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Recommendations Report ARCHIVED 2012

Diagnostic Imaging in Breast Cancer

*A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)*

**This Practice Guideline Report was reviewed in Sept 2011 and
ARCHIVED in 2012.**

The reviewed report consists of:

- 1. Guideline Overview**
- 2. Full Report**

and is available on the CCO website at:

<http://www.cancercare.on.ca>

Release Date: April 3, 2012

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Diagnostic Imaging in Breast Cancer

Guideline Report History

| GUIDELINE VERSION | SYSTEMATIC REVIEW | | PUBLICATIONS | NOTES AND KEY CHANGES |
|--------------------------------|-------------------|-------------|-------------------------|------------------------------------|
| | Search Dates | Data | | |
| Original version April 2006 | 1980-2004 | Full Report | Web publication | Not applicable (NA) |
| Reviewed Version April 2012 | N/A | N/A | Updated Web publication | Guideline ARCHIVED |



Recommendations Report ARCHIVED 2012

Diagnostic Imaging in Breast Cancer

Guideline Review Summary

Review Date: September 2011

The 2006 guideline recommendations are

ARCHIVED

This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

OVERVIEW

Evidence-based Series History

This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 2006. In September 2011, the PEBC guideline update strategy was applied, and the recommendations were archived. The Full Report in this version is the same as April 2006 version.

Update Strategy

The PEBC update strategy includes an annual screening of our guidelines and if necessary, an updated search of the literature is conducted with the review and interpretation of new eligible evidence by the clinical experts from the authoring panel and consideration of the guideline and its recommendations based on the new available evidence.

Impact on Guidelines and Its Recommendations

During the annual screening process, it was agreed that this document will no longer be maintained by PEBC therefore an update literature search was not conducted. The 2006 guideline and its recommendations on Diagnostic Imaging in Breast Cancer are ARCHIVED (Appendix 3).



Recommendations Report ARCHIVED 2012

Diagnostic Imaging in Breast Cancer

R. Myers, T. Minuk, M. Johnston, and the Diagnostic Imaging Guidelines Panel

Report Date: April 12, 2006

I. QUESTIONS

1. In patients with breast cancer, when should ultrasonography (US), computed tomography (CT) scan, or magnetic resonance imaging (MRI) be used:
 - for the initial staging of patients with newly diagnosed breast cancer,
 - to assess tumour response in patients with breast cancer undergoing chemotherapy,
 - to detect disease recurrence in patients who have completed primary treatment for breast cancer?
2. How often should imaging be repeated during treatment and follow-up?

II. INTRODUCTION

Diagnostic imaging is essential to determine the staging of disease in patients with an established diagnosis of cancer. Such staging is critical for determining the type and aggressiveness of treatment options to be offered to patients. Where needed, imaging is also used to assess the response of the cancer to therapy and to determine the extent of the disease when recurrence is found.

There are concerns with the current state of diagnostic imaging delivery for cancer. There is a perception among Canadians that waiting times for many medical services are excessive, which may be harmful to patients. Those concerns about excessive waits apply to diagnostic imaging, particularly cross-sectional imaging modalities such as computed tomography (CT), and magnetic resonance imaging (MRI). Of importance, radiologists have identified cross-sectional imaging for cancer as the major determinant of CT and MRI use in the province. As well, some have suggested that many imaging studies ordered during active treatment among patients with cancer are done so for uncertain reasons and that results will often have no impact on clinical care. Moreover, significant expansion in the number of CT and MRI machines has not meaningfully influenced wait times for those investigations.

For those reasons, Cancer Care Ontario established a small working group to review cancer treatment guidelines published during the last five years. After examining documents from nineteen guideline developers, the group concluded that the available guidelines did not adequately address the use of cross-sectional imaging in oncology. The lack of guidance on the use of those tests during active treatments was of particular concern. Therefore, a Diagnostic Imaging Guidelines Panel was established to develop practice guidelines for Ontario on the use of CT, MRI, and ultrasound for the initial staging, assessment of tumour response during active

treatment, and follow-up for patients with six types of cancer: lymphoma, breast cancer, colorectal cancer, prostate cancer, lung cancer, and ovarian cancer. Positron emission tomography (PET) was not considered in the guidelines because PET is not currently available across Ontario, and clinical trials are ongoing. The Institute for Clinical Evaluative Sciences (ICES) has completed a systematic review on PET scanning in oncology that is available on the Web at http://www.ices.on.ca/file/Pet_jan20041.pdf.

A systematic review of the literature on CT, MRI, and US revealed that there are few randomized studies that provide guidance on the use of cross-sectional imaging in the management of patients with cancer. The guideline panel determined that it would have to evaluate both randomized trials and cohort studies, and incorporate expert opinion, to make its recommendations. This current guideline will deal with diagnostic imaging for patients with breast cancer. Use of mammography was systematically reviewed in this guideline; the focus is only on cross-sectional imaging.

III. METHODS

This guideline is one of a set developed by the Program in Evidence-Based Care's (PEBC) Diagnostic Imaging Guidelines Panel, using methods adapted from the Practice Guidelines Development Cycle (1). These guidelines are intended to:

- promote evidence-based practice,
- provide guidance to clinicians about which imaging techniques are the most appropriate to use in the workup and management of their patients,
- provide information that is useful to those charged with planning for the number of imaging machines needed for patients with cancer in Ontario,
- assist in monitoring the use of imaging modalities in patients with cancer.

Panel members included medical, radiation, and surgical oncologists; diagnostic radiologists; and methodologists. Prior to embarking on the guideline development, members were asked to disclose information on any potential conflicts of interest, but there were none. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-term Care.

The Diagnostic Imaging Guideline panel:

1. Formulated a set of guideline questions relevant to cancer care in Ontario,
2. Systematically reviewed existing evidence-based guidelines and evidence from primary studies.

The Breast Working panel:

1. Considered the quantity, quality, consistency, completeness and relevance of the available evidence,
2. Drafted recommendations, and,
3. Consulted members of relevant PEBC Disease Site Groups and external reviewers for feedback.

Evidence and expert opinion were considered in determining whether imaging should be conducted (e.g., How often would diagnostic imaging with CT, MRI, or US revise staging in patients with cancer?) and then which imaging test would be most appropriate (e.g., Should CT, MRI, or US be used to detect liver metastases?). An informal consensus process was used to reach agreement on recommendations.

A focused external review process was planned for each document, utilizing the expertise of a small panel of experts. That was obtained through a mailed survey consisting of items that addressed the quality of the draft report and recommendations and whether the recommendations should serve as a practice guideline.

Literature Search Strategy

An inventory of diagnostic imaging guidelines published in English after 1998 was completed by the PEBC in October 2003 and used to identify existing evidence-based guidelines. MEDLINE (Ovid–1980 to 23 September 2004), EMBASE (Ovid–1980 to 23 September 2004), and the Cochrane Databases of Systematic Reviews and Abstracts of Reviews of Effects (2nd Quarter 2004) were searched for meta-analyses, primary studies, and additional guidelines.

Search strategies were modified for each database and disease site. Searches of MEDLINE and EMBASE relied primarily on subject headings, with appropriate terms chosen for each database from the list in Appendix A. MEDLINE and EMBASE searches were conducted for breast neoplasms and breast cancer. Supplementary searches were conducted across disease sites for randomized trials and for studies reporting sensitivity/specificity; those searches used broader (i.e., less specific) search strategies in order to ensure that no relevant studies were missed. Titles, abstracts, full text, and keywords in the Cochrane databases of reviews were searched using text works such as ultrasound, computed tomography, magnetic resonance, cancer, and :carcinoma.

Study Selection/Eligibility Criteria

The Research Coordinator working with the guideline panel applied the eligibility criteria below to the titles and abstracts of the citations listed in output from the literature searches. Where titles and abstracts provided insufficient information to determine a study's eligibility for inclusion in the systematic review, the full report was examined online or in paper form.

Inclusion Criteria

Studies were included if they:

1. included patients with confirmed cancer of the breast,
2. evaluated CT, MRI, or US,
3. reported data for disease recurrence, quality of life, survival, frequency of true- and false-positive tests for extent of disease, or sensitivity, specificity, positive predictive value, or negative predictive value to detect distant metastases.
4. were randomized trials, comparative cohort studies, case series (prospective or retrospective) with more than 12 consecutive patients, meta-analyses (published in English after 1998) of data from randomized trials, comparative cohort studies, or case series.

Literature searches for primary studies were not restricted by language, but, because resources for translation were limited, evidence was abstracted only from English-language papers. Evidence-based guidelines from the PEBC or other guideline developers were reviewed. Those guidelines provide descriptive and interpretive summaries of the evidence, as well as recommendations based on evidence, values, and expert opinion. Clinical practice guidelines were eligible if they stated objectives or guideline questions, described the literature searched, and cited references for the evidence described.

Exclusion criteria

Letters, editorials, and meeting abstracts were not included.

Collating and Synthesizing the Evidence

The Research Coordinator extracted the following information from the published reports eligible for inclusion in the systematic review:

- recommendations and qualifying statements for evidence-based practice guidelines;
- survival, recurrence, surgery, and quality-of-life data for randomized trials;

- the percent of cases categorized as true positive and false positive, sensitivity, specificity, positive predictive, negative predictive value, and proportion of patients with disease from case series.

Where necessary, true positive, false positive, sensitivity, specificity, positive predictive value, and negative predictive value rates were calculated from data provided in primary reports, using the Predictive Value Calculator available on the Web at <http://www.azzopardi.freemove.co.uk/easycalc/Additions/predict.htm>.

Sets of tables summarizing the available evidence were distributed for review to individual panel members according to their area of practice, along with copies of guidelines and primary study reports. The guideline authors did not pool data from individual studies, but published meta-analysis were considered with the other evidence.

Study Quality

No attempt was made to systematically measure the quality of the studies included in the systematic review. However, note was made as to whether the imaging tests were interpreted without the knowledge of other clinical information. Only studies with an objective diagnostic standard were included. Case series that did not enter consecutive patients were excluded.

IV. RESULTS: SUMMARY OF THE EVIDENCE AND ISSUES RELATED TO CROSS-SECTIONAL IMAGING IN BREAST CANCER

Literature Available for Review

Twenty-three citations published in languages other than English could not be ruled out as potentially eligible for inclusion in the systematic review; all were case series, one of which was described as “consecutive” in English-language abstracts. No randomized trials or other comparative studies were found among the non-English-language citations. Eligible papers for the systematic review on imaging in breast cancer included four practice guidelines (2,14-16), one randomized trial (17), and 12 case series (3-13,18).

How often would diagnostic imaging with CT, MRI, ultrasound, chest x-ray, or nuclear medical scan revise staging in patients with newly diagnosed cancer?

Staging of cancer in general and for breast cancer in particular is done to determine the extent of disease, prognosis, and appropriate therapy needed and to allow comparison of treatment programs at different centres. In a new breast cancer patient who is well and who has a normal physical exam, normal complete blood count, and routine biochemical testing, the chance of detecting metastatic disease is quite small. The chance of finding metastatic disease does increase according to the TNM stage. In most new breast cancer patients, surgery is the usual initial treatment, provided the patient is fit and the breast tumour is resectable. Most often, staging is done postoperatively, and the amount of testing done is dependent on the TNM stage of the patient.

Imaging to detect metastatic disease

One evidence-based practice guideline released after 1999 examined the role of diagnostic imaging to detect distant metastases in stage I through III breast cancer (2). In February 2000, the PEBC's Breast Cancer Disease Site issued a guideline on baseline staging tests in primary breast cancer. The latest update search for new evidence was conducted in April 2003.

The guideline panel considered the role of staging in breast cancer at diagnosis to be effectively dealt with by PEBC guideline, which addressed the following questions:

1. Does evaluation with bone scanning, liver ultrasonography, and chest radiography help to determine the extent of metastatic disease in women with newly diagnosed operable breast cancer who are otherwise asymptomatic ?
2. In what stages of breast cancer is the prevalence of detectable metastatic disease high enough to justify routine testing with bone scanning, liver ultrasonography, and chest radiography?
3. Is there a role for performing those tests before surgery or for cases where they are necessary should they be performed only after surgery?

The guideline made the following recommendations for women with newly diagnosed breast cancer who have undergone surgical resection and who have no symptoms, physical signs, or hematologic or biochemical evidence of metastases:

- Routine bone scanning, liver ultrasonography, and chest radiography are not indicated before surgery.
- In women with intraductal and pathological stage I tumours, routine bone scanning, liver ultrasonography, and chest radiography are not indicated as part of baseline staging.
- In women who have pathological stage II tumours, a postoperative bone scan is recommended as part of baseline staging. Routine liver ultrasonography and chest radiography are not indicated in this group but could be considered for patients with four or more positive lymph nodes (now considered as stage 3).
- In women with pathological stage III tumours, bone scanning, liver ultrasonography, and chest radiography are recommended postoperatively as part of baseline staging.
- In women who are asymptomatic with stage 2 or 3 disease, for whom treatment options are restricted to tamoxifen or aromatase inhibition therapy, or for whom no further treatment is indicated because of age or other factors, routine bone scanning, liver ultrasonography, and chest radiography are not indicated as part of baseline staging.

There were no new series related to bone scan or chest x-ray to change our philosophy. However, in ultrasound, there were new published series. Since the original guideline was written, new information has been published about ultrasound. The recommendations related to ultrasound were based on a review of four case series (1625 women in total) reported between 1988 and 1993; liver ultrasound detected hepatic metastases in no patients with stage I disease, in 0.4% with stage II, and in 2.0% with stage III. Those recommendations are reinforced by the more recent study by Ravaioli et al that reported abdominal ultrasound data by stage of disease for a large consecutive series of patients (3). In that study, the true-positive rate for liver metastases was 0.8%, and the false-positive rate was 0.4%. Furthermore, the detection (true-positive rate) was 0% for stage 1 breast cancer, 0.5% for stage 2 with <4 nodes, 2.1% in stage 2 with >3 nodes involved (now considered stage 3), and 2.9% in stage 3 patients. The specificity of ultrasound was 62%, sensitivity 99%, positive predictive value 67%, and negative predictive value 99%, using distant metastases confirmed by CT or MRI during the six-month follow-up as the reference standard.

Imaging to determine extent of disease in the breast

Five case series examined imaging of the breast with ultrasound or MRI to determine the extent of disease prior to surgery (Table 1). Currently most centres in Ontario use mammography for that purpose, although MRI may be considered as an option in the future.

One study by Snelling et al (4) evaluated whole-breast ultrasound versus clinical measurement in differentiating tumours larger than 3 cm from smaller ones, using pathological tumour size as the gold standard. That study found low sensitivity for both modalities but found higher overall accuracy using whole-breast ultrasound (94% versus [vs.] 83%, $p=0.007$ on McNemar's test).

Four studies evaluated different imaging modalities for the detection of multifocal or diffuse disease, using final histopathological results as the gold standard. The Park et al (5) study found high sensitivity but moderate (67%) specificity for breast sonography. The Schelfout et al (6) study compared MRI, ultrasound, and mammography in the detection of multifocal, multicentric, and bilateral disease. That study found high specificity (100%) for all modalities, with high sensitivity for MRI but low to moderate sensitivity for ultrasound (9% to 56%) and mammography (18% to 56%). In contrast, Liberman et al (7) reported only 53% positive predictive value of MRI in detecting cancer in the ipsilateral breast. The Zhang et al (8) study found the combination of ultrasound and mammography to have a low sensitivity (26%) but high specificity (100%) compared to the MRI high sensitivity (100%) and good specificity (85%).

Table 1. Assessing extent of disease before surgery – test characteristics* from case series.

| Study | Patients | N | Prevalence | Imaging test | Sensitivity | Specificity | PPV | NPV |
|---|--|-----|------------------|------------------------------|-------------|-------------|------|------|
| Detecting tumours larger than 3 cm | | | | | | | | |
| Snelling, 2004 (4) | Candidates for breast cancer surgery | 111 | 24% | Whole-breast ultrasound | 26% | 94% | 58% | 80% |
| | | | | Clinical measurement | 30% | 83% | 36% | 79% |
| Detecting multifocal or diffuse disease | | | | | | | | |
| Park, 2003 (5) | Candidates for breast-conserving surgery | 183 | NR | Breast sonography | 100% | 67% | 75% | 100% |
| Schelfout, 2004 (6) | Candidates for breast-conserving surgery | 170 | multifocal 16% | MRI of breast | | | | |
| | | | | - multifocal disease | 96% | 100% | 100% | 99% |
| | | | multicentric 13% | - multicentric disease | 95% | 100% | 100% | 99% |
| | | | | - bilateral disease | 100% | 100% | 100% | 100% |
| | | | vs. Ultrasound | | | | | |
| | | | | - multifocal disease | 41% | 100% | 100% | 90% |
| | | | bilateral 5% | - multicentric disease | 9% | 100% | 100% | 88% |
| | | | | - bilateral disease | 56% | 100% | 100% | 98% |
| vs. Mammography | | | | | | | | |
| | - multifocal disease | 37% | 100% | 100% | 89% | | | |
| | - multicentric disease | 18% | 100% | 100% | 89% | | | |
| | - bilateral disease | 56% | 100% | 100% | 98% | | | |
| Liberman, 2003 (7) | Candidates for breast-conserving surgery | 70 | 27% | MRI of breast | NR | NR | 53% | NR |
| Zhang, 2002 (8) | Candidates for breast-conserving surgery | 54 | 37% | MRI of breast | 100% | 85% | 79% | 100% |
| | | | | vs. Ultrasound + mammography | 26% | 100% | 100% | 70% |

* using pathology results as the reference standard

PPV, positive predictive value; NPV, negative predictive value; NR, not reported

In what circumstances and with what frequency would diagnostic imaging with CT, MRI, or ultrasound be useful in determining tumour response in patients undergoing chemotherapy or radiotherapy?

Five case series have examined the role of MRI in assessing tumour response to neoadjuvant chemotherapy in patients with locally advanced breast cancer (Table 2), which occurs in <5% of breast cancer patients. There is no strong evidence that MRI was better than clinical examination for assessing tumour shrinkage. There were no studies on the use of imaging to monitor response to chemotherapy for metastatic disease.

Table 2. Detecting complete tumour response to neoadjuvant chemotherapy in locally advanced breast cancer - case series.

| Study | Patients | N | Imaging test | Complete response on imaging test* | | | |
|-----------------------|---|----|---------------|------------------------------------|-------------|------|------|
| | | | | Sensitivity | Specificity | PPV | NPV |
| Abraham, 1996 (9) | Stage II-IV undergoing chemotherapy prior to surgery | 40 | breast MRI | 27% | 90% | 50% | 76% |
| Cocquyt, 2002 (10) | Stage II-III undergoing chemotherapy prior to surgery | 42 | breast MRI | 0 | 97% | 0 | 83% |
| | | | clinical exam | 71% | 77% | 38% | 93% |
| Partridge, 2002 (11) | Undergoing chemotherapy prior to surgery | 52 | breast MRI | 38% | 100% | 100% | 90% |
| | | | clinical exam | 38% | 86% | 38% | 86% |
| Bodini, 2004 (12) | Stage II-III undergoing chemotherapy prior to surgery | 73 | breast MRI | 25% | 86% | 9% | 95% |
| | | | clinical exam | 4% | 10% | 10% | 4% |
| Martincich, 2004 (13) | Stage II-III undergoing chemotherapy prior to surgery | 30 | breast MRI | 100% | 92% | 75% | 100% |

*complete response on MRI or clinical evaluation confirmed by pathologic findings at surgery
PPV, positive predictive value; NPV, negative predictive value

The follow-up of patients undergoing treatment for metastatic disease is quite variable. In those patients, treatment is palliative and so, palliative end points should be followed and assessed. However, knowing whether a given treatment is successfully causing tumour regression or stability is important, in order to make decisions about continuing, changing or stopping therapy. To that end, imaging tests that are abnormal at baseline would usually be repeated every three or four months in order to decide whether the current therapy should continue or be changed. The one exception to that practice would be bone scanning, which can be misleading in follow-up, as healing can look very similar to new disease in bone.

What is the role of CT, MRI, and ultrasound in the detection of recurrent disease during the follow-up of patients who have completed primary treatment for cancer, and what should be the frequency of use of those tests during follow-up?

If local recurrence develops in a breast cancer patient, the goals of therapy become palliative. The exception is the patient who develops an ipsilateral or contralateral breast recurrence or a regional nodal recurrence, as many of those patients will be cured with further surgery.

Evidence-based guidelines on follow-up after curative treatment for breast cancer have been developed by two Canadian groups, the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer and the Canadian Task Force on Preventive Health Care (14,15). Neither of those guidelines nor a set of clinical indicators from the RAND Health group (16) recommend routine blood work or imaging, except for routine

breast imaging with mammography, during the follow-up of women who have completed primary treatment for breast cancer.

The Diagnostic Imaging Guidelines Panel endorses the recently updated Steering Committee guideline. Among other recommendations, that Canadian guideline concluded that:

- All patients with breast cancer should have regular follow-up surveillance.
- Annual visits should include mammographic examination.
- Routine laboratory and radiographic investigations should not be carried out for the purpose of detecting distant metastases.

What is the role of CT, MRI, or ultrasound imaging in assessing patients who develop symptoms of disease recurrence or elevated biochemical markers after primary treatment for cancer?

Patients who develop symptoms or signs of recurrence require individual testing to determine if recurrence has actually occurred and to determine the extent of the recurrence. The tests used to detect local recurrence usually include mammography, US, and clinical assessment, and when those are inconclusive, Breast MRI is often required and in some cases, biopsy may be necessary to confirm the presence of recurrent disease.

In general, once recurrence has been found, it is necessary to completely restage the patient with ultrasound, a bone scan, blood work, and biochemical markers, with MRI and CT being used as needed, but not necessarily routinely, to aid with the treatment decision of whether radiotherapy, hormonal therapy, or chemotherapy is required.

There is new information related to the problem of axillary pain or lymphedema. Not all affected patients require imaging of the axilla, but, when it is performed, one RCT has shown that CT is equivalent to MRI (Table 3), and a case series has shown similar results (Table 4).

The RCT did not detect a significant difference between CT and MRI (17). Dixon et al randomized 58 patients with axillary symptoms (e.g., pain or edema) after primary therapy for breast cancer to CT (n=29) or MRI (n=30), in order to determine if the axillary symptoms were due to metastatic breast cancer or to the fibrotic effects of previous surgery and radiotherapy. One patient in the MRI group dropped out immediately after randomization, and another crossed over to the CT group. Analysis was conducted according to the test given, rather than on an intent-to-treat basis. Outcomes reported included agreement between the radiologic diagnosis and diagnosis after six months of follow-up. Quality of life was assessed at the time of imaging and six months later.

Table 3. Detecting recurrence in axilla - randomized trial of CT versus MRI.

| | CT (n=29) | MRI (n=28) | |
|--|----------------------------|----------------------------|---|
| <i>Axillary findings – diagnosis of recurrence</i> | | | |
| Sensitivity | 80% | 88% | using 6-month diagnosis as gold standard |
| Specificity | 100% | 100% | |
| Positive predictive value | 100% | 100% | |
| Negative predictive value | 76-90% | 81-100% | |
| <i>Metastatic disease elsewhere</i> | | | |
| Known metastatic disease at referral | 1 | 3 | |
| Additional metastatic disease detected by imaging | 7 (24%) | 6 (21%) | |
| <i>Quality of life (N=37)</i> | | | |
| Change in score over 6 months (95% confidence interval) | -0.119 (-0.269 to 0.03) | 0.001 (-0.005 to 0.008) | p=0.10 |

Table 4. Detecting recurrence - case series.

| Study | Patients | N | Imaging test | Test characteristics* | |
|--------------------|--|-----|--------------|-----------------------|------|
| Bradley, 2000 (18) | Symptoms related to ipsilateral axilla | 105 | Axillary MRI | Sensitivity | 89% |
| | | | | Specificity | 100% |
| | | | | PPV | 100% |
| | | | | NPV | 90% |

* clinical outcome ≥ 12 months after MRI used as reference standard
 PPV, positive predictive value; NPV, negative predictive value

V. ONGOING TRIALS

One relevant trial was listed as open to recruitment in the National Cancer Institute's clinical Trials Database (<http://www.cancer.gov/search>). The American College of Radiology Imaging Network and the Cancer and Leukemia Group B are collaborating on a trial titled "Diagnostic Study of Contrast-Enhanced Magnetic Resonance Imaging and Correlative Molecular Studies in Women With Locally Advanced Breast Cancer Who Are Receiving Neoadjuvant Chemotherapy. That diagnostic trial is a study of MRI and biomarkers in women receiving chemotherapy before surgery for locally advanced breast cancer. More information is available online at <http://www.cancer.gov/clinicaltrials/CALGB-150007>.

VI. DISCUSSION AND CONSENSUS

How often would diagnostic imaging with CT, MRI, or ultrasound revise staging in patients with newly diagnosed cancer?

Imaging to detect metastatic disease

The guideline panel considered the role of staging in breast cancer at diagnosis to be effectively dealt with by the PEBC guideline (2). However, two issues were not directly assessed in that original guideline. First, there is no evidence to help determine what blood work is needed preoperatively in patients undergoing breast cancer surgery. Generally, that would be decided by each local hospital in accordance with the anesthesia requirements and general health of the patient. The second issue involves patients found to have clinical stage III cancers preoperatively, a group not commonly seen now because of more aggressive screening and increasing breast cancer awareness. They can be assessed in the same way as other patients with earlier stage disease. If they are clinically operable, surgery is still usually the best initial approach unless there are features in their physical exam that would suggest inoperability. If surgery is not felt to be initially possible then referral to a multidisciplinary clinic consisting of a general surgeon, radiation oncologist, and medical oncologist is advised to determine their optimal management. At that clinic, they would be staged through a bone scan, abdominal ultrasound, and a chest radiograph. Although diagnostic imaging tests continue to evolve rapidly, there is, unfortunately, no conclusive evidence to support changing the approach discussed above.

Imaging to determine extent of disease in the breast

Limited evidence was identified on the use of imaging to determine the extent of disease in the breast, and some of the evidence was contradictory. In general, ultrasound was found to have a relatively low sensitivity and high specificity, with the exception of the study by Park et al (5). Mammography was similar to ultrasound in performance. MRI was generally found to have high sensitivity and good specificity. The weight of the identified evidence is in favour of MRI for the detection of multifocal or diffuse disease.

In what circumstances and with what frequency would diagnostic imaging with CT, MRI or ultrasound be useful in determining tumour response in patients undergoing chemotherapy or radiotherapy?

Only evidence that evaluated chemotherapy in the neoadjuvant setting with regard to detecting tumour response was available. No studies were identified addressing chemotherapy in the adjuvant or metastatic setting or radiotherapy. In the neoadjuvant studies, both the clinical examination and MRI had generally high specificity. Clinical examination had a generally low sensitivity (11% to 39%), while MRI had widely varying sensitivity (0% to 100%, median 74%). That wide variation in sensitivity for MRI was not immediately explained through this review of the studies.

What is the role of CT, MRI, and ultrasound in the detection of recurrent disease during the follow-up of patients who have completed primary treatment for cancer, and what should be the frequency of use of those tests during follow-up?

No evidence beyond existing systematic reviews and guidelines (14-16) was obtained for this review. The Diagnostic Imaging Guidelines Panel endorses the recently updated Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer guideline (14).

What is the role of CT, MRI, or ultrasound in assessing patients who develop symptoms of disease recurrence or elevated biochemical markers after primary treatment for cancer?

Only one study was identified that looked at imaging modalities in assessing patients who developed symptoms of disease recurrence. The RCT (17) did not detect a significant difference between CT and MRI.

VII. EXTERNAL REVIEW

The draft report, with recommendations developed by a small panel of experts in oncology and radiology, was distributed with a 4-item survey in February and March 2006 for review as part of an external consultation process to a broader group of Ontario radiologists and oncologists. The external consultation included the 24 members of the provincial Breast Cancer Disease Site Group and 20 other Ontario health care providers. Among the 15 respondents (34%), which included four radiologists, one pathologist, three radiation oncologists and seven medical oncologists, fourteen filled in the questionnaire and eleven provided written comments. Fourteen agreed that the methods used in the report development were appropriate. Thirteen agreed with the draft recommendations as stated, and would follow the recommendations of the report whereas one would neither agree nor disagree to those statements. Twelve respondents agreed that the recommendations should be approved as guidelines for practice, one neither agreed nor disagreed and one disagreed.

Radiology Perspective

Most comments reflect how the respondents supported guidelines and the need to disseminate the information. There were many comments reflecting concerns regarding the lack of current institutional capacity for MRI and the need for some type of training or accreditation process for Breast MRI. One respondent commented that MRI is not 100% accurate and should not be used as a screening tool. This is not the suggestion of the panel but for MRI to be used to stage certain populations. Another respondent felt that in cases of inconclusive liver ultrasonography (fatty liver, etc) further evaluation by abdominal CT should be considered. The panel feels that, in general, there are a certain percentage of patients who have an ultrasound that is felt to be non-diagnostic, which may be for several reasons, including:

- a. Fatty liver. Fatty infiltration of the liver can limit the overall visualization of the liver in some patients and a CT scan would be of benefit in that group. It is important to note that many patients with a fatty liver will still have a diagnostic ultrasound and do not need CT;
- b. Position of the liver high under the rib cage. If the entire liver cannot be visualized for anatomic reasons, then a CT would be of benefit; and
- c. Obesity. The liver may not be optimally visualized in the obese and a CT would better visualize the liver in these patients.

If an ultrasound of the liver is felt to be non-diagnostic, for whatever reason, a CT scan could be obtained. In general, liver CT tends not to be limited by those factors that limit the quality of an ultrasound exam. One respondent commented that staging for metastatic disease with a chest X-ray did not exist nowadays and that the greater sensitivity of CT over chest X-ray meant that CT would be the modality of choice. However, the panel disagreed and felt that routine chest x-ray is the screening test of choice for lung metastasis in breast cancer patients. Chest CT scanning is certainly more sensitive at detecting metastatic disease in the chest, but is not the primary investigation and should only be used if there is some other reason, such as an abnormal chest x-ray that is suspicious for, but not diagnostic of metastatic disease.

Oncology Perspective

Again most respondents had comments supporting the recommendations. However, there were some concerns about possible missing articles from the literature review. The search criteria was very stringent to reduce possible biases, and many of those articles suggested did not meet the selection criteria either due to the use of non-consecutive patients or the lack of an outcome of interest. There was some concern that some recommendations were not always reflective of the points made in the body of the review. However due to the paucity of the literature in some areas, expert opinion and consensus carried more weight in the development of some of the recommendations. One respondent felt that a patient with a stage IIII surgically inoperable cancer should not wait to see an oncologist before being full staging workup is done since it would delay the time from referral to optimal treatment. The panel feels that if the surgeon or referring physician wants to do staging that is a fine option. Another felt that in the recommendations after surgery, those women whose treatment options may be limited to hormone therapy should not be discriminated against and that some of those with more advanced N2+ disease may harbour significant slowly growing bone metastases that could put them at risk of fracture and therefore a bone scan with X-rays of suspicious strategic areas would seem appropriate to minimize morbidity. The panel recognizes that this is a guideline only and although there may be patients that harbour asymptomatic bone metastases, the risk of bone metastases if there are no symptoms and the alkaline phosphatase level is normal, is small, irrespective of stage. A fracture, although possible, is rare in the asymptomatic patient.

Report Approval Panel

The PEBC Report Approval Panel felt that the guideline was well written, the recommendations were clear and that the authors appropriately balanced the input coming from the limited published literature, other guidelines, and a consensus process.

VIII. CONCLUSIONS

In general, the evidence base available to evaluate the relative merits of CT, MRI, and ultrasound is limited. Several well-written clinical practice guidelines are available that address some of the questions in this report, but, where existing guidelines are not available, the evidence on which to base a guideline is poor. There is a great need for further comparative

studies, preferably randomized studies that are designed and powered to provide definitive evidence regarding the utility of the different modalities.

Because of this lack of evidence, the Diagnostic Imaging Guidelines Panel has developed the recommendations presented below through a consensus process, using the existing evidence, professional experience, and clinical judgement to arrive at recommendations that the panel believes will improve patient care and outcome.

IX. RECOMMENDATIONS

Based on the evidence described above and their expert clinical opinion, the Diagnostic Imaging Guidelines Panel drafted the following recommendations. There is a summary of the recommendations at the end of the report (Table 5).

Staging

Before Surgery

Until further information becomes available, MRI and mammography are both useful tools to determine the extent of disease in women with operable breast cancer. The choice between those modalities should be made based on the particular conditions of each patient and the equipment availability to handle the increased workload that would entail. However, MRI should not be used as a substitute for detailed mammographic or sonographic work-up of any abnormalities detected at a routine screening or as a substitute for the clinical or image-guided core biopsy of mammographic, sonographic, or clinical abnormalities. Pathology is the gold standard.

Subsets of patients that may benefit from MRI include:

- Women with clinically palpable and mammographically occult breast cancer.
- Women with metastatic adenocarcinoma to axillary lymph nodes, with an unknown primary (normal mammogram and ultrasound)—75% to 85% of breast malignancies will be detected by MRI in these cases, and most will be <2cm.
- Women with lobular carcinoma. That histology is associated with a higher risk of multifocal and multicentric spread, and the extent is frequently underestimated mammographically and sonographically. MRI is not perfect in this area and may also underestimate the extent of disease; however, it is more sensitive than standard imaging.
- Patients who require re-excision because of positive surgical margins may benefit from the increased sensitivity of MRI. The group of patients with > 50% dense fibroglandular tissue (BIRADS densities 3 or 4), may benefit the most.
- Patients with a high risk of multifocal disease may warrant an MRI. The youngest patients (24-39 years) have significant multifocality not detected on routine imaging. Their surgical treatment is frequently dramatically altered by MRI.

After Surgery

The practice guideline issued by Cancer Care Ontario's PEBC should be followed. That guideline applies to women with newly diagnosed breast cancer who have undergone surgical resection, and who have no symptoms, physical signs, or hematological or biochemical evidence of metastases.

- In women with intraductal and pathological stage I tumours, routine bone scanning, liver ultrasonography, and chest radiography are not indicated as part of baseline staging.
- In women who have pathological stage II tumours, a postoperative bone scan is recommended as part of baseline staging. Routine liver ultrasonography and chest radiography are not indicated for that group.
- In women with pathological stage III tumours, bone scanning, liver ultrasonography, and chest radiography are recommended postoperatively as part of baseline staging.

- In women for whom treatment options are restricted to tamoxifen or hormone therapy, or for whom no further treatment is indicated because of age or other factors, routine bone scanning, liver ultrasonography, and chest radiography are not indicated as part of baseline staging.

Response

Locally Advanced Breast Cancer

In the follow-up of locally advanced breast cancer patients receiving adjuvant chemotherapy, mammography and ultrasound are not accurate at assessing tumour response. Clinical assessment is subjective and lacks accuracy as well. MRI will determine whether the tumour is responding to chemotherapy, which does have long-term prognostic implications. As well, it will determine which tumours do not respond to chemotherapy, in which case the therapeutic regime could be altered.

Metastatic Breast Cancer

In order to determine if a treatment is successfully causing tumour regression or stability and inform decisions about continuing, changing, or stopping therapy, imaging tests that are abnormal at baseline could be repeated every three or four months. The one exception to this process would be bone scanning, which can be misleading in follow-up, as healing can look very similar to new disease in bone. If a patient is diagnosed with metastatic breast cancer, staging is required to identify the full extent and patterns of spread to determine if the patient should be treated with hormonal therapy instead of chemotherapy.

Follow-up

The Canadian practice guideline issued by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer should be followed. In patients who have been treated curatively, routine imaging tests to detect distant metastases should not be carried out.

Diagnosing Recurrence

Patients who develop symptoms or signs suggestive of recurrence require individualized testing to determine if recurrence has occurred. Recurrent breast cancer may be difficult to fully assess on mammography due to scarring and inflammation from previous surgery or radiation. If the patient is a candidate for repeat lumpectomy, MRI should be considered.

X. ACKNOWLEDGEMENTS

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Table 5. Summary of recommendations.

| Clinical/ Diagnostic Problem | Investigation | Recommendation | Comment |
|---|------------------------------|------------------------------------|---|
| Staging | Mammogram | Indicated | <ul style="list-style-type: none"> • Best modality to stage. |
| | MRI | Indicated and Specialized Study | <ul style="list-style-type: none"> • Subsets of patients that may benefit from MRI: <ul style="list-style-type: none"> ◦ Women with clinically palpable and mammographically occult breast cancer. ◦ Women with metastatic adenocarcinoma to axillary lymph nodes, with an unknown primary. ◦ Extent of disease needs better delineation, e.g. women with lobular carcinoma. ◦ Patients who require re-excision because of positive surgical margins. ◦ Patients with a high risk of multifocal disease. |
| | US | Indicated (supplementary) | <ul style="list-style-type: none"> • Preoperatively to assess multifocal disease, and determine method of biopsy • Postoperatively to detect liver metastases in women with stage III tumours |
| | CT | Not Indicated | |
| Response Assessment | MRI | Indicated | <ul style="list-style-type: none"> • In women with locally advanced breast cancer: <ul style="list-style-type: none"> ◦ MRI will determine whether the tumour is responding to chemotherapy. ◦ Mammogram, CT and US not indicated |
| | Mammogram MRI CT US | Indicated | <ul style="list-style-type: none"> • In women with metastatic breast cancer: <ul style="list-style-type: none"> ◦ Imaging tests that were abnormal at baseline could be repeated every 3-4 months |
| Follow-up | Mammogram | Indicated | <ul style="list-style-type: none"> • Annual routine follow-up is recommended. |
| | MRI CT US | Not Indicated | <ul style="list-style-type: none"> • Routine imaging tests should not be carried out to detect distant metastases. |
| Investigation of a Suspected Relapse | Mammogram | Indicated | |
| | MRI | Indicated | <ul style="list-style-type: none"> • Recurrent breast cancer may be difficult to fully assess on mammography due to scarring and inflammation of previous surgery or radiation, so consider when: <ul style="list-style-type: none"> ◦ The patient is a candidate for repeat lumpectomy ◦ Discordant clinical and imaging findings ◦ Imaging findings unclear or uncertain |

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Appendix 1. Literature search terms.

MEDLINE

exp breast neoplasms/
lung neoplasms/sc [secondary]
liver neoplasms/sc
brain neoplasms/sc
bone neoplasms/sc
exp abdominal neoplasms/sc
exp neoplasms/sc
neoplasm staging/
staging.mp.
exp neoplasm metastasis/
neoplasm recurrence, local/
neoplasm, residual/

ultrasonography/
ultrasonography, doppler/
exp ultrasonography, doppler, duplex/
endosonography/
exp tomography, x-ray/
exp tomography, x-ray computed/
exp magnetic resonance imaging/
neoplasm metastasis/di, ra, ri, sc, us

randomized.mp.
randomized controlled trials/
randomized controlled trial.pt.
clinical trial.pt.
exp case-control studies/
exp cohort studies/
cross-sectional studies/
exp clinical trials/
control groups/
double-blind method/
matched-pair analysis/
random allocation/
single-blind method/
exp "sensitivity and specificity"/

sensitivity.mp.
follow-up studies/
follow-up.mp.
surveillance.mp.
guidelines/
practice guidelines/
guideline.pt.
practice guideline.pt.
(Medline.mp. or systematic.mp.) and
(review.mp. or review.pt.)
meta-analysis.pt.
meta-analysis/

EMBASE

exp breast cancer/
exp metastasis/di
cancer staging/
cancer recurrence/

diagnostic imaging/
echography/
exp computer assisted tomography/
nuclear magnetic resonance imaging/

"sensitivity and specificity"/
case control study/
prospective study/
retrospective study/
clinical trial/
multicenter study/
randomized controlled trial/
systematic review.mp.
systematic review/
meta-analysis/

Appendix 2. Stage grouping for breast cancer (TNM staging).

Primary tumor (T)

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

Tis Carcinoma in situ

Tis (DCIS) Ductal carcinoma in situ

Tis (LCIS) Lobular carcinoma in situ

Tis (Paget) Paget's disease of the nipple with no tumor

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

T1 Tumor ≤ 2 cm in greatest dimension

T1mic Microinvasion ≤ 0.1 cm in greatest dimension

T1a Tumor > 0.1 cm but not > 0.5 cm in greatest dimension

T1b Tumor > 0.5 cm but not > 1 cm in greatest dimension

T1c Tumor > 1 cm but not > 2 cm in greatest dimension

T2 Tumor > 2 cm but not > 5 cm in greatest dimension

T3 Tumor > 5 cm in greatest dimension

T4 Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below

T4a Extension to chest wall, not including pectoralis muscle

T4b Edema (including peau d'orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast

T4c Both T4a and T4b

T4d Inflammatory carcinoma

Regional lymph nodes (N)

NX Regional lymph nodes cannot be assessed (e.g., previously removed)

N0 No regional lymph node metastasis

N1 Metastasis in movable ipsilateral axillary lymph node(s)

N2 Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis

N2a Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures

N2b Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis

N3 Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement

N3a Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s)

N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)

N3c Metastasis in ipsilateral supraclavicular lymph node(s)

Regional lymph nodes (pN)**

pNX Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)

pN0 No regional lymph node metastasis histologically, no additional examination for isolated tumor cells***

pN0(i-) No regional lymph node metastasis histologically, negative IHC

pN0(i+) No regional lymph node metastasis histologically, positive IHC, no IHC cluster > 0.2 mm

pN0(mol-) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)

pN0(mol+) No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)

pN1mi Micrometastasis (> 0.2 mm, none > 2.0 mm)

pN1 Metastasis in one to three axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent§

pN1a Metastasis in one to three axillary lymph nodes

pN1b Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent§

pN1c Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent§¶

pN2 Metastasis in four to nine axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis

pN2a Metastasis in four to nine axillary lymph nodes (at least one tumor deposit > 2.0 mm)

pN2b Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis

pN3 Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph

nodes; or in ipsilateral supraclavicular lymph nodes

pN3a Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit > 2.0 mm), or metastasis to the infraclavicular lymph nodes

pN3b Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent§

pN3c Metastasis in ipsilateral supraclavicular lymph nodes

Distant metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

NOTE. Adapted with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the *AJCC Cancer Staging Manual, Sixth Edition* (2002) published by Springer-Verlag New York, <http://www.springer-ny.com>.

Abbreviations: IHC, immunohistochemistry; RT-PCR, reverse transcriptase polymerase chain reaction.

* "Clinically apparent" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

** Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node" (e.g., pN0(i+)(sn)).

*** Isolated tumor cells are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical or molecular methods but which may be verified on hematoxylin and eosin stains. Isolated tumor cells do not usually show evidence of metastatic activity (e.g., proliferation or stromal reaction).

§ Not clinically apparent" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.

¶ If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as N3b to reflect increased tumor burden.

Stage Grouping

| | | | |
|------|-------|-------|----|
| 0 | Tis | N0 | M0 |
| I | T1* | N0 | M0 |
| IIA | T0 | N1 | M0 |
| | T1* | N1 | M0 |
| | T2 | N0 | M0 |
| IIB | T2 | N1 | M0 |
| | T3 | N0 | M0 |
| IIIA | T0 | N2 | M0 |
| | T1* | N2 | M0 |
| | T2 | N2 | M0 |
| | T3 | N1 | M0 |
| | T3 | N2 | M0 |
| IIIB | T4 | N0 | M0 |
| | T4 | N1 | M0 |
| | T4 | N2 | M0 |
| IIIC | Any T | N3 | M0 |
| IV | Any T | Any N | M1 |

NOTE. Adapted with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. Original: AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, <http://www.springer-ny.com>.

* T1 includes T1mic.

Source: Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol*. 2002;20(17):3628-36.

Appendix 3. Review outcomes definitions.

1. **ARCHIVED** - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “ARCHIVED”.
2. **ENDORSED** - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.
3. **DEFERRAL** - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool
4. **UPDATE** - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.