRI ***is recommended***, based on the opinion of the Working Group, in the following situations:

a) To aid in surgical planning of BCS in patients with suspected or known multicentric or multifocal disease.
b) To identify additional lesions in patients with dense breasts.
c) To determine the presence of pectoralis major muscle/chest wall invasion in patients with posteriorly located tumours or when invasion of the pectoralis major muscle or chest wall is suspected.
d) To aid in surgical planning for skin/nipple-sparing mastectomies or for autologous reconstruction, oncoplastic surgery, and BCS with suspected nipple/areolar involvement.
e) Patients with familial/hereditary breast cancer but who have not had recent breast MRI as part of screening or diagnosis.

Qualifying Statements for Recommendation 3

Preoperative breast MRI is recommended in the above situations if additional information about disease extent could influence treatment. The decision of whether to conduct MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences.

Preoperative Breast Magnetic Resonance Imaging Guideline

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To make recommendations about whether preoperative breast magnetic resonance imaging (MRI) should be added to conventional imaging (mammography and/or ultrasound) in patients with newly diagnosed breast cancer, and to make recommendations about specific indications if evidence allows.

TARGET POPULATION

Patients diagnosed with breast cancer of any stage for which additional information on disease location or extent in the breast obtained prior to surgery may influence staging, treatment, or prognosis. The guideline does not address patients diagnosed with breast cancer but without an identified cancerous lesion in the breast (occult breast cancer).

INTENDED USERS

1. Radiologists, surgeons, and other clinicians involved in determining extent of disease and treatment of patients diagnosed with breast cancer.
2. Members of the Breast Cancer Advisory Committee, Ontario Health (Cancer Care Ontario) (OH [CCO]) staff, and others involved in the review and update of the Breast Cancer Pathway Map [see https://www.cancercareontario.ca/en/pathway-maps/breast-cancer].

BACKGROUND

Suspected breast cancer based on clinical examination or screening mammography is generally confirmed by diagnostic mammography (with or without ultrasound) and biopsy. Surgery may be preceded by further advanced imaging of higher sensitivity or diagnostic utility, with contrast-enhanced breast MRI (CE-MRI, often referred to as MRI) being the most widely used to characterize locoregional extent of breast cancer. It has been established that MRI has higher sensitivity than mammography and ultrasound; however, there is less consensus on whether the additional information provided by MRI, including detection of additional lesions, improves patient outcomes. Use of breast MRI after diagnosis of cancer but prior to surgery to detect additional breast lesions or provide additional information on disease distribution or extent to guide surgery or systemic therapy is the topic of our recent Evidence Summary (systematic review) (1) and this guideline.

Breast MRI has sensitivity for detecting cancer of greater than 90%, and as high as 97% to 100% (2-5) in some studies of screening or for preoperative use after diagnosis. Studies published prior to 2000 had suggested poor sensitivity for ductal carcinoma in situ (DCIS); however, with improved equipment and radiologist expertise this is no longer the case (6-8). MRI specificity depends on study populations, technical methods, and criteria for interpretation. It is generally greater than 70%, and up to 97% has been reported (2). The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) Atlas sets a benchmark for specificity in screening MRI as 85% to 90% (9).

Benefits and harms of preoperative MRI

It has been established that breast MRI can provide additional information on lesion presence, size, location, and distribution; it is less certain in what circumstances this will lead to better patient outcomes. There are both potential benefits and harms to consider (see

Section 4 and Table 2-1), and the relative importance will vary depending on patient and disease characteristics; technical considerations related to equipment and radiology team expertise; and system considerations such as cost, availability of equipment and staff, and wait lists for MRI and other procedures and consultations.

Table 2-1. Potential benefits and harms of preoperative MRI

Factor	Potential Benefits	Potential Harms
High Sensitivity	• MRI is not impacted by breast density which limits the sensitivity of mammography. • Higher cancer detection rates with MRI than mammography, with greater ability to detect occult cancer in the ipsilateral breast with multifocal and multicentric disease. • More accurate staging of the contralateral breast reduces the rate of breast cancer detected in follow-up. • Allows detection of all cancerous lesions at the start so they can be treated at one time instead of having pre-existing cancers only being detected on short-term follow-up; this can have cost benefit (patient and health-care system), reduce anxiety, and improve quality of life of patients. • Confirmation of limited disease may allow more conservative treatment such as partial breast irradiation (including patients with previous radiotherapy), omission of systemic therapy. • May allow a longer interval between initial treatment and follow-up imaging. • Additional information from MRI reduces the frequency of reoperations to achieve clear margins and reduces rate of unplanned (salvage) mastectomy subsequent to initial BCS. This can have cost benefit (patient and health-care system), reduce surgical complications, reduce anxiety, and improve quality of life of patients. • May confirm or rule out the feasibility of nipple-sparing mastectomy. • In the setting of Paget disease with negative conventional imaging studies, MRI can identify underlying breast malignancy, facilitating proper treatment planning.	• Higher breast biopsy rates, including some lesions that will be negative for cancer (i.e., false-positive by MRI). • Higher mastectomy rates with MRI when disease extent is greater than shown on conventional imaging. • Repeat (short interval follow-up) MRIs may be required for BI-RADS 3 lesions if MRI-guided biopsy was not conducted or with benign breast biopsies. • More aggressive surgery or other treatment due to knowledge of additional lesions may not change survival outcomes. • MRI is not necessarily more accurate in estimating tumour size than other imaging; the optimal modality may vary with tumour characteristics.
Specificity	• Specificity is generally greater than 70%, and up to 97% has been reported (2). MRI specificity depends on study populations, technical methods, and criteria for interpretation.	• Specificity may be lower than mammography in some MRI centres or for some applications. • MRI-detected lesions require biopsy for tissue confirmation and may include false-positive lesions.
Patient Factors	• May reduce the mastectomy rate in patients initially opting for mastectomy due to fear of more extensive disease and not due to clinical factors. • Reduction in anxiety for some patients as they are more confident regarding appropriateness of treatment planned or received.	• Some patients are not suitable for MRI (anxiety, claustrophobia, MRI does not accommodate body habitus, other patient concerns) or do not want to undergo this procedure. • Increased anxiety for some patients regarding MRI procedure or biopsies, or while waiting for these to occur or results to be reported.

Adverse Effects		• Gadolinium contrast agents may cause allergic reactions (≈0.1% of patients). • Gadolinium retention, especially after multiple MRIs, has been reported in the brain; long-term effects are uncertain but have not been reported to date. Accumulation depends on type of contrast agent and cumulative exposure. • Nephrogenic systemic fibrosis may occur in patients with acute kidney injury or severe chronic kidney disease; risk varies with type and volume of gadolinium contrast agent used.
Delay in treatment		• Breast MRI use may potentially lead to delays in treatment due to both MRI scheduling and characterization of any identified lesions (biopsies and histopathology analysis/reporting). • May increase anxiety for patients while waiting for treatment.
Equity	• Universal access to preoperative MRI would result in more health care equity, provided equivalent facilities and staffing are available.	• Breast MRI, including expertise for interpretation, is not available in all centres and some patients may need to travel long distances.
Cost	• Better lesion characterization may reduce operative costs by reducing rates of reoperations (direct surgical costs for multiple operations, treating surgical complications, patient time), costs to treat metachronous contralateral breast cancer, and longer-term costs due to decreased recurrence.	• Addition of MRI and subsequent biopsy of lesions will add to the initial diagnostic cost.

Abbreviations: BCS, breast conserving surgery; BI-RADS, Breast Imaging Reporting and Data System; MRI, magnetic resonance imaging

Evidence Base for Recommendations

The Evidence Summary (systematic review) on preoperative breast MRI (1) is the primary evidence base for this guideline. Embase, MEDLINE, and EBM Reviews (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews) were searched until January 18, 2021. A focused search was conducted in July 2022 (see Section 4), to locate any subsequent publications of the included randomized controlled trials (RCTs) and studies previously indicated to be in progress. The review included eight RCTs, two prospective cohort studies, and forty-three retrospective comparative studies. Minor revision and additional quality assessment of the included studies was conducted as part of the guideline development process (see Section 4 of this document). The Evidence Summary should be consulted for details of each study. Forest plots provide a concise summary of studies for each outcome both overall and for various subgroups (see Figures in Section 4) and data based on the forest plots are provided in Table 4-3. The other tables in Section 4 provide quality assessment according to GRADE (Grading of Recommendations, Assessment, Development and Evaluations; see https://www.gradeworkinggroup.org/) (10, 11). As an aid in interpretating magnitude of effect, an approximation of absolute effects is reported in Tables 4-4 and 4-5 and reproduced in the Key Evidence accompanying the recommendations. Conclusions in Section 4 use standardized wording suggested by Santesso et al (12) and have been modified slightly for use in the Key Evidence.

RECOMMENDATIONS, KEY EVIDENCE[1], AND JUSTIFICATION

Recommendation 1

Preoperative breast MRI ***should be considered*** on a case-by-case basis in patients diagnosed with breast cancer for whom additional information about disease extent could influence treatment. The ensuing decision of whether to conduct MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences.

Stronger recommendations for specific situations are provided in Recommendations 2 and 3.

Qualifying Statements for Recommendation 1

- Benefits and harms (see Key Evidence and Table 2-1) may vary depending on patient and disease characteristics such as breast density, tumour size, tumour stage, number and distribution of tumours (multicentric or multifocal), subtype of cancer, type of surgery being considered or preferred, adjuvant treatment, and patient factors/comorbidities.
- System issues such as MRI availability may result in treatment delays that may modify the decision.
- "Treatment" in the recommendation includes surgery as well as radiation and systemic treatment.
- In patients with strong preference for mastectomy or with contraindications to breast conserving surgery (BCS), MRI is unlikely to change surgical planning in the ipsilateral breast. Breast MRI may still impact treatment if mammographically occult contralateral breast cancer (CBC) is detected.
- Contrast-enhanced mammography (contrast-enhanced spectral mammography, contrast-enhanced digital mammography), diffusion-weighted imaging (DWI) MRI, magnetic resonance spectroscopy, or other advanced imaging techniques are known to provide additional information beyond that of conventional imaging and be suitable instead of or in addition to CE-MRI. Potential adverse effects due to contrast agent and radiation exposure vary among these techniques, whereas many other potential benefits and harms in Table 2-1 would be relevant. These are mentioned briefly in the systematic review, but evaluation was outside of scope. They are less widely available and there is much less evidence regarding their effect on patient outcomes.

Key Evidence for Recommendation 1

The literature review (1) compared patients with and without preoperative MRI. Re-analysis reported in Section 4 reached the following conclusions:

Recurrence

- Use of MRI is associated with a reduction of recurrence of any type (hazard ratio [HR]=0.77, 95% confidence interval [CI]=0.65 to 0.90) [moderate level of certainty].

[1] Odds ratios (OR) or hazard ratios (HR) and 95% confidence intervals (CI) are from the forest plots. The absolute (percent) results are estimates of the magnitude of effect. GRADE uses terminology *certainty of evidence*, *quality of evidence, strength of evidence,* and *confidence in the evidence* interchangeably and assigns 4 categories (high, moderate, low, and very low) for each outcome based on the overall body of evidence. This evaluation includes assessment of risk of bias, inconsistency, indirectness, imprecision, size of effect (if large), and dose response (if present).

Approximate recurrence 8.2% versus 10.5%; 2.3% less (1% to 3.6% fewer). See Figure 4-5a, Table 4-4e, and Table 4-5e.

Contralateral Cancer

- Use of MRI is associated with an increase in detection of synchronous CBC (prior to initial surgery) (HR=2.52, 95% CI=1.75 to 3.62; HR>1 indicates increased detection with MRI) [moderate level of certainty]. Approximate synchronous CBC detection 4.7% versus 1.9%; 2.8% more (1.4% to 4.8% more). See Figure 4-4a and Tables 4-3, 4-4d, and 4-5d.
- Use of MRI is associated with a slight reduction in metachronous CBC (HR=0.71, 95% CI=0.59 to 0.85) [moderate level of certainty]. Approximate metachronous CBC 1.7% versus 2.4%; 0.7% fewer (0.4% to 1.0% fewer). See Figure 4-4b and Tables 4-3, 4-4d, and 4-5d.

Conversion Mastectomy

- Use of MRI is associated with a reduction in the rate of conversion mastectomy (odds ratio [OR]=0.76, 95% CI=0.58 to 0.99) [low level of certainty]. Approximate conversion mastectomy rate 5.5% versus 7.1%; 1.6% fewer (95% CI=0.1% to 2.9% fewer). See Figure 4-3f and Tables 4-3, 4-4c, and 4-5c.

Positive Margins

- Use of MRI reduced the rate of positive margins in studies with low or low-moderate risk of bias (OR=0.57, 95% CI=0.36 to 0.89) [moderate level of certainty]. Approximate rate of positive margins 6.5% versus 10.9%; 4.4% fewer (95% CI=1.1% to 6.7% fewer). See Tables 4-3, 4-4b and 4-5b.

Reoperations and Re-excisions

- Use of MRI is associated with a reduction in the rate of reoperation (OR=0.73, 95% CI=0.63 to 0.85) [low level of certainty]. Approximate rate of reoperation 14.4% versus 18.7%; 4.3% fewer (95% CI=2.3% to 6.0% fewer). See Figure 4-3b and Tables 4-3, 4-4c, and 4-5c.
- Use of MRI is associated with a reduction in the rate of re-excision (OR=0.63, 95% CI=0.45 to 0.89) [low level of certainty]. Approximate rate of re-excision 6.9% versus 10.5%; 3.6% fewer (95% CI=1.0% to 5.5% fewer). See Figure 4-3d and Tables 4-3, 4-4c, and 4-5c.

Mastectomy Rates

- Use of MRI is associated with an increase in the initial mastectomy rate in patients planned (prior to MRI) for BCS (OR=5.18, 95% CI=2.37 to 11.29) [very low level of certainty]. Approximate initial mastectomy rate 5.5% versus 1.1%; 4.4% more (95% CI=3.6% to 11.5% more). Use of MRI is associated with an increase in final mastectomy rate (OR=1.87, 95% CI=1.23 to 2.85) [very low level of certainty]. Approximate final mastectomy rate 14% versus 8%; 6% more (95% CI=1.7% to 11.9% more). See Figures 4-1a and 4-1c and Tables 4-3, 4-4a and 4-5a.
- Studies including all patients diagnosed with breast cancer (not restricted to predetermined BCS) showed that use of MRI is associated with an increase in initial mastectomy rate (OR=1.29, 95% CI=1.09 to 1.35) [low level of certainty]. Approximate initial mastectomy rate 38.0% versus 32.3%, 5.8% more (95% CI=1.9% to 9.9% more). Use of MRI is associated with an increase of final mastectomy rate (OR=1.19, 95% CI=1.06 to 1.33). Approximate final mastectomy rate 41.8% versus 37.6%, 4.2% more (95% CI=1.4% to 6.9% more). There was no difference in final mastectomy rate when the trials using

registry data were excluded (OR=0.98, 95% CI=0.82 to 1.17). See Figures 4-1a and 4-1c and Tables 4-3, 4-4a, and 4-5a.

Other supporting studies (not part of the meta-analysis)

- A meta-analysis of 22 studies by Brennan et al. found the incremental CBC detection rate over conventional imaging to be 4.1% (13). This is much higher than the cancer rate of 1.4% in the High Risk Ontario Breast Screening Program (14) in which MRI is routinely used.
- Two studies which characterized mammographically occult ipsilateral lesions (>2 cm away or in different quadrants than the index tumour) found that they were larger than the index lesion in approximately 20% of cases (15, 16). In the absence of MRI, such tumours, unless detected coincidentally during operation of the index tumour, would be untreated surgically.
- Guidelines by The Canadian Association of Radiologists (17), the European Society of Breast Imaging (EUSOBI) (18, 19), and Blue Shield of California/Blue Cross Blue Shield Association (20, 21) have similar recommendations.

Justification for Recommendation 1

- We consider the significant reduction in recurrence, probable improvement in disease-free survival (DFS) and metachronous CBC, and reduction in reoperations (re-excisions and conversion mastectomies) evidence of benefit that outweighs the potential negative effects overall. This recommendation places higher value on treating cancer in a single operation and avoidance of recurrence than on avoidance of discomfort of MRI and potential additional biopsies.
- While absolute benefit is small for most outcomes and not always statistically significant, the trend is toward MRI being beneficial for each outcome, and therefore this consistency strengthens the conclusion that preoperative MRI has a positive impact in general.
- While MRI use is associated with an increase in mastectomy rate, reasons are likely to be multifactorial, including to encompass additional foci of cancer, lack of BCS/oncoplastic surgery expertise for more complex cases, and patient preferences. In retrospective studies (and some of the RCTs) MRI was used for clinical reasons that may not have been recorded or adjusted for but that could be related to mastectomy use. As mastectomy rates may vary by country, region, hospital, and surgeon, and due to patient factors such as age, relationship status, and race/ethnicity, the additional effect of MRI for mastectomy outcomes is difficult to assess.

Recommendation 2

Preoperative breast MRI ***is recommended*** in patients diagnosed with invasive lobular carcinoma (ILC) for whom additional information about disease extent could influence treatment. The decision of whether to conduct MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences.

Qualifying Statements for Recommendation 2

- Risks and benefits will vary depending on patient and disease characteristics.
- System issues such as MRI availability may result in treatment delays that may modify the decision.

Key Evidence for Recommendation 2

Evidence for Recommendation 1 would apply, in addition to stronger evidence specifically for ILC:

- Use of MRI is associated with a reduction in the rate of conversion mastectomy in patients with ILC (OR=0.38, 95% CI=0.25 to 0.56) [high certainty of evidence]. Approximate conversion mastectomy rate in ILC 5.9% versus 14.2%; 8.3% fewer (5.7% to 10.3% fewer).
- Use of MRI is associated with a reduction in the rate of positive margins in patients with ILC (OR=0.63, 95% CI=0.49 to 0.82) [moderate level of certainty]. Approximate rate of positive margins 18.9% versus 27.0%; 8.1% fewer (3.7% to 11.7%).
- Use of MRI is associated with a large reduction in the rate of reoperation in patients with ILC (OR=0.30, 95% CI=0.13 to 0.72) [moderate level of certainty]. Approximate rate of reoperation 12.3% versus 31.9%; 19.6% fewer (6.77% to 26.1% fewer).
- Lobbes et al (22) found MRI increased detection of synchronous CBC in ILC (OR=4.07, 95% CI=1.73 to 3.61, p<0.001) (HR>1 indicates increased detection with MRI).
- A review of the literature by Mann et al (23) found synchronous CBC detected by MRI in 7% of patients (95% CI=4% to 12%), and that the rate was almost twice as high as for invasive ductal carcinoma. The recommendation is consistent with guidelines by EUSOBI (19), the European Society of Breast Cancer Specialists (EUSOMA) (24), Institut national d'excellence en santé et en services sociaux (INESSS) (25), and The Royal College of Radiologists (London) (26).

Justification for Recommendation 2

- We consider the significant reduction in positive margins resulting in a large reduction in reoperations (including conversion mastectomy), in addition to the benefits in survival and recurrence for all patients (see Recommendation 1) to be evidence of benefit that outweighs the potential negative effects overall. This recommendation places higher value on treating cancer in a single operation and avoidance of recurrence than on avoidance of discomfort of MRI and potential additional biopsies. The benefit of MRI is consistent with results of studies which reported that compared to invasive ductal carcinoma, ILC has been found more difficult to detect by mammography, more likely multifocal, more often occurs with synchronous CBC, and has more involved margins after initial resection (27-32).

Recommendations related to MRI and treatment planning but without comparative studies in the Evidence Summary

Recommendation 3

Preoperative breast MRI ***is recommended***, based on the opinion of the Working Group, in the following situations:

f) To aid in surgical planning of BCS in patients with suspected or known multicentric or multifocal disease.
g) To identify additional lesions in patients with dense breasts.
h) To determine the presence of pectoralis major muscle/chest wall invasion in patients with posteriorly located tumours or when invasion of the pectoralis major muscle or chest wall is suspected.

i) To aid in surgical planning for skin/nipple-sparing mastectomies or for autologous reconstruction, oncoplastic surgery, and BCS with suspected nipple/areolar involvement.
j) Patients with familial/hereditary breast cancer but who have not had recent breast MRI as part of screening or diagnosis.

Qualifying Statements for Recommendation 3

Preoperative breast MRI is recommended in the above situations if additional information about disease extent could influence treatment. The decision of whether to conduct MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences.

Key Evidence and Justification for Recommendation 3

Comparative studies meeting the evidence review inclusion criteria were not found. These uses are recommended based on expert opinion of the authors, and are consistent with recommendations in other guidelines (19-21, 24-26, 33, 34). Some of these situations are implicit in Recommendation 1; however, the authors wanted to draw attention to these uses.

a) Most studies in the literature review (1) either excluded multicentric and multifocal disease or included these in the list of factors used to adjust results in multivariate analysis, indicating these are known to influence outcomes, but with the result that we did not find direct comparison of outcomes according to MRI use. The presence of multicentric and multifocal disease increases complexity of surgical planning and in older guidelines was a contraindication to BCS. When the disease is well-characterized, possibility of BCS may be increased in some cases and ruled out in others, and likelihood of incidental finding during surgery decreased. Consensus of the authors is that the increased sensitivity of MRI justifies its use in suspected/known multicentric or multifocal disease if BCS is desired.

b) Several studies mentioned in the literature review (1) reported that sensitivity of mammography decreases as breast density increases, while sensitivity of MRI is high and independent of breast density. GEMMA (Gadobutrol-Enhanced MR Mammography) trials studied MRI in patients with newly diagnosed and histologically proven breast cancer. In GEMMA1, MRI sensitivity was 83% (independent of density), while sensitivity of mammography decreased from 79% to 62% as breast density increased (35). Corresponding results in the GEMMA2 trial were 91% (independent of density) for MRI and 82% (low density) to 64% (high density) for mammography. The Ottawa study of preoperative MRI found additional lesions changing surgical management in 31% of patients with low density (fat density) and 62% with dense breasts (36). Screening studies reported similar variations in sensitivity of mammography with breast density. The Supplemental MRI Screening for Women with Extremely Dense Breast Tissue (DENSE trial) randomized 40,373 women with extremely dense breast tissue and normal screening mammography to either supplemental MRI or only mammography, and found MRI reduced interval cancers by 50% in those offered MRI, and 80% in those who agreed to have an MRI (37-39). A systematic review and meta-analysis (40) found breast density is one of the strongest risk factors for breast cancer.

c) Tumours near the chest wall may invade the pectoralis major muscle or involve the chest wall and thus accurate knowledge of tumour extent will influence treatment planning. MRI has been found to have high sensitivity in detecting muscle or chest wall involvement (41-44).

d) Standard BCS may lead to fair to poor esthetic and functional results (45) and more complex oncoplastic surgery or mastectomy may be more appropriate if the optimal tumour-to-breast ratio for each quadrant is exceeded. Breast MRI or other advanced imaging (e.g., positron emission tomography/computed tomography) may be a prerequisite for extreme oncoplasty (46). MRI is frequently used prior to nipple-sparing mastectomy, especially in the case of centrally located tumours (47-51). MRI may rule out nipple involvement such that 2 cm is no longer considered a minimum tumour-to-nipple distance; 5 mm (52) or 1 cm (53-58) may be sufficient.

e) Hereditary cancer patients have a high risk of synchronous and metachronous CBC. A systematic review reported 10-year CBC rates of 25% to 31% for patients with germline mutations compared to 4% to 8% for sporadic cases (59).

Other Comments

Several other applications of breast MRI are generally accepted but outside the scope of the current work. This includes breast cancer screening, use prior to definitive diagnosis in cases with diagnostic uncertainty, occult breast cancer, or Paget disease of the breast. MRI or other advanced imaging may be used to localize the tumour prior to and following neoadjuvant therapy and to monitor response during treatment (17-21, 24, 26, 33, 60, 61).

TECHNICAL FACTORS FOR MRI USE

MRI is one of the most sensitive imaging techniques in detecting breast tumours, with the potential to be highly specific. Performance depends on the equipment and MRI techniques used and expertise of those conducting the analysis. The literature review (1) identified several technical documents and standards for MRI use. Guidance on performance of CE-MRI and biopsies by the Canadian Association of Radiologists (17), American College of Radiology (ACR) (61-72), EUSOBI (19, 73), and others may be useful; however, these were not critically reviewed or compared in this evidence summary. Several studies used technical standards for MRI set by the American College of Radiology Imaging Network (ACRIN) 6667 trial (74-77) and EUSOBI as well as the ACRIN 6698 trial for DWI (78).

Best practice is that additional suspicious lesions detected by preoperative MRI be biopsied or otherwise confirmed if they could alter surgical procedures. Sites performing MRI should have the capacity for MRI-directed biopsy. This minimizes the need for repeat MRIs and associated costs, delays due to transfer of care (ultimately resulting in delay to definitive treatment) (79), and risk of patients not receiving follow-up. Familiarity with the complete process may also result in better expertise in reading and interpreting MRI (80).

IMPLEMENTATION CONSIDERATIONS

In Ontario there are currently capacity constraints that affect the availability of MRI. Additional MRI use will add system pressures unless capacity issues are resolved and may increase treatment delays beyond what are considered acceptable in some cases. Availability/accessibility varies among regions.

Patient input indicated education on benefits and risks as outlined in Table 2-1 and subsequent shared decision-making is crucial. For patients expressing reluctance about MRI due to the equipment (e.g., claustrophobia and noise), discussion could include ways to make it more acceptable such as sedation or alternative MRI units (some MRI equipment may be larger). Local availability of breast MRI and projected surgical delays due to addition of preoperative MRI may be major issues in deciding whether MRI is used. Patients indicated that they would like to be aware of these issues and whether they were modifiable in their situation.

Abbreviated or Shortened MRI

Limited availability and high cost are in part due to the long time of a full MRI scan (30-45 min). Many studies have investigated whether scan time can be reduced without sacrificing sensitivity and specificity or loss of other information. As MRI has been found of benefit in screening women at high risk of cancer (81-83), as well as intermediate risk (2, 84, 85) including patients with dense breasts (37), the majority of evidence comes from screening studies or those enriched in cancerous lesions.

The first major study of abbreviated MRI (AB-MRI) in screening by Kuhl et al. was published in 2014 (86). Women at mildly to moderately increased risk of breast cancer with negative digital mammography underwent full diagnostic MRI (8 pulse sequences). For AB-MRI, only the first two sequences (precontrast and first postcontrast acquisition) were read. Acquisition time for AB-MRI sequences was 3 min, compared to 17 min for the full protocol. Additional cancer yield was 18.2/1000. Sensitivity was 100% and specificity was similar to the full protocol (94.3% vs. 93.9%). Based on this work, many other studies of AB-MRI have been conducted. Specificity was lower in some studies (though generally >80%), and variations in protocol including additional sequences have been investigated. Adding a T2-weighted sequence and having at least two post-contrast sequences does not increase the scan time by more than 3 to 4 min and allows improved specificity equivalent to the full protocol. Ultrafast MRI involving a fast post-contrast acquisition capturing the inflow of contrast agent and may be used on its own, or together with abbreviated MRI; in the latter case it adds information but does not take additional time (87). DWI has the advantage of not requiring contrast agent and provides additional functional information but has lower sensitivity. DWI may also be used in conjunction with AB-MRI. AB-MRI has been reported for over 5400 women in 21 studies published from 2014 to 2018 (88), with overall sensitivity of 94% and specificity of 90%. A later review identified 41 studies until 2020 involving 15,680 MRI examinations (89). There is not a common definition of AB-MRI, and it sometimes refers to just the precontrast and postcontrast sequence, sequences less than 7 to 10 min, or to any protocol that is significantly shorter than the standard (full) MRI protocol.

The ECOG-ACRIN EA1141 trial "Comparison of Abbreviated Breast MRI and Digital Breast Tomosynthesis in Breast Cancer Screening in Women With Dense Breasts" found a cancer detection rate of 15.2 per 1000 women with AB-MRI and 6.2 with digital breast tomosynthesis; corresponding sensitivity was 95.7% versus 39.1% (90, 91). A similar study in Korea conducted in women with a history of breast cancer found sensitivity of 100% for AB-MRI and 54.6% for digital breast tomosynthesis (92). Of more direct relevance to the current guideline, two studies used MRI after diagnosis to guide treatment. Girometti et al. used a 3-min AB-MRI in patients with biopsy-proven lesions to detect additional disease in staging (93). Institutional policy was to refer all women with histological diagnosis of breast cancer to staging MRI. There were 36 additional lesions (confirmed by pathology) in 87 patients. Four readers found a cancer detection rate for additional lesions of 88.9% to 94.4% using AB-MRI and 91.7% to 94.4% using full protocol MRI. Lee-Felker et al used MRI to determine extent of disease in diagnosed breast cancer (94). In their study of 81 patients, sensitivity was 99% and specificity 97% with AB-MRI sequences and 98% and 94% with full MRI. MRI detected eight additional cancers (8%) of which five were ipsilateral and three were contralateral. AB-MRI scan time was approximately 3.5 min, and a full scan was 16 to 17 min.

The ACR accreditation requirements for breast MRI include a precontrast sequence (T2 weighted/bright fluid series, multi-phase T1-weighted series, and pre-contrast T1; these may be separate or combined), and early postcontrast and delayed postcontrast T1-weighted sequences (95). Massachusetts General Hospital (Boston, Massachusetts) since 2016 has used a rapid abridged multiphase (RAMP) breast MRI protocol that met ACR requirements and has a scan time of 10 min (96).

In Ontario, use of the full diagnostic protocol is common and requires 30 to 45 min. Some cancer centres including those in Ottawa and London use a shortened protocol that requires a scan time of 12 min and meets Canadian Association of Radiologists (17) and Ontario Breast Screening Program guidelines.

GUIDELINE LIMITATIONS

This literature review referred to in this guideline included primarily retrospective studies that may have additional confounding factors for which adjustment was not made. While the benefits of MRI use in these studies are generally consistent, the magnitude of benefit is less certain due to differences in patient populations, study designs, and methods of adjustment for confounders. Comparative studies on use of MRI versus no MRI that met our inclusion criteria were not found for many of the subgroups of interest, including use of systemic therapy or radiotherapy. Cost analysis was outside the scope of this work.

FURTHER RESEARCH

Advances in contrast-enhanced MRI, as well as in complementary techniques such as DWI-MRI and growing expertise of those interpreting output, have improved the sensitivity and specificity of MRI in detecting lesions and reduced the proportion of lesions that require biopsy. Accelerated or abbreviated MRI techniques may significantly reduce the acquisition time and related costs without sacrificing performance in most cases; this is a topic of recent and ongoing clinical trials.

Preoperative Breast Magnetic Resonance Imaging Guideline

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario) supported by the Ontario Ministry of Health (OMH). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control. All work produced by the PEBC is editorially independent from the OMH.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

BACKGROUND

An evidence summary (1) was prepared to provide guidance on when to use preoperative MRI to inform the Breast Cancer Pathway Map (https://www.cancercareontario.ca/en/pathway-maps/breast-cancer). Based on the findings from the completed Evidence Summary, the primary goal of the Guideline is to translate the evidence into clinical guidance recommendations regarding when preoperative breast MRI should be considered. To aid in guideline development, further analysis and quality assessment of data was conducted (see Section 4).

GUIDELINE DEVELOPERS

This guideline was developed by the Preoperative Breast MRI Guideline Development Group (Appendix 1), which was convened at the request of the Cancer Imaging Program of OH (CCO) and Disease Pathway Management of OH (CCO).

The project was led by a small Working Group of the Preoperative Breast MRI Guideline Development Group, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in radiology, surgery, medical oncology, and health research methodology. Other members of the Preoperative Breast MRI Guideline Development Group served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1 and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle (97, 98). This process includes a systematic review, interpretation of the evidence and draft recommendations by the Working Group, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework (99) as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development and to improve the completeness and transparency of reporting in practice guidelines.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence-base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers), and the potential impact on equity, acceptability, and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues) is outside of scope, but known issues are provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

GUIDELINE REVIEW AND APPROVAL

Patient and Caregiver-Specific Consultation Group

Five people with personal experience with cancer (patients/survivors/caregivers) participated as Patient Consultation Group members. They reviewed copies of the draft recommendations and provided feedback on their comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

Internal Review

Approval required that 75% of the content experts who comprised the GDG Expert Panel cast a vote indicating whether or not they approved the document, or abstained from voting for a specified reason, and of those that voted, 75% had to approve the document. In addition, the PEBC Report Approval Panel, a three-person panel with methodology expertise, had to unanimously approve the document. The Expert Panel and Report Approval Panel members could specify that approval was conditional, and that changes to the document were required.

External Review

Feedback on the approved draft guideline was obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise were identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline were contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, the ECRI Guidelines Trust, and the Guidelines International Network (GIN) Library.

ACKNOWLEDGEMENTS

The Preoperative Breast MRI Guideline Development Group would like to thank the following individuals for their assistance in developing this report:

- Michelle Ghert, Mona el Khoury, Renee Hanrahan, Donna Maziak, Sheila McNair, Amanda Roberts, Jonathan Sussman, Emily Vella, and Xiaomei Yao for providing feedback on draft versions.
- Sara Miller for copy editing.

We also acknowledge the work of Neety Panu, Christina Lacchetti, Karen Spithoff, Sarah Kellett, and Caroline Hamm in preparing an earlier unpublished review and guideline on this topic (3).

Preoperative Breast Magnetic Resonance Imaging Guideline

Section 4: Evidence Base

INTRODUCTION

The evidence base for this guideline is an evidence summary/systematic review (1) completed by OH (CCO) PEBC in December 2021. The systematic review should be consulted for further details of the methodology, data extracted from included studies, and discussion of results. Subsequent to the review, a targeted search was conducted in July 2022 to identify any additional publications related to the included RCTs and updates of any ongoing studies identified in the systematic review. Additional quality assessment and data analysis were conducted, and the GRADE approach was used to facilitate recommendation development.

RESEARCH QUESTION

In patients with newly diagnosed breast cancer, does additional information on extent of disease obtained by use of preoperative breast MRI after mammography and/or ultrasound (a) change the type or extent of surgery (BCS, unilateral or bilateral mastectomy), type or extent of radiation therapy, or use of adjuvant therapy; or (b) improve patient outcomes such as recurrence, DFS or event-free survival, distant metastasis-free survival, OS, rates of re-excision or re-operation, or quality of life?

TARGET POPULATION

Patients diagnosed with breast cancer for which additional information on disease location or extent obtained prior to surgery may influence staging, treatment, or prognosis. Individuals at high risk[2] of breast cancer who have already had MRI as part of screening are not included in the current review. It does not address patients diagnosed with breast cancer but without an identified cancerous lesion in the breast (occult breast cancer).

METHODS

The 2021 report details methods used in conducting the systematic review (1). To aid in recommendation development, the risk of bias was subsequently assessed per outcome for each study by GGF using methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (100). The Cochrane risk-of-bias (RoB) tool (revised version RoB 2) for RCTs and ROBINS-I for non-RCTs are described in this handbook and other publications (101-103). The RoB 2 tool version is available as an MS Excel-based form; the 22 August 2019 version was used and can be downloaded from https://www.riskofbias.info/welcome/rob-2-0-tool/current-version-of-rob-2. Risk of bias for RCTs was determined for categories of outcomes: mastectomy rates; resection margins; reoperations, re-excisions, conversion mastectomy; and recurrence and survival outcomes. Choices were low risk, some concerns, or high risk. For ROBINS-I the same categories of outcomes were used except that resection margins were combined with reoperations, re-excisions, and conversion mastectomy. Choices were low risk of bias (similar to a good RCT), moderate (good non-RCT but worse than good RCT), serious (important problems), critical (too problematic to be useful).

[2] For high-risk individuals, use of MRI together with mammography is the standard of care for screening in Ontario as part of the Ontario Breast Screening Program (see https://www.cancercareontario.ca/en/guidelines-advice/cancer-continuum/screening/breast-cancer-high-risk-women).

Forest plots had been created for data presentation in the evidence review using Review Manager 5.4 software (RevMan) provided by the Cochrane Collaboration (104). Those plots considered important in development of recommendations were revised. Additional sensitivity analysis was conducted excluding studies based on extraction of data from registries outside of individual institutions (e.g., regional, or country-wide databases) and excluding two RCTs with high risk of bias for non-mastectomy outcomes. Subgroup analysis was conducted for categories of in situ disease, invasive disease, and ILC; RCTs and non-RCTs; and subtypes of recurrence (local, locoregional, ipsilateral, or combination of these three subtypes, and distant recurrence).

The GRADE approach (see https://www.gradeworkinggroup.org/) was used to rate the overall quality of evidence for outcomes of mastectomy rates, positive margins, reoperations, re-excisions, conversion mastectomy, recurrence (and specific types of recurrence), DFS or recurrence-free survival (RFS), and OS. The GRADEPro guideline development tool (105) was used to determine the GRADE rating and present the results. A summary evaluation of risk of bias for each outcome and data from the forest plots was input, as well as a judgement for the other GRADE fields. As part of imprecision evaluation, the number of subjects for each outcome (optimal information size) was compared to a sample size calculation using the tool available at https://www.stat.ubc.ca/~rollin/stats/ssize/b2.html, using an alpha=0.05 and power of 0.80. Studies not meeting this sample size were judged to have serious or very serious imprecision. A factor in "other considerations" is magnitude of effect; outcomes with a large effect of preoperative MRI (OR<0.5) or very large effect (OR<0.2) were upgraded by one or two levels, respectively. GRADEPro requires entry of the baseline event rates in order for it to calculate anticipated absolute effects. This was estimated from control data (no MRI) after excluding outliers that were much higher than the other studies. GRADE uses terminology "certainty of evidence", "quality of evidence" "strength of evidence" and "confidence in the evidence" interchangeably and assigns 4 categories (high, moderate, low, and very low) for each outcome based on the overall body of evidence (10-12). These reflect "the extent to which we are confident that an estimate of the effect is correct" or "the extent to which our confidence in an estimate of the effect is adequate to support a particular recommendation" (11).

RESULTS

A publication of recurrence and survival data for the POMB trial was recently published (106). At a median of 10 years of follow-up they reported the following results: DFS 85.5% versus 80.0% (p=0.099), OS 90.9% versus 88.6% (p=0.427), breast cancer-specific survival 92.3% versus 89.5% (p=0.321), locoregional recurrence 5.9% versus 8.6% (p=0.275), contralateral recurrence 0.9% versus 2.3%, distant recurrence 7.3% versus 11.8% (p=0.116), and any recurrence (locoregional + contralateral + distant combined) 11.8% versus 19.1% (p=0.048; for stage I-III subgroup p=0.057).

RoB is one component of the GRADE assessment. RoB for RCTs is illustrated in Table 4-1. RoB was high for the outcome of mastectomy rate for all RCTs. For other outcomes, the RoB was evaluated as high for the COMICE (107) and MONET trials (108). Table 4-2 shows evaluation for each component of bias assessment for non-RCTs, as well as the overall RoB for RCTs. For non-RCTs, we only included studies with equivalent groups (historical, propensity-score matching, multivariate analysis) and therefore RoB from confounding was rated as low in some studies and moderate in most of the others. Studies with high likelihood of confounding were not included according to the inclusion/exclusion criteria of the literature review. Trials using registry data had less information available and residual confounding was more likely. With the exception of two studies (22, 109), no MRI methodology was provided for studies using

registry data; classification bias existed except for the Lobbes study which used EUSOBI criteria and Vos which indicated use of dynamic contrast-enhanced MRI.

Forest plots were recreated (see Figures 4-1 to 4-5) with the following revisions from the initial evidence summary(1):

- Inclusion of the new POMB data (106).
- Removal of data from the MIPA trial because a new publication (110) indicated that it did not meet the review criteria.
- Removal of data from Sung et al, 2014 (111) as groups are not well matched/not equivalent.
- Removal of data from Wang et al, 2018 (112) as they reported subsequent mastectomy as a surrogate for recurrence, and breast cancer-specific survival but not OS or DFS. These outcomes are not equivalent to those in other trials.
- An abstract of the B-Smart trial (113) had been included only in the data tables; re-excision data was therefore added to the revised forest plots.
- For studies with both overall and subgroup data by stage/subtype (22, 109, 114), the previous forest plots had used only the subgroup data. Plots were redone to use the overall study data except when analyzing by subgroup by stage/subtype.
- It was previously overlooked that in one study (114) propensity-matching was used for most outcomes but not re-excision results; re-excision data for this study are no longer included in the plots.
- During risk of bias evaluation, it was noted that studies using registry data had less information available and residual confounding was more likely. With the exception of two studies (22, 109), no MRI methodology was provided for studies using registry data. Table 4-3 shows ORs overall and without registry studies.
- RoB was high for the COMICE (107) and MONET randomized trials (108). Table 4-3 shows ORs overall and without these two RCTs.
- For recurrence data, outcomes have been regrouped as locoregional (ipsilateral breast or regional lymph nodes), distant, or any recurrence (locoregional + distant, and sometimes metachronous CBC). Duplicate inclusion of studies in forest plots and duplicate inclusion in summary data due to inclusion in more than one category has been corrected.
- Contralateral data had been reported as a separate category as well as in recurrence. Duplication has been eliminated.
- For synchronous CBC, HRs are now reported so that HR>1 corresponds to an increase in CBC detection with use of MRI.
- For CBC, recurrence, and survival outcomes, most studies reported HR and therefore for these outcomes all ratios were converted to HR. For other outcomes, most studies reported OR and no change was made.

GRADE results are reported in the Summary of Findings (Table 4-4) and Grade Profiles (Table 4-5). Absolute effects are given for ease of interpretation; however, these should be considered as only rough approximations due to assumptions of a single average baseline risk for each outcome or subgroup instead of a range of risks for each study used in the multivariate analyses in determining ORs.

INTERPRETATION AND CONCLUSIONS

- Based on the data presented in the summary of findings and grade profiles from GRADEPro (see Tables 4-4 and 4-5), the conclusions below were reached. Uniform

wording as suggested by Santesso et al (12) has been used[3]. The forest plots (Figures 4-1 to 4-5) should be consulted for a comparison of outcomes for each study. ORs or HRs and 95% CIs are from the forest plots and are the main results used in interpreting the effect of preoperative MRI. The absolute (percent) results are for ease of interpretation and portray the magnitude of effect; however, the calculation of CIs for these absolute effects does not take into account that baseline risks are only approximations. MRI probably increases OS slightly (HR=0.89, 95% CI=0.74 to 1.07) [moderate level of certainty]. Approximate OS 93.8% versus 93.0%; 0.7% greater survival (0.5% less to 1.8% more).

- MRI probably increases RFS/DFS (HR=0.77, 95% CI=0.53 to 1.12) [moderate level of certainty]. Approximate RFS 91.6% versus 89.3%; 2.4% greater DFS (1.2% less to 4.9% more).
- MRI probably reduces recurrence of any type (HR=0.77, 95% CI=0.65 to 0.90) [moderate level of certainty]. Approximate recurrence 8.2% versus 10.5%; 2.3% less (1% to 3.6% fewer).
    - MRI may reduce locoregional recurrence slightly (HR=0.85, 95% CI=0.69 to 1.04) [low level of certainty]. Approximate locoregional recurrence 4.8% versus 5.7%; 0.8% fewer (1.7% fewer to 0.2% more).
    - MRI may reduce distant recurrence slightly (HR=0.77, 95% CI=0.56 to 1.07) [low level of certainty]. Approximate distant recurrence 4.7% versus 6.1% (1.4% fewer (2.6% fewer to 0.4% more).
- MRI increases detection of synchronous CBC (prior to initial surgery) (HR=2.52, 95% CI=1.75 to 3.62; HR>1 indicates increased detection with MRI) [moderate level of certainty]. Approximate synchronous CBC detection 4.7% versus 1.9%; 2.8% more (1.4% to 4.8% more). A meta-analysis of 22 studies found the incremental cancer detection rate in the contralateral breast over conventional imaging to be 4.1% (13).
- MRI probably reduces metachronous CBC slightly (HR=0.71, 95% CI=0.59 to 0.85) [moderate level of certainty]. Approximate metachronous CBC 1.7% versus 2.4%; 0.7% fewer (0.4% to 1.0% fewer).
- MRI may reduce the rate of conversion mastectomy (OR=0.76, 95% CI=0.58 to 0.99) [low level of certainty]. Approximate conversion mastectomy rate 5.5% versus 7.1%; 1.6% fewer (95% CI=0.1% to 2.9% fewer).
    - MRI reduces the rate of conversion mastectomy in patients with ILC (OR=0.38, 95% CI=0.25 to 0.56) [high certainty of evidence]. Approximate conversion

[3] For MRI as the intervention, each recommendation is of the form *MRI reduces/increases outcome*, or *MRI results in a reduction/increase in outcome*. The modifier before reduce/increase (or reduction/increase) will depend on certainty of evidence. "May" or "evidence suggests" indicates low certainty evidence while "likely" or "probably" indicate moderate certainty evidence; for high certainty a modifier can be omitted (e.g., X results in a large reduction…). Magnitude of effect is divided into four categories with the modifier either before reduction/increase or after reduces/increases outcome: large effect (large reduction/increase in outcome); moderate effect (this is the default, no descriptor is needed); small important effect, (slight reduction/increase, or increases slightly); or trivial, small unimportant effect, or no effect. For very low certainty of evidence, this can be stated directly as "the evidence is very uncertain about the effect…"

mastectomy rate in ILC 5.9% versus 14.2%; 8.3% fewer (95% CI=5.7% to 10.3% fewer).

- MRI may reduce the rate of positive margins (OR=0.89, 95% CI=0.74 to 1.06) [low level of certainty]. Approximate rate of positive margins 16.5% versus 18.2%; 1.7% fewer (95% CI=4.1% fewer to 0.9% more).
    - MRI probably reduces the rate of positive margins in studies with low or low-moderate RoB (OR=0.57, 95% CI=0.36 to 0.89) [moderate level of certainty]. Approximate rate of positive margins 6.5% versus 10.9%; 4.4% fewer (95% CI=1.1% to 6.7% fewer).
    - MRI probably reduces the rate of positive margins in patients with ILC (OR=0.63, 95% CI=0.49 to 0.82) [moderate level of certainty]. Approximate rate of positive margins 18.9% versus 27.0%; 8.1% fewer (95% CI=3.7% to 11.7%).
- MRI may reduce the rate of reoperation (OR=0.73, 95% CI=0.63 to 0.85) [low level of certainty]. Approximate rate of reoperation 14.4% versus 18.7%; 4.3% fewer (95% CI=2.3% to 6.0% fewer).
    - MRI probably results in a large reduction in the rate of reoperation in patients with ILC (OR=0.30, 95% CI=0.13 to 0.72) [moderate level of certainty]. Approximate rate of reoperation 12.3% versus 31.9%; 19.6% fewer (95% CI=6.77% to 26.1% fewer).
- MRI may reduce the rate of re-excision (OR=0.63, 95% CI=0.45 to 0.89) [low level of certainty]. Approximate rate of re-excision 6.9% versus 10.5%; 3.6% fewer (95% CI=1.0% to 5.5% fewer).
- The evidence is uncertain about the effect of MRI on initial mastectomy rate (OR=1.42, 95% CI=1.19 to 1.69) [very low level of certainty]. Approximate rate of initial mastectomy 34.6% versus 27.1%; 7.5% more (3.6% more to 11.5% more).
    - In studies restricted to BCS candidates, the evidence is uncertain about the effect of MRI on initial mastectomy rate (OR=5.18, 95% CI=2.37 to 11.29) [very low level of certainty]. Approximate rate of initial mastectomy 5.5% versus 1.1%; 4.4% more (95% CI=1.5% to 10.2% more).
    - In studies not restricted to type of surgery (determined prior to MRI), MRI may increase the initial mastectomy rate (OR=1.29, 95% CI=1.09 to 1.53) [low level of certainty]. Approximate rate of initial mastectomy 38.0% versus 32.3%; 5.8% more (95% CI=1.9% to 9.9% more).
- The evidence is uncertain about the effect of MRI on final mastectomy rate (OR=1.24, 95% CI=1.11 to 1.39) [very low level of certainty]. Approximate rate of final mastectomy was 37.7% versus 32.8%; 4.9% more (95% CI=2.3% to 7.6% more).
    - In the subset of studies for which registry data was excluded (studies not restricted to initial BCS determination), MRI probably results in little to no difference in final mastectomy rates (OR=0.98, 95% CI=0.82 to 1.17).

As seen in the forest plots and the above summary, the evidence for benefit of preoperative MRI is stronger for ILC than for the overall data. This is consistent with results of studies that reported that, compared to invasive ductal carcinoma, ILC has been found more difficult to detect by mammography, more likely multifocal, more likely to have synchronous CBC, and with a higher rate of involved margins after initial resection (27-32). There was insufficient information to report on other subtypes of cancer separately.

The summary indicates a benefit of MRI in reducing positive margins and reoperations. These outcomes were measured in a large number of studies and with data available for most patients. Included studies also indicate an increase in synchronous CBC and corresponding decrease in metachronous CBC; this is consistent with more rigorous studies designed specifically to investigate CBC (see systematic review). MRI resulted in a decrease in rates of recurrence of any type. Subtype of recurrence was not reported consistently among the studies and therefore subgroup information was limited and therefore less likely to be statistically significant due to low number of participants and events for each outcome. Due to the long follow-up required, potential to retreat patients upon recurrence, and generally high survival in early breast cancer, survival outcomes are less sensitive to interventions than the other outcomes. Overall survival results were only available from five studies, of which four suggest there may be a small (not statistically significant) OS benefit of MRI; the combined data for OS were similar with and without MRI (OR=0.90, 95% CI=0.75 to 1.09). RFS or DFS was also reported in a small number of studies and with lower number of events than for short-term outcomes that could be measured in all patients. As RFS or DFS includes a component of recurrence, these results are similar to recurrence results.

While degree of benefit appears small for most outcomes and not always statistically significant, for all outcomes (except perhaps mastectomy rates, see evidence summary for a discussion of this) the trend is towards MRI being beneficial for each outcome, and therefore this consistency strengthens the conclusion that preoperative MRI has a positive impact in general. It is recognized that this may be higher for patients with certain characteristics such as high breast density or risk factors for (or diagnosis of) multifocal or multicentric cancer and may be lower for patients with a single small well-defined lesion and no other risk factors. While these factors are of interest and are briefly discussed in the literature review, data were not available for them in the comparative studies meeting the review inclusion criteria.

Table 4-1. Risk of bias for RCTs.

Table 4-1a. Risk of bias using ROB2 for mastectomy rates.

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
ICRIS	Balleyguier, 2019	MRI in BCS	no MRI	Mastectomy rate	14.8	-	!	+	+	+	-
Turku	Bruck, 2018	MRI in BCS	no MRI	Mastectomy rate	2.3	-	+	+	+	+	-
Breast-MRI	Mota, 2019	MRI in BCS	no MRI	Mastectomy rate	3.9	-	!	+	+	!	-
COMICE	Turnbull, 2010	MRI in BCS	no MRI	Mastectomy rate	21.9	-	-	+	-	+	-
POMB	Gonzalez, 2014	MRI	no MRI	Mastectomy rate	35.2	-	-	+	+	+	-
MONET	Peters, 2011	MRI	no MRI	Mastectomy rate	21.9	-	-	!	+	!	-

+ Low risk; ! Some concerns; - High risk

D1 - Randomization process; D2 - Deviations from the intended interventions; D3 - Missing outcome data; D4 - Measurement of the outcome; D5 - Selection of the reported result; ; BCS, breast conserving surgery; MRI, magnetic resonance imaging; RCT, randomized controlled trial; ROB, risk of bias.

Table 4-1b. Risk of bias using ROB2 for positive resection margins.

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
COMICE	Turnbull, 2010	MRI in BCS	no MRI	Margins	100	!	-	+	-	+	-

+ Low risk; ! Some concerns; - High risk

D1 - Randomization process; D2 - Deviations from the intended interventions; D3 - Missing outcome data; D4 - Measurement of the outcome; D5 - Selection of the reported result; BCS, breast conserving surgery; MRI, magnetic resonance imaging; RCT, randomized controlled trial; ROB, risk of bias

Table 4-1c. Risk of bias using ROB2 for reoperations, re-excisions, and conversion mastectomy.

Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
IRCIS	Balleyguier, 2019	MRI in BCS	no MRI	Reoperations*	20.5	!	!	+	+	+	!
Turku	Bruck, 2018	MRI in BCS	no MRI	Reoperations*	7.8	+	+	+	+	+	+
Breast-MRI	Mota, 2019	MRI in BCS	no MRI	Reoperations*	13.7	!	!	+	+	!	!
COMICE	Turnbull, 2010	MRI in BCS	no MRI	Reoperations*	29.5	!	-	+	-	+	-
POMB	Gonzalez, 2014	MRI	no MRI	Reoperations*	13.3	!	!	+	+	+	!
Monet	Peters, 2011	MRI	no MRI	Reoperations*	12.4	-	-	!	+	!	-
B-SMART	Rahman, 2012	MRI	no MRI	Re-excisions	4.1	+	!	+	+	!	!

*Reoperations, re-excisions, and conversion mastectomy

+ Low risk; ! Some concerns; - High risk

D1 - Randomization process; D2 - Deviations from the intended interventions; D3 - Missing outcome data; D4 - Measurement of the outcome; D5 - Selection of the reported result; BCS, breast conserving surgery; MRI, magnetic resonance imaging; RCT, randomized controlled trial; ROB, risk of bias

Table 4-1d. Risk of bias using ROB2 for recurrence and survival outcomes.

Unique ID	Study ID	Experimental	Comparator	Outcome	D1	D2	D3	D4	D5	Overall
Turku	Bruck, 2018	MRI in BCS	no MRI	Distant recurrence	+	+	+	+	+	+
Breast-MRI	Mota, 2019	MRI in BCS	no MRI	Local recurrence, distant recurrence, overall survival	!	!	+	+	!	!
POMB	Gonzalez, 2014, 2021	MRI	no MRI	Locoregional recurrence, distant recurrence, disease-free survival, overall survival	!	!	+	+	+	!

+ Low risk; ! Some concerns; - High risk

D1 - Randomization process; D2 - Deviations from the intended interventions; D3 - Missing outcome data; D4 - Measurement of the outcome; D5 - Selection of the reported result; BCS, breast conserving surgery; MRI, magnetic resonance imaging; RCT, randomized controlled trial; ROB, risk of bias

Table 4-2. Risk of bias for included studies.[4]

Table 4-2a. Mastectomy rates - Patient population not defined by type of surgery planned before MRI.

Study name	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
In situ or DCIS									
Lebanon, NH	Davis, 2012 (115)	Low-moderate	Low	Low	Low	Low	Low	Low	Low-moderate
Netherlands Cancer Registry	Keymeulen, 2019 (116)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
University of Ulsan College of Medicine, Gangneung, Korea	Yoon, 2020 (117)	Low	Low	Low	Low	Low	Low	Low	Low
Eindhoven Cancer Registry	Vos, 2015 (109)	Serious	Low	Moderate	Low	Low	Low	Low	Serious
In situ and invasive									
POMB (RCT)	Gonzalez, 2014 (118)								High
Monet (RCT)	Peters, 2011 (108)								High
Mayo Clinic, Rochester	Katipamula, 2009 (119)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Magee-Womens Hospital - tumour registry	Sorbero, 2009 (120)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
4 registries of BCSC (USA)	Onega, 2017 (121)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate

[4] Evaluation of RCTs is reported in Table 4-1. These studies have been included in Table 4-2 for comparison, however only the overall evaluation is provided here, and other columns are blank and shaded .

Study name	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
SEER-Medicare database registry	Ozanne, 2017 (122)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
4 registries of BCSC (USA)	Goodrich, 2016 (123)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Germany registry	Heil, 2013 (124)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
University of Ulsan College of Medicine, Seoul, South Korea	Choi, 2017 (125)	Low	Low	Low	Low	Low	Low	Low	Low
Changhua Christian Hospital	Lai, 2016 (126)	Low-moderate	Low	Moderate	Low	Low	Low	Low	Low-moderate
Mercy Hospital, Oklahoma City	Hollingsworth, 2008 (127) & 2015 (80)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Single institution in USA	Grady, 2012 (128)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Invasive									
NCCN centres 2000-2009	Luis, 2015 (129) [abstract]	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
McGill University	Parsyan, 2016 (130)	Moderate-serious	Low	Low	Low	Low	Low	Low	Moderate-serious
Administrative data in Ontario registry	Arnaout, 2015 (131)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Memorial Sloan-Kettering	Kapoor, 2013 (132)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate

Study name	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
SEER-Medicare database registry	Killelea, 2013 (133)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Eindhoven Cancer Registry	Vos, 2015 (109)	Moderate-serious	Low	Moderate	Low	Low	Low	Low	Moderate-serious
Netherlands Cancer Registry	Vriens, 2017 (134)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Netherlands Cancer Registry	Lobbes, 2017 (22)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
SEER-Medicare linked dataset registry	Fortune-Greeley, 2014 (114)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
ILC									
Radboud University Nijmegen	Mann, 2010 (135)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Seoul, Korea	Ha, 2018 (136) Overlaps with pts in Ha, 2019 (137)	Low	Low	Low	Low	Low	Low	Low	Low

Abbreviations: BCSC, Breast Cancer Surveillance Consortium; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; RCT, randomized controlled trial; SEER, Surveillance, Epidemiology, and End Results Program (National Cancer Institute, USA)

Table 4-2b. Mastectomy outcome in studies with only breast conserving surgery candidates.

Study name or location	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
IRCIS BCS-DCIS: RCT	Balleyguier, 2019 (138)								High
BREAST-MRI BCS – in situ or invasive: RCT	Mota, 2019 (139) [Abstract]								High
COMICE BCS – in situ or invasive: RCT	Turnbull, 2010 (107, 140)								High
Turku University Hospital BCS- invasive: RCT	Bruck, 2018 (141)								High
Breast Cancer Surgical Outcomes (BRCASO) database 2003-2008 Registry data	Feigelson, 2013 (142)	High	Low	Moderate	Low	Low	Low	Low	High

Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Table 4-2c. Positive margins, reoperation, re-excision, conversion to mastectomy.

Study name or location	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
In situ, DCIS									
Lebanon, NH	Davis, 2012 (115)	Low-moderate	Low	Low	Low	Low	Low	Low	Low-moderate
Netherlands Cancer Registry	Keymeulen, 2019 (116)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
University of Ulsan College of Medicine	Yoon, 2020 (117)	Low	Low	Low	Low	Low	Low	Low	Low
DCIS – BCS planned									
IRCIS (RCT)	Balleyguier, 2019 (138)								Some concerns
In situ or invasive									
POMB (RCT)	Gonzalez, 2014 (118)								Some concerns
Monet (RCT)	Peters, 2011 (108)								High
SEER-Medicare database	Wang, 2013 (143)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Mercy Hospital, Oklahoma City	Hollingsworth, 2008 (127) Hollingsworth, 2015 (80)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Single institution in USA	Grady, 2012 (128)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
University of Ulsan College of Medicine, Seoul, South Korea	Choi, 2017 (125)	Low	Low	Low	Low	Low	Low	Low	Low
Changhua Christian Hospital	Lai, 2016 (126)	Low-moderate	Low	Moderate	Low	Low	Low	Low	Low-moderate

Study name or location	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
SEER-Medicare database	Ozanne, 2017 (122)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Eindhoven Cancer Registry, The Netherlands	Vos, 2015 (109)	Moderate-serious	Low	Moderate	Low	Low	Low	Low	Moderate-serious
In situ or invasive – BCS only									
BREAST-MRI	Mota, 2019 (139) [Abstract]								Some concerns
COMICE	Turnbull, 2010 (107, 140)								High
Memorial Sloan Kettering Cancer Center, New York	Sung, 2014 (111)	Low	Low	Low	Low	Low	Low	Low	Low
Lynn Sage Comprehensive Breast Center	Zeng, 2020 (144)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Rotterdam, The Netherlands	Obdeijn, 2013 (145)	Low-moderate	Low	Low	Low	Low	Low	Low	Low-moderate
Invasive									
Breast Cancer Treatment Disparity Study in New Jersey State Cancer Registry	Chandwani, 2014 (146)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
SEER-Medicare linked dataset	Fortune-Greeley, 2014 (114)	Low-moderate	Low	Moderate	Low	Low	Low	Low	Moderate
McGill University Health Centre	Parsyan, 2016 (130)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Memorial Sloan-Kettering	Kapoor, 2013 (132)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate

Study name or location	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
Netherlands Cancer Registry	Vriens, 2017 (134)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Netherlands Cancer Registry	Lobbes, 2017 (22)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
University of Pennsylvania	Burkbauer, 2020 (147) [abstract]	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Invasive - BCS									
Turku University Hospital,	Bruck, 2018 (141)								Low
ILC									
Radboud University Nijmegen Medical Centre (RUNMC)	Mann, 2010 (135)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Seoul, Korea	Ha, 2018 (136) Overlaps with pts in Ha, 2019 (137)	Low	Low	Low	Low	Low	Low	Low	Low
Ongoing Trials									
B-SMART (terminated)	Rahman, 2012 (113) [Abstract]								Some concerns

Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial; SEER, Surveillance, Epidemiology, and End Results Program (National Cancer Institute, USA)

Table 4-2d. Contralateral breast cancer, recurrence, and survival.

Study name or location	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
DCIS – all surgeries									
SEER-Medicare dataset	Wang, 2016 (148)	Moderate	Low	Moderate	Low	Low	Low	Low	Low-moderate
DCIS – BCS planned									
Memorial Sloan-Kettering Cancer	Pilewskie, 2014 (149)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
In situ or invasive- all surgeries									
University of Ulsan College of Medicine, Seoul, South Korea	Choi, 2017 (125)	Low	Low	Low	Low	Low	Low	Low	Low
Seoul National University College of Medicine	Kim, 2013 (150)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
POMB	Gonzalez, 2014 (118); Gonzalez, 2021 (106)								Some concerns
In situ or invasive – BCS only									
Enterprise Data Warehouse of Northwestern Medicine, Chicago	Amin, 2015 (151) [abstract]	Low-moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Samsung Medical Center	Ko, 2013 (152)	Low-moderate	Low	Low	Low	Low	Low	Low	Low-moderate
Dartmouth Hitchcock Medical Center	Hill, 2017 (153)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Memorial Sloan Kettering Cancer Center, New York	Sung, 2014 (111)	Low	Low	Low	Low	Low	Low	Low	Low

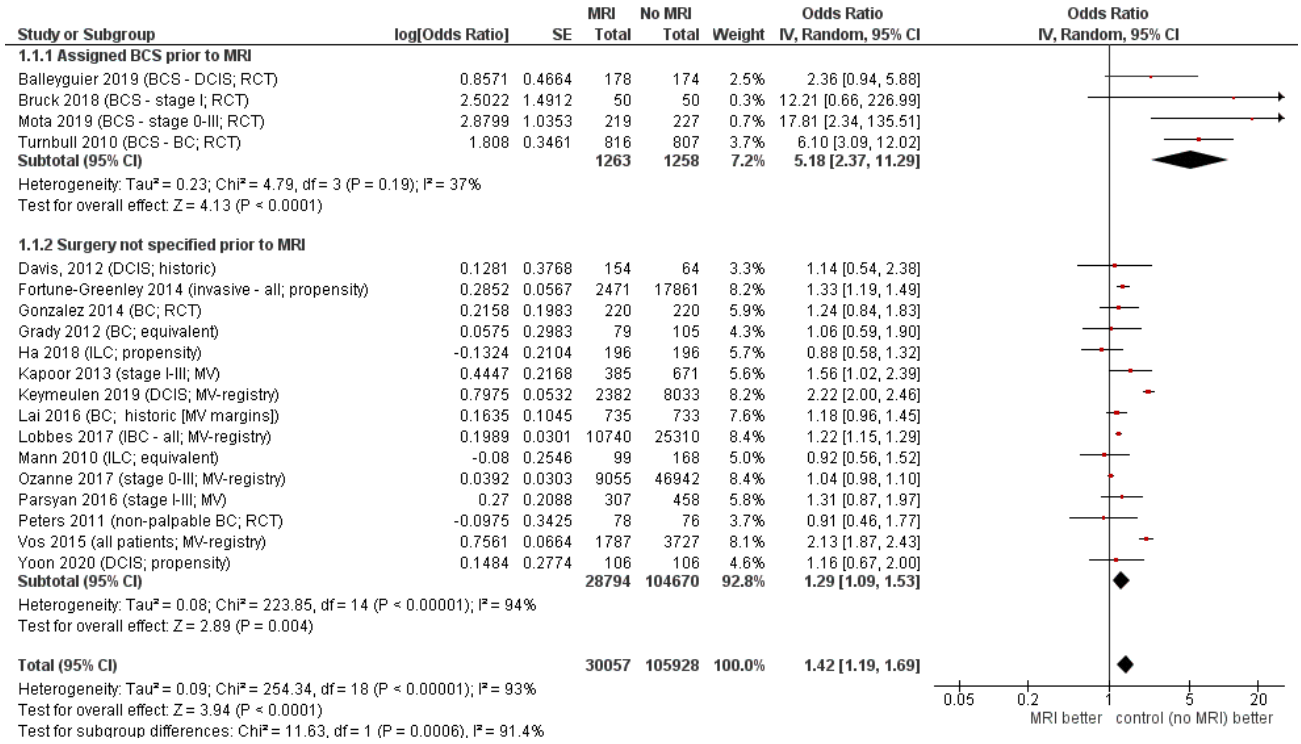
Study name or location	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
Lynn Sage Comprehensive Breast Center	Zeng, 2020 (144)	Low	Low	Moderate	Low	Low	Low	Low	Moderate
Invasive									
Seoul National University Hospital, Seoul, Korea	Bae, 2016 (154)	Low	Low	Low	Low	Low	Low	Low	Low
Netherlands Cancer Registry	Lobbes, 2017 (22)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Netherlands Cancer Registry	Van Nijnatten, 2020 (155)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Netherlands Cancer Registry	Vriens, 2017 (134)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
SEER-Medicare dataset	Wang, 2016 (156)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Invasive – BCS only									
Princess Margaret Hospital, Toronto	Hwang, 2009 (157); Gervais, 2017 (158)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Yonsei University Hospital, Seoul, Korea	Ryu, 2016 (159)	Moderate	Low	Low	Low	Low	Low	Low	Moderate
SEER-Medicare dataset Registry	Wang, 2018 (112)	Moderate	Low	Moderate	Low	Low	Low	Low	Moderate
Invasive Ductal Carcinoma – BCS only									
Turku University Hospital	Bruck, 2018 (141)								Low
ILC									
Seoul, Korea	Ha, 2018 (136)	Low	Low	Low	Low	Low	Low	Low	Low

Study name or location	Author and source	Confounding	Selection bias	Classification bias	Departure from interventions	Missing Data	Measurement of outcomes	Selection of results to report	Overall
	Overlaps with pts in Ha, 2019 (137)								
Ongoing Trials									
BREAST-MRI	Mota, 2019 (139) [Abstract] Interim analysis for recurrence; final results not available								High (interim data, abstract)

Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial; SEER, Surveillance, Epidemiology, and End Results Program (National Cancer Institute, USA)

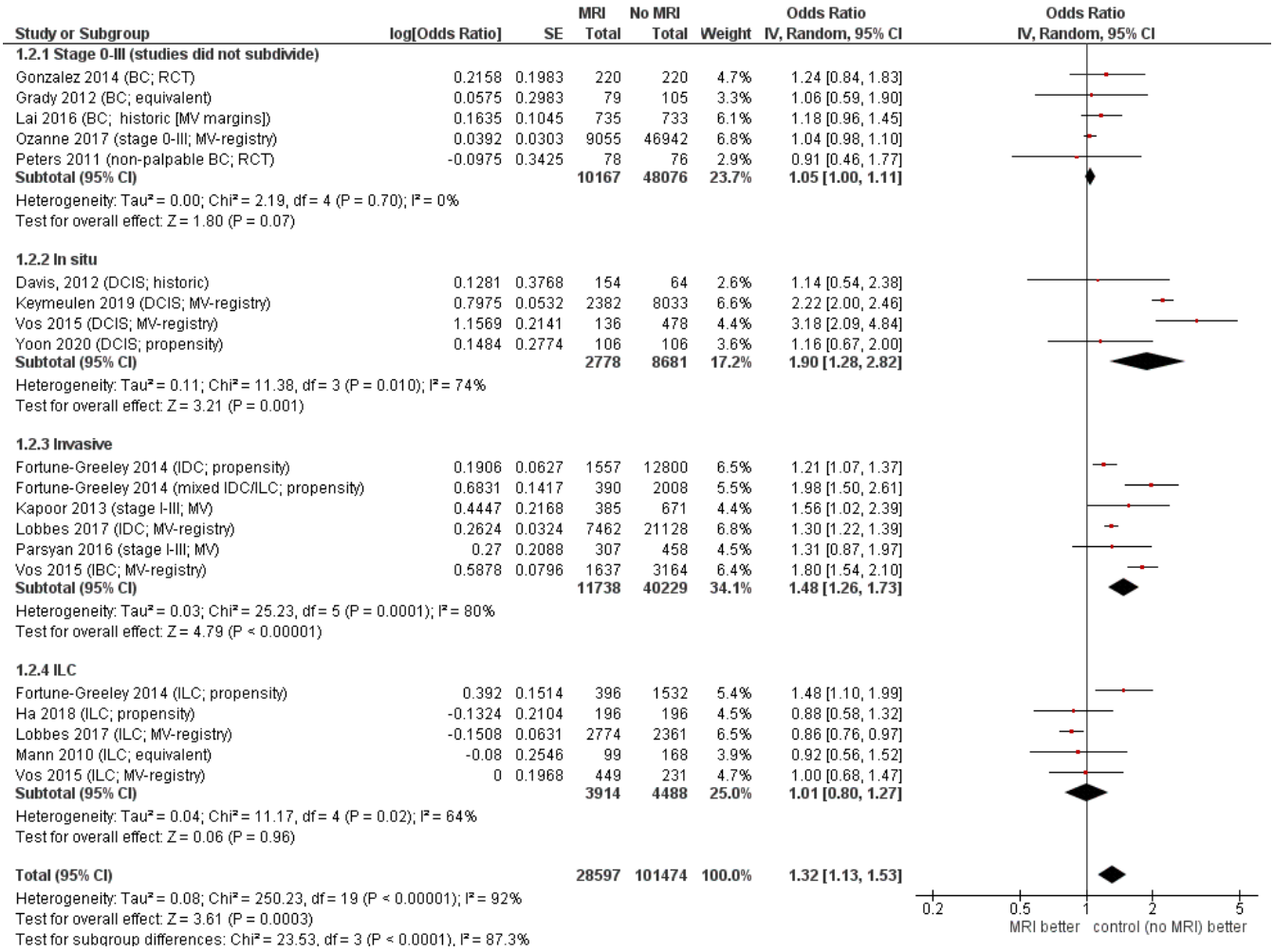
Figure 4-1. Forest plots for mastectomy rates.

Figure 4-1a. Initial mastectomy rate, subdivided by studies where patients were restricted to those assigned to breast conserving surgery prior to MRI or all preoperative patients were allowed.



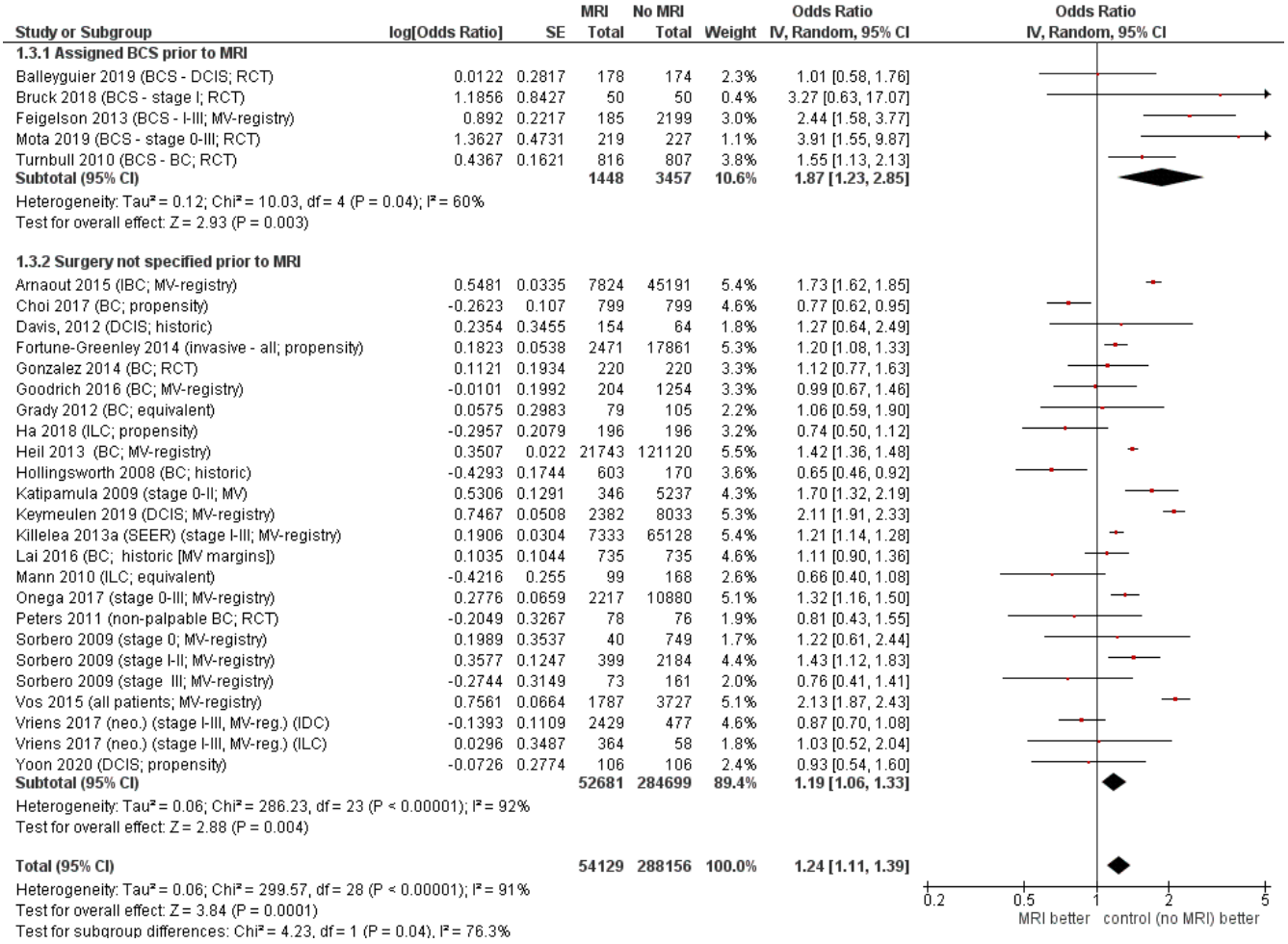
Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Figure 4-1b. Initial mastectomy rate by cancer subtype/stage (excluding studies restricted to breast conserving surgery).



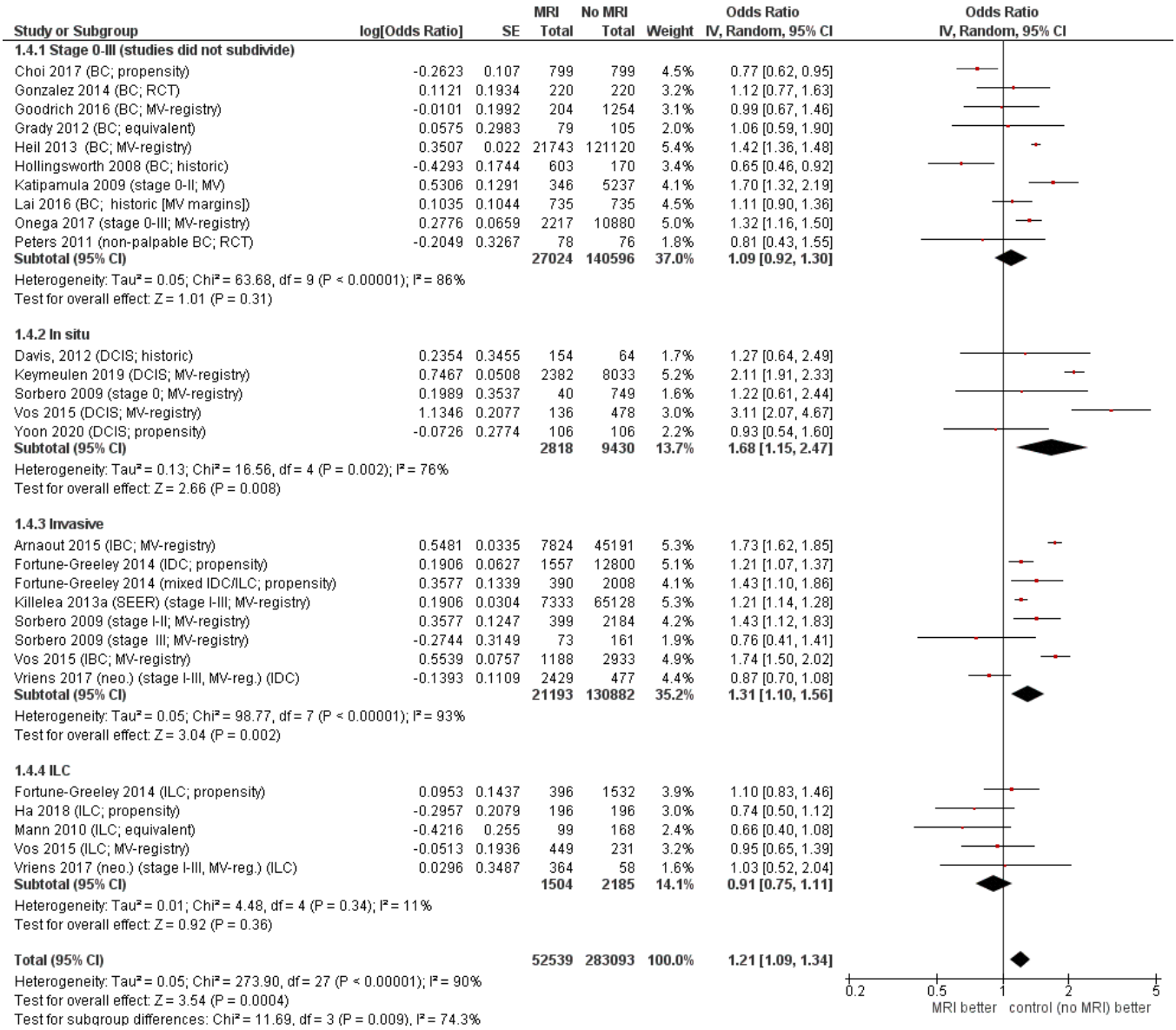
Abbreviations: BCS, breast conserving surgery; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Figure 4-1c. Final (overall) mastectomy rate, subdivided by studies where patients were restricted to those assigned to breast conserving surgery prior to MRI or all preoperative patients were allowed.



Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial; SEER, Surveillance, Epidemiology, and End Results Program (National Cancer Institute, USA)

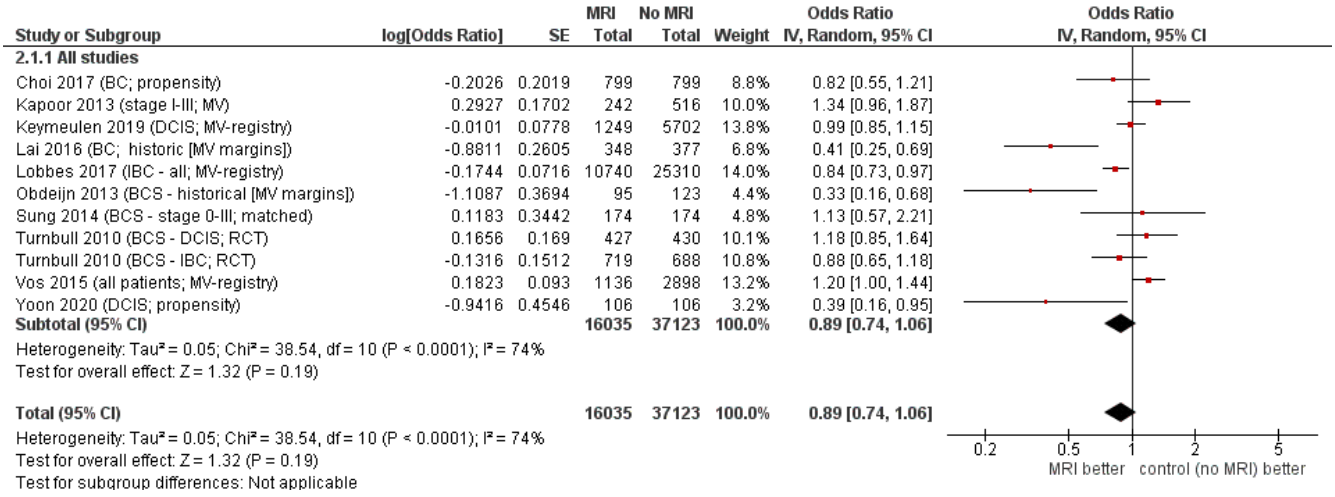
Figure 4-1d. Final mastectomy rate by cancer subtype/stage (excluding studies restricted to breast conserving surgery).



Abbreviations: DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial; SEER, Surveillance, Epidemiology, and End Results Program (National Cancer Institute, USA)

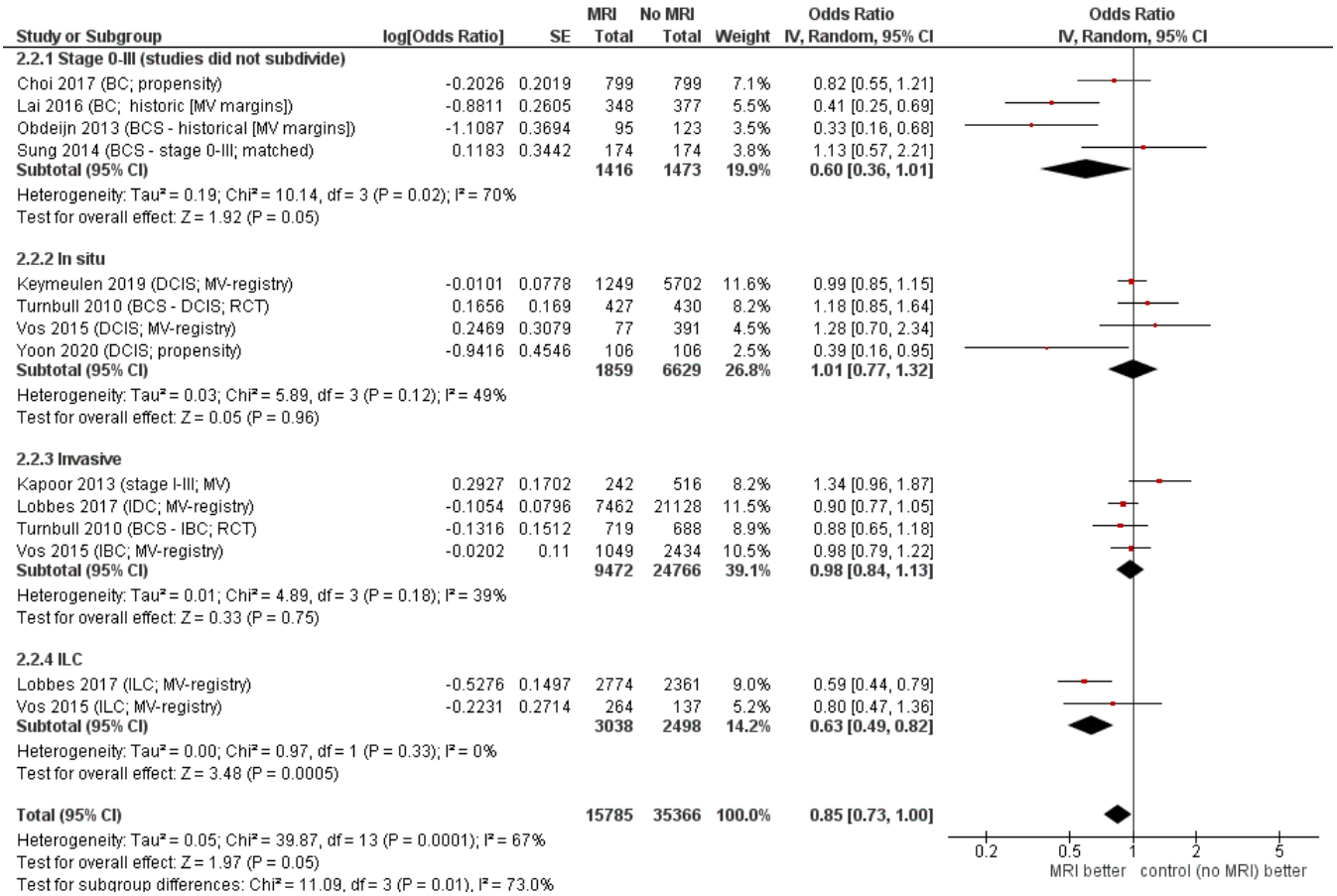
Figure 4-2. Forest plots for positive margins

Figure 4-2a. Positive margins (all studies).



Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; IBC, inflammatory breast cancer; MRI, magnetic resonance imaging; RCT, randomized controlled trial

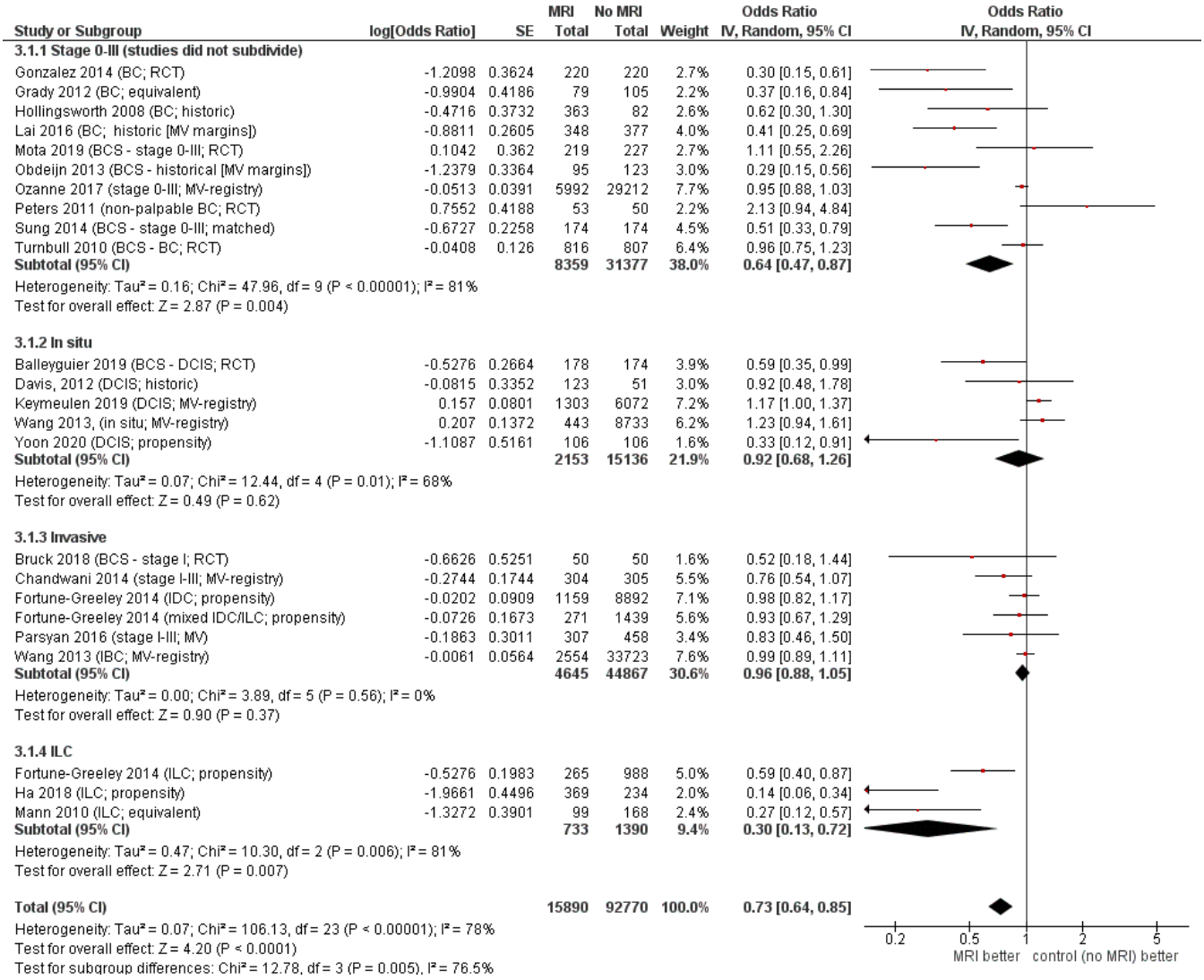
Figure 4-2b. Positive margins by cancer stage/subtype.



Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

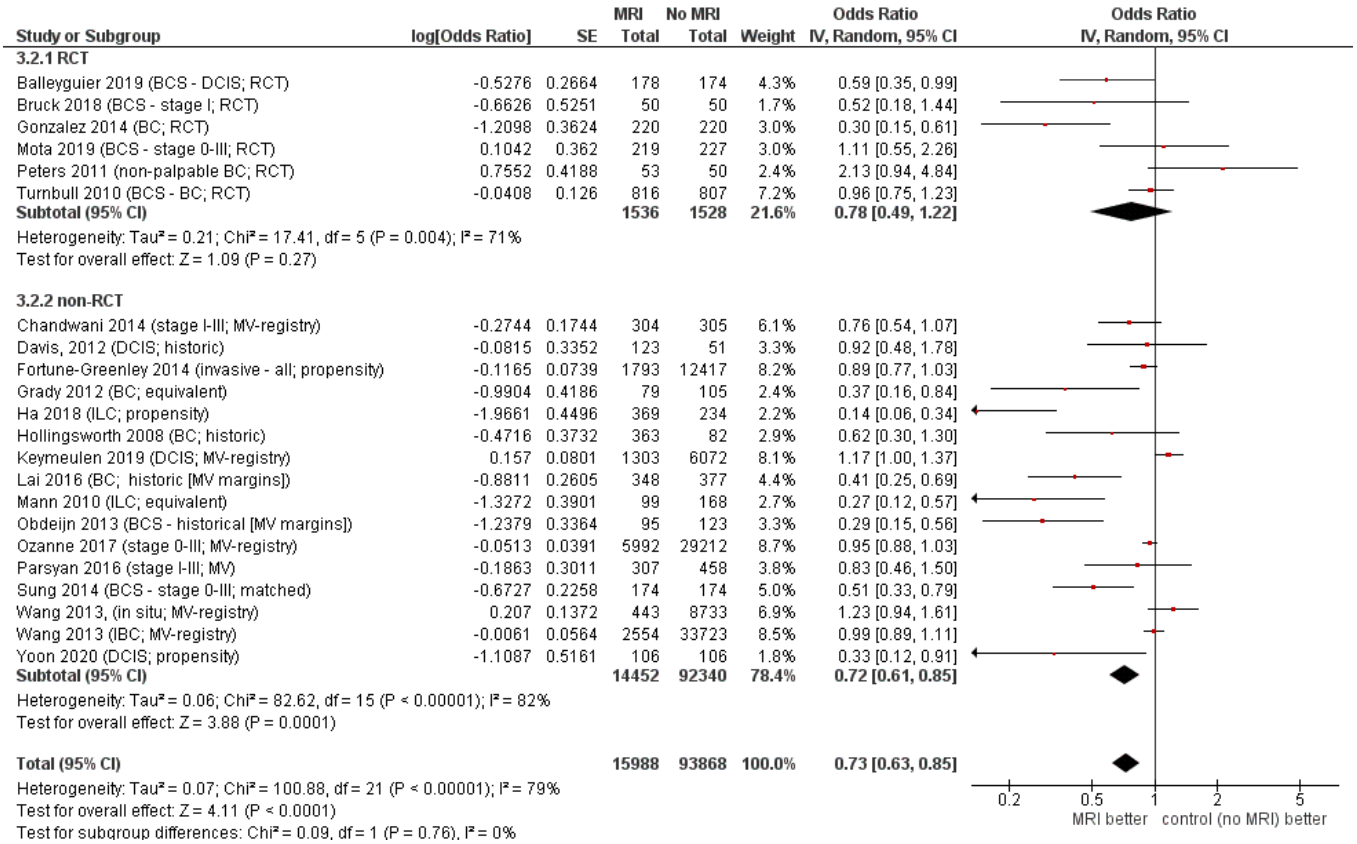
Figure 4-3. Forest plots for additional surgery.

Figure 4-3a. Reoperations, by stage/subtype



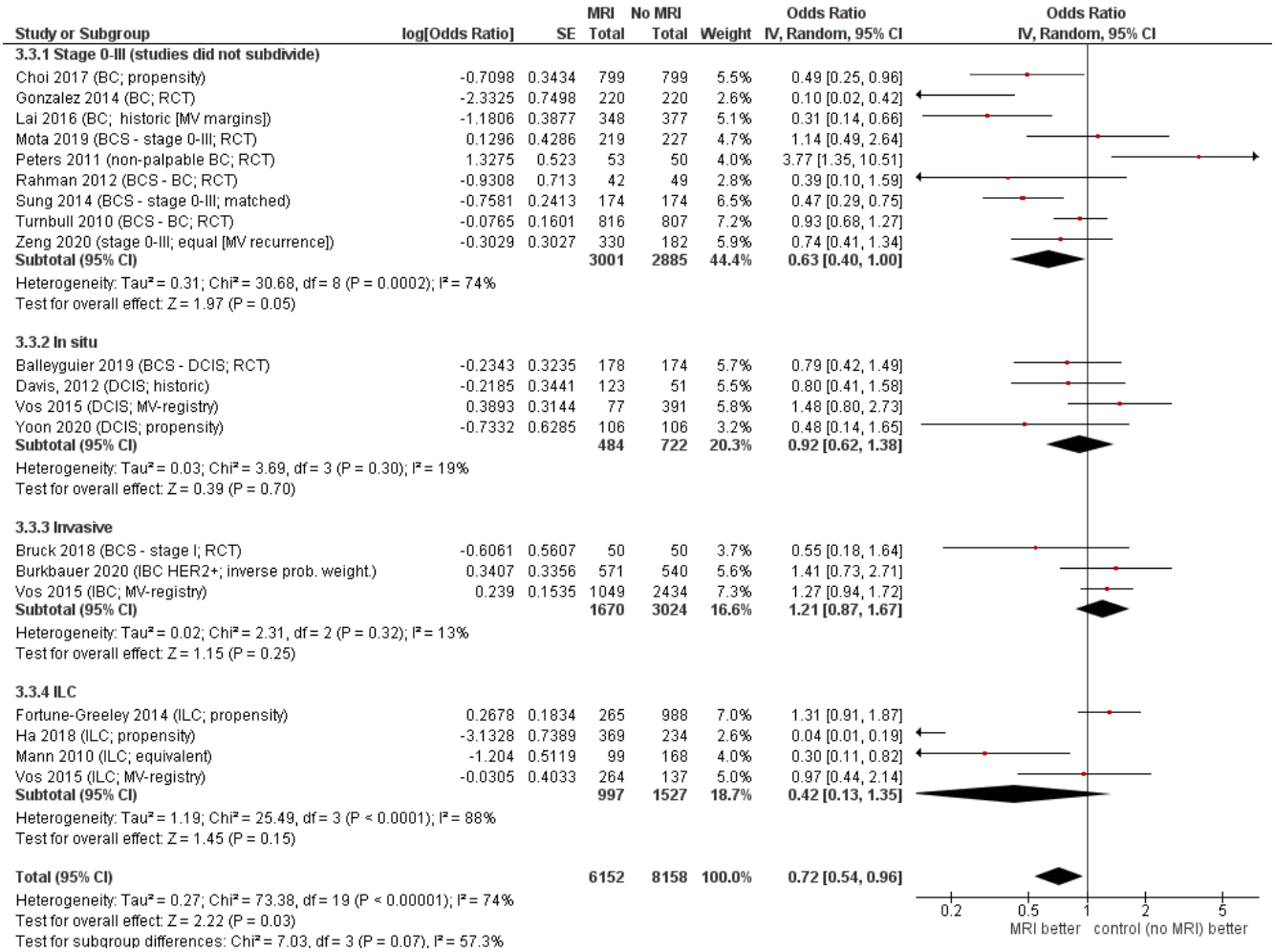
Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Figure 4-3b. Reoperations, by RCT or non-RCT studies



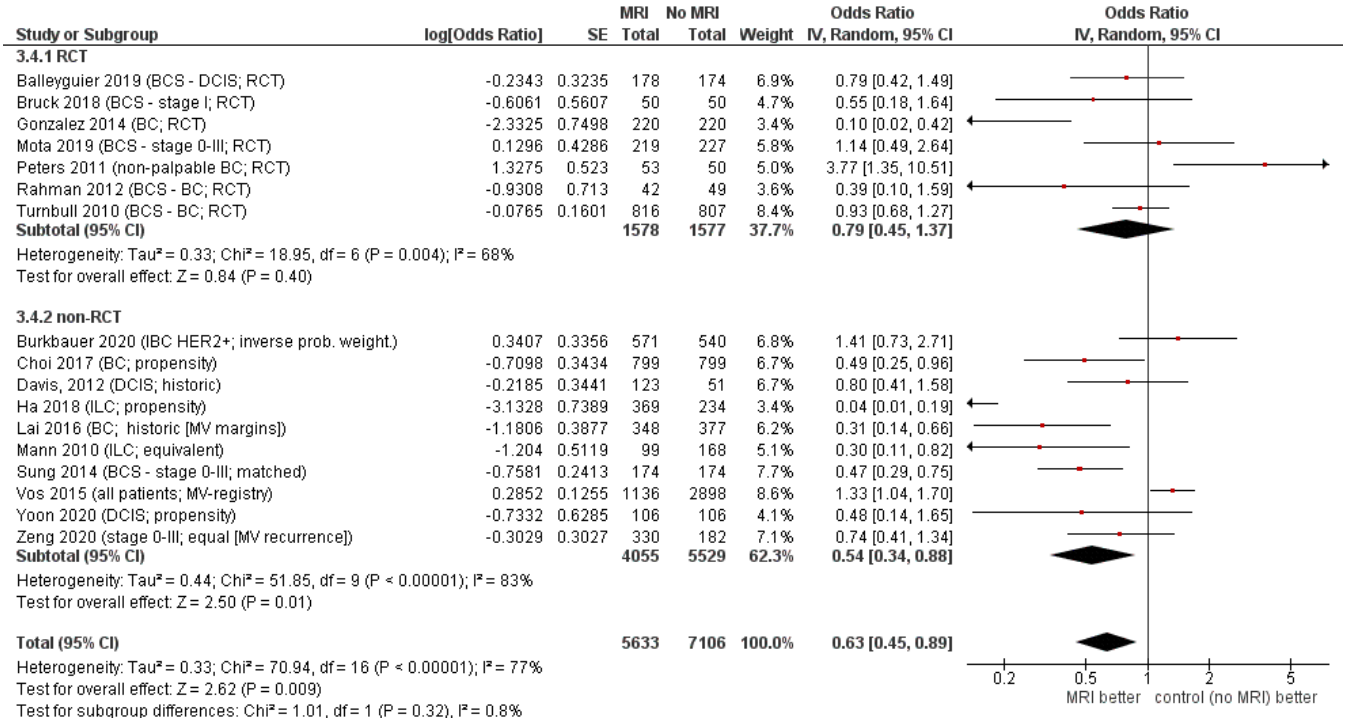
Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Figure 4-3c. Re-excisions, by stage/subtype.



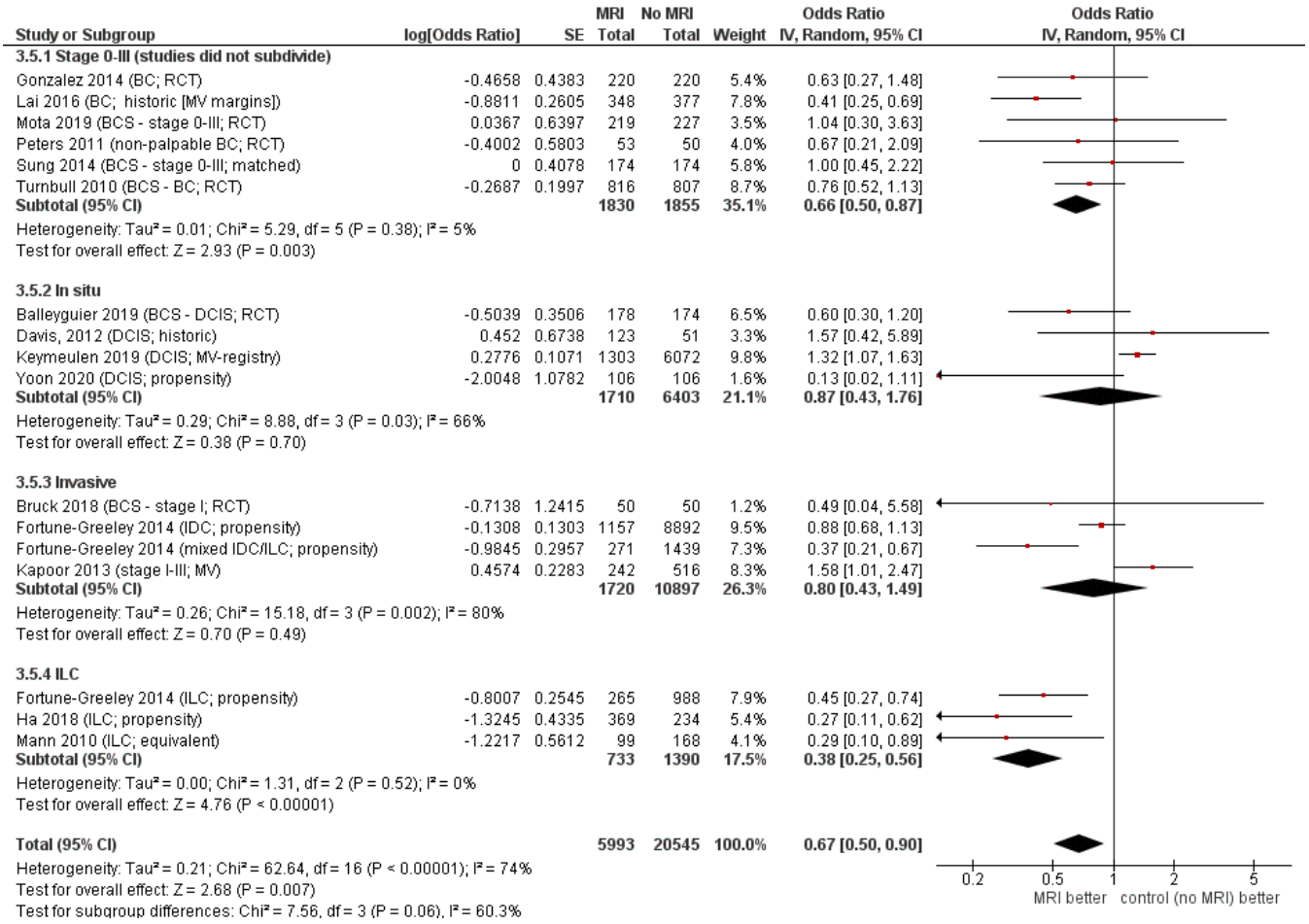
Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; IBC, inflammatory breast cancer; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Figure 4-3d. Re-excisions, by RCT or non-RCT studies



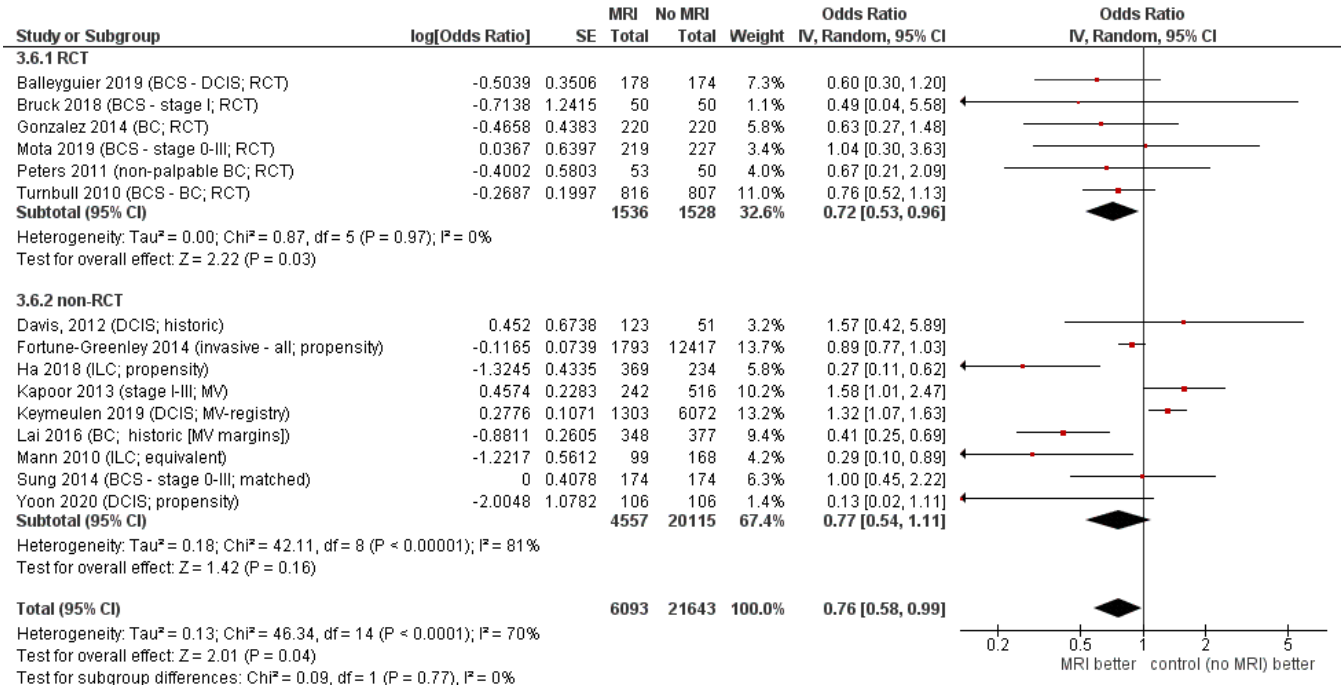
Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; IBC, inflammatory breast cancer; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Figure 4-3e. Conversion mastectomy, by stage/subtype.



Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

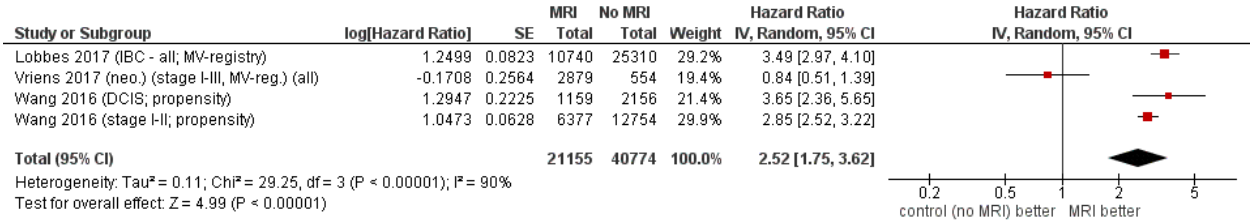
Figure 4-3f. Conversion mastectomy, by RCT or non-RCT.



Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

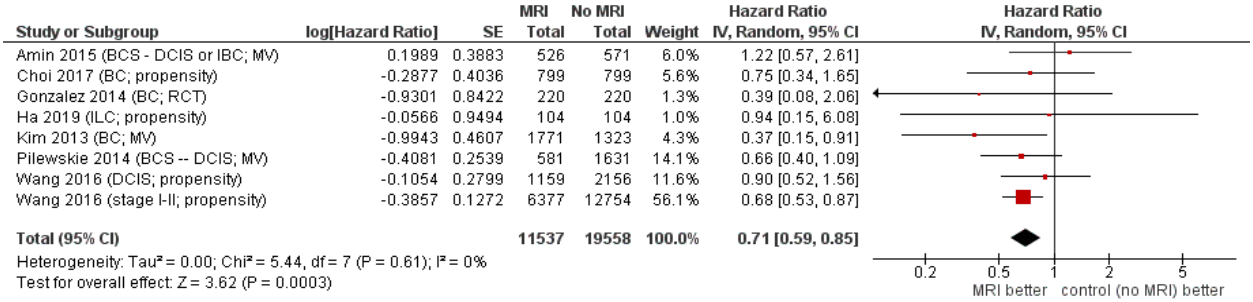
Figure 4-4. Forest plots for contralateral breast cancer.

Figure 4-4a. Synchronous contralateral breast cancer.



Abbreviations: DCIS, ductal carcinoma in situ; IBC, inflammatory breast carcinoma; MRI, magnetic resonance imaging

Figure 4-4b. Metachronous contralateral breast cancer.



Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

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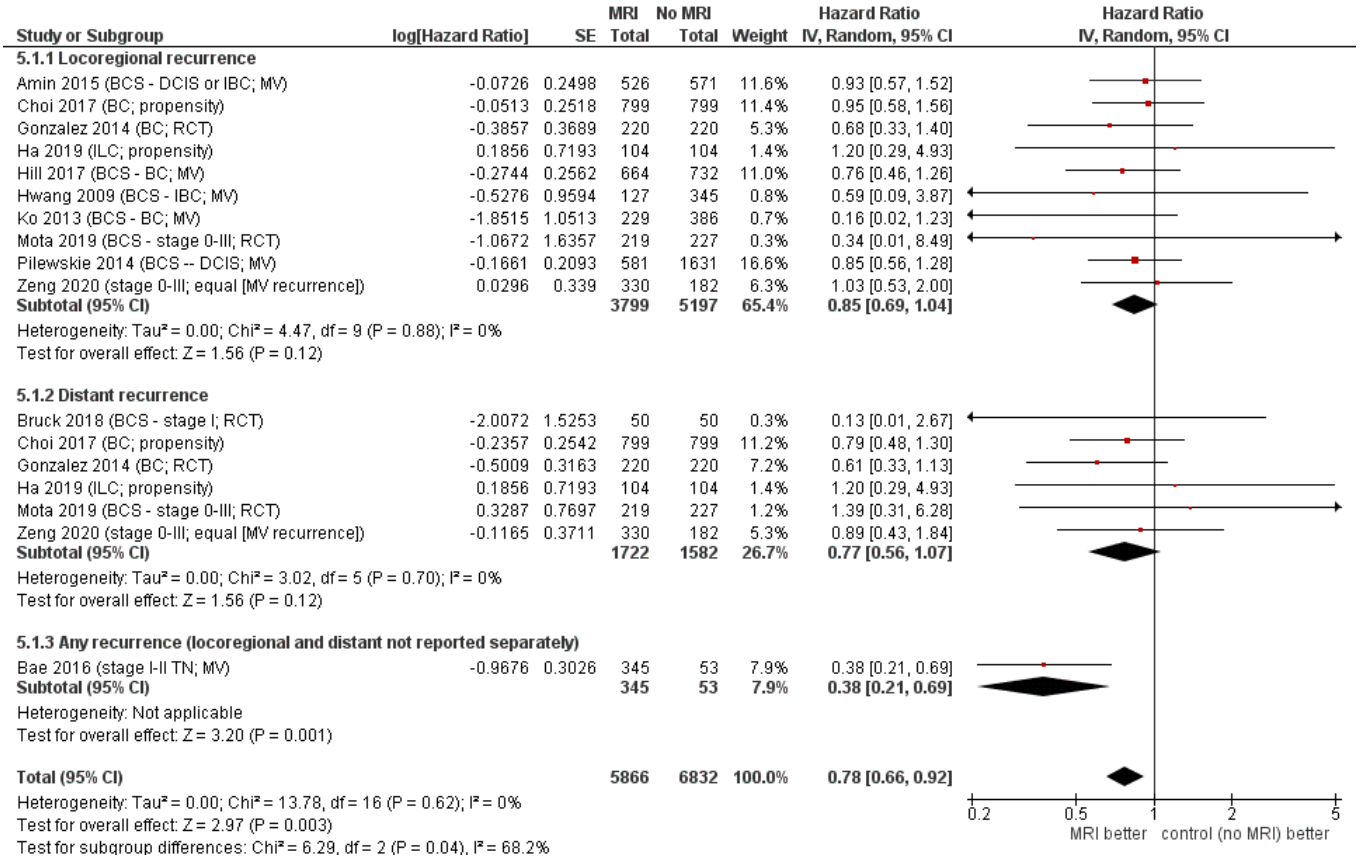
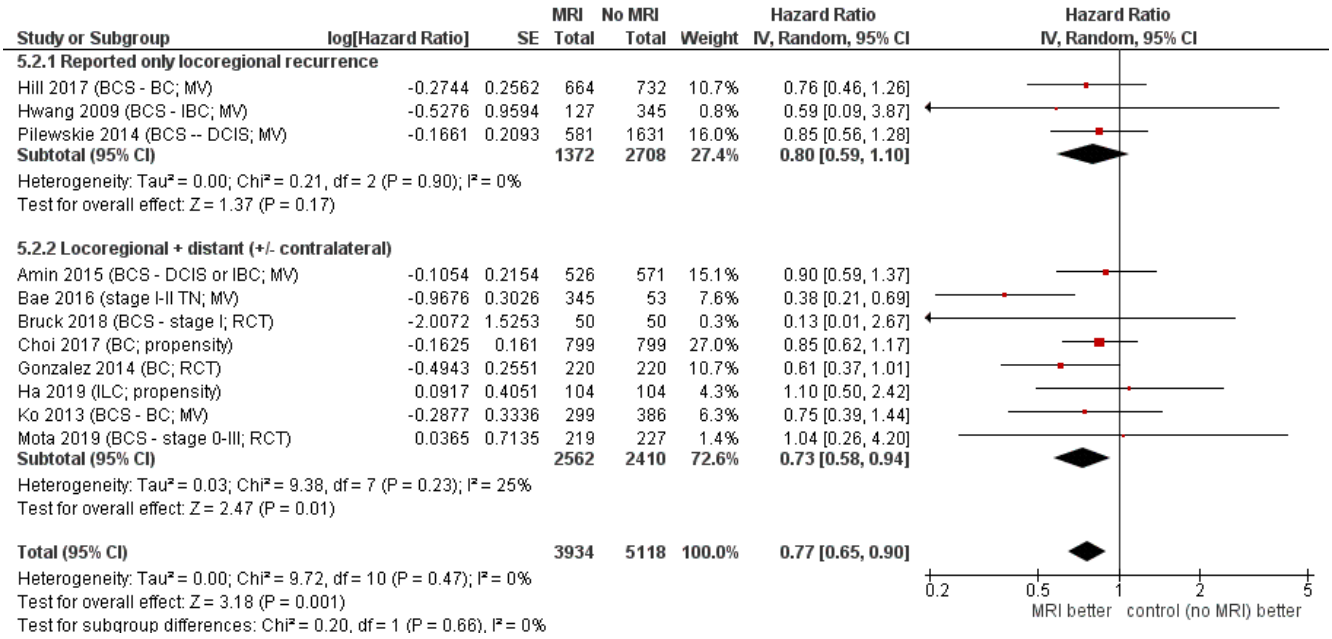
Figure 4-5. Forest plots for survival or recurrence.

Figure 4-5a. Recurrence by recurrence type reported.



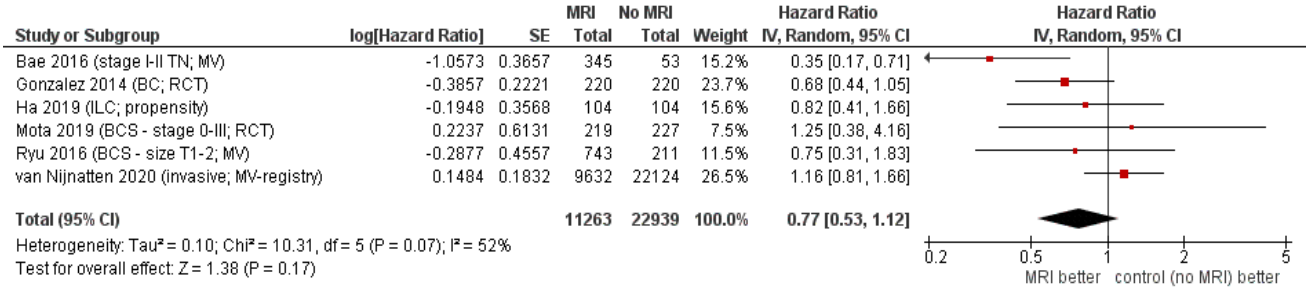
Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; IBC, inflammatory breast cancer; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Figure 4-5b. Recurrence (any type)



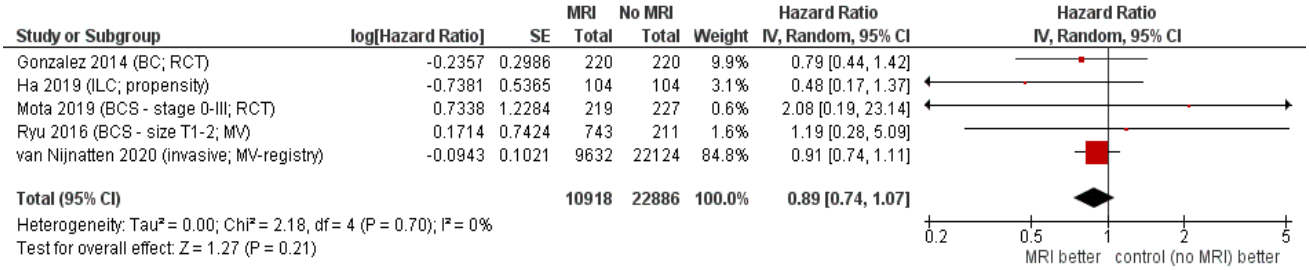
Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ; IBC, inflammatory breast carcinoma; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Figure 4-5c. Recurrence-free survival/disease-free survival.



Abbreviations: BCS, breast conserving surgery; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Figure 4-5d. Overall survival.



Abbreviations: BCS, breast conserving surgery; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Table 4-3. Summary of odds or hazard ratios and confidence intervals from forest plots.

Outcome	Group	Subgroup	OR or HR and 95% CI*	OR and 95% CI excluding registry data
Initial mastectomy	All		1.42 (1.19-1.69)	1.34 (1.11-1.62)
	Patients initially assigned BCS only**		5.18 (2.37-11.29)	No registry data
	Not restricted to BCS**		1.29 (1.09-1.53)	1.25 (1.15-1.36)
	Not restricted to BCS**	In situ	1.90 (1.28-2.82)	1.15 (0.74-1.78)
	Not restricted to BCS**	Invasive	1.48 (1.26-1.73	1.47 (1.12-1.92)
	Not restricted to BCS**	ILC	1.01 (0.80-1.27)	1.10 (0.76-1.59)
Final mastectomy	All		1.24 (1.11-1.39)	1.07 (0.90-1.27)
	Patients initially assigned BCS only**		1.87 (1.23-2.85)	1.72 (1.02-2.87)
	Not restricted to BCS**		1.19 (1.06-1.33)	0.98 (0.82-1.17)
	Not restricted to BCS**	In situ	1.68 (1.15-2.47)	1.05 (0.69-1.60)
	Not restricted to BCS**	Invasive	1.31 (1.10-1.56)	1.14 (0.89-1.47)
	Not restricted to BCS**	ILC	0.91 (0.75-1.11)	0.88 (0.68-1.15)
Positive margins	All		0.89 (0.74-1.06)	0.78 (0.56-1.07)
	Low or low/moderate RoB studies only		0.57 (0.36-0.89)	No registry data
	All	In situ	1.01 (0.77-1.32)	0.74 (0.25-2.15)
	All	Invasive	0.98 (0.84-1.13)	1.08 (0.71-1.63)
	All	ILC	0.63 (0.49-0.82)	(no studies)
Reoperations	All		0.73 (0.63-0.85)	0.56 (0.44-0.73)
	Excluding high risk of bias RCTs		0.69 (0.59-0.81)	0.50 (0.37-0.66)
	RCTs only		0.78 (0.49-1.22)	(not applicable)
	RCTs, excluding high risk of bias RCTs		0.57 (0.33-0.97)	(not applicable)
	Non-RCTs		0.72 (0.61-0.85)	0.47 (0.33-0.67)
	All	In situ	0.92 (0.68-1.26)	0.62 (0.38-1.00)
	All	Invasive	0.96 (0.88-1.05)	0.95 (0.81-1.10)
	All	ILC	0.30 (0.13-0.72)	No registry data
Re-excisions	All		0.63 (0.45-0.89)	0.59 (0.42-0.84)
	Excluding high risk of bias RCTs		0.54 (0.37-0.80)	0.51 (0.35-0.73)
	RCTs only		0.79 (0.45-1.37)	(not applicable)
	RCTs, excluding high risk of bias RCTs		0.54 (0.27-1.08)	(not applicable)
	Non-RCTs		0.54 (0.34-0.88)	0.49 (0.31-0.76)
	All	In situ	0.92 (0.62-1.38)	0.75 (0.49-1.15)
	All	Invasive	1.21 (0.87-1.67)	0.97 (0.39-2.41)
	All	ILC	0.42 (0.13-1.35)	0.29 (0.05-1.81)
Conversion mastectomy	All		0.76 (0.58-0.99)	0.70 (0.53-0.93)
	RCTs only		0.72 (0.53-0.96)	(not applicable)
	RCTs, excluding high risk of bias RCTs		0.66 (0.41-1.07)	(not applicable)
	Non-RCTs		0.77 (0.54-1.11)	0.67 (0.42-1.05)
	All	In situ	0.87 (0.43-1.76)	0.63 (0.23-1.74)
	All	Invasive	0.80 (0.43.-1.49)	No registry data

Outcome	Group	Subgroup	OR or HR and 95% CI*	OR and 95% CI excluding registry data
	All	ILC	0.38 (0.25-0.56)	No registry data
Synchronous CBC	All		2.52 (1.75-3.62) [HR>1 indicates higher detection with MRI]	2.94 (2.50-3.46) [2/4 studies]
Metachronous CBC	All		0.71 (0.59-0.85) [HR<1 indicates lower rate in MRI group]	No registry data
Recurrence	Any recurrence		0.77 (0.65-0.90)	No registry data
	Locoregional		0.85 (0.69-1.04)	No registry data
	Distant		0.77 (0.56-1.07)	No registry data
DFS/RFS			0.77 (0.53-1.12)	0.66 (0.47-0.92)
OS			0.89 (0.74-1.07)	0.77 (0.48-1.24)

OR were generally reported for short-term outcomes, while HR were generally reported for recurrence and survival outcomes. OR and HR were both used for CBC and therefore data for these CBC were converted to HR.

**Some studies (mostly RCTs) made a decision prior to MRI on the type of surgery that would be conducted, and then only included patients who (in the absence of MRI results) would receive BCS.

Abbreviations: BCS, breast conserving surgery; CBC, contralateral breast cancer; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; OR, odds ratio; OS, overall survival; RFS, recurrence-free survival; RCT, randomized-control trial

Table 4-4. Summary of findings from GRADEPro.

Table 4-4a. MRI versus no MRI for treatment planning (outcome is mastectomy rate).

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Risk with MRI (%)	Risk without MRI (%)	Difference	
Initial mastectomy rate Number of participants: 135,985 (19 observational studies)	**OR 1.42** (1.19 to 1.69)	**34.6%** (30.7 to 38.6)	27.1%	**7.5% more** (3.6 more to 11.5 more)	⊕◯◯◯ Very low[a,b]
Initial mastectomy rate - Assigned BCS prior to MRI Number of participants: 2,521 (4 RCTs)	**OR 5.18** (2.37 to 11.29)	**5.5%** (2.6 to 11.3)	1.1%	**4.4% more** (1.5 more to 10.2 more)	⊕◯◯◯ Very low[c,d]
Initial mastectomy rate - Surgery not specified prior to MRI Number of participants: 133,464 (15 observational studies)	**OR 1.29** (1.09 to 1.53)	**38.0%** (34.2 to 42.1)	32.3%	**5.8% more** (1.9 more to 9.9 more)	⊕⊕◯◯ Low[a,b]
Initial mastectomy rate by subtype (excluding studies restricted to BCS candidates) - In situ Number of participants: 11,459 (4 observational studies)	**OR 1.90** (1.28 to 2.82)	**37.4%** (28.7 to 47)	23.9%	**13.5% more** (4.8 more to 23.1 more)	⊕◯◯◯ Very low[a,b]
Initial mastectomy rate by subtype (excluding studies restricted to BCS candidates) - Invasive Number of participants: 51,967 (6 observational studies)	**OR 1.48** (1.26 to 1.73)	**32.4%** (29 to 35.9)	24.5%	**7.9% more** (4.5 more to 11.4 more)	⊕⊕◯◯ Low[a,b]
Initial mastectomy rate by subtype (excluding studies restricted to BCS candidates) - ILC Number of participants: 8,402 (5 observational studies)	**OR 1.01** (0.80 to 1.27)	**39.0%** (33.6 to 44.5)	38.7%	**0.2% more** (5.1 fewer to 5.8 more)	⊕◯◯◯ Very low[a,b,e]
Final (overall) mastectomy rate Number of participants: 342,285 (29 observational studies)	**OR 1.24** (1.11 to 1.39)	**37.7%** (35.1 to 40.4)	32.8%	**4.9% more** (2.3 more to 7.6 more)	⊕◯◯◯ Very low[a,b]
Final (overall) mastectomy rate - Assigned BCS prior to MRI Number of participants: 4,905 (5 RCTs)	**OR 1.87** (1.23 to 2.85)	**14.0%** (9.7 to 19.9)	8.0%	**6.0% more** (1.7 more to 11.9 more)	⊕◯◯◯ Very low[b,c,d]
Final (overall) mastectomy rate - Surgery not specified prior to MRI Number of participants: 337,380 (24 observational studies)	**OR 1.19** (1.06 to 1.33)	**41.8%** (39 to 44.5)	37.6%	**4.2% more** (1.4 more to 6.9 more)	⊕⊕◯◯ Low[a,b]
Final (overall) mastectomy rate by subtype (excluding studies restricted to BCS candidates) - In situ Number of participants: 12,248 (5 observational studies)	**OR 1.68** (1.15 to 2.47)	**40.7%** (32 to 50.2)	29.0%	**11.7% more** (3 more to 21.2 more)	⊕⊕◯◯ Low[a,b]
Final (overall) mastectomy rate by subtype (excluding studies restricted to BCS candidates) - Invasive Number of participants: 152,075 (8 observational studies)	**OR 1.31** (1.10 to 1.56)	**40.4%** (36.2 to 44.6)	34.1%	**6.3% more** (2.2 more to 10.6 more)	⊕⊕◯◯ Low[a,b]
Final (overall) mastectomy rate by subtype (excluding studies restricted to BCS candidates) - ILC Number of participants: 3,689 (5 observational studies)	**RR 0.91** (0.75 to 1.11)	**44.1%** (36.4 to 53.8)	48.5%	**4.4% fewer** (12.1 fewer to 5.3 more)	⊕⊕◯◯ Low[a,e]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Low to moderate risk of bias for most studies; b. I^2 >50%; c. High risk of bias due to study design; d. Only included patients determined prior to MRI as BCS candidates; e. Less than optimal sample size

Abbreviations: BCS, breast conserving surgery; CI, confidence interval; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk

Table 4-4b. MRI versus no MRI for treatment planning (outcome is positive margins).

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Risk with MRI (%)	Risk without MRI (%)	Difference	
Positive margins - All studies Number of participants: 53,158 (11 observational studies)	**OR 0.89** (0.74 to 1.06)	**16.5%** (14.1 to 19.1)	18.2%	**1.7% fewer** (4.1 fewer to 0.9 more)	⊕⊕◯◯ Low[a,b]
Positive margins, subset with low or low-moderate RoB Number of participants: 3,101 (5 observational studies)	**OR 0.57** (0.36 to 0.89)	**6.5%** (4.2 to 9.8)	10.9%	**4.4% fewer** (6.7 fewer to 1.1 fewer)	⊕⊕⊕◯ Moderate[b]
Positive margins by subtype - In situ Number of participants: 8,488 (4 observational studies)	**OR 1.01** (0.77 to 1.32)	**22.5%** (18.1 to 27.5)	22.3%	**0.2% more** (4.2 fewer to 5.2 more)	⊕◯◯◯ Very low[a,c]
Positive margins by subtype - Invasive Number of participants: 34,238 (4 observational studies)	**OR 0.98** (0.84 to 1.13)	**9.1%** (7.9 to 10.4)	9.3%	**0.2% fewer** (1.4 fewer to 1.1 more)	⊕◯◯◯ Very low[a,c]
Positive margins by subtype - ILC Number of participants: 5,536 (2 observational studies)	**OR 0.63** (0.49 to 0.82)	**18.9%** (15.3 to 23.3)	27.0%	**8.1% fewer** (11.7 fewer to 3.7 fewer)	⊕⊕⊕◯ Moderate[a]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; OR: odds ratio
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Risk of bias is moderate in most studies; b. I^2 >50%; c. Less than optimal sample size

Abbreviations: CI, confidence interval; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; OR, odds ratio; RoB, risk of bias

Table 4-4c. MRI versus no MRI for treatment planning (outcome is additional surgery).

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Risk with MRI (%)	Risk without MRI (%)	Difference	
Reoperations, all patients Number of participants: 109,856 (22 observational studies)	**OR 0.73** (0.63 to 0.85)	**14.4%** (12.6 to 16.3)	18.7%	**4.3% fewer** (6 fewer to 2.3 fewer)	⊕⊕◯◯ Low[a,b]
Reoperations, RCT only Number of participants: 3,064 (6 RCTs)	**OR 0.78** (0.49 to 1.22)	**16.6%** (11.1 to 23.7)	20.3%	**3.7% fewer** (9.2 fewer to 3.4 more)	⊕◯◯◯ Very low[b,c,d]
Reoperations, non-RCT Number of participants: 106,792 (16 observational studies)	**OR 0.72** (0.61 to 0.85)	**13.7%** (11.9 to 15.8)	18.1%	**4.4% fewer** (6.2 fewer to 2.3 fewer)	⊕⊕◯◯ Low[a,b]
Reoperations, by subtype - In situ Number of participants: 17,289 (5 observational studies)	**OR 0.92** (0.68 to 1.26)	**20.0%** (15.6 to 25.5)	21.4%	**1.4% fewer** (5.8 fewer to 4.1 more)	⊕⊕◯◯ Low[a,b]
Reoperations, by subtype - Invasive Number of participants: 49,512 (6 observational studies)	**OR 0.96** (0.88 to 1.05)	**17.5%** (16.3 to 18.8)	18.1%	**0.6% fewer** (1.8 fewer to 0.7 more)	⊕⊕◯◯ Low[a,d]
Reoperations, by subtype - ILC Number of participants: 2,123 (3 observational studies)	**OR 0.30** (0.13 to 0.72)	**12.3%** (5.7 to 25.2)	31.9%	**19.6% fewer** (26.1 fewer to 6.7 fewer)	⊕⊕⊕◯ Moderate[a,b]
Re-excisions, all patients Number of participants: 12,739 (17 observational studies)	**OR 0.63** (0.45 to 0.89)	**6.9%** (5 to 9.5)	10.5%	**3.6% fewer** (5.5 fewer to 1 fewer)	⊕⊕◯◯ Low[a,b]
Re-excisions, RCT Number of participants: 3,155 (7 RCTs)	**OR 0.79** (0.45 to 1.37)	**8.4%** (5 to 13.7)	10.4%	**2.0% fewer** (5.4 fewer to 3.3 more)	⊕◯◯◯ Very low[b,c,d]
Re-excisions, non-RCT Number of participants: 9,584 (10 observational studies)	**OR 0.54** (0.34 to 0.88)	**6.0%** (3.9 to 9.4)	10.5%	**4.6% fewer** (6.7 fewer to 1.1 fewer)	⊕⊕◯◯ Low[a,b]
Re-excisions, by subtype - In situ Number of participants: 1,206 (4 observational studies)	**OR 0.92** (0.62 to 1.38)	**11.2%** (7.8 to 15.9)	12.0%	**0.9% fewer** (4.2 fewer to 3.9 more)	⊕◯◯◯ Very low[a,d]
Re-excisions, by subtype - Invasive Number of participants: 4,694 (3 observational studies)	**OR 1.21** (0.87 to 1.67)	**12.0%** (9 to 15.9)	10.2%	**1.9% more** (1.2 fewer to 5.7 more)	⊕⊕◯◯ Low[a,d]
Re-excisions, by subtype - ILC Number of participants: 2,524 (4 observational studies)	**OR 0.42** (0.13 to 1.35)	**8.3%** (2.7 to 22.5)	17.7%	**9.4% fewer** (15 fewer to 4.8 more)	⊕⊕◯◯ Low[a,b]
Conversion mastectomy, all patients Number of participants: 27,736 (15 observational studies)	**OR 0.76** (0.58 to 0.99)	**5.5%** (4.3 to 7.1)	7.1%	**1.6% fewer** (2.9 fewer to 0.1 fewer)	⊕⊕◯◯ Low[a,b]
Conversion mastectomy, RCT Number of participants: 3,064 (6 RCTs)	**OR 0.72** (0.53 to 0.96)	**6.6%** (5 to 8.6)	9.0%	**2.3% fewer** (4 fewer to 0.3 fewer)	⊕◯◯◯ Very low[c,d]
Conversion mastectomy, non-RCT Number of participants: 24,672 (9 observational studies)	**OR 0.77** (0.54 to 1.11)	**4.9%** (3.5 to 7)	6.3%	**1.4% fewer** (2.8 fewer to 0.6 more)	⊕⊕◯◯ Low[a,b]
Conversion mastectomy, by subtype - In situ Number of participants: 8,113 (4 observational studies)	**OR 0.87** (0.43 to 1.76)	**6.4%** (3.3 to 12.2)	7.3%	**0.9% fewer** (4 fewer to 4.9 more)	⊕◯◯◯ Very low[a,b,d]

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Risk with MRI (%)	Risk without MRI (%)	Difference	
Conversion mastectomy, by subtype - Invasive Number of participants: 12,617 (4 observational studies)	**OR 0.80** (0.43 to 1.49)	**4.7%** (2.6 to 8.3)	5.8%	**1.1% fewer** (3.2 fewer to 2.6 more)	⊕◯◯◯ Very low[a,b,d]
Conversion mastectomy, by subtype - ILC Number of participants: 2,123 (3 observational studies)	**OR 0.38** (0.25 to 0.56)	**5.9%** (4 to 8.5)	14.2%	**8.3% fewer** (10.3 fewer to 5.7 fewer)	⊕⊕⊕⊕ High[a]

*****The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Risk of bias is moderate in most studies; b. I^2 >50%; c. Risk of bias some concerns or high; d. Less than optimal sample size.

Abbreviations: CI, confidence interval; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; **OR,** odds ratio; RCT, randomized controlled trial

Table 4-4d. MRI versus no MRI for treatment planning (outcome is contralateral cancer).

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Risk with MRI (%)	Risk without MRI (%)	Difference	
Synchronous Contralateral Breast Cancer (CBC) Number of participants: 61929 (4 observational studies)	**HR 2.52** (1.75 to 3.62)	4.7%	1.9%	**2.8% more** (1.4 more to 4.8 more)	⊕⊕⊕◯ Moderate [a,b]
Metachronous Contralateral Breast Cancer Number of participants: 31095 (8 observational studies)	**HR 0.71** (0.59 to 0.85)	1.7%	2.4%	**0.7% fewer** (1 fewer to 0.4 fewer)	⊕⊕⊕◯ Moderate [a]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; HR: hazard ratio
GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Risk of bias is moderate in most studies; b. I^2 >50%

Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging

Table 4-4e. MRI compared to no MRI for treatment planning (outcome is survival or recurrence).

Outcome Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)			Certainty
		Risk with MRI (%)	Risk without MRI (%)	Difference	
Recurrence: Locoregional + Distant (+ contralateral in some studies) Number of participants: 9,052 (11 observational studies)	**HR 0.77** (0.65 to 0.90)	**Recurrence**			⊕⊕⊕◯ Moderate[a]
		8.2% (7 to 9.5)	10.5%	**2.3% fewer** (3.6 fewer to 1 fewer)	
Locoregional Recurrence (ipsilateral breast or lymph nodes) Number of participants: 8,996 (10 observational studies)	**HR 0.85** (0.69 to 1.04)	**LRR**			⊕⊕◯◯ Low[a,b]
		4.8% (3.9 to 5.9)	5.7%	**0.8% fewer** (1.7 fewer to 0.2 more)	
Distant Recurrence Number of participants: 3,304 (6 observational studies)	**HR 0.77** (0.56 to 1.07)	**Distant Recurrence**			⊕⊕◯◯ Low[a,b]
		4.7% (3.5 to 6.5)	6.1%	**1.4% fewer** (2.6 fewer to 0.4 more)	
Recurrence-Free Survival (Disease-Free Survival) Number of participants: 34,202 (6 observational studies)	**HR 0.77** (0.53 to 1.12) [recurrence or death]	**DFS**			⊕⊕⊕◯ Moderate[a]
		91.6% (88.1 to 94.2)	89.3%	**2.4% more DFS** (1.2 fewer to 4.9 more)	
Overall Survival Number of participants: 33804 (5 observational studies)	**HR 0.89** (0.74 to 1.07) [death]	**Overall Survival**			⊕⊕⊕◯ Moderate[a]
		93.8% (92.6 to 94.8)	93.0%	**0.7% more OS** (0.5 fewer to 1.8 more)	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
a. Risk of bias is low to moderate in most studies; b. Less than optimal sample size

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; MRI, magnetic resonance imaging; OS, overall survival

Table 4-5. Grade profiles from GRADEPro

Table 4-5a. MRI compared to no MRI for treatment planning (outcome is mastectomy rate).

Certainty assessment							Summary of findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no MRI	With MRI		Risk with no MRI	Risk difference with MRI
Initial mastectomy rate											
135,985 (19 observational studies)	very serious[a]	serious[b]	not serious	not serious	none	⨁◯◯◯ Very low	28,723/105928 (27.1%)	10,405/30,057 (34.6%)	**OR 1.42** (1.19 to 1.69)	271 per 1,000	**75 more per 1,000** (from 36 more to 115 more)
Initial mastectomy rate - Assigned BCS prior to MRI											
2,521 (4 RCTs)	very serious[c]	not serious	very serious[d]	not serious	none	⨁◯◯◯ Very low	14/1,258 (1.1%)	70/1,263 (5.5%)	**OR 5.18** (2.37 to 11.29)	11 per 1,000	**44 more per 1,000** (from 15 more to 102 more)
Initial mastectomy rate - Surgery not specified prior to MRI											
133,464 (15 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	33,758/104,670 (32.3%)	10,957/28,794 (38.1%)	**OR 1.29** (1.09 to 1.53)	323 per 1,000	**58 more per 1,000** (from 19 more to 99 more)
Initial mastectomy rate by subtype (excluding studies restricted to BCS candidates) - In situ											
11,459 (4 observational studies)	very serious[a]	serious[b]	not serious	not serious	none	⨁◯◯◯ Very low	2,075/8,681 (23.9%)	1,039/2,778 (37.4%)	**OR 1.90** (1.28 to 2.82)	239 per 1,000	**135 more per 1,000** (from 48 more to 231 more)
Initial mastectomy rate by subtype (excluding studies restricted to BCS candidates) - Invasive											
51,967 (6 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	9,836/40,229 (24.5%)	3,797/11,738 (32.3%)	**OR 1.48** (1.26 to 1.73)	245 per 1,000	**79 more per 1,000** (from 45 more to 114 more)
Initial mastectomy rate by subtype (excluding studies restricted to BCS candidates) - ILC											
8,402 (5 observational studies)	serious[a]	serious[b]	not serious	very serious[e]	none	⨁◯◯◯ Very low	1,739/4,488 (38.7%)	1,571/3,914 (40.1%)	**OR 1.01** (0.80 to 1.27)	387 per 1,000	**2 more per 1,000** (from 51 fewer to 58 more)
Final (overall) mastectomy rate											
342,285 (29 observational studies)	very serious[a]	serious[b]	not serious	not serious	none	⨁◯◯◯ Very low	94,444/288,156 (32.8%)	20,393/54,129 (37.7%)	**OR 1.24** (1.11 to 1.39)	328 per 1,000	**49 more per 1,000** (from 23 more to 76 more)
Final (overall) mastectomy rate - Assigned BCS prior to MRI											
4,905 (5 RCTs)	very serious[c]	serious[b]	very serious[d]	not serious	none	⨁◯◯◯ Very low	277/3,457 (8.0%)	203/1,448 (14.0%)	**OR 1.87** (1.23 to 2.85)	80 per 1,000	**60 more per 1,000** (from 17 more to 119 more)
Final (overall) mastectomy rate - Surgery not specified prior to MRI											
337,380 (24 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⨁⨁◯◯ Low	107,052/284,699 (37.6%)	22,022/52,681 (41.8%)	**OR 1.19** (1.06 to 1.33)	376 per 1,000	**42 more per 1,000** (from 14 more to 69 more)

Certainty assessment							Summary of findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no MRI	With MRI		Risk with no MRI	Risk difference with MRI
Final (overall) mastectomy rate by subtype (excluding studies restricted to BCS candidates) - In situ											
12,248 (5 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	2,734/9,430 (29.0%)	1,147/2,818 (40.7%)	**OR 1.68** (1.15 to 2.47)	290 per 1,000	**117 more per 1,000** (from 30 more to 212 more)
Final (overall) mastectomy rate by subtype (excluding studies restricted to BCS candidates) - Invasive											
152,075 (8 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	44,598/130,882 (34.1%)	8,557/21,193 (40.4%)	**OR 1.31** (1.10 to 1.56)	341 per 1,000	**63 more per 1,000** (from 22 more to 106 more)
Final (overall) mastectomy rate by subtype (excluding studies restricted to BCS candidates) - ILC											
3,689 (5 observational studies)	serious[a]	not serious	not serious	serious[e]	none	⊕⊕◯◯ Low	1,059/2,185 (48.5%)	693/1,504 (46.1%)	**RR 0.91** (0.75 to 1.11)	485 per 1,000	**44 fewer per 1,000** (from 121 fewer to 53 more)

Explanations
a. Low to moderate risk of bias for most studies; b. I^2 >50%; c. High risk of bias due to study design; d. Only included patients determined prior to MRI as BCS candidates; e. Less than optimal sample size

Abbreviations: BCS, breast conserving surgery; CI, confidence interval; ILC, invasive lobular carcinoma; OR, odds ratio; MRI, magnetic resonance imaging; RR, relative risk

Table 4-5b. MRI compared to no MRI for treatment planning (outcome is positive margins).

Certainty assessment							Summary of findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no MRI	With MRI		Risk with no MRI	Risk difference with MRI
Positive margins - All studies											
53,158 (11 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	6,746/37123 (18.2%)	2,641/16,035 (16.5%)	**OR 0.89** (0.74 to 1.06)	182 per 1,000	**17 fewer per 1,000** (from 41 fewer to 9 more)
Positive margins, subset with low or low-moderate RoB											
3,101 (5 observational studies)	not serious	serious[b]	not serious	not serious	none	⊕⊕⊕◯ Moderate	172/1,579 (10.9%)	99/1,522 (6.5%)	**OR 0.57** (0.36 to 0.89)	109 per 1,000	**44 fewer per 1,000** (from 67 fewer to 11 fewer)
Positive margins by subtype - In situ											
8,488 (4 observational studies)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ Very low	1,480/6,629 (22.3%)	419/1,859 (22.5%)	**OR 1.01** (0.77 to 1.32)	223 per 1,000	**2 more per 1,000** (from 42 fewer to 52 more)
Positive margins by subtype - Invasive											
34,238 (4 observational studies)	serious[a]	not serious	not serious	very serious[c]	none	⊕◯◯◯ Very low	2,303/24,766 (9.3%)	862/9,472 (9.1%)	**OR 0.98** (0.84 to 1.13)	93 per 1,000	**2 fewer per 1,000** (from 14 fewer to 11 more)
Positive margins by subtype - ILC											
5,536 (2 observational studies)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ Moderate	674/2,498 (27.0%)	574/3,038 (18.9%)	**OR 0.63** (0.49 to 0.82)	270 per 1,000	**81 fewer per 1,000** (from 117 fewer to 37 fewer)

Explanations
a. Risk of bias is moderate in most studies; b. I2 >50%; c. Less than optimal sample size

Abbreviations: CI, confidence interval; ILC, invasive lobular carcinoma; OR, odds ratio; MRI, magnetic resonance imaging; RoB, risk of bias

Table 4-5c. MRI compared to no MRI for treatment planning (outcome is additional surgery).

Certainty assessment							Summary of findings				
Participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no MRI	With MRI		Risk with no MRI	Risk difference with MRI
Reoperations, all patients											
109,856 (22 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	17,524/93,868 (18.7%)	2,297/15,988 (14.4%)	**OR 0.73** (0.63 to 0.85)	187 per 1,000	**43 fewer per 1,000** (from 60 fewer to 23 fewer)
Reoperations, RCT only											
3,064 (6 RCTs)	serious[c]	serious[b]	not serious	serious[d]	none	⊕◯◯◯ Very low	310/1,528 (20.3%)	255/1,536 (16.6%)	**OR 0.78** (0.49 to 1.22)	203 per 1,000	**37 fewer per 1,000** (from 92 fewer to 34 more)
Reoperations, non-RCT											
106,792 (16 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	16,700/92,340 (18.1%)	1,978/14,452 (13.7%)	**OR 0.72** (0.61 to 0.85)	181 per 1,000	**44 fewer per 1,000** (from 62 fewer to 23 fewer)
Reoperations, by subtype - In situ											
17,289 (5 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	3,239/15,136 (21.4%)	431/2,153 (20.0%)	**OR 0.92** (0.68 to 1.26)	214 per 1,000	**14 fewer per 1,000** (from 58 fewer to 41 more)
Reoperations, by subtype - Invasive											
49,512 (6 observational studies)	serious[a]	not serious	not serious	serious[d]	none	⊕⊕◯◯ Low	8,121/44,867 (18.1%)	813/4,645 (17.5%)	**OR 0.96** (0.88 to 1.05)	181 per 1,000	**6 fewer per 1,000** (from 18 fewer to 7 more)
Reoperations, by subtype - ILC											
2,123 (3 observational studies)	serious[a]	serious[b]	not serious	not serious	strong association[e]	⊕⊕⊕◯ Moderate	443/1,390 (31.9%)	90/733 (12.3%)	**OR 0.30** (0.13 to 0.72)	319 per 1,000	**196 fewer per 1,000** (from 261 fewer to 67 fewer)
Re-excisions, all patients											
12,739 (17 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	746/7,106 (10.5%)	389/5,633 (6.9%)	**OR 0.63** (0.45 to 0.89)	105 per 1,000	**36 fewer per 1,000** (from 55 fewer to 10 fewer)
Re-excisions, RCT											
3,155 (7 RCTs)	very serious[c]	serious[b]	not serious	serious[d]	none	⊕◯◯◯ Very low	164/1,577 (10.4%)	133/1,578 (8.4%)	**OR 0.79** (0.45 to 1.37)	104 per 1,000	**20 fewer per 1,000** (from 54 fewer to 33 more)
Re-excisions, non-RCT											
9,584 (10 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	583/5,529 (10.5%)	241/4,055 (5.9%)	**OR 0.54** (0.34 to 0.88)	105 per 1,000	**46 fewer per 1,000** (from 67 fewer to 11 fewer)

Re-excisions, by subtype - In situ											
1,206 (4 observational studies)	serious[a]	not serious	not serious	very serious[d]	none	⊕◯◯◯ Very low	87/722 (12.0%)	54/484 (11.2%)	**OR 0.92** (0.62 to 1.38)	120 per 1,000	**9 fewer per 1,000** (from 42 fewer to 39 more)
Re-excisions, by subtype - Invasive											
4,694 (3 observational studies)	serious[a]	not serious	not serious	serious[d]	none	⊕⊕◯◯ Low	307/3,024 (10.2%)	201/1,670 (12.0%)	**OR 1.21** (0.87 to 1.67)	102 per 1,000	**19 more per 1,000** (from 12 fewer to 57 more)
Re-excisions, by subtype - ILC											
2,524 (4 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	270/1,527 (17.7%)	83/997 (8.3%)	**OR 0.42** (0.13 to 1.35)	177 per 1,000	**94 fewer per 1,000** (from 150 fewer to 48 more)
Conversion mastectomy, all patients											
27,736 (15 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	1,543/21,643 (7.1%)	294/6,093 (4.8%)	**OR 0.76** (0.58 to 0.99)	71 per 1,000	**16 fewer per 1,000** (from 29 fewer to 1 fewer)
Conversion mastectomy, RCT											
3,064 (6 RCTs)	very serious[c]	not serious	not serious	serious[d]	none	⊕◯◯◯ Very low	137/1,528 (9.0%)	102/1,536 (6.6%)	**OR 0.72** (0.53 to 0.96)	90 per 1,000	**23 fewer per 1,000** (from 40 fewer to 3 fewer)
Conversion mastectomy, non-RCT											
24,672 (9 observational studies)	serious[a]	serious[b]	not serious	not serious	none	⊕⊕◯◯ Low	1,272/20,115 (6.3%)	224/4,557 (4.9%)	**OR 0.77** (0.54 to 1.11)	63 per 1,000	**14 fewer per 1,000** (from 28 fewer to 6 more)
Conversion mastectomy, by subtype - In situ											
8,113 (4 observational studies)	serious[a]	serious[b]	not serious	serious[d]	none	⊕◯◯◯ Very low	470/6,403 (7.3%)	110/1,710 (6.4%)	**OR 0.87** (0.43 to 1.76)	73 per 1,000	**9 fewer per 1,000** (from 40 fewer to 49 more)
Conversion mastectomy, by subtype - Invasive											
12,617 (4 observational studies)	serious[a]	serious[b]	not serious	serious[d]	none	⊕◯◯◯ Very low	627/10,897 (5.8%)	80/1,720 (4.7%)	**OR 0.80** (0.43 to 1.49)	58 per 1,000	**11 fewer per 1,000** (from 32 fewer to 26 more)
Conversion mastectomy, by subtype - ILC											
2,123 (3 observational studies)	serious[a]	not serious	not serious	not serious	strong association[e]	⊕⊕⊕⊕ High	198/1,390 (14.2%)	43/733 (5.9%)	**OR 0.38** (0.25 to 0.56)	142 per 1,000	**83 fewer per 1,000** (from 103 fewer to 57 fewer)

Explanations
a. Risk of bias is moderate in most studies; b. I^2 >50%; c. Risk of bias some concerns or high; d. Less than optimal sample size; e. Outcomes with a large effect of preoperative MRI (OR<0.5) or very large effect (OR<0.2) were upgraded by one or two levels, respectively.

Abbreviations: CI, confidence interval; ILC, invasive lobular carcinoma; OR, odds ratio; MRI, magnetic resonance imaging

Table 4-5d. MRI compared to no MRI for treatment planning (outcome is contralateral cancer).

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no MRI	With MRI		Risk with no MRI	Risk difference with MRI
Synchronous Contralateral Breast Cancer											
61,929 (4 observational studies)	serious[a]	serious[b]	not serious	not serious	strong association[c]	⊕⊕⊕◯ Moderate	770/40,774 (1.9%)	992/21,155 (4.7%)	HR 2.52 (1.75 to 3.62)	19 per 1,000	28 more per 1,000 (from 14 more to 48 more)
Metachronous Contralateral Breast Cancer											
31,095 (1 RCT and 7 other studies)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ Moderate	478/19,558 (2.4%)	201/11,537 (1.7%)	HR 0.71 (0.59 to 0.85)	24 per 1,000	7 fewer per 1,000 (from 10 fewer to 4 fewer)

Explanations
a. Risk of bias is moderate in most studies; b. I^2 >50%; c. Outcomes with a large effect of preoperative MRI (OR<0.5) or very large effect (OR<0.2) were upgraded by one or two levels, respectively.

Abbreviations: CI, confidence interval; HR, hazard ratio; ILC, invasive lobular carcinoma; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Table 4-5e. MRI compared to no MRI for treatment planning (outcome is survival or recurrence).

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no MRI	With MRI		Risk with no MRI	Risk difference with MRI
Recurrence: Locoregional + Distant (+ contralateral in some studies)											
9,052 (3 RCT and 8 other studies)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ Moderate	5,118 participants	3,934 participants	**HR 0.77** (0.65 to 0.90) Recurrence	**Recurrence**	
										105 per 1,000	**23 fewer per 1,000** (from 36 fewer to 10 fewer)
Locoregional Recurrence (ipsilateral breast or lymph nodes)											
8,996 (2 RCT and 8 other studies)	serious[a]	not serious	not serious	serious[b]	none	⊕⊕◯◯ Low	5,197 participants	3,799 participants	**HR 0.85** (0.69 to 1.04) Recurrence	**Locoregional Recurrence**	
										57 per 1,000	**8 fewer per 1,000** (from 17 fewer to 2 more)
Distant Recurrence											
3,304 (3 RCT and 3 other studies)	serious[a]	not serious	not serious	serious[b]	none	⊕⊕◯◯ Low	1,582 participants	1,722 participants	**HR 0.77** (0.56 to 1.07) Recurrence	**Distant Recurrence**	
										61 per 1,000	**14 fewer per 1,000** (from 26 fewer to 4 more)
Recurrence-Free Survival (Disease-Free Survival)											
34,202 (2 RCT and 4 other studies)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ Moderate	22,939 participants	11,263 participants	**HR 0.77** (0.53 to 1.12) Recurrence or death	**Disease-free Survival**	
										893 per 1,000	**24 more per 1,000** (from 12 fewer to 49 more)
Overall Survival											
33,804 (2 RCT and 3 other studies)	serious[a]	not serious	not serious	not serious	none	⊕⊕⊕◯ Moderate	22,886 participants	10,918 participants	**HR 0.89** (0.74 to 1.07) Death	**Overall Survival**	
										930 per 1,000	**7 more per 1,000** (from 5 fewer to 18 more)

Explanations
a. Risk of bias is low to moderate in most studies; b. Less than optimal sample size.

Abbreviations: CI, confidence interval; HR, hazard ratio; MRI, magnetic resonance imaging; RCT, randomized controlled trial

Preoperative Breast Magnetic Resonance Imaging Guideline

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Patient and Caregiver-Specific Consultation Group

Five patients/survivors/caregivers participated as Consultation Group members for the Working Group. They reviewed the draft recommendations and provided feedback on its comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The main comments from the Consultation Group are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Patient Consultation Group.

Comments	Responses
1. In recommendations, be more explicit that decision should be made after consultation between physician and patient	We have added a phrase in the recommendations: The decision of whether to conduct MRI should be made ***in consultation with the patient and*** …
2. The additional situations for breast MRI (following Recommendation 2) should be labelled as Recommendation 3	This change has been made
3. The table of risks and benefits indicates current delays due to MRI are 6 to 12 days; this seems to be too optimistic	We have removed the time estimate and reworded this to indicate MRI may result in delays, both while waiting for the MRI, and for subsequent biopsies (if needed).
4. The patient population regarding stage of breast cancer is unclear.	The Target Population and Background have been edited to more clearly indicate it applies to any breast cancer for which breast MRI may provide additional information on the extent of disease in the breasts.
5. Education of patients is critical, and the table of Benefits and Risks is useful	Education has been mentioned in Implementation Considerations
6. In some cases, patients may be reluctant to have MRI due to fear of the machine (claustrophobia, loud noise). Doctors should discuss whether there can be modifications made such as sedation or larger machine. Comment that despite claustrophobia, they	This has been added to implementation considerations

would tolerate it because MRI was so important in treatment of cancer.	
7. Quality of life was not listed and realize information may not be available. It was stressed that additional information from MRI allows better decision making and therefore better quality of life.	Due to retrospective nature of most studies, quality of life was usually not recorded as an independent outcome; however, the outcomes reported are all know to impact quality of life: positive margins result in reoperation and/or increased risk of recurrence and sometime unplanned and medically unnecessary mastectomy; recurrence requires additional surgery and/or other treatment and possible result in death; BCS may result in less complications and shorter surgery than mastectomy, more natural breasts, and less psychosexual effects
8. Access to MRI may not be available in some communities where the patients live, or the wait time locally is unacceptable. Patients do not know how to navigate the health system, and therefore doctors should let them know the possibility of going to a more distant location for MRI.	A statement about access, delays, and individual situations has been added to implementation considerations. We are cautious about use of more distant MRI locations (other than proposed treatment centres) as MRI, additional testing, follow-up, and surgery are generally preferred to be at the same institution/location.

Expert Panel Review and Approval

The GDG Expert Panel consisted of eight members. All members voted and approved the document. The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. Consider adding the following to Table 2-1: • In patients with initial diagnosed occult breast cancer, may identify the breast lesion allowing more specific treatment, including less aggressive surgeries, including BCS. • In the setting of Paget disease with negative conventional imaging studies, can identify underlying breast malignancy, facilitating proper treatment planning.	Occult cancer was specifically excluded from the literature review; however, we note this was not mentioned in this document. A statement has been added to the Target Population section to reflect this. The comment on Paget disease has been added to the table.
2. Table 2-1. Concerns of brain gadolinium accumulation may not be applicable to this scenario, because we are discussing a single specific preoperative study.	Degree of accumulation depends on degree of exposure and type of agent used. It can occur after a single MRI and therefore is kept in the table but reworded.
3. Table 2-1. It is missing discussion of MRI cost, which may represent a real impediment to the global adoption of preoperative MRI, mainly in the sense that it is not feasible in countries with limited resources.	Cost has been added to Table 2-1, and a comment under limitations that cost analysis was outside the scope.

	When reviewing the document, the costs were considered outside the scope of the review, but it is so important that I suggest bringing it briefly here, with details considered out of the scope of the work.	
4.	Under Evidence Base in Section 2. It is suggested to include time period of search strategy to show it was the most up-to-date systematic review.	This has been added.
5.	Consider including Paget disease in Other Comments and/or Table 2-1 (see previous comment)	This has been added.
6.	Recommendation 1 and the key evidence for recommendation 1 support the routine use of MRI in patients diagnosed with breast cancer, other than in patients unlikely to have BCS (or MRI contraindicated). If such is the intent of Recommendation 1, then this could be more explicit in the wording of recommendation one.	We believe the recommendation accurately reflects our intent. The recommendation indicates it applies to patients for whom additional information about disease extent could influence treatment. We have clarified in the qualifying statement that treatment includes surgery and adjuvant therapy. The recommendation applies to both patients who (in the absence of MRI) will have BCS or mastectomy as both type of surgery and adjuvant treatment can change with additional information, depending on the rational for the initial decision. Contraindications to MRI are part of the assessment of risks and benefits.
7.	I approve with condition that Recommendation 1 could be revisited to be less vague - it seems to say that the overall objective of these guidelines is to find which patients would benefit from preop diagnostic MRI and summary of recommendation says that it could be used in anyone with cancer for which there may be benefit… sort of a circular comment ?	The first objective is to find whether MRI is beneficial in an overall sense. If data exist for more specific situations, then these would also be dealt with. Data found in the evidence summary were insufficient to make more specific recommendations.
8.	This recommendation seems somewhat vague/ non-prescriptive. As a surgeon, the goal is to excise "all" known areas of identifiable disease. Often the decision for breast conservation versus mastectomy hinges on understanding of the extent of disease. The recommendation invites MRI for all patients who are not committed to mastectomy based on extent of disease identified by conventional imaging or upfront patient preference for mastectomy independent of disease extent. Is there guidance for individualizing the use of MRI for patients in whom conventional imaging is more likely to underestimate disease extent (e.g., patient age, multifocal or multicentric disease, breast density, previous breast surgery- cancer surgery or reduction mammoplasty, tumour histology etc.)? How should some of the factors in the first qualifying statement be used to selectively choose preoperative MRI for the patients who are most likely to benefit from the intervention?	Recommendation 1 suggests use of MRI *be considered* for all patients except in those for which any results would not make a difference to treatment. Recommendations 2 and 3 provide specific situations where MRI is recommended. While it is tempting to recommend MRI in cases with higher probability of recurrence, the evidence in the literature search was insufficient to reach this conclusion.
9.	Since there are other competing imaging modalities (for example, I see a lot of contrast-enhanced	Background information on other techniques was provided in the systematic

mammogram being done locally), the qualifying statements for Recommendation 1 should make some reference at least to their existence and insufficient data.	review. An additional qualifying statement has been added to Recommendation 1 to reflect that other advanced imaging may be suitable.
10. Among the key evidence for Recommendation 1, it would be useful to know whether more weight was given to DFS versus reduced rate of positive margins, for example. The eight bullet points of key evidence could be grouped according to those given more importance as outcomes versus less importance and/or according to those where the evidence is low to moderate versus moderate to strong.	Some more discussion of outcomes has been added to Section 4. The importance of outcomes was considered as part of the guideline development process and all those outcomes presented in this document were considered very important or critical. Strength of evidence varies, but all effects were in the same direction (MRI benefit) so all these together contribute to the recommendation. Survival and recurrence outcomes are generally the most important (unless adverse effects have large impact on quality of life) and therefore listed first.
11. Key Evidence Recommendation 1: For the study by Wang et al, 2018 on MRI in patients with or without radiation therapy, did any patients receive endocrine therapy and were patients selected appropriately for radiation therapy omission?	This study was reviewed, and it was decided due to limitations in design it should not be included as key evidence
12. Recommendation 3, Preoperative breast MRI is recommended to confirm suitability for partial breast irradiation (PBI): The suitability for PBI is typically based on the final pathology after BCS and review of the CT-simulation plan to ensure that the tumour bed/seroma is visible (assisted by the placement of surgical clips) so that the clinical target volume receives the planned dose. PBI eligibility includes (ASTRO guidelines): unifocal T size <2cm, invasive ductal carcinoma only (no ILC), clear margins, age >50 years. Reference #37 found a higher likelihood of PBI ineligibility for young pts and ILC – but these are contraindications for PBI anyway. Age is clear cut and ILC would need preop MRI anyway for surgical planning. The EUSOMA guideline is based on older retrospective studies and does not consider the more recently published RCTs which demonstrated non-inferiority of PBI versus whole breast irradiation in carefully selected patients with early breast cancer, none of which mandated MRI. NSABP B39 eligibility was broader than RAPID or other PBI trials (B39 permitted women 18 years or older to participate in the trial, and was a negative trial – non-inferiority was not met). Maybe I am missing something, but based on my review I suggest removing this recommendation from the document. In current practice, PBI eligibility is restricted by age, only invasive ductal carcinoma or DCIS, size, non-G3, no lymphovascular invasion, negative margin status and only unifocal focal disease. Multifocal or multicentric disease is also contraindication for PBI.	Based on this and the following reviewer comment we have removed the recommendation for preoperative MRI in patients being considered for PBI.

The ASTRO guidelines outline suitability for PBI, and patients are carefully selected.	
13. Recommendation 3d (PBI): Please clarify. Patients are considered for PBI after surgery based on gross tumour characteristics and microscopic staging and postoperative planning T (NSABP B 39 criteria). How does preoperative breast MRI impact decision for PBI?	Response for previous comment applies.
14. I would question the capacity of our current system to perform the number of MRIs and follow-up mammograms and ultrasounds that may follow from these recommendations. The guideline reports superior performance on all measures for MRI over conventional imaging and suggests consideration of MRI for all patients to best define disease extent and recommends all patients with lobular carcinoma (up to 10% of all breast cancer) have MRI.	Capacity issues are beyond the scope of this work; however, they are noted in the implementation considerations section, where is stated that "In Ontario there are currently capacity constraints that affect the availability of MRI. Additional MRI use may increase treatment delays beyond what are considered acceptable in some cases. Availability/accessibility varies among regions."
15. For key evidence in Recommendation 1, the confidence interval includes 1, suggesting a trend but not statistical significance. Is the benefit overstated?	While some outcomes are not statistically significant at the 95% level, they are at 93%. We have made recommendations based on the overall evidence for all outcomes, not one outcome in isolation. This has been added to Justification for Recommendation 1 and to Interpretations and Conclusions in Section 4.
16. Recommendation 2 suggests MRI for almost all patients with lobular histology. Should this be individualized for certain patients who may be more likely to benefit from the additional testing (e.g., age, breast density, etc.)?	Studies did not provide additional information based on patient or disease characteristics.
17. Recommendation 3c: CT is a more accessible study; does it provide equal value for evaluating pectoralis invasion?	Techniques other than MRI were outside scope unless as a third comparison to MRI and to no additional imaging.

Report Approval Panel Review and Approval

Three Report Approval Panel members reviewed this document during November to December 2022 and approved the document on December 5, 2022. The main comments from the Report Approval Panel and the Working Group's responses are summarized in Table 5-3.

Table 5-3. Summary of the Working Group's responses to comments from the Report Approval Panel.

Comments	Responses
1. In the Objectives, the phrase "about whether or in what situations" would be clearer if reworded "indications for"	This has been reworded.
2. It is unclear in Section 2 and not described in Section 4 why there is a separate recommendation for breast cancer and another for ILC.	We have added a note to Recommendation 1 to indicate specific situations are covered in Recommendations 2 and 3. Some additional information has been added to Recommendation 2 justification and Section 4 noting that ILC is a specific type of breast cancer that is more difficult to diagnose by mammography and more likely to be

	multifocal; higher rates of contralateral cancer were already noted in key evidence statements.
3. An explanation of 'levels of certainty' prior to the Recommendation tables would be helpful. Or perhaps as a foot note on the tables themselves would assist in providing clarify.	This has been added as a footnote to the Recommendation section.
4. Table 2-1 lists anxiety as both benefit and harm. Is this patient dependent?	Further explanation has been added.
5. The phrase 'should be considered' is not helpful because 'should' and 'consider' are directive and open ended, respectively. Perhaps 'could be considered'? Or 'may be considered'?	The wording reflects the intent that consideration of MRI use should occur (i.e., the physician should think about whether MRI is appropriate). We believe consideration is important, and will be followed by a decision as to whether MRI is appropriate for the particular circumstances. Decision has been replaced by "ensuing decision" to emphasize that consideration is only the first step. We have clarified that the consideration is on an individual basis.
6. In the qualifying statements for Recommendation 1, the phrase '…Treatment in the recommendation includes surgery as well as radiation and systemic treatment' would be clearer' if 'treatment' were in quotations to indicate that word is extracted from the Recommendation.	This change has been made.
7. How were the outcomes of interest chosen? Was patient input used to prioritize the outcomes of interest? The patient reviewers inquired into quality of life and the authors acknowledge that as a limitation in that the available evidence does not address this outcome. This issue could be a 'qualifier' or 'limitation' within the document itself.	The controversy in use of breast MRI is whether the information just detects more cancer or improves surgical and cancer-related outcomes. The outcomes were thus chosen to match the research question and objectives. Quality of life was not addressed as such (as a composite outcome); however, all the outcomes are acknowledged to have an impact on quality of life: positive margins result in reoperation which is negative; recurrence is negative as it requires additional surgery and/or other treatment and possible result in death; BCS may result in less complications and shorter surgery than mastectomy, more natural breasts, and less psychosexual effects.
8. The health or research question is described in Section 2 but not Section 4.	Section 4 directs the reader to the systematic review previously completed where all details are available. However, for ease of reading, the Research Question and Target Population have been added to Section 4 of this guideline document.
9. Limitations of the body of evidence are not indicated in the Results section of Section 4.	The Results and Discussion sections of the systematic review should be consulted.
10. Health benefits, side effects, and risks have been considered. This is in Section 2 but not other sections.	Side effects and risks are generally well known and were not within scope of the literature review. To provide context to the reader, these are summarized in Table 2-1. Health benefits are improvement in outcomes and are clearly described in results and discussion section of the systematic review and reanalysis of data presented in Section 4 of the current document.

11. Section 4, Interpretation and Conclusions: Is recurrence here local or local and distant? Not sure why recurrence and death were combined? This is not routinely done in oncology trials and the link between them (especially local recurrence and OS) is not very clear.	All studies on recurrence and survival were reviewed to confirm the type of recurrence, and were reclassified into locoregional recurrence, distant recurrence, or total (any) recurrence. Two studies were removed from the meta-analysis. The remaining studies included locoregional and distant recurrence (and most included contralateral cancer) in their definition of DFS. RFS or DFS is a commonly reported outcome in breast cancer trials, at least in part to the high survival rate in early breast cancer and extremely long time required to accumulate sufficient OS events. DFS is an outcome that patients often rate as very important, even if there is no difference in OS.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Three targeted peer reviewers from Ontario and Quebec who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group and agreed to be reviewers. Three responses were received. Results of the feedback survey are summarized in Table 5-4. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-5.

Table 5-4. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.			1	1	1
2. Rate the guideline presentation.			1	1	1
3. Rate the guideline recommendations.			1	1	1
4. Rate the completeness of reporting.				2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?		1		1	1
6. Rate the overall quality of the guideline report.			1	1	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.			1	1	1
8. I would recommend this guideline for use in practice.			1	1	1

9. What are the barriers or enablers to the implementation of this guideline report?	The main barriers would be on one hand, the limited availability of MRI mainly in remote areas and on the other hand, the very few benefits that were statistically significant and/or associated with a high level of certainty when scrutinized properly. Timely access to MRIs and subsequent biopsies is a barrier. In addition, the need for multiple follow-up MRIs for benign biopsies is a deterrent. Outlining very specific and clear benefits for MRI in specific populations (i.e., lobular) will help enable the guidelines. My concern is that if the evidence is only a trend toward positive impact, this may result in an unnecessary increase in MRIs in patients who may not otherwise benefit from an MRI. This guideline is needed and in keeping with current practice.

Table 5-5. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
Guideline Development: All the items were taken into account and addressed properly. The development is sound with appropriate stakeholders. Good language around alternatives, risks, etc. Good discussion of evidence and recommendations. Strong approach. The guideline process is clear, complete, and well-analyzed.	Thank you for the comments.
In Section 2: Guideline Recommendation and Evidence - Implementation Consideration: I wonder why accelerated or shortened MRI was listed only under the Research section when many studies in the literature highlight its advantages and contribution to decreasing the cost of standard MRI protocols and increasing MRI's availability. I would add a section on the benefit of considering shortened MRI protocols with a few references.	A discussion of abbreviated or shortened MRI has been added under technical considerations.
Under the section of Interpretation and Conclusion: In the last paragraph, I would add in the summary that preoperative MRI has a positive impact on patients with certain characteristics among them ILC histology in addition to the other factors listed.	The report indicates "As seen in the forest plots and the above summary, the evidence for benefit of preoperative MRI is stronger for ILC than for the overall data" and gives some additional details.
What about the age of occurrence of breast cancer? Would the young age at onset of breast cancer be one of the indications for preoperative MRI? (Although, young age may indirectly assume dense breasts	We did not find evidence that young patients should preferentially have MRI as part of breast cancer staging. Dense breasts at any age (and more common at younger age) are a risk factor

nonetheless, I think it deserves to be mentioned under the indications).	for cancer and a risk factor for underdiagnosis by mammography. Some younger patients may be eligible for high-risk screening programs and have had screening MRI that led to the initial diagnosis. Patients values and preferences may differ according to age, and should be part of the joint decision making.
In the summary, I would highlight more the benefits that were associated with a high and moderate level of certainty and keep those with a low level of certainty in the results section so that the former ones do not get diluted with the latter.	We have removed those without statistically significant results. Only recurrence and contralateral cancer (plus margins in higher quality studies) have moderate-high certainty. While mastectomy rates and reoperations have less certainty, we believe the consistency of all outcomes strengthens the evidence.
Recommendation 1 is dense. Perhaps the key evidence section could be organized further into sub-sections with headings for ease of identifying the relevant evidence – i.e., recurrence and survival outcomes, surgical planning, positive margins/reoperations, etc.	Headings have been added to categorize types of outcomes.
Recommendation 1 is very broad and some of the benefits seem to be overstated. One could look at a lot of the results and come to the opposite conclusion that the evidence is weak, with many studies demonstrating no significant difference between preoperative MRI and no MRI and therefore preoperative MRI should be considered in very few patients (i.e., only lobular). I understand the intention to draw attention to the trend toward some benefits (i.e., reduction in positive margins, reoperations) but I feel there could be more definitive statements for certain aspects or patient populations (i.e., synchronous CBCs, patients with dense breasts, etc).	We have removed DFS/RFS outcomes from the key evidence. We have removed margin status overall and only kept the subgroup data for higher quality studies. The remaining outcomes all indicate benefit for preoperative MRI. It is a judgement call as to whether these are clinically significant, and different patients may reach different conclusions. We believe the evidence is clear for synchronous CBC, and this on its own could be considered justification for MRI in all patients; however, we realize not all physicians would have the same view.
I do not feel convinced that MRIs are useful overall when looking at the forest plots and then reading the statements (and I actually use MRIs quite often in the preoperative setting)	Data from each of the primary studies is provided in the systematic review and may be more useful for some readers.
In the local recurrence + distant (+/- contralateral) recurrence; why is CBC included in this? Are these confirmed metastases in the contralateral breast? I understand the data is not duplicated but this is a bit confusing.	Metachronous contralateral breast cancer is included because that is how several of the publications defined total recurrence. Contralateral cancer could be either metastasis or new cancers and no distinction was usually made. Similarly, there was no attempt to determine whether new cancer in the ipsilateral breast was recurrence or a new cancer.
Some data on the average number of recalls and additional follow up MRIs (i.e., 6-month, 12-month, etc.) could be included to give more context to the harms/risks section.	In this review of preoperative MRI (as opposed to use in screening), the focus was on the influence of MRI on the immediate surgery. Patterns of follow-up due to suspicious but not biopsied lesions were not commonly reported.

Figure 4-4a is confusing – the HR is >1 but the horizontal axis label suggests that the Control (no MRI) is better.	Thank you for noticing this. This was an error and the axis labels have been corrected.
I needed more clarity about what "initial mastectomy" versus "final mastectomy" as outcomes are and their clinical significance/impact.	Initial mastectomy is mastectomy in the initial operation, whereas final mastectomy is the outcome after any reoperations generally due to positive margins or addition disease detected on final pathology. It would not include subsequent mastectomy due to recurrence.
I think this is an important guideline to have as there is a lot of variability in preop MRI use, but it is not as definitive as I was hoping for in terms of which specific patients or clinical scenarios would benefit most from preoperative MRI.	This is a limitation of the data available.
There is a comment at the end of the Justification for Recommendation 1, that states, "Mastectomy rates, while of interest, were therefore not considered a critical outcome in deriving this recommendation." This statement seems a little dismissive of the significance of patient centred outcomes associated with the long-term deformity of mastectomy. Would suggest removing. Does not add value to the justification.	This terminology has specific meaning in the guideline development field, but appreciate the comment that it might not be clear to the reader and have deleted it.
Consider adding a comment about lack of sensitivity for lymph node evaluation with MRI.	Lymph node evaluation depends on the equipment and field of observation. Using specific protocols, MRI is very sensitive; breast MRI is generally not optimized for this. This is noted under Other Considerations in the systematic review (1).
Consider commenting on patients undergoing neoadjuvant chemotherapy, utilization for pre- and post-treatment for surgical planning.	Under Other Comments we noted "Several other applications of breast MRI are generally accepted but outside the scope of the current work. This includes breast cancer screening, use prior to definitive diagnosis in cases with diagnostic uncertainty, occult breast cancer, or Paget disease of the breast. MRI or other advanced imaging may be used to localize the tumour prior to and following neoadjuvant therapy and to monitor response during treatment."

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. The list for professional consultation included professionals in Ontario marked as active in the PEBC database not already involved in the project and who a) had indicated an interest in breast cancer, or b) were surgeons and radiologists who had not indicated a particular area of specialty. Imaging Leads for the Ontario Breast Screening Program were also contacted in advance, and those who agreed to participate were included in professional consultation.

Of 321 professionals contacted, 61 responses were received (19%). Twenty stated that they did not have interest in this area or were unavailable to review this guideline at the time.

The results of the feedback survey from 41 people are summarized in Table 5-6. The main comments from the consultation and the Working Group's responses are summarized in Table 5-7.

Table 5-6. Responses to four items on the professional consultation survey.

	Reviewer Ratings (N=41)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			7	19	15
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1	1	7	15	17
3. I would recommend this guideline for use in practice.	1	1	5	17	17
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers • Access to timely MRI and wait times • Availability/accessibility varies among regions (inequitable distribution) • Access to radiologists with expertise in MRI interpretation • Technical considerations of equipment and its operation • Access to biopsy after MRI; lack of MRI-directed biopsy capability • Delay of surgery due to MRI and follow-up procedures for biopsy and results • Anxiety due to treatment delay may lead to clinically unnecessary mastectomy. • Possible overtreatment surgically for the inevitable "gray zones"; repeated biopsies or long-term follow-up may further contribute to patient stress. • Access to oncoplastic surgery for multiple lesions and to reconstruction if mastectomies increase • Increase in bilateral surgery, which takes more time/resources. • Capacity issues for system • Quality of studies is more limited than usual. • Push-back back by surgeons or others who focus only on recurrence and mortality rates • Adverse effects of MRI, false negative cases may lead to a wrong decision in surgery Barriers and Enablers • Recommendations are very general and MRI may apply to most patients, even when mastectomy is being considered. Perhaps we should be doing more routine preoperative MRI. • The guidelines are based on survival outcomes but do not take into account breast reconstruction decisions that are greatly influenced by preoperative findings and affect				

	quality of life decisions by patients . Now that oncoplastic surgery and immediate breast reconstruction is considered, MRI would be beneficial in surgical planning and may improve quality of life. Enablers • Good language around breast MRI being considered in consultation with the patient. • As MRI use increases and radiologists become more familiar with reading MRI/MRI guided biopsies, the false negative rate will decrease. • Guideline is thorough and well written.

Table 5-7. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
Lack of MRI biopsy capability is an issue. I think this needs to be stronger. If a centre is going to do MRI then they MUST have MRI biopsy capability. It significantly increases time to first treatment (associated with worse survival outcomes) if a patient has an MRI at one centre without biopsy capability and biopsy is recommended. The patient needs to start over in another centre to have an MRI biopsy, and often requires another MRI to assess the outside MRI finding.	The section in technical issues has been reworded to address this.
Overall, I think the guideline plays down the increased biopsy rate with MRI (and increased benign biopsy rate would be interesting) and downplays the lower specificity and time to surgery and increased mastectomy rate.	It was outside the scope of the review to gather information on false positive rates; however, the first point under potential harms in Table 2-1 is an increase biopsy rates including false negatives, so do not think this is downplayed. We did state in the Introduction that "MRI specificity depends on study populations, technical methods, and criteria for interpretation. It is generally greater than 70%, and up to 97% has been reported (2). The American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) Atlas (cited in (72)) sets a benchmark for specificity in screening MRI as 85% to 90%." If centres are achieving this benchmark, then specificity is as high as for mammography, and much better in patients with dense breasts (see Recommendation 3). The potential delays due to MRI are mentioned several times. These are primarily system issues as opposed to intrinsic issues and may vary from a few days to several months. High mastectomy rates, as illustrated by the extremely wide range among different institutions, are less due to disease factors, and more influenced by physician and institutional factors and patient

	preferences. We reported a final mastectomy rate of 41.8% with MRI versus 37.6% without.
In Recommendation 1 there are a number of strong statements about RFS and DFS but the confidence intervals cross 1 (0.53 to 1.12), which I thought made the finding non-significant. Same for use of MRI and reducing positive margin (0.74 to 1.06). If I have interpreted the statistics correctly, I thought this meant this was a non-significant finding. The use of MRI is associated with an improvement in RFS or DFS: HR 0.77 (95% CI 0.53 to 1.12). One cannot make this claim with these data. Similarly, the use of MRI is associated with a reduction in the rate of positive margins HR 0.89 (95% CI 0.74 to 1.06). One cannot make a definitive claim of benefit here either.	While we did not comment on statistical significance in the document, we recognize "use of MRI is associated…" may be overstating the results. We have removed RFS/DFS from Key Evidence. For positive margins, we have removed overall data from the Key Evidence but kept the subgroup data for which OR=0.57, 95% CI=0.36 to 0.89).
I think this is an area of heterogeneous study quality that is not adequately addressed by the guideline. Specifically, RCTs and observational studies are afforded similar weight (at least based on relative sample sizes). I am concerned by the rigour of the meta-analysis and whether the data reported can be trusted.	This is addressed in the systematic review (1).
Non-significant effects (e.g., recurrence risk) are incorrectly reported as significant.	As suggested in the Cochrane Handbook, we have avoided statements of significance. However, recurrence results (HR=0.77, 95% CI=0.65 to 0.90) would be statistically significant.
I am unsure where HRs for recurrence have been extracted from. Specifically, in the Turku study, I am not aware of a time to event analysis for recurrence risk. Similarly, the POMB study did not report these data to my knowledge.	Most HRs are as reported in the publications. For a small number of RCTs (including the Turku study) or studies with propensity score matching, other reported data was entered in RevMan which then calculated HRs. The 2021 publication of the POMB trial mentioned in Section 4 (106) reported rates and HRs for locoregional recurrence, distant recurrence, contralateral recurrence, any recurrence, any event (DFS) death (OS), and breast cancer deaths.
There was also little mention of the effect of age on MRI studies. For example, in the POMB study (which is one of the larger RCTs), all patients were 56 years of age or younger. Benefit for patients older than 75 years is unclear for me.	We have no information to indicate that age is an independent factor determining whether MRI is of benefit. Age may be associated with comorbidities, suitability of any or specific surgeries, life expectancy, menopausal status, hereditary cancers, breast density, patient preferences for BCS, effect of surgery on quality of life, acceptable risk of recurrence, etc., While we required age or menopausal status to be a factor in matching/adjusting the MRI and no MRI groups, we are not aware of studies comparing MRI versus no MRI and reporting relative benefits of MRI according to age.

	These factors could be part of the consideration as to whether MRI is appropriate for a specific patient.
This is an excellent guideline. I rated it 4 because it does not address the research question which includes effects on use of radiation and systemic therapy. This should be mentioned somewhere, I think. I know the title is preoperative MRI but then the research question should be different or at least say why these issues were not included in the guideline.	The research question for the literature review (see Section 4 or previous publication (1) included effects on radiation and systemic therapy. Studies which met the inclusion criteria did not provide sufficient information to make specific recommendations, and therefore radiation and systemic therapy were not part of the guideline objective (see Section 2). An additional statement under limitations has been added.
As well the breast pathway has no link and is not defined. Users of the guideline may not be aware a pathway exists as it is not advertised or published in any journals	A link has been added.
I do not think the guideline should be implemented as I do not agree with it. As written, it makes preoperative MRI the default, asking surgeons to consider it in ALL cases and then decide in which specific cases not to perform it. The default should be to NOT perform MRI and then choose to do it in specific cases, for example in which the extent of disease is difficult to assess and the surgeon is uncertain whether the disease is resectable (e.g., invading chest wall) or whether breast conserving therapy is possible (e.g., lobular cancer). Besides the fact that overuse of MRI is a waste of a valuable, costly resource in a very cash-strapped system, there are many downstream negative effects for the patient.	It makes consideration about MRI the default. That is not the same as making use of MRI the default. We disagree the default should be to not perform MRI. We have acknowledged that resource limitations are a concern. While outside the scope of this work, there are studies suggesting preoperative MRI is cost effective. There are both potentially positive and negative effects for the patient, as outlined in Table 2-1. We have clearly stated in the recommendations that “the ensuing decision of whether to conduct MRI should be made in consultation with the patient and must take into account the balance of benefits and risks and patient preferences”.
The false positive rate leads to unnecessary unilateral and bilateral mastectomies as well as the need for follow-up MRIs for at least an additional two years. And preoperative MRI leads to overdiagnosis of ipsilateral and contralateral cancers as the incidence of these cancers far exceeds the incidence of these cancers over the following years in the absence of MRI (many of these cancers are likely cured by current systemic treatments and radiation).	It is essential that no change in management occurs due to additional lesions without confirmation by biopsy. Except in studies that did not follow this requirement, evidence reviewed did not indicate that MRI leads to overdiagnosis. The document does not suggest the need for additional follow-up due to MRI, and follow-up requirements after surgery for breast cancer was not a part of this guideline.
This guideline reads like it was driven by radiology special interest groups rather than clinicians who actually deal with patients and their decision-making. I see patients who remain anxious for years because their preoperative MRI showed lots of 'stuff' that cannot all be biopsied, and they then want MRI screening to be done in perpetuity.	This would be most appropriately addressed as part of the joint and informed decision of whether to conduct MRI (see risks and benefits in Table 2-1), as well as the decision whether to have mastectomy or breast-conserving surgery. Furthermore, the decision for surveillance imaging should be a shared process between the patient and the healthcare provider.

I would avoid the statement "too large for the MR" - maybe a softer wording "MR does not accommodate body habitus" or something else	This change has been made.
In Recommendation 3, MRI is recommended to identify additional lesions in women with dense breasts. It would be helpful if there could be some quantification to this recommendation (i.e., what percentage dense breast tissue should trigger MRI).	The percentage is not clear. We have declared in Recommendation 3 that there is limited evidence, and the recommendations are based on expert opinion. MRI has been shown to reduce interval cancer rates in women with dense breasts (DENSE trial) compared to mammography. This and other studies would lend support to the panel recommending MRI on this basis.
Why are there blank cells in Table 4-2b and others?	RCTs were evaluated in Table 4-1 and therefore only summary data for RCTs is included in Table 4-2. A footnote to this effect has been added to the table.
I think another important endpoint is mastectomy rate with and without MRI and this should be emphasized in summary comments as well.	We have reported this but chose not to emphasize this, as additional factors also contribute to the decision of whether to have a mastectomy.
I was interested in the statement of "performance depends on the equipment and MRI techniques used and expertise of those conducting the analysis". The latter comment regarding expertise is interesting from a pathology point of view. As a breast pathologist, I often find that there are overcalls in breast MRI and we are forced in pathology to hunt down many lesions described on MRI that turn out to be benign/inconsequential (this takes up considerable pathology resources). I sometimes wonder if this is related to whether the radiologist reading the breast MRI has fellowship experience or not. I realize that not everyone can be expected to have this experience, but I wonder about how the specificity of the test is influenced by one's experience/criteria for interpretation.	Publications of studies using multiple readers for the same MRI output have found differences in sensitivity and specificity among readers.
It would be helpful to include a definition of some terms, e.g., is there a time limit after an initial surgery to qualify as a conversion mastectomy? Also, what is the time threshold between synchronous and metachronous additional breast cancer cases?	The systematic review indicates that conversion mastectomy occurs when patients had an initial BCS, but due to reasons such as positive margins or detection of additional tumours, a subsequent mastectomy was performed. It would not include reoperation for recurrence or additional cancers detected on follow-up. The systematic review notes that synchronous cancers are those occurring and detected at the same time, and that some publications include contralateral cancer detected within six months as synchronous.
In our centre, patients with newly diagnosed breast cancer routinely have a contrast	This was outside the scope but mentioned briefly in the systematic review as well as qualifying statements

mammography. What is the advantage of an MRI over contrast mammography? Growing rate of use of contrast-enhanced mammography should promote developing future guidelines regarding the use of contrast enhanced mammography preoperatively.	in Recommendation 1. MRI has the advantage of not using radiation.
I completely agree that preoperative MRI brings lots of benefit for patient with ILC and multifocal tumours.	
It would be extremely useful to develop guidelines for MRI screening in patients with dense breasts (maybe with abbreviated protocols). This would be preferable to ultrasound screening.	
There is also a need for guidance on the use of MRI in the follow up/surveillance of people with previously treated breast cancer	
Would like to see recommendations regarding extensive cases of DCIS.	

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC Report Approval Panel.

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Appendix 1. Affiliations and Conflict of Interest Declarations

Table A1-1. Members of the Preoperative Breast MRI Working Group

Name and profession	Affiliation	Declarations of interest
Derek Muradali Radiologist	• Professor, University of Toronto • Staff Radiologist, St Michael's Hospital, Toronto	None
Andrea Eisen Medical Oncologist	• Ontario Breast Cancer Lead, Ontario Health (Cancer Care Ontario) • Medical Oncologist and Head Familial Cancer Program, Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto • Associate Professor, Department of Medicine, University of Toronto	None
Erin Cordeiro Surgeon	• General Surgeon, The Ottawa Hospital • Attending Surgeon, Breast Surgical Oncology Unit, Division of General Surgery, The Ottawa Hospital • Assistant Professor, Division of General Surgery, Department of Surgery, University of Ottawa	None
Samantha Fienberg Radiologist	• Clinical Lead for the Ontario Breast Screening Program (OBSP), Cancer Screening, Ontario Health (Cancer Care Ontario) effective January 10, 2020 • Assistant Clinical Professor Radiology, Faculty of Health Sciences, McMaster University, Hamilton • Radiologist, Grand River Hospital, Kitchener • Regional Breast Imaging Lead, Waterloo Wellington Regional Cancer Program	None
Glenn Fletcher Health Research Methodologist	• Health Research Methodologist, Program in Evidence-Based Care, Department of Oncology, McMaster University, Hamilton	None
Ralph George Surgeon	• Medical Director, CIBC Breast Centre, St. Michael's Hospital, Toronto • Associate Professor, Department of Surgery, University of Toronto	Co-Principle Investigator, PET ABC study looking at PET for staging LABC
Supriya Kulkarni Radiologist	• Assistant Professor, Medical Imaging, University of Toronto • Department of Medical Imaging, Princess Margaret Hospital	None

Jean Seely Radiologist	• Professor, Department of Radiology, University of Ottawa • Head, Breast Imaging Section, Department of Medical Imaging, The Ottawa Hospital • Regional Breast Imaging Lead, Ontario Breast Screening Program, Champlain LHIN, Cancer Care Ontario	• Site principal investigator for the TMIST (Tomosynthesis Mammography Intervention Screening Trial) in Ottawa, funded by National Cancer Institute, to the Canadian Clinical Trials Group; voluntary role and employ staff research team to perform study. • Consultant to the Canadian Breast Cancer Network in 2022; received honoraria of $750. • Visiting professor to Queen's university and received honorarium of 750$.
Rola Shaheen Radiologist	• Regional Breast and Cancer Imaging Lead (RBCIL) for the Central East Regional Cancer Program & Regional Breast Imaging Lead (RBIL) for the Mississauga Halton and Central West Regions • Chief of Radiology and Medical Director at Peterborough Regional Health Centre	None

Table A1-2. Members of the Preoperative Breast MRI Patient Consultation Group

Name	**Declaration of Conflicts of Interest**
Joan Conrad	Board member (unpaid) for Peterborough Regional Health Centre
Randy Conrod	None
Lise Craig	None
Lauri Petz	None
Bob Tuck	None

Table A1-3. Members of the Preoperative Breast MRI Expert Panel

Name	Profession	Declarations of interest
Brian Pinchuk	Surgical Oncologist	None
Muriel Brackstone	Surgical Oncologist	None
Petrina Causer	Radiologist	None
Vivianne Freitas	Radiologist	None
Francisco Perera	Radiation Oncologist	None
Anne Koch	Radiation Oncologist	None
Sonal Gandhi	Medical Oncologist	>$500 as consultant on Advisory Board for Novartis
Anita Bane	Pathologist	None

In accordance with the PEBC Conflict of Interest (COI) Policy, the Preoperative Breast MRI Guideline Development Group members and internal and external reviewers were asked to disclose potential conflicts of interest. Authors and internal reviewer declarations are recording in the preceding tables. Report Approval Panel members and targeted external reviewers indicated they had no conflicts. The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca.