MAGNETIC RESONANCE IMAGING FOR BREAST CANCER SCREENING, PRE-OPERATIVE ASSESSMENT, AND FOLLOW-UP

Effective Date: January 2012

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

Diagnostic imaging is now an essential part of breast cancer screening, assessment, and follow-up. Mammography has been the gold standard for screening and surveillance. Ultrasound is an accepted adjunct to mammography in the diagnostic work-up of suspicious lesions. Increasingly, magnetic resonance imaging (MRI) is also being used in the work-up and surveillance of breast cancer. Given the issues of accuracy, access and cost, the appropriate use of MRI in the context of breast cancer requires clarification and ongoing review.

GUIDELINE QUESTIONS

- Should MRI be used for breast cancer screening?
- Should MRI be used for preoperative assessment of breast cancer?
- Should MRI be used for the follow up of patients treated for breast cancer?
- In which patients is the use of MRI appropriate?
- Are there other considerations?

DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Breast Tumour Team. Members of the Alberta Provincial Breast Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, pharmacists, and radiologists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Breast Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in October 2010. This guideline was revised in January 2012.

SEARCH STRATEGY

A systematic search for relevant, existing practice guidelines, systematic reviews, health technology assessments, meta-analyses, and randomized controlled trials was conducted of: MEDLINE, CINAHL, EMBASE, CancerLit, the Cochrane Library, and the National Guidelines Clearinghouse.

The search terms included “breast neoplasm” and “magnetic resonance imaging.” The search covered the period between 1965 and July 2010. A total of 95 articles were returned. The majority was review articles; there were seven clinical trials, nine meta-analyses, 12 comparative studies, and nine guidelines.

There is a paucity of data on many of the uses of MRI in the context of breast cancer. As such, the guideline developers have chosen to make provincial recommendations for use of MRI, by adapting from existing evidence-informed guidelines elsewhere. A recommendations matrix highlighting key guidance from nine existing guidelines on the use of MRI for breast cancer assessment, staging, and follow-up, is included in the Appendix.

RECOMMENDATIONS
1. Screening

The following sources were considered in developing the screening recommendations: the Alberta Breast Cancer Screening Program,1 the National Comprehensive Cancer Network,2,3 the National Institute for Health and Clinical Excellence,4 Cancer Care Ontario,5 the American Cancer Society,6 and the American College of Radiology.7

Mammography is the recommended modality for screening breast cancer in the general population of asymptomatic women.8,9

- The Alberta Breast Cancer Screening Program1 recommends:
  - Encouraging eligible women age 50 to 69 to have a screening mammogram every two years,
  - Advising them of their results, and
  - Reminding them if they are overdue for a repeat screening.
- Women aged 40 to 49 and over 70 may be referred to the Program by a family physician.

MRI should be used in addition to mammography, at an interval of every 12 months, for screening high-risk category patients; these include women who:2-4,7

- Have known personal history of deleterious mutation(s) in either BRCA1, BRCA2, TP53 or PTEN.
- Have never been tested personally but have a first degree relative with known BRCA1, BRCA2, TP53 or PTEN.
- Have a personal lifetime risk of developing breast cancer of 20-25 percent or more according to models that are largely dependent on family history.
- Are under 50 years of age and have received radiation treatment to the chest between ages 10 and 30 (e.g. thoracic radiation therapy for Hodgkin’s disease)

A more detailed guideline, Risk Reduction and Surveillance Strategies for Individuals at High Genetic Risk for Breast and Ovarian Cancer, developed by Alberta Health Services in 2011 is available at the following website: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-br011-hereditary-risk-reduction.pdf.10

There is insufficient evidence to recommend routine use of MRI screening in women who:5-7

- Have a lifetime risk of breast cancer of 15–20 percent, as defined by models that are largely dependent on family history.
- Have only had lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH).
- Have only had atypical ductal hyperplasia (ADH).
- Have heterogeneously or extremely dense breasts on mammography with no other risk features.
- Have personal history of breast cancer, but do not otherwise fit into the high-risk category as noted above.

2. Pre-operative Assessment

The following sources were considered in developing the pre-operative assessment recommendations: the National Comprehensive Cancer Network2,3 and Cancer Care Ontario.5

Pre-operative MRI may be considered in the following circumstances:

- Biopsy proven axillary nodal adenocarcinoma with no primary identified on mammography, ultrasound, and physical examination.
Discordant clinical and mammogram/ultrasound findings.

Pre-operative MRI may be used in the following situations where the patient desires breast conserving surgery and:2,3,10

- There is high risk for multifocal/multicentric disease.
- The extent of disease is unclear.

MRI may be used for breast cancer evaluation before, during and after neoadjuvant therapy to help evaluate response to systemic treatments.11,12

- MRI may overestimate response to neoadjuvant chemotherapy and should not be used to plan post-chemotherapy breast conserving surgery.
- MRI accurately predicts lack of response to neoadjuvant chemotherapy and may be used to support a change in therapy.

3. Problem Solving

The following sources were considered in developing the recommendation on problem solving: the National Institute for Health and Clinical Excellence,4 the BC Cancer Agency,13 and the Scottish Intercollegiate Guidelines Network.14

MRI may be considered only after high quality mammogram and ultrasound have been carried out and the results are inconclusive or discordant. MRI should not be used in lieu of biopsy if more appropriate or in cases where clinical and radiological suspicion is low.

MRI is not recommended for the routine screening of patients with nipple discharge.

4. Follow-up

The following recommendation has been adapted from the National Comprehensive Cancer Network.2,3

There is insufficient evidence to recommend MRI for follow-up screening of the ipsilateral and contralateral breast of women with prior breast cancer unless they are in the high-risk category, as per the recommendations in the section on Screening.

5. Operational Considerations

The following recommendations have been adapted from the National Comprehensive Cancer Network.2,3

Breast MRI examinations require a dedicated breast coil and breast imaging radiologists familiar with the optimal timing sequences and other technical details for image interpretation.

Breast MRI examinations should be performed and interpreted by an experienced radiologist with training in breast MRI, working in concert with the multidisciplinary treatment team.

Patients meeting the criteria for MRI should be referred to a centre with an MRI machine that has been configured with a dedicated breast coil.

DISCUSSION
Screening

Several meta-analyses have examined the sensitivity and specificity rates of MRI. Warner, et al. (2008), conducted a meta-analysis of 11 prospective studies to compare the sensitivity and specificity of mammography alone, MRI alone, and mammography plus MRI in patients with known BRCA mutations and/or patients with various family history criteria but no known mutation (median age, 40-47 years). The analysis included 15,496 mammographies, 15,576 MRIs, and 6,781 mammography plus MRI screenings and revealed sensitivity and specificity rates of 39% and 95%, respectively, for mammography in BI-RADS 3+ patients (32% and 98.5%, respectively, in BI-RADS 4+ patients) versus 77% and 86%, respectively, for MRI in BI-RADS 3+ patients (75% and 96%, respectively, in BI-RADS 4+ patients). The combined (mammography plus MRI) rates were 94% and 77%, respectively, in BI-RADS 3+ patients (84% and 95%, respectively, in BI-RADS 4+ patients).

Another meta-analysis of nine prospective studies and one retrospective study evaluating the use of MRI for screening of women at high risk for breast cancer also showed sensitivity rates ranging from 71-100% for MRI. Thus, the mean positive predictive value of biopsies resulting from a positive MRI screen was 45% (range, 17-89%), which is close to or exceeds the 25-40% desirable positive biopsy rate range recommended by the ACR BI-RADS. MRI was also shown to detect unsuspected malignancies in the ipsilateral and contralateral breasts as well as malignancies in patients with metastatic axillary adenocarcinoma and unknown primary at rates of 15.9%, 4.4%, and 60.9%, respectively.

An analysis of the correlation between mammography and MRI in women at increased risk of developing breast cancer revealed correlation coefficients ranging from -0.38 to 0.18, among seven included studies. In all but one study, the 95% confidence interval for the correlation coefficient included 0.0, indicating no significant correlation; however, because the sensitivity of combined mammography and MRI is higher than each modality alone, MRI alone is not recommended for screening for high risk women and should always be used in conjunction with mammography. Using both tests for breast cancer screening is likely to improve the early detection of breast cancer in women at increased risk. Prior to partaking in a high risk screening program using MRI, patients should be made aware of the risk of false positives.

In women with newly diagnosed invasive breast cancer, there is insufficient evidence to recommend routine MRI unless there is a specific problem to be addressed. MRI has been used to screen for contralateral lesions. A systematic review and meta-analysis of 22 studies revealed a positive predictive value of 47.9% (95% CI, 31.8% to 64.6%) and a sensitivity (true positive to false positive ratio) of 0.92 (95% CI, 0.47 to 1.82) for MRI in this setting. However, caution is warranted before recommending that this group of women undergo routine contralateral MRI, as 35.1% of the MRI-detected cancers were ductal carcinoma in situ and the majority were stage pTis or pT1 and node negative; nevertheless, many women were reported as having undergone contralateral mastectomy. Women should be informed that MRI does not reliably distinguish benign from malignant findings and that they may be at risk of additional investigations or unnecessary surgery, as a result of the MRI findings.

Pre-Operative Assessment

Despite the high sensitivity rates reported for MRI, there is a need to reduce false positive rates in MRI detection. A meta-analysis of 19 retrospective and prospective studies that examined MRI detection or accuracy in local staging (or in determining disease extent) in women with proven or suspected breast cancer (n = 2,610) showed that the diagnostic odds ratio (a measure of both sensitivity and specificity)
was 88%, while the area under the curve (a global measure of accuracy) was 96%. However, the positive predictive value (a ratio of true positive results to all positive results) was only 66% (95% CI, 52-77%). This resulted in a change in surgical management for patients with multifocal/multicentric histologically-proven cancer from wide local excision (WLE) to mastectomy of 8.1% (95% CI, 5.9-11.3%) and from WLE to more extensive surgery (i.e. wider/additional excision or mastectomy) of 11.3% (95% CI, 6.8-18.3%). In patients who did not have additional malignancy on histology (false positive detection), a change from WLE to mastectomy of 1.1% (95% CI, 0.3-3.6%) and from WLE to more extensive surgery of 5.5% (95% CI, 3.1-9.5%) was made.

A more recent comparative study by Pengel, et al. (2009)\textsuperscript{21} showed that in women with invasive breast cancer, the rate of incomplete tumour excisions in wide local excisions was not significantly different among 176 patients eligible for breast-conserving therapy (on the basis of conventional imaging and palpation only) versus 173 who had an additional preoperative MRI (19.4% vs. 13.8%, respectively; P = 0.17). The large COMICE trial\textsuperscript{22} showed that the addition of MRI to conventional assessment (e.g. mammography, ultrasound, and physical exam) was not significantly associated with a reduction in re-excision rates (odds ratio 0.96, 95% CI 0.75-1.24; p=0.77); however, breast cancer patients with all histologies were included in the analysis and other research has shown a decrease in excision rates.\textsuperscript{23} The utility of MRI in this setting may be limited to patients with certain breast cancer subtypes; for example, Mann, et al. (2008) showed that in patients with invasive lobular carcinoma, the sensitivity of MRI was 93.3% and correlation with pathology ranged from 0.81 to 0.97; MRI resulted in a change in surgical management in 28.3% of cases.\textsuperscript{24} In patients with occult breast cancer (i.e. no primary tumour identified on physical examination, mammography or ultrasound), MRI was shown to detect the tumour in more than two thirds of patients and provided the possibility of breast conserving surgery in one third of patients.\textsuperscript{25} However, in patients with ipsilateral breast tumor recurrence, MRI evaluation in the planning of initial lumpectomies was not associated with improved local outcomes, as it did not influence the achievement of negative margins and was not associated with lower rates of re-excision (MRI: 11.8% versus no-MRI: 13.3%; P=0.50).\textsuperscript{26} Until more conclusive data is available, surgical decisions should not be based solely on MRI findings.

MRI has demonstrated high specificity but a low sensitivity in assessing response to neoadjuvant chemotherapy.\textsuperscript{11} MRI has been shown to accurately evaluate the size of non-responders to neoadjuvant chemotherapy (r > 0.87)\textsuperscript{22,27-29} Compared to ultrasound or physical exam, MRI was found to correlate most closely with pathologic tumour size (r = 0.749) in breast cancer patients (n = 68) who underwent MRI, ultrasound, and physical exam prior to the start of neoadjuvant chemotherapy and one week after completion of treatment.\textsuperscript{30} However, five out of six smaller studies\textsuperscript{31-36} conducted in patients with locally advanced breast cancer have provided no clear evidence that MRI is advantageous over physical examination, for assessing tumour response. An ongoing study at the Cross Cancer Institute in Edmonton, Alberta is collecting data on the use of MRI in this setting and may be able to provide clarification once the data have been analyzed. In the mean time it is recommended that, although MRI may be used support a change in therapy upon detecting a non-response to neoadjuvant chemotherapy, it should not be used to plan post-chemotherapy breast conserving surgery.\textsuperscript{12}

**Problem Solving**

Breast MRI is often used to further assess equivocal mammographic and ultrasound findings. The use of breast MRI in this mode, over guided biopsy or short term follow-up, often depends on the particular case, as well as the preferences of the radiologist, patient, primary physician, or surgeon. The use of breast MRI as a means for problem-solving has been supported in by several other organizations, including the
National Institute for Health and Clinical Excellence, the BC Cancer Agency, and the Scottish Intercollegiate Guidelines Network. These guidelines specifically recommend, however, that MRI be used to further assess inconclusive or discordant clinical and imaging findings, only after mammography and ultrasound have been carried out. Further, a recent retrospective study by Moy, et al. (2009) showed that, in cases in which mammographic or sonographic findings are inconclusive, MRI performed for the indication of problem-solving (i.e. asymmetry and architectural distortion) had a sensitivity of 100% and compared with mammography had significantly higher specificity (91.7% vs. 80.7%, p = 0.029), positive predictive value (40% vs. 8.7%, p = 0.032), and overall accuracy (92.2% vs. 78.3%, p = 0.0052). The frequency of incidental lesions detected at MRI was high (15.7%), all of which were subsequently found to be benign; therefore, strict patient selection criteria should be employed.

Follow-up

MRI may be used to diagnose local relapses of breast cancer; however, the accuracy of MRI can be affected by inflammatory changes in the breast tissue operative bed after surgery, for up to 6 months, and after radiation therapy, for up to 24 months; it is generally after this time period that local tumour recurrence appears, making the timing of MRI important. MRI may be used to identify and differentiate tumour recurrence from post-surgical or post-radiation scar when conventional imaging is indeterminate. In a study of patients with suspected tumour recurrence after lumpectomy, with or without radiotherapy and chemotherapy, Lewis-Jones, et al. (1991) reported a sensitivity of 100% and a specificity of 94% for MRI in detecting new tumour versus post-treatment fibrosis. However, a retrospective study (Gorechlad, et al. 2008) in patients treated with breast-conserving therapy and followed for a median of 5.4 years showed that the recurrence rate (1.7% of patients, ipsilateral breast) and risk of contralateral disease (2.3% of patients) were both very low and the authors concluded that MRI screening would not have been cost-effective and was unlikely to have improved overall survival. Therefore, MRI is not recommended for the follow-up of women with prior breast cancer unless they are in the high-risk category.

Operational Considerations

The use of MRI should be limited to trained and experienced radiologists, as there is evidence of a learning curve, especially for ductal carcinoma in situ (DCIS). In general, the sensitivity of MRI increases with experience, while the number of benign lesions investigated unnecessarily decreases with experience. The American College of Radiology (ACR) has introduced a voluntary accreditation program that evaluates the qualifications of personnel, the quality control program, MRI safety policies, and image quality specific to MRI. The program also defines the physician’s and the medical physicist’s qualifications (experience and education) and continuing medical education requirements in order to be accredited. The physician’s responsibility includes reviewing all indications for the examination, specifying the pulse sequences to be performed, specifying the use and dosage of contrast agents, interpreting images, generating written reports, and assuring the quality of both the images and interpretations. The medical physicist must be familiar with the principles of MRI safety, the Food and Drug Administration’s guidance for MRI diagnostic devices, and other regulations pertaining to the performance of the equipment being monitored; knowledgeable in the field of nuclear physics and MRI technology (e.g. function, clinical uses, performance specifications, calibration processes); and have an understanding of clinical imaging protocols and methods of their optimization.

The minimal technical requirements to adequately perform breast MRI include high spatial resolution with a breast coil on a high field magnet (minimum 1.5 T), with thin slices and high matrix (approximately 1 mm in-plane resolution). This will help to ensure better quality imaging and a higher signal-to noise ratio,
which are imperative for MRI to be able to detect breast cancer. Annual evaluation of MRI equipment should be performed and should include the following tests: magnetic field homogeneity, slice position accuracy, slice thickness accuracy, radiofrequency calibration for all coils, frequency and gain/attenuator verification, image signal-to-noise ratio (SNR) for all coils, intensity uniformity for all volume coils, phase stability and image artifact assessment for all coils, and softcopy (monitor) fidelity. In addition, the safety standards (e.g. signage, access control, screening procedures, and cryogen safety) should be assessed annually. Facilities performing breast MRI should have the capacity to perform MRI-guided intervention or to create a referral arrangement with a cooperating facility that could provide the service. In Alberta, the current availability of MRI machines that have been configured with a dedicated breast coil may be limited to the larger centres. Patients meeting the criteria for MRI should be referred to a centre with an MRI machine capable of performing breast MRI, if one is not available locally.

Cost-Effectiveness

The large COMICE trial out of the UK showed that in women with biopsy-proven primary breast cancer who had undergone conventional assessment followed by MRI (1.5 T or 1.0 T) with a dedicated bilateral breast coil \( (n = 816) \), the re-excision rates were similar (odds ratio = 0.96, 95% CI 0.75-1.24, \( p = 0.7691 \)) to those of women who had not undergone MRI \( (n = 807) \) and there were no significant differences in the proportion of patients receiving chemotherapy, radiotherapy or additional adjuvant therapies, local recurrence-free interval rates, quality of life measures, or economics. As such, the use of MRI in this setting may be limited in cost-effectiveness. However, preoperative biopsy of MRI-only-detected lesions (i.e. occult breast cancer) could minimize the incidence of inappropriate mastectomy, as MRI has been shown to provide the possibility of breast conserving surgery in as many as a third of patients with occult breast cancer. Furthermore, MRI may be cost-effective in patients with invasive lobular carcinoma, in which a sensitivity of MRI of 93.3% has been demonstrated and resulted in a change in surgical management in 28.3% of cases. More research is needed in order to identify the subtypes of breast cancer patients that may benefit most from MRI assessment, thereby maximizing the cost-effectiveness of this application.

Within CancerControl Alberta, access to MRI machines configured with a dedicated breast coil may be limited to the larger urban centres. As such, patients presenting with indications for breast MRI, as outlined in the recommendations section, may require a referral to a larger centre if an MRI machine capable of imaging the breast is not available locally or if local expertise in breast MRI is limited. The cost of a typical MRI scan in 2004/2005 in Alberta was approximately $500. The number of additional MRI scans, as a result of this guideline, is expected to be minimal. In 2011, there are expected to be 2,090 new diagnoses of breast cancer. Assuming conservatively that up to 15% of new breast cancer cases require MRI for the purposes of problem solving or pre-operative assessment, and that 1% of the population of women in Alberta fall into the high-risk category, an estimated 330 breast MRI scans will be performed annually, as a result of this guideline. This would result in a total cost per year of $165,000. Other possible costs would include staffing and travel expenses for remote patients.

Safety in Pregnancy and Breast-Feeding

Contrast enhanced MRI, using Gadolinium-based contrast agent, is contraindicated during pregnancy, as there are no adequate and well-controlled studies of its use in pregnant women. However, in rare and extenuating circumstances, whereby the health of the mother and/or fetus would be significantly compromised without a contrast enhanced MRI, and after all other imaging options (i.e. ultrasound, CT,
nuclear scintigraphy, fluoroscopy, etc.) have been exhausted, MRI with a Gadolinium-based contrast agent could be considered. Patients should be informed of the risks and benefits of the procedure.

GLOSSARY OF ABBREVIATIONS

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<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ACR</td>
<td>American College of Radiology</td>
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<tr>
<td>ADH</td>
<td>atypical ductal hyperplasia</td>
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<td>ALH</td>
<td>atypical lobular hyperplasia</td>
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<td>AUC</td>
<td>area under the curve</td>
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<td>CE</td>
<td>contrast enhanced</td>
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<td>DCIS</td>
<td>ductal carcinoma in situ</td>
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<td>DOR</td>
<td>diagnostic odds ratio</td>
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<td>LCIS</td>
<td>lobular carcinoma in situ</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>PPV</td>
<td>positive predictive value</td>
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<td>SNR</td>
<td>signal-to-noise ratio</td>
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<td>US</td>
<td>ultrasound</td>
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<td>WLE</td>
<td>wide local excision</td>
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<td>XRM</td>
<td>x-ray mammography</td>
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DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta

MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2012. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.
CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Breast Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Breast Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES

48. Turnbull LW, Brown SR, Olivier C, Harvey I, Brown J, Drew P, et al. Multicentre randomised controlled trial examining the cost-effectiveness of contrast-enhanced high field magnetic resonance imaging in women with primary...

